ACS POLYMERS Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/polymerau
Review

Polysaccharide-Based Hydrogels for Advanced Biomedical Engineering Applications

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Cite This: ACS Polym. Au 2024, 4, 463−486
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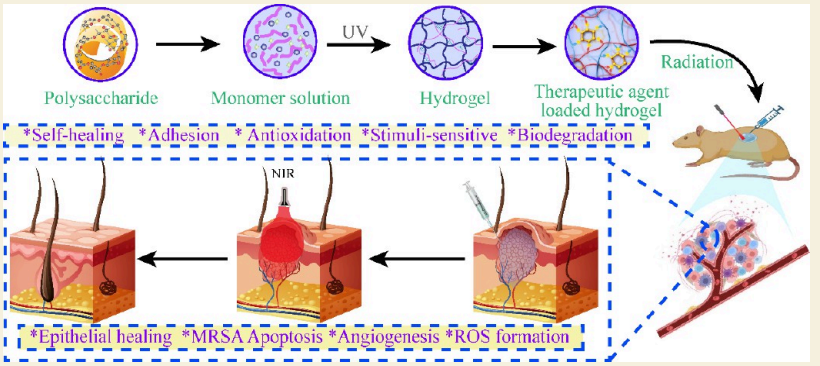


ABSTRACT: In recent years, numerous applications of hydrogels using polysaccharides have evolved, benefiting from their widespread availability, excellent biodegradability, biocompatibility, and nonpoisonous nature. These natural polymers are typically sourced from renewable materials or from manufacturing processes, contributing collaboratively to waste management and demonstrating the potential for enhanced and enduring sustainability. In the field of novel bioactive molecule carriers for biotherapeutics, natural polymers are attracting attention due to their inherent properties and adaptable chemical structures. These polymers offer versatile matrices with a range of architectures and mechanical properties, while retaining the bioactivity of incorporated biomolecules. However, conventional polysaccharide-based hydrogels suffer from inadequate mechanical toughness with large swelling properties, which prohibit their efficacy in real-world applications. This review offers insights into the latest advancements in the development of diverse polysaccharide-based hydrogels for biotherapeutic administrations, either standalone or in conjunction with other polymers or drug delivery systems, in the pharmaceutical and biomedical fields.

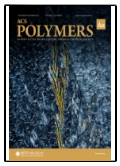
KEYWORDS: *Polysaccharides, Hydrogels, Stimuli-sensitive, Swelling, Drug delivery, Cancer Treatment, Diabetic Wound Treatment, Tissue Engineering*

1. INTRODUCTION

Hydrogels, composed of a 3D cross-linked hydrophilic polymer architecture holding a significant amount of water, are applicable across a wide range of applications, including biomedical, sensory, self-healing, energy, and water sustainability fields.[1−5] The synthesis of these hydrophilic polymers involves both physical and chemical cross-linking.[6,7] Chemical cross-linking employs conventional techniques such as redox, thermal processes, photochemical reactions, and radiation-initiated free radical polymerization.[8,9]

Noncovalent interactions, such as hydrophobic interactions, $\pi-\pi$ interactions, hydrogen bonding, and host−guest interactions play a crucial role in shaping the network structure of hydrogels, endowing them with distinctive self-healing properties.[10−12] However, the low binding capability and weak noncovalent chain interactions lead to low mechanical properties with inadequate modulus.[13−15] The mechanical properties of hydrogels have been improved in a number of ways, including by changing the topological structure of the matrix, copolymerizations, hybrid cross-linking systems, double-network polymerization, and nanocomposite approaches.[16] Despite these efforts, synthetic hydrogels often struggle to provide biocompatibility and high mechanical toughness simultaneously within emerging biomaterials.[17,18]

Received: March 25, 2024
Revised: August 7, 2024
Accepted: August 7, 2024
Published: August 20, 2024



https://doi.org/10.1021/acspolymersau.4c00028
ACS Polym. Au 2024, 4, 463−486

Advancements in engineering hydrogels employing natural polysaccharides have gained a driving force, particularly owing to the growth of biological applications for being elastic substances.[19] Interestingly, polysaccharide-based hydrogels address the problem with synthetic hydrogels by being biocompatible and nontoxic by nature, which are problems with regular hydrogels. The main feature of polysaccharide hydrogels is their natural origin, derived from renewable resources, such as starch, cellulose, alginate, or chitosan. This natural origin enhances the biocompatibility and makes them more environmentally friendly. However, hydrogels from natural resources like cellulose, alginate, pectin,[20] and chitosan are being extensively explored as renewable alternatives to address the global energy crisis.[21] Polysaccharide biomass resources, made up of repeating units of monosaccharides, are more common, cheaper, biocompatible, nontoxic, tough, adhesive, and able to heal themselves compared to synthetic polymer alternatives. Polysaccharides containing −OH, −COOH, or -NH_2 groups provide an accessible platform for enhancing different functionalities with premodification and/or postmodification.[22,23] However, dissolving cellulose and chitosan to synthesize polymeric composite gels in a water medium faces challenges due to extensive hydrogen bonding.[24] Several approaches have addressed these issues, like aqueous base/urea systems, cyclic Freeze−thaw processes, and oxidation modification.[25] Polysaccharide derivatives formed through these methods exhibit intriguing features, including stimuli-responsiveness and self-healing behavior, but often demonstrate low mechanical performance and poor stability.[25,26] Combining chemical and physical cross-linking, the double-network strategy is a promising approach to develop composite gels based on highly stable, strong, and tough polysaccharides.[8,27]

The functional groups within the glucose unit of a polysaccharide moiety allow them to attach various chemical modifications, such as fluorescent dyes, metal nanoparticles, and drug molecules, to enhance the properties and applications of polysaccharides.[28] Furthermore, polysaccharides' unique physicochemical properties, such as their biodegradability and biocompatibility, make them ideal for various practical applications. These encompass the development of artificial tissue, the treatment of wounds, the packaging of food, the treatment of wastewater, and the delivery of drugs and bioactive molecules.[3,29] Using polysaccharide biomass resources is not a sustainable solution to the energy crisis and opens up opportunities for developing eco-friendly and biocompatible materials. However, while polysaccharides offer opportunities for eco-friendly materials, their limited stability in physiological conditions and high-water solubility can hinder drug delivery systems and limit their use in food packaging applications.[30] Additionally, a current problem with polysaccharide hydrogels is their relatively weak mechanical strength and poor stability, which can limit their practical applications, especially in load-bearing situations or long-term use. To address these challenges, researchers have explored various modification techniques to enhance stability and water resistance of polysaccharide-based materials. Recent developments in polysaccharide hydrogels focus on enhancing their mechanical properties and stability through various strategies, such as cross-linking methods, blending with other polymers, and incorporating reinforcing agents. Additionally, incorporating nanoparticle fillers or functional groups onto polysaccharides can enhance their properties, such as controlled release capabilities or antimicrobial properties. By overcoming these limitations, polysaccharide-based materials hold great potential in revolutionizing industries and promoting a more sustainable and environmentally friendly future. These advancements are crucial for expanding the utility of polysaccharide hydrogels in real-world applications, particularly in the biomedical field, where robust and durable materials are often required.

This Perspective offers comprehensive guidelines for the rational design and synthesis of polysaccharide-based hydrogels. We explore the traditional toughening mechanisms, their experimental support, and the fundamental characteristics and gelling properties of various polysaccharides used in composite hydrogels in different sections. This exploration aims to elucidate the rationale behind the utilization of polysaccharide-based hydrogels. Numerous theories pertaining to hydrogel behavior are presented, paving the way for more in-depth investigations and study. Emphasis is placed on the distinctive properties conferred by polysaccharides and other filler materials alongside their applications, fostering insights into future polysaccharides application in hydrogels. Most importantly, considering these insights from previous reviews on hydrogels, this Perspective aids in the judicious selection of polysaccharides and enhances discussions on mechanical properties, thereby propelling further research in polysaccharide-based hydrogels.

2. HYDROGELS DERIVED FROM POLYSACCHARIDES

Biopolymers, primarily obtained from biological resources such as polysaccharides, proteins, and nucleic acids, demonstrate extensive biocompatibility and biodegradability.[31] Through minor chemical adjustments, they retain their viability in the environment. This characteristic makes them a preferred option for the creation of hydrogels. Hydrogels, along with their modified forms, are effectively produced by integrating polysaccharides like cellulose, chitosan, pectin, dextran, hyaluronic acid, starch, alginate, heparin, peptidoglycan, and glycogen.[32] Natural polymers boast various functional groups, accelerating the development of polysaccharide-based hydrogels achieved through chemical or physical cross-linking. Moreover, protein-based polymers,such as collagen, gelatin, and fibrin form nanometer-wide fibrils and micrometer-length structures. These structures emerge from both intermolecular and intramolecular forces, encompassing hydrogen bonding, ionic bonding, van der Waals interactions, and so on, with or without permanent electrostatic moments. These mechanisms are significant in enabling the creation of three-dimensional polymeric gels architecture through self-arrangement and entanglement under suitable environments.[33]

Polysaccharides possess inherent functional groups, making them suitable for engineering hydrogels through various cross-linking techniques, both noncovalent and covalent. However, preparing hydrogels using cellulose and chitosan in aqueous solutions poses a considerable challenge owing to the extensive intermolecular as well as intrachain hydrogen bonding. Solvents, for example, aqueous base/urea systems, have been studied to dissolve cellulose through continuous freezing-thawing processes. Additionally, modifying polysaccharides through oxidation to produce carboxylated derivatives has proven to be effective. These derivatives can form gels through hydrogen bonds, ionic interactions, or coordination interactions with metal ions and organic molecules, and most commonly, host−guest interactions. For instance, alginate can form egg-box-like structures with calcium ions, and cyclo-

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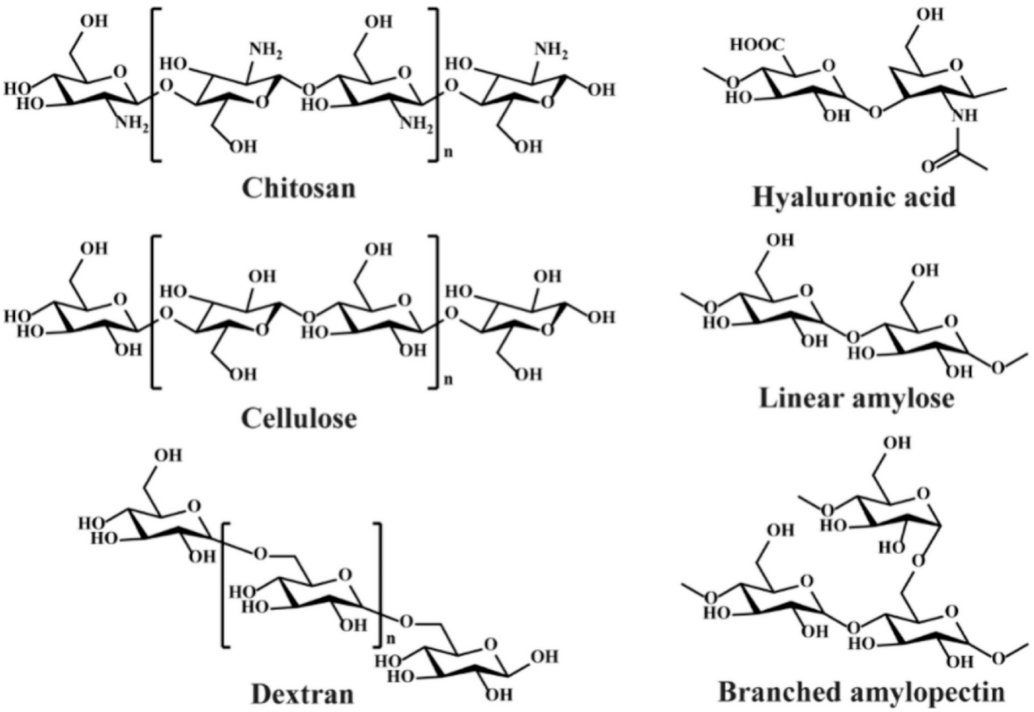

Figure 1. Structural representations of different polysaccharides such as chitosan, cellulose, dextran, hyaluronic acid, linear amylose, and branched amylose.

dextrins (CDs) can create inclusion complexes with various guest molecules through host−guest interactions to form hydrogels.

