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Posted Date: 3 February 2023

doi: 10.20944/preprints202302.0061.v1

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*Review*

# Structural Strategies of Supramolecular Hydrogels and Their Applications

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**Abstract:** Supramolecular structures are of great interest due to their applicability in various scientific and industrial fields. These fields of scientific action include promising applications i biomedical areas, in sensing, and in conductive and electrical phases. The sensible definition of supramolecular molecules is being set by investigators, who, because of the different sensitivities of their methods and observational timescales, may have different views as to what constitute these supramolecular structures. Besides, diverse polymers can be found to offer unique avenues for multifunctional systems with properties in medicine industrial applications. Aspects of this review provide different conceptual strategies to address molecular design, properties, and potential applications of self-assembly materials and the use of metal coordination as a feasible and useful strategy for constructing complex supramolecular structures. In this order of appreciations and ideas order, it is that this review report involves classic topics such as hydrogels that range from their relationship with drug delivery systems, to metallo-supramolecular materials, through applications in ophthalmic systems, in applications that require adhesiveness and electrically conductive hydrogels. This review also addresses systems that are largely based on hydrogel chemistry and the enormous opportunities to design very specific structures for applications that demand enormous specificity.

**Keywords:** supramolecular hydrogels, hydrogel chemistry; self-healing hydrogels, adhesive hydrogels, conductive hydrogels, clays, 3D structures

## 1. Introduction

Supramolecular chemistry is considered as one of the most important areas related with many classes of materials including hydrogels for uses in drug delivery and as biomaterials. This, coupled by practicing of the cross-linking based on host-guest recognition provides supramolecular hydrogels with the underlying affinity and dynamics to control key factors of stability of their mechanics properties [1,2] as well as offering the ability to protect and control the release of therapeutics [3].

In the construction of a network of supramolecular hydrogels a gelling molecule or macromolecule is necessary to form non-covalent intermolecular dynamic bonds such as hydrogen bonds, van der Waals interactions, electrostatic interactions, hydrophobic interactions, π−π bonds, metal-ligand coordination, and host-guest interactions [4]. In contrast, these properties are much less easily achievable by fully covalently cross-linked hydrogels whose degradation is practically negligible due polymer network is made by strong and irreversible covalent bonds [5].

One characteristic of molecular hydrogels lies in the fact that are materials which have a three-dimensional network structure and can hold or absorb water in each cross-link junctions, this unbound water molecules show no evidence of order. The design of the adhesion junctions depends on the way in which the adherends are joined to give rise to a topology and obviously to the surface properties in relation to adhesion [6].

Hydrogels are widely used in tissue engineering, implantable devices, and drug delivery systems due to their biocompatibility, controllable physical and mechanical properties [7]. Hydrogels

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include cross-linked three-dimensional (3D) networks containing an extensive range of structural forms and chemical compositions [8,9]. The static behavior of conventional hydrogels versus the dynamic behavior of smart hydrogels are two extremes of behavior that can significantly affect the performance of drug delivery systems among other technologies. In this sense, the dynamic nature of supramolecular chemistry is applicable to the development of smart hydrogels. Indeed, every time new technologies advance for specific demands, the structural chemistry of hydrogels is emphasized [10]. In contrast, in comparison with supramolecular hydrogels, specific properties of conventional hydrogels are much less easily achievable as the polymer network is permanently joined together by strong and irreversible covalent bonds [5].

This review addresses issues around macromolecular and supramolecular structures that are dominated by nanosciences and even nanotechnology since they allow a straightforward transition between different length scales. Research in biointerfaces comprises the development of a specific molecular patterns found in complex biological systems and their applications in controlled release of therapeutic agents. This discipline of technology integrates molecular assembly and nanoscale design to provide control over biological processes. We also emphasize, as far as possible the analyses of significant technological advances in supramolecular materials all those boosted by the hydrogels and their derivatives. By highlighting the importance of supramolecular hydrogels, this review will present a set of rational guidelines for the development of future supramolecular hydrogels even beyond tissue engineering applications as well as its implications for pharmacological and clinical effects as future research.

## 2. Hydrogels and their Relationship with Drug Delivery Systems (DDS)

The field of tissue engineering comprises a constant evolution that involves the regeneration of functional tissues [11]. Drug delivery systems focus on temporal control to deliver the proper dosage during a given time interval and the spatial control to deliver the pharmaceutical agents to the precise site in the human body. This control spatiotemporal control of the any drug release can reduce the off-target release and the subsequent degradation of active therapeutic agents upon administration by protecting the payload from harsh in vitro or in vivo environments. Additionally, it is worth noting that the inclusion of a photosensitive element allows for the delivery of higher concentrations of the drug to the target site in a more controllable manner. This peculiarity of drug manipulation enhances its effectiveness and at the same time minimizing off-target toxicity [12]. In an extensive review of Bernhard et al., two main areas of research on drug delivery systems are specified; the use of supramolecular binding systems to design hydrogels as injectable materials for local drug delivery and the adaptation of supramolecular hydrogels in drug delivery by adjusting the affinity between the drug and the material [13].

This characteristic impact and particularize the chemical properties that can dictate the way in which hydrogels can be delivered into the human body. It is so that hydrogel delivery systems can be classified based on their size as macroscopic hydrogels, microgels and nanogels [14]. However, regardless of the variety of packaging, transport, and storage both the drug and the hydrogel must be chemically and physically stable to hydrogel can be delivered by various means, such as surgical implantation, local needle injection or systemic delivery via intravenous infusion.

It is so that several enhanced biomaterial systems with controlled release properties guarantee the efficacy of therapies. At the same time, it is plausible a broad in a range of possibilities about the drug carrier interface modification al-ways keeping side effects under control in very low levels [15]; a miscellaneous of nanostructures for drug loading inherent to the incorporation of stimuli responsive agent are demonstrative illustrate in Figure 1. In a study directed by Vermonden it is specified an overview on supramolecular hydrogels containing hyaluronic acid (HA) as one of the building blocks. The authors argue that being HA present in many tissues and extracellular matrix (ECM) makes it amenable to designing supramolecular materials for biomedical applications and that by having excellent processing properties makes them more attractive [16]. Furthermore, this approach is mentioned in a very descriptive work in which it is emphasized that for enhance

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mechanical properties of hydrogels prepared through self-assembly is necessary increase the ability to fabricate complex and precise hydrogel tailored for drug delivery applications [17].

