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From Lab to Use: A Comprehensive Review of Chitosan Hydrogel Fabrication and Applications

Sravan Kumar Abburi[1]; DhruvaKumar Chatrajupalli[2]; Lahari Vuddanti[3]; Seetharam Gude[4]*

[1]QC Chemist, Sofie Biosciences, Totowa, New Jersey, USA.
[2]Health data science, Saint Louis university, Missouri, USA.
[3]Quality Control Scientist, Pherros Biosciences, Florida, USA.
[4]Research and Development, Aurobindo Pharma Limited, Hyderabad, India.

***Corresponding Author(s): Seetharam Gude**
Research and Development, Aurobindo Pharma Limited,
Hyderabad, India.
Email: seethasaiofficial@gmail.com

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Abstract

Chitosan, a natural biopolymer obtained through the deacetylation of chitin, has gained significant attention due to its biodegradability, safety, and multifunctional biological properties. This review summarizes recent advances in the design, synthesis, and application of chitosan-based hydrogels in the food sector, emphasizing their roles in preservation, sensing, and safety enhancement. A comprehensive literature survey was conducted to explore synthesis strategies, including physical, chemical, and enzymatic cross-linking methods, as well as structural modifications and functionalization approaches. Particular focus was placed on biological evaluations such as antimicrobial, antioxidant, and biocompatibility assessments relevant to food applications. Chitosan-based hydrogels exhibit structural versatility arising from their reactive amino and hydroxyl groups, enabling the development of three-dimensional networks suitable for diverse uses. They have been successfully employed as food freshness indicators, intelligent packaging systems, contaminant detectors, dye adsorbents, and nutrient delivery matrices. Their inherent antimicrobial and antioxidant activities further support their potential in maintaining food quality and safety. Despite these advantages, certain limitations remain, including insufficient mechanical strength, limited scalability, and regulatory challenges, which hinder broader industrial application. In conclusion, chitosan-based hydrogels hold promise as sustainable, multifunctional materials for intelligent food systems. Overcoming current barriers through advanced cross-linking strategies, reinforcement techniques, and harmonized regulatory frameworks may accelerate their transition from laboratory research to commercial implementation. This review highlights both their potential and the critical steps required to ensure their integration into next-generation food safety and innovation platforms.

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Introduction

Hydrogels are viscoelastic, highly hydrated polymeric systems defined by a three-dimensional, crosslinked macromolecular network that can absorb and retain significant quantities of water often exceeding hundreds of times their dry weight without undergoing dissolution [1,2]. This extraordinary water uptake capacity is not merely due to the hydrophilic nature of their constituent monomers, but also a result of the loose, highly porous, and interconnected spatial architecture that enables capillary flow, osmotic diffusion, and physical entrapment of water molecules [3]. Such characteristics lend hydrogels not only their pliability and softness mimicking the extracellular matrix but also enable the modulation of their rheological behavior and mechanical performance for diverse biomedical applications [4].

Structurally, hydrogels can be engineered to exhibit varying degrees of swelling, elasticity, and degradation kinetics by manipulating the crosslinking density, polymer chain length, and inclusion of ionic or responsive moieties [5]. These materials are broadly classified into natural and synthetic hydrogels, based on the origin of their polymeric constituents. Natural hydrogels, particularly those derived from polysaccharides, are gaining unprecedented interest due to their innate biocompatibility, renewable sourcing, and enzyme-mediated biodegradability features highly favorable in applications such as wound healing, tissue engineering scaffolds, and localized drug delivery systems [6]. Among these, Chitosan (CS), a partially deacetylated derivative of chitin obtained predominantly from crustacean exoskeletons, is receiving extensive attention in post-2023 bioengineering literature [7]. Molecularly, chitosan is composed of randomly distributed β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine units. Its primary amino groups protonated under acidic conditions impart a positive surface charge, distinguishing it as the only naturally occurring cationic polysaccharide, which is a rare biochemical trait [8]. This unique feature plays a pivotal role in its biological activities. The antibacterial activity of chitosan is attributed to its ability to electrostatically bind to the negatively charged phospholipids on bacterial cell membranes [9]. This interaction perturbs the integrity of the membrane, leading to leakage of intracellular contents, disruption of essential cellular processes, and ultimately, cell lysis [10].

Modern studies using membrane potential-sensitive dyes and electron microscopy have confirmed this bactericidal mechanism in both Gram-negative and Gram-positive species. Moreover, its antioxidant properties arise from the presence of free amino (–NH_2) and hydroxyl (–OH) groups, which can chelate metal ions and scavenge Reactive Oxygen Species (ROS). When these functional groups interact with free radicals, they donate hydrogen atoms, forming stable ammonia ions (–NH_3^+), thereby halting the radical chain reactions involved in oxidative damage [11]. However, a persistent challenge in utilizing chitosan lies in its limited solubility at physiological pH, as it is only soluble in dilute acidic environments (pH<6.5), which restricts its formulation flexibility and in vivo compatibility [12]. To overcome this, various chemical modification strategies have been employed, each aimed at introducing hydrophilic, ionizable, or reactive groups to improve water solubility and functional integration [13]

Carboxymethyl Chitosan (CMC) is one such derivative synthesized by the substitution of carboxymethyl groups at the hydroxyl or amino sites of the chitosan backbone. These amphoteric derivative displays both positive and negative charges along the polymer chain and exhibits high solubility in neutral and alkaline solutions [14]. Its polyelectrolyte nature not only enhances aqueous dispersion but also facilitates ionic crosslinking with divalent cations or anionic co-polymers, thereby expanding its utility in pH-responsive drug delivery, injectable hydrogels, and bioadhesive formulations [15]. In parallel, Hydroxyethyl Chitosan (HE-CS) is formed by etherification reactions that introduce hydroxyethyl groups, thereby replacing the labile hydrogen atom of the amine or hydroxyl moieties with hydrophilic side chains. This modification significantly improves hydrophilicity, reduces viscosity at high concentrations, and enhances compatibility with proteins and biologics qualities currently being explored in ophthalmic formulations and injectable wound sealants [16]. Another promising derivative, N-Succinyl Chitosan (CH-Su), involves the insertion of succinyl groups specifically at the N-position of glucosamine units, yielding a polymer that not only demonstrates increased aqueous solubility across a broad pH range but also displays superior cytocompatibility and cellular uptake compared to unmodified chitosan [17].

Recent 2024 biofabrication studies report its successful incorporation in 3D-bioprinted constructs, where it enhanced fibroblast proliferation, sustained cell viability over extended culture periods, and promoted ECM deposition indicating its potential as a biofunctional scaffold in soft tissue engineering [18]. Collectively, these advances reflect a transformative shift in hydrogel science from inert, water-swollen carriers to intelligent, bioactive, and structurally programmable materials that respond to physiological stimuli and enable controlled therapeutic delivery, cellular modulation, and precision tissue regeneration [19]. The future trajectory of chitosan-based hydrogels is now converging with nanotechnology, CRISPR-Cas mediated drug activation, and personalized medicine, suggesting a broader role beyond traditional biomedical domains into biosensing, immunoengineering, and responsive implantable systems [20] (Figure 1).

Recent investigations into chitosan-based hydrogels have illuminated their role as an adaptable, multifunctional platform, particularly distinguished by their capacity to integrate a diverse array of bioactive agents while maintaining mechanical resilience and biodegradability [21]. Emerging data from 2023 onwards have significantly advanced our understanding of how chitosan's intrinsic polycationic nature and modifiable amine groups facilitate controlled gelation and crosslinking through ionic interactions (e.g., with multivalent anions like tripolyphosphate) or more contemporary strategies such as photoinduced click chemistry and enzyme-mediated covalent bonding [22-25]. The tunable network density achieved via such methods directly influences swelling behavior, porosity, and stimuli-responsiveness critical attributes for applications in precision drug release and tissue scaffolding [26].

From a food technology perspective, recent studies have focused on the hydrogel's capacity to act as carriers for antimicrobial peptides, antioxidants, or probiotics, enhancing shelf life and nutrient stability in functional food systems [27]. The intersection of green chemistry and hydrogel design has further led to the proliferation of eco-friendly synthesis protocols, minimizing residual toxicity through the use of plant-based crosslinkers like genipin and citric acid [28]. Moreover, advancements in 3D printing of chitosan-based hydrogels particularly when blended with reinforcing biopolymers such as alginate or cellulose nanofibers have enabled the creation of complex architectures suitable for bioactive food packaging and regenerative scaffolds with cell-instructive microenvironments [29]. Notably, integrated omics analyses and real-time release monitoring via embedded biosensors are now being explored to understand hydrogel–cell or hydrogel–food interactions at a systems biology level. Collectively, these multidimensional innovations underscore the shift from static hydrogel systems toward dynamic, smart biomaterials, aligned with the global emphasis on sustainability, functionality, and biomedical efficacy [30].

