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REVIEW

Carbohydrate-Based Hydrogels: Weaving Nature's Versatility into Biomedical Innovation

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Abstract: During the past few years, the development of innovative hydrogels for biomedical applications has undergone significant advancements. Among the diverse classes of soft biomaterials, carbohydrate-based hydrogels have attracted particular attention due to their intrinsic biocompatibility, biodegradability, and high versatility in chemical modification. Their structural diversity enables finely tunable biological interactions, and recent approaches increasingly focus on receptor-mediated targeting to improve cellular recognition and therapeutic precision. These properties position carbohydrate-based hydrogels as promising platforms in three major application areas: drug delivery, tissue engineering, and wound healing. In addition, their high water-retention capacity supports favourable healing environments and allows sustained drug release, while their natural origin helps reduce production costs and environmental impact. Despite these advantages, important challenges remain—such as achieving controlled degradation, ensuring long-term mechanical stability, and balancing bioactivity with safety—to fully exploit their clinical potential. To better align with emerging trends, this review also highlights recent advancements involving the integration of carbohydrate-based hydrogels with smart materials and nanocomposites, which are expected to further enhance their performance and expand their biomedical applications. Overall, this review provides a comprehensive overview of current progress in carbohydrate-based hydrogels, emphasizing their bio-interactions, existing limitations, and future directions in this rapidly evolving field.

Keywords: hydrogels, carbohydrates, drug delivery, tissue engineering, wound healing, biopolymer

Introduction

Recent advancements in biomaterials research have catalysed extensive investigations into alternative biocompatible materials, with a focus on understanding their properties, benefits, limitations, and the potential of alternative sources such as carbohydrates and proteins for their synthesis and/or functionalization[1–6] Among the numerous explored biomaterials, hydrogels have emerged as particularly promising due to their unique combination of biocompatibility, biodegradability, favourable mechanical properties, and responsiveness to external stimuli.

Structurally, hydrogels consist of three-dimensional networks of hydrophilic polymers, cross-linked either physically or chemically, that have the capacity to absorb significant amounts of water—ranging from 10% to several thousand times their own weight—while maintaining their structural integrity (Figure 1A). This ability to retain water while preserving stability and their unique properties makes hydrogels ideal for a wide array of biomedical applications,[7–11] from tissue engineering to smart drug delivery systems.[8,12–20]

A distinct and widely studied subclass of hydrogels is supramolecular hydrogels, which are composed of low molecular weight gelators (LMWGs) that self-assemble into fibrillar networks, trapping water within their structure. These hydrogels form through non-covalent interactions such as hydrogen bonding, hydrophobic interactions, π–π stacking and van der Waals forces (Figure 1B). Their reversible nature and tunable properties offer significant advantages, making them highly promising for biomedical applications such as drug delivery, wound healing, and tissue regeneration.

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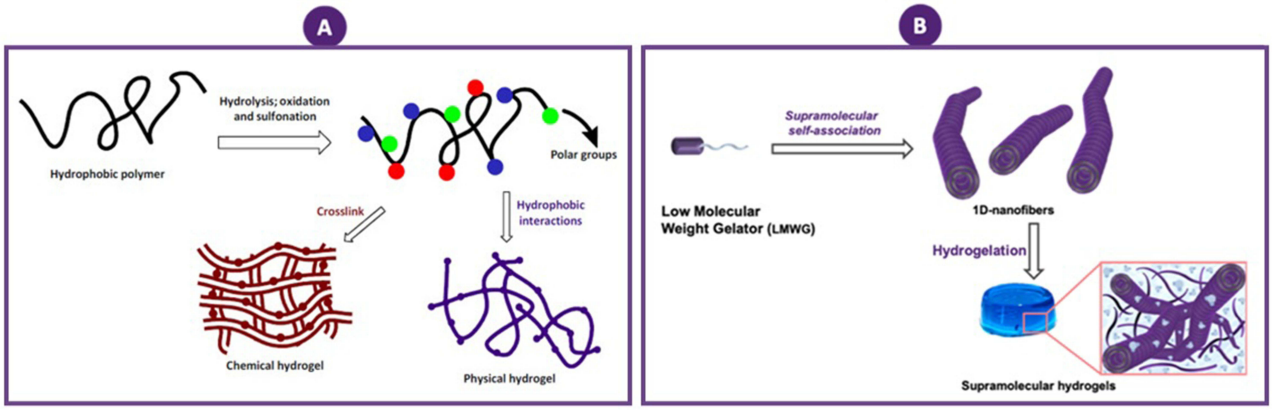

Figure 1 Schematic representation of the two type of hydrogels: (**A**) physically and chemically crosslinked polymer hydrogels. Taken from ref.[20] published by Elsevier. (**B**) Supramolecular hydrogels form LMWGs.

The development of hydrogels originated with the pioneering work of Wichterle and Lim in the 1960s, who first introduced poly-2-hydroxyethyl methacrylate for use in contact lenses and ocular applications.[21] Since then, hydrogels have expanded significantly, evolving into implantable, injectable, and sprayable forms, each specifically designed for distinct medical applications. Injectable hydrogels, for example, are widely used for localized drug delivery, while sprayable hydrogels provide innovative wound healing solutions by forming protective barriers over injured tissues.[22] Beyond the medical field, recent advancements have demonstrated the potential of hydrogels in environmental engineering and soft robotics, showcasing their versatility. Despite these expanding applications, the biomedical sector continues to dominate research, with over 25,000 references to hydrogels in biomedical contexts published in recent years. This surge in scientific interest highlights the immense potential of hydrogels in medicine, as illustrated in Figure 2.

The adaptability of hydrogels for such many different applications lies in their tuneable physical properties, which can be precisely engineered by modifying structural components. Key parameters influencing these characteristics include the ratio of hydrophilic to hydrophobic elements, polymer concentration, and reaction conditions like temperature and time.[23] By manipulating these factors, researchers can tailor hydrogels to exhibit specific properties—such as controlled swelling and deswelling rates, enhanced mechanical strength, and customizable degradation profiles—making them

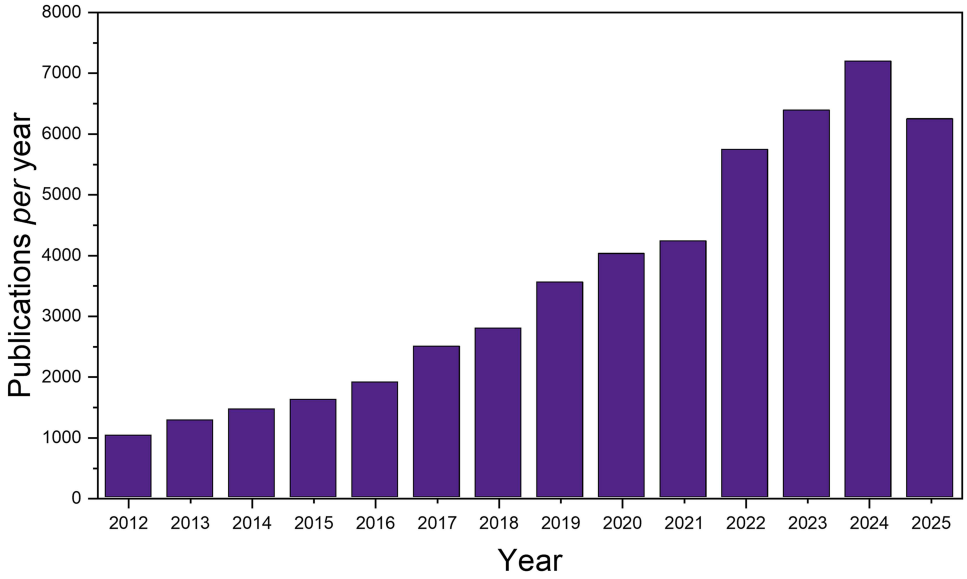

Figure 2 Publications related to hydrogels in the biomedical field over the last 14 years (2012 to 2025). The citation report graphic was generated using Clarivate Web of Science by searching for "hydrogels" and refining the results to the "biomedical" research area (updated to February 2026).

suitable for a broad range of biomedical applications.[24] This versatility has been essential in advancing their use in drug delivery, tissue engineering, wound healing, and regenerative medicine. In particular, in biomedical applications, the three critical characteristics of hydrogels are:[25]

Biocompatibility, which ensures that the hydrogel interacts with biological tissues without causing adverse effects like toxicity or inflammation, a feature commonly seen in hydrogels made from natural polymers, which helps minimize immune responses and promotes healing.

Biodegradability, which is essential particularly in tissue engineering, where the hydrogel must break down into non-toxic by-products that are safely absorbed or eliminated by the body, while supporting cellular migration and growth.[26]

Biological recognition, involving the hydrogel ability to mimic the natural extracellular matrix by incorporating ligands that facilitate cell interaction and adherence to the gel matrix.

Among the various materials utilized in hydrogel engineering, carbohydrates have received significant attention due to their inherent biocompatibility, biodegradability, and versatility.[27–30] For example, common carbohydrates like alginate, chitosan, cellulose, and hyaluronic acid are abundant in nature and exhibit desirable properties for biomedical applications.[31,32] Alginate, derived from brown seaweed, is extensively used in wound dressings and drug delivery systems due to its biocompatibility and mild gelation process. Chitosan, a cationic polysaccharide with antibacterial properties, is valuable in tissue engineering for promoting wound healing and biodegradability.[33] Cellulose, known for its mechanical strength and water retention, is utilized in wound dressings, drug delivery, and scaffolds for tissue engineering.[34] Hyaluronic acid, found in connective tissues and synovial fluid, is appreciated for its viscoelastic properties and water-binding capacity, making it useful in clinical fields such as cosmetic surgery and orthopaedics.[35] The versatility of carbohydrate-based hydrogels is further enhanced by the functional groups—hydroxyl, amino, and carboxyl—that are abundant on carbohydrate chains.[26] These groups provide numerous sites for chemical and physical cross-linking, allowing the modification of hydrogels to achieve specific physical and chemical properties tailored to different biomedical needs. By adjusting these features, hydrogels can be designed to exhibit controlled swelling behaviours, tuneable mechanical strength, and customized degradation rates.[36]

More in general, the merge of carbohydrates and hydrogels, offers a range of exceptional characteristics including:[11]

Superior biocompatibility, minimizing the likelihood of adverse immune reactions when introduced into the body, supporting cell adhesion, proliferation, differentiation, and facilitating more effective healing and seamless integration with surrounding tissues.[24]

Biodegradability, forming non-toxic by-products that can be absorbed or eliminated via natural metabolic pathways. This characteristic is particularly valuable in tissue engineering, where temporary scaffolds need to degrade over time, providing support only until natural tissue regeneration occurs.[37]

Sustainability, supported by the natural availability of carbohydrates which reduces the environmental impact, particularly when compared to conventional hydrogels that often depend on petrochemical-derived polymers with significant ecological footprints.

Versatility and tunability, through various chemical and physical modifications.[38] Factors such as cross-linking density, polymer concentration, and mechanical strength can be customized to meet the specific requirements. This tunability allows for precise control over swelling behaviour, degradation rates, and mechanical properties.

Excellent water retention, making them ideal for applications like wound dressings, where maintaining a moist environment is crucial for promoting healing, reducing infection risk, and facilitating cell migration.[24] This water retention also enhances their effectiveness as carriers for controlled and sustained drug release.

Functional properties, allowing incorporation of functional groups, bioactive molecules, or targeting ligands, which enhance their interaction with biological systems.[39] This functionalization enables hydrogels to release growth factors or therapeutic agents in a controlled manner, improving treatment outcomes and expanding their potential for targeted therapies and personalized medicine.

Bioactivity: Many carbohydrate-based hydrogels exhibit inherent bioactivity, promoting cell adhesion and growth, which makes them particularly suited for use as scaffolds in tissue engineering.[40] This bioactivity is essential for supporting cellular functions that are critical for successful tissue regeneration.

Cost-effectiveness, thanks to the widespread availability of carbohydrates. This affordability is especially advantageous in resource-limited settings, where access to low-cost biomedical materials can significantly impact patient care.

It should be highlighted that many of these features of carbohydrate-based hydrogels can aid in the shift towards a sustainable society, as called for by several national and international policies and public pressure.[41,42] In particular, some characteristics are directly connected to various United Nations Sustainable Development Goals (SDGs).[43] Firstly, they contribute to the SDG 3, "Good Health and Well-being", by offering advanced medical treatments, enhancing healing processes, and providing sustained release of therapeutic agents, all of which are essential for maintaining and improving health outcomes. Moreover, advancements in carbohydrate-based hydrogels represent significant innovations in the biomedical field, aligning with the SDG 9, "Industry, Innovation, and Infrastructure". Indeed, these advancements involve the development of new materials that can be integrated into healthcare infrastructure, fostering innovation and supporting the creation of resilient healthcare systems. Furthermore, the natural origin of carbohydrate-based hydrogels aligns with the SDG 12, "Responsible Consumption and Production" and the SDG 13, "Climate Action", by reducing the carbon footprint associated with biomedical material production. Lastly, the use of natural, biodegradable materials derived from carbohydrates promotes the sustainable use of terrestrial ecosystems, supporting the SDG 15, "Life on Land", by aiding in the conservation of biodiversity and encouraging the use of renewable biological resources. Nevertheless, the successful translation of carbohydrate-based hydrogels into clinical practice[44] still requires addressing several challenges, primarily related to a deeper understanding of bio-interactions at the molecular level, scalability, and improved mechanical strength. In particular, the in-depth use of carbohydrate chemistry for the rational design of compounds for specific targeting remains practically unexplored in this field, significantly limiting the full potential of these hydrogels. Consequently, continued research and innovation remain essential.

Numerous recent reviews in the literature explored the diverse biomedical applications of hydrogels, including their roles in drug delivery, tissue engineering, and wound healing treatment.[23,25,45] For instance, some studies focus on sprayable hydrogels for biomedical applications, such as the work by Liao et al[46] and others investigate hydrogel-based devices for biomedical applications, as reviewed by Deligkaris et al.[47] Other reviews specifically addressing carbohydrates and hydrogels focus on chitosan-based hydrogels,[33] and alginate-based hydrogels for biomedical applications.[48] Additionally, a book chapter explores carbohydrate-based nanohydrogels for drug delivery systems.[36]

As a tool for guiding research in this area, the present review offers an in-depth look at recent advancements in carbohydrate-hydrogels, emphasizing their bio-interactions, structural modifications, and functional capabilities. Unlike broader hydrogel reviews, this manuscript specifically focuses on carbohydrate-based systems, providing a detailed analysis of how their molecular composition and architecture influence biological performance and material properties. Supported by selected case studies, it not only highlights current limitations in synthesis, stability, and functionality but also critically evaluates innovative strategies aimed at overcoming these challenges. Furthermore, the review synthesizes insights from interdisciplinary studies—spanning chemistry, biology, and materials science—to propose future research directions that may expand the applicability of carbohydrate hydrogels in areas such as drug delivery, tissue engineering, and biosensing. By offering both a comprehensive overview and a targeted critique, this work serves as a unique reference for researchers seeking to leverage the distinct advantages of carbohydrate-based hydrogels while addressing gaps in current knowledge (Figure 3).

Fundamentals of Carbohydrate-Based Hydrogels

Carbohydrates play a crucial role in living organisms, serving structural functions, providing energy, and participating in cellular signalling and communication.[49] Among the most studied carbohydrates for the preparation of hydrogel are polymeric materials, including chitosan, alginate, dextran, cellulose, and hyaluronic acid.[50] Only a few examples involve the use of monosaccharides of small molecules, such as mannose, sucrose, fructose[51] and galactose. This substantial limitation highlights the challenge of designing hydrogels with specific bio-interactions, which can be addressed by creating carbohydrate-based molecules tailored for targeted interactions exploiting the chemistry of carbohydrates. Their individual contributions to hydrogel performance are discussed below, with an emphasis on biological interactions (summarized in Figure 4) and applications (summarized in Table 1).

