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Stimulus-Responsive Cellulose-Based Hydrogels for Drug Delivery

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Abstract. Stimulus-responsive cellulose-based hydrogels combine the advantages of being widely sourced, renewable, biocompatible, and biodegradable. With their three-dimensional porous networks and high water content, they provide an ideal environment for drug loading, diffusion, and cell growth. Through chemical modification, physical crosslinking, chemical crosslinking, or composite network design, cellulose-based hydrogels can respond to pH, temperature, light, and multi-stimuli, and achieve controlled drug release by adjusting network pore size, swelling behavior, crosslinking density, or degradation rate. This review summarizes the structural characteristics of cellulose and its derivatives, the main preparation methods of cellulose-based hydrogels, their stimulus-responsive mechanisms, and recent advances in their application for drug delivery. It focuses on their potential applications in anticancer drug delivery, wound dressings and antimicrobial delivery, ophthalmic drug delivery, oral-intestinal drug delivery, as well as tissue engineering and regenerative medicine. Finally, this paper summarizes the challenges facing these materials in terms of mechanical properties, release behavior stability, in vivo compatibility, and large-scale application, and outlines future directions for their development.

Keywords: stimulus-responsive, hydrogel, cellulose-based, drug deliver

1. Introduction

Traditional drug administration methods include oral, injectable, inhaled, transdermal, and mucosal routes, among others; however, their practical application is often limited by factors such as drug stability, bioavailability, distribution in the body, and frequency of administration. In order to boost how well a treatment works and cut down on unwanted side effects, drug delivery systems (DDS) have been getting more and more attention over time. These systems can make drugs work better—by controlling things like how fast the drug is released, where in the body it acts, and how it spreads around. To some degree, DDS also make targeted delivery and controlled-release therapy possible [1].

Among different drug delivery carriers, hydrogels are often considered suitable candidates because their internal structure is close to the basic requirements of a drug reservoir. Their three-dimensional cross-linked networks contain a large amount of water and provide spaces for drug molecules to be incorporated. More importantly, drug release from hydrogels is not only a passive diffusion process; it can also be affected by the pore structure, cross-linking density and degradation

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rate of the network [2]. Stimulus-responsive hydrogels are developed on this basis. Unlike ordinary hydrogels, they can respond to environmental changes, such as pH, temperature, light and redox conditions, and then alter their swelling state, network structure or degradation behavior. These changes further influence the release of loaded drugs. Therefore, stimulus-responsive hydrogels are more adaptable to complex physiological or pathological environments. In tumor therapy, for example, the acidic microenvironment of tumor tissues or externally applied stimuli can be used to trigger drug release at the lesion site, which may increase local drug concentration, reduce systemic toxicity and prolong the therapeutic effect.

Cellulose is often selected as a starting material for biomedical hydrogels because of its renewable origin, low cost and generally good biocompatibility. More importantly, its molecular structure contains many hydroxyl groups, which can be used for etherification, esterification, oxidation or grafting reactions. Through these modifications, native cellulose can be converted into derivatives such as carboxymethyl cellulose, methyl cellulose and hydroxypropyl methyl cellulose. These derivatives partly overcome the limited solubility and processability of cellulose and can also provide sites for constructing gel networks or introducing responsive units [3]. In this sense, stimulus-responsive cellulose-based hydrogels are not simply a combination of cellulose and hydrogels. Their value lies in linking the modifiable cellulose backbone with a network structure that can regulate drug loading and release.

This review discusses stimulus-responsive cellulose-based hydrogels from the perspective of drug delivery. Instead of treating cellulose only as a natural polymer matrix, we focus on how its molecular structure, derivative forms and cross-linked networks affect drug loading and release. The review first introduces the structural features of cellulose and commonly used cellulose derivatives, followed by a discussion of physical and chemical cross-linking methods used to construct hydrogel networks. Particular attention is then given to pH-, temperature- and light-responsive systems, since these responses directly influence swelling behavior, network stability and drug release profiles. Finally, recent applications in anticancer therapy, wound healing, ophthalmic delivery, intestinal delivery and tissue engineering are summarized, and the remaining challenges in material design and biomedical translation are discussed.

2. Structure and properties of cellulose and its derivatives

Out in nature, cellulose is one of the most abundant natural polysaccharides you can find. It mainly comes from three sources: plant cellulose, bacterial cellulose, and animal-derived cellulose. Take plant cellulose—it's the main stuff in plant cell walls and a big part of plant biomass. The good things about it? It's everywhere, cheap, and easy to use on a large scale. But there's a catch: in natural plant tissues, cellulose usually hangs out with other components like lignin and hemicellulose. So before you can actually use it, you often have to go through steps like delignification, purification, and structural modification. Now, bacterial cellulose is different. It's made by certain microorganisms, and it generally doesn't carry impurities like lignin or hemicellulose. That means it's pretty pure, with a well-developed nanofiber network. It also holds water well, has good mechanical properties, and is biocompatible. That's why it's so valuable for things like wound dressings, tissue engineering, and drug delivery carriers. Then there's cellulose of animal origin. This one mostly comes from tunicates. It has high crystallinity, good orientation, and nice structural regularity. But the downsides? Limited sources and high extraction costs. That's why it's still mostly used for lab research at this point.