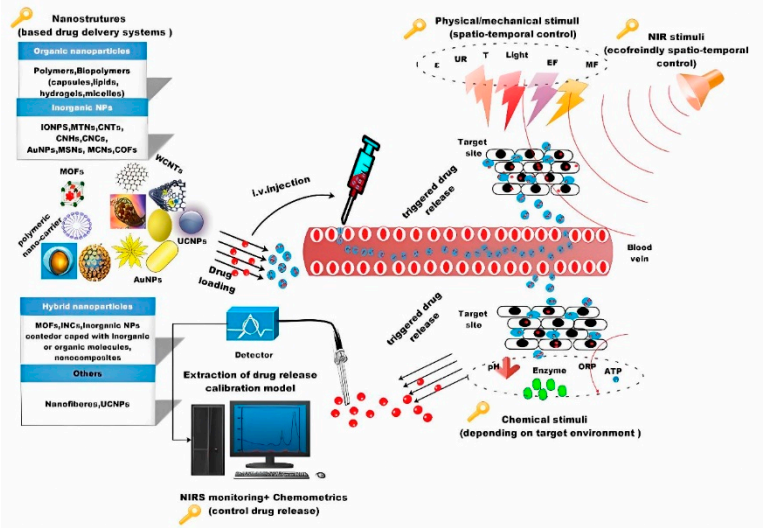


**Figure 1.** Scheme of basic nanostructures for DDS and different stimulation. Reprinted from Ref. [15] with permission.

In order to structure a injectable hydrogels platform based on hydrophilic thermosensitive linear-bottlebrush-linear (LBL) triblock copolymers that self-assemble at body temperature, a research group has developed systems to systematic control of the mechanical mismatch in an implant under controlled water environment, and other factors such as low viscosity at high concentrations of the hydrogel to facilitate injectability, physical cross-linking to eliminate any percolate of chemical into the body, and mechanical resilience [18]. Besides, in 2020, Ahsan et al., reported a thermosensitive, physically cross-linked injectable hydrogel was formulated for the effective and sustained delivery of disulfiram (DSF) to cancer cells [19]. In the same idea, a polyhistidine (Phis)-based Ni-coordinated hydrogel with physiologically relevant pH responsiveness, injectability, and stability in neutral buffer was prepared [20]. Alternatively, a series of injectable conductive self-healed hydrogels have been investigated based on quaternized chitosan-g-polyaniline (QCSP) and benzaldehyde group functionalized poly(ethylene glycol)-co poly(glycerol sebacate) (PEGS-FA) for cutaneous wound healing [21]. The adequate incorporation of chemically cross-linked domains and physically cross-linked domains effectively enhances the mechanical properties of the double-cross-linked (DC) cellulose hydrogels [22]. In the same way, as the capabilities of hydrogels have dramatically increased over time, they have unsurprisingly become useful tools for a wide range of fields and disciplines [23,24]. This is how works of researchers such as Correa et al, primarily focus on the contributions of injectable hydrogel systems, with an admirable emphasis on dynamic hydrogels [25].

The combined nanoparticle-hydrogel structures typically used in the conventional drug delivery can modulate the release kinetics of immunotherapeutic agents and functioning as tissue scaffolds [26]. Based on this, some drugs interact with enzymes in a way that changes the way the enzyme does its job. In this category, a particular emphasis on discussing the advantages in which a compound could interact with an enzyme in a way that increases expression, known as induction, or in a way that reduces or blocks its function, referred to as inhibition is of valuable importance. This means that one drug's impact on an enzyme or transporter could alter another drug's pharmacokinetics. In these scenarios, the former is commonly known as the perpetrator drug, which negatively affects the processing and physiological effects one second drug. For the above, some research that involve chitosan/glycerophosphate (CS/GP) hydrogel/microparticles assembly loaded with lornoxicam, a non-steroidal anti-inflammatory drug, presented a lower concentration into the blood, not so a direct injection of a lornoxicam solution in the delivery site, this is considered proof of a sustained delivery of this drug. In this setting, microparticles are embedded into hydrogel before its gelation process by

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mixing the microparticle suspension and the CS solution. The method is used with thermosensitive hydrogels for which the microparticle suspensions are pre-formed controlling the microparticle size to later mix them with a CS solution [27].

Other authors strategy has been to induce chemically and physically cross-linking domains within chitin hydrogels by sequential chemical cross-linking with epichlorohydrin (ECH) involving hydrogen bonding, hydrophobic interactions, and the formation of crystalline hydrates in aqueous ethanol solution. Due to behave coordinated to avoid stress concentration, there is an increase in the stress at fracture, higher deformation, and energy dissipation mechanism [28].

Physical networks typically employ enthalpy-dominated cross-linking interactions. That is why is that through mathematical relationship between cross-linking interaction thermo-dynamics and bulk viscoelasticity of the resulting physical networks, an entropy-driven physical network based on dynamic and multivalent polymer-nanoparticle (PNP) inter-actions were created hydrogels that exhibit temperature independent viscoelasticity [29]. Zeng et al., explored His-$Zn^{2+}$ binding, and showed that the coordination number is an important parameter for the mechanical strength of the hydrogels. By adjusting the His and $Zn^{2+}$ concentrations, demonstrated the hydrogels can achieve a set of demanding mechanical features, including the young's modulus of 7-123 kPa, fracture strain of 434-781%, toughness of 630-1350 $kJm^{-3}$ [30].

In 2018, Caruso and co-workers implemented a supramolecular gel media for the crystallization of active pharmaceutical ingredients (APIs) for controlling crystal size, morphology, and polymorphism, as these features determine a performance of pharmaceutical formulations. They reported the crystallization of APIs in a titanium (IV) ($Ti^{IV}$) medium with a natural polyphenol like tannic acid without the need of a heat cool trigger, which is used as a medium for API crystallization [31].

Personalized therapies are extremely diverse, this opens opportunities in a wide range of options for a diversity of drugs, their include drug's toxicities, pharmacokinetics and biodistribution. In another instance, materials-based strategies, such as nano-particles derivatized with targeting ligands, are less specific than antibody-drug conjugates and, consequently, could best be used to deliver a cargo with more specificity to molecular or cellular targets [32]. In this context, the release of a drug with high specificity must be constant and pharmacokinetically controlled. In this way and with the advent and discovery of new drugs to attack complex diseases is that perfectly designed materials must be outlined. The required duration of drug availability and its release profile continuous or pulsatile depend on the specific application. As the drug decreases at indicate site, the hydrogel should be structure either to degrade to avoid surgical removal or to be reused by drug refilling or adapt for tissue regeneration.

## 3. D-Printed Hydrogels

The 3D structures are the product of a series of two-dimensional (2D) layers. This approach therefore has obvious advantages, to tell the truth, the printing process is the simultaneous deposition, that entails for instance cells and biomaterials, using systems of high precision to build architectures in a layer-by-layer fashion [33,34]. By conventional techniques it is practically impossible to structure highly aligned supramolecular domains to reproducibly model hydrogels in 3D. In order to reduce non-reproducibility, Sather et al. designed a method for 3D printing of ionically cross-linked liquid crystalline hydrogels from aqueous supramolecular polymer inks where pH is important to establish intermolecular interactions between the self-assembled structures [35]. At the same time, a strategy for the specific hydrogels is currently being used in 3D printing scaffolds that may be employed to create scaffolds effective of stimulating the alignment of cells and fabricate materials with anisotropic ionic and electronic conductivity [34].