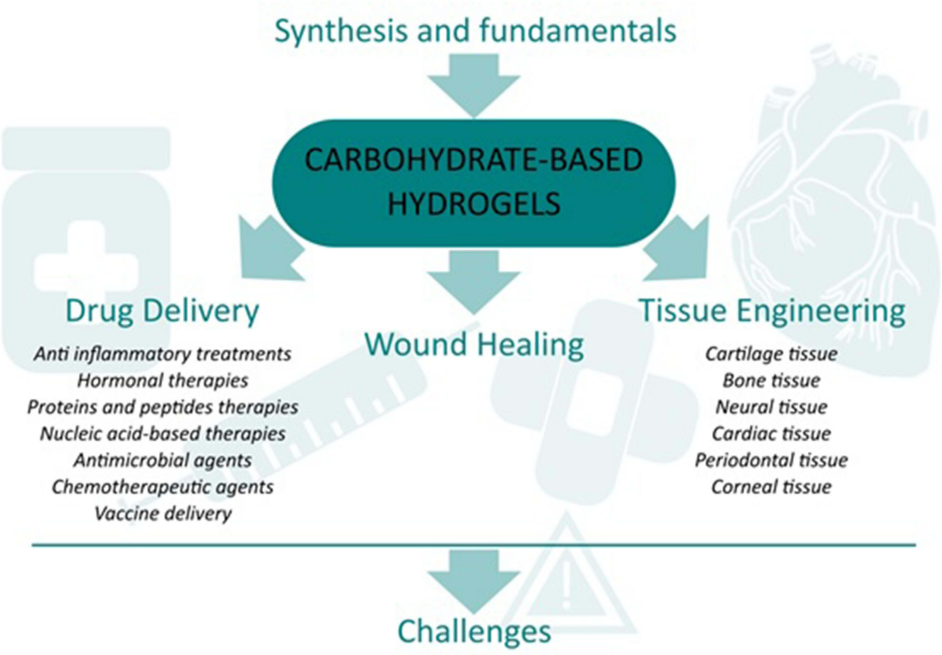

Figure 3 Scheme of the key topics of the review.

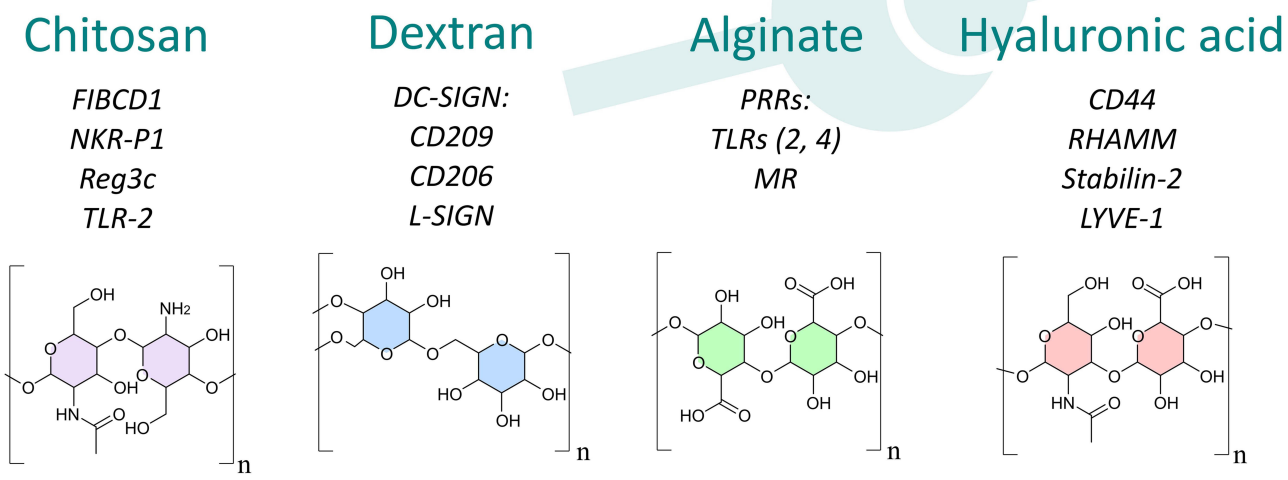

Figure 4 Chemical structure and main biological interactions of the most widely studied carbohydrates used in hydrogel preparation.

Chitosan

Chitosan is a linear polysaccharide derived from the deacetylation of chitin, which is abundant in crustacean shells,[52] consists of linear chains of β-(1→4)-linked D-glucosamine (deacetylated unit) and N-Acetyl-D-glucosamine units (acetylated unit).[53] Its unique properties, including the presence of reactive amino and hydroxyl groups, enable its modification for specific applications. Chitosan hydrogels are pH-responsive and exhibit high biocompatibility, biodegradability, and water retention, making them versatile for drug delivery, wound healing, and tissue engineering.[33] In drug delivery, these hydrogels control the release of therapeutic agents, enhancing their bioavailability and reducing side

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Table 1 Properties and Applications of Key Carbohydrate-Based Hydrogels in Biomedical and Therapeutic Fields

Carbohydrate	Physical Properties	Mechanical Properties	Biological Properties	Applications
Chitosan	Swelling ratio: 10–15 g/g; Porosity: 50–70%; Gelation time: 10–30 min; Moderate viscosity	Modulus: 50–150 kPa; Moderate stiffness; Compressive strength: 20–60 kPa; Elastic	Antibacterial, biocompatible	Wound healing, drug delivery, bone tissue engineering, antibacterial coatings
Dextran	Swelling ratio: 15–25 g/g; Porosity: 55–75%; Gelation time: 10–20 min; Tuneable viscosity	Modulus: 20–100 kPa; Variable stiffness; Compressive strength: 10–50 kPa; Elastic	Biocompatible	Drug delivery, plasma expanders, targeted cancer therapies
Alginate	Swelling ratio: 20–25 g/g; Porosity: 60–80%; Gelation time: 2–5 min; High water retention	Modulus: 10–50 kPa; Soft, low stiffness; Compressive strength: 5–20 kPa; Elastic	Biocompatible, biodegradable	Cell encapsulation, wound dressings, controlled drug release, tissue scaffolding, oral drug delivery
Cellulose	Swelling ratio: 15–30 g/g; Porosity: 60–80%; Gelation time: 5–15 min; Moderate to high water retention	Modulus: 50–200 kPa; Moderate–high stiffness; Compressive strength: 30–100 kPa; Elastic	Biocompatible, biodegradable	Tissue engineering, drug delivery systems, wound dressings, cartilage regeneration
Hyaluronic acid	Swelling ratio: 30–35 g/g; Porosity: 65–85%; Gelation time: 5–15 min; High water retention	Modulus: 5–20 kPa; Soft, elastic; Compressive strength: 5–15 kPa; Highly elastic	Biocompatible, enzymatically degradable	Osteoarthritis treatment, dermal fillers, tissue regeneration, drug delivery, ophthalmic drug delivery (contact lens)

effects. In wound healing, chitosan hydrogels promote moisture retention and create barriers against infection, while in tissue engineering, they act as scaffolds supporting cell growth and regeneration.[33,54–57]

Chitosan is a biopolymer with significant biological activity due to its unique chemical structure, particularly its abundant amino groups (-NH_2). These groups enable chitosan to interact effectively with cellular receptors, influencing cell behaviour. Its positive charge at physiological pH enhances its affinity for negatively charged cell membranes and specific receptors, crucial for cell adhesion, migration, and proliferation. This interaction can activate intracellular signalling pathways that promote tissue repair.[58]

Chitosan is not naturally present in mammals, giving it the capacity to cause recognition by the mammalian immune system.[59] Several chitin-binding receptors have been identified in mammals, including fibrinogen C domain containing 1 (FIBCD1), natural killer cell inhibitory receptor (NKR-P1), and Regenerating islet-derived protein 3-c (Reg3c).[60–62] For instance, FIBCD1 is a transmembrane receptor that specifically detects chitin and chitosan. Its expression has been observed in various tissues, such as the gastrointestinal tract and lungs, and it plays a significant role in activating immune cells and host defence mechanisms.[63] When chitosan interacts with FIBCD1, it triggers several signalling pathways. One potential pathway involves the stimulation of intracellular signalling molecules, such as protein kinases, leading to the phosphorylation and activation of downstream signalling proteins. This cascade of events regulates immune cell activation and cytokine production, which are critical for the immune response. The activation of FIBCD1 can enhance the phagocytic capacity of immune cells like macrophages and neutrophils, contributing to the body defence mechanisms.[60]

Moreover, the interplay between chitosan and Toll-like receptor 2 (TLR-2) initiates signalling cascades that are crucial for immune reactions. When chitosan binds to TLR-2, it activates various signalling pathways, notably the Myeloid Differentiation Factor 88 (MyD88)-dependent pathway. This pathway utilizes the adaptor protein MyD88 to trigger the activation of downstream signalling molecules, including interleukin-1 receptor-associated kinase (IRAK) and tumour necrosis factor receptor-associated factor 6 (TRAF6).[60,64] Upon activation, these molecules initiate a cascade of

reactions that amplify the activity of transcription factors like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and activator protein 1 (AP-1).[65] The subsequent production and release of pro-inflammatory cytokines such as Interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), and Interleukin 1 beta (IL-1β) are critical for initiating and regulating immune responses, promoting inflammation, and coordinating the recruitment and activation of immune cells. Interestingly, chitin has been shown to expedite the wound healing process through pathways that involve MyD88, which is subsequently linked to the Transforming growth factor beta (TGFβ)/ small mother against decapentaplegic (Smad) signalling pathway.[66]

Dextran

Dextran is a branched polysaccharide composed of glucose units linked primarily by α-(1→6) glucosidic linkages, with occasional α-(1→3) branches. Dextran is notable for its excellent biocompatibility and biodegradability. These properties make dextran-based hydrogels ideal for drug delivery and tissue engineering. In drug delivery, dextran hydrogels provide controlled release of encapsulated drugs, such as anticancer agents, ensuring sustained therapeutic efficacy while minimizing toxicity. In tissue engineering, they serve as scaffolds that support cell attachment and growth, contributing to tissue regeneration.[67–69]

Dextran interacts with several receptors and proteins in the body, particularly in the immune system and the vascular system. In humans, receptors that bind to dextran include a group known as the DC-SIGN (dendritic cell–specific intercellular adhesion molecule 3-grabbing nonintegrin) family. This group comprises receptors such as DC-SIGN (CD209) and L-SIGN, which is a homologue of DC-SIGN found in the liver and lymphatic endothelium. Additionally, the mannose receptor (CD206) and langerin are also part of this receptor family. These receptors play a crucial role in the uptake of pathogens by dendritic cells and macrophages. Furthermore, they may influence the modulation of immune responses, typically favouring the pathogens themselves rather than the host organisms.[70]

Alginate

Alginate is an anionic polysaccharide primarily extracted from the cell walls of brown seaweeds and algae. It consists of two monomeric units, β-D-mannuronic acid (M blocks) and α-L-guluronic acid (G blocks), linked by β-(1→4) glycosidic bonds.[71] Alginate hydrogels are known for their ease of gelation in the presence of divalent cations like calcium and their ability to encapsulate and release drugs in a controlled manner. Their biocompatibility and biodegradability make them suitable for drug delivery, wound healing, and tissue scaffolds.[72] Alginate hydrogels support cell growth and tissue regeneration by creating a porous structure that facilitates nutrient and oxygen diffusion.

In mammals, alginate does not naturally occur, enabling it to be recognized by the immune system through various receptors. Notable among these are the pattern recognition receptors (PRRs), which include Toll-like receptors (TLRs) and the mannose receptor (MR). TLRs, particularly TLR2 and TLR4, are essential for detecting foreign materials and initiating immune responses.[59] The mannose receptor is crucial for recognizing glycoproteins and polysaccharides, including alginate, facilitating endocytosis and immune activation.

When alginate interacts with these receptors, several signalling pathways are activated. For example, the binding of alginate to TLR2 and TLR4 initiates a cascade of events leading to the activation of the MyD88-dependent signalling pathway. This pathway triggers the production of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, which play vital roles in modulating immune responses. The engagement of alginate with the mannose receptor can also enhance phagocytosis, enabling immune cells to recognize and eliminate foreign materials effectively.

Moreover, alginate can influence cellular behaviour through its interactions with integrins and other adhesion receptors. By modulating the extracellular matrix (ECM), alginate affects cell attachment, proliferation, and differentiation, which are critical for tissue regeneration. The ability of alginate to form hydrogels can mimic the ECM, providing a supportive environment for cell growth and development.

Cellulose

Cellulose is a natural polymer composed of β-D-glucose units linked by β (1→4) glycosidic bonds. It is the primary structural component of the cell walls in plants and is the most abundant organic polymer on Earth.[73] Cellulose-based

hydrogels are highly hydrophilic and provide excellent water retention, making them effective for wound healing and tissue engineering. Chemical modifications, such as carboxymethylation, enhance cellulose gel-forming properties, allowing for controlled drug release and scaffold formation in tissue engineering applications. Cellulose itself does not interact with specific receptors and is typically used as a matrix for loading other compounds or as a hydration source.[74]

Hyaluronic Acid

Hyaluronic acid, a non-sulphated glycosaminoglycan, is composed of alternative units of D-glucuronic acid and N-acetyl glucosamine linked by β-1,3 and β-1,4 glycosidic bonds. Hyaluronic acid a naturally occurring biopolymer in connective tissues and synovial fluid, is prized for its biocompatibility, viscoelasticity, and high water-binding capacity.[75] In biomedical applications, hyaluronic acid hydrogels serve as scaffolds for tissue engineering, promoting cell proliferation and differentiation. Their hydrophilic nature is also advantageous in wound healing, as they maintain a moist environment that accelerates tissue repair. In ophthalmology and orthopaedics, hyaluronic acid is used for eye surgeries and joint lubrication, respectively.[76]

Beyond its physicochemical properties, hyaluronic acid exhibits significant biological effects through specific interactions with hyaluronic acid -binding proteins, known as hyaladherins, including CD44, Receptor for hyaluronan-mediated motility (RHAMM), Stabilin-2 and lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1).[77,78] These interactions are pivotal in influencing cell behaviour, immune responses, and tissue regeneration, making hyaluronic acid a critical component in both health and disease.

Hyaluronic acid interacts with several key receptors, primarily CD44, which is a glycoprotein expressed on the surface of most cell types, including skin keratinocytes and fibroblasts.[79] CD44 is involved in various signal transduction pathways, making it a critical mediator of hyaluronic acid biological activities. The binding of hyaluronic acid to CD44 initiates multiple intracellular signalling pathways that regulate essential biological processes, such as cell proliferation, migration, wound healing, and tissue regeneration. These pathways are particularly important in contexts like wound healing, where hyaluronic acid promotes cellular movement to injury sites and stimulates growth factor production. CD44 involvement in cancer is of significant interest, as overexpression of CD44 is observed in various cancer types, including breast, pancreatic, gastric, prostate, ovarian, and colon cancers.[80,81] Consequently, CD44 hyaluronic acids emerged as a biomarker for cancer cells, making targeting overexpressed CD44 an important strategy in cancer therapy.