Building on recent investigations, this article explores the multifunctional role of chitosan-based hydrogels across food-related applications by consolidating evidence from diverse synthesis strategies and performance evaluations. Similar to earlier works that emphasized biomedical and pharmaceutical potentials, the present review extends the discussion into food packaging, biosensing, and nutrient delivery, thereby highlighting the translational opportunities of these systems. By synthesizing current findings and identifying gaps, this review positions chitosan hydrogels as a sustainable and innovative platform that bridges laboratory research with practical applications in food safety and preservation.

Formation mechanisms and design strategies of chitosan-based hydrogels

Chitosan-based hydrogels represent a highly tunable class of biomaterials whose formation mechanisms are governed by an intricate interplay of physicochemical and covalent interactions, including ionic crosslinking, hydrogen bonding, and dynamic covalent bond formation such as Schiff base reactions, particularly with aldehyde-containing compounds [31-35]. Recent studies published in 2024 have elucidated that the hierarchical assembly of chitosan networks can be significantly influenced by the degree of deacetylation, molecular weight, and the environmental pH, which collectively dictate the sol-gel transition behavior and resultant mechanical properties [36-41]. Physical hydrogels, often stabilized through non-covalent interactions like van der Waals forces and hydrophobic interactions, offer shear-thinning and self-healing capabilities ideal for minimally invasive delivery systems, whereas chemically crosslinked hydrogels formed via agents such as genipin, glutaraldehyde, or enzymatic triggers demonstrate enhanced stability and prolonged retention under physiological stress [42]. Comparative rheological profiling between thermosensitive and pH-responsive variants has revealed distinct viscoelastic signatures, indicating potential for precise tuning in drug delivery and tissue engineering contexts [43,44].

Interdisciplinary insights from supramolecular chemistry and nanofabrication have further expanded the design of hybrid hydrogels, integrating nanoparticles or bioactive peptides into the chitosan matrix to create stimuli-responsive systems with improved loading efficiency and controlled release profiles. Importantly, the integration of microfluidic synthesis and 3D bioprinting in 2023–2025 innovations has facilitated the fabrication of architecturally complex hydrogels with spatially controlled properties, thereby aligning material design more closely with regenerative medicine and personalized therapy paradigms. These advances collectively signal a paradigm shift in the development of next-generation hydrogels, moving beyond static scaffolds toward dynamic, intelligent biomaterials [45-50].

Physical crosslinking is predicated on the establishment of supramolecular interactions primarily hydrogen bonding, ionic interactions, hydrophobic effects, and van der Waals forces rather than permanent covalent bonds, thus preserving the environmental responsiveness and biodegradability of the hydrogel matrix [51]. Emerging evidence from 2023–2024 studies indicates that the mechanical and rheological integrity of these hydrogels can be finely tuned by modulating parameters such as polymer concentration, degree of deacetylation, and ionic strength of the surrounding medium [52]. This has led to the stratification of physically crosslinked hydrogels into ‘strong’ and ‘weak’ classes, the former being characterized by robust entanglement networks and the latter by transient, stimulus-sensitive linkages [53]. For instance, the integration of multivalent counterions (e.g., sulfate or phosphate ions) has been shown to enhance crosslink density and improve resistance to enzymatic degradation, a feature increasingly desirable in mucosal or wound-healing applications [54]. In addition, thermosensitive chitosan derivatives are gaining attention for their ability to form in situ gelling systems at body temperature, as evidenced by recent in vivo evaluations in ocular and injectable drug delivery platforms [55]. Compared to traditional chemically crosslinked systems, these physically crosslinked constructs exhibit markedly improved cytocompatibility, reduced inflammatory response, and minimal risk of leachable impurities traits that align with the current regulatory emphasis on green and patient-centric biomaterials. Collectively, these developments affirm the translational potential of physically crosslinked chitosan hydrogels in next-generation biomedical and pharmaceutical formulations [56-58].

Ionic interactions represent a fundamental and versatile strategy for establishing physical cross-linking in chitosan-based hydrogels [59]. These interactions arise through the electrostatic attraction between the functional groups of chitosan primarily amino and hydroxyl moieties and various multivalent metal ions, resulting in the formation of robust and three-dimensional network structures [60]. This ionic-mediated cross-linking significantly enhances the mechanical integrity, elasticity, and structural coherence of the hydrogel system, which is crucial for biomedical and pharmaceutical applications where resilience under physiological conditions is required [61]. Recent advancements in this field have highlighted the nuanced ability of ionic interactions to tailor not just mechanical strength but also the microarchitecture of the hydrogel matrix, such as pore size distribution and surface topology [62]. These morphological modulations have a direct influence on the hydrogel’s permeability, swelling behavior, and diffusion kinetics, which are vital for applications in drug delivery, wound healing, and tissue engineering [63]. Notably, the use of metal ions like Fe^{3+}, Al^{3+}, and Ca^{2+} has emerged as particularly effective due to their varying ionic radii and charge densities, which facilitate differential cross-linking efficiencies and coordination behaviors with chitosan derivatives [64]. One compelling example of this approach is demonstrated by Mitsuhashi and colleagues (2019) [59], who engineered a chitosan derivative hydrogel using N-Succinyl Chitosan (CH-Su) cross-linked with trivalent and divalent metal ions [65], CH-Su, being rich in both amino and hydroxyl groups, readily interacts with these metal ions to form ionic bridges, thereby promoting a tightly woven and stable hydrogel network. Upon the introduction of multivalent cations such as Fe^{3+} and Al^{3+}, ion-pairing occurs due to the strong affinity between the positively charged ions and the negatively charged functional groups on CH-Su. This interaction results in an intricate mesh-like network with notable physicochemical properties. The CH-Su/Al^{3+} variant, in particular, exhibited superior mechanical robustness, structural integrity, and a moderate degradation profile suitable for biomedical applications, such as the prevention of peritoneal adhesions. Furthermore, FT-IR spectral analysis indicated a pronounced binding affinity of CH-Su towards Fe^{3+} and Al^{3+}, likely attributable to the high charge densities of these ions [66]. These ions effectively coordinate with the carboxyl and amide groups of succinylated chitosan, promoting the formation of succinate-metal ion complexes, which are thermodynamically stable and less prone to hydrolytic breakdown under physiological conditions. In addition to these findings, recent studies have delved deeper into how manipulating the ionic environment during synthesis can lead to hydrogels with switchable mechanical and chemical characteristics, opening new frontiers in energy-responsive materials and controlled release systems. The potential to exploit these ionic interactions for dynamic hydrogel systems lies in their reversible nature an aspect increasingly explored for stimuli-responsive platforms. For instance, by varying the valency and coordination number of the introduced ions, or by modulating the pH and ionic strength of the medium, one can finely tune the gelation behavior, degradation rate, and swelling kinetics of the chitosan-based network. Moreover, advancements in nanocomposite hydrogel design have integrated metal ion cross-linking with inorganic nanomaterials, amplifying the hydrogel's biofunctionality, antibacterial properties, and responsiveness to external stimuli such as pH, light, or magnetic fields [67].

Collectively, ionic cross-linking offers an elegant and environmentally benign route to engineer chitosan hydrogels with customized performance attributes. It leverages the inherent bioactivity and chemical reactivity of chitosan in tandem with the coordination chemistry of metal ions, resulting in materials that are not only biocompatible and biodegradable but also highly adaptable for emerging biomedical technologies. As research progresses, the refinement of these systems using multivalent ions, coupled with advanced characterization techniques, continues to deepen our understanding of how to precisely control the micro- and macro-structural properties of chitosan hydrogels for next-generation therapeutic applications [68].