The design of 3D-printed living materials is led by quantitative models that establish the responses of programed cells in printed microstructures of hydrogels [36,37]. For the non-submerged printing approach, a highly viscous Alg/MC hydrogel blend and cell-GelMA mixture were printed alternately on top of each other in order to obtain cell-laden structures. The gelatin methacrylate (GelMA) reinforced the whole structure after printing, additionally, the cross-linking was enhanced

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using UV light [38]. A feasible "gelation and soaking" method was applied to convert chitosan-gelatin (CS-Gel) composite hydrogels to stiff and tough chitosan-gelatin-phytate (CS-Gel-P) hydrogels in sodium phytate solution [28]. Considering further expanded the scope in the response of hydrogels according to its natural chemical properties, the Sun research group has successfully been exploring the adenosylcobalamin (AdoB12)-dependent C-terminal adenosylcobalamin binding domain (CarHC) proteins tetramerization which is essential for the formation of an elastic hydrogel which can undergo a rapid gel-sol transition caused by light induced disassembly [39].

In recently contribution in the item 3D bioprinting, the system of oxidized hyalu-ronate, glycol chitosan, adipic acid dihydrazide, and alginate (OHA/GCS/ADH/ALG) hydrogels for potential applications in cartilage regeneration were investigated in vitro. The study emphasizes that using ALG and calcium ions enhanced the mechanical stiffness of the resulting material [40]. In addition, significant studies based on the viscosities and shear moduli of alginate and alginate/carrageenan hydrogels with different printing parameters was evaluated [41].

As progress has been made in the design of matrices for 3D cell cultures have emerged strategies such as cell spreading, migration, signaling, and mechanotransduction under physiological conditions. The flexibility of many "smart" materials have integrated responsive moieties to specific biological targets, particularly for drug delivery applications [42], in order to achieve specific interaction and responses from cellular systems by regulating key variables of chemokines and cytokines [43] because in biological materials, cross-links are often considerably weaker than the covalent backbone that holds the structure together [44].

A suitability for 3D printing of self-healing hydrogels obtained through vat photopolymerization (VP) has been developed at room temperature without any stimulus. Excellent results were obtained through dispersive forces using poly(vinyl alcohol) (PVA) and photocurable species, such as acrylic acid (AAc) and poly(ethylene glycol) diacrylate (PEGDA) [45]. VP is a class of additive manufacturing processes to create 3D objects by selectively curing liquid polymer through targeted light-activated polymerization.

An outstanding work describes design considerations for gel-phase materials such as self-healing and slimming bioinks, with a focus on dynamic, biochemical, and mechanical gel properties. These inks take advantage of the ability of guest-host complexes to disassemble upon the application of physical force, and then reform once the force is removed [46].

Following the basic design principle of 3D printing, which is to digitally cut a 3D object into multiple thin 2D layers and then recreate that object by depositing materials in a layer-by-layer 2D pattern, suitable structures have been designed for the immobilization of enzymes in a complete framework (post-impression) or incorporated into impression materials during framework fabrication (entrapment) [47].

The 4D bioprinting, using smart materials that can stimuli-responsive, could also be used to create dynamic 3D-printed biological architectures adapted for changing their sizes and shapes based on an applied stimulus [34]. Besides, photo-cross-linkable hydrogels, and natural proteins, are among the most well-known material for the fabrication of microrobots using 3D printing through a photochemical reaction method, with multiples application, from environmental to biomedical [48].

Of note is the development of a partially automated portable bioprinter capable of in situ printing and cross-linking of hydrogel scaffolds. The printer includes an ultraviolet light source to photocross the bioink hydrogels deposited on the geometry of surfaces that could present some defect. Surfaces may not necessarily be flat at the site of an injury [49]. Several factors are driving profound changes in the way chemical science organize their workflow, whether in basic research of hydrogels or in obtaining supramolecular hydrogels for specific and applications. For be explicit, this requires increasingly sophisticated in molecular construction to self-assembly diverse molecules with diverse properties.

## 4. Clays into Hydrogels

Successful formation of nanocomposite particles has been recently evidenced in some works on Laponite®. The studies of Boyes and Thorpe tested that combined effects of hy-poxia [5% $O_2$] and the

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structural environment of the hydrogel poly(N-isopropylacrylamide)-*N*,*N*′-dimethylacrylamide-Laponite® (pNIPAM-DMAc-Laponite®) could differentiate the human mesenchymal stem cells (hMSCs) towards a central gelatinous nucleus pulposus cell phenotype without the need for additional chondrogenic inducing factors. The inherent simplicity showed the clinical convenience of such a method could provide an effective and minimally invasive treatment platform for regeneration of the nucleus pulposus as a treatment strategy for intervertebral disc (IVD) degeneration [50,51]. In an extensive work, Chakraborty et al. reported the surface coating of MOF nanoparticles with the Laponite®. They chose a prototypic ZIF-8 framework ($Zn[MeIm]_2$, where MeIm = 2-methylimidazolate. A charge-assisted self-assembly of ZIF-8 nanoparticles having surface positive charge with Laponite® with negatively charged faces results in a ZIF-8-LP hydrogel nanocomposite. Hydrogel composite of 5-fluorouracil (FU)-encapsulated ZIF-8 (FU@ZIF-8+Laponite®) shows the controlled release of FU. They also reported the synthesis of a fluorescent hydrogel by first encapsulating the fluorescent "drug mimic" fluorescein inside ZIF-8 and subsequently performing gelation with Laponite® [52]. For his part, Hu research group reported a novel injectable hydrogel sealant of catechol CS-hydrogel with self-contractile characteristic, formed through Schiff base reaction between catechol-functionalized CS (CCS) and dibenzaldehyde-terminated polyethylene glycol [53]. The authors found the mussel-inspired catechol groups and remnant aldehyde groups contributed to the superior wet adhesion to tissues.

On the other hand, Chen et al., propose a postsynthetic modification of molecular architecture of nanoMOFs using phosphate functionalized methoxy polyethylene glycol (mPEG–$PO_3$) groups for guide to the formation of redispersible solid materials. The authors mention that these resulting nanoMOFs can favor the loading of drugs [54]. In other contribution, were fabricated smart hydrogels using poly(N-isopropylacrylamide-co-acrylamide) (poly(NIPAM-co-AM)) hydrogels with in-homogeneous structures by assembling subunits of nano-clay (Laponite®) via rearranged strong hydrogen bonding between polymers and clay nanosheets of Laponite®. The assembled hydrogel complexes can realize a variety of diversified deformations in response to environmental stimuli for soft robots, actuators, and artificial muscle [55]. In the same circumstances, the ability of the cell morphology, extracellular matrix (ECM) synthesis, expression of chondrogenic marker proteins and mechanical properties of the newly formed cartilage tissue derived from the chondrocytes/hydrogel constructs have been examined [56].

Moreover, there is an increase in the surface area, the porosity and the clay bonding sites increase their surface area with the mixture of a nano-clay by incorporating it into a hydrogel. Of course, uniformity is a factor that should not be neglected together with the synthetic way to obtain the clay and hydrogel nanocomposite, for example via free radical polymerization or supramolecular assembly [57].