Furthermore, pH-dependent dynamic and reversible covalent interactions, such as the Diels−Alder reaction, imine bonds, disulfide linkages, and boronate ester bonds, have been employed to introduce the cross-linked hydrogels. These interactions endow polysaccharide-based hydrogels with desirable features, such as responsiveness to stimuli and self-healing capabilities, though they often exhibit low mechanical strength and stability. The double-network strategy, which combines chemical and physical cross-linking, offers a promising approach to enhance these hydrogels' strength, toughness, and stability. Extensive research has focused on developing polysaccharide-based hydrogels due to their exceptional properties. They have been widely used in various applications, including catalysis, tissue engineering, sensing, self-healing materials, and energy storage and conversion.

Polysaccharides are natural polymers consisting of monosaccharides connected through glycosidic bonds. These complex carbohydrates exhibit diverse chemical structures, compositions, and ionic properties. To be classified as polysaccharides, these compounds must contain at least ten sugar units; otherwise, they fall under the category of oligosaccharides. The general formula for polysaccharides is $C_x(H_2O)_y$. The properties of polysaccharides are largely determined by the unique features of their repeating units, which include the size of the sugar rings, their specific configurations, and the types of bonds that link them together.[21]

Considering the chemical structures, a polysaccharide is formed by the dehydration condensation of monosaccharide molecules. The common monosaccharides are listed as follows: hexose (D-glucose, d-mannose, d-fructose, d-galactose, and l-altrose); pentose (d-xylose); and hexuronic acid (D-glucuronic acid, d-galacturonic acid, d-mannuronic acid, and l-iduronic acid), among others, where d and l are used to distinguish two particular stereoisomers. These monosaccharides are linked by glycoside bonds, such as α-1,4-, β-1,4-, and α-1,6-glycoside bonds, where α and β are classified by the position of the −OH group on the C-1 carbon atom and the ending −OH group of the molecule. Furthermore, the structural units can form different morphologies of the molecule chain, namely, straight-chain or branched-chain structures. The straight chains are generally connected by α-1,4-glycoside bonds (such as starch) and β-1,4-glycoside bonds (such as cellulose), whereas in the branched chains, the connection point linkage is usually an α-1,6-glycoside bond. Therefore, polysaccharides can be categorized according to the differences in monosaccharide composition and linkage type, such as homopolysaccharides and heteropolysaccharides based on their composition or linear and branched polysaccharides based on their structures.[22] The polysaccharides can also be divided according to their electrical charges or functions. Some of the chemical structures of the popular polysaccharides are present in Figure 1.

The position of the α-linkages within a polysaccharide molecule can significantly affect its mechanical and biological properties. Polysaccharides are complex carbohydrates composed of long chains of monosaccharide units linked together by glycosidic bonds. The arrangement of these bonds, whether α or β, and their positions along the polysaccharide chain influence their physical, mechanical, and biological characteristics.

The position of α-linkages of two glucose units is a key factor in shaping the flexibility, structural rigidity, and overall mechanical properties of polysaccharides-based hydrogels. This understanding opens up exciting possibilities for innovation in polysaccharide-based materials. For instance, polysaccharides with α-linkages in certain positions may exhibit greater

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ACS Polym. Au 2024, 4, 463−486

flexibility due to the ability of the α-glycosidic bond to adopt a conformation that is more extended than that of β-linkages. This flexibility can affect the material's tensile strength, elasticity, and resistance to deformation. The position of these linkages can influence the polymer's ability to form hydrogen bonds or interact with other molecules, thereby impacting its tensile strength and elasticity. Moreover, the spatial arrangement of α-linkages can dictate the ability to withstand mechanical behavior, especially compression, tensile, and shear forces, making them significant in real-world applications ranging from biomedical to agricultural products. The position of α-linkages in cellulose significantly affects its tensile strength and elastic modulus, with α(1 → 4) linkages contributing to higher mechanical properties compared to α(1 → 6) linkages. Understanding how the positioning of α-linkages influences mechanical properties enables an adapted design of polysaccharide-based materials for specific applications.

The position of the α-linkages within the polymer network can notably affect the biological properties of biopolymers. This understanding opens up new possibilities for developing polysaccharide-based materials for various biomedical applications. These linkages play a crucial role in determining polysaccharides' bioavailability, biocompatibility, and bioactivity. For example, specific orientations of α-linkages can enhance the recognition and binding of polysaccharides to cell receptors, influencing processes such as cellular adhesion, signaling, and immunomodulation. Moreover, the arrangement of α-linkages can impact the enzymatic degradation of polysaccharides in the body, affecting their metabolic fate and biological half-life. The α-linkages of natural polysaccharides have a huge significance in terms of bioactivity. Polysaccharides with specific α-linkages exhibited enhanced antioxidant and immunomodulatory activities compared to others. Structural characterization and antioxidant activity of a novel polysaccharide derived from Pteris multifida Poiret. Therefore, understanding the relationship between the position of α-linkages and biological properties is crucial for developing polysaccharide-based materials for various biomedical applications, including drug delivery systems, tissue engineering scaffolds, and regenerative medicine approaches.

The toughening mechanisms of polysaccharides can vary depending on the position of α-linkages.[34] This variability presents rich ground for future advancements in polysaccharide-based materials. Toughness refers to the ability of a material to absorb energy and deform plastically before fracturing.[35] Polysaccharides with α-linkages in specific positions may exhibit enhanced toughness due to intermolecular interactions, chain entanglement, hydrogen bonding, and crystallinity.[34,36−38] However, the position of α-linkages can also affect the sacrificial bonding, energy dissipation, and crack deflection on the toughening mechanisms by altering the molecular interactions within the polysaccharide matrix, leading to differences in fracture toughness and resistance to mechanical stress.[39,40] The position of α-linkages can affect the formation of hydrogen bonds and other intermolecular interactions within polysaccharide chains, contributing to their toughening mechanisms.[41,42] Understanding these toughening mechanisms is essential for developing polysaccharide-based materials with improved mechanical properties for various applications, including tissue engineering, drug delivery, and food packaging. On the other hand, the position of the α-linkage can affect the ability of the polysaccharide material to dissipate energy and the chain entanglement upon deformation, thereby influencing its toughness. Certain linkage positions may facilitate mechanisms, such as crack deflection, crack bridging, and plastic deformation, leading to enhanced toughness. Changes in the arrangement of α-linkages can induce microstructural modifications in the polysaccharide matrix, impacting toughening mechanisms such as strain hardening or stress redistribution.[34] This potential for future advancements in polysaccharide-based materials should inspire hope and optimism in researchers and professionals.

2.1. Cellulose

Cellulose, earth's most abundant biodegradable polymer, is made up of D-glucopyranose connected by the β-1,4-glycosidic bonds. On the other hand, the presence of numerous free hydroxyl groups in cellulose contributes significantly to the formation of abundant intra- and intermolecular hydrogen bonds.[43] These bonds facilitate the association of individual chains with cellulose fibers. These fibers are characterized by a combination of highly ordered (crystalline) and disordered (amorphous) regions arranged alternately.[44] Traditionally, cellulose fibers have been used in the production of paper and textiles, and more recently, they have found applications in the composite industry. However, the robust network of hydrogen bonds also renders cellulose insoluble in most common solvents.[45] To address this challenge, chemical modifications of cellulose are employed to create cellulose derivatives with diverse properties and applications.[46] For example, commercially available cellulose derivatives include carboxymethyl cellulose (CMC), methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, and mixed ethers such as hydroxyethyl methylcellulose, which are produced by reacting cellulose fibers with alkyl halides in an alkaline medium.

However, the applications of cellulose-based hydrogels in materials science still need to be improved due to their poor solubility. Cellulose exhibits poor solubility, mainly due to strong hydrogen bonding among its alcohol groups and the inherent stiffness of the molecules.[47] Various modification techniques enhance solubility by disrupting these hydrogen bonding interactions. A deep understanding of the principles of solvation is crucial for anticipating and manipulating the solubility of polymers such as cellulose in other liquid systems and under different chemical modifications. For instance, derivatives such as methyl cellulose become soluble in water with the increasing substitution of hydroxyl groups by methyl groups.[48] At the same time, further methylation renders cellulose soluble in organic solvents like dichloromethane.

Temperature adjustments play a significant role in altering intermolecular interactions and solvation dynamics, thereby enhancing the absorbency properties of polymers.[49] Solvation power can also be enhanced by incorporating strongly ionic or hydrogen bonding agents such as lithium chloride, urea, or sodium hydroxide into solvent systems.[50] Synthetic polymers are engineered with specific solubility profiles, rheological properties, and absorbency capacities tailored to diverse applications. Modifications involving solvent systems like water-urea mixtures or acid−base reactions are explored to increase cellulose solubility.[51] Polymer−polymer interactions can also be minimized through structural adjustments, reduction of functional groups, or enhancement of chain symmetry. Examples such as poly(vinyl alcohol), derived from poly(vinyl acetate), demonstrate how controlled hydrolysis

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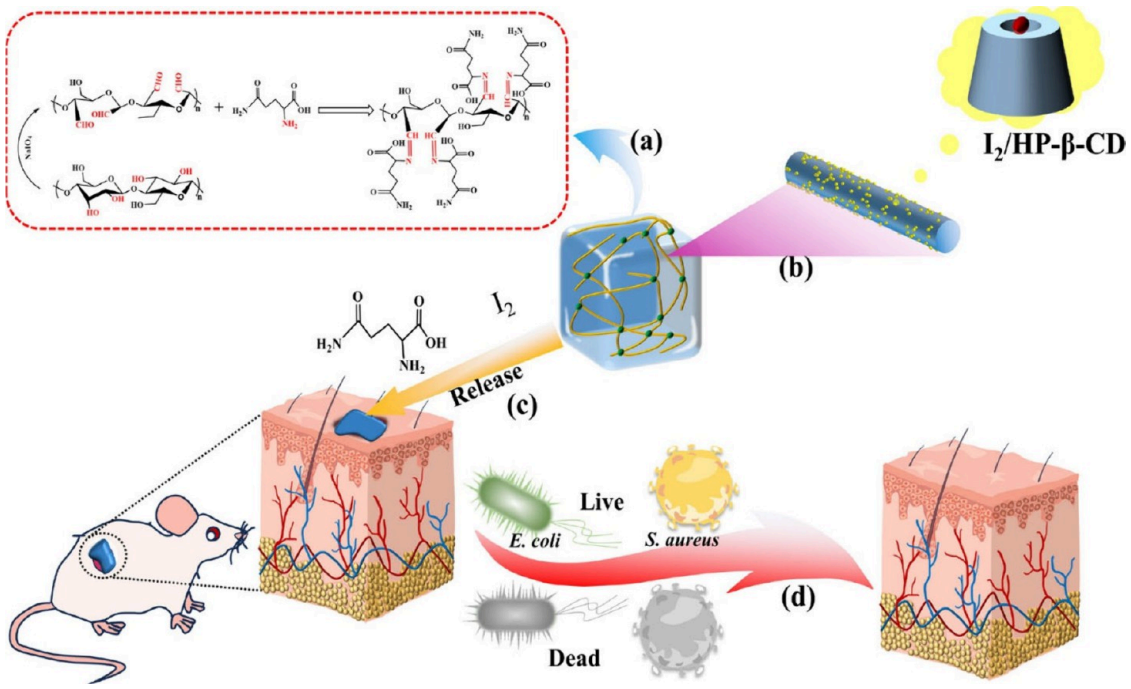

Figure 2. Illustration depicting (a) The reaction mechanism involved in the hydrogel preparation process. (b) Modification of I2/HP-*β*-CD to the fibers of the gel skeleton. (c) The ability of the hydrogel to release L-glu and iodine in contact with the infected wound site, (d) Bacterial death and the subsequent wound recovery.[59] Reprinted with permission from ref 59. Copyright (2024) American Chemical Society.

optimizes water solubility, illustrating broader principles applicable to cellulose and synthetic polymers like poly-(hydroxyethyl methacrylate) and poly(*N*-isopropylacrylamide), known for their complex interactions with water and versatile phase behavior.[52,53]

The biomedical field benefits greatly from its extensive applications, owing to its biocompatibility, biodegradability, minimal toxicity, and cost-effectiveness. Mansur et al.[54] conducted a recent study where they developed polymeric gels using carboxymethyl-cellulose (CMC) cross-linked with citric acid (CA) and enhanced with poly(ethylene glycol) (PEG) through an environmentally friendly aqueous method. Another investigation by Tan et al.[55] introduced a chitosan-cellulose composite hydrogel with pH-sensitive properties designed for drug delivery and wound treatment purposes. This hydrogel, formed by oxidizing adjacent OH groups on CMC, presented Schiff base derivative hydrogels with carboxymethyl chitosan (CMCh). The hydrogel loaded with silver sulfadiazine demonstrated controlled release under both acidic (pH 5.5) and alkaline (pH 9.5) conditions. However, one-pot radical graft copolymerization was used in order to produce a hydrogel with a spongy-like architecture denoted as QHM, consisting of mesocellular silica foam (MCF) and quaternized hydroxyethyl cellulose.[56] The QHM gel, containing 9.8% MCF, could rapidly expand upon contact with water, enhancing blood component concentration, activating coagulation factors, and promoting hemostasis and wound management. Cellulose-based gels, like the bacterial cellulose/acrylic acid (BC/AA) polymeric film, have shown promise for use in the treatment of burn wounds as potential nanocarriers for human skin epidermal keratinocytes and dermal fibroblasts. Nanocellulose, especially cellulose nanocrystals (CNs), played a significant role in hydrogel preparation owing to their exceptional characteristics, including high mechanical toughness with sufficient strength, elastic modulus, high active surface area, low polymer density, and reactive functionalities.[55,57] Chen and colleagues developed a copolymer reinforced with CN and pH dependent Schiff-base bonds among the -NH_2 of CMC and the −CHO groups of aldehyde-functionalized nanocrystals cellulose (DANCC) for cross-linking.[58] DANCC acted as active junctions for rapid self-healing and included reinforcing fillers to enhance the hydrogel strength.