Furthermore, since hyaluronic acid receptors were found to be overexpressed on chondrocytes, different hyaluronic-based hydrogels have been broadly developed for these purposes, showing promising results for osteoarthritis therapies.[82]

In addition to CD44, hyaluronic acid also binds to RHAMM,[83] which affects cell migration and tissue remodelling, and LYVE-1, which mediates hyaluronic acid uptake in lymphatic vessels, playing a role in fluid homeostasis and immune responses.[84]

Summarizing Table 1 shows the key properties of the carbohydrate-based hydrogels presented above.[85,86]

Monosaccharides

While polysaccharides such as chitosan, hyaluronic acid, and alginate have been extensively studied for hydrogel applications, monosaccharides-such as mannose, sucrose, fructose, and galactose-also offer promising opportunities for the design of functional hydrogels with targeted bio-interactions.[87] A common strategy entails conjugating specific sugars, notably mannose and galactose, to nanoparticles, which are subsequently embedded within the hydrogel matrix to enhance its biological functionality and targeting capabilities.[88,89] This strategy enables the creation of hydrogels with specific bioactivity, as the sugars on the nanoparticle surface can interact with cell surface receptors, promoting cellular uptake, migration, and other biologically relevant processes. For instance, a study involving D-mannose, a monosaccharide, demonstrated its incorporation into an injectable nanocomposite hydrogel for anti-inflammatory applications in osteoarthritis treatment.[90] Network-pharmacology analyses help clarify how the stereochemical configuration of D-mannose, particularly the orientation of its hydroxyl groups, underlies its selective interaction with specific cellular receptors and signalling proteins. Based on its 2D molecular structure, 84 potential pharmacological targets were identified, with 39 overlapping genes associated with osteoarthritis. Another approach involves crosslinking hydrogels

whose structures are based on hydrogen bonds, hydrophobic interactions, or ionic interactions. In this context, the use of natural crosslinkers, such as monosaccharides like glucose, sucrose, and fructose, is becoming an increasing trend.[51,91]

Concerning specifical interactions, D-mannose, for example, have been demonstrated to increase the receptor mediated uptake of nanocarriers of drugs. Indeed, mannose receptors overexpressed on antigen presenting cells such as macrophages or dendritic cells and are necessary targets for treating cancer and other infectious diseases.[92]

Galactose has been shown to specifically target the asialoglycoprotein receptor (ASGP-R), which is abundantly expressed on the membrane of HepG2 cells.[93] Indeed, the ASGP-R displays high specificity for galactose. The ligand-binding site is formed by a cluster of residues—Asp241, Asp265, Asn264, Glu252, Gln239, and Trp243—within the H1 subunit of the receptor. Binding is initiated through coordination between a receptor-associated calcium ion and the oxygen atoms of the galactose molecule. The spatial arrangement of amide and carboxylate side chains in the binding pocket enforces a strict requirement for hydrogen bonding with the 3- and 4-hydroxyl groups of galactose. In addition, galactose recognition is further stabilized by hydrophobic contacts between its C3, C4, C5, and C6 positions and Trp243, along with the formation of four hydrogen bonds involving residues of the H1 subunit.[94]

Methodologies for the Synthesis of Carbohydrate-Based Hydrogels

The design of carbohydrate-based hydrogels involves both physical and chemical crosslinking strategies, each contributing differently to the material properties and potential applications.[23,25,95]

Physical Crosslinking

Physical crosslinking relies on non-covalent interactions that create reversible bonds, allowing the hydrogel to maintain its structure without permanent chemical modifications. Several approaches are employed to design carbohydrate-based hydrogels through physical crosslinking, including hydrogen bonding, amphiphilic grafting, crystallization, ionic interactions, and protein interactions.[24]

Hydrogen Bonding

Hydrogen bonds form principally between molecules with -OH and -NH groups, such as those found in polysaccharides like chitosan, alginate, and dextran. These interactions stabilize the hydrogel network and contribute to its water retention capacity. The establishment of hydrogen bonds between the polysaccharide chains and water molecules enhances the swelling behaviour and overall mechanical stability of the hydrogel, making it particularly suitable for applications requiring high moisture retention.[96]

Amphiphilic Grafts and Block Polymers

Amphiphilic grafts and block copolymers, which consist of both hydrophilic and hydrophobic segments, can self-assemble into micellar structures within the hydrogel matrix. This structural organization enhances both water retention (due to hydrophilic domains) and mechanical strength (due to hydrophobic regions). This dual functionality is particularly useful for creating hydrogels with tuneable properties for applications such as drug delivery and tissue scaffolding.[97,98]

Crystallization

Under controlled conditions, some polysaccharides can form crystalline domains within the hydrogel matrix, further stabilizing the network. Methods like freeze-thaw cycles or heat-induced crystallization can promote the formation of such crystalline regions, enhancing the hydrogel mechanical properties and structural integrity.[99]

Ionic Interactions

Carbohydrate-based hydrogels, especially those derived from anionic polysaccharides like alginate, often rely on ionic interactions for crosslinking. When exposed to divalent cations (eg, calcium ions), the negatively charged carboxylate groups on alginate form ionic bonds, leading to gelation. This method is advantageous because it operates under mild conditions, preserving the bioactivity of sensitive molecules or cells encapsulated within the hydrogel matrix.[100,101]

Protein Interactions

Carbohydrates can form physical crosslinks through interactions with proteins. Some polysaccharides have specific binding sites for proteins, enabling the formation of hydrogels through protein-carbohydrate complexation. This approach is particularly beneficial in biomedical applications, where the bioactive properties of both proteins and carbohydrates can be exploited for drug delivery or tissue engineering purposes.[102,103]

Supramolecular Self-Assembly of Amphiphiles

Supramolecular hydrogels form through the self-assembly of amphiphilic molecules driven by non-covalent interactions, such as hydrogen bonding, van der Waals forces, and hydrophobic interactions. These amphiphiles organize into structured networks without requiring covalent modifications, leading to highly dynamic and reversible hydrogel systems. This method is particularly advantageous for biomedical applications, including drug delivery, wound healing, and tissue engineering, where controlled degradation and responsiveness to environmental stimuli are desirable.[104,105]

Chemical Crosslinking

Chemical crosslinking involves the formation of covalent bonds between polymer chains, resulting in a stable and irreversible hydrogel network. Various methods are used to chemically crosslink carbohydrate-based hydrogels, offering precise control over the material properties.[106]

Enzymatic Reactions

Enzymes such as transglutaminase or laccase facilitate the formation of covalent bonds between carbohydrate molecules.[107] Enzymatic crosslinking is biocompatible and allows for precise control over the crosslinking density, enabling the design of hydrogels with tailored mechanical properties and degradation rates for specific biomedical applications.[108,109]

Chemical Reactions

Chemical crosslinking can be achieved through reactions like esterification or amidation, where functional groups (eg, carboxyl, hydroxyl, or amine groups) on the polysaccharide chains are modified to form stable covalent bonds. This method provides a high degree of control over the hydrogel properties, including its mechanical strength and responsiveness to environmental conditions.[110,111]

High-Energy Radiation

High-energy radiation (eg, gamma rays or electron beams) induces crosslinking by generating free radicals in the polymer chains, which then form covalent bonds. This technique offers the dual benefit of sterilizing the hydrogel while simultaneously enhancing its structural integrity without the need for chemical additives.[112,113]

Free-Radical Polymerization

Free-radical polymerization is a widely used chemical crosslinking method where a radical initiator triggers the polymerization of monomers or oligomers, leading to the formation of a cross-linked network. This approach is commonly used in hydrogel design due to its versatility and ability to produce hydrogels with tuneable mechanical and swelling properties.[114,115]

Click Reactions

Click chemistry, particularly azide-alkyne cycloaddition[116] offers a highly selective and efficient method for crosslinking carbohydrate-based hydrogels.[117] This technique operates under mild conditions, allowing for the incorporation of bioactive molecules, such as drugs or growth factors, into the hydrogel network. The precision of click chemistry makes it ideal for creating hydrogels for drug delivery and tissue engineering, where controlled functionality and biodegradability are essential.[117]

In conclusion, Table 2 provides a comparative overview of the different methods used for hydrogel synthesis.

Table 2 Comparison of Hydrogel Synthesis Methodologies

Synthetic Methodologies	Advantages	Disadvantages	Applications
Physical crosslinking	Simple, often solvent-free or mild aqueous conditions; no toxic reagents needed; reversible and dynamic networks allow self-healing and injectability; can respond to environmental stimuli (temperature, pH, ionic strength)	Limited mechanical strength, not suitable for load-bearing applications; less stable over time, prone to dissolution in physiological conditions; properties strongly dependent on environmental conditions	Soft tissue engineering; Injectable hydrogels for drug delivery; Temporary scaffolds or in situ gelation
Chemical crosslinking	Strong, permanent networks with high mechanical stability; tuneable stiffness and degradation rates; precise control of functional group incorporation; can include stimulus-responsive linkages for controlled drug release	May require potentially toxic crosslinkers or initiators; longer and more complex preparation; often requires careful removal of unreacted reagents	Load-bearing tissue scaffolds; long-term implants; hydrogels with controlled and site-specific drug delivery; Stimulus-responsive or functionalized hydrogels

Biomedical Applications and Selected Examples

Various hydrogels made from carbohydrates have been developed as drug carriers, cell delivery systems, scaffolds for tissue engineering, and more, offering versatile platforms for medical applications.

Drug Carriers for Drug Delivery

Drug delivery systems offer innovative approaches to disease treatment through the encapsulation of active pharmaceutical ingredients within carriers. This encapsulation allows for controlled and sustained release at targeted sites, thereby minimizing the risk of overdose and reducing adverse side effects.[52,118] Among these systems, carbohydrate-based hydrogels are primarily owing to their excellent biocompatibility and biodegradability, which closely mimic the extracellular matrix found in biological tissues.[119] Their inherent nontoxicity ensures patient safety, while their high water content and absorption capacity create a hydrated microenvironment that enhances drug stability and facilitates molecular transport.

From a mechanistic perspective, the transfer of drug molecules from carbohydrate-based hydrogels to the surrounding bulk solution is predominantly governed by diffusion through the hydrated polymer network. This process is strongly influenced by key structural parameters of the hydrogel, including mesh size, crosslinking density, and polymer chain mobility. Highly crosslinked networks with smaller mesh sizes typically restrict molecular diffusion, leading to prolonged and sustained release profiles, whereas more loosely crosslinked structures allow faster drug transport.

In addition to diffusion-driven mechanisms, hydrogel swelling and polymer relaxation play a significant role in modulating drug release kinetics. Upon exposure to the release medium, water uptake induces network expansion, increasing chain flexibility and facilitating molecular migration. This phenomenon is particularly relevant during the initial stages of release and may account for the presence of an early burst effect, especially for drug molecules weakly bound or located near the hydrogel surface.

Drug–polymer interactions further contribute to the controlled release behaviour observed in carbohydrate-based hydrogels. Hydrogen bonding, electrostatic interactions, and hydrophilic affinity between the carbohydrate matrix and the encapsulated drug can temporarily retain the active molecules within the network, delaying their diffusion into the bulk solution. These interactions, together with the tunable degradation rates of carbohydrate-based hydrogels, provide an effective means to tailor release kinetics for specific therapeutic requirements. For instance, in some forms of cancer, carbohydrates can bind to receptors like CD44, which is commonly associated with tumour progression and metastatic invasion. This interaction not only enhances drug accumulation in target tissues but also promotes a targeted and controlled release of the active ingredient, thereby optimizing treatment efficacy and minimizing systemic side effects.

One significant area of application for carbohydrate-based hydrogels is in anti-inflammatory treatments. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly employed to manage pain and inflammation associated with conditions such as arthritis, muscle injuries, and post-surgical recovery. However, the prolonged use of these medications often leads to adverse effects, including gastrointestinal irritation and cardiovascular risks. Carbohydrate-based hydrogels can enhance NSAID delivery by minimizing side effects while maximizing therapeutic efficacy.[24,120,121] For instance, a study demonstrated the development of an alginate hydrogel designed for localized ibuprofen delivery. This hydrogel was engineered to swell in response to inflammatory signals, allowing for the rapid release of ibuprofen directly at the site of inflammation. Such localized delivery not only improved the drug efficacy but also mitigated the systemic side effects typically associated with oral administration.[118,122] Similarly, research by Suhail et al involved the development of an alginate hydrogel for the delivery of diclofenac. The hydrogel exhibited significant swelling in response to physiological conditions, enabling controlled and sustained diclofenac release (Figure 5A), which improved drug availability at the site of action while reducing gastrointestinal side effects.[123]

Proteins and peptides present unique challenges in drug delivery due to their larger molecular sizes and complex structures, which can be destabilized by environmental factors such as temperature, pH, and enzymatic degradation.

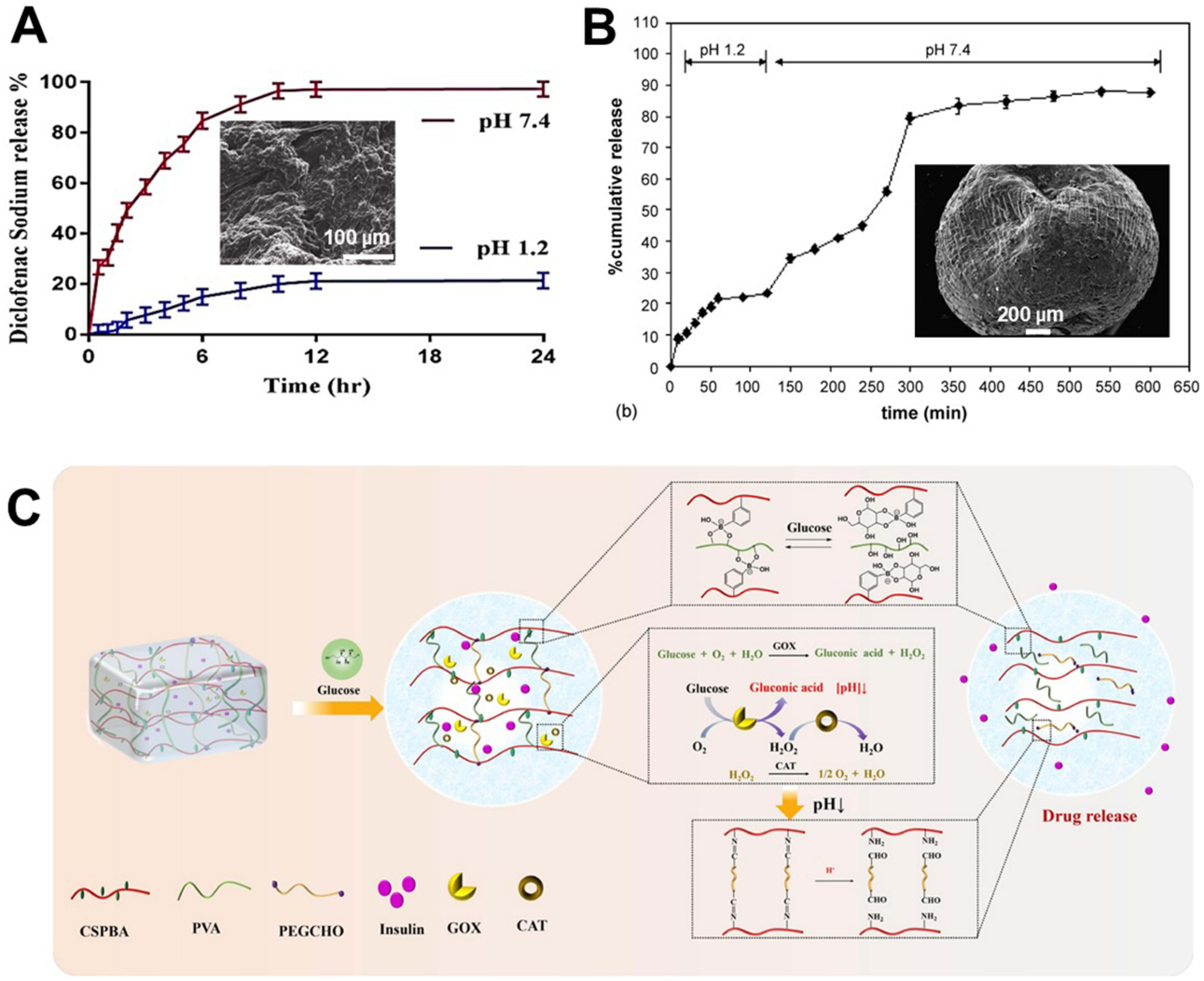

Figure 5 (**A**) Kinetic of release of diclofenac loaded into alginate hydrogel at different pH and surface morphology of alginate hydrogels. Taken from ref.[123] (**B**) Kinetic of release of bovine serum albumin loaded into alginate/guar gum hydrogel crosslinked with glutaraldehyde at different pH and scanning electron micrographs of air-dried beads. Taken from ref[124] (**C**) A hydrogel containing dual glucose sensors and dual glucose-responding elements based on phenylboronic acid-modified chitosan, formyl terminated polyethylene glycol and polyvinylacohol through the cross-linking of two dynamic covalent bonds, phenylborate ester and imine, and glucose oxidase and catalase. Taken from ref.[125]

