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Novel Studies in the Designs of Natural, Synthetic, and Compound Hydrogels with Biomedical Applications

Novedosos Estudios en el Diseño de Hidrogeles Naturales, Sintéticos y Compuestos con Aplicaciones Biomédicas

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ABSTRACT

Hydrogels are gaining widespread popularity in the biomedical field due to their extraordinary properties, such as biocompatibility, biodegradability, zero toxicity, easy processing, and similarity to physiological tissue. They have applications in controlled drug release, wound dressing, tissue engineering, and regenerative medicine. Among these applications, hydrogels as a controlled drug delivery system stands out, which releases active substances in precise amounts and at specific times. To explore the latest advances in the design of hydrogels, a literature review of articles published in indexed scientific journals, in Scopus and Science Direct, was carried out. This review aimed to discover and describe the most innovative hydrogel research with applications in the biomedical field; hydrogels synthesized with polymers of different origins were selected, such as; i. Natural (dextran, agarose, chitosan, etc.); ii. Synthetic (polyacrylamide, polyethylene glycol, polyvinyl alcohol, etc.); iii. Composites (interpenetrants, hybrid crosslinkers, nanocomposites, etc.). Comparative analysis revealed that hydrogels with composite materials show the most promise. These composite hydrogels combine the advantages of different polymers or incorporate additional components, offering enhanced properties and functionalities. In summary, hydrogels are versatile biomaterials with immense potential in biomedicine. Their unique properties make them suitable for diverse applications. However, innovative designs and formulations must continue to be explored to further advance the capabilities of hydrogels and expand their biomedical applications.

KEYWORDS: drug delivery system, hydrogel, regenerative medicine, wound repair

RESUMEN

Los hidrogeles están ganando una extensa popularidad en el campo biomédico gracias a que presentan propiedades extraordinarias como biocompatibilidad, biodegradabilidad, nula toxicidad, fácil procesamiento, y similitud con el tejido fisiológico. tienen aplicaciones en la liberación controlada de fármacos, el vendaje de heridas, la ingeniería de tejidos y la medicina regenerativa. Entre estas aplicaciones, destaca el uso de hidrogeles como sistema de administración controlada de fármacos, que liberan sustancias activas en cantidades precisas y en momentos concretos. Para explorar los últimos avances en el diseño de hidrogeles, se realizó una revisión bibliográfica de artículos publicados en revistas científicas indexadas, en Scopus y Science Direct. El objetivo de esta revisión fue descubrir y describir las investigaciones de hidrogeles más innovadoras con aplicaciones en el campo biomédico, se seleccionaron hidrogeles sintetizados con polímeros de diferente índole como; i. Naturales (dextrano, agarosa, quitosano, etc.); ii. Sintéticos (poliacrilamida, polietilenglicol, alcohol polivinílico, etc); iii. Compuestos (interpenetrantes, reticulantes híbridos, nanocompuestos, etc.). El análisis comparativo reveló que los hidrogeles que utilizan materiales compuestos son los más prometedores. Estos hidrogeles compuestos combinan las ventajas de distintos polímeros o incorporan componentes adicionales, ofreciendo propiedades y funcionalidades mejoradas. En resumen, los hidrogeles son biomateriales versátiles con un inmenso potencial en biomedicina. Sus propiedades únicas los hacen adecuados para diversas aplicaciones, sin embargo, se debe seguir explorando diseños y formulaciones innovadores para seguir avanzando en las capacidades de los hidrogeles y ampliar sus aplicaciones biomédicas.

PALABRAS CLAVE: hidrogel, medicina regenerativa, sistema de liberación de fármacos, reparación de heridas

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INTRODUCTION

Hydrogels are soft polymeric materials formed by three-dimensional networks that have a high content of water or biological fluid while maintaining their structure without dissolution [1][2], in addition to being biodegradable, biocompatible, and flexible thanks to the water content that makes them very similar to natural tissue [3][4][5][6][7]. They can have a variety of applications in different areas, such as agriculture, biomedicine, or food. However, one of the most researched approaches in recent years is the use of hydrogels in biomedicine, as they provide a versatile platform for the supply of drugs, wound dressings, engineering tissue, and regenerative medicine, such as being applied in cartilage regeneration and as scaffolds for cell proliferation and growth [8].

In recent years, a significant focus has been put on the development of controlled-release drug delivery systems, since in conventional delivery systems, the dose of the drug increases dramatically in the blood and then decreases, causing organ toxicity and body tissues before the drug, reaches the target site [9]. The controlled drug delivery system must provide the correct amount of the active substance to the desired site within a specified period [10]. There has been a significant boom in the application of hydrogels as drug delivery vehicles since their three-dimensional network allows them to retain liquids, which helps them to encapsulate hydrophilic drugs and release them in a controlled way. The basic growth factor of fibroblasts is widely used (bFGF) since it is a hydrophilic drug that can be incorporated into hydrogels to repair damaged tissue since it has the property of attracting cells and fibroblasts to the site of injury; it also helps in angiogenesis and metabolism [11].

Different presentations of dressings are used for wound healing, including gauze, gels, hydrogels, foams, hydrocolloids, etc. Within these presentations, hydrogels are the most promising for wound treatment since they can retain large amounts of liquid inside, providing a moist wound environment, removing exudates, preventing infection, and providing a suitable environment for wound healing tissue regeneration [11] [12].

This review explores and describes the most innovative research on the use of hydrogels in the biomedical field, mainly for controlled-release drug applications, wound dressings, and tissue engineering, opening an overview of new composite hydrogels, which improve the properties of conventional hydrogels designed from natural or synthetic polymers. It also aims to open the reader's view toward designing new smart hydrogels with more unique properties that aid in rapid and effective patient recovery.

MATERIALS AND METHODS

A review of the literature of articles related to the design of hydrogels was carried out. Investigations were chosen in which hydrogels were made from natural, synthetic, or composites. These articles selected for this review were published in scientific journals indexed in Scopus and Science Direct. No limit was selected for the publication date. However, articles published in the last 5 years mainly provide information on the most recent advances in this field.

The following parameter was determined for selecting the articles: obtaining hydrogels based on natural, synthetic, or composite sources with promising results to be used exclusively in medical applications.

RESULTS AND DISCUSSIONS

Hydrogel structure and crosslinkin strategies

The mesh size and molecular weight of the crosslinked polymer chain are essential properties of the hydrogel at the molecular level [11]. The final application of the hydrogel generally determines the strategy for

selecting crosslinking. They can be prepared by physical or chemical crosslinking, and the first ones are formed by ionic bonds, hydrogen bonds, or Van der Waals forces [13], which makes hydrogels dynamic, while in chemical crosslinking, hydrogels are formed by covalent bonds, which gives them better stability [14] [15]. Different molecules have been used to crosslink such networks as dialdehydes, diisocyanate, and diacrylate, among others [4]. Among the most widely used crosslinking agents are glutaraldehyde, poly(itaconic acid) and genipin [16]. Genipin is 5,000 to 10,000 times less toxic than glutaraldehyde, although its price is high [4]. Another way to crosslink relatively stable hydrogels is by enzymatic crosslinking. The most important advantages of this type of crosslinking are that hydrogels have a greater cytocompatibility than chemical crosslinking, the possibility of kinetic manipulation of gel formation by controlling the concentration of enzymes, and the gel time is fast, and strong covalent bonds are formed. Transglutaminase and horseradish peroxidase are the enzymes most used for manufacturing and crosslinking hydrogels [17].