Hydrogen bonding interactions serve as a critical molecular mechanism in the physical cross-linking of hydrogels, significantly determining their structural conformation, physico-mechanical behavior, and overall stability [69]. These non-covalent interactions arise when a hydrogen atom, covalently bonded to an electronegative donor such as nitrogen, oxygen, or fluorine, experiences an electrostatic attraction to another electronegative atom acting as an acceptor [70]. In polymeric hydrogel systems, particularly those derived from natural biopolymers like chitosan, this type of bonding facilitates the aggregation of polymer chains into a three-dimensional network, thereby enabling the formation of hydrogels with unique morphologies and responsive characteristics [71]. The dynamic and reversible nature of hydrogen bonding is especially significant in designing stimuli-responsive or "smart" hydrogels, where changes in environmental conditions such as pH, temperature, and ionic strength can induce the reversible dissociation or formation of hydrogen bonds, leading to alterations in hydrogel swelling, porosity, and mechanical strength [72]. This mechanism has been strategically exploited to develop advanced chitosan-based hydrogels with high degrees of environmental responsiveness and biomedical applicability [73]. For instance, when carboxymethyl chitosan is mixed with sodium alginate under acidic conditions, extensive hydrogen bonding between hydroxyl and carboxyl groups can induce the formation of a stable hydrogel matrix with pronounced pH sensitivity and reversibility, making it a promising candidate for protein encapsulation and controlled release systems [74]. The pH-triggered conformational changes enabled by hydrogen bonding allow the hydrogel to load and release biomolecules in response to specific physiological cues [75]. Similarly, short-chain chitosan has been shown to significantly enhance the mechanical properties of Polyacrylamide (PAM) hydrogels by integrating into their network via hydrogen bonds, thus improving elasticity and compressive strength without requiring chemical cross-linkers. Notably, Budianto and colleagues (2020) [76], explored the synergistic use of chitosan, acetaldehyde, and N,N'-methylenebisacrylamide (NNMBA) to engineer pH-responsive hydrogels with Interpenetrating Polymer Networks (IPNs) [77]. These hydrogels exhibited a high degree of cross-linking and structural integrity, attributes largely attributed to the formation of hydrogen bonds and imine linkages via Schiff base reactions. The interplay between hydrogen bonding and dynamic covalent chemistry here results in hydrogels with enhanced resilience and potential for drug delivery under varying pH conditions. Moreover, advancements in supramolecular chemistry have enabled the development of hydrogels where chitosan is functionalized with orotic acid, introducing carboxyl groups that form complementary hydrogen bonds with molecules such as 2,6-diaminopurine. These interactions facilitate a hierarchical self-assembly process, generating supramolecular networks that are both pH- and temperature-responsive. Such designs offer dual-responsive release kinetics ideal for gastrointestinal drug delivery, where localized pH fluctuations can trigger site-specific release of therapeutic agents. Recent studies have begun exploring the hybridization of chitosan with synthetic and natural polymers using hydrogen bonding as a central mechanism to fine-tune properties like biodegradability, protein affinity, and mucoadhesiveness [78]. The integration of computational modeling and molecular dynamics simulations is further refining our understanding of hydrogen bond formation and rupture under physiological conditions, thereby guiding the rational design of next-generation hydrogels. Collectively, these advancements underscore the pivotal role of hydrogen bonding in creating versatile, adaptive, and functional chitosan-based hydrogel systems for biomedical, pharmaceutical, and tissue engineering applications [79].

Hydrophobic interactions, a key non-covalent force, play a pivotal role in the formation and stabilization of physically cross-linked hydrogels [80]. These interactions occur when hydrophobic moieties within a polymeric matrix tend to associate in aqueous environments to minimize their exposure to water, thereby driving the self-assembly and aggregation of polymer chains [81]. The fundamental driving force behind this phenomenon is the acid-base-free energy of cohesion among water molecules, which leads to the exclusion of non-polar groups and a consequential increase in entropy [82]. In hydrogel systems, this behavior results in the spontaneous organization of hydrophobic domains within the polymer network, promoting the development of more stable and mechanically robust hydrogel architectures. The aggregation of hydrophobic molecules into larger clusters reduces the system's free energy and promotes structural integrity in the absence of chemical crosslinkers, making hydrophobic interactions particularly attractive in the design of biocompatible and stimuli-responsive hydrogels. The utility of hydrophobic interactions in tailoring hydrogel microstructures, such as modifying porosity, surface area, and overall network density, thereby influencing crucial parameters like drug release kinetics, swelling behavior, and mechanical strength. For instance, Han et al. (2019) [83] investigated hydrophobically associating polymers, including Hydrophobically Attached Polymers (HAP) and Hydrophobically Attached Polyelectrolytes (HAPE), and found that manipulating the molecular architecture such as altering molecular weight, sequence distribution of hydrophobic moieties, type and density of hydrophobic and ionic groups, and their spatial arrangement could significantly enhance hydrophobic interactions and thus the performance of these hydrogels [84]. This level of tunability makes HAPs and HAPEs promising candidates for biomedical and industrial applications where controlled mechanical and release properties are critical. In another noteworthy study, Enache et al. (2022) [85] utilized chitosan hydrogels loaded with NYSm (a mycobacterial suspension), relying on both the amino functionalities of chitosan and the physical crosslinking facilitated by hydrophobic interactions and hydrogen bonding [86]. These hydrogels demonstrated superior performance in fungal inhibition, swelling capacity, and controlled drug release across variable pH conditions when compared to chemically crosslinked counterparts [87]. Moreover, chitosan-based hydrogels can be further modified by introducing hydrophobic functional groups, thereby enhancing their ability to interact with hydrophobic drugs or biomolecules. Huang et al. (2021) [88] demonstrated a sophisticated approach involving thiolated chitosan and maleic anhydride-modified chitosan to construct hydrogels through dual crosslinking mechanisms, incorporating both click chemistry and physical interactions [89]. The resulting materials exhibited minimized hydrogel size and enhanced mechanical strength without compromising cytocompatibility, highlighting the advantage of integrating covalent and non-covalent strategies [90]. These findings align with the growing emphasis on engineering hydrogels with hierarchical structures and multi-responsive behavior to meet the complex demands of advanced therapeutic delivery, tissue engineering, and wound healing [91,92].

Electrostatic interactions play a pivotal role in the assembly and stabilization of chitosan-based hydrogels, as these interactions arise naturally between oppositely charged moieties [94]. When charged molecular entities are in close proximity, electrostatic forces either attractive or repulsive are generated, which in turn influence the aggregation behavior of molecules and the structural integrity of hydrogels. In the case of chitosan, a cationic biopolymer obtained from the deacetylation of chitin, electrostatic interactions predominantly involve the positively charged amino groups on its polymer chain and the negatively charged functional groups of various anionic polymers [95]. These interactions facilitate the formation of Polyelectrolyte Complexes (PECs), whose formation and strength are highly dependent on parameters such as the density and spatial distribution of charges within the hydrogel network, as well as the ionic strength, pH, and polarity of the surrounding medium [96]. Under suitable pH conditions, particularly in mildly acidic environments, chitosan exhibits enhanced solubility and ionization, which promotes more efficient complexation with anionic polymers. For instance, Papagiannopoulos and colleagues in 2023 [93]. successfully constructed physical hydrogels from carrageenan and chitosan (Car/Chit) by harnessing their inherent electrostatic compatibility. The negatively charged sulfate groups of carrageenan interacted with the protonated amino groups of chitosan, leading to a pronounced increase in the viscoelastic properties of the resulting hydrogel, especially under acidic pH conditions [97]. The swelling behavior of these hydrogels was simultaneously reduced, a consequence attributed to the densification of the polymer matrix through ionic bonding. Another significant advancement was reported by Wang et al. [96] in the same year, where they employed high-degree deacetylated chitosan (greater than 90%) as the backbone for the synthesis of an injectable, adhesive hydrogel system. By leveraging the catechol groups inspired by mussel adhesion proteins, and introducing them to interact electrostatically with sulfonic acid-containing monomers like N-isopropyl acrylamide, the team developed a thermo-responsive and biocompatible hydrogel capable of in situ gelation [98]. The electrostatic interactions between the cationic amino groups of chitosan and the anionic sulfonic acid moieties facilitated rapid gel formation and strong tissue adhesion, highlighting the utility of such systems in biomedical applications including wound healing, tissue regeneration, and drug delivery. Further extending the versatility of electrostatic interactions, Wan et al. (2022) [99] explored the formation of mesoporous hydrogel adsorbents through a synergistic combination of chitosan and Polyethyleneimine (PEI) [100]. In this study, acrolein was employed as a crosslinking agent, forming covalent C–N bonds with chitosan and partially altering the hydrogen bonding network. The introduction of PEI further enhanced the C–N bonding and supported the creation of a stable mesoporous framework [101]. This framework demonstrated a strong electrostatic affinity for anionic dyes, particularly under acidic conditions where the protonation of amino groups on the chitosan backbone significantly increased the positive surface charge of the material. As a result, anionic azo dye molecules such as Acid Blue 93 (AB93) were efficiently adsorbed through electrostatic attraction and π–n interactions involving the dye's aromatic rings. Overall, chitosan-based hydrogels formed through electrostatic interactions offer an expansive and evolving platform for developing multifunctional biomaterials [102]. The inherent tunability of chitosan's charge density, combined with advances in polymer conjugation and environmental responsiveness, continues to drive innovations in fields such as environmental remediation, pharmaceutical drug delivery, tissue engineering, and regenerative medicine. Recent literature underscores the growing potential of these electrostatically assembled systems, particularly in designing stimuli-responsive hydrogels with enhanced mechanical strength, controlled swelling, degradability, and targeted interaction with biological or environmental analytes [103] (Table 1).