These destabilizing conditions can significantly reduce the bioavailability and therapeutic efficacy of these biomolecules. Thus, careful formulation is essential to ensure that proteins and peptides maintain their integrity from the point of delivery to their target site within the body.[126,127] Carbohydrate-based hydrogels provide an innovative solution for encapsulating these biomolecules, creating a protective matrix that shields them from harsh environmental conditions.[125] For instance, Abraham et al developed a pH-sensitive alginate/guar gum hydrogel crosslinked with glutaraldehyde for the controlled delivery of bovine serum albumin, achieving an optimal drug release of approximately 90% at pH 7.4 (Figure 5B).[128]

Carbohydrate-based hydrogels also play a crucial role in hormonal therapies, which are essential for managing conditions such as diabetes, hormonal imbalances, and certain cancers. These hydrogels provide sustained release of hormones, thus improving therapeutic outcomes and enhancing patient adherence.[129] For example, insulin, a critical hormone for regulating blood glucose levels, is typically delivered via injections, which can be inconvenient and painful for patients.[130] Zhang et al formulated a chitosan hydrogel that encapsulated insulin and demonstrated its capacity to maintain stable blood glucose levels in diabetic animal models. This hydrogel was designed to swell in response to glucose concentration, facilitating controlled insulin release in correlation with rising blood sugar levels, thereby mimicking physiological insulin release (Figure 5C).[131] Similarly, Burova et al[124] utilized dextran as a hydrogel to protect insulin, yielding promising results that contribute to the development of oral protein pharmaceutical preparations.

As therapeutic applications become more complex, nucleic acid-based therapies, including DNA and RNA, have garnered attention for their potential in treating genetic disorders and cancers. However, delivering these molecules safely and effectively poses challenges due to their inherent instability.[132] Carbohydrate-based hydrogels can address these challenges by facilitating the delivery of nucleic acids while protecting them from degradation.[133,134] For example, Yalcin et al utilized dextran-coated iron oxide nanoparticles to deliver miR-29a to tumors, aiming to inhibit the expression of tumor-associated microRNAs. Despite miRNA short half-life and susceptibility to degradation, the developed platform effectively protected miR-29a using dextran-coated magnetic nanoparticles for cancer therapy. The results demonstrated that this formulation is a safe delivery system, with the magnetic nanoparticles safeguarding the unstable miR-29a from decomposition while facilitating its uptake by cancer cells.[135] In another innovative application, Segura et al developed a hyaluronic acid-based hydrogel for targeted gene therapy delivery. This hydrogel encapsulated plasmid DNA and exhibited stability under physiological conditions. It was engineered to degrade in response to elevated levels of hyaluronidase, an enzyme presented in tumor tissues. Upon degradation, the hydrogel released the encapsulated DNA, enabling its uptake by cancer cells and leading to the expression of therapeutic proteins that inhibit tumor growth.[136] Xiao et al[137] designed a supramolecular hydrogel formed by spiropyran conjugated with galactose for the release of miR-122 and the delivery of the miRNA into HepG2. The presence of galactose, which target the asialoglycoprotein receptor (ASGP-R) that is highly expressed on the membrane of HepG2 cells, enables targeted delivery of miRNA (Figure 6A).

Carbohydrate-based hydrogels also allow for the incorporation of various antimicrobial agents, enabling localized treatment strategies. For instance, curcumin, a natural compound derived from turmeric, demonstrates significant antimicrobial and anti-inflammatory properties. Researchers have developed alginate and chitosan-based hydrogels to encapsulate curcumin, enhancing its delivery while protecting the compound from degradation and providing controlled release.[139] Another study by Prusty et al reported on a dextran-based hydrogel system that incorporated covalently bound silver nanoparticles. The researchers evaluated the swelling, deswelling, and water retention characteristics of these hydrogel composites to assess the release rate of ornidazole, an antibacterial medication. The in vitro results indicated a remarkable release rate of 98.5% of ornidazole within six hours.[140]

Furthermore, the effective delivery of chemotherapeutic agents is crucial for maximizing therapeutic efficacy while minimizing side effects. Several polysaccharides have the unique, innate ability to recognize specific receptors overexpressed on the surfaces of diseased cells, enabling the design of targeted drug delivery systems that can selectively deliver therapeutic agents through receptor-mediated endocytosis.[141] Yang et al developed a range of hyaluronic acid-based nanogels through the copolymerization of methacrylated hyaluronic acid with di(ethylene glycol) diacrylate. The resulting nanogels, which exhibited a spherical shape and measured approximately 70 nm in diameter, were subsequently loaded with doxorubicin using an incubation method. In vitro experiments demonstrated that cellular uptake of these

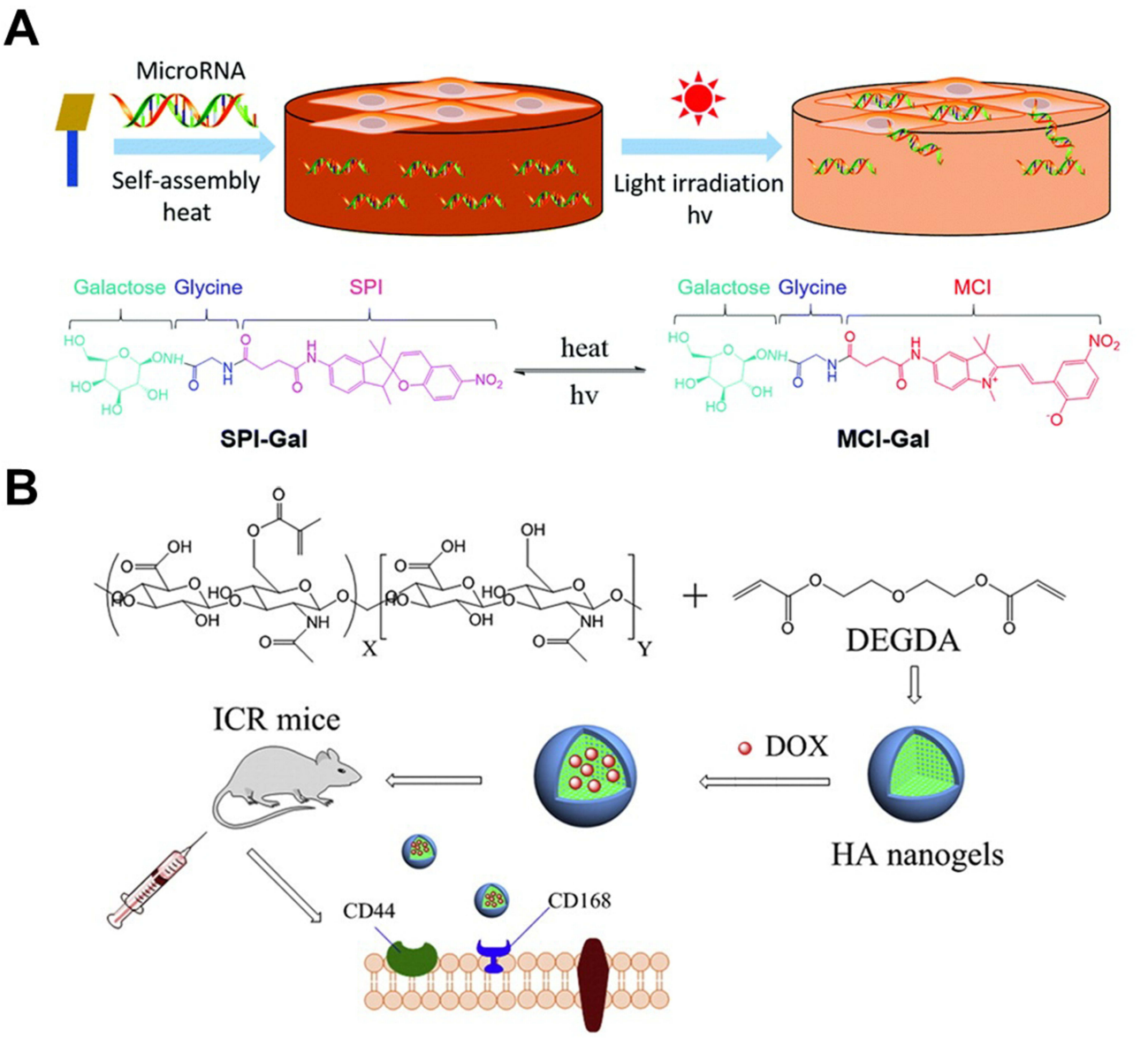

Figure 6 (**A**) Dual-functional supramolecular hydrogel, able to release encapsulated miRNA in a light-controlled manner. The presence of galactose targets the asialoglycoprotein receptor. Details of the merocyanine moiety that undergoes photo-isomerization into spiropyran. Taken from ref.[137] (**B**) Doxorubicin-loaded hyaluronic acid nanogels synthesized using a methacrylated strategy. Cellular uptake studies show preferential internalization by CD44 or CD168-overexpressed cancer cells in vitro. In vivo antitumor evaluations demonstrate distinct suppression of tumor growth by these nanogels. Taken from ref.[138]

nanogels was dependent on CD44, leading to enhanced internalization in tumor cell lines that overexpress the CD44 receptor (Figure 6B).[138]

An outstanding study reported the encapsulation of doxorubicin within a pH-responsive chitosan/poly (acrylamide-co -maleic acid) hydrogel system. This system was designed to preferentially release doxorubicin in the acidic microenvironment of tumours, thereby enhancing drug efficacy and minimizing systemic side effects. In vitro experiments demonstrated that the chitosan hydrogel could sustain the release of doxorubicin over an extended period, effectively inhibiting cancer cell proliferation.[142] Additionally, biodegradable carboxymethyl cellulose/graphene oxide nanocomposite hydrogel beads prepared by Namazi et al using physical crosslinking with $FeCl_3 \cdot 6H_2O$ were evaluated as a drug delivery system for doxorubicin. Their findings indicated that hydrogen bonding interactions were stronger in basic conditions than in acidic conditions, resulting in higher drug release at pH 6.8 compared to pH 7.4 (Figure 7A).[143] Moreover, hyaluronic acid-based hydrogels have been developed for encapsulating paclitaxel, facilitating controlled

release for intraperitoneal chemotherapy. However, despite the prolonged local retention of paclitaxel observed in vivo (Figure 7B), this approach did not translate into an enhanced anti-tumor effect. This discrepancy may stem from limitations inherent to the hydrogel system, such as insufficient penetration of paclitaxel into peritoneal tumor nodules due to the hydrogel's viscosity and limited diffusivity, premature degradation or dilution within the peritoneal cavity, or suboptimal release kinetics that fail to achieve therapeutic drug concentrations at the tumor site. These considerations highlight the need for further optimization—including modulation of crosslinking density, tuning of mesh size, or incorporation of responsive degradation mechanisms—to improve the therapeutic performance of hyaluronic acid–based intraperitoneal drug delivery platforms.[144] A supramolecular gel based on structurally related diazobenzene/diacetylene glycolipids was also reported to encapsulate and release hydrophobic drugs such as docetaxel in

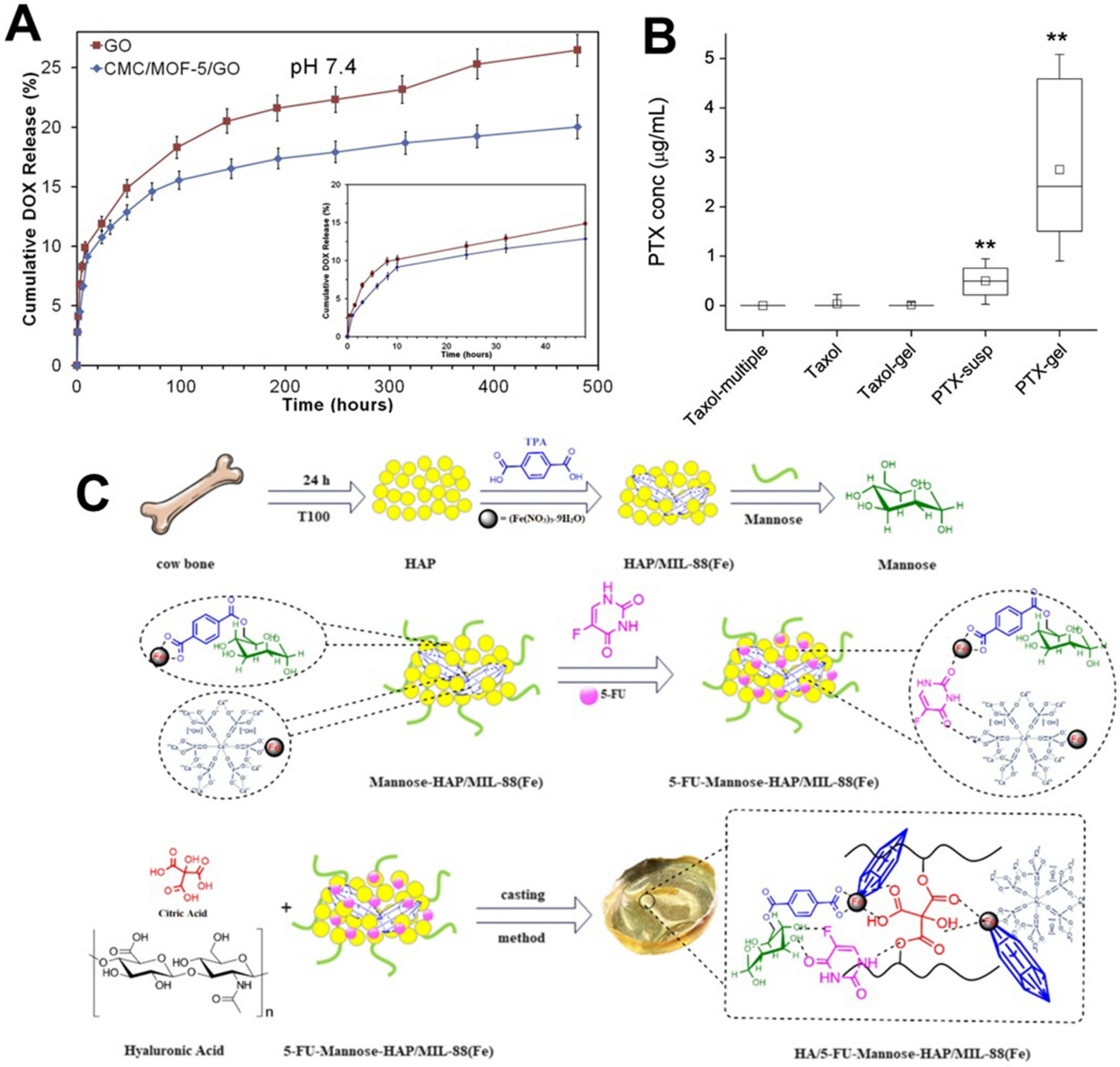

Figure 7 (**A**) Superior drug loading capacity of carboxymethylcellulose/Zn-based metal-organic framework/graphene oxide bio-nanocomposite compared to graphene oxide. Taken from ref.[143] (**B**) Hyaluronic acid-based in-situ crosslinkable hydrogel developed as a paclitaxel (PTX) carrier. In tumor-bearing nude mice, PTX-gel demonstrated superior retention in the peritoneal cavity, with microparticulate PTX entrapped in the hyaluronic acid gel, while Taxol-gel and other Taxol-based formulations showed negligible PTX levels in the cavity after 14 days. Taken from ref.[144] (**C**) Dual-targeted oral anticancer delivery system for 5-fluorouracil delivery, composed of mannose-functionalized hydroxyapatite nanoparticles/metal organic frameworks embedded into a hyaluronic acid edible hydrogel film. Taken from ref.[89]

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a controlled manner. The system relies on the photoswitching of azobenzene-based amphiphiles, allowing for reversible gel–sol transitions under UV irradiation, which could enable precise spatiotemporal drug release. The presence of mannose in the gel have demonstrated selective interactions with lectins, which could be exploited for targeted drug delivery in cancer therapy.[145] Poursadegh et al[89] reported the synthesis of a MIL-88 (Fe) metal-organic framework using the in situ method in the presence of hydroxyapatite nanoparticles (HAP). It was then functionalized with mannose as an anticancer receptor through the Steglich esterification method. For drug release investigation, 5-fluorouracil was loaded into the as synthetized structure, which was then coated with a hyaluronic acid hydrogel film (Figure 7C). Cytotoxicity tests on HT29 cancer cells showed increased effectiveness due to the presence of mannose and hyaluronic acid, highlighting the dual-targeted delivery system. Mannose-binding lectins are commonly overexpressed in many cancer cells, making them an ideal target for drug delivery. Additionally, hyaluronic acid selectively binds to the overexpressed CD44 receptor on tumor cells, further enhancing the targeted delivery of the drug.