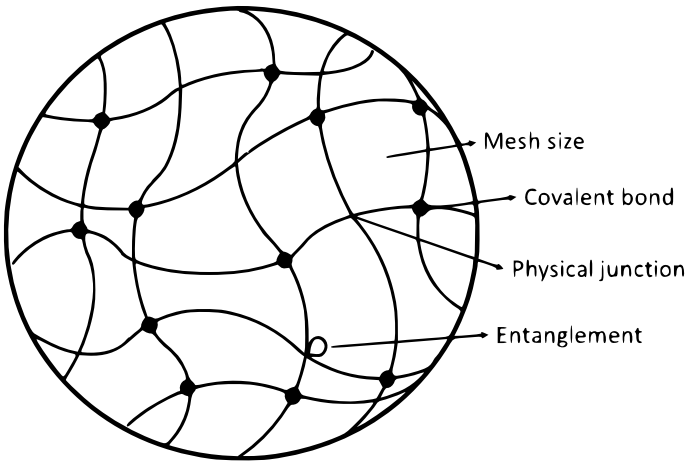

FIGURE 1. **Hydrogel structure at the molecular level. Adapted from [11].**

The degree and speed of swelling in the hydrogel depend on the crosslinking density and the concentration of the polymer. The swelling of the hydrogel has three stages: 1) Water joins the hydrophilic group, 2) the interaction of water with hydrophobic groups, and 3) free water in equilibrium, water fills the spaces gaps [11]. Denser crosslinked materials swell less compared to more freely crosslinked hydrogels. Another property determined during the crosslinking stage is porosity which determines the ability to adequately exchange nutrients and debris for the encapsulated cells [12]. Figure 1 shows the hydrogel structure at the molecular level presenting the mess size and the two main types of crosslinking: covalent bonds (chemical crosslinking) and non-covalent bonds (physical crosslinking).

Classification of hydrogels according to the type of material

Hydrogels can be classified as natural, synthetic, and composite, depending on the type of material with which they are formed [18]. Hydrogels based on natural polymers have physicochemical and biological characteristics that make them interesting for biomedical applications, such as biocompatible, biodegradable, non-toxic, and promoting cell adhesion [4][5]. Among these applications are used as controlled release drug delivery systems (hydrogels sensitive to stimuli such as pH changes; in response, the hydrogel swelling percentages vary, causing the release of drug molecules), wound dressings (used due to their ability to absorb wound exudate while allowing oxygen to pass to the wound site) [19][20]. Natural biopolymers are generally polysaccharides and proteins such as -dextran, hyaluronic acid, alginate, agarose, pectin, cellulose, carrageenan, or chitosan. On the other hand, synthetic polymers include polyethylene glycol (PEG) and polyacrylamide [12]. These polymers are promising candidates for preparing hydrogels because they form hydrophilic gels that retain water or biological fluids without collapsing their structure and are biocompatible and biodegradable [5][9][14]. In addition, hydrogels can improve their mechanical and adhesive properties through crosslinking concentration and additives, improving or optimizing their functionality for various applications. [13][21]. Composite hydrogels are a combination of a natural polymer with a synthetic one that

gives the hydrogel both mechanical and biological properties [11] since the use of synthetic materials gives it better mechanical resistance properties while using of biological materials gives the compound hydrogel biological properties that allow it to be self-healing [12]. Table 1 presents the classification of hydrogels according to the type of material with which they have been synthesized, the materials most used to synthesize hydrogels, and their applications in biomedicine and properties.

TABLE 1. Classification of hydrogels with their applications and properties.

Hydrogel	Material and Application	Properties
Natural	**Dextran:** Tissue engineering, drug administration	Biocompatible, biodegradable, non-toxic
	Hyaluronic acid: Tissue engineering, drug administration	Biocompatible, biodegradable, non-immunogenic, high viscoelasticity
	Alginate: Wound healing, drug administration	Biocompatible, biodegradable, non-immunogenic, crosslinking with divalent cations
	Gelatin: Bone regeneration., wound management	Biocompatible, biodegradable, non-toxic, good adhesiveness
	Agarose: Cell growth and adhesion, drug administration	Biocompatible, biodegradable, self-gelling
	Chitosan: Tissue engineering, drug administration, wound dressing	Biocompatible, biodegradable, non-toxic, non-allergic, bioavailable
	Xylene: Skincare, drug administration, bone regeneration	Biocompatible, biodegradable, non-toxic, anti-inflammatory, antioxidant, and anticancer effects
	Silk fibroin: Wound healing	Biocompatible, biodegradable, good mechanical properties, hardness, and stability
Synthetics	**Polyacrylamide:** Cartilage regeneration, tissue engineering	Controllable hardness, a high degree of swelling
	Poly (N-isopropyl acrylamide): Drug administration, medical diagnosis	Temperature-induced sol-gel transition ability
	Polyethylene glycol: Drug administration, tissue engineering	Good mechanical properties
	Poly (methyl methacrylate-co-methacrylic acid): Cartilage regeneration, tissue engineering	Biocompatible, hydrophilic
	Pluronic diacrylate: Cell growth and proliferation	Biocompatible, hydrophilic, self-gelling
	Polyvinyl alcohol: Wound healing, regenerative medicine	Controllable hardness, a high degree of swelling
Composites	**Interpenetrating polymer networks:** Wound healing	Biocompatible, good mechanical properties
	Crosslinking hybrids: Wound healing	7 Biocompatible, good mechanical properties
	Nanocomposites: Wound healing, cell growth, and proliferation	Biocompatible, good mechanical properties

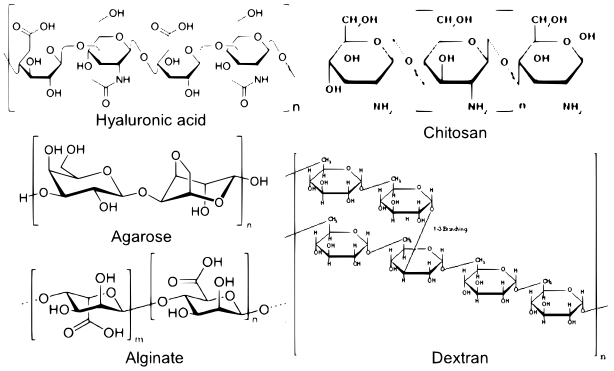

FIGURE 2. Structure of the natural hydrogels used for the biomedical area.

Natural hydrogels

Natural hydrogels are made from natural polymers

(alginate, chitosan, hyaluronic acid) or proteins (gelatin, silk fibroin) [22]. They have zero toxicity, biodegradability, and biocompatibility [23], making them promising candidates for biomedical applications such as tissue engineering, drug administration, etc. The most significant limitation of natural hydrogels is their poor stability, so their use decreases in applications where high-resistance hydrogels are required [24]. Figure 2 shows the structures of the most applied natural hydrogels in biomedicine. Table 2 shows the advantages and disadvantages of natural hydrogels.

TABLE 2. Advantages and disadvantages of natural hydrogels used in the biomedical area.