An example of the modulation of the adhesion of hydrogels by adjusting the content of dopamine (DA) and nano-clay is studied by Gu and Wen and their group of researchers, who specify that there is a dissipation layer by providing the intrinsic strength of the hydrogel enhanced by physical cross-linking of Gel, chemical cross-linking of Gel with polydopamine via Michael addition or Schiff base reaction, and a restriction of the molecular chain induced by the nano-clay [58]. On the contrary, hydrogels made with Carrageenan and CS were prepared by electrostatic complexation in aqueous solutions avoiding the use of chemical reactions or toxic solvents. Additionally, the Lap nano-clay is incorporated as an inorganic material with potential for drug delivery applications. When the two polysaccharides are both fully charged (pH 5), their electrostatic attraction is very strong the swelling ratio is lower and viscoelastic moduli presents a maximum [59]. Supramolecular hybrid hydrogel cucurbit[7]uril and clay nanosheets contain electrostatic interactions of a custom-designed cationic copolymer. This hydrogel shows high mechanical strength (>50 kPa), selfheal rapidly in ~1 min, and dissolve quickly (4–6 min) using an amantadine hydrochloride solution that breaks the supramolecular interactions [60].

On the other hand, the print of a 3D high strength supramolecular polymer/clay nanocomposite hydrogel scaffold was proposed; the composition of hydrogel involve a hydrogen bonding monomer (*N*-acryloyl glycinamide) (NAGA) and Laponite cross-linkage would eventually result in high

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strength and swelling stable hydrogels providing reliable loading support [61]. There is no doubt that hybrid nanoparticles will accentuate a pathway to build engineering scaffolds for precise repairs and individualized such as bone defects and degenerative.

## 5. Selected Applications of Hydrogels based on Supramolecular Strategies

The supramolecular interaction between some materials and guest molecules endowed gels with reversible gel−sol transformation. A plausible example has to do with self-healing that is one of the most intriguing characteristics of biological or artificial systems, such as the particular and specific applications described below due to their intrinsic importance. Thermodynamic stability plays an important role, for example in the preparation of ophthalmic hydrogels and metallo-supramolecular hydrogels. The above is descriptive of the excellent self-healing ability of an explosive network of applications of various hydrogel systems [62].

### *5.1. Ophthalmic Hydrogels*

The first choice for ocular treatment is eye drops, that is the most preferred noninvasive way to deliver drugs for treating ophthalmic diseases. Consequently, it is important for drug transport to overcome multiple ocular barriers, such as corneal epithelium, choroid, retinal pigmented epithelium, choroidal and conjunctival blood flow, lacrimation, and lymphatic drainage, restrict the drug transport into the ocular tissues. Less than 5% of drugs have been reported to enter the aqueous humor, this result in a sub-therapeutic drug concentration in these ocular tissues [63]. To overcome this situation, it has developed polypseudorotaxane hydrogels were developed by mixing polyvinyl caprolactam-polyvinyl acetate-polyethylene (Soluplus®) micelles about 99.4 nm and cyclodextrins solution as a prominent example [64].

About ophthalmic gels, the eye drops exist as viscous solutions before application to the eye and normally are used for dry eyes. In situ gels, by comparison, are liquids that are applied as drops to the eye and only after administration they experience a transition from sol-gel to gel in the conjunctiva through stimuli, such as pH, temperature, or ions, with a significant improvement in the ocular bioavailability [65]. Alginate-based nanoparticles were prepared using W/O emulsion technology and coated with CS and Gel. The mean diameter of prepared nanoparticles was in the range of 150–270 nm, a suitable size in ocular drug delivery that does not cause irritation [66].

Dana and Annabi and co-workers designed a biocompatible adhesive hydrogel for corneal tissue repair, which can be used for quick and long-term repair of corneal stromal defects. The bioadhesive hydrogel is made of a chemically modified form of gelatin (Gel) and photoinitiators, which can be photocross-linked after short-time exposure to visible light (450 to 550 nm). Gel is chemically functionalized with methacryloyl groups to form a bioadhesive gel for corneal regeneration (GelCORE). Additionally, the authors shown that physical properties and adhesion strength of GelCORE bioadhesives can be tuned by changing GelCORE concentration and light exposure time [67]. In this same situation, an efficient antibiotic gel for clinical treatment of bacterial keratitis was suggested. For such purposes, a supramolecular hydrogel was fabricated via the electrostatic interactions between guanosine 5′-monophosphate disodium salt (GMP) and tobramycin (TOB) that is a kind of aminoglycoside antibiotic bearing multiple primary amine groups in his structure. Obviously, electrostatic interaction between the primary amine groups of TOB and negatively charged phosphates on assembled GMP nanofibers could facilitate the formation of a supramolecular GMP-TOB gel [68].

Cyclodextrin (CD)-based supramolecular hydrogels was studied for the potential to prolong precorneal retention and increase ocular bioavailability [69]. This effort has also opened a beneficial channel between the thermodynamics of an equilibrium system to achieve the gradual and controlled release and capture of cyclodextrin (guest) using a coordination polymer (Mg-CP) as a host and temperature as a stimulus [70].

An excellent supramolecular hydrogel based on β-CD and adamantane for corneal wound healing was well designed by Fernandes-Cunha et al. In these the supramolecular hyaluronic acid hydrogel was formed based on the host–guest interaction. Compared to the free hyaluronic acid

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solution, the supramolecular hyaluronic acid hydrogel had prolonged residence time on the cornea without complication [71]. In similar points of view but with different materials, the design architecture has included supramolecular hydrogels DNA-based which could form gel under physiological conditions and bring a promising candidate for vitreous substitute because is colorless and transparent, with a similar density to that of natural vitreous [72].

*5.2. Adhesive Hydrogels*

A cooperative structural effect of hydrogels for adhesive applications is falls on creating systems for surgical adhesion, tissue engineering, transdermal drug delivery systems, and soft devices such as sensors, and actuators and in the design of inks for additive manufacturing [73–78].

With a high potential impact, a significant progress has been achieved in the field of adhesive hydrogels, considerably around supramolecular adhesive hydrogels with inherent applications to the tissue engineering. In this regard, an exhaustive review of structural strategies for the formation of supramolecular adhesive hydrogels and their application in tissue engineering has been reported by Zhao et al. [79]. Shin et al., demonstrated the feasibility of bioinspired hyaluronic acid modified with catechol (HA-CA) hydrogel for effective in tissue engineering. Also, they shown the adhesiveness of HA-CA hydrogel [80]. On the other hand, the outstanding gelation of HA-CA and chitosan modified with catechol (CS-CA) allows obtaining highly cross-linked systems and an enhanced adhesive ability to the tissues [81].