Chemically crosslinked chitosan hydrogels:

Chemical crosslinking in chitosan-based hydrogels involves the establishment of covalent bonds between polymer chains, resulting in the formation of a highly stable, three-dimensional network structure [104]. This process takes advantage of the abundant reactive functional groups present in chitosan, particularly the amino ($-NH_2$) and Hydroxyl ($-OH$) groups, which readily participate in reactions with various crosslinking agents. Upon exposure to suitable chemical crosslinkers, these functional groups form strong covalent bonds, thereby producing a gel matrix that exhibits superior rigidity and long-term stability compared to physically crosslinked systems [105]. These covalent connections are not reversible under physiological conditions, making the resulting hydrogels significantly more robust and less prone to disintegration under mechanical or environmental stress. The chemically crosslinked hydrogels, often referred to as "true gels," are typically permanent in nature, with enhanced mechanical properties that are vital for numerous biomedical and pharmaceutical applications [106].

Moreover, the versatility of chitosan and its derivatives allows for extensive chemical modification, enabling the design of hydrogels with tailored physicochemical properties. The introduction of additional functional moieties into the chitosan backbone can facilitate further crosslinking, thereby enhancing structural integrity and endowing the gel with additional functional attributes such as improved biocompatibility, controlled degradation, and antimicrobial activity [107]. These modifications are particularly advantageous for applications that require prolonged residence time, mechanical resilience, or sustained drug release profiles. Compared to their physically crosslinked counterparts, chemically crosslinked chitosan hydrogels demonstrate superior resistance to environmental changes such as pH, ionic strength, or enzymatic degradation, which might otherwise compromise gel integrity [108]. This increased resistance, combined with their enhanced mechanical strength, makes chemically crosslinked hydrogels particularly suitable for use in tissue engineering, wound healing, and controlled drug delivery systems where long-term performance and mechanical robustness are crucial [109].

The Schiff base reaction plays a pivotal role in modifying natural polymers like chitosan to enhance their structural and functional characteristics, particularly in the development of advanced drug delivery systems and biomaterials [110]. This reaction typically proceeds under mildly acidic conditions to promote the condensation between a primary amine group and a carbonyl group, generally an aldehyde or ketone, resulting in the formation of an imine linkage commonly referred to as a Schiff base [112]. In the case of chitosan, which possesses abundant amino groups along its polymer backbone, this reaction becomes especially significant, as it enables the covalent attachment of various aldehyde-containing functional molecules or catalysts [113]. The resultant imine (C=N) bond formation not only provides a stable linkage but also facilitates the development of three-dimensional cross-linked networks, enhancing the mechanical integrity and resilience of the modified hydrogel systems. When chitosan is functionalized through Schiff base chemistry, the introduction of cross-links between polymer chains results in a robust hydrogel matrix with superior mechanical strength, improved stability, and tailored porosity [114] This structural modification is highly advantageous for pharmaceutical and biomedical applications, particularly in the controlled release of therapeutic agents. One compelling example of such a modification involves the grafting of Gallic Acid (GA), a natural polyphenolic compound, onto the chitosan backbone. In a study conducted by Park et al. (2023), [107] the synthesis of a Chitosan-Gallic Acid (CS-GA) conjugate was achieved using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) in combination with N-hydroxysuccinimide (NHS) [115]. EDC served to activate the carboxylic group of gallic acid, which in turn formed a stable intermediate with NHS. This intermediate then reacted with the amino groups present on the chitosan chains, leading to the formation of amide bonds and successful conjugation of GA onto the polymeric backbone. Subsequent formation of CS-GA hydrogel beads was accomplished by dropping the sol of this conjugate into a Tri-borate Buffer Solution (TBS), initiating ionic gelation [116]. Interestingly, the CS-GA hydrogels exhibited varied dissolution behavior when tested under different pH conditions, suggesting pH-responsive characteristics likely influenced by the Schiff base dynamics. Specifically, hydrogels formed at pH 4 (CSGAXM) demonstrated different solubility and drug release patterns compared to those formed at pH 8.5 (CS-GAXT), indicating that the degree of crosslinking and stability of the imine bonds are modulated by environmental pH. This tunability is a critical feature in the design of smart drug delivery systems, as it allows for site-specific release profiles, especially within pH-variable biological environments [117].

In another notable study by Dziadek et al. (2022) [108], the application of Schiff base chemistry was extended to create multifunctional chitosan-based hydrogels through cross-linking with 2,3,4-Trihydroxybenzaldehyde (THBA). This aldehyde compound offered not only a reactive aldehyde group to form imine linkages with the amino groups of chitosan but also three hydroxyl groups that provided additional binding potential with other components under acidic conditions [118]. The synthesized hydrogels were further functionalized with Pectin (PC), Biologically Active Glass (BG), and Rosmarinic Acid (RA), each contributing unique physicochemical and biological properties. Pectin formed electrostatic complexes with chitosan due to interactions between their oppositely charged groups, while rosmarinic acid participated in hydrogen bonding through its oxygen atoms. Moreover, calcium ions from the bioactive glass engaged in ionic interactions with the carbonyl functionalities of pectin, establishing a multi-layered network of synergistic interactions [119]. Despite the presence of various non-covalent interactions such as hydrogen bonding and ionic attractions, the imine bonds resulting from Schiff base formation exhibited superior strength and stability, thereby dominating the overall structural framework of the hydrogel [120]. The resultant biomaterials not only displayed excellent mechanical strength and antioxidant activity but also demonstrated cytocompatibility and anticancer potential, likely due to the bioactivity of the incorporated natural compounds and the robustness of the cross-linked network. These studies highlight the profound versatility and utility of Schiff base reactions in tailoring the architecture and performance of chitosan-based hydrogels for advanced biomedical applications [121].

The Diels–Alder reaction serves as a cornerstone in synthetic organic chemistry, enabling the efficient construction of six-membered cyclic compounds through a [4+2] cycloaddition mechanism. This pericyclic reaction typically involves the interaction of a conjugated diene and a dienophile, facilitating the formation of a new cyclic structure in a highly stereoselective and regioselective manner. Its utility extends far beyond conventional organic synthesis, finding critical applications in the development of natural products, therapeutic agents, and complex molecular architectures. In particular, the adaptation of the Diels–Alder reaction to the realm of biomaterials has opened new pathways for designing functional hydrogels with tunable physicochemical properties. Among such innovations, the incorporation of Diels–Alder chemistry into chitosan-based hydrogels has garnered significant attention. Chitosan, a natural polysaccharide derived from chitin, provides a reactive framework due to its abundant amine and hydroxyl groups. When modified via Diels–Alder chemistry, chitosan hydrogels can exhibit remarkable features such as injectability, autonomous self-healing, and enhanced mechanical strength. These attributes arise from structural modifications involving either the introduction of novel functional groups or alterations of existing moieties within the chitosan matrix, which influence the crosslinking density and dynamic bonding characteristics of the hydrogel network. An illustrative example of this approach is the development of pectin-chitosan hybrid hydrogels via Diels–Alder click chemistry, as demonstrated by Li D and colleagues (C. H. Chen et al., 2021) [111]. In their study, furfural was employed to modify pectin, thereby introducing conjugated diene functionalities. Concurrently, chitosan was grafted with 6-maleimidohexanoic acid to yield maleimide-bearing protodiol components. Upon mixing the furfural-modified Pectin

(PF) with maleimide-modified Chitosan (CA), a spontaneous Diels–Alder reaction occurred, forming a robust crosslinked network without requiring external catalysts or harsh reaction conditions. The resulting hydrogel system exhibited extraordinary load-bearing capacity, capable of supporting weights up to 500 grams without structural failure, which underscores the material's mechanical resilience. Furthermore, the hydrogels demonstrated rapid self-repair behavior when damaged, attributed to the reversible nature of Diels–Alder linkages and the dynamic physical interactions that re-establish the crosslinked network upon deformation. Another noteworthy property of these hydrogels is their dual responsiveness to environmental pH and temperature. This stimuli-responsive behavior is grounded in the amphoteric nature of both pectin and chitosan, which display ionization-dependent transformations in their functional groups under varying pH conditions. Specifically, in acidic environments, the carboxylic acid groups of pectin protonate to form $–COOH_2^+$, while the amine groups of chitosan protonate to $–NH_3^+$. At alkaline pH levels above 7, these groups deprotonate to yield $–COO^-$ and neutral $–NH_2$, respectively. Such reversible ionization modulates the hydrogel's swelling behavior, crosslinking dynamics, and overall stability, enabling tailored performance under physiological and process-specific conditions. Collectively, these Diels–Alder modified chitosan-pectin hydrogels present a versatile and highly functional material platform with immense potential in biomedical applications, controlled drug delivery, and catalytic support systems, where their mechanical integrity, environmental responsiveness, and self-healing capabilities can be strategically harnessed [122].