Hydrogel material	Advantages	Disadvantages
Dextran	Biocompatible, biodegradable, non-toxic	Low biological activity
Hyaluronic acid	Biocompatible, biodegradable, non-immunogenic, high viscoelasticity	Low mechanical properties
Alginate	Biocompatible, biodegradable, non-immunogenic, crosslinking with divalent cations	Low tensile strength, limited mechanical properties
Gelatin	Biocompatible, biodegradable, non-toxic, good adhesiveness	Requires chemical agents as crosslinking agents to stabilize
Agarose	Biocompatible, biodegradable, self-gelling	Not present bioactivity for cell proliferation
Chitosan	Biocompatible, biodegradable, non-toxic, non-allergic, bioavailable	Low mechanical properties
Xylene	Biocompatible, biodegradable, non-toxic, anti-inflammatory, antioxidant, and anticancer effects	Low mechanical properties
Silk fibroin	Biocompatible, biodegradable, good mechanical properties, hardness, and stability	From wake and brittle biomaterials

Dextran hydrogels

Dextran is a carbohydrate biopolymer, which breaks down in specific physical environments without any effect on cell viability [25], is produced by bacterial species from sucrose or by chemical synthesis, is non-toxic, it is also biocompatible and biodegradable [5][26], it promotes wound healing due to the existence of specific glucan receptors in human fibroblasts where glucan stimulates the expression of fibroblasts that help cell proliferation [27], the disadvantage of dextran is that they have relatively low biological activity, but it can be improved with the incorporation of another polymer capable of improving said activity [28]. Also, they have low load capacity and ease of deformation, which restricts their use for hard-tissue engineering applications [25]. However, the hydroxyl groups that dextran presents can be oxidized, alkylated, and esterified to obtain various derivatives, which are expected to be beneficial in the design of new polymeric materials in which various properties can be controlled, for example, the degradation rate [29][30]. Solomevich *et al.*, 2019, designed a hydrogel based on a dextran phosphate derivative with the final drug release application for local tumor chemotherapy. Dextran phosphate hydrogels were loaded with prospidine. Hydrogels are sensitive to pH thanks to phosphate groups; in a low-pH environment, the swelling was significantly less than in a neutral environment. Tests for drug release showed that prospidine was released depending on the pH of the external media, and the loaded hydrogels were able to inhibit the proliferation of cancer cells depending on the dose delivered. Hence, the application of the hydrogel was successful with an effective antitumor [29].

On the other hand, Ghaffari *et al.* 2020, synthesized dextran hydrogels with the incorporation of nanoparticles of β-nanocrystalline tricalcium phosphate (β-TCP) as scaffolds for bone tissue engineering and reported that the effect of β-TCP improved the activity exhibiting an increased ability to interact with body fluids and specifically produced active sites for cell anchoring and mineral precipitation in vitro [28]. Dong-Soo *et al.* 2022,

prepared a hydrogel matrix by introducing a functional group capable of forming crosslinks between natural polymers to create a basis for preparing a favorable microenvironment for cell adaptation in biotissues. The modified dextran hydrogel polymer was designed to mimic the extracellular matrix conditions as a scaffold. The results showed that the functional groups of the polymers helped with self-assembly due to intermolecular interactions. The dextran residues in the molecular structure of the hydrogel helped to keep the scaffold self-assembled by undergoing interactions due to Van der Waals forces, electrostatic forces, and the ability to form intramolecular hydrogen bonds [31]. Jintao *et al.* 2023, designed injectable hydrogels modified with dextran and gallic acid to accelerate wound healing by scavenging reactive oxygen species (ROS) in burn and combined radiation injuries. These composites showed good self-healing ability, excellent injectability, strong antioxidant activity, and favorable biocompatibility. In addition, they exhibited excellent antibacterial properties, which facilitated wound healing [32].

Hyaluronic Acid Hydrogels

Hyaluronic acid is a natural unbranched polysaccharide part of the extracellular matrix of human tissue. It is highly hydrated and negatively charged, consisting of glucuronic acid and N-acetylglucosamine; it is biocompatible, biodegradable, non-immunogenic, high viscoelastic, and high-water holding capacity [17] [33][34]. It is currently used for wound healing, cell augmentation and proliferation, angiogenesis, and drug delivery [22]. Menezes *et al.* 2020, manufactured a collagen-based hydrogel (extracted from the skin of Nile tilapia fish) / hyaluronic acid with 1-ethyl-3- (3-dimethyl aminopropyl) carbodiimide(EDC) and NHS as crosslinking agents, the hydrogel presented a robust reticulated network with high potential for its use in tissue engineering [33]. Luo *et al.* 2020, synthesized a hyaluronic acid hydrogel loaded with 5-fluorouracil, cisplatin, and paclitaxel to function as a multi-drug delivery system. *In vivo* studies in mice presenting with colorectal peritoneal carcinomatosis showed that the hydrogel decreased the formation of ascites, inhibited tumor growth and metastasis in the liver and lungs, and also prolonged the survival time of the mice; therefore, the hyaluronic acid hydrogel is a promising tool in the treatment of colorectal peritoneal carcinomatosis [35]. In 2023, Weinqian *et al.* synthesized in situ an injectable hydrogel with good swelling resistance using hyaluronic acid and aldehyde β-cyclodextrin (ACD) via Schiff base reaction for long-term controlled drug release. They concluded that hyaluronic acid-based injectable hydrogel prepared by Schiff base reaction provides a new option for long-term controlled drug release in the course of disease treatment from a material perspective [36]. Nam-Gyun *et al.* 2023, fabricated a hydrogel with fast self-healing properties and high antibacterial activity by testing various proportions of hyaluronic acid and pectin mixture using Fe^{3+} as a crosslinker. The proposed hydrogel demonstrated antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* due to the release of Fe^{3+} during the hydrogel degradation process without being toxic to human dermal fibroblast cells. These results suggest that the proposed hyaluronic acid/PT hydrogel holds great promise for tissue regeneration [37].

Alginate hydrogels

Alginate is a natural linear and anionic glycan [38] [39], it is extracted from brown algae, but it is also produced by *Azotobacter* and *Pseudomonas* bacteria [22]; it can absorb wound exudate, so it has been widely used as a wound dressing, as well as providing protection to the wound against bacterial load, providing a humid environment and helping the formation of granulation tissue causing faster wound closure. It is also biocompatible, biodegradable, non-immunogenic, and has controlled release properties [40][41]. It can crosslink with divalent cations such as Calcium (Ca^{2+}) [38] or Magnesium (Mg^{2+}) [37]. Despite their efficient application in wound healing, they have the disadvantage of having low tensile strength and limited mechanical properties [40]. Zhang *et al.* 2019, manufactured a hydrogel for the

controlled release of dexamethasone sodium phosphate (Dexp). The hydrogel was formed based on alginate with the crosslinking of Ca^{2+}. The *in vivo* pharmacological analysis indicated that the hydrogel significantly improved the bioavailability of the drug since the hybrid hydrogel had a slower drug release rate than the hydrogel without alginate [42]. In another study, Abbasi *et al.* 2020, also synthesized a hydrogel with a final application of wound dressing, using a combination of a thermosensitive polymer (formulated for accelerated wound healing), sodium alginate, which due to its properties, is being widely used in wound healing, and polyvinyl alcohol (PVA) as a crosslinker. The crosslinking of the chosen materials showed the hydrogel's good tensile strength, mechanical properties, and pharmaceutical viability and efficacy in wound healing [40]. Sun *et al.* 2020, made a sulfanilamide-loaded alginate hydrogel using a combination of Ca^{2+} ions and crosslinked with glutaraldehyde that helped it to have an improved mechanical resistance, which had the adjustable fluid absorption capacity and controlled release of the drug, improved cell adhesion and proliferation without cytotoxicity, making it promise to be used as a wound dressing [43]. In another study, Yang *et al.* 2023, fabricated an alginate hydrogel loaded with chitosan nanoparticles and Fumaria officinalis extract, which was evaluated for its wound healing capacity compared to a commercial product with that function. The hydrogel was tested on diabetic rats' wounds, obtaining a promising dressing, and carrying out the healing process with comparable results to the commercial product tested [44].