Xielong et al.[59] have introduced innovative methods for developing a multifaceted gel wound management system (Figure 2). This system highlights iodine's role in eliminating bacteria, emphasizes the functional significance of L-glutamine (L-glu) as an essential active ingredient, and hydrogel effectively mimics the extracellular matrix (ECM). Specifically tailored for chronic wound treatment, this novel system harnesses multiple synergistic effects. The hydrogel received an innovative modification by incorporating amino acids using Schiff base interaction. Noteworthy is the fact that human skin typically maintains a pH range of 4 to 6. However, during an infection, the pH of the wound tends to decrease gradually. Dissociating the Schiff base bond automatically while the pH declines below 6.6 is significant progress. DANCC stimulates the aggregation of red blood cells, leading to clots to stop bleeding effectively. Meanwhile, releasing amino acids from the tissue effectively enhances cellular immunity, while iodine penetrates the targeted infected area by diffusion, offering a novel method for eliminating germs. The synergistic interaction of several elements, emphasizing unprecedented unity, facilitates the quick progression of wound recovery.

2.2. Alginate-Based Hydrogels

Alginate is a linear polysaccharide extracted from seaweed, comprised of homopolymer subunits consisting of *α*-*L*-guluronate (G) and *β*-*D*-mannuronate (M) residual units. Its widespread application in wound treatment hydrogels is due to its biocompatibility and easy modification process. The

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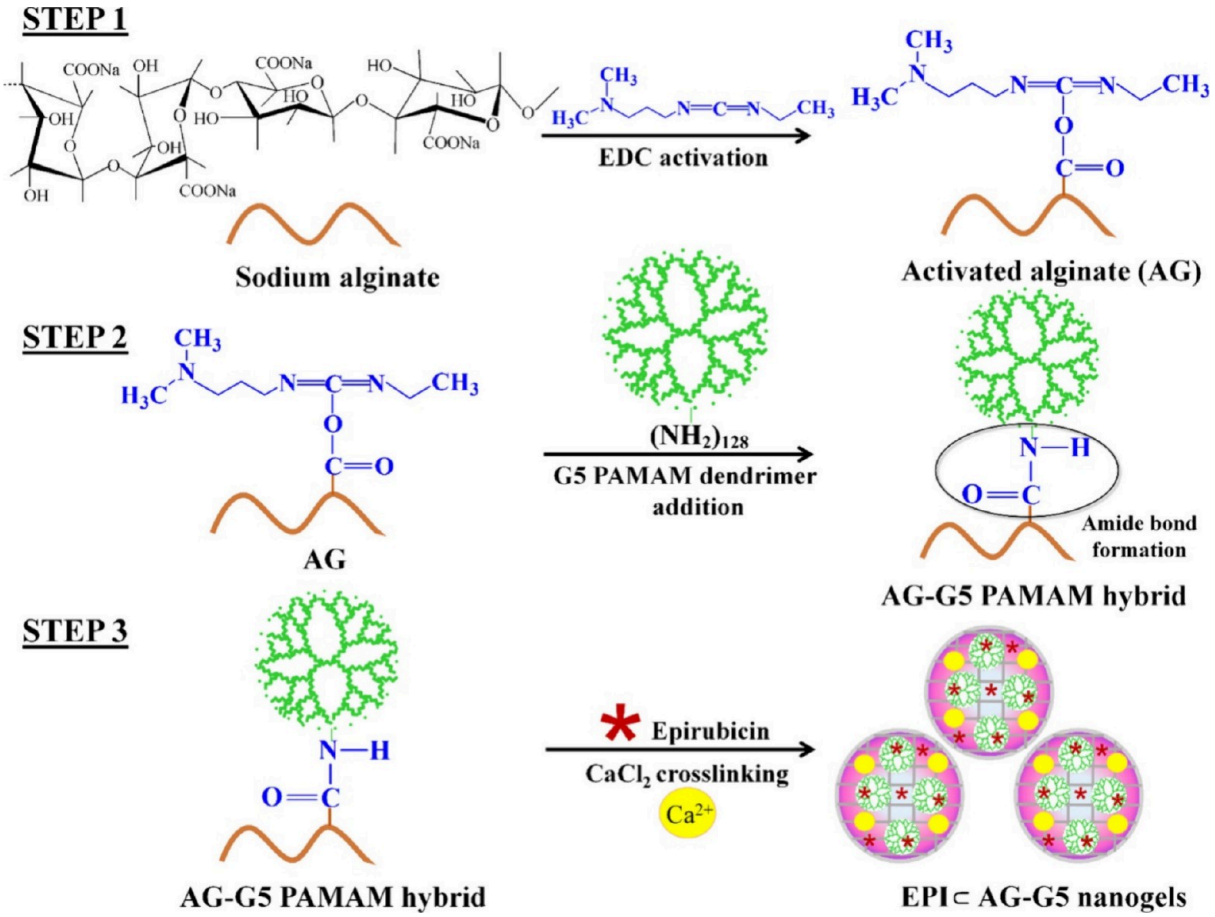
Scheme 1. Stepwise Illustration of the Preparation Process for EPI⊂AG-G5 Gels [a]



[a]Adapted from Matai, I. and P. Gopinath, chemically cross-linked hybrid nanogels of alginate and PAMAM dendrimers as efficient anticancer drug delivery vehicles.[64] Reprinted with permission from ref 64. Copyright (2016) American Chemical Society.

hydrogel synthesis process involves cross-linking of G-blocks with M^{2+} ions (especially Ca^{2+}, Mg^{2+}, Ba^{2+}, and Fe^{2+}). Therefore, the physical behavior of as-prepared alginate-based composite hydrogel can be influenced by several factors, like the molecular weight, M/G ratio, sequences of the repeated moiety, and length of G-block units.[60]

A composite hydrogel, introduced by Chang and colleagues,[61] combines glass mass that is biologically compitable and oxidized sodium alginate (OSA), cross-linked by adipic acid dihydrazide (ADH)-functionalized γ-polyglutamic acid (γ-PGA). The gel system facilitates wound closure and recovery processes through several mechanisms. It releases alkaline ions from the glass mass, which aid in imine linkage formation. Additionally, it promotes the release of Ca^{2+} from the glass mass, enhancing adhesion with biomaterials. Moreover, the hydrogel promotes blood flow in the affected area by releasing Si-ions. On the other hand, Sui et al. engineered a porous, ultrastrong chitosan/sodium alginate composite film using a diffusion process, showcasing superfast programmable deformations triggered by pH, charged ions, magnetic field, and temperature. Hytönen et al.[62] presented an alginate-based hydrogel infused with nano cellulose tailored explicitly for 3D printing. This innovative method aims to prevent deformation of the printing paste, ensuring the preservation of shape fidelity in the printed pattern. It represents a unique approach to wound repair. Doping various ions in alginate-based gels imparts diverse properties; for example, investigating antibacterial properties involved doping Rb^{+}, Cu^{2+}, Zn^{2+}, and Sr^{2+} in gels.[63]

Ishita et al.[64] used a simple synthetic process to develop nanocomposite hydrogels for administering drugs toward the target carcinoma cells. Scheme 1 represents the stepwise preparation process for EPI-AG gels. The −COOH groups of alginates were activated using 1-ethyl-3-(3-dimethylamino propyl) carbodiimide hydrochloride (EDC), a zero-length cross-linker, to form an amide bond (−CONH−) with the $-NH_2$ groups of Polyamidoamine (PAMAM) dendrimer. This resulted in the formation of permanent, irreversible amide bonds between alginate and the PAMAM moieties. Following this, Ca^{2+} from $CaCl_2$ was employed to form cross-links with the remaining carboxylate groups depicted in Scheme 1. The structural stability and superior drug entrapment efficiency were achieved through the synergistic interplay of covalent and electrostatic bonding interactions within the alginate-dendrimer network. To assess these properties, exocrine pancreatic insufficiency (EPI) was employed as a model drug, investigating the psychological implications associated with the prepared hydrogels. The anticancer efficacy of prepared nanocomposite hydrogels in human breast cancer cells was also examined using the natural red fluorescence of EPI to monitor its distribution within the cells. This fluorescence-based approach allows for the monitoring of cancer growth and therapy.

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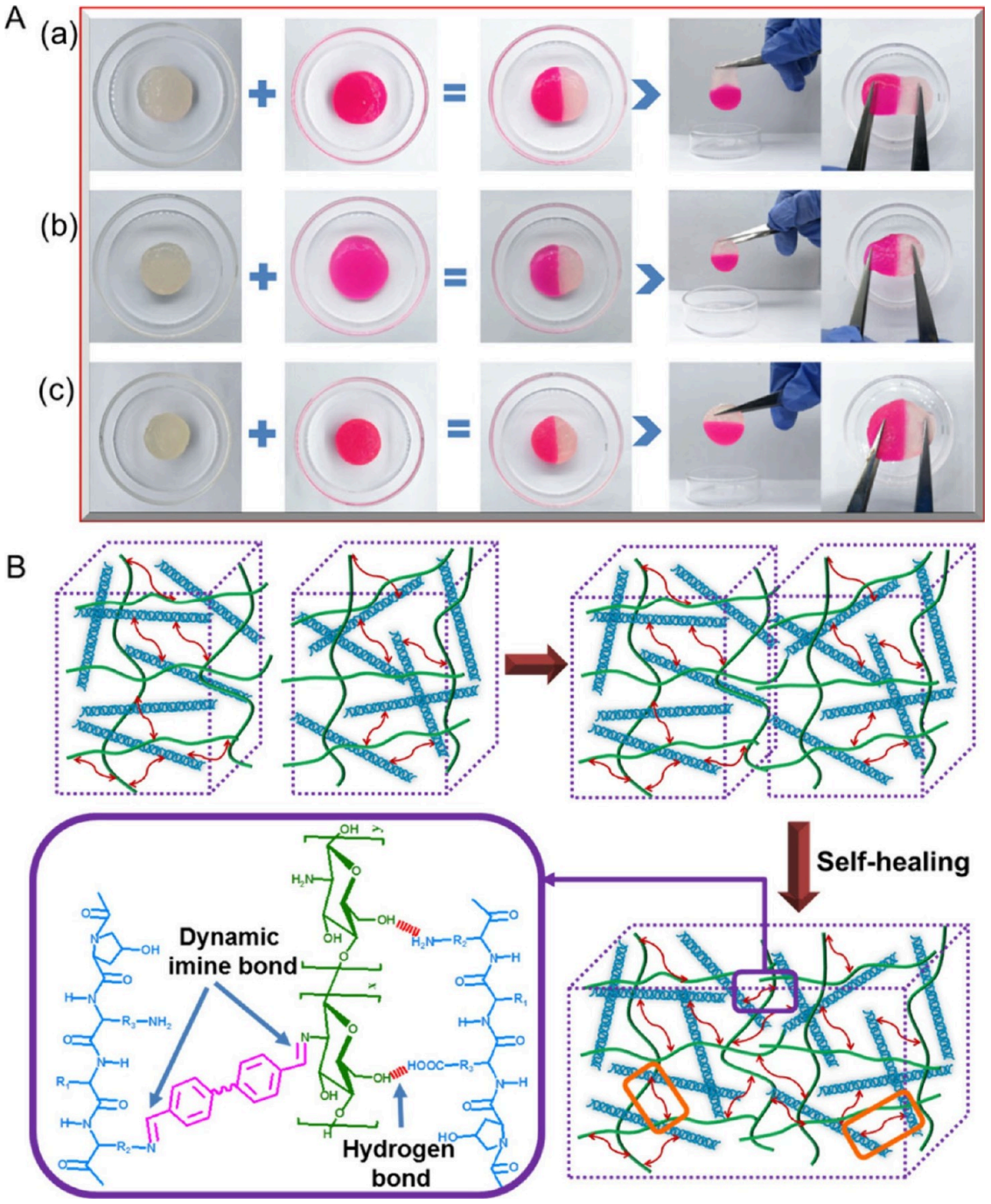

Figure 3. (A) Representation of real images of virgin and healed gel sample of COL-CS hydrogels: (a) COL-CS (1:1), (b) COL-CS (1:2), and (c) CS; (B) Illustration depicting the proposed healing mechanism.[72] Reprinted with permission from ref 72. Copyright (2020) American Chemical Society.