Due to their dynamism about advances functionality, a key advantage of supplanting stitches with an adhesive is that the adhesive covers an entire wound as a continuum, because conventional suture materials, such as stitches, staples, or wires, are not the ideal choices to achieve minimally invasive surgeries. Other advantages of gluing the tissue are that the method is quick, save surgery time, is inexpensive, does not require stitch removal, and is waterproof [82]. In this terrain, the designed adhesive should be biocompatible and nonimmunogenic, should comply with the tissue mechanical properties, should develop adhesion over specified time periods, should adhere strongly and, in some cases, the adherence must behave reversibly. The design of hydrogel adhesives is complicated by the inherent nature of these materials, as most of their volume is water and, under physiological conditions, the functional groups needed must have permanent adherence and the covalent junctions are strong and durable; however, they are essentially static and not reversible [73,83]. In biomedicine, there is specific interest in adhering hydrogels to tissues for the closure of wounds, sealing of damaged sections of organs [84]. and the development of stretchable electronics [85,86]. In addition, the hydrogels adhesion to hard and dry surfaces is useful for engineering adaptive and responsive devices. By virtue of this, tissue adhesives require interdisciplinary efforts that span chemistry, mechanics, and biology, as the performance of the adhesive is primarily determined by the adhesive's physicochemical properties, chemical and mechanical interactions with the tissue, host immune response, and local environment characteristics [87], and of course, often they are not properly developed for specific tissue applications [88]. Also, it is important to outline that some of mechanical relationships do not apply directly to most biological tissues [89]. By contrast, anti-adhesion approaches, including the use of impermeable barriers that block fibroblast penetration from surrounding tissues for prevent postoperative adhesion are finally essential, principally to establisher a permanent membrane that can be governed by expanded polytetrafluoroethylene (ePTFE) providing a barrier beneath the sternum reducing the adhesions between the sternum and the epicardium [90]. Newly, a hydrogel has been developed for uterine applications and prevent adhesion, the compound was developed using 3D printing technology to encapsulate human amnion mesenchymal stem cells (hAMSCs) from a human amniotic membrane. In this setting, using natural biopolymers such as Gel and collagen (Col) and the importance of its unique biocompatibility and biodegradability properties, methacrylated gelatin (GelMA) and methacrylated collagen (ColMA) polymers were synthesized [91]. In addition, Yang et al., studied the effect of imidazolidinyl urea (IU) content and the molecular weight of PEG on the mechanical properties. The energy dissipation efficiency and shape memory behavior were also investigated.

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Moreover, they tested the hemolytic activity, cytocompatibility, in vivo retention time, and tissue compatibility of the supramolecular hydrogels [92].

Several studies, such as those reported by Zhang, X. and Zhang, J. and co-workers detail the reversible adhesive properties of multistimuli-responsive supramolecular hydrogels based on hydrogen bonding. They reported networks formed by adding poly(ethylene polyamine) (PPA) to an aqueous dispersion of oxidized multiwalled carbon nanotubes (ox-MWCNTs). The resulting materials were cross-linked through a combination of weak (N−H···N) and strong (N−H···O) hydrogen bonding [93]. Other findings provided by Burattini et al. include to the designed healable supramolecular polymers from chain-folding polyimide and pyrenyl functionalized polyurethanes. These materials are held together by aromatic π–π stacking between the π–electron-deficient diimide groups and the π–electron-rich pyrenyl units. It is noteworthy that π–π interactions are complemented by hydrogen bonding between urea and diimide residues [94].

A comprehensive study directed by Liu and his group was focused using hydroxypropyl-modified $\alpha$-cyclodextrin (Hy-$\alpha$-CD) and acrylamide-PEG$_{20000}$-acrylamide (ACA-PEG$_{20000}$-ACA) to con-struct a polypseudorotaxane with good water solubility. The attraction of this research was that through photo-initiated polymerization of polypseudorotaxane with acrylamide in-situ, for obtain a capped polyrotaxane cross-linked with 1,4-butanediol diglycidyl ether in basic solution to form a slide-ring supramolecular hydrogel that can be stretched to 25.4 times its original length, which recovers rapidly on unloading. Also, these hydrogels $Ca^{2+}$-doped are used to prepare wearable strain sensors for monitoring human motion [95]. In another line of research, hydrogels of peptide-DNA based that are organized into superstructures interlaced that deconstruct upon the addition of molecules or changes in charge density have been well reported. In this regard, experimental simulations suggest that chemically reversible structures can only occur within a limited range of supramolecular cohesive energies [96].

### *5.3. Self-Healing Hydrogels Systems*

Self-repairing behavior originating from dynamic covalent bonds, can includes disulfide exchange, diselenide exchange, and Schiff bases (imine bonds). Consequently, breaking and remaking the covalent bonds requires appropriate conditions of reaction. Conversely, in dynamic non-covalent hydrogels, mostly known as autonomous self-repair hydrogels, the mechanism is based on hydrogen bond interactions, metal-ligand interactions, host-guest interactions, hydrophobic interactions, supramolecular interactions, and entanglement of polymeric chains as illustrated in Figure 2 [97].

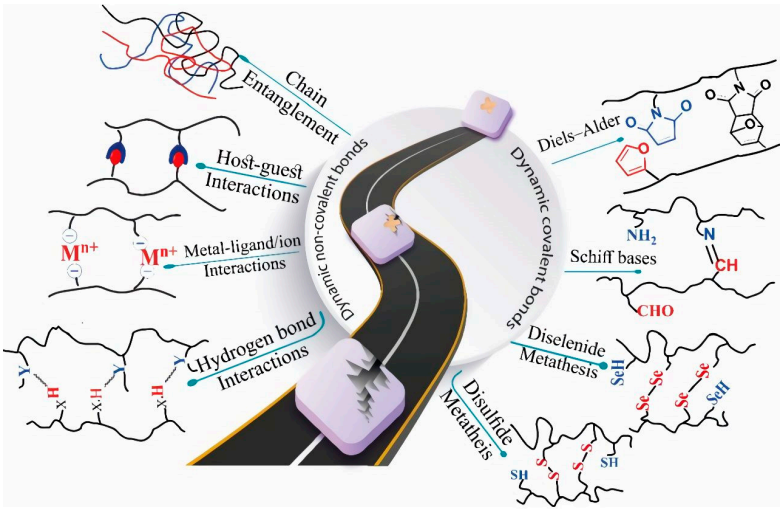


**Figure 2.** Schematics of dynamic covalent and no-covalent bonds operation in the self-healing process. Reprinted from Ref. [97] with permission.

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The specificity of hydrogels for self-repair is due to its reversibility properties after being subjected to stress and evidently in the nature of its physical bonds. This is how the hydrogel structured using hyaluronic acid behaves together with gallol when exhibiting spontaneous loading approximately 93% of a solution of proteins in a concentration of 270 ug/mL in phosphate-buffered saline (PBS, pH 7.4) [98]. In this regard are reported by Hardman and coworkers particularly concerns on hydrogels for soft sensing applications. They explain very accurately the electrical and mechanical properties of an ionically sensorized self-healing Gel hydrogel at room temperature and can undergo strains of up to 454%, furthermore, presents stability over long periods of time, and a formidable biocompatibility and biodegradability. The hydrogel is Gel and glycerol based and can be 3D printed to create customizable sensor networks [99].

New research based on supramolecular chemistry establishes that ionic gels self-healing does not require any external stimuli. For instance, polymer design and architecture have a great impact on the creation of ion gels with self-healing abilities as well as other functionalities, such as high stretchability and toughness and the compatibility with ionic liquids, here the interaction of synthetic polymers such as polyacrylamides and polymethacrylates and the ionic liquid is relevant [100]. In addition, self-healing sodium cellulose ionic conducting hydrogels (Na-CICH) with an ionic conductivity of $\approx 10^{-4}$–$10^{-3}$ S $cm^{-1}$ have been developed using an aqueous NaOH/urea cellulose solution system [101].