Gelatin hydrogels

Gelatin is a biocompatible and biodegradable polymer derived through the physical or chemical partial hydrolysis of native collagen in bone, tendon, and skin. It has attractive characteristics such as low cost, colorless and non-toxic adhesiveness [45][46]. Generally speaking, there are two types of gelatin, Type A, processed by acid collagen treatment, and Type B, obtained by alkaline hydrolysis [17]. The aqueous gelatin solution spontaneously forms a hydrogel when it is cooled by the molecules that form a triple helix, but at physiological temperature, it returns to the liquid state, so chemical agents such as crosslinking agents are required to stabilize the hydrogel [47]. Anamizu and Tabata 2019, designed an injectable hydrogel based on the physicochemical interaction between gelatin/alginate/ Fe^{3+} to evaluate cells encapsulated in hydrogels and evaluated whether the cells were able to survive, proliferate and carry out osteogenic differentiation. The cells were encapsulated by the hydrogel and injected into the posterior subcutis of mice. The percentage of cells retained at the injected site was higher than those injected in a phosphate buffer suspension, so the cells were successfully transplanted with the hydrogel for bone regeneration [48]. Takei *et al.* 2020, manufactured a hydrophobically modified gelatin hydrogel to form a physical crosslink that would stabilize the hydrogel and limit chemical agents' use as crosslinking agents. The researchers loaded the hydrogel with two drugs, one with basic fibroblast growth factor (bFGF) (hydrophilic drug) and the other with fluorescein sodium (hydrophobic drug). *In vivo* tests showed that bFGF is released gradually as the hydrogel breaks down, aiding therapeutic angiogenesis. The same result occurred with fluorescein sodium, which proposes the hydrogel as a drug delivery system that can release both hydrophilic and hydrophobic drugs controllably [47]. Gonzalez-Ulloa *et al.* developed and characterized polymeric hydrogels based on gelatin and collagen. Different studies were performed to evaluate their mechanical, thermal, and microstructural properties and biocompatibility. The results showed that hydrogels formed from the mixture of collagen and gelatin retain, to a large extent, the good viscoelastic properties of collagen while showing low levels of cytotoxicity and hemocompatibility. However, due to the nature of the materials used, the thermal characteristics are not ideal for use in biomedicine, so further studies are required to overcome these drawbacks [49].

Agarose hydrogels

Agarose is a carbohydrate with self-gelling properties

and is converted into a gel without the need for chemical crosslinking agents [50][51]; it is composed of 1-4-anhydrous-α derivatives -1-galactose linked to 1,4 and derivatives of β-D-galactose linked to 1,3, which is extracted from seaweed [52]. It is soluble in water at temperatures above 65 °C, and depending on the molecular weight and functional groups, it gels between 17 °C and 40 °C. Once the agarose gel is stable, it cannot swell or liquefy until heated to 65 °C. [53]. Agarose produces mechanically robust networks with long-term stability and is widely used in hydrogels as a rigid component to improve the mechanical properties of hydrogels. Agarose chains can generate porous scaffolds that allow cell mobility and transport oxygen and nutrients to cells embedded in the hydrogel matrix. However, agarose hydrogels have the disadvantage of not having bioactivity to promote binding and cell proliferation [54]. Topuz *et al.* 2018, developed agarose hydrogels incorporating 2D anisotropic nano silicates (Laponite), which enhanced the bioactivity of the hydrogel by aiding cell growth and proliferation, finding that nano silicates do not affect the structure of the hydrogel but revealed greater incorporation of fibroblasts, which is never seen in pure agarose hydrogels [54]. In another investigation, Yuan *et al.* 2018, also made agarose hydrogels, incorporating Konjac glucomannan (KGM) to improve the properties of the agarose hydrogel, the hydrogel was loaded with the drug ciprofloxacin, and its release behavior was evaluated. KGM was able to significantly reduce the hardness and stiffness of hydrogels. It also improved agarose hydrogels' encapsulation, drug loading efficiency, and sustained release ability [52]. Qi *et al.*, 2019, successfully built an agarose-based hydrogel and introduced salt to the hydrogel matrix. Only these natural biopolymers were used without the help of chemical crosslinkers or monomers. The hydrogel resulted in good biocompatibility, serving as a cellular framework because it supports cell adhesion and growth [55]. Patiño-Vargas *et al.* 2022, synthesized a human agarose/plasma hydrogel as a wound-healing dressing. In this work, they varied the concentrations of agarose in hydrogels: 0 %, 0.5 %, 1 %, 1.5 %, and 2 % (w / v), to evaluate the activity of fibroblasts present in the hydrogel, obtaining that fibroblasts propagate faster at low concentrations of agarose present in the hydrogel [56].

Chitosan hydrogels

Chitosan, a partially deacetylated chitin product, is a natural polyamine saccharide made up of two common sugars, glucosamine, and N-acetylglucosamine, that has attracted attention because it is non-toxic, odorless, non-allergenic, biocompatible, biodegradable and bioavailable [4][6][9][57][58][59][60][61][62]. These characteristics make chitosan be used as a vehicle for drug delivery, in tissue engineering, and as a dressing in wound healing due to its anticancer, antimicrobial, and antioxidant properties [60][63][64]. Low molecular weight chitosan can protect RNA from degradation by inhibiting the RNAse. Chitosan has a primary amino group and needs to be dissolved in an acidic medium to protonate its amino group and have a positive charge [18]. Songkroh *et al.* 2015, manufactured a hydrogel with a new surgical approach as a sealant for treating biological reduction in lung volume. This chitosan-based hydrogel was crosslinked with genipin and loaded with sodium orthophosphate hydrate ($Na_3PO_4 \cdot 12H_2O$); the hydrogel was evaluated in Chinese dogs, presented good mechanical resistance, and proved to be promising as a lung sealant [65]. For their part, Dehghan-Banani *et al.* 2020, formed a modified chitosan hydrogel using N-(β-maleimidopropyloxy) succinimide ester (BMPS), incorporating ketogenic (KGN) to promote the chondrogenesis of stem cells in the hydrogel, suggesting a solution for the regeneration of cartilage defects in the form of an injectable platform [66]. In another investigation, Thongchai *et al.* 2020, obtained a hydrogel based on chitosan and collagen using tetraethyl orthosilicate as a crosslinking agent; the purpose of the hydrogel was to be loaded with caffeic acid as a controlled drug delivery system, which was satisfactory since caffeic acid decreased the degradation behavior of the hydrogel, gradually releasing over 8 hours. The antioxidant properties of the hydrogel demonstrated potential utility

for cosmetic and pharmaceutical research [67]. Wang *et al.* 2023 prepared an injectable chitosan hydrogel with catechol and 4-glutenolic acid to prevent swelling and promote wound healing. The hydrogel showed antimicrobial efficacy against *Escherichia coli* and *Staphylococcus aureus*. In vitro evaluation showed that the hydrogels contributed to coagulation by absorbing red blood cells and platelets. In vivo, evaluation in mice showed that they stimulated fibroblast migration and epithelialization, which may be a promising option for wound healing treatment [68].