2.3. Chitosan-Based Hydrogels

The preparation of Chitosan, derived through the deacetylation of chitin found in the exoskeletons of crustaceans, is a linear polymer composed of *N*-acetylglucosamine units.[19,65,66] Among natural polysaccharides, chitosan is the fundamental polymer that is special primarily because of its abundance of amino groups distributed throughout its structural chains, which offer it a positive charge. However, Chitosan-based hydrogels are natural polymer hydrogels formed via a variety of physicochemical interactions.[67] One key factor influencing their gelation is pH: chitosan, initially insoluble in water at neutral pH, becomes soluble in acidic conditions when its amine groups are protonated.[68] Neutralizing a chitosan solution with a strong base above pH 6.5 triggers rapid formation of a hydrated gel-like precipitate by removing positive charges from its amine groups. Another mechanism involves ionic interactions, where gradual interactions occur between molybdate polyoxyanion and D residues on chitosan under acidic conditions, contributing to gelation.[68] Additionally, chitosan hydrogels can be physically or covalently cross-linked to stabilize the network and tailor properties for specific applications. Some studies also explore combinations of these mechanisms. Furthermore, employing a polyol base facilitates

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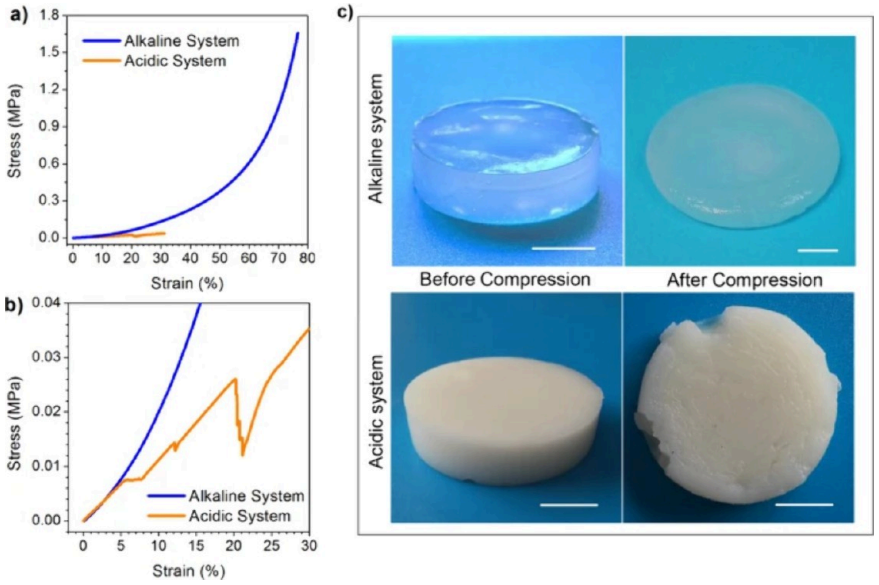

Figure 4. Mechanical behavior of CS gel using alkaline and acidic solvents. (a) Compressive analysis of as-prepared composite hydrogels. (b) Compressive analysis of as-prepared composite hydrogels at low strain range. (c) Real images of CS hydrogels before and after compression tests.[74] Reprinted or adapted with permission under a Creative Commons (http://creativecommons.org/licenses/by/4.0/) from ref 74. Copyright (2016) Springer Nature.

gelation of these hydrogels at body temperature (37 °C). This phenomenon arises from interactions within the hydrogel matrix, including reduced electrostatic repulsion between chitosan chains and enhanced hydrophobic interactions between polymer chains. Its distinctive characteristics, such as antimicrobial activity and nonantigenicity, have spurred extensive research in different applications, particularly drug and therapeutic molecule delivery, antibacterial, wound healing, soft robotics, and biomedical applications.[66] The antibacterial attributes of chitosan contribute to enhancing the versatility of the hydrogels.

In contrast to conventional dressings that release antibacterial agents, chitosan-based dressings with inherent antibacterial properties might exhibit sustained antibacterial effects while minimizing cytotoxicity to organoids.[69] Ma et al.[70] introduced an injectable hydrogel with antibacterial and conductive behavior by incorporating glycidyl methacrylate-modified quaternized chitosan and carbon nanotubes (CNTs). This innovative gel is designed to address noncompressible hemorrhage, promote hemostasis, and facilitate wound recovery. The hydrogel demonstrated strong mechanical resilience, swift shape memory, and self-assembly stimulated by blood, rapid absorption, and a notable capacity for blood uptake. Tao and Wang[71] introduced hydrogels built with dynamic chemical connections such as disulfide, esterification, Schiff-base, hydrazine, acetal, etc. These hydrogels exhibit the ability to undergo shape changes autonomously, guided by various forces, especially surface tension and gravitational forces, without the need for external stimuli. Ding et al.[72] use the telechelic cross-linking technique to introduce a pH-dependent self-healing behavior of a chitosan and difunctional poly(ethylene glycol) (DF-PEG)-based composite hydrogel (DF-PEG) shown in Figure 3. During the recovery phase of rat-liver laceration, the application of a thrombin-loaded hydrogel (CPT) to the liver capsule resulted in a sleek appearance and a vibrant color indicative of its promise as a highly effective drug carrier for in vivo injured wound dressing. Yao and colleagues[73] designed chitosan-based hydrogels with thermosensitive properties to deliver external recombinant human stromal cell-derived α factor-1 to treat damaged eyes. The approach aimed at enhancing the regeneration of the corneal epithelium, promoting its restoration with enhanced natural structural and functional characteristics. This resulted in enhanced local proliferation of important growth factors that are required for corneal epithelial repair.

Jingyi et al.[74] investigated the gelation process in an acidic medium, with a specific focus on developing multilayers and orientation in hydrogels. To gain a comprehensive understanding, exploration of alkaline systems becomes essential, as a crucial missing puzzle piece. The peculiarities of alkaline systems impose limitations on the choice of characterization techniques. Traditional methods such as SEM and TEM suffer from drawbacks such as sacrificing the hydrogel's native state and interference from the crystal formation of LiOH and urea. Conversely, techniques such as light scattering offer insights into the native state but lack direct observation capabilities. Additionally, the need for quick data acquisition to capture the entire gelation process further complicates the selection of suitable methods. Considering these factors, fluorescent imaging has emerged as an ideal strategy. Here, in situ fluorescent imaging was used to observe the gelation process dynamically in real-time (Figure 4). The differences between basic and acidic systems were investigated by analyzing the gelation mechanism and structural properties and conducting other in situ experiments.

2.4. Collagen-Based Polysaccharide/Protein Composite

Collagen, cellulose, and chitosan are noteworthy examples of highly abundant natural biopolymers that offer renewability. Because of its dominant physical and chemical attributes, collagen/protein-based hydrogel has crucial importance in the biomedical domain as a structural protein in different tissues, including epidermis, muscles, veins, bones, cartilage, etc.[75] With functional groups like hydroxyl, amino, carboxyl, and imidazole, collagen naturally forms a trihelical fibrous architecture under physiological atmosphere, imparting sig-

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ACS Polym. Au 2024, 4, 463−486

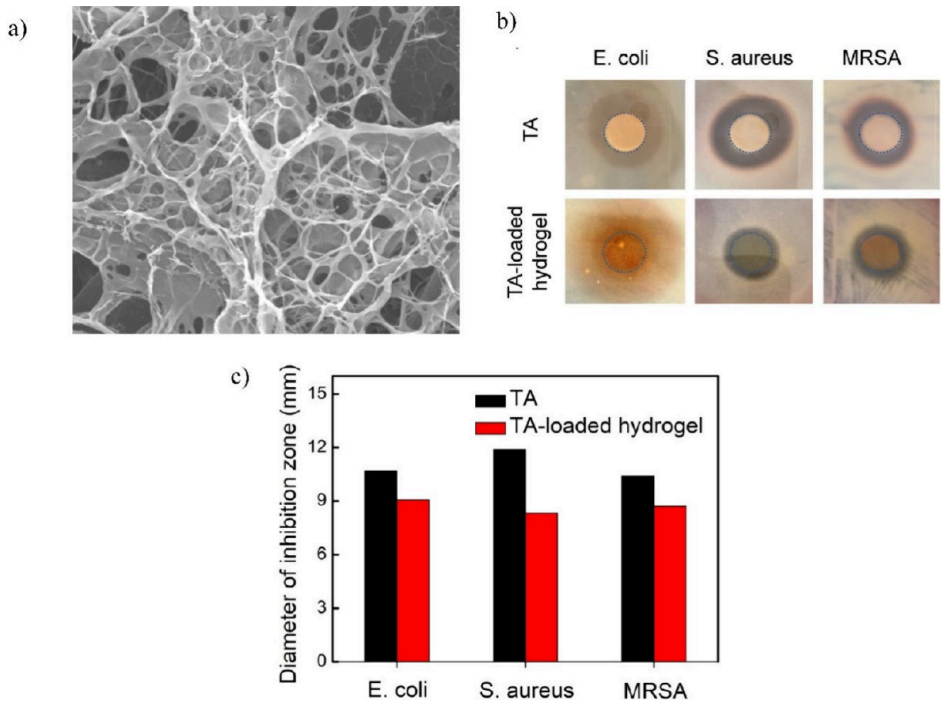

Figure 5. (a) Scanning Electron Microscope (SEM) image of composite hydrogel. (b) Photographic representation of agar diffusion analysis for both Tannic Acid (TA) and TA-loaded blend hydrogels. (c) Determination of inhibition zone diameters for *E. coli*, *S. aureus*, and MRSA in the presence of TA and TA-loaded hydrogels.[81] Reprinted with permission from ref 81. Copyright (2018) American Chemical Society.

nificant tensile strength and durability.[54] The inherent features of collagen, encompassing hydrophilicity, biocompatibility, biodegradability, nonimmunogenicity, and mechanical resilience, render it indispensable for biomedical research. However, the gelation process of collagen hydrogels involves the fibrillogenesis of collagen molecules, initiated by temperature elevation and pH neutralization within the collagen solution.[76] Over time, solubilized fibrils interact and assemble into networks and fibers. The kinetics of collagen hydrogel gelation vary with temperature and pH, exhibiting maximal storage modulus at 37 °C and pH 8.[77] Gelation denotes the transition of a polymer system into a gel, where branched polymers gradually link chains, forming larger polymers. Upon reaching the gel point, these interchain links create a cohesive, highly viscous gel with reduced fluidity. The gel, or network, represents a macroscopic polymer structure that exhibits nonsolubility in the solvent but can undergo swelling within it.

However, the primary sources of collagen are animals, pork skin, bovine tendon, rabbit tail, or marine resources, and it can be extracted using chemical or enzyme methods.[78] Alternatively, recombinant collagen produced through technologies including *Escherichia coli*, insect cells, tobacco plants, yeast, mammalian cells, and corn seeds offers an alternative source.[79] Chemical modification is often required to achieve the desired properties, and various methods can be employed to prepare hydrogels with specific characteristics. Gelatin, derived from collagen through irreversible hydrolysis, is a denatured, water-soluble polypeptide.[80] Despite its challenges in terms of usability under physiological conditions due to a low melting temperature, gelatin methacrylate (GelMA) and similar modifications have become noteworthy in biological domains. They provide photo-cross-linking capabilities along with the ability to regulate stiffness and porosity. Alginate, a biopolymer of natural origin, consists of recurring α-L glucuronate and β-D mannuronate residues. It offers biocompatibility, biodegradability, lack of antigenicity, and stability. Alginate hydrogels, obtained from brown algae or produced by bacterial biosynthesis, share structural similarities with the ECM of tissues. Various methods, such as ionic and covalent cross-linking, thermal gelation, and in situ copolymerization, are utilized to prepare alginate-based hydrogels. Amphiphilic and cell-interactive alginate derivatives hold promise in drug delivery and tissue regeneration applications.