In another sense, no less relevant, the formation of Cu(II) metallohydrogel com-pounds with third-order nonlinear optical activity based on the self-repairing protein Bo-vine Serum Albumin (BSA) is pursued in order to produce semiconductor devices due to the large contribution of$\pi$-electrons to photosensitivity [102].

Coordination bonds have utility for constructing self-healing polymers and, evidently, because of the presence of metal ligands and metal-ligand dynamic bonds, self-healing polymers can exhibit various functions such as dielectric materials, luminescence, magnetism, catalysis, responsiveness to stimuli and shape memory behavior. However, there are coordination compounds that are labile and can undergo a variety of reactions, including electron transfer, ligand exchange, and associated processes. All of this depends on the d-electron configuration of the central metal ion [103,104]. In the event of mechanical damage, chain deformation or chemical degradation suffered by self-healing hydrogels made up of reversible dynamic covalent or non-covalent bonds, they can easily recover their original properties [97]. This process is the product of the division and reformation of dynamic links, in response to various external triggers or autonomously.

The characteristics of a self-healing hydrogel based on the specific coordination of $Ni^{2+}$ with a polymeric ligand made by polyaddition of 2,6-diethynylpyridine and diazido-poly(ethylene glycol) have been developed. The choice of $Ni^{+2}$ is due to the great selectivity due to the high chain length of the polymeric linker, which can hinder the formation of efficient intermolecular cross-links of $Ni^{+2}$ and 2,6-bis(1,2,3-triazol-4-yl)-pyridine ($Ni^{+2}$-btp) complexes with high thermodynamic stability. The impact on hydrogelation is selective due to metal-ligand coordination interactions between the $Ni^{2+}$ and btp residues, while the addition of other divalent metal ions such as $Zn^{2+}$, $Fe^{2+}$, $Cu^{2+}$, $Mg^{2+}$, $Mn^{2+}$, $Ca^{2+}$, and $Cd^{2+}$ only induce a color change or precipitation [105].

### *5.4. Electrically Conducting Hydrogels*

Conducting hydrogels are being used in different scientific settings. Indeed, versatile biochemical sensors using conventional hydrogels based on carbohydrates, polymers, DNA, and peptides are expansively studied. An illustrative example of the use of a 3D hydrogel is exposed through the use of amyloid beta 42 (A$\beta$42) peptide for prostate-specific antigen (PSA) detection was reported using a hydrogel based on poly(ethylene glycol) diacrylate. In this way, an interdigitated microelectrode (IME) with a dynamic range was substantially improved with an enviable sensitivity for biosensing has been structured for peptides as the A$\beta$42 [106].

All cellular communication occurs through electrical signals impacting critical mechanisms and the functionality of biological tissues. This principle, address skeletal muscle tissue engineering (SMTE) to fabricate in vitro bioartificial muscle tissue to assist and accelerate a regeneration process

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using electrically conductive hydrogels as establish engineered platforms that can guarantee a tissue-like microenvironment [107].

Conductive hydrogels can also be obtained by including electrical fillers into the hydrogel network. As described by Farr et al., by including graphene oxide (GO) and reduced GO (rGO), metal nanowires, and carbon nanotubes (CNTs) as an alternative to promote skeletal muscle repair and regeneration [108].

There are three reviews with extensive information regarding the performance of electrically conductive hydrogels in technological applications such as biosensing, flexible electronics, and tissue engineering [109–111]. It is noteworthy the strategies to produce conductive hydrogels whose focus includes the polymerization of a conducting monomer in a prefabricated hydrogel, a mixture of conductive systems by instance a simultaneous or stepwise cross-linking of monomers to synthesize conductive hydrogels, and self-assembling of the modified electrically conductive materials [110]. In another instance, Figure 3 illustrates the main approaches employed to design electrically conductive hydrogels [111].

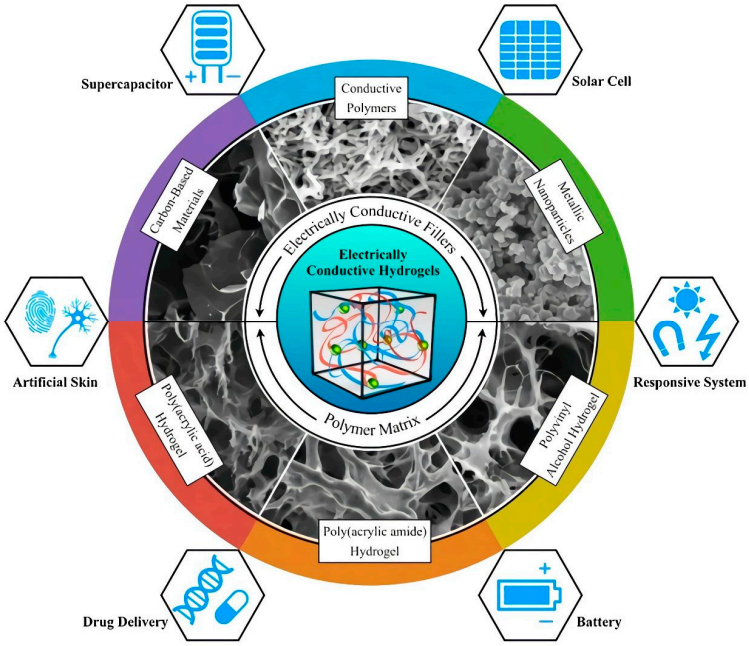


**Figure 3.** Electrically conductive hydrogels are an emerging class of hydrogels combining a hydrophilic matrix with conductive fillers, and they have exceptional promises in a wide range of applications. Reprinted from Ref. [111] with permission.

In the same direction, have been designed electrically conductive hydrogels for active electrode materials for supercapacitors and lithium-ion batteries with specifically morphology and composition. Classic examples about electrically conductive hydrogels are encompasses in Figure 4 [111].

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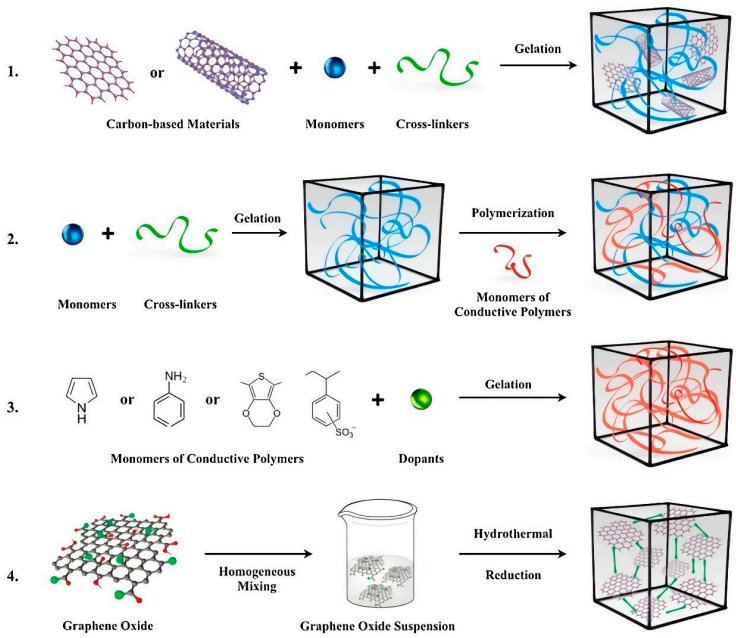


**Figure 4.** Four main approaches used to obtain ECAs: (1) Hydrogel formation from a conductive filler suspension; (2) Polymerization within a preformed hydrogel matrix; (3) Crosslinking conductive polymers by dopant molecules; (4) Self-assembly of Graphene Hydrogel via Supramolecular Interactions. Reprinted from Ref. [111] with permission.