Finally, the role of carbohydrate-based hydrogels extends to vaccine delivery, which is crucial for preventing infectious diseases. These hydrogels can function as adjuvants, enhancing immune responses while allowing for controlled release of vaccine components. Hyaluronic acid-based hydrogels have been effectively employed for delivering vaccine antigens, such as those targeting influenza and COVID-19. The sustained release of antigens from these hydrogels promotes stronger and longer-lasting immune responses. Studies indicate that encapsulating vaccine components within carbohydrate-based hydrogels can enhance immunogenicity, resulting in improved antibody responses and potentially reducing the number of doses required for effective vaccination. This innovative approach not only boosts vaccine efficacy but also simplifies vaccination schedules, ultimately contributing to better public health outcomes.[146]

Some of the most recent and relevant publications related to carbohydrate-based hydrogels for drug delivery are reported in Table 3.

Table 3 Selected Publications Related to Carbohydrate-Based Hydrogel for Drug Delivery

Therapeutic Application	Carbohydrate Hydrogel Formulation	Drug	Ref.
Anti-inflammatory	Sodium alginate/co-poly(2-acrylamido-2-methyl propane sulphonic acid)	Diclofenac	[123]
	Alginate/magnetic nanocellulose	Ibuprofen	[147]
	Carboxymethyl chitosan/poloxamer 407	Nepafenac	[148]
	Dextran/poly(2-ethylaniline)	Diclofenac	[149]
	Alginate/brushite	Ibuprofen	[150]
Hormonal Therapy	Chitosan	Insulin	[125]
	Dextran I	Insulin	[128]
Protein and peptide	Alginate/guar gum/glutaraldehyde	Bovine Serum Albumin	[124]
	Carboxymethyl chitosan/oxidized chondroitin sulfate/chitosan microspheres	Bovine Serum Albumin	[151]
	Aldehyde-modified xanthan/carboxymethyl-modified chitosan	Bovine Serum Albumin-FITC	[152]
	N,O-carboxymethyl chitosan and alginate blended with genipin	Bovine Serum Albumin	[153]
Nucleic Acid Therapy	Chitosan	siRNA	[77]
	Dextran-coated Iron oxide nanoparticles	miR-29a	[135]
	Spiropyran/galactose	miR-122	[137]

(*Continued*)

Table 3 (Continued).

Therapeutic Application	Carbohydrate Hydrogel Formulation	Drug	Ref.
Antimicrobial agents	Dextran/Silver nanoparticles	Ornidazole	[140]
	Alginate	Curcumin	[154]
	Chitosan/poloxamer 407	Fluconazole	[155]
	Chitosan/gelatine/dopamine	Metronidazole	[156]
	Chitosan/xanthan gum/monomer 2-acrylamido-2-methylpropane sulfonic acid	Acyclovir	[157]
Chemotherapeutic agents	Hyaluronic acid	Doxorubicin	[138]
	Chitosan/poly(acrylamide-co-maleic acid)	Doxorubicin	[142]
	Carboxymethyl cellulose/graphene oxide nanocomposite	Doxorubicin	[143]
	Supramolecular gel formed by mannose-functionalized 1D-glyconanotube	Doxorubicin	[145]
	Hyaluronic acid	Paclitaxel	[144]
	Mannose/hydroxyapatite/metal-organic framework/hyaluronic acid	5-fluorouacil	[89]
	N-(2-carboxybenzyl)chitosan	5-fluorouacil	[158]
	Carboxymethyl cellulose/graphene oxide nanocomposite	Doxorubicin	[159]
	Chitosan/xanthan gum/cellulose nanocrystals	5-fluorouacil	[160]
	N-carboxyethyl chitosan/ dibenzaldehyde-terminated poly(ethylene glycol)	Doxorubicin	[161]
	Chitosan/hyaluronic acid/sodium glycerophosphate	Doxorubicin	[162]
Vaccines	Hyaluronic acid	mRNA Vaccine	[146]

The field of drug delivery is undergoing significant advancements, driven by the unique properties of carbohydrate-based hydrogels. These hydrogels, with their highly porous structures, serve as versatile carriers capable of encapsulating a wide range of therapeutic agents, including small molecules, peptides, proteins, and nucleic acids. The porous network of these hydrogels not only enables efficient drug entrapment but also provides a suitable microenvironment that preserves the stability of the encapsulated therapeutics, ensuring their integrity throughout the delivery process.

A key advantage of carbohydrate-based hydrogels in drug delivery is their ability to offer controlled and sustained release profiles.[163] This feature is especially critical in the management of chronic diseases, where prolonged therapeutic intervention is required to maintain efficacy and avoid frequent dosing.

Moreover, carbohydrate-based hydrogels can be functionalized by integrating bioactive molecules, further enhancing their therapeutic capabilities. For example, by incorporating growth factors or anti-inflammatory agents, hydrogels can be designed to actively promote tissue regeneration and healing in addition to delivering drugs.

Recent advances in this field have also seen the incorporation of nanomaterials into carbohydrate-based hydrogels, further increasing their drug delivery potential. Nanoparticles can be embedded within the hydrogel matrix to enhance its mechanical strength, improving the stability of the hydrogel in physiological environments.[164] Additionally, these nanomaterials can provide multifunctional properties, such as targeted drug delivery or enhanced antimicrobial activity.

Tissue Engineering

Tissue engineering is an innovative and rapidly evolving field that merges concepts from biology, materials science, and engineering. Its primary focus is on creating biological substitutes that can restore, maintain, and enhance the function of damaged tissues. This interdisciplinary approach hinges on the development of scaffolds-structural frameworks that facilitate cellular growth and tissue regeneration. By replicating the natural extracellular matrix, scaffolds play a pivotal role in guiding cellular behaviour, enabling attachment, proliferation, and differentiation.[165–168] The design and materials of scaffolds are fundamental to the success of tissue engineering. Ideal scaffolds exhibit several key characteristics: they must be biocompatible to prevent immune responses, biodegradable to allow for the seamless integration of new tissue, and possess mechanical properties that mimic those of the target tissue. For instance, while bone scaffolds require stiffness and strength to endure physiological forces, those designed for softer tissues may need to be more flexible. Moreover, the porosity and surface topography of scaffolds significantly influence cellular processes such as nutrient exchange and migration. High porosity facilitates these essential functions, while surface features enhance cell attachment and proliferation.

Recent advancements in biomaterials have transformed the landscape of tissue engineering, particularly with the emergence of biopolymer-based hydrogels. Unlike traditional scaffold materials that often struggle to replicate the hydrated, dynamic environment of native tissues, hydrogels offer a compatible and moist environment conducive to cell growth. Carbohydrate-based hydrogels, including alginate, chitosan, and hyaluronic acid, are particularly promising in tissue engineering due to their intrinsic biocompatibility and bioactivity. Hydrogels derived from these materials can promote cell adhesion, proliferation, and differentiation by mimicking native extracellular matrix cues; reduce the risk of immune reactions compared to synthetic polymers; facilitate the incorporation of growth factors or signaling molecules, supporting functional tissue regeneration.[169,170]

Cartilage tissue engineering faces significant challenges due to the limited regenerative capacity of cartilage, particularly in the context of injuries and degenerative conditions such as osteoarthritis. Since the 1990s, researchers have explored a variety of biomaterials, including natural and synthetic materials, chondrocytes, stem cells, and growth factors, to develop effective strategies for cartilage repair through the injection or implantation of scaffolds. Among the various types of scaffolds studied, hydrogels derived from natural resources have gained increasing importance due to their structural and biological similarities to the native extracellular matrix. These properties facilitate cell transplantation, proliferation, and differentiation, making hydrogels a central topic in contemporary CTE research.[171–174] Recent advancements have shown that combining alginate with growth factors like transforming growth factor-beta (TGF-β) significantly enhances chondrocyte proliferation and matrix production.[175] Innovations in alginate formulations, such as incorporating bioactive materials like hydroxyapatite nanowires (HAPNWs), have significantly improved the mechanical properties and cellular interactions of hydrogels, enhancing their clinical applicability for cartilage and bone defects (Figure 8A and B). Specifically, studies on Bovine serum albumin /alginate/HAPNW scaffolds demonstrate that the addition of HAPNWs increases the compressive modulus from 389.7 ± 29.6 kPa to 682.6 ± 51.0 kPa, highlighting a ~75% improvement in stiffness. This enhancement is largely due to the high aspect ratio of the nanowires, which facilitates effective stress transfer, formation of a percolating reinforcement network, and energy dissipation under cyclic loading, analogous to steel reinforcement in concrete. Furthermore, hydroxyapatite concentration plays a key role in tuning mechanical performance: optimized loadings increase stiffness and toughness without compromising elasticity or porosity, while excessive concentrations may reduce flexibility or alter the interconnected pore network essential for nutrient transport and cell infiltration. These structure–property relationships emphasize that both the morphology and loading of hydroxyapatite must be carefully controlled to achieve scaffolds with robust mechanical behavior and excellent biocompatibility.[176]

Chitosan, derived from chitin, is notable for its structural similarity to glycosaminoglycans found in cartilage. It can encapsulate chondrocytes and deliver growth factors, facilitating cartilage repair while exhibiting antimicrobial properties that reduce infection risks during implantation.[174] For instance, hydrogels prepared with glycerol phosphate, chitosan, and hydroxyethylcellulose as a cross-linker were used to prepare an injectable hydrogel for cartilage repair.[179]

Hyaluronic acid also exhibits chondroprotective and anti-inflammatory properties. Additionally, several studies have reported an overexpression of the CD44 receptor on human articular chondrocytes. Consequently, hyaluronic acid-based hydrogels are extensively studied and applied as viscosupplements and drug delivery systems for treating osteoarthritis.[180]

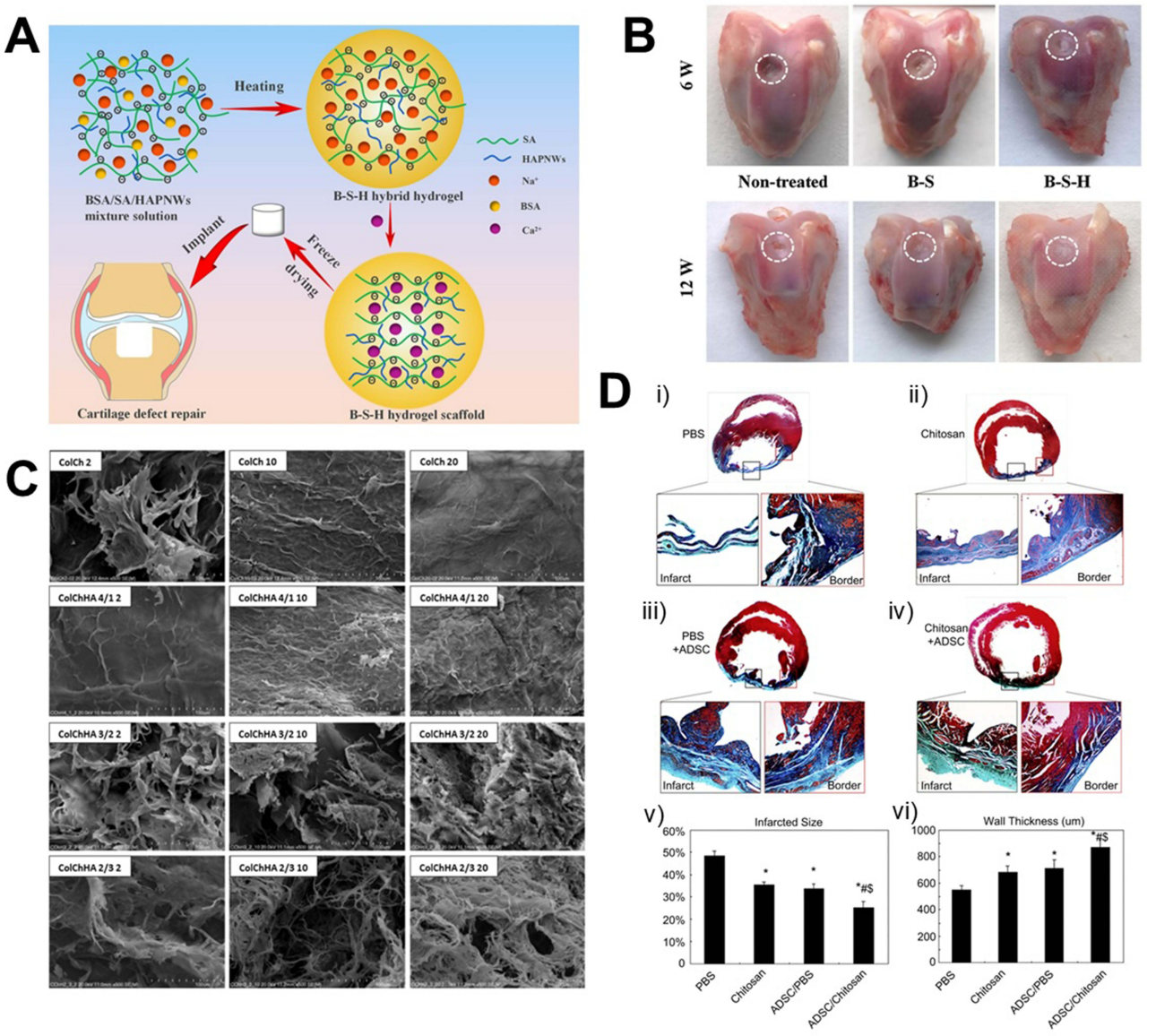

Figure 8 (**A**) representation of the structures of bovine serum albumin/sodium alginate hydrogel scaffolds incorporated with hydroxyapatite. Taken from ref.[176] (**B**) Macroscopic comparison of defects (white dotted circles) across three groups at 6- and 12-weeks post-surgery. Taken from ref.[176] A novel bovine serum albumin and sodium alginate hydrogel scaffold doped with hydroxyapatite nanowires for cartilage defects repair. (**C**) Scanning electron micrographs of collagen/chitosan and collagen/chitosan/hyaluronic acid hydrogels crosslinked with genipin at 2, 10, and 20 mM concentrations. Taken from ref.[177] (**D**) Infarct size and wall thickness. Representative Masson's trichrome-stained myocardial sections from PBS group (i), chitosan group (ii), PBS/ADSCs group (iii), and chitosan/ADSCs group (iv). Photomicrographs show two cases of representative myocardial sections in each group (Scale bar = 200 μm). Infarct size (v) and infarct wall thickness (vi) were statistically compared across different groups. Data are mean ±SEM *p < 0.05 versus PBS group; #p < 0.05 versus chitosan group; $p < 0.05 versus PBS/ADSCs group. Taken from ref.[178]