The Michael addition reaction, commonly referred to as the Michael reaction, is a type of conjugate addition that plays a significant role in organic synthesis. This reaction involves the addition of a nucleophilic species to an α,β-unsaturated carbonyl compound, which contains one or more carbon–carbon double bonds adjacent to electron-withdrawing functional groups. The ability of this reaction to form carbon–carbon bonds at mild conditions makes it an invaluable tool in the construction of complex molecular architectures. Because of its versatility and efficiency, the Michael addition has found widespread application across various scientific domains, including the synthesis of natural products, pharmaceutical agents, advanced biomaterials, and functional polymers. Its utility lies not only in its tolerance for a wide range of substrates but also in its potential to introduce a variety of functional groups into conjugated systems, which is particularly useful in modifying the physicochemical properties of macromolecular structures. A noteworthy application of this reaction is illustrated by the work of Guaresti and colleagues (2019) [110], who leveraged the Michael addition mechanism to develop innovative chitosan-based materials with enhanced properties. In their study, they first modified chitosan, a naturally derived polysaccharide known for its biocompatibility and biodegradability, by introducing sulfhydryl groups using thiolactic acid. This functionalization yielded water-soluble thiolated chitosan derivatives, which served as reactive building blocks for subsequent hydrogel formation. By reacting these sulfhydryl-modified chitosan polymers (denoted as CsSH) with a bifunctional Michael acceptor specifically, a water-soluble bis-maleimide compound (BMI) they were able to induce covalent crosslinking through a sulfhydryl-Michael addition process. The result was the formation of a robust, pH-sensitive hydrogel network. The resulting hydrogels exhibited several desirable characteristics. Mechanically, they showed excellent structural integrity and a high degree of stability under physiological conditions, making them promising candidates for biomedical applications such as drug delivery or tissue engineering. The materials also demonstrated favorable in vivo degradability and thermal resistance, indicating their potential for long-term functional performance within biological environments. Notably, increasing the concentration of bis-maleimide in the formulation led to a significant rise in the hydrogel's storage modulus, indicating enhanced stiffness and mechanical strength. Concurrently, the same increase in crosslinker content also accelerated the degradation profile of the hydrogel, suggesting a tunable system wherein mechanical and degradation properties can be modulated by adjusting the crosslinking density. This dual responsiveness to compositional variations underscores the flexibility and adaptability of the sulfhydryl-Michael addition approach in designing smart polymeric materials tailored for specific applications.

The thiol-ene reaction, also referred to as the thiol-ene click chemistry, represents a highly efficient, regioselective, and versatile chemical transformation that has garnered significant attention in polymer and materials science. This reaction involves the addition of a thiol group (–SH) to an alkene (a carbon–carbon double bond), leading to the formation of a stable thioether linkage (C–S bond). This mechanism is typically initiated by Ultraviolet (UV) light or radical initiators, promoting a rapid and near-quantitative reaction that proceeds under mild conditions with high specificity and minimal byproducts. Because of these advantageous features, the thiol-ene reaction has become a powerful tool for the functionalization and post-polymerization modification of macromolecular frameworks, allowing for the precise incorporation of sulfur-containing moieties into diverse polymeric backbones. This strategy offers opportunities to tailor mechanical properties, enhance chemical stability, and introduce biological responsiveness in polymer-based materials, thus expanding their utility across biomedical, pharmaceutical, and engineering domains. A particularly compelling application of the thiol-ene reaction has been demonstrated in the design and development of chitosan-based hydrogels modified with liposomes for biomedical use. In an insightful study conducted by Li and colleagues in 2018 [111], thiol-ene chemistry was harnessed to create multifunctional hydrogels through the reaction of thiol-modified chitosan derivatives and maleate-functionalized liposomal systems. Specifically, thioglycolic acid-modified chitosan (bearing free thiol groups) was reacted with chitosan-maleate or methacrylated chitosan-coated liposomes, forming a covalently cross-linked hydrogel network via the thiol-ene mechanism. Nuclear Magnetic Resonance (NMR) spectroscopy data revealed notable shifts in the chemical environment of vinyl protons after methacrylic acid modification, confirming successful grafting onto the chitosan backbone. The resulting hydrogel matrices exhibited enhanced porosity, and their structural and functional attributes could be fine-tuned by altering the stoichiometric ratio of thiol to alkene groups (n-SH/n-C=C). These variations significantly influenced the gelation kinetics and swelling behaviors of the hydrogels, suggesting a high degree of control over their physicochemical characteristics.

Furthermore, the inclusion of liposomes within the chitosan matrix played a pivotal role in enhancing the mechanical robustness, surface morphology, and biological performance of the resulting hydrogels. Compared to native chitosan hydrogels, these thiol-ene cross-linked systems displayed a finer and more compact crystalline structure, translating to improved dimensional stability and mechanical integrity. The presence of liposomes not only imparted additional functional attributes but also contributed to better biocompatibility and potential for controlled drug delivery. These advancements highlight the superior versatility of chitosan-based hydrogels synthesized through thiol-ene reactions, where both physical and chemical cross-linking methods contribute to an expanded scope of practical applications. By facilitating the construction of structurally sophisticated and functionally rich materials, thiol-ene click chemistry continues to serve as a cornerstone for the next generation of smart polymeric systems, particularly in regenerative medicine, tissue engineering, and targeted therapeutics.

Nucleophilic ring-opening reactions are a crucial class of organic transformations that involve the cleavage of strained cyclic systems through the action of nucleophiles such as alcohols, amines, and thiols. These reactions generally occur at electron-deficient centers within cyclic molecules, especially those containing heteroatoms like oxygen, nitrogen, or sulfur. The fundamental driving force behind these reactions is the relief of ring strain and the formation of more thermodynamically stable, acyclic or expanded structures. In these processes, nucleophiles target electrophilic sites on the ring, initiating a bond-breaking and bond-forming sequence that disrupts the cyclic architecture. This typically results in the generation of reactive intermediates such as cyclic sulfur ions, sulfates, or other heteroatom-containing compounds, which can further participate in downstream modifications. These transformations are notable for their high regioselectivity and efficiency under relatively mild reaction conditions, which can include aqueous acidic media or even solvent-free systems, making them particularly attractive for applications in the synthesis of functional materials and biologically active molecules. An illustrative example of such a transformation is found in the work of Wang and colleagues (2019), who engineered a functionalized chitosan derivative through a sulfation process involving nucleophilic ring opening. In their study, chitosan was chemically modified using a combination of formamide, formic acid, chlorosulfonic acid, and N,N-dimethylformamide to produce 2-N,6-O-sulfated chitosan (2-N,6-O-SCS). This modified polymer was then immobilized on gelatin sponges to fabricate bioactive scaffolds with the capacity to act as cytokine reservoirs. During the sulfation step, the reactive chlorosulfate group from chlorosulfonic acid underwent protonation, forming a positively charged intermediate that facilitated electrophilic interaction with the nucleophilic hydroxyl groups present on the chitosan backbone. This interaction led to the cleavage of the oxygen-sulfur bond in the intermediate, followed by the formation of a new ester linkage between the sulfate group and the chitosan molecule. As a result, the hydroxyl groups of the chitosan were replaced with sulfate esters, yielding a sulfated chitosan derivative capable of enhanced biological functionality. The biological relevance of this reaction was highlighted through the scaffold's ability to selectively capture Vascular Endothelial Growth Factor (VEGF) from the bloodstream, demonstrating its potential as a localized cytokine depot. The modified scaffold exhibited the ability to promote angiogenesis by concentrating endogenous growth factors at targeted vascular sites, obviating the need for the exogenous delivery of stem or progenitor cells. This function is particularly significant in tissue engineering and regenerative medicine, as it suggests that such chemically modified biopolymers can create microenvironments conducive to neovascularization through purely biochemical means. Overall, the integration of nucleophilic ring-opening strategies in polymer chemistry represents a versatile and bio-compatible route to tailoring material properties for advanced biomedical applications [123].