Yueyuan et al. developed a nanofiber-based, injectable, self-healing, and adhesive gel comprising gelatin and gellan gum for wound treatment. The composite gels demonstrated notable shear-thinning and self-healing behavior.[81] To enhance its benefits, tannic acid was incorporated, although caution is needed to avoid potential side effects. An SEM analysis confirmed that the composite hydrogels consist of a nanoporous chain network with a 2−3 μm pore size, shown in Figure 5. These nanofiber-based wound dressings have received interest due to their enormous surface area, substantial porosity, and outstanding permeation, which promote cell adhesion, migration, and proliferation.

2.5. Starch-Based Hydrogel

Starch, a natural polysaccharide, comprises repeated sugar units connected via α-*D*-(1−4) and α-*D*-(1−6)-glycosidic bonds. Its cost-effectiveness, renewability, biodegradability, and biocompatibility make it widely used in the food, agriculture, biological, and drug sectors.[82] In its natural form, starch displays a granular structure, termed a starch granule, containing minimal amounts of proteins, fatty acids, and minerals. The starch structure is predominantly characterized by two polysaccharides: Amylose and amylopectin. With its linear configuration, Amylose is known for forming a double helix owing to a left-handed helical conformation and can create supramolecular inclusion complexes with guest molecules. Conversely, amylopectin possesses a more extensively

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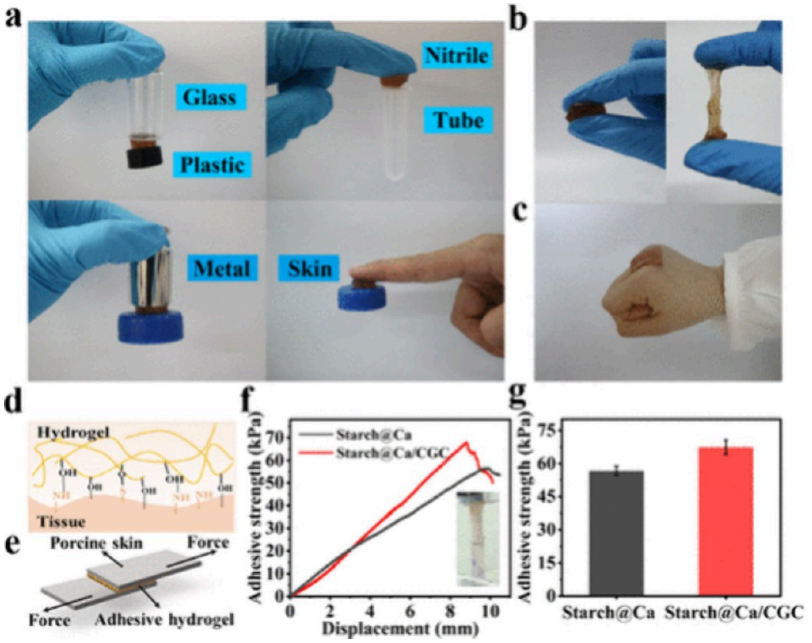

Figure 6. Demonstration of adhesive behavior of as-prepared Starch-Ca/CGC hydrogels; (a) Depicting the adhesion property of the Starch@Ca/CGC hydrogel to various substrates. (b) Compression, stretching state; (c) Images illustrating the resilient resistance to joint bending exhibited by the pliable and flexible Starch@Ca/CGC hydrogel. (d) Schematic representation of the characteristic interactions involved in the adhesion of hydrogels to biological tissues. (e) Schematic illustration of the lap shear test. (f, g) Determination of tissue adhesive strength in Starch@Ca and Starch@Ca/CGC hydrogels through a lap shear test on porcine skin, with a representative test image inset.[92] Reprinted with permission from ref 92. Copyright (2024), American Chemical Society.

branched structure compared to Amylose, resulting in a helical formation and crystallization, which has a significant role in stabilizing the structure of starch granules.[83]

Creating a well-defined 3D network structure is essential for maximizing the biomedical utility of hydrogels derived from starch.[84] Various techniques are employed to achieve this, each offering distinct advantages tailored to specific applications. Chemical cross-linking involves the formation of covalent bonds between polymer chains within the hydrogel matrix. Agents like glutaraldehyde, genipin, and carbodiimides facilitate cross-linking by reacting with hydroxyl groups on starch molecules, thereby stabilizing the structure and influencing mechanical and swelling properties.[85,86] Adjustment of agent concentration and reaction time allows precise control over cross-link density, enhancing customization for diverse biomedical needs. Physical cross-linking techniques, in contrast, utilize physical interactions to create 3D networks without chemical reactions.[87] Thermoresponsive hydrogels integrate polymers like poly(*N*-isopropylacrylamide), exhibiting sol−gel transitions based on temperature fluctuations.[88] Below the LCST, hydrophobic interactions induce network formation, while the hydrogel reverts to a solution state above this temperature. Similarly, pH-responsive hydrogels incorporate polymers such as poly(acrylic acid), responding to pH changes by swelling or contracting due to ionization of acidic groups, thereby modulating the 3D network structure.[89] These methods offer versatility in designing starch-based hydrogels with tailored architectures suitable for various biomedical applications.

Starch extraction is feasible from diverse sources, including seeds, foliage, roots, fruits, and vegetables. The composition of Amylose and amylopectin within starch exhibits variations based on the plant's origin. For example, corn starch possesses roughly 28 wt % Amylose, cassava starch showcases approximately 17 wt % amylose, and waxy potato starches exhibit 8 wt % amylose.[90] Starch-based gels can be prepared using biofriendly physical approaches, like starch retrogradation and extrusion. The retrogradation process involves the reorganization of Amylose during the fridge-throwing process. Additionally, diverse chemical techniques, such as etherification and coating, can be used to prepare starch-based hydrogel.[91] Etherified starches result from substituting OH groups with ether groups such as carboxymethyl in the starch moiety. Various vinyl monomers, including acrylamide and acrylic acid, can be applied to starch by using the coating strategy. A distinctive composition of light-curing gels, derived from starch and incorporating Fe_3O_4 nanoparticles, was created through the alteration of starch using acrylic glycol and cross-linking it using blue light. The gels exhibit customizable quercetin release, increased bioavailability, and enhanced mechanical properties.

Ke Xu and colleagues[92] have a novel method: a protocol for functionalizing starch-based hydrogels with Cu-gallic acid-carvacrol nanospheres (CGC NPs). This biomineralization technology enhanced the hydrogel properties, including injectability, self-repairing ability, adhesion, and antibacterial properties, for improved wound healing. The process included generating Cu-gallic acid cross-linked nanosphere (CG NS) systems using both ultrasonication and hydrothermal-assisted techniques. These methods were employed to improve the notable adhesion behavior, as illustrated in Figure 6. Simultaneously, the CG NSs exhibited a significant photothermal ability. Carvacrol, known for its antibacterial and antioxidant properties, was emulsified with CG NSs to form CGC NPs for functionalizing starch-based hydrogels. The experimental confirmation involved testing potato starch, selected for its distinct thermal transition temperature, viscosity characteristics influenced by extended amylopectin

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ACS Polym. Au 2024, 4, 463−486

Table 1. Applications of stimuli-sensitive polysaccharide-based hydrogels[a]

Polysaccharides	Cross-linking	Stimuli sensitive	Model	Mechanical analysis	Swelling	Applications	ref.
CMCh	Both Physical and Chemical cross-linking	Temperature/Salt/ Redox	GA/CCS/ DNSA/Eu^{3+}	Tensile properties (0.8)		Anticounterfeiting	93
Guar gum	Chemical	pH/Salt/ Temperature	PAA- and MBA		About 2400 g/g At 37 °C	Drug delivery	94
CA	Chemical	pH/Temperature/ Magnetic	NIPAM, PAA and Fe_3O_4		650 g/g At pH 7.5 and 25 °C	Drug delivery	95
Salecan	Chemical	pH/Temperature/ Magnetic	PDMAEMA		20 g/g at pH 7.4 at 25 °C	Drug delivery	96
Linseed	Physical	pH/Ionic			8.5 after 1000 min	Drug delivery	97
Glucuronoxylan	Both Physical andChemical cross-linking	pH/Saline			210 g/g at pH 7.4	Drug delivery	98
Xanthan maleate	Chemical (ionic)	pH/Temperature	NIPAm		8000 g/g at 25 °C	Biomedical andBiotechnological	99
Ch	Physical	pH/Temperature			170g/g at 35 °C and pH 7.4	Doxorubicindelivery in breast cancer	100
Carboxymethyl Starch	Physical	pH/Temperature			1100 g/g at 37 °C and pH 7.4	Anti-Inflammatory drug delivery	101
HA	Chemical	pH/Reduction	THA			Cancer therapy	102
Ch	Chemical	pH/Redox	Oxidized Dex			Anticancer drug delivery	103
Alg	Physical	pH	Protein			Protein carrier	104
Ch	Chemical	pH/Glucose	Oxidized Dex	Rheological Analysis		Anticancer drug delivery	105
MC	Physical	Temperature				Ophthalmic drug delivery	106
Ch (PNIPAAm)	Physical	Temperature	NIPAM			Drug treatment	107
Ch/Disulfiram	Physical	Temperature		Rheological Analysis		Anticancer drug carrier	108
Chitosan	Chemical	Temperature		Rheological and self-healing Analysis		Cancer therapy	109
Alg	Chemical	Temperature	NIPAM	Tensile properties (o. 9 MPa)		4D printing	110
S-ch	Chemical	pH		Rheological Analysis		Breast tumor therapy	111
Sodium Alg	Chemical	pH			8.5 m/m_o at pH 1.2	Drug release	112
Sodium Alg and CMCh	Physical	pH			400 g/g at pH 7.4	Drug release	113
Ch			PEG	Rheological Analysis	20% at pH 2.0 and −75% at pH 10	Drug release	114
Cel		pH		Rheological and self-healing Analysis		Cancer treatment	115
Cel	Chemical	Magnetic	Hemicellulose		27 at pH 7.0	Drug release	116
Ch	Chemical	Magnetic	DT-PEG		4000%	Breast Cancer treatment	117
Alg	Physical	Magnetic	g-Heparin		7.5 au with 15% NaCl	TGF- β- treatment	118
Dextran	Chemical	Magnetic				Biomedical	119
Alg	Physical cross-linking	Light	Iron	Viscosity		Drug release	120
Alg and Ch	Physical cross-linking	Electric	Agarose		60% after 160 min	Neural disorder treatment	121
Alg	free radical polymerization	pH	BSA/5-ASA	Texture analysis	760% at 37 °C and pH 7.4	Protein and drug delivery	122
Alg/Ch	Schiff-base reaction	magnetic	5-FlU	Compressive strength andSelf-healing	110% after 6h at 37 °C	Drug delivery	123
Cel	one-pot method	magnetic	5-FlU		57%	Drug delivery	124
cel	*in situ* method	pH and magnetic	naringin		35%	Drug delivery	125
β-glucan	redox polymerization	temperature	ASA		6 m/m_o at 25 °C	Drug delivery	126
Konjac glucomannan	Chemical cross-linking	pH sensitive	nicotinamide	Rheological Analysis	22 g/g	Drug delivery	127
CMCh	Chemical cross-linking	pH and temperature	quercetin		6300% at pH 7.4 and 35 °C	Drug delivery	128
sodium Alg	Chemical cross-linking	pH	5- FlU		300% at pH 7.4	Drug delivery	129
CMC/Ch	*in situ* method	pH and magnetic	methotrexate		9 g/g	Drug delivery	130
sodium Alg	blending method	Temperature, pH and magnetic	Dox HCl		850 g/g at 35 °C	Drug delivery	131
pullulan/Ch	Schiff-base reaction	pH	Dox	Rheological Analysis	4500% at pH 7.4	Drug delivery	132
starch/CMC	blending method	pH	Dox. HCl/5-FlU		1600% at pH 7.4	Drug delivery	133
starch	blending method	pH/temperature	amoxicillin		585% after 45h	Drug delivery	134

[a]Hyaluronic Acid (**HA**); Thiolated Hyaluronic Acid (**THA**); Poly(dimethylaminoethyl methacrylate) (PDMAEMA); κ-carrageenan (**CA**);Poly(*N*-isopropylacrylamide) (NIPAM); Polyacrylic acid;[62] *N*,*N*-methylene bis(acrylamide) (**MBA**) Gelatin (GA); 3,5-dinitrosalicylic acid (DNSA);

https://doi.org/10.1021/acspolymersau.4c00028
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Table 1. continued

Alginate;[135] Chitosan(**Ch**); Cellulose (Cel); carboxymethylcellulose(CMC); carboxymethyl chitosan (CMCH); Bovine Albumin Serum (BSA); Aminosalicylic acid (ASA); Fluorouracil(FlU); Doxorubicin (DOC), Polyethylene glycol,[136] Difunctional telechelic poly(ethylene glycol) (DT-PEG), Dextran;[137] Methylcellulose (**MC**); Succinated Chitosan (S-Ch).

contents, elevated levels of phosphate-ester groups, and a crystalline structure of the B-type. Notably, the study showcased the preparation of starch@Ca^{2+}, a retrogradation-resistant and eco-friendly starch-based hydrogel using only starch and Ca^{2+} through a facile and "green" method without involving chemical reactions (Figure 6).