Transitioning to bone tissue engineering, the focus shifts to addressing critical defects that arise from trauma, disease, or surgical intervention.[181,182] A recent study explores the synthesis and properties of novel injectable hydrogels made from collagen, chitosan, and hyaluronic acid, chemically crosslinked with genipin (Figure 8C). The hydrogels exhibit good biocompatibility, supporting the proliferation and adhesion of MG-63 cells, indicating potential for bone regeneration, especially for small bone losses. The findings suggest that these materials could serve as effective injectable scaffolds.[177]

In the field of neural tissue engineering, unique challenges arise, particularly concerning directional growth and functional recovery following nerve injuries. Chitosan, a carbohydrate polymer derived from chitin, has emerged as a promising material for supporting neuronal growth. According to reports by Cao et al,[183] neural cells showed improved attachment and growth when exposed to a blended hydrogel containing agarose and chitosan. They proposed that the steric hindrance effect of chitosan may contribute to the morphological variations and promote optimal cell attachment

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and outgrowth. Alizadeh et al[184] synthetized a hydrogel composed of chitosan-aniline pentamer, alginate, and agarose, which was loaded with olfactory stem cells for neural tissue engineering. The chitosan-aniline component enhanced the hydrogel conductivity. This hydrogel promoted cellular activity and facilitated the differentiation of olfactory stem cells into neuron-like cells when exposed to various neurotrophic factors. Additionally, the hydrogel was fully resorbable, and the aniline oligomer could be readily eliminated through the kidneys.

In cardiac tissue engineering, repairing myocardial tissue damaged by infarction is critical for restoring heart function. In light of the limited efficacy of current treatments for cardiac regeneration, tissue engineering approaches have been explored for their potential to provide mechanical support to injured cardiac tissues, deliver cardio-protective molecules, and improve cell-based therapeutic techniques.[185] Enhancing the microenvironment of myocardial infarction to improve the engraftment, survival, and homing of stem cells presents a significant challenge. In this context, Liu et al[178] created an injectable chitosan hydrogel designed for delivering adipose-derived mesenchymal stem cells (ADSC) into the ischemic heart. They found that reactive oxygen species (ROS) in damaged tissue may adversely affect the adhesion molecules of ADSC (αV, β1, p-FAK, and p-Src) that are crucial for engraftment and homing. Additionally, ROS can disrupt host myocardial ligands such as ICAM1 and VCAM1, which play a role in stem cell engraftment. The chitosan hydrogel developed could enhance cell engraftment by reducing ROS levels and increasing cytokines associated with stem cell homing, such as SDF-1 (Figure 8D).

The regeneration of periodontal tissues[186] is equally critical for maintaining oral health, particularly in cases of periodontal disease. In recent years, hydrogels have been utilized as carriers for delivering and releasing bioactive molecules, such as growth factors and anti-inflammatory agents. These bioactive molecules facilitate tissue regeneration and repair, speeding up the healing process of periodontal tissues. Some research has also explored loading both growth factors and antibacterial drugs into hydrogels. This dual-purpose hydrogel can control infection and inflammation while also enhancing the regeneration and repair of periodontal tissues.[187] Tan et al[188] developed a chitosan-based thermo-sensitive hydrogel containing β-tricalcium phosphate, confirming its three-dimensional network structure and demonstrating notable biocompatibility with pre-osteoblastic MC3T3-E1 cells and human gingival fibroblasts. This hydrogel shows considerable potential for periodontal tissue regeneration. Hyaluronic acid hydrogels have proven effective in enhancing cell migration and supporting tissue integration in periodontal applications. Clinical studies have shown that patients treated with hyaluronic acid hydrogels experience improved outcomes regarding tissue regeneration and reduced inflammation.[186] The development of composite hydrogels that combine hyaluronic acid with other biomaterials, such as collagen or chitosan, is currently being explored to further augment the regenerative potential in periodontal treatments, providing a multifaceted approach to restore periodontal health. Recent research reported the synthesis of a chitosan-hyaluronic acid hydrogel scaffold for periodontal tissue regeneration without extraneous chemical agents from the crosslinking reactions.[189] Hyaluronic acid-based scaffolds and their interactions with CD44 have been primarily studied in stem cells[190] and cancer stem cells.[191] These interactions have been shown to promote cell migration and tissue regeneration. Additionally, research indicates that the binding of hyaluronic acid to CD44 can inhibit the activation of matrix metalloproteinases (MMPs) such as MMP-1, MMP-3, and MMP-13 in chondrocytes, as well as reduce MMP-9 expression in osteoclasts. Since MMPs are key players in periodontal disease, these findings support the idea that CD44-hyaluronic acid interactions are important for regulating MMP activity, making hyaluronic acid -based scaffolds promising materials for periodontal regeneration.[192]

Finally, corneal tissue engineering aims to restore vision by repairing or regenerating damaged corneal tissue. Hyaluronic acid hydrogels have demonstrated considerable potential due to their excellent biocompatibility and moisture-retaining capabilities. Research indicates that hyaluronic acid hydrogels can enhance the proliferation of corneal epithelial cells, facilitating the healing of corneal wounds and improving visual outcomes.[193] Notably, studies have shown that hyaluronic acid-based hydrogels can serve as effective drug delivery systems, releasing therapeutic agents such as anti-inflammatory drugs or growth factors to promote corneal regeneration. This localized treatment enhances the healing process while maintaining the optical properties essential for vision, an aspect that is critical in clinical applications. For instance, Kang et al[194] developed an in-situ hydrogel composed of collagen and hyaluronic acid, enriched with growth factors, and evaluated its potential for corneal repair. Upon gelation, the hydrogel exhibited strong mechanical and biological properties (Figure 9). To assess its cytocompatibility, the researchers seeded corneal

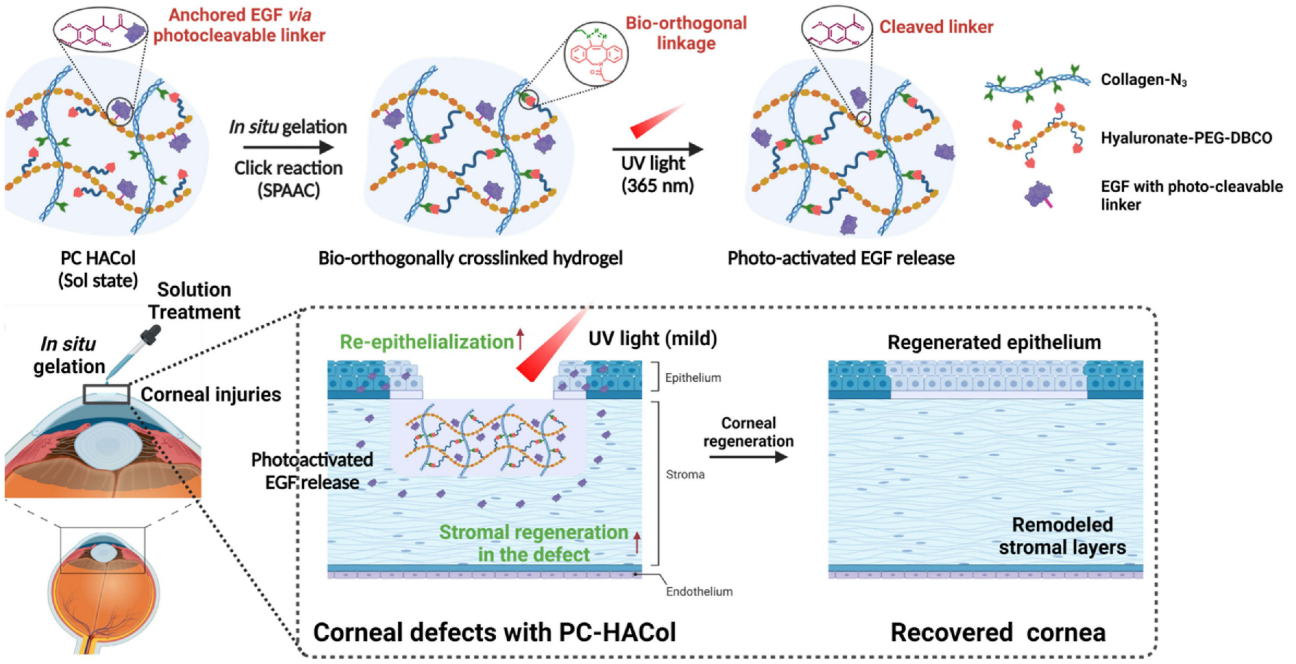

Figure 9 Schematic illustration of bio-orthogonally crosslinked hyaluronic acid/collagen-based hydrogel treatment. The gelation and photoactivated release of hydrogel. The application of hydrogel pre-solution for corneal reparation. Taken from ref.[194]

endothelial cells onto the scaffold and observed nearly 100% cell viability and proliferation. In their in vivo rat model, the treated corneas showed full recovery of corneal thickness, minimal scarring, and no epithelial hyperplasia within just 7 days.

A summary of recent and key studies on carbohydrate-based hydrogels for tissue engineering can be found in Table 4.

Carbohydrate-based hydrogels are becoming crucial in tissue engineering, helping create biomimetic scaffolds that support cell growth and tissue regeneration. These hydrogels mimic the natural extracellular matrix, fostering key cellular

Table 4 Selected Publications Related to Carbohydrate-Based Hydrogel for Tissue Engineering

Tissue Application	Carbohydrate Hydrogel Formulation	Ref.
Cartilage	Bovine serum albumin/sodium alginate/hydroxyapatite nanowires	[176]
	Glycerol phosphate/chitosan/ hydroxyethylcellulose	[179]
	Cellulose/chitosan/alginate-gelatin	[195]
	Chitosan/carboxymethyl chitosan/ethylenediaminetetraacetic acid/EDC-HCl	[196]
	Alginate/gelatin/$CaCl_2$	[197]
Bone	Collagen/chitosan/hyaluronic acid	[177]
	N-carboxyethyl chitosan/oxidized dextran	[198]
	Montmorillonite/chitosan/glycerophosphate	[199]
Neural	Agarose/chitosan	[183]
	Agarose/alginate/chitosan	[184]
	Glycol chitosan/DF-PEG	[200]

(*Continued*)

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Table 4 (Continued).

Tissue Application	Carbohydrate Hydrogel Formulation	Ref.
Cardiac	Chitosan	[178]
	Collagen/chitosan	[201]
	Pluronic/chitosan/gold nanoparticles/poly glycerol sebacate	[202]
	Hyaluronic Acid/chitosan/β-Glycerophosphate	[203]
Periodontal	Chitosan/ β-tricalcium phosphate	[188]
	Chitosan/hyaluronic acid	[189]
	Alginate/hydroxyapatite	[204]
Corneal	Hyaluronic acid/collagen	[194]
	Chitosan/oligoethylene glycol	[205]
	Chitosan/sodium alginate	[206]

behaviours like adhesion, proliferation, and differentiation.[207] Their properties, such as porosity, stiffness, and degradation rates, can be customized for specific tissues—stiffer hydrogels for cartilage repair and softer ones for soft tissue regeneration. Advanced techniques like 3D bioprinting enable precise control over hydrogel structure, creating complex microstructures that replicate natural tissue. Incorporating bioactive factors like growth factors, cytokines, or cell adhesion peptides enhances cell survival and differentiation, boosting the regenerative potential of stem cells. Stimuli-responsive hydrogels, which change properties in response to signals like pH or temperature, provide dynamic control over cellular behaviour. Integrating stem cell therapy with carbohydrate-based hydrogels supports stem cell viability and differentiation, offering promising solutions for treating degenerative diseases and injuries through regenerative therapies.

Wound Dressings for Wound Healing

Wound healing is a complex biological process designed to restore tissue integrity and function following an injury. This multifaceted process unfolds through several coordinated phases: haemostasis, inflammation, proliferation, and remodelling.[208] Wounds can generally be categorized into two main groups based on the duration of the injury: acute and chronic. Acute wounds arise suddenly and typically heal rapidly, often resolving without complications. Common examples include surgical incisions, minor abrasions, and moderate burns. In contrast, chronic wounds are characterized by prolonged healing periods. These include severe burns, pressure ulcers, diabetic foot ulcers, and ulcers resulting from radiation or chemotherapy.

While traditional wound care methods have been effective for many cases, they often fall short in creating optimal conditions for healing, particularly in chronic or complex wounds. This inadequacy has led to the exploration of advanced materials, such as carbohydrate-based hydrogels, which have emerged as promising candidates for enhancing wound healing outcomes. These hydrogels possess high biocompatibility, reducing the risk of immune responses and ensuring safe integration within biological systems. Their hydrophilic nature allows them to retain substantial moisture at the wound site, which is essential for cellular activities such as migration, proliferation, and differentiation—key processes in effective healing.[209] Moreover, they are characterized by additional characteristic such as anti-inflammatory, antibacterial and antioxidant abilities that can help the process of healing.[164]

Chitosan, in its topical formulation, plays a significant role in promoting wound healing. Its mechanism of action involves several key processes, including the infiltration of inflammatory cells, such as polymorphonuclear leukocytes, and the secretion of inflammatory mediators like TNF-α. This process is accompanied by the migration of macrophages

and an increase in collagen production, which are essential for tissue repair. The presence of N-acetyl-D-glucosamine, a component of chitosan, enhances the binding to specific receptors in the body, leading to increased activation of macrophages. This activation triggers a cascade of events, including the release of various biological mediators that facilitate the healing process. Furthermore, chitosan has been shown to activate the complement system, an integral part of the immune response, while also stimulating fibroblasts to produce interleukin-8 (IL-8) and other cytokines,[210] thereby contributing to the inflammatory response and tissue regeneration. For this scope, Del Olmo et al[211] prepared chitosan hydrogel crosslinked with genipin. These hydrogels demonstrated antibacterial properties and proved effective in treating ulcerative wounds in both in vitro and in vivo assays. To enhance their therapeutic potential, hydrogels were loaded with acetylsalicylic acid and antibiotics, including cefuroxime, tetracycline, and amoxicillin. The combination of acetylsalicylic acid with these antibiotics exhibited significant anti-inflammatory activity. Zhang et al[212] developed a novel alginate-chitosan oligosaccharide-ZnO composite hydrogel (Figure 10A) with antibacterial and healing-promoting properties. This innovative polysaccharide composite hydrogel showed significant advantages in wound healing combined with antibacterial infection and water retention (Figure 10B). In a more recent research, Mohanty et al[213] developed a multifunctional film containing silver-doped zinc oxide nanoparticles, using chitosan and guar gum, for potential applications in wound healing, antibacterial activity, and haemostasis. The nanoparticle-infused film demonstrated 90% and 94% inhibition of gram-negative and gram-positive bacteria, respectively. It also promoted enhanced wound closure, showing 100% cell migration at 24 hours, compared to just 66% in the control group. In vitro testing revealed 80% inhibition of bacterial biofilm after 72 hours, with good cytocompatibility and hemocompatibility in L929 mouse fibroblast cells, making it an excellent candidate for wound healing applications.