Xylene hydrogels

Xylene is one of nature's most abundant hemicellulosic polysaccharides, a predominant by-product of chemical and mechanical pulps [45]. Xylene hydrogels have biodegradability and non-toxicity properties. They have anti-inflammatory effects, immune functionality, antioxidant, and anticancer. They are used as carriers of biological and pharmacological macromolecules [2]. Gami *et al.* 2020, prepared xylene and β-cyclodextrin based hydrogels using ethylene glycol diglycidyl ether (EDGE) as crosslinking chemical; the hydrogels were loaded with curcumin and 5-fluorouracil to analyze their release kinetics, having promising applications as a drug delivery system [2]. Fu *et al.* 2020, made a hydrogel mainly of dialdehyde xylene (DAX) and gelatin; DAX was produced by direct oxidation of the xylene obtained from a viscous fiber mill and was used as a crosslinker to allow the formation of a network of 3D gel, glycerol, and nicotinamide were introduced to adjust the texture and function of the hydrogel. The hydrogel was a promising skincare application and a strategy for manufacturing crosslinked hydrogels from biomass [45]. Gutiérrez-Hernández *et al.* 2023, evaluated a xylene hydrogel mixed with functionalized multi-walled carbon nanotubes (MWCNTs) with biomedical applications as a scaffold for *in vitro* culture of osteoblastic cells. The results show that the developed hydrogels have a high potential to be bionanomaterials for bone regeneration due to increased cell viability, proliferation, and adhesion [69].

Silk fibroin hydrogels

Some lepidopteran larvae manufacture silk. Silk is made of two proteins: fibroin is the central protein covered by sericin, similar to glue. Silk fibroin is a natural copolymer formed by hydrophobic and hydrophilic segments that provide it with hardness and stability; it is also biocompatible, biodegradable, with good mechanical properties, relatively low molecular weight, and acceptable immunogenicity, which makes it attractive in tissue engineering [17][70]. It is also widely used in preparing controlled-release drug delivery systems, biosensors, and wound repair [71]. Despite having good mechanical properties, most biomaterials made from silk fibroin are usually weak and brittle [71]. Li *et al.* 2020, manufactured a hydrogel based on silk fibroin from cocoons of *Bombyx mori* to evaluate the therapeutic effects of the hydrogel on hypertrophic scars on the ears of white rabbits from New Zealand; the results obtained showed that the hydrogel had favorable biocompatibility, and hypertrophic scars showed a decrease in scar color in addition to a reduction in thickness [72]. For their part, Wang *et al.* 2023, developed a silk fibroin-based hydrogel for use in the controlled release of miR-29a nanoparticles, aiding peripheral nerve regeneration. The results indicated that the silk fibroin hydrogels promoted myelination and neuronal differentiation of PC12 cells. This indicates a potential application as a nerve guidance conduit in peripheral nerve repair [73].

Synthetic hydrogels

Synthetic hydrogels are formed from synthetic polymers such as polyacrylamide, polyethylene glycol, and polyvinyl alcohol, among others. They are candidates in various implantable devices, including controlled-release drug depots and tissue engineering [74]. They exhibit good mechanical strength; however, the human body recognizes synthetic materials as foreign materials, provoking an immune response. Its properties can be improved by redesigning the hydrogel, as with controlled degradation or alterations in crosslinking density [75]. There are several methods to produce synthetic

hydrogels, such as photopolymerization or crosslinking by chemical agents; these two methods are the most used to synthesize hydrogels with biomedical applications [74]. Figure 3 shows the structures of the most applied synthetic hydrogels in biomedicine. Table 3 shows the advantages and disadvantages of synthetic hydrogels.

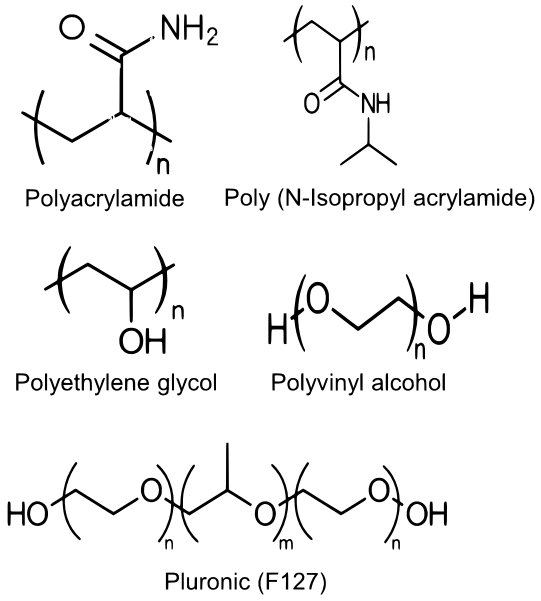

FIGURE 3. Structure of the synthetic hydrogels used for the biomedical area.

TABLE 3. Advantages and disadvantages of synthetic hydrogels used in the biomedical area.

Hydrogel material	Advantages	Disadvantages
Poly acrylamide	Controllable hardness, a high degree of swelling	Brittleness, low biodegradability
Poly (N-isopropyl acrylamide)	Temperature-induced sol-gel transition ability	Low biological activity
Pluronic (F127)	Good mechanical properties	Low biological activity
Polyethylene glycol	Biocompatible, hydrophilic	Limited metabolism in the human body
Polyvinyl alcohol	Biocompatible, hydrophilic, self-gelling	Minimal cellular and protein adhesion

Polyacrylamide hydrogels

Polyacrylamide is a polymer that can be synthesized from the acrylamide monomer in an aqueous solution with the addition of N, N' methylene bisacrylamide (crosslinking agent), ammonium persulfate (photothermal initiator), N, N, N ', N' - tetramethylene diamine (crosslinking accelerator) [52]. It has been extensively studied for its compatible applications as a hydrogel [76] [77][78]. It is a type of hydrogel with easily controllable hardness; polyacrylamide allows the hydrogel to form quickly and has a high degree of swelling; the disadvantages are brittleness and low biodegradability [79]. Depending on the application of the hydrogel, the properties can be adjusted by altering the synthesis conditions, polymerizing it with other monomers, or chemically modifying the hydrogel [22]. McClure and Wang 2017 evaluated a 4 % polyacrylamide hydrogel to investigate its effect on horses with natural osteoarthritis. 28 horses with the disease were evaluated, obtaining that 23 horses reduced the problem and could walk better on day 45 of the evaluation. The mechanism of action that causes improvement when walking is unknown, but it is attributed to the fact that the viscosity of the hydrogel polyacrylamide is similar to that of normal synovial fluid at 37 °C. Polyacrylamide can protect the cartilage surface in horses with osteoarthritis, allowing quality fibrocartilaginous healing [80]. Chen *et al.* 2023, prepared a hydrogel with a double polyacrylamide network, to which they introduced carboxymethyl chitosan, exhibiting excellent mechanical properties and stability. The carboxymethyl chitosan provided the hydrogel with antibacterial and biocompatible properties, resulting in a hydrogel with promising applications as an implantable biosensor [81].