3. PROPERTIES OF STIMULI-SENSITIVE POLYSACCHARIDE-BASED HYDROGEL

Stimuli-sensitive polysaccharide-based hydrogels possess remarkable properties that render them exceptionally versatile in various biomedical and industrial applications. These hydrogels possess a unique sensitivity to changes in atmospheric stimuli, such as specific ionic species, pH, temperature, magnetic and electrical fields, etc., enabling precise control over their swelling behavior, disintegration rate, and mechanical properties. Their biocompatibility and biodegradability make them excellent options for therapeutic delivery systems, tissue engineering scaffolds, wound healing, and biosensors. Moreover, their tunable responsiveness to environmental cues allows for tailored responses, enhancing their efficacy in targeted therapies and controlled-release applications. The remarkable properties of stimuli-sensitive polysaccharide-based hydrogels continue to inspire innovative advancements in diverse fields, promising new avenues for therapeutic interventions and technological advancements. Table 1 represents some of the well-known stimuli-responsive hydrogels for various applications.

3.1. Swelling

Hydrogels derived from polysaccharides can absorb water due to cross-linked networked structures.[5] The ionic groups in the hydrogel govern the liquid absorption capacity. An increased concentration of ionic groups enhances water-holding capacity, which is significant for facilitating the transfer of nutrients and cellular molecules within the gel matrix.[138]

As a result, the enhancement is crucial in boosting the effectiveness of the drug release from hydrogels. A study by Suflet and colleagues[139] demonstrated that combining covalent bonding with physical cross-linking methods can lead to polymers with fast swelling and a decreased elastic modulus. Several factors, including the cross-linking density, ionic strength, synthetic routes, and type of bonding, can impact the equilibrium and swelling kinetics of gels. The swelling ratio (SR), denoting the weight-swelling ratio of a swollen gel to its dry state, stands out as a critical parameter for evaluating the swelling properties of polymers. It is crucial to understand that the cross-linking process is a determining factor in the SR of a gel. Hamdy et al.[140] reported that hydrogel with robust cross-linking displays a reduced SR, while those with insufficient cross-linking showcase an elevated SR. Moreover, the SR of hydrogel can be affected by the presence of hydrophobic and hydrophilic groups, along with their chemical composition. Hydrogels based on polysaccharides with a higher proportion of hydrophilic groups have a tendency to exhibit greater water up-taking ability compared to those with predominantly hydrophobic functionalities.[141]

3.2. pH Sensitivity

A gel sensitive to pH can experience either expansion or contraction in response to alterations in the chemically reactive surroundings.[142] These polymeric gels, fabricated through in situ polymerization techniques, are ideal for incorporation into microfluidic devices. Their potential applications encompass the development of pH-sensitive control valves and systems capable of releasing substances in response to pH changes.[143] These biomaterials, exhibiting beneficial physical and chemical properties in defined pH ranges, comprise polymer chains connected with acidic or alkali groups. Hydrogels facilitate the drug release through different mechanisms like diffusion, swelling, and chemically stimulated techniques.[144]

The diffusion-regulated approach, grounded in Fick's law of diffusion, is widely recognized, wherein drug release correlates with the hydrogel diffusion coefficient when the molecular dimensions are significantly smaller than the pore size.[145] The proximity of porous structure and drug size inhibits drug release through cross-linked polymer chains.[146] When swelling exceeds the drug release rate, swelling governs drug release by absorbing water molecules and desorbing the drug. Dry polymer hydrogels are responsive to shape and volume changes during hydration, and they control drug release by managing gel composites and the degree of cross-linking. These structures permit the permeation of physiological fluid, mainly water, through skin interfaces, leading to swelling due to solvent circulation.[147] After gradual drug release, swelling diminishes as desorption takes place. An example of dermal drug release involves the top layer of the human epidermis, the stratum corneum, influenced by skin pH (usually 5.0 to 6.0). Changes in the acid mantle, influenced by age, gender, glands, and cells, can result in disruption like inflammation. Maintaining an appropriate tissue pH is vital for patch dermal therapy, as exemplified by Kwon et al.,[148] who synthesized a pH-sensitive hydroxyethyl cellulose/hyaluronic acid nanocomposite gels for controlled drug release in treating propionibacterium acnes. Dipankar et al.[149] explored the unique properties of dextrin and methacrylic acid (MAA) in coating a hybrid polymeric network using in situ coating and chemical cross-linking strategies. This composite network, termed Dxt-MAA, combines natural polysaccharide-dextrin and synthetic polymer-MAA. The preparation involved in situ polymerization of MAA through free radical polymerization and was followed by chemical cross-linking using *N,N′*-methylene bis(acrylamide) (MBA). The main objective of chemical cross-linking was to conquer the limitations associated with PMAA, such as uncontrolled swelling behavior and dextrin, which exhibits aqueous solubility issues. The examination encompassed an analysis of the chemical composition and structure of the hydrogel, exploring its responsiveness to pH, rheological traits, and compatibility with cells. Additionally, a study was conducted on releasing two antimicrobials from tablets based on the hydrogel. The correlation between Dxt-PMAA hydrogel morphology at various pH values (1.2 and 7.4) and different SR values was observed. The results suggested that the synthesized Dxt-PMAA gel demonstrates compatibility with MCF7 cells and

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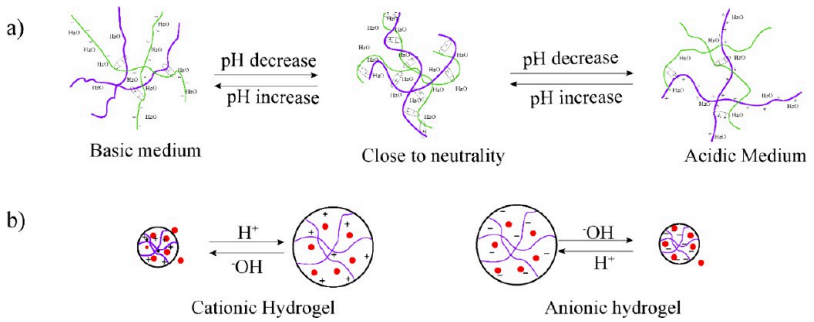

Figure 7. (a) General mechanism of pH-dependent structure and swelling in polysaccharide-based polyelectrolyte complex hydrogels. (b) Typical behavior of a pH-responsive polymer hydrogel for drug delivery applications. The cationic hydrogel swells in acidic conditions and shrinks in basic conditions, releasing its cargo. Conversely, anionic hydrogels swell in basic conditions and shrink in acidic conditions.

efficiently maintains the sustained release of antimicrobial agents.

However, polyelectrolyte complex hydrogels are synthesized through ionic cross-linking, which involves ions or ionic molecules of high molecular weight, mainly in polyelectrolytes with a specific molecular weight distribution.[150,151] The principal and most robust interaction in this polyelectrolyte complex is the electrostatic attraction between the cationic amino groups of one polysaccharide (such as chitosan) and the anionic carboxyl groups of another polysaccharide (cellulose),[152,153] as illustrated in Figure 7 (a). The general mechanism for the pH-sensitive hydrogel is closely related to the volume phase transition. It is influenced by changes in pH and the ionic strength of the surrounding environment. Adjusting the pH level of a polysaccharide solution can trigger the process of pH-induced gelation. This technique is often used alone or alongside other gelation methods to create gel particles from substances, such as chitosan, pectin, and alginic acid. The mechanism for the pH-sensitive hydrogel is closely related to the volume phase transition and is influenced by changes in pH and the ionic strength of the surrounding environment. These materials contain ionic pendant groups, such as carboxylate (COO^-) and amine (−NH) groups, that can either accept or donate protons when the pH of their environment changes. When a droplet of polymer solution contacts an acidic or alkaline bath, gelation begins at the interface, forming an initial shell. This shell thickens and completes as ions diffuse through it. In the case of alginic acid, gels form when the solution's pH drops below the polymer's dissociation constant.[154] The rate at which the pH decreases significantly impacts the gel properties: a rapid pH drop causes alginic molecules to precipitate into aggregates, while a gradual decline results in a continuous alginic acid bulk gel. Unlike ionic gels, alginate acid gels are stabilized by intermolecular hydrogen bonds between carboxylic groups of different chains with M-block residues contributing to gelation. Similarly, pectin gelation is stabilized by hydrophobic interactions among the methylated groups. Chitosan gel particles, on the other hand, are formed at higher pH levels. Initially dissolved in a mildly acidic environment (commonly using acetic acid to protonate the amine functional groups), chitosan gel particles are produced in an alkaline medium (typically with NaOH). The pH of the alkaline solution must remain above the pK_a value (6.3) of the $-NH_2$ groups to deprotonate the amines. Cellulose is coagulated using strong acidic solutions such as H_2SO_4, HNO_3, or HCl. These acids act as nonsolvents, inducing the formation of a gel-like structure.

Consequently, the ionization level of the hydrogel varies with the medium's pH.[154] When the external pH shifts, there is a corresponding change in the ionization of these groups, leading to fluctuations in internal and external ion concentrations.[155] This causes a sudden change in volume due to the altered osmotic pressure and modified hydration properties driven by electrostatic repulsion among the ionized groups. Eventually, this results in the collapse of the hydrogel's hydrogen-bonded three-dimensional structure. These pH-sensitive hydrogels can be utilized for drug-controlled release under physiological pH conditions for both cationic and anionic hydrogels as shown in Figure 7(b).[156] Both natural and synthetic polymer-based hydrogels have been developed for applications in drug delivery systems for cancer treatment and textile-based transdermal therapy.[157]

3.3. Temperature Sensitivity

Researchers have focused on addressing the acidity in tumors, ischemia, and wound healing sites by developing drug delivery approaches that specifically treat local acidosis.[158] Dual pH and temperature-sensitive hydrogels have been explored for this purpose. The gel achieves temperature responsiveness through meticulous control of the interaction between hydrophobic and hydrophilic moieties within the polymeric matrix, displaying distinct properties for hydrophobicity and hydrophilicity.[136] Temperature changes alter the interactions of these segments with water molecules, modifying the disintegration of the cross-linked architecture and phase separation. Unlike the moving sol phase, the gel phase remains stable without migration. The interplay between hydrophilicity and hydrophobicity dictates the overall disintegration phase of the cross-linked network in a water-based medium. However, the gelation process is initiated once the mixture solution containing the monomer and other reactive species of the thermoresponsive hydrogels reaches either the upper critical solution temperature (UCST) or the lower critical solution temperature (LCST).[136] At the LCST, the polymer becomes hydrophobic and insoluble, offering a gelation process.