Bioactive potential of chitosan-based hydrogels

Chitosan-based hydrogels have emerged as a promising class of bioactive materials, primarily due to their biodegradability, biocompatibility, non-toxicity, and renewability, which render them ideal for various applications, particularly in the food and biomedical sectors [124]. As a natural polysaccharide obtained from the deacetylation of chitin, chitosan possesses inherent functional properties that have been increasingly explored for enhancing the safety, shelf life, and nutritional value of food products [125]. Within the realm of food engineering, the antioxidant and bacteriostatic potential of chitosan hydrogels is particularly noteworthy. Antioxidants are indispensable in modern food processing, as they prevent oxidative degradation of lipids and essential nutrients, thereby preserving flavor and extending shelf life. Concerns surrounding the adverse health effects of synthetic antioxidants have intensified the demand for natural, safer alternatives [126]. Chitosan, with its intrinsic free radical scavenging ability, meets this demand effectively. For instance, studies by Hashim and colleagues demonstrated that chitosan, when combined with alginate and further loaded with bioactive components such as Omega-3 fatty acids and curcumin, forms microbeads exhibiting enhanced antioxidant performance. The incorporation of curcumin significantly elevated the antioxidant activity, as evidenced by DPPH assays and peroxide value analysis [127] The observed enhancement was attributed to polyelectrolyte complexation between cationic chitosan and anionic alginate, which stabilized the system and slowed down the oxidative degradation of encapsulated fish oils. Additionally, the complexation between chitosan and polyethylene glycol was found to regulate the release of turmeric compounds, further maintaining the antioxidant efficacy during storage. In a similar vein, Li and coworkers [128]. engineered chitosan-gelatin cryogels using tannic acid as a cross-linking agent and explored their antioxidant dynamics through peroxide and Thiobarbituric Acid (TBA) value measurements. The results indicated that the networked structure of the hydrogels, enriched with tannins' polyphenolic hydroxyl groups, effectively delayed the oxidative processes over time compared to the individual polymer constituents. The ability of chitosan hydrogels to serve as a chain-breaking antioxidant system highlights their potential as a natural preservative medium in food packaging and storage. Beyond their antioxidative function, chitosan hydrogels also serve as potent bacteriostatic agents, essential in minimizing microbial contamination in food systems [129]. Bacterial contamination not only results in food spoilage but poses significant health risks to consumers, necessitating the integration of safe and effective antimicrobial agents. The mechanism underlying the antimicrobial activity of chitosan is primarily electrostatic in nature, where positively charged $–NH_3^+$ groups in the chitosan matrix interact with the negatively charged bacterial cell membranes, leading to membrane disruption, leakage of intracellular contents, and ultimately bacterial cell death. This mechanism offers broad-spectrum activity against both Gram-positive and Gram-negative bacteria, though varying degrees of efficacy are observed based on differences in cell wall composition. In one study, Hao and collaborators developed a curcumin-loaded cyclodextrin-grafted chitosan hydrogel that exhibited substantial inhibitory effects against Staphylococcus aureus and Escherichia coli [130-132]. The superior efficacy against S. aureus was attributed to its thick peptidoglycan layer, which interacts more readily with the cationic chitosan framework compared to the lipid-rich outer membrane of Gram-negative bacteria.

Additionally, research by Wang et al. [133] introduced chitosan nanohydrogels incorporated with tanshinone, aimed at combating Streptococcus pyogenes and inhibiting biofilm formation. These hydrogels demonstrated pH-responsive release capabilities, leveraging the protonation of residual amino groups in acidic environments typically associated with infection sites. The hydrogel not only disrupted microbial cell membranes directly but also ensured sustained release of tanshinone, which exerted additional antimicrobial effects. The inhibition of biofilm formation, which was sustained over a 48-hour period with a significant reduction in biofilm density by nearly 29%, underlines the practical utility of such chitosan-based systems in addressing persistent microbial threats in food preservation and packaging. These findings collectively emphasize that chitosan hydrogels, owing to their dual function as antioxidants and antimicrobials, represent a versatile and sustainable approach in developing next-generation food safety technologies [134].

Chitosan hydrogel, a biocompatible natural polymer, is widely recognized for its safe interaction with biological systems, making it a suitable candidate for food-related applications [135]. Its use aligns with the growing demand for environmentally friendly and non-toxic materials. Evaluating its biocompatibility, particularly through cytotoxicity assays like the MTT test, ensures its safety in routine human exposure and guides the development of advanced food packaging solutions. For example, Liu et al. (2022) [136] created antimicrobial hydrogels using chitosan, gelatin, and 3-phenyl lactic acid, which showed over 90% cell viability in Caco-2 and SW480 cells, indicating excellent biocompatibility. Similarly, Fletes-Vargas et al. (2023) [137] used sodium bicarbonate to cross-link chitosan hydrogels of varying concentrations and molecular weights, and MTT tests on HT-29 cells confirmed their non-toxic nature and high metabolic activity. Further enhancement using selenium nanoparticles (SeNPs), as explored by Wu et al. (2021), [138] improved mechanical and antioxidant properties of chitosan/β-glycerophosphate hydrogels. However, this study highlighted the importance of controlling SeNP concentration, as excessive amounts led to cytotoxic effects. Collectively, these findings support chitosan hydrogel's promise as a safe and functional material, provided that its composition is carefully optimized [139].

In biosensor technology, chitosan hydrogels serve either as active or passive sensing matrices. Stimulus-responsive hydrogels, representing one category, do not contain specific receptor units; instead, they undergo reversible changes in volume, porosity, or phase in response to external physicochemical cues such as pH shifts, temperature variations, ionic strength, and external fields like magnetic or electric forces [140]. These changes can be harnessed to detect environmental fluctuations or biochemical transformations in real-time. In contrast, the second type of hydrogel biosensors often referred to as passive or functionalized hydrogels are embedded with specialized recognition elements. These can include metal ions, nanoparticles, enzymes, bioactive molecules, or even living cells. The presence of such functional agents enables these hydrogels to participate in highly specific interactions with target analytes, facilitating precise biochemical recognition and signal generation. Applications of these systems span multiple domains, including food preservation where they scavenge free radicals and prevent microbial contamination, adsorption technologies for the removal of synthetic food colorants, and the controlled, localized delivery of nutrients or bioactives in targeted nutritional interventions. Taken together, the integration of chitosan's intrinsic biocompatibility with hydrogel technology offers a versatile and tunable platform for developing advanced materials capable of addressing critical challenges in food safety, environmental monitoring, and biomedical diagnostics. Their structural adaptability, coupled with a broad range of functional customization options, continues to drive innovation in smart material systems and next-generation biosensors [141].

These systems are particularly effective in enhancing food safety and quality control, as they can detect the presence and concentration of specific biochemical compounds associated with spoilage or degradation. Among the promising technologies in this field are hydrogel-based indicators, which stand out due to their exceptional water retention and hydrophilic nature. The high moisture content of these hydrogels significantly improves their sensitivity, making them ideal for applications that rely on visible changes, such as colorimetric shifts in response to environmental variations [142]. This enhanced responsiveness enables real-time and accurate detection of quality deterioration. Moreover, when pH-sensitive sensors are strategically positioned near food products, they allow for the continuous monitoring of key microenvironmental conditions, including pH, temperature, and humidity. Gathering such real-time data plays a critical role in preserving product freshness and preventing contamination, ultimately contributing to better food safety and reduced waste across the supply chain [143].