If you look at it from a molecular structure standpoint, cellulose is made up of D-glucose units that are linked together in a straight line by β(1→4) glycosidic bonds [4]. But here's the trade-off:

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this tightly ordered hydrogen-bonded structure makes the material very stable, but it also means natural cellulose doesn't dissolve well in water or in most organic solvents. That poor solubility ends up limiting how we can directly process it and use it to make gels. So, to get around this and make cellulose more useful in areas like hydrogels and drug delivery, a key approach is to either chemically modify it or design composites based on it.

As shown in Figure 1, various cellulose derivatives can be produced through different modification processes. By using processes like etherification and esterification, you can attach all kinds of different substituents to the hydroxyl groups on cellulose molecular chains, which gives you a whole range of functional cellulose derivatives. Some common examples? For cellulose ethers, you've got methyl cellulose (MC), carboxymethyl cellulose (CMC), hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), and hydroxypropyl cellulose (HPC). And if you're looking at cellulose esters, cellulose acetate (CA) is a good representative. After modification, cellulose no longer behaves only as a rigid and poorly soluble polysaccharide. Substituents such as carboxyl, hydroxypropyl, methyl and acetyl groups can alter its interaction with water and surrounding polymer chains, thereby affecting hydrophilicity, dispersion, swelling and gel formation. These structural changes are also important for hydrogel design, because they create sites that can participate in cross-linking, drug loading or the introduction of stimulus-responsive components.

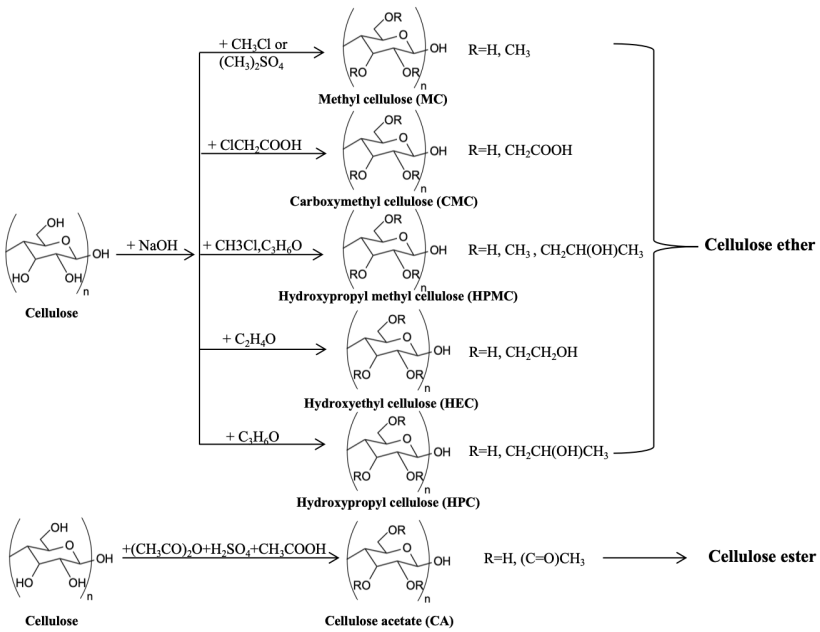

Figure 1. Different cellulose derivatives are obtained through various modification processes

3. Method for the preparation of cellulose-based hydrogels

Cellulose-based hydrogels typically form three-dimensional network structures through physical or chemical cross-linking. The choice of cross-linking method directly influences the hydrogel's pore structure, swelling behaviour, mechanical properties, degradation rate and drug release process; it is therefore a critical aspect of cellulose-based hydrogel design.

Physical cross-linking relies primarily on non-covalent interactions such as hydrogen bonding, ionic coordination and electrostatic interactions, and offers advantages such as mild processing

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conditions, high reversibility and the absence of the need for additional cross-linking agents. As the forces within a physically cross-linked network are dynamic and reversible, hydrogels are capable of undergoing a certain degree of structural rearrangement in response to external stimuli or mechanical forces, thereby exhibiting properties such as self-healing, energy dissipation and responsive release. Taking hydrogen-bond cross-linking as an example, the molecular chains of cellulose and its derivatives contain a large number of hydroxyl groups, which can form intermolecular hydrogen bonds with other hydrophilic polymers, thereby constructing a stable network structure. Poly(vinyl alcohol) (PVA)/cellulose nanofibril (CNF) hydrogels can enhance their strain at break, strength and toughness through strong hydrogen bonds and chain orientation between PVA and CNF [5]. Ionic cross-linking typically relies on the coordination of multivalent metal ions such as Ca^{2+}, Zn^{2+} and Al^{3+} with carboxyl groups to form dynamic cross-linking sites. Such coordination not only enhances network stability but also acts as a reversible sacrificial bond to dissipate energy under loading, thereby conferring on the material good self-recovery capability, deformation resistance and mechanical reinforcement. Electrostatic interactions, on the other hand, primarily form polyelectrolyte composite networks through Coulombic forces between oppositely charged species. For example, the interaction between anionic CMC and cationic polymers or chitosan can improve network stability and influence drug loading and release behaviour by modulating electrostatic interactions [6].