Great developments about conductive nonocomposites have come true, especially those based on CNTs, graphene, transition metal carbides (MXenes), and metal nanofibers. Of these, carbonitrides, nitrides, and transition metal carbides are the most attractive of 2D materials, which together are known as MXenes. There are various synthetic routes of MXene derived its precursor MAX phase: M represents a transition metal, A is the main group element, generally, Si or Al, and X is N or C. Through MXene materials has been produced some ordered-oriented intelligent tunable hydrogel materials (PMZn) with biocompatible polymers and $ZnSO_4$ solution as precursor. This leading to the manufacture PMZn-GL conductive hydrogels that can be used as wearable flexible sensor for detecting a series of human activities such as hand and facial movements [112]. Similarly, the conductive material $Ti_3AlC_2$ precursor is processed into MXene nanosheets, that at the same time a solution of PVA and $ZnSO_4$ are mixed. The anisotropic PMZn-GL hydrogel obtained presents good tensile properties, and conductive faculties that could well be used as a wearable flexible sensor for comprehensive human motion biomonitoring [113]. There is no doubt that the transistors technology into bioelectronic interfaces, as well as its high spatial resolution upon bioelectronic signals recording is expanding its unprecedented coverage degree [114].

A way to make a patch as biomarker in sweat can incorporate a transducing layer of nanoporous carbon and MXene (NPC@MXene). The composition of resulting product is composed of a glucose biosensor go along by pH and temperature sensors to precisely quantify glucose that, together with biopotential electrodes is feasible to record electrophysiological signals in real-time [115].

Recently, Wu et al., exposed new developments of hydrogel-based triboelectric nanogenerators (H-TENGs). They explain in a pertinent review the recent progress on the subject about the flexible TENGs. The authors emphasis the advanced functions to enhance outputs and stability of H-TENGs on practical applications such as biomedical electronics as represented in Figure 5 [116].

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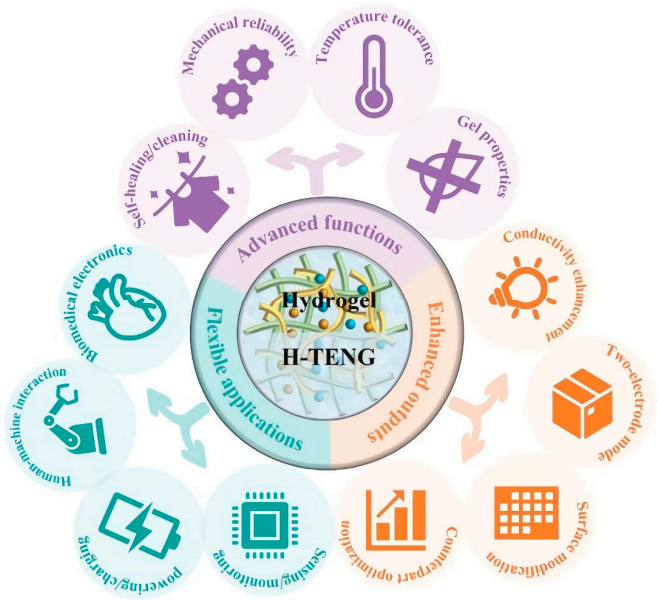


**Figure 5.** Development of H-TENGs: advanced functions, enhanced outputs, and flexible and wearable applications. Reprinted from Ref. [116] with permission.

In a very eloquent work, structures were designed 1D fiber-shaped supercapacitors (FSCs) cellulose composed to produce recyclable ionic hydrogels to establish the foundations of a system of a fully sustainable energy storage fiber system made from reused/recycled materials for wearable Internet of Things (IoT). Such hydrogels were produced from aqueous system cellulose and lithium hydroxide (LiOH) in the presence of urea and later a regeneration process was carried out directly in carbon fiber wire electrodes. In this way, a pair stretch-broken carbon fiber yarns (SBCFYs) as current collectors to fabricate 1D FSCs was obtained. Additionally, a specific capacitance of up to 433.02 $\mu F \cdot cm^{-2}$ at 5 $\mu A \cdot cm^{-2}$ is reported, simultaneously the specific energy density reached a value of $1.73 \times 10^{-2}$ $\mu Wh \cdot cm^{-2}$. Besides, a maximum achieved specific power density was $5.33 \times 10^{-1}$ $mW \cdot cm^{-2}$ at 1 $mA \cdot cm^{-2}$ [117].

Lately, great advances about the impact of complex and intelligent machines are more noticeable especially when it comes to the biomedical engineering sciences. Such is the case of computers, mobile device, sensor, actuators, and robots. Because of this, unconventional materials have been designed for bridging human and machines through hydrogels interfaces in a broad range of applications [118].

### *5.5. Metallo-Supramolecular Hydrogels*

One paper demonstrating ion size variation is that presented by Dubey and co-workers, who reported on a series of fluorescent metallohydrogels with attached alkali metal ions that show large conductance and rheological properties consistent with alkali metal ion size variation [119].

Following this order of ideas, the use of 3,6-bis(2-pyridyl)-1,2,4,5-Tetrazines (bptz) ligands for the synthesis of supramolecular gels based on metal-ligand coordination has been described, showing notable dynamic mechanical properties; These materials have the advantage that they can be easily functionalized by Diels-Alder reactions, therefore metallohydrogel scaffolds have been prepared for the release of small molecules activated by photoactivation and enzymatically. The Diels-Alder functionalization of the bptz ligands attached to the ends of the PEG chains is ensured by gelation induced by metal coordination in the presence of $Ni^{2+}$ and $Fe^{2+}$ cations [120].

One aspect of complex peptides is obtained by the coordination of metal ions that impact their functionality; however, they are also participants in self-assembly and, at the same time, in the structuring of supramolecular gels. In this context, His-copper (His-Cu) coordination in the supramolecular assembly of gelators is used to improve the understanding and development of these materials. Metal-gel coordination mimics biologically relevant metal-peptide coordination,

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influencing hydrogel self-assembly and mechanical properties, biodegradability, biocompatibility, adjustability, and recycling, while metal coordination allows for widespread applications in the biomedical, waste management and catalysis industries [121]. This has led to studies reporting a peptide based as a simple drug delivery system (DDS) for doxorubicin (DOX) delivery as an anticancer system (Das et al. 2018). This DDS is structured in tripeptides that form a metal-peptide coordination center with Cu(II) to self-assemble and thus generate structures whose morphology allows the controlled and sustained release of DOX. of the His residue at the site [122]. The choice of His to displace drug molecules from the metallopeptide network, this is because among the essential amino acids the His can easily bind strongly to the $Cu^{2+}$ center. Regarding the above, for example, it is noteworthy that one of four peripheral ZnII ions is anchored by Glu and His side chains from one monomer and His from another [123]. Thus, the Lys amine group completes the tetrahedral coordination geometry. In another study, the kinetic and thermodynamic characteristics of pyridinedicarboxamide (PDCA) complexes with a series of transition metal ions are established that could provide the basis for the development of new metallo-supramolecular polymeric networks and hydrogels. By means of the condensation of linear PEG segments with the PDCA ligand via urethane bonds and the complexation of PDCA with various metal ions under basic conditions, the rheological peculiarities were investigated [124].