Conversely, the hydrogels experience a transition in their state from soluble to insoluble at the UCST when nearing the critical temperature.[159] The LCST is determined by the ratio of hydrophilic to hydrophobic groups. Temperature-responsive gels have shown significant progress in releasing bioactive ingredients continuously based on temperature. These gels offer advantages as a delivery mechanism, particularly in injectable applications where the heat-responsive gel eliminates the need for denaturing cross-linking agents.[160] The sol−gel transition triggered by temperature is secure when it occurs

https://doi.org/10.1021/acspolymersau.4c00028
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within the body. Flowable administration ensures a good distribution of therapeutic drugs within the gel matrix, with a rapid sol-to-gel transition at body temperature preventing premature release of therapeutics, thus facilitating controlled drug release. Additionally, flowable administration contributes to the stability of the gel structure.[161]

3.4. Biodegradability

Polysaccharide-based polymers offer significant benefits in biological and environmental contexts due to their inherent ability to experience spontaneous degradation. Biodegradability, however, refers to the ability of a material to undergo chemical processes that are allowed by microbes or enzymes, leading to material decomposition into simpler substances within a specific scale. To improve the efficacy and minimize the adverse effects of polysaccharide hydrogels, it is necessary to understand the time scale, various factors, and approaches that affect biodegradability.[162] However, the biodegradability rate significantly depends on numerous factors, such as the degree of cross-linking, chemical structure with different functionalities, and the overall environmental status (including temperature, pressure, pH, and the amount of enzyme or microorganism present in the material's circumstances).[163] Generally, for polysaccharide-based hydrogels, the biodegradable process takes over a range of time scales; it could be a day to a couple of months, and sometimes it takes years. On the other hand, the degradation process also depends on the chemical structure of the polysaccharides. For instance, naturally occurring chitosan, a derivative of chitin biopolymer, has been extensively studied for its degradability, and it was found that the time scale for chitosan-based hydrogels ranges from a few weeks to several months.[164] The decomposition mainly depends on the total molecular weight of the polymer and the number of cross-linking. Sometimes, the degree of deacetylation also impacts the breakdown process. While alginate-based hydrogels isolate alginate from seaweed, the breakdown process takes a few weeks to months under physiological conditions. Similarly, hydrogels with hyaluronic acid can decompose within a couple of days to a week, while the time scale for cellulose-based hydrogels ranges from months to a year.

However, the biodegradability of this biopolymer-based hydrogel is required to control for enhancing its applicability in diverse applications. Several strategies can be responsible for the decomposition process. The chemical structural modifications, including cross-linking, grafting, or introducing active functional groups, might significantly affect the rate of breakdown of biopolymer.[6] For example, there is a negative impact on the degree of cross-linking; as the number of cross-linking increases, it prolongs the degradation time scale by limiting the accessibility to the degrading enzymes or microorganisms and also reduces the water absorbing ability. Meanwhile, the introduction of hydrolytically labile bonds or enzymatically cleavable moieties can accelerate degradation. Conversely, physiological conditions, such as temperature, pressure, pH, and the number of active enzymes or microbes present in the system, can significantly influence the decomposition rate.[165] Changing certain physiological factors can help in managing how quickly polysaccharide-based hydrogels break down in certain situations. For example, pH-sensitive hydrogels can be designed to degrade more rapidly under the acidic conditions typically found in inflamed tissues.

4. APPLICATIONS OF POLYSACCHARIDES-BASED HYDROGEL

Hydrogels made from natural polysaccharides present promising alternatives to the ECM in biomedical uses.[8] They are notable for their distinct combination of traits, including biodegradability, biocompatibility, adjustable mechanical properties, biomimicry, and responsiveness.[27] This unique amalgamation of features can establish microenvironments that maintain cellular functions, enhance cell health, and facilitate tissue formation. Hydrogels with biopolymer-based cross-linkers and/or fillers have been engineered for diverse applications, including drug delivery, cell transport systems, and tissue engineering scaffolds.[19] This diversity offers flexible platforms for medicinal purposes.

4.1. Drug Carriers for Drug Delivery

Hydrogel-based drug delivery systems have proven to be highly effective in delivering medications. These hydrogels, characterized by entangled polymer networks, can retain water and hydrophilic drugs, forming a protective barrier against harsh conditions like enzymes and low pH values.[166] Hydrogel, equipped with biosensor moieties responsive to physical and chemical stimuli, can undergo reversible phase transitions based on environmental changes, offering them an ideal candidate for controlled and stepwise drug release.

The rising demand for hydrogel in drug delivery has spurred the development of multifunctional varieties, including those with conductivity and self-healing capabilities.[167] Beyond natural polymer-based hydrogels, materials integrating natural polymers with synthetic components or inorganic particles exhibit diverse functions. This review explores recent advancements in natural polymer-based hydrogels for controlled drug release, encompassing composite gels synthesized by combining natural polysaccharides with inorganic nanoparticles. For example, a self-healing chitosan-based hydrogel has been designed for stroke therapy, encapsulating hydrophilic and hydrophobic drugs with asynchronous releasing behavior.[168] Another example is a multidomain peptide gel for cyclic dinucleotide transport, surpassing conventional collagen-based hydrogels in release and survival rates.[169] Moreover, chitosan/poly(glutamic acid)/alginate nanocomposite hydrogels with an analogous chain network and superior efficiency have been developed for controlled colon drug release, minimizing gastrointestinal irritation side effects. A controlled drug release system, responsive to temperature, has been developed using chain functionalities coordinated with azobenzene side chains to regulate the release of α-CD.[170] Magnetic nanoparticles, such as Fe_3O_4 particles, are frequently incorporated into drug delivery systems for targeted and controlled delivery. Magnetic hydrogel microrobots, designed for inner ear administration, effectively prevent deafness in cisplatin-deafened mice.[171] Combining chitosan and Fe_3O_4 modified with PEG, hybrid gel beads exhibit pH and magnetic field responsiveness in drug delivery applications.[172]

Inorganic materials, especially carbon quantum dots, have been extensively studied for drug delivery.[173,174] Hydrogel nanocomposite films incorporating graphene quantum dots display pH-responsive, controlled, and prolonged doxorubicin release.[175] pH-sensitive bionano gels, formed through chemical cross-linking of carbon dots and gelatin, demonstrate controlled release for curcumin and doxorubicin, exhibiting superior anticancer effects compared to free drugs. Wu et al.[176,177] developed a nanocomposite hydrogel for delivering

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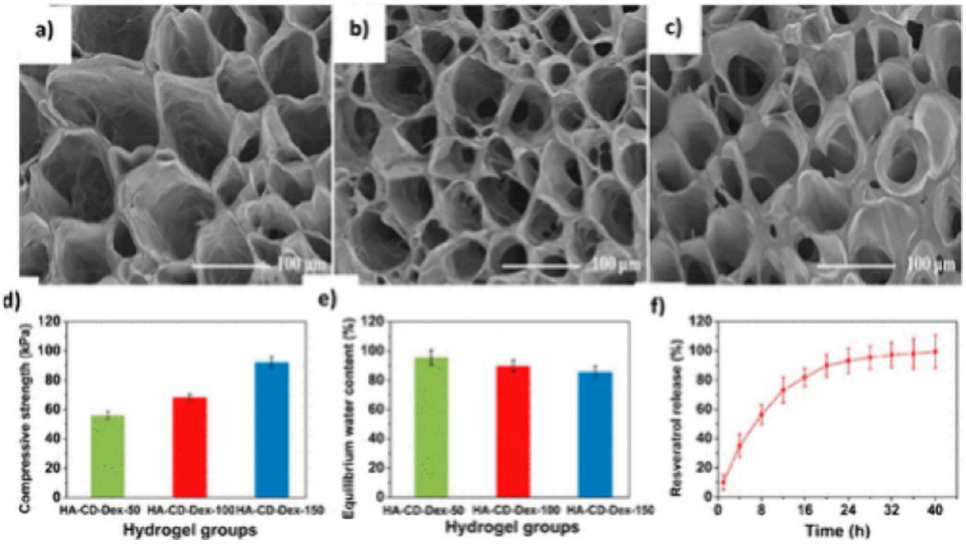

Figure 8. SEM images showcasing the porous structure of (a) HA-CD-DEX-50, (b) HA-CD-DEX-100, and (c) HA-CD-DEX-150 hydrogels, (d) compressive properties, (e) equilibrium water content in PBS, and (f) resveratrol release from HA-CD-DEX-150 hydrogel. Reproduced with permission from ref 179. Copyright (2019), Elsevier.

two cytokines and doxorubicin. To create this hydrogel, they utilized ionically cross-linked 4-arm PEG-*b*-poly(L-glutamic acid) and hydroxypropyl CH/4-arm PEG-*b*-poly(*l*-lysine), followed by the chemical linkage of cholesterol-bearing DEX to the CH counterpart. This engineered injectable gel exhibited the capacity to protect cytokines from disintegration.

Additionally, it sustained the simultaneous release of IL-2, IFN-γ, and doxorubicin into tumors, effectively inhibiting cancer growth.[178] In a separate study, Wang et al.[179] formulated hydrogels using *N*-hydroxyethyl acrylamide-DEX and HA methacrylate cross-linked with PEG-methyl-acrylate-β-cyclodextrin. Encapsulation of resveratrol, an anti-inflammatory agent, took place within cyclodextrin. Simultaneously, a hydrogel was loaded with a complex consisting of PEI and a plasmid encoding VEGF. This gel can suppress inflammation and promote vascularization in a burn wound interface, thereby boosting the recovery process (Figure 8).

4.2. Wound Dressings

Hydrogels have showcased their promises as wound dressings, attributed to their three-dimensional hydrophilic polymeric networks with high water content.[180] These networks promote a moist atmosphere at the interface of the infected wound, cool the affected skin, alleviate pain, and promote faster wound healing. Moreover, hydrogels featuring porous and continuous networks can absorb wound fluids, facilitate nutrient and metabolite exchange, adjust oxygen concentration, and protect against infection.[181] However, wound repair is a multifaceted process comprising four steps: hemostasis, inflammation, proliferation, re-epithelialization, and remodeling, which demand coordinated activity from various cell types.[182,183]

For the antibacterial and wound-repairing analysis, sodium alginate-polyacrylamide-based gel was synthesized by applying a sophisticated cross-linking process with M^{2+} ions such as Cu, Zn, Sr, and Ca.[184] Zn^{2+} coordinated hydrogels displayed effective antibacterial activities and enhanced wound healing. Another approach involved the preparation of antibacterial gels with conductive, adhesion, and self-repairing properties.[185] These hydrogels demonstrated photothermal antibacterial properties and better wound healing in affected skin wounds in rats. On the other hand, MXene, a stimuli-sensitive material-based gel, was developed for light and magnet-sensitive drug delivery systems in chronic wound treatment.[154] The hydrogel offered a precise and controlled release profile for various therapeutic biomolecules, significantly improving the chronic diabetes wound treatment. Additionally, a functionalized nanocomposite DN hydrogel based on cellulose-γPGA with biocompatibility and antimicrobial activity was investigated for wound dressing, showing an enhanced wound-repairing performance in infected skin wounds.[186]

Nanocomposite polymeric hydrogel formulating with bioactive molecules, for example, live cells, drugs, polypeptide genes that influence cell growth, and protein, were introduced for wound treatment, especially for diabetic wounds with a lower healing rate.[187] Glucose-sensitive gels were prepared for enhanced performance in this particular nonhealable wound treatment, incorporating fulvic acid for antibacterial and anti-inflammatory abilities. Nanocomposite hydrogel based on sodium alginate combined with deferoxamine was developed for diabetic wound dressing and showed enhanced vascularization. A nanocomposite polymeric gel based on epigallocatechin-hyaluronic acid and tyramine-coated human-like collagen, coupled with nanoparticles, exhibited significant enhancement of angiogenesis and diabetic wound dressing. Exosome-containing gels based on α-Lipoic acid functionalized chitosan were designed for diabetic wound repair, showing strong adhesion, light-induced self-repairing, and sensitivity to pH/H_2O_2/glucose for targeted exosome release. Fei et al.[188] studied a nanocomposite hydrogel with enhanced mechanical toughness, cell-to-cell adhesion, rapid self-repairing, and antioxidant properties, with an optimistic combination of boric acid as a physical cross-linker for Enteromorpha prolifera (PEP) and covalently cross-linked PAM (referred to as PEP–PAM). To further enhance its capability to promote cell proliferation and migration, human epidermal growth factor (EGF) was encapsulated into the gel matrix, as shown in Figure 9. This conducted study provides a comprehensive in vitro and in vivo attempt to exhibit the potential of the PEP–PAM gel as a suitable candidate for wound healing without specifying citation numbers.