The pH value of a food product serves as a key indicator of its acidity or alkalinity and provides essential insights into the transformations that may occur within a specific environment. This parameter is closely associated with critical aspects such as the shelf life, quality, and freshness of the product [144]. In the domain of food packaging, continuous monitoring of pH is instrumental in maintaining freshness and ensuring the product meets safety standards. Owing to the importance of pH in determining food safety and quality, the integration of pH-sensitive hydrogels into packaging materials has garnered increasing attention. These hydrogels possess the unique ability to respond swiftly and effectively to pH variations, allowing for the controlled release of bioactive agents, which offers a distinct advantage over traditional hydrogel systems [145]. Chitosan, a naturally derived polymer, exhibits notable pH sensitivity, particularly in mildly acidic environments such as those around pH 6.2. This sensitivity is attributed to chitosan's hydrophilic properties and its ability to mediate the transport of hydrogen and hydroxide ions, as well as its interactions involving the protonation and binding of $-NH_2$ functional groups [146]. A study by Athauda and colleagues in 2020 (134). introduced an innovative application in which chitosan-based hydrogels were integrated with chipless Radio Frequency Identification (RFID) resonators to impart electromagnetic properties at ultra-wideband frequencies. These sensors were engineered to operate across a pH spectrum of 4 to 10, making them suitable for detecting both acidic and basic conditions. The hydrogel demonstrated expansion under acidic circumstances and a reduction in amplitude in more alkaline settings [147]. The hydrophilic nature of chitosan facilitates ion exchange and enhances interactions between protonated amine groups and the hydrogel matrix, thereby influencing its swelling behavior. Furthermore, the ability of chitosan hydrogels to modulate the release of encapsulated compounds in response to environmental pH changes is a critical functional advantage [148]. In a study by Li et al. in 2022, chitosan was combined with Chlorella through physical cross-linking to form hydrogel beads. These beads exhibited optimal swelling in the pH range of 6 to 8, a behavior likely driven by the hydrogel's intricate three-dimensional structure and the water-retention capacity of Chlorella. Electrostatic interactions between the positively charged ammonium groups (NH_3^+) of chitosan further supported the network's expansion. The controlled-release tests confirmed that the hydrogel beads were responsive to pH shifts in their surrounding medium, demonstrating high water absorption and enhanced efficiency in the release of active components [149].

Temperature plays a pivotal role in numerous scientific and industrial domains, and materials that can respond to thermal variations are of significant interest. Among such materials, hydrogels exhibit outstanding temperature-sensitive properties, making them ideal for real-time temperature sensing in both environmental and liquid systems [150]. These hydrogels not only help in monitoring thermal conditions but also assist in regulating temperature during chemical reactions or manufacturing processes, leading to improved precision and product quality. Their ability to undergo structural or visual changes in response to temperature variations also makes them useful as indicators in applications such as drug delivery and tissue regeneration. For example, thermoresponsive hydrogels can facilitate the controlled release of therapeutics or aid in scaffold-mediated tissue repair by responding to physiological temperature shifts. These versatile applications open up new research directions in biomedical engineering, advanced drug delivery systems, and material science. A notable advancement in this area was reported by Bi and colleagues in 2020, [151] where they synthesized a Hydroxybutyl Chitosan (HBC) solution using epoxy butane in a homogeneous system comprising potassium hydroxide and urea. This approach led to the development of chitosan nanohydrogels with distinctive thermoresponsive behavior. When dispersed in deionized water, these modified chitosan derivatives demonstrated reversible amphiphilic self-assembly depending on the ambient temperature. Unlike conventional hydrogels, these nanohydrogels exhibited enhanced biocompatibility and biodegradability, alongside stable, reversible transformations in structure and color with temperature fluctuations. Experimental observations showed that increasing the temperature induced a color change from transparent to opaque, signifying heightened internal hydrophobic interactions. Conversely, cooling caused the hydrogels to transition from a uniform, spherical morphology to smaller dispersed particles, revealing the reversible nature of their thermal response. Such features underscore the potential of these temperature-sensitive hydrogels in creating intelligent systems for biomedical and industrial applications [152].

The surrounding humidity plays a critical role in shaping their water uptake behavior, release kinetics, fabrication efficiency, structural integrity during storage, and their overall functional responsiveness. Effective humidity control is essential to enhance the practical utility and stability of these hydrogels across various applications, as highlighted in earlier literature (Ahmed, 2015). In an innovative study, Shao and colleagues (2020) developed an edible, bilayer membrane system designed for directional humidity regulation [153]. This system combined hydrophobic Ethyl Cellulose (EC) as the external barrier with a hydrophilic internal layer comprising carboxymethyl chitosan and genipin. The outer EC film was fabricated via solvent casting, while the interior chitosan-based hydrogel was cross-linked with genipin, a naturally derived and biocompatible agent. The cross-linking interaction between genipin and chitosan led to a reduction in free amino groups, lowered water solubility, and improved mechanical strength, enhancing the film's structural performance [154]. This composite membrane demonstrated promising utility in food preservation, particularly for maintaining the post-harvest quality of shiitake mushrooms. Through effective moisture regulation, the membrane was able to suppress microbial growth, mitigate oxidative stress during storage, and stimulate the activity of Phenylalanine Ammonia-Lyase (PAL), an enzyme associated with the biosynthesis of bioactive phenolic compounds and anthocyanins. This indicates the hydrogel's potential not only as a functional humidity sensor but also as a smart packaging material that supports food stability and nutritional value [155].

Food preservation plays a crucial role in public health, and effective packaging is key to maintaining the freshness and safety of food over time. Conventional plastic packaging offers strong mechanical properties but presents significant environmental challenges due to its poor biodegradability, low recycling rates, and limited release of bioactive substances. In contrast, chitosan hydrogels have gained attention as sustainable alternatives, offering enhanced biodegradability and the ability to release bioactive compounds in response to stimuli such as pH, temperature, or magnetic fields [156]. These properties not only improve the stability and bioavailability of active agents but also help reduce environmental impact. Chitosan-based materials, especially in hydrogel form, are particularly valuable in food packaging due to their antimicrobial and antioxidant properties, which contribute to extending the shelf life of food without relying on chemical preservatives. Additionally, these hydrogels can manage moisture inside packages by absorbing water or exudates, helping to preserve fruits, vegetables, and meat products. For instance, hydrogels developed from double aldehyde guar gum and pomegranate peel extract combined with chitosan have shown promising results due to their porous structure, enhanced solubility, mechanical integrity, and biological activity. These hydrogels are effective in absorbing excess moisture and extending freshness. Similarly, chitosan-based nano silica hydrogel films incorporating β-acid have demonstrated excellent performance in food packaging by improving antimicrobial properties, UV resistance, and water vapor control, while also enabling the gradual release of active substances. Such innovations highlight the potential of chitosan hydrogels to serve as eco-friendly, functional packaging materials that support long-term food preservation [157].

Dye-contaminated wastewater, a significant environmental concern stemming from food industry effluents, is notoriously difficult to treat due to its non-biodegradable, chemically stable macromolecular structure [158]. Its resistance to degradation, high toxicity, and persistence in aquatic ecosystems, particularly in photosynthetic environments, poses serious threats to biological health. Among various remediation strategies, chitosan hydrogel stands out as a sustainable adsorbent owing to its low energy demands, operational simplicity, high biodegradability, and excellent dye-binding capacity. The hydrogel's pronounced swelling facilitates water and dye diffusion, enabling hydroxyl and amino groups to effectively capture dye molecules, particularly under acidic conditions where chitosan behaves similarly to cationic polymers. This property allows it to interact efficiently with anionic pollutants, thus enhancing dye removal [159].

Research by Huy Q. Le and colleagues demonstrated that activating chitosan with carbon dioxide leads to the formation of functional groups protonated amines, carbamates, and bicarbonates that increase dye affinity and hydrogel stability, especially at higher temperatures [160]. This CO_2-activated chitosan showed improved adsorption of food dyes like vivid blue FCF and

Congo red [161]. Another study by Zhang and co-researchers introduced a dual-network hydrogel combining carboxymethyl chitosan and poly(vinyl alcohol), strengthened through freeze-thaw cycles and calcium chloride crosslinking. This hydrogel's porous structure and multiple functional groups significantly enhanced dye adsorption via electrostatic, hydrogen bonding, and van der Waals interactions. Beyond wastewater treatment, chitosan hydrogels have proven valuable in controlled nutrient delivery systems. They can be engineered into beads to encapsulate bioactives like quercetin and linseed oil, as shown by Huang et al., ensuring slow release and protection against degradation [162]. These beads maintained structural integrity in simulated digestion environments, improving bioavailability. Similarly, Duffy et al. developed iron-loaded chitosan beads that exhibited excellent swelling and iron release in both water and milk, fulfilling daily nutritional requirements without affecting pH or sensory properties. These findings highlight the multifaceted potential of chitosan hydrogels in environmental and nutritional applications [163].

Table 1: Chitosan hydrogels prepared by physical methods.