The strength, stability, and connectivity of the coordination bonds can be largely tuned without significant synthetic effort, solely through the simple choice of metal ion. Thus, it has been shown that energy dissipation modes are relevant in metallo-supramolecular systems, even more so by introducing a mixture of metal ions with different complex stabilities [125]. To a large extent, different binding constants of bis(terpyridine) and Mn(II) and Zn(II) complexes have been demonstrated. Multivalent effects are influenced by increasing binding affinity [104]. Through connectivity mismatches, supramolecular hydrogels have been developed by systematically introducing different percentages of connectivity defects into a model supramolecular network and the resulting macroscopic elastic response by oscillatory shear rheology, microscopic autodiffusivity by fluorescence recovery after photobleaching (FRAP) and characterizing and testing the specific type of defects by double quantum NMR (DQ-NMR). With the work developed by Nicolella et al. It is highlighted that with connectivity defects, the hydrogel becomes softer and autodiffusivity increases inside [126].

In order to visualize the modes of energy dissipation, hydrogel models with metal-ligand coordination have been developed of divalent metal ions in the formation of stable biscomplex, evidencing significant linearity in the energy dissipation. Deviation from linear behavior is to be expected in cases where metal ions and ligands show weak coordination affinity and even more so if metal ions compete to form mono, bis or tris complexes [127].

Molecular interactions have been observed when producing a metallogel with vanadium pentoxide. The metallogel was obtained by reacting (E)-N'-((2-hydroxynaphthalen-1-yl)methylene)benzohydrazide with vanadium pentoxide in methanol solution. Surprisingly, a ligand gelation test showed that the ligand could not gel in both polar and nonpolar solvents. However, when the warm DMF solution of the ligand was reacted with the warm vanadium pentoxide solution in DMF/$H_2O$ (2:1 v/v) spontaneous gelation occurred when cooled to room temperature [128]. The metallogels show weak C–H---O and N–H---O bonding interactions. In a molecular packing diagram, it is possible to observe that the dioxovanadium (V) molecules are linked by N–H---O intermolecular hydrogen bonds, to form a one-dimensional ziz-zag linear arrangement.

In another case, amphiphilic peptides (AP) have been studied for the construction of molecular blocks, especially in the manufacture of supramolecular soft materials with potential for various applications in fields of science and technology. Especially, in recent years various amphiphilic peptides have been designed and synthesized [129]. Amphiphilic peptides are divided into two different subclasses, namely peptides containing alternating hydrophilic/hydrophobic amino acid residues and a long hydrophobic stretch of amino acids attached to a hydrophilic sequence. Obviously, the impact on the aggregation properties of these designer amphiphiles vary markedly.

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Metallo-supramolecular polymer networks (MSPN) are the subject of study to detail certain biomimetic functions such as self-healing and stimuli-responsiveness. A good example is the use of His, which is an $\alpha$-amino acid of great importance in enzyme function. It is found abundantly in the soft, collagen-like core of the byssus threads of marine mussels. It contains an a-amino group capable of being protonated under biological conditions and a carboxylic acid, in addition to containing an imidazole group. The nitrogen atom of the imidazole group is protonated at pH < 6 (pKa 6.5), while under neutral and basic conditions it falls apart, what a magnificent property. Thus, depending on the pH conditions, His may have the feasibility of forming compounds with various transition metal ions and shaping various coordination geometries.

Metal ions are essential in controlling the structural properties and catalytic function of many proteins required for proper physiological function. Thus, artificial metalloproteins are built by introducing metallocofactors into a natural protein. Detailed examples of bioinorganic active sites of cupredoxins, commonly known as blue copper proteins, are presented by Borovik and his team [130]. The transfer of electrons between the $Cu^{2+}$ and $Cu^{+}$ redox states causes the active sites of cupredoxins to present a distorted trigonal monopyramidal coordination geometry for the Cu(I) and Cu(II) states. The highly covalent nature of the Cu−$S_{cys}$ bond Cys (cysteine) results in charge transfer from the S$\pi$−Cu ligand to the metal, responsible for the characteristic blue color ($\lambda_{max} \approx 600$ nm) and the small hyperfine coupling constant observed by EPR spectroscopy (A ≈ 180 MHz).

## 6. Conclusions and Perspectives

We have summarized the main synthetic strategies and recent functional applications of supramolecular chemistry based on hydrogels and their derivatives which are a big topic of hierarchically materials experiencing explosive growth, especially in the last two decades, and the situation continues. In view of the above, a wealth of peculiar information about supramolecular hydrogels visualizes non-covalent interactions to modulate gel properties and establishes many opportunities for current and future research to make the most out of combining a larger number of supramolecular interactions to optimize many characteristics of the hydrogels to design cautiously tailored properties. Moving forward, the fine collaboration between scientists should be visualized and emphasized at the same time a higher-performing and realistic biomimetic materials. Without being onerous, research in tissue engineering should incorporate additional biocompatibility and should include in vivo animal studies to monitor the long-term immune response. In this way, ophthalmic issues and adhesiveness that have to do with biological task are addressed.

In other ideas order, this review report involves classic topics such as hydrogels that range from their relationship with drug delivery systems, to metallo-supramolecular materials, through applications in ophthalmic systems, in applications that require adhesiveness and electrically conductive hydrogels. This review also addresses hydrogels systems called TENGs with ionic conductive capacities, stretchability, flexibility, and biocompatibility; and more generally, electrically conductive hydrogels are discussed through this review. Of course, the exciting topic of self-healing hydrogels is not left aside. The requirements that are relevant of self-healing hydrogels are the phase mobility, requisitioned rate of self-recovery, multiple healing cycles, and usually autonomous healing in different environmental conditions that a common hydrogel with a dynamic bond would not gather each aforesaid requirement.

With an expanding in the fundamental understanding of the impact of hydrogels to improve our daily lives, hydrogel for drug delivery systems, self-healing hydrogels and electrically conducting hydrogels, are likely to further change the scale, efficacy, and cost of constitutive effort in areas not considered within the academic and industrial field.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

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**Conflicts of Interest:** The authors declare no conflict of interest.

**Acknowledgments:** Rodrigo Cue-Sampedro of the School of Engineering and Sciences at Tecnologico de Monterrey, Campus Monterrey, is gratefully acknowledged for graciously providing his technical support.

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