Poly (N-isopropyl acrylamide) hydrogels

It is the most studied synthetic polymer with a polar peptide group in the side chain. This polymer forms a thermo-reversible/thermo-responsive hydrogel. This property allows the hydrogel to act according to the temperature at which it is found; at low temperatures, it is in a liquid state and gradually transforms into a

semi-solid gel as the temperature increases [82]. This phenomenon occurs when the aqueous solution of poly (N-isopropyl acrylamide) (PNIPAM) below 30-32 °C remains hydrated, but phase separation occurs when heated above 32 °C, forming a two-phase system. The polymer will precipitate out of a clear solution. The polymer-rich phase is insoluble in water. This temperature-induced sol-gel transition is a reversible process [52][83]. This property makes it suitable for drug delivery; applying a PNIPAM-based gel on the skin can increase drug retention in the epidermis and reduce drug penetration into the skin [84]. Shivshetty *et al.* 2022, developed a poly(N -isopropyl acrylamide) hydrogel used for etiologic diagnosis of corneal infection of bacteria and fungi without using a microbiology laboratory. This research was carried out on ex vivo rabbit eyes infected with the microorganisms *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Candida albicans*. They found with this work a hydrogel easy to use and with potential in the diagnosis of infected eyes since the hydrogel was able to collect the three microorganisms only 30 minutes after being in place. These results were confirmed by conventional microbiology techniques and fluorescence signals [85]. Damonte *et al.* in 2023 developed a work whose objective was to improve the properties of poly(N-isopropyl acrylamide) (PNIPAAm)-based hydrogels in terms of mechanical characteristics and functionality by combining the polymer with a star-shaped tetra functional polycaprolactone (PCL), which was synthesized ad-hoc and introduced into the reaction mixture. This work developed novel PNIPAAm-based hydrogels with high mechanical strength, the ability to interact with positively charged molecules with tunable kinetic release and swelling ratio, biocompatibility, and thermo-reactivity [86].

Polyethylene glycol hydrogels

It is one of the best synthetic polymers widely used in biomedicine. It is highly hydrophilic and has excellent biocompatibility; the kidney and liver are metabolized in the human body and remove the complete polymer chains according to their molecular weight. The kidney eliminates it if its weight is <30 kDa and the liver if its weight is > 30 kDa. Only polyethylene glycol with a molecular weight <50 kDa is considered for use in biomedicine to ensure its complete elimination from the human body [52]. Janse van Rensburg *et al.* 2017, synthesized a polyethylene glycol (PEG) hydrogel that contained heparin (Hep) and heparan sulfate (HS) and loaded with growth factors to be administered in a controlled way and thus can improve angiogenesis in applications of tissue regeneration. These hydrogels were able to release heparin and growth factors on a sustained basis to increase the vascularization of scaffolds *in vivo*. These hydrogels are potentially valuable for tissue engineering or regenerative medicine applications where the hydrogel is required to be anti-thrombogenic [87]. In another study, Navaratman *et al.* 2020, evaluated a PEG hydrogel in patients undergoing proton beam radiotherapy to treat prostate cancer. Seventy-two patients with the disease were evaluated, of whom 51 patients had the hydrogel placed before radiation; after introducing the hydrogel, the prostate-rectum separation was measured and correlated with the rectal radiation dose and toxicity rectal. The result showed a 42.2 % decrease in the rectal radiation dose in patients with the hydrogel due to the degree of sagittal separation from the midline created by the PEG hydrogel [88]. In 2023, Fan *et al.* fabricated PEG-based synthetic hydrogels with placenta powder for application in tissue engineering. PEG hydrogels with placenta powder and pristine hydrogels were evaluated. All hydrogels showed *in vitro* viability greater than 91%. The hydrogels with placenta powder showed bioactivity, as cell adhesion and proliferation were propagated, while the pristine hydrogels remained bioinert. The bioactivity property makes the hydrogels promising for applications in tissue regeneration [89].

Poly (methylmethacrylate-co-methacrylic acid) hydrogels

It is a polymer of hydrophobic nature, used in drug delivery and tissue engineering; however, one of its main applications is as a biomaterial for bone tissue; it

has the advantages of being easy to process and low cost [90]. Jiménez *et al.*, 2020, created a hydrogel based on poly (methylmethacrylate-co-methacrylic acid), using poly (ethylene glycol) diacrylate and polyethylene glycol as a sporogenous agent as a crosslinking agent; *In vitro* and *in vivo* biological tests showed that the chondrocytes grown in the hydrogel were capable of producing an extracellular matrix similar to hyaline cartilage and that it can promote cell proliferation, being an optimal candidate for cartilage tissue regeneration and as scaffolds in osteoarthritis treatment [91].

Pluronic diacrylate hydrogels

Pluronic diacrylate is a nonionic, water-soluble, biocompatible copolymer that can form solid hydrogels after chemical crosslinking and release drugs and active substances. It self-assembles in the presence of polar and non-polar solvents, making it useful for forming hard materials and bone nanocomposites [92]. Bao *et al.* 2020, made a hydrogel scaffold composed of nanoparticles of calcium carbonate (nanoCaCO3)/multiple hydro cyclone diacrylates (F127-DA) as an option for bone regeneration. Control of the nano space distribution of the $CaCO_3$ in the hydrogel matrix improved and regulated the mechanical properties and also acted as an intelligent source of calcium by promoting a weakly acidic environment at the bone defect site. The hydrogel obtained a gradient distribution of Ca^{2+} in its matrix, which promoted the scaffold's migration, cell growth, and osteogenic capacity, achieving controllable bone regeneration. [93]. In another study, Li e*t al.* 2023, fabricated a hydrogel based on methacrylate gelatin (GelMA)/ F127DA and Pluronic F127 aldehyde (AF127) micelles and type I collagen, applied to repair the damaged cornea. Multiple crosslinking imparts toughness to the hydrogel. White male rabbits underwent lamellar keratoplasty to evaluate the hydrogel, where the lamella was removed, and the hydrogels were applied and spread as a thin film. The evaluation was carried out for 4 weeks, resulting in a regeneration of the corneal stroma, so it has great potential for ophthalmic surgeries [94].

Polyvinyl alcohol hydrogels (PVA)

Polyvinyl alcohol is a synthetic hydrophilic biocompatible polymer with a high affinity for water, processability, and minimal cell and protein adhesion. It is used in various pharmaceutical applications, such as drug delivery, scaffolding, contact lenses, dialysis membranes, and artificial cartilage [95]. Chunshom *et al.* 2018, manufactured a hydrogel based on polyvinyl alcohol and bacterial cellulose, with which hydrogen bonds were formed along with the crosslinked hydrogel network. The hydrogel showed outstanding swelling, the presence of bacterial cellulose had an essential effect on pore size, and it presented high water absorption [96]. Shefa *et al.*, 2020, implemented a polyvinyl alcohol hydrogel (PVA) for its gelling capacity and oxidized cellulose nanofiber to improve porosity, loaded with curcumin to treat skin wounds, curcumin had to be solubilized in pluronic (F127) to solve the hydrophobicity problem it presents. A freeze-thaw process physically crosslinked the hydrogel; as the concentration of PVA increased, the viscosity also increased. In vitro tests revealed that L929 fibroblast cells absorbed curcumin, improving wound healing [97]. Huang *et al.* 2023, developed a PVA hydrogel used in regenerative medicine as a cell releaser. Evaluations showed that the hydrogel was biocompatible with stem cells, but more importantly, stem cells cultured within the hydrogel showed high viability, making the hydrogel an interesting tool in regenerative medicine [98].

Composite hydrogels

The high-water content in the hydrogel can represent a disadvantage because water swells the hydrogel's three-dimensional network, thus reducing mechanical resistance. To prepare high-resistance hydrogels, researchers have considered the introduction of different energy dissipation mechanisms in the last decades in hydrogels. The new type of compound hydrogels has significantly improved mechanical resistance and has obtained other characteristics such as self-healing and electrical conductivity. The following compound hydrogel types have been designed: interpenetrating

polymer networks (IPNs), hybrid crosslinking hydrogels, nanocomposite hydrogels, and hydrogels composed of macromolecular microspheres [13].