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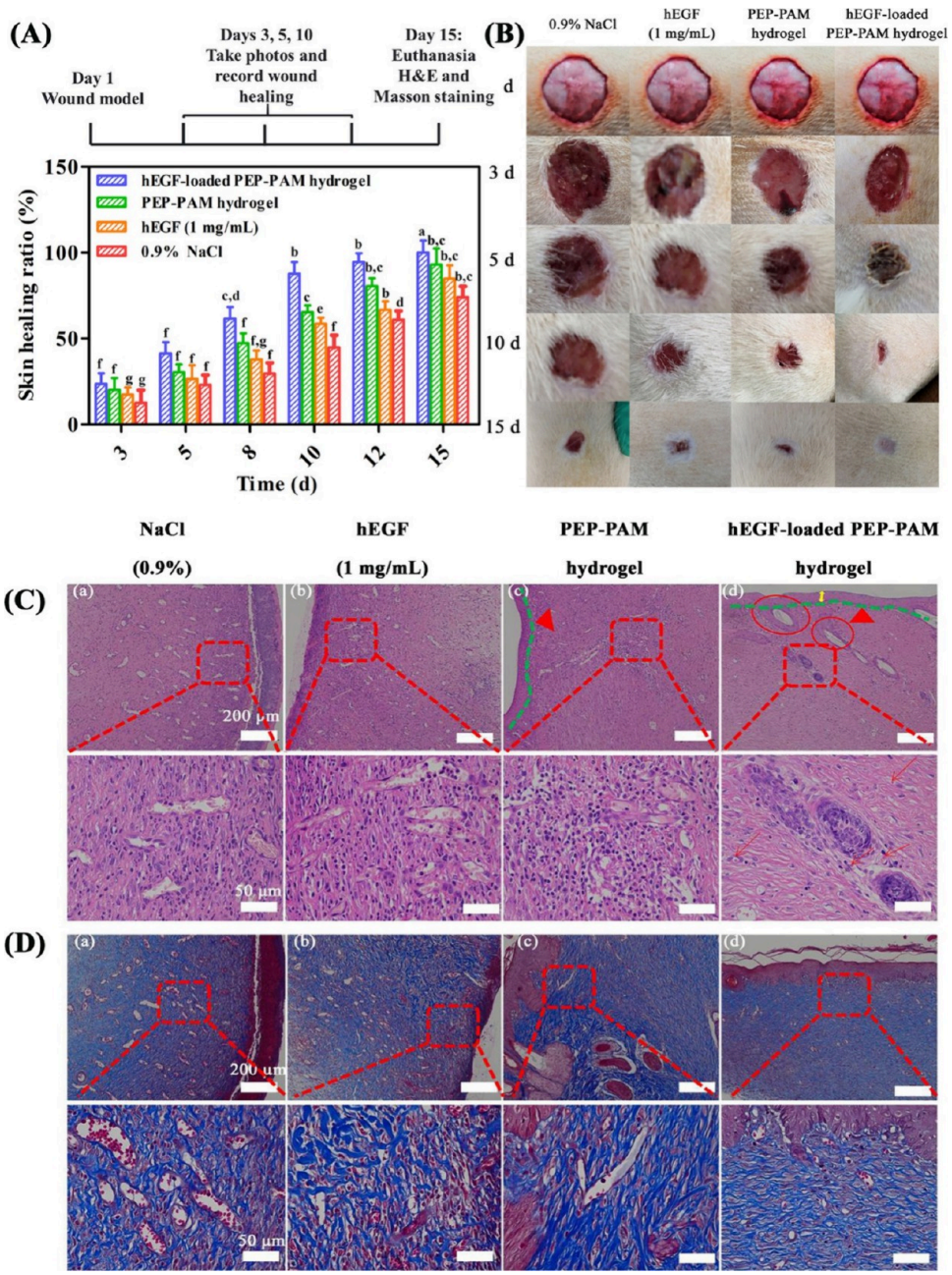

Figure 9. An in vivo study involved the application of hEGF-loaded PEP−PAM hydrogels for treating full-thickness skin wounds on the backs of rats. The digital paragraphs encompass different aspects of the study, including quantitative analysis of wound healing (A), the progress at 3, 5, 10, and 15 days (B), histomorphology observation of wound healing with different treatments (C), and Masson's staining assessment on the 14th day (D) treating with 0.9% NaCl, hEGF (1.0 mg/mL), hydrogel, and hEGF-loaded hydrogel.[188] Reprinted with permission from ref 188. Copyright (2021) American Chemical Society.

4.3. Scaffolds for Regenerative Medicine

Hydrogel has garnered significant interest as scaffolds for regenerative pharmaceutical products. Their inherent capacity to take off the ECM involves characteristics like water content, targeted cell engraftment capability, and advancement of cell growth.[189] The exceptional permeability of gels facilitates the exchange of O_2, nutrients, and soluble metabolic byproducts, making them suitable replacements for tissue engineering and regenerative drug applications. Natural polysaccharide-based gels possess a universal platform for biomedical engineering, exhibiting unique combinations of compatibility, biodegradability, biomimetics, stimuli sensitivity, and mechanical stiffness tunability that mirror the native ECM.[190] These hydrogels provide spatial support, preserve cell activities, and encourage tissue regeneration. For instance, collagen/alginate/fibrin-based hydrogels, developed for biomedical use, exhibit thermo-sensitivity and mechanical elasticity similar to natural tissues, demonstrating significant improvement in osteogenic functions and improved cell aggregation.[191]

Composite hydrogels, which incorporate inorganic fillers like bioactive materials, including clay, biomass, ceramics, and graphene-based materials, have been reported to enhance mechanical and biological performance in biomedical applications.[192] Functional nanomaterials incorporated composite hydrogels prepared for treating osteoporotic bone

https://doi.org/10.1021/acspolymersau.4c00028
ACS Polym. Au 2024, 4, 463−486

defects, effectively mitigating intracellular ROS, fostering the polarization of M2 macrophage, and diminishing inflammation.[193] A functionalized alginate-based osteoconductive gel, developed for MSC delivery in craniofacial bone treatment, exhibits tunable mechanical toughness, leading to a complete dental bone regeneration experiment in a rat model.[194]

In the context of anisotropic tissue regeneration, anisotropic cell capsulation in a 3D network of gel matrix plays a crucial role.[195] Hydrogel based on GelMA for scaffold experiments contains several anisotropic microchannels developed using vertical 3D cryo-printing techniques, enabling the fabrication of muscle-tendon and muscle-microvascular units with improved robustness and versatility.[196,197] A patterned magnetic micropillar cellular gel, synthesized by incorporating methacrylate-functionalized hyaluronic acid using UV-cross-linking, allows the prepositioning of diamagnetic objects in 3D hydrogels, leading to the creation of engineered cartilage constructs with cell gradients and complex tissue design capabilities after long-term culture.

4.4. Therapy and Cell Delivery

Drug discovery plays a significant role in treating critical diseases through chemotherapy. Analyzing binding signals between small molecule drugs and their target proteins is essential for drug discovery, repositioning, or repurposing.[198] Zhou et al.[199] have introduced a gel chip based on 3D-dextran, enabling the label-free detection ability of small molecule drugs and high-throughput DNA sequencing. This innovative chip combines surface plasmon high resonance microscopic imaging techniques with a protein microarray function on the polymeric chip, ensuring uniform and high-quality binding signals without needing citation numbers.

Cell interaction with the ECM significantly influences cell behavior and response to drug treatment.[200,201] Creating 3D multicellular tumor spheroid cells plays a significant role in assessing anticancer drugs.[202] These spheroids provide a more accurate and precise model than traditional 2D monolayer-based studies and resemble the relationship between the uncontrolled tumor cell and the ECM.[203] Karamikamkar et al.[204] fabricated alginate and collagen-based 3D hydrogel and applied a series of in vitro cancer spheroid models. Breast cancer cells that begin to grow abnormally in the breast, capsulated in these gel beads, maintained cellular viability with proliferation, producing homogeneous TSs without the need for citation numbers.[205] The physical environment of Embryonic stem cells substantially influences pluripotency and is preserved throughout self-renewal, differential activity, and growth of tissues.[206] In vivo embryonic cell areas are structurally adaptive microenvironments that regulate the development of tissues and cell function.[207] Modeling or remodeling of ECM has remarkable influence in controlling the behavior of embryonic cells. Hydrogel systems especially Magneto-responsive GelMA-based hydrogels with incorporated Fe_3O_4@SiO_2 magnetic nanorods, were developed.[208,209] Prealigning nanorods in an applied magnetic field allows for dynamic and reversible hydrogel modulus adjustment. Control of the mechanical toughness of gel considerably affected the development of human induced pluripotent stem cells by controlling mechano-responsive signaling pathways. Dual-cross-linked alginate gels with 3D micropatterns have been developed for tumor necrosis factor immobilizing and embryonic stem cell encasing, showing how the micro-patterned polymer is a feasible substrate for promoting stem cell activity in the area of artificial tissue engineering.

5. FUTURE PERSPECTIVES

Recently, there has been significant interest in natural polysaccharides or polymers derived from animals or plants.[210] This fascination arises from their unique characteristics, including chemical compatibility, structural flexibility, and biocompatibility.[211,212] These inherent properties hold promise for diverse biomedical applications such as drug delivery and tissue regeneration. Despite their potential, most natural polymers' purification or extraction processes are intricate, and their material properties can vary based on sources.[213] To enhance the structural properties, various technologies have been explored. For instance, enzymatic methods have been used to develop hyaluronic acid with specific characteristics, and biological technologies like recombinant systems have been employed for collagen synthesis.[214,215]

Moreover, chemical modifications have been applied to design and synthesize derivatives that bring the superiorities of both natural and synthetic polymers, finding extensive use in diverse biomedical fields.[216] The ongoing challenge is to develop new natural-based polymers with advanced structural behavior and reaction sensitivity within affected cells and tissues, aiming for enhanced in vivo performance in biomedical applications.[217,218] While natural polysaccharides-based hydrogels have shown their promise in biomedical applications owing to their natural abundance, biodegradability, and compatibility with soft natural tissues, they face limitations in mechanical strength.[219] Several approaches have been developed to address these limitations including composite hydrogels, DN gels, and copolymer gels. For instance, nanocomposite hydrogels utilize micro- or nanofillers like carbon materials or inorganic nanoparticles to enhance mechanical performance.[220] In addition, novel hydrogels with specific characteristics have been introduced for effective biomedical use. Smart polymeric gels, responsive to environmental stimuli, are advantageous for smart drug delivery, targeting specific sites, reducing drug toxicity, and improving bioavailability.[221] Injectable hydrogels, cross-linked by dynamic bonds, offer a nonsurgical implantation option, facilitating in situ cell encapsulation for tissue repair.[222]

Numerous technologies, including 3D printing and 4D printing, have been explored to fabricate sophisticated hydrogel-based suitable products for biomedical applications.[223] Notably, 3D bioprinting enables the fabrication of polymeric gels containing cells that feature biomimetic structures for regenerative drugs. The limitations of static 3D printing have led to the development of 4D printing, allowing dynamic changes in structure and function over the response time to external stimuli. These advancements underscore the continuous efforts to harness natural polymers for innovative biomedical solutions.

6. CONCLUSIONS

Polysaccharide-based polymeric gels have significantly garnered attention as biomaterials due to their distinctive and outstanding characteristics. This involves an examination of the polymeric structure and synthesis techniques for frequently applied natural polysaccharides for gel preparation. The subsequent section delves into hydrogels based on natural polymers, addressing aspects such as the gelation process and

https://doi.org/10.1021/acspolymersau.4c00028
ACS Polym. Au 2024, 4, 463−486

their mechanical and other properties. The effective applications of these gels in biomedicine include pharmaceutical molecule delivery, tissue repair, wound treatment, and other areas such as drug design, cell-to-cell interaction, cell-to-ECM interaction, and stem cell guiding. Due to the progress in pharmaceutical products, specifically drugs, there is a growing demand for polymeric gels that exhibit high performance. Consequently, novel techniques, like enzymatic approaches, are devised to enhance polysaccharides' mechanical and swelling properties and generate innovative, high-performance derivatives. In addition, efforts have been made to develop new hydrogel materials that meet advanced needs in biomedical applications. This includes the development of composite gel matrixes and intelligent gel materials with stimuli-sensitive and injectable hydrogels. Innovative designs, such as in situ cross-linking, dual-cross-linking, 3D/4D bioprinting, and double network hydrogels, are inspected to manufacture smart gel materials with specific properties tailored for advanced medical applications.

■ ASSOCIATED CONTENT

Data Availability Statement

Data are available in this article. There is no supporting document.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work is supported by the fund allocated from the Ministry of Science and Technology, Government of the People's Republic of Bangladesh (SRG-232377). The authors sincerely acknowledge the infrastructure support of the Energy Research Laboratory, BUET, established by a project funded by the Bangladesh Energy and Power Research Council (EPRC/58-2019-001-01). Support from the University Grants Commission (UGC) of Bangladesh and the Committee for Advanced Studies and Research (CASR), BUET, are appreciated.

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