Hyaluronic acid plays numerous critical physiological roles for wound healing due to its distinct molecular structure and physicochemical characteristics.[214] These roles include joint lubrication, modulation of vascular wall permeability, and facilitation of the diffusion and function of proteins, water, and electrolytes. As a vital extracellular matrix component, it promotes initial inflammation, supports cell infiltration, accelerates the formation of granulation tissue matrices, and aids in tissue remodelling. For example, Liu et al[215] developed an electrospun thioether-grafted hyaluronic acid nanofiber that can spontaneously form a nanofibrous hydrogel in situ on wound sites, thereby modulating the inflammatory microenvironment and accelerating the healing of chronic diabetic wounds. As illustrated in Figure 11A, the acute wound model was established in Kunming mice, while Figure 11B shows markedly improved closure following nanofiber dressing and subsequent hydrogel treatment.

Shah et al[216] developed an injectable hydrogel composed of hyaluronic acid, pullulan-grafted Pluronic F127, designed as a sustained and targeted delivery system for curcumin to promote skin regeneration in diabetic wounds. Biological testing demonstrated that curcumin within the hydrogel boosted cell proliferation, reduced inflammatory cell presence, and ultimately improved wound closure. Additionally, these studies indicated that curcumin release was enhanced with higher levels of hyaluronic acid. Wang et al[217] developed an advanced wound dressing by incorporating hyaluronic acid-grafted pullulan succinate with chitosan (Figure 12), aiming to enhance antimicrobial properties and expedite skin wound healing. The resulting film exhibited a highly organized three-dimensional structure, along with a superior swelling index compared to the individual polymers, enabling efficient absorption of exudates from the wound site. When tested in vitro with L929 cells, the film displayed no cytotoxicity and actively promoted cell proliferation. Moreover, the composite demonstrated significant antibacterial efficacy against *Staphylococcus aureus* and *Escherichia coli*. In in vivo studies, the film dressings exhibited superior performance in reducing inflammation and accelerating the healing of skin wounds in rat models.

Alginate also play a key role in the healing of chronic wounds. Their high M block content effectively stimulates cytokine production by human monocytes.[218] Alginate properties include strong biological activity, high adsorption capacity, bio-stability, anionic nature, hydrophilicity, non-toxicity, lack of immunogenic responses, hydrogel-forming ability, and cost-effectiveness. Alginate can form bonds with metal ions through various mechanisms, including electrostatic interactions and coordination. When guluronate blocks interact with calcium ions (Ca^{2+}), they create an egg-box structure that facilitates cross-linking, making alginate suitable for numerous advanced applications, especially in wound healing.[219] Alginate maintains a moist wound environment and reduces bacterial infection, both essential for rapid healing. Upon contact with wound exudates, alginates partially dissolve, forming a gel matrix that protects against

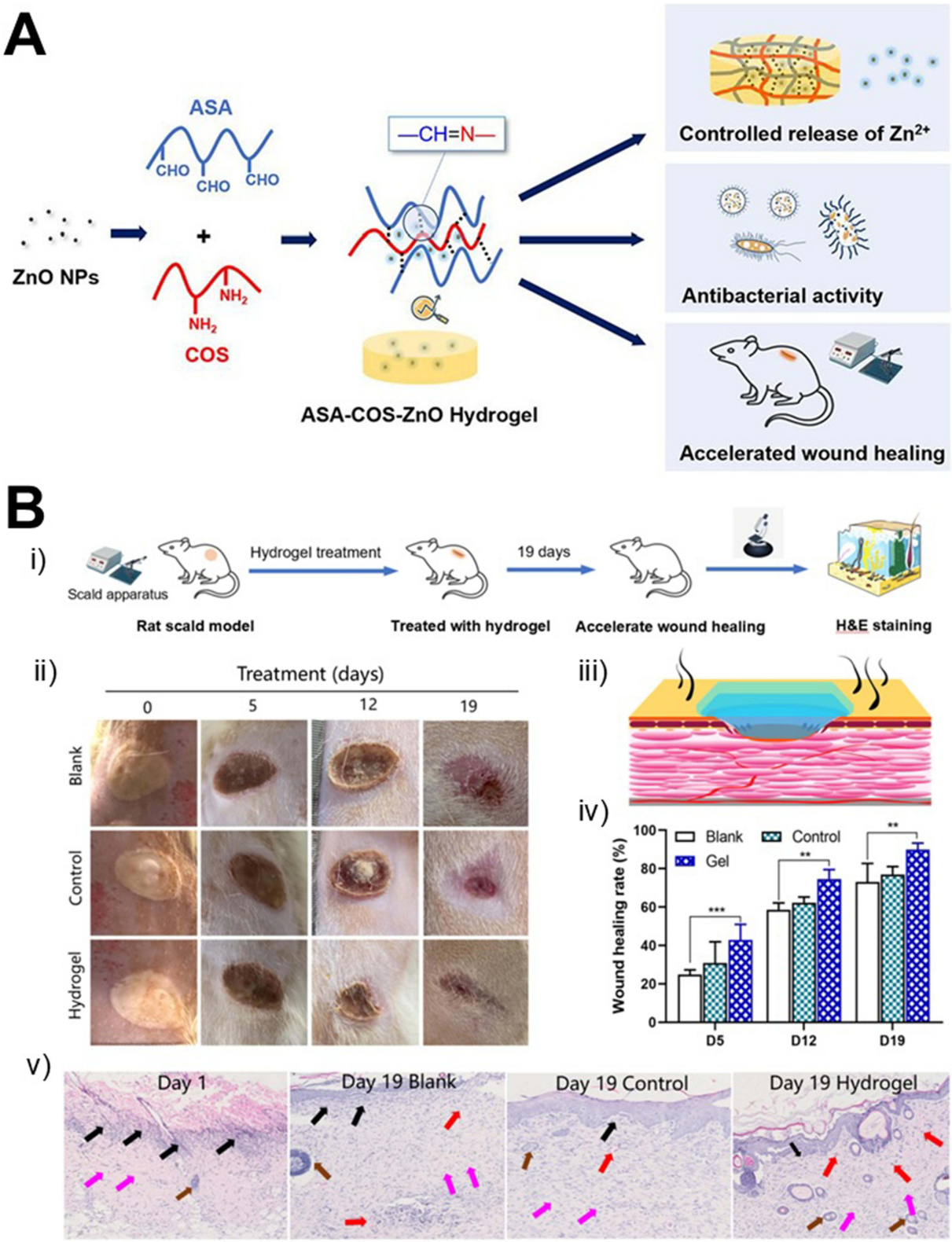

Figure 10 (**A**) Schematic illustration of preparation of sodium alginate-chitosan oligosaccharide-zinc oxide hydrogel with controlled release of Zn^{2+}, antibacterial activity, and accelerated wound healing. (**B**) (i) Wound formation and treatment; (ii) representative digital images of the wound at specific time points for the blank, positive control, and sodium alginate-chitosan oligosaccharide-zinc oxide hydrogel groups; (iii) interactions between the hydrogel and wound tissues; (iv) quantification of wound closure over 19 days (** and *** indicate levels of statistical significance $p < 0.01$ and $p < 0.001$, respectively); v) photomicrographs of histological staining of wound sites on day 0 and day 19 (inflammatory cells: black arrows, blood vessels: red arrows, hair follicles: brown arrows, fibroblasts: purple arrows). Taken from ref.[212]

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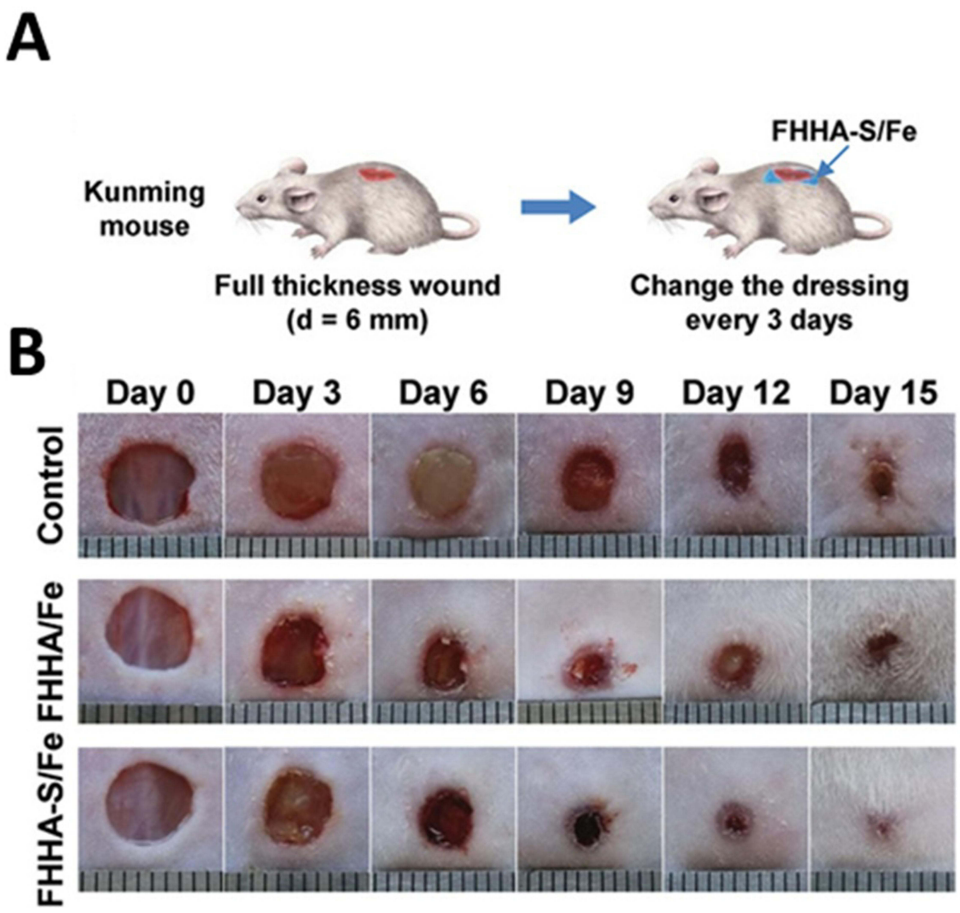

Figure 11 Electro spun thioether-grafted hyaluronic acid nanofiber hydrogel enhanced the healing effect in an acute wound model. (**A**) Schematic representation of the establishment and treatment of the acute wound model. (**B**) Representative images of wounds following different treatments at the specified days. Taken from ref.[215]

microbes while providing an optimal moist environment. This process promotes cell proliferation and granulation tissue formation, accelerating wound healing.[220] Additionally, alginate-based dressings demonstrate excellent haemostatic properties and can be easily removed from the wound site. An example of this is the alginate-fibrinogen-based composite hydrogels created by Soleimanpour et al[221] for skin wound healing. The findings indicated that this synthesized system possesses excellent characteristics for wound healing applications, thanks to its suitable mechanical properties and biocompatibility. Furthermore, in vivo studies using Wistar rat models demonstrated that the bio composite hydrogel exhibited significant antibacterial effects and efficacy in treating chronic wounds. In a recent study, sodium alginate and arginine were crosslinked with zinc to form a hydrogel for use in skin wound dressings. The hydrogel demonstrated an enhanced swelling capacity, which was advantageous for absorbing wound exudate. Additionally, it exhibited notable antioxidant activity and strong inhibitory effects against *Escherichia coli* and *Staphylococcus aureus*.[222]

Dextran exhibits several distinctive properties, including enhanced water absorption, non-toxicity, and the capacity for polymer cross-linking. These characteristics promote angiogenesis, stimulate cell proliferation, and accelerate wound healing, thereby facilitating superior skin regeneration.[223] Furthermore, dextran plays a critical role in the removal of wound exudates, metabolic by products, and other detrimental substances, thus creating an optimal environment for healing. It also supports angiogenesis, fostering the formation of new blood vessels, and protects the epidermis from ischemic damage. Additionally, dextran contributes to collagen deposition and influences tissue remodelling during the late stages of wound healing.[220]

Due to their excellent biocompatibility, cellulose-based hydrogel bio-adhesives are commonly used for loading and releasing various substances in wound treatment.[208]

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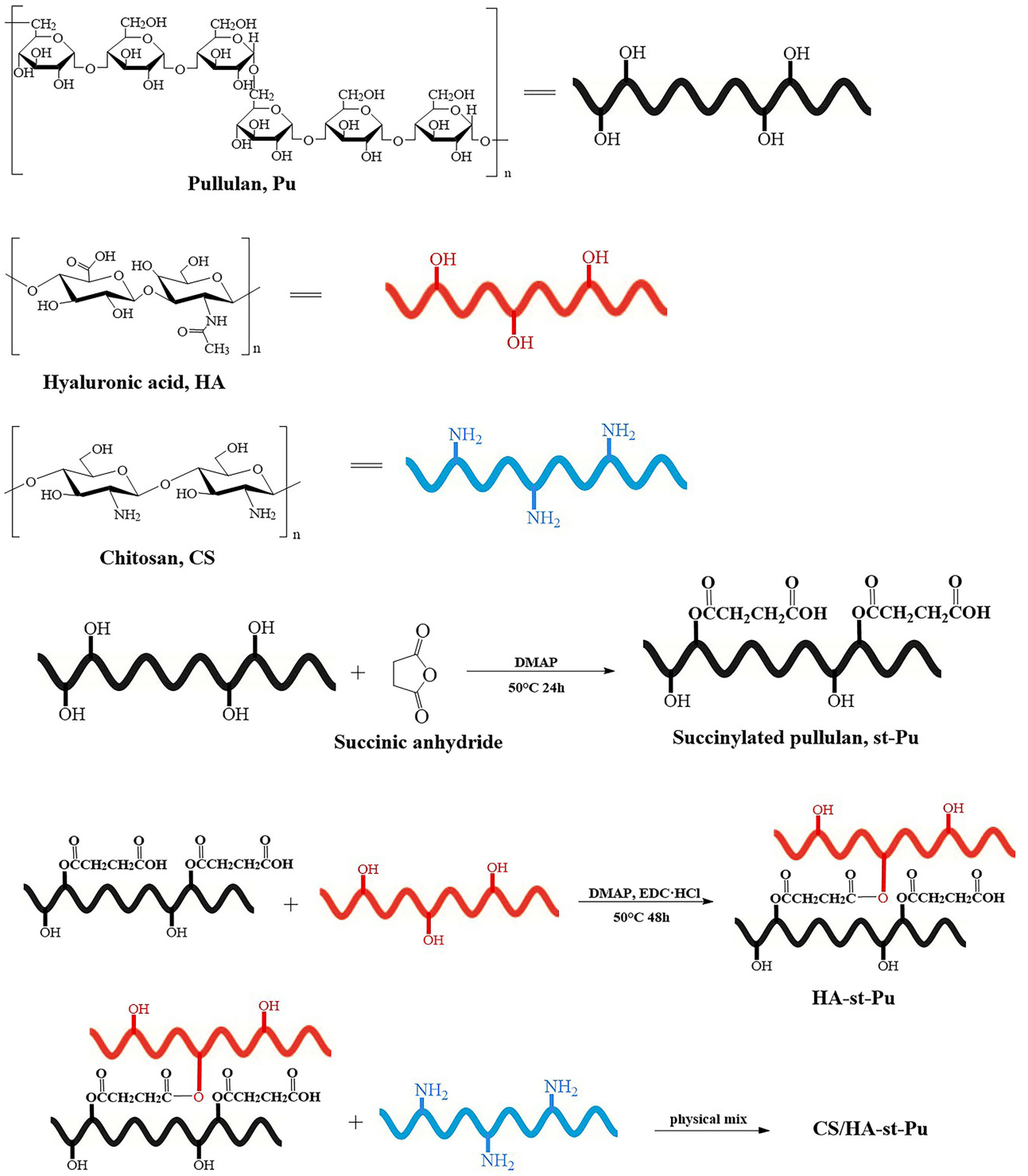