Interpenetrating polymer networks

According to IUPAC, an interpenetrating polymer (IPN) has at least one pair of partially interlocking networks, but there is no covalent bond between the networks. The most representative characteristic is phase separation, which is why heterogeneous phases are formed. The IPN hydrogels can respond to stimuli such as temperature, pH, electricity, and magnetic field since the networks have different characteristics from the hydrogel. The first network is rigid and gives it firmness and rigidity; the second network presents a low degree of crosslinking and functions to fill the gaps in the first network [13]. Kim *et al.*, 2018, synthesized hydrogels of interpenetrating polymer networks composed of poly (N-isopropyl acrylamide) (PNIPAM) and hyaluronic acid to administer luteolin in a controlled way for psoriasis disease. They first prepared a primary network with PNIPAM. The secondary network was hyaluronic acid and divinyl sulfone (DVS) as a crosslinking agent (Figure 4). The hydrogels were loaded with luteolin. The results showed that the hydrogel did not show cytotoxicity regardless of the concentration of the crosslinking agent; it was able to incorporate 48.2 % of luteolin and to release this drug while inflammation was produced, hydrogels were considered powerful candidates for the relief of psoriasis when inhibiting hyperproliferation of keratinocytes present in the epidermis [83]. For their part, Zhang *et al.* 2020, developed an interpenetrating network hydrogel based on polyacrylamide and serine. Polyacrylamide was the basis for the hydrogel due to its easily controllable hardness and a high degree of swelling, while sericin provided antibacterial, antioxidant, and anticancer properties, stimulating cell growth and wound healing. They used hydrogen peroxide (H_2O_2) as a chemical crosslinking agent and horseradish peroxidase as a catalyst to apply it as a dressing for skin repair due to its highly transparent, biocompatible, and bioactive properties. The hydrogel was successfully synthesized without presenting cytotoxicity and with good adhesiveness and proliferation in cell culture in mouse skin fibroblasts [79]. In 2023, Sanchez-Cid *et al.* fabricated a chitosan-based hydrogel with a semi-IPN network by dissolving chitosan in glacial acetic acid and then adding synthetic polymers crosslinked with the chitosan solution. UV light was used to form the semi-IPN network. The results reported that the degree of crosslinking affects the properties of the resulting hydrogel. As the monomer is increased, the degree of crosslinking increases; however, it decreases the wettability and hinders the formation of the hydrogel. This study concluded that a hydrogel with adequate properties is obtained if a 1/1 ratio is used, potentially for future applications in tissue engineering or drug delivery [99].

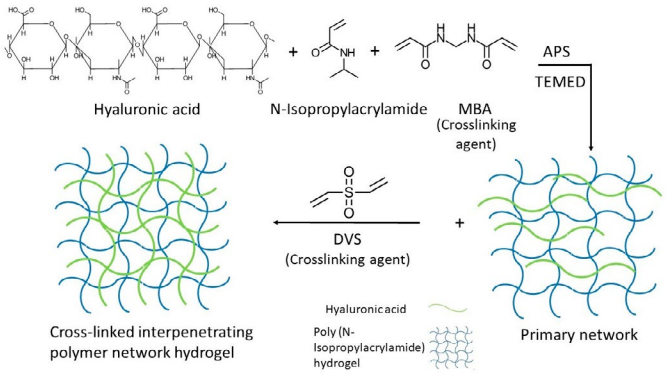

FIGURE 4. Schematic representation of an interpenetrating network hydrogel formed based on hyaluronic acid and poly (N-isopropyl acrylamide). Adapted from [13].

Hybrid crosslinking hydrogels

Covalent crosslinks and non-covalent crosslinks characterize it. Correct covalent crosslinking helps improve the hydrogel's mechanical strength, while proper non-covalent crosslinking allows the hydrogel to dissipate much energy during the deformation process [13]. Xue *et al.*, 2019, designed a hydrogel with a double physical-chemical network. The hydrogel was formed by mixing chitosan and acrylamide separately in deionized water. To continue mixing both solutions, then

liquid matrigel was added. The acrylamide and matrigel monomers formed a hybrid hydrogel by radical polymerization and physical crosslinking. The hydrogel exhibited good characteristics such as low cytotoxicity, high swelling, good stretching, and compression. The results of the in vivo tests showed that the hydrogel improved skin regeneration and consequently significantly favored wound healing [100]. In other research, Zhang et al., 2018 made an adhesive hydrogel using a hybrid crosslinking strategy. To the polyacrylamide-based hydrogel, adenine and MBA were introduced by free radical polymerization, and a hybrid network of crosslinking hydrogel was formed; adenine could generate intermolecular hydrogen-adenine bonds- Adenine and MBA served as a chemical crosslinker to form covalent bonds. The hydrogel exhibited excellent adhesiveness and toughness, capable of adhering to various surfaces of biological materials and tissues [101]. Gong *et al.* 2023, developed a gallic acid-agarose-based double network hydrogel with potential applications in wound healing. The hydrogel exhibited excellent porosity, good water retention, antimicrobial effect, and biocompatibility in vitro, while in vivo tests accelerated wound healing [102].

Nanocomposite hydrogels

Nanocomposite hydrogels are obtained by combining inorganic nanoparticles with organic polymers. Commonly used nanoparticles are silica, graphene, and silver. There are five methods to achieve a uniform distribution of nanoparticles in a hydrogel:

1) Formation of a hydrogel directly by the suspension of nanoparticles
2) Nanoparticles physically embedded in a pregelatinized hydrogel matrix
3) Formation of a hydrogel within pregelatinized nanoparticles
4) Formation of a hydrogel with nanoparticles mediated as crosslinkers
5) Formation of a hydrogel by adding a mixture of unique molecules of gellingagent

Many nanoparticles have attractive biological activities such as antioxidant, antimicrobial, antiangiogenic, anti-inflammatory, and antiplatelet properties [13]. Various types of silver, particularly silver halides, have superior bacterial properties. Pasaribu *et al.* 2018, synthesized a self-healing hydrogel based on polyacrylic acid (PAA), crosslinked with Al^{3+}, incorporating silver chloride nanoparticles; the resulting hydrogel had good antibacterial properties against Escherichia coli and improved the proliferation of L929 mouse fibroblast cells, this hydrogel could be suitable for self-healing applications [103]. On the other hand, Narayanan *et al.* 2019, made a *Lysinibacillus sphaericus* reduced graphene oxide (L-rGO) -polyacrylamide nanocomposite polymeric hydrogel, used as a scaffold to support the growth and proliferation of fibroblasts in the skin. Hydrogels were prepared using acrylamide, MBA as the crosslinking agent, and ammonium persulfate as the initiator. The results showed that hydrogels are biocompatible with human skin fibroblasts, providing an ideal extracellular matrix for the growth of human cells in tissue engineering [104]. Kumar and Kaur, 2019, prepared a polyvinyl alcohol/chitosan nanocomposite hydrogel incorporating silver nanoparticles. Adding more chitosan produces a high swelling, and adding silver nanoparticles provides mechanical resistance and flexibility. The PVA/chitosan nanocomposite hydrogels and silver nanoparticles are antimicrobial against *Staphylococcus aureus* and *Escherichia coli*, which makes them beneficial for wound dressings [105]. In another study, Chen *et al.* 2023, synthesized carboxylated polyvinyl alcohol nanocomposite hydrogels by photopolymerizing PVAGMACOOH and hydroxyapatite at nanoscale to increase cell adhesion. The carboxylated polyvinyl alcohol nanocomposite hydrogels exhibited excellent compressive strength and tensile strength. The introduction of nanoscale hydroxyapatite significantly improved the cytocompatibility and cell adhesion of the hydrogels [106]. Almajidi *et al.* 2023, In their research, they developed a novel nanocomposite scaffold based on a natural chitosan gelatin hydrogel (CS-Ge) by incorporating synthetic polyvinyl alco-

hol (PVA) and MnFe layered double hydroxides (LDH) to increase biological activity. Biological tests performed showed healthy cell line cell viability higher than 95 % after 48 and 72 h. In addition, the nanocomposite demonstrated high antibacterial activity against *Pseudomonas aeruginosa* bacterial biofilm, as confirmed through Anti-biofilm assays. In addition, mechanical tests revealed that the storage modulus was higher than the loss modulus (G'/G" > 1), confirming the appropriate elastic state of the nanocomposite [107].