Hydrogel	Primary Materials	Crosslinking Method	Crosslinking Agent	Application
Cat-CH/ Hydrogel	Sodium bicarbonate, chitosan, EDC	Physical crosslinking (ionic interactions)	Sodium Bicarbonate	Injectable Adhesion carries drug delivery vehicles
OS Chitosan based Hydrogel	Chitosan, tapioca starch, sodium periodate	Physical Crosslinking		Injectable Adhesion carries drug delivery vehicles
SG/CS Hydrogel	Succinoglycan (SG), chitosan, 5-fluorouracil	Electrostatic interactions		pH responds to changes in drug delivery systems
Dual crosslinked CMC-ALG Hydrogels	Carboxymethyl chitosan, alginate, calcium chloride, EGF powder	Electrostatic interactions		Clinical wound care
CCHs hydrogel	Carboxymethyl chitosan powder, allyl glycidyl ether (AGE), ammonium persulfate (APS), calcium chloride ($CaCl_2$)	Hydrogen Bonding Interactions, Ionic Interactions	Allyl Glycidal Ether	As flexible sensors, Wearable devices, and Energy harvesting devices
TEPA – COS hydrogel	Tetraacetylethylenediamine (TEPA), epichlorohydrin (ECH), low chitosan	Hydrogen Bonding Interactions	TEPA	
(Fe^{3+-}PCS/CSfHNTs NC hydrogel)	Acrylamide (AAm), acrylic acid (AAc), ammonium persulfate (APS), kaolin nanotubes (HNTs), hyperbranched polysiloxane (HSiv)	Ionic Interactions, hydrogen Bonding Interaction, Chemical Crosslinking	HSiv	For load-bearing structural materials
CSTPP hydrogel	Chitosan, tripolyphosphate (TPP), SQR22 dye, dimethyl sulfoxide (DMSO)	Electrostatic Interactions	TPP	
CS/SP printing inks	Chitosan powder, two-component silicone elastomer (ACEO), sulfate (SP)	Electrostatic Interactions	SP	Composite chitosan/silk particle scaffolds
Chitosan Hydrogel modified Cotton fabrics	Chitosan polymer, amylase, sodium bisulfite (Na2S2O4), monochloroacetic acid (CAA), sodium carbonate (Na2CO3), reactive dye (Supra rouge SPX)	Electrostatic Interactions		A functional cotton

Table 2: Chitosan hydrogel preparation by chemical crosslinking.

Hydrogel	Primary Materials	Crosslinking Method	Crosslinking Agent	Application
API-CS-oxCS/oxHA	Chitosan, sodium periodate, hyaluronic acid	Schiff base reaction	oxCS, oxHA	For wound care
Cn-Nm hydrogel	Chitosan, aldehyde-4-arm polyethylene glycol, amino-4-arm polyethylene glycol, potassium hydroxide, sodium chloride	Schiff base reaction	4r-PEG-CHO	Antimicrobial wound aids for traumatic wounds
PVA/dextran/chitosan hydrogel	Glutaraldehyde, polyvinyl alcohol, chitosan, dextran	Chemical Crosslinking	Glutaraldehyde	For healing of burns, bedsores, etc.
Chitosan-based isothiocyanato-trimellitic anhydride cross-linked hydrogels	Br12 dye, chitosan, Isothiocyanatotriphthalic anhydride	Chemical Crosslinking	Isothiocyanatotrityl-triphthalic anhydride	Highly Effective Alternative Adsorbents
PC/CS (PCCS) hydrogels	Chitosan hydrochloride, carboxylated polyvinyl alcohol (PC), succinic anhydride, triethylamine (TEA)	Amidation reaction	Carboxy polyvinyl alcohol (PC)	Adhesive dressings for Dynamic traumatic wounds
BC-Ch Hydrogel	Genipin, chitosan, bacterial cellulose (BC)	Chemical Crosslinking	Genipin	Drug carrier
Frozen-Thawed CMC-CSCA hydrogels	Chitosan, carboxymethyl cellulose sodium salt,	Hydrogen bonding Interactions, Electrostatic interactions	Citrate	A device for green storage of electrolytes
Hierarchical microCS hydrogel scaffold	Chitosan powder, LiOH, epichlorohydrin (ECH)	Chemical Crosslinking	Epichlorohydrin	Stents mimicking the dura mater
(CS-PEG-HA) hybridized hydrogels	Methacrylic anhydride and dibenzocyclotitani- peg4 - hydroxy succinimide ester (dbco - peg4 - nhss -ester), chitosan, 4-arm PEG-azide (2 KDa), 1-(3-dimethyl aminopropyl)-3-ethyl Carbodimide hydrochloride	Chemical Crosslinking	Polyethylene glycol	Novel materials to accelerate wound healing in the body or on the skin

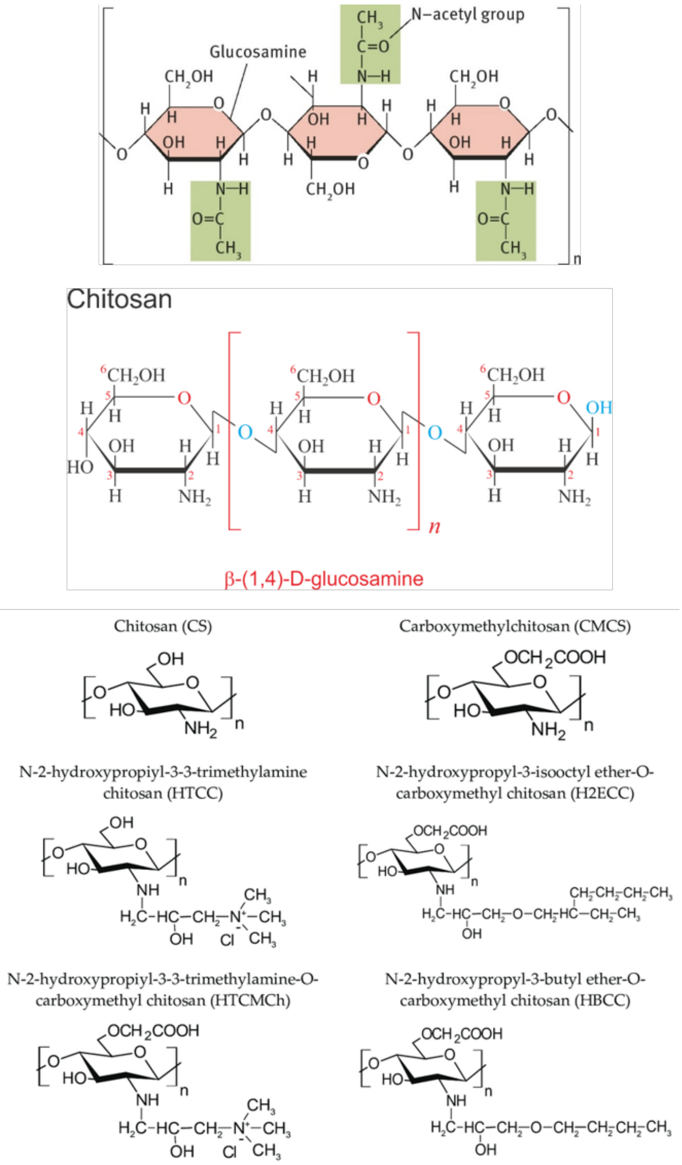

Figure 1: Structural formulas of chitosan derivatives.

Conclusion

Chitosan-based hydrogels have emerged as versatile and sustainable materials with significant potential across environmental, biomedical, and food-related applications. Their unique molecular structure rich in reactive amino and hydroxyl groups enables the formation of hydrogels with tunable properties such as swelling behavior, mechanical strength, and bioactivity. These characteristics facilitate their application in critical areas like dye wastewater remediation, where chitosan's high adsorption capacity and eco-friendly nature offer efficient removal of toxic, non-biodegradable dyes. Advanced fabrication strategies, including CO_2 activation and dual-network formation with polymers like PVA, have further enhanced their structural integrity and adsorption performance through electrostatic and hydrogen bonding interactions. In the food and nutrition sector, chitosan hydrogels support encapsulation and controlled release of bioactive compounds, ensuring nutrient stability and improved bioavailability. Their ability to function under gastrointestinal conditions while protecting sensitive compounds like quercetin and iron underscores their relevance in nutraceutical development. Additionally, chitosan hydrogels contribute to food safety through antimicrobial and antioxidant actions, aligning with green packaging innovations. The integration of these materials into biosensors and smart delivery systems highlights their adaptability in real-time environmental and physiological monitoring. As research advances, chitosan hydrogels stand poised to address pressing global challenges in sustainability, health, and food security through their multifunctional and responsive design.

Author declarations

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Conflict of interest

There is no conflict of interest regarding this article.

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