Figure 12 Synthetic route of hyaluronic acid-grafted pullulan succinate and the preparation of the chitosan/ hyaluronic acid-grafted pullulan succinate film. Taken from ref.[217]

For example, a cellulose-based hydrogel film was synthesized through a multistep process involving cellulose dissolution in a NaOH/urea system, crosslinking with chitosan, and subsequent incorporation of carboxylated multi-walled carbon nanotubes, resulting in a conductive composite hydrogel (Figure 13). This system exhibited enhanced structural integrity and functional performance, highlighting its potential for advanced biomedical applications.[224]

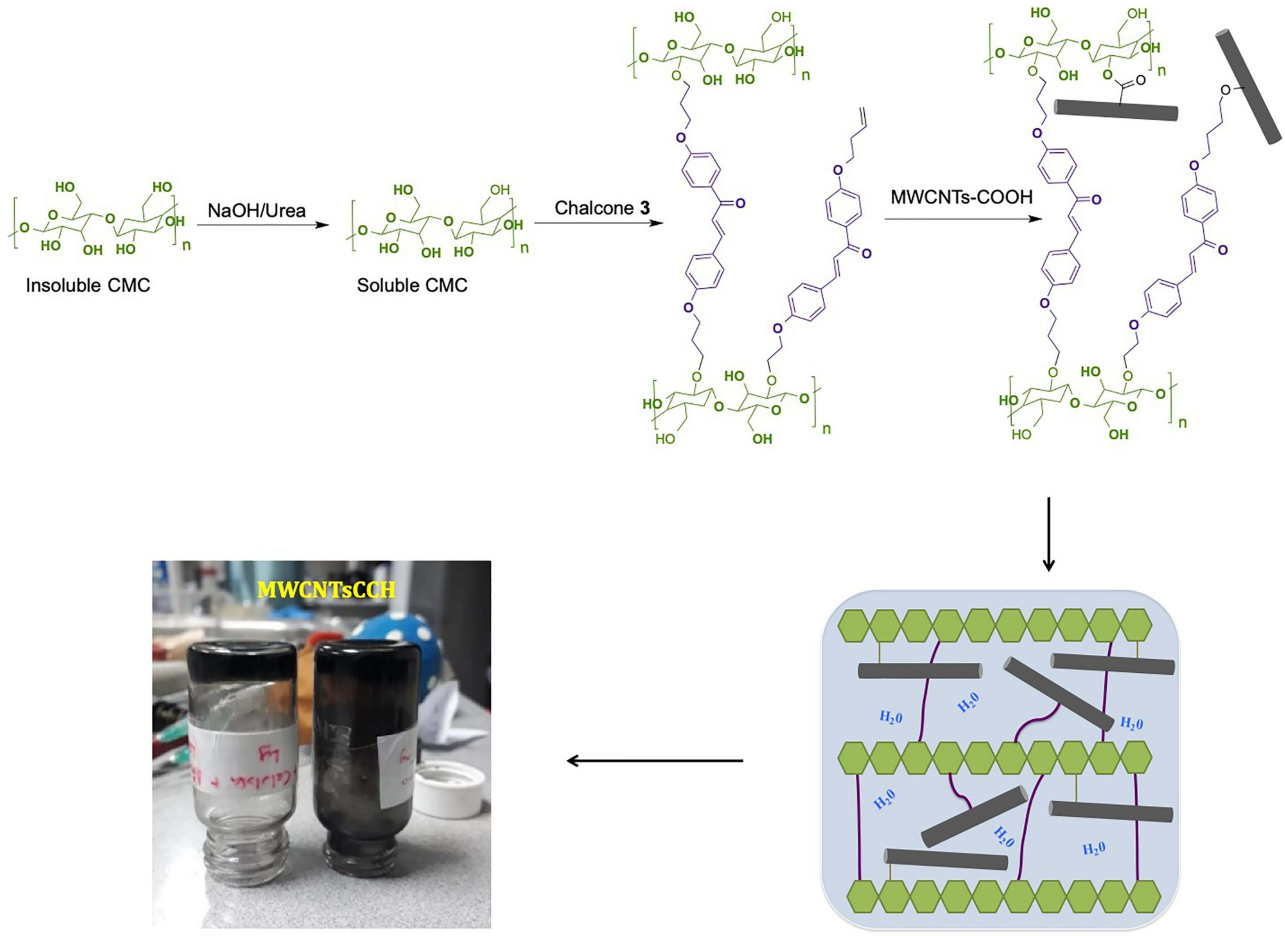

Figure 13 Schematic representation of the multistep synthesis of a cellulose–chitosan hydrogel, including cellulose dissolution, chitosan-mediated crosslinking, incorporation of carboxylated multi-walled carbon nanotubes, and formation of the final hydrogel film. Taken from ref.[224]

Table 5 presents a selection of the most recent and significant publications on carbohydrate-based hydrogels for wound healing.

Recent research has focused on enhancing the healing properties of carbohydrate-based hydrogels through innovative approaches. One significant advancement involves the incorporation of growth factors into these hydrogels. For example, chitosan-based hydrogels loaded with epidermal growth factor have been developed to promote faster epithelialization

Table 5 Selected Publications Related to Carbohydrate-Based Hydrogel for Wound Healing

Carbohydrates	Role in Wound Healing	Ref
Chitosan	Enhancing cell migration; reducing infection; stimulating tissue regeneration through its antimicrobial and haemostatic properties.	[211–213,225–228]
Hyaluronic acid	Promoting cell migration, angiogenesis and inflammation modulation; enhancing reepithelialisation and collagen synthesis.	[215–217,229,230]
Alginate	Forming a gel-like matrix that maintains moisture, supports cell migration, and reduces infection risk.	[221,222,231,232]
Dextran	Anti-inflammatory properties; improving cell proliferation; acting as a scaffold for tissue regeneration.	[233,234]
Cellulose	Provide a supportive matrix for cell attachment and migration, maintaining a moist wound environment to facilitate healing.	[224,235,236]

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and granulation tissue formation. In preclinical models, these epidermal growth factor -loaded hydrogels have demonstrated significantly enhanced healing rates compared to control groups without growth factors.[237]

Moreover, composite hydrogels that combine carbohydrate-based materials with synthetic polymers have shown promise in improving mechanical strength and flexibility.[24]

In recent years, the development of smart hydrogels has garnered considerable attention. These responsive materials can adapt to changes in their environment, such as pH, temperature, or ionic strength. This dynamic behaviour enables them to optimize drug release and hydration based on the specific conditions of the wound, providing a more personalized approach to wound management.[238–242]

Antimicrobial properties are another focal point in the advancement of carbohydrate-based hydrogels. By integrating antimicrobial agents—such as silver nanoparticles or essential oils—into the hydrogel matrix, researchers aim to combat bacterial infections that can complicate wound healing. This is particularly important for chronic and complex wounds, where the risk of infection is significantly elevated.[243]

Advantages and Challenges

Carbohydrate-based hydrogels are increasingly recognized for their significant advantages in biomedical applications, particularly due to their tuneable properties. The structure of carbohydrates can be easily modified through chemical or physical methods, enabling researchers to customize characteristics such as swelling behaviour, degradation rates, and mechanical strength. This versatility is essential for tailoring hydrogels for specific biomedical applications, ranging from drug delivery systems to tissue engineering scaffolds. The ease of modification further enhances the appeal of carbohydrate-based hydrogels, as functional groups inherent in saccharides provide multiple sites for chemical alterations, facilitating the incorporation of bioactive compounds, growth factors, or nanoparticles. Biocompatibility is another critical advantage. Many carbohydrate-based hydrogels are derived from natural sources, which reduces the risk of adverse immune responses when used in vivo. Their biodegradability ensures that they can be safely absorbed by the body, minimizing the need for surgical removal post-application.

The increasing number of research articles and patents underscores the growing interest and significant industrial investment in this field. For instance, EP4188468A1 discusses a method for enhancing the mechanical properties of carbohydrate-based hydrogels through specific crosslinking agents, demonstrating their potential for improved performance in tissue engineering. Similarly, CN113797385B is related to a chitosan/polyethylene glycol hydrogel with potential applications in promoting drug release and wound healing.

However, despite their advantages, carbohydrate-based hydrogels must address several challenges to achieve broader biomedical use.

- Firstly, the rational design of carbohydrate-based compounds within the hydrogel matrix for specific biological interaction is rarely investigated. The precise design of carbohydrate components—such as selecting the right monosaccharides, modifying the monosaccharides, or functionalizing them with bioactive molecules—is essential for promoting desired cellular behaviours and improving the performance of hydrogels in applications like drug delivery and tissue engineering. A more systematic approach to designing these hydrogels could enhance their biological activity, allowing for better targeting, controlled release, and integration with biological environments.[244]

- One other significant limitation is related to their mechanical strength. While suitable for soft tissue applications, many carbohydrate hydrogels lack the robustness required for hard tissue engineering. Indeed, on the contrary of many organogels[245] natural polymer-based hydrogel possesses low mechanical strength which restricts its application in various fields.[246,247] This shortcoming often necessitates reinforcement through composites or crosslinking, which can complicate the fabrication process. Therefore, improving their mechanical strength has become very challenging.[248–250]

- Stability is another challenge. Environmental factors such as temperature, pH, and ionic strength can adversely affect hydrogel properties, leading to variability in performance. This instability can be particularly concerning in applications requiring precise control over release rates or mechanical properties.[85]
- Scalability in production is a crucial issue as well. While laboratory synthesis of carbohydrate-based hydrogels can yield desirable properties, translating these methods to large-scale production, ie, multi-kilo, without compromising quality remains a challenge.[251]
- Sustainability. To mitigate this challenge, researchers are exploring greener synthesis methods that employ low-energy consumption processes and less hazardous solvents. Such approaches not only enhance sustainability but also aim to preserve the biological properties of the resulting hydrogels.[25] To this end, sustainability characteristics should always be demonstrated and described using green metrics calculations and, where applicable, life cycle assessment (LCA).[252]
- Sterilization: hydrogels intended for biomedical applications must be sterilized without compromising their structure, functionality, or bioactivity. Common sterilization methods, such as autoclaving or gamma irradiation, can alter the mechanical properties, swelling capacity, or degradation profile of carbohydrate-based hydrogels, requiring careful optimization.[253]
- Regulatory Compliance: Translation to clinical use requires adherence to strict regulatory standards regarding safety, efficacy, and biocompatibility. Demonstrating long-term stability, predictable degradation, absence of immunogenicity, and consistent performance under physiological conditions are essential for regulatory approval.[254]

To address these issues, recent studies have explored a variety of design strategies.

One widely studied approach is the incorporation of nanoparticles or nanofibers into the polysaccharide matrix.[85] For example, adding nano-silica to an alginate–chitosan–gelatin hydrogel improved mechanical strength and promoted osteogenic differentiation of pre-osteoblastic cells.[255] Similarly, embedding nano-hydroxyapatite into alginate scaffolds enhanced structural stability and bioactivity, making them suitable for bone tissue engineering.[256] While these nanocomposite hydrogels improve stiffness, durability, and porosity, challenges remain, such as ensuring uniform dispersion of fillers and avoiding potential cytotoxicity or immunogenicity.

Another effective strategy involves double-network or interpenetrating polymer networks, where two polymer networks interpenetrate each other. One network provides stiffness, while the second contributes elasticity, resulting in hydrogels with significantly enhanced mechanical strength and resilience.[257] For example, dual-network hydrogels combining modified alginate and chitosan demonstrated self-healing, injectability, and mechanical robustness suitable for drug and cell delivery.[258] Although highly effective, these hydrogels require careful synthesis to maintain porosity and uniformity.

Chemical crosslinking using bio-orthogonal reactions, such as Schiff-base formation, thiol–ene chemistry, or click reactions, offers another route to improve hydrogel stability. Covalent networks are more resistant to physiological degradation than ionically crosslinked hydrogels and allow for precise control over degradation kinetics and bioactive molecule incorporation.[259] However, the choice of crosslinking chemistry must balance stability with biocompatibility, and complex chemistries can complicate large-scale production.

Self-assembling peptide–polysaccharide hybrids represent an innovative approach to enhance hydrogel performance. Here, peptides form a nanofibrillar network within the polysaccharide matrix, providing mechanical reinforcement and bioactive domains for cell adhesion. These hybrids allow tunable degradation and hydration while maintaining biocompatibility.[260] The main limitations are higher cost and complexity in synthesis, as well as the need for thorough in vivo validation.

Finally, incorporating biodegradable micro- or nanoparticles within the hydrogel provides both reinforcement and controlled release of therapeutic agents. For instance, poly(lactic-co-glycolic acid) microspheres embedded in polysaccharide hydrogels allow sustained drug release while enhancing mechanical stability.[261] Care must be taken to maintain uniform particle distribution and preserve hydrogel porosity and swelling properties.

In conclusion, while each of these strategies addresses specific limitations, trade-offs remain between mechanical strength, biocompatibility, degradability, and manufacturability. No single approach provides a universal solution; the optimal design depends on the intended clinical application. Successful translation requires application-specific optimization, reproducible synthesis, and thorough in vitro and in vivo validation to ensure safety, functionality, and scalability.

Conclusions and Outlook

Looking ahead, the potential for clinical translation of carbohydrate-based hydrogels is vast. As these materials become increasingly sophisticated, they can be tailored to meet specific medical needs, enhancing patient outcomes across various therapeutic domains.[26] The integration of smart technologies into hydrogel design offers a pathway for innovation that could fundamentally change how treatments are administered.[239] For example, hydrogels embedded with biosensors could monitor wound conditions in real-time, providing healthcare providers with critical information regarding the status of a wound and the need for intervention.[25] The development of multifunctional hydrogels that integrate various therapeutic properties—such as haemostatic capabilities, antimicrobial activity, and the delivery of growth factors—holds great promise for simplifying wound management.[262,263] Such multifunctional dressings could address multiple aspects of healing, improving overall treatment efficiency and patient comfort, while also reducing the need for additional interventions. Despite these promising advances, several challenges must still be addressed before widespread clinical adoption can be achieved. Issues of reproducibility, batch-to-batch variability, and the lack of standardized evaluation protocols remain significant barriers. Establishing robust manufacturing processes and harmonized testing criteria will be essential to ensure consistent performance and regulatory approval. Looking toward the future, emerging trends are expected to shape the next generation of carbohydrate-based hydrogels. AI-guided material design could accelerate the discovery of optimized formulations with enhanced biological responses. Another promising avenue for future research involves the customization and personalization of hydrogel.[264] Continued progress in 3D and 4D bioprinting, organ-on-chip systems, organoid biomanufacturing enable the fabrication of patient-specific hydrogel architectures with complex geometries and spatially controlled properties, while organ-on-chip systems and organoid biomanufacturing facilitate in vitro modelling of tissue physiology and personalized therapeutic testing. Additionally, the incorporation of advanced biosensing capabilities and responsive behaviours will further expand their functionality, paving the way for intelligent, dynamic wound-care systems.[265] Overall, carbohydrate-based hydrogels stand at the forefront of biomedical innovation, and ongoing interdisciplinary research will continue to unlock their full potential.

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Disclosure

There are no conflicts to declare.

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