Hydrogels are composed of microspheres

For the preparation of these compound hydrogels, microspheres are used as initiators and crosslinking agents; these microspheres trigger a large amount of polymerized monomers on the surface of the macromolecules to obtain the hydrogel compounds of high-resistance microspheres. The structure of this type of hydrogel is more regular. The mechanical resistance of these hydrogels depends on the following factors: the initiation time of the radicals, the concentration of the macromolecular monomers and microspheres, and the initiation temperature [13]. Imaizumi *et al.* 2019, designed a gelatin microsphere hydrogel as a scaffold to be loaded with bFGF (basic fibroblast growth factor with a short half-life) for slow release in the vocal cords as a preventive approach to minimize the risk of tumor growth. BFGF is a chemoattractant for endothelial cells and fibroblasts, and it also stimulates angiogenesis, metabolism, and extracellular matrix deposition. This investigation used bovine bone collagen to isolate gelatin through an alkaline process and crosslinking with glutaraldehyde. The study was conducted on Japanese white rabbits, where the gelatin hydrogel microspheres were injected into the injured vocal cords. To avoid leakage to the microspheres, a gelling material was added 4 to 5 minutes after mixing; if more time were allowed to gel, the needle would become clogged. The volume to be injected was careful not to cause excessive tissue swelling to avoid obstructing the airways of the rabbits. As the gelatin hydrogel microspheres were degraded, they released bFGF. The results demonstrated the regenerative potential of the growth factor contained in biodegradable gelatin hydrogel microspheres as a drug delivery system applied immediately after vocal cord injury due to the interaction of bFGF with cells that modulate the environment of the wound. The bFGF significantly helped to repair the injured vocal cords; however, hoe repaired cords do not return as whole strings [108]. Xiang-Ping *et al.*, 2023, fabricated agarose and alginate (Ag/Al) based hydrogel microspheres for stem cell encapsulation. The hydrogel obtained was required to degrade, releasing the stem cells at the desired site. This was achieved for at least 10 days, when the stem cells survived without needing nutrients or temperature control, making this hydrogel a promising device for cell-based transport and therapy [109].

Plasma modified hydrogels

Hydrogels can be used as screens during treatment with cold plasma at atmospheric pressure, or they can also be used as reservoirs for gases generated by liquid plasma, such as oxygen and nitrogen. Complex research is required to assess possible modifications to polymers in solution when exposed to cold plasma reactivity. The primary products of plasma hydrogel treatment are free radicals, unsaturated organic compounds, crosslinks between polymers, products of polymer chain destruction, and gas-phase products. The radical formation is mainly due to the impact of electrons and UV radiation. The efficacy of plasma treatment is related to generating reactive oxygen and nitrogen species in biological tissues or liquids [110]. Cyganowski *et al.*, 2019, produced a new gold nanoparticle catalyst (AuNP), synthesized by direct current cold plasma glow discharge, applied to a hydrogel used in the catalytic reduction of 4-nitrophenol (4- NP) to 4-aminophenol (4-AP), which is a fundamental substance in the elaboration of several drugs (Figure 5). Chemically synthesizing AuNPs by providing and controlling NP size was difficult but solved using cold plasma at atmospheric pressure. The results obtained

showed that the AuNPs had an average size of 7 nm, so the size could be controlled without altering the polymer matrix where they were found. The hydrogel prepared with AuNP completely reduced 4-NP to 4-AP (Figure 5) [111].

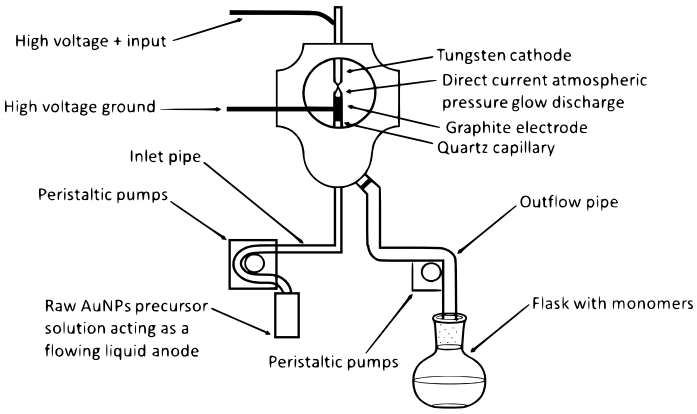

FIGURE 5. **The schematization of the plasma reactor. Adapted from [111].**

Future directions

Science has evolved, and although various hydrogels are still manufactured with only one polymeric material with good properties, the development of hydrogels currently focuses on compound hydrogels that have had a more extraordinary upswing than conventional hydrogels due to the deficiency that the material presents. It can be supplemented with another polymer so that the designed hydrogel can provide excellent mechanical and biological properties. Compound hydrogels are potential candidates for application in many fields, especially biomedical ones. The primary commitment of these new hydrogels is to comply with the requirements to be used in physiological tissues, improving their biocompatibility, biodegradability, zero toxicity properties, and increasing their mechanical properties. Achieving this continues to be a significant challenge for researchers in the coming years, so this review provides a guide for constructing hydrogels according to their final application.

CONCLUSIONS

Despite the significant progress in biomedicine, there are still many areas of opportunity to advance in the research of hydrogels to be candidates for applications in this field. Before choosing the design of the hydrogel, we should think about the final application that will have such hydrogel, as well as take into account what biological and mechanical properties are the most important that present the hydrogel to be used in wound healing, tissue engineering, regenerative medicine or for the controlled release of drugs, which any of these applications remains a significant challenge, due to the high complexity of recovery in an injured organ or wound, as well as to improve the controlled release of drugs since the traditional release can cause toxicity in an undesired site. Hydrogel is a promising dressing material due to its excellent biocompatibility, high water retention, and immune cell activation to accelerate wound healing. They have also been successfully used for scaffolding in tissue engineering. Hydrogels based on a single polymer, either natural or synthetic, continue to be widely used; however, composite hydrogels are now being heavily investigated, as using two or more polymers confers a wide range of biological and mechanical properties to the hydrogel.

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AUTHOR CONTRIBUTIONS

C.G.C.G. reviewed literature and participated in the writing and editing of the original manuscript. M.C.I.A. prepared the tables and performed the drafting of the manuscript. R.I.N.C. participated in the review, editing and the validation of the final version of the manuscript. R.R.M. elaborated the figures and performed the

drafting of the manuscript. M.M.T.R. participated in the review and editing of the different stages of the manuscript. M.P.L.E. translated the manuscript to English language. All authors reviewed and approved the final version of the manuscript.

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