Compared to physical cross-linking, chemical cross-linking forms a more stable three-dimensional network structure through covalent bonds, and typically exhibits higher environmental tolerance, structural stability and sustained-release capacity. Common chemical cross-linking methods include the use of small-molecule cross-linking agents, radical polymerisation and the Schiff base reaction. Small-molecule cross-linking agents react with functional groups such as hydroxyl and carboxyl groups on cellulose chains to form stable cross-linking sites, thereby modulating the hydrogel's swelling properties, interfacial characteristics, water resistance and degradation behaviour. Radical polymerisation, on the other hand, involves the initiation of chain polymerisation of monomers by an initiator, followed by the formation of a covalent network under the action of a cross-linking agent. This method can be used to construct composite hydrogels that combine porous structures, mechanical stability and mass transfer capabilities, facilitating the loading, diffusion and sustained release of drug molecules. The Schiff base reaction is one of the commonly used methods for dynamic covalent cross-linking in cellulose-based hydrogels. It involves the condensation of an aldehyde group with a primary amine or hydrazine group to form a dynamic C=N bond, enabling the construction of networks with reconfigurability and a certain degree of pH responsiveness under mild conditions. For example, oxidized carboxymethyl cellulose/polyacryloyl hydrazide (oxi-CMC/PAH) hydrogels exhibit tunable gelation times, degradability and sustained release capabilities [7].

Overall, physical cross-linking is better suited to the development of systems characterised by mild conditions, reversible responses and good biocompatibility, whereas chemical cross-linking is more conducive to enhancing network stability, environmental tolerance and sustained-release capabilities. In practical design, these two types of cross-linking are often combined to achieve a balance between the hydrogel's mechanical support, stimulus responsiveness, degradation control and controlled drug release.

4. Stimulus-response mechanisms and drug release

What really matters here is adding responsive groups, dynamic bonds, or functional components into the cellulose hydrogel network. Once you do that, the material becomes sensitive to changes in its

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surroundings and can adjust its structure—either in a reversible way or not. When we're talking about drug delivery, hydrogels normally release drugs through a mix of processes like drug diffusion, network swelling, and degradation. But if you bring in stimulus-responsive structures, the system can react to environmental shifts by tweaking things like network pore size, how hydrophilic it is, cross-linking density, or how fast it degrades. And that means you can actually control the release rate. Compared to regular hydrogels, stimulus-responsive hydrogels don't just rely on passive diffusion anymore. Instead, the release process can be actively adjusted based on the disease microenvironment or external triggers. That's a big plus—it improves the spatiotemporal selectivity of drug release, cuts down on off-target release, and makes the whole drug delivery process much closer to what on-demand therapy really needs.

So where does pH responsiveness come from? Mostly from how ionisable groups—like carboxyl and amino groups—behave under different pH conditions. When the environment gets more acidic or more alkaline, these groups either gain or lose protons (that's protonation or deprotonation). As a result, the charge density on the polymer chains changes, which in turn affects things like electrostatic repulsion between chains, hydrogen bonding, and osmotic balance. And that's what makes the hydrogel either swell or shrink. Let's break it down for cellulose derivatives that carry carboxyl groups. Under higher pH conditions, those carboxyl groups lose protons and turn into negatively charged carboxylate groups. That increases repulsion between chains, so the network soaks up more water and swells. On the flip side, in acidic conditions, the carboxyl groups get protonated, the charge drops, and the interactions between chains get stronger. That makes the network tighten up or stay pretty stable. Now, if you're dealing with systems that have amino groups, the opposite happens—protonation under acidic conditions changes the charge state and swelling behavior too. All these shifts affect how drugs diffuse through the network and how fast they get released. That makes pH-responsive hydrogels a good fit for situations like the weakly acidic tumor microenvironment, infected wounds, and gastrointestinal delivery. Here's one example: injectable hydrogels made from oxidized carboxymethyl cellulose and hydrazine-modified CMC. They can control drug release through a pH-triggered mechanism [8].

How do hydrogels respond to temperature? Well, it usually comes down to two things: either they contain components that have a lower critical solution temperature (LCST), or they rely on a shift between hydrophilic and hydrophobic states when the temperature changes. Here's how it works. When the temperature is below that phase transition point, the polymer chains and water molecules stick together tightly through hydrogen bonding. So the hydrogel is generally more hydrophilic and stays swollen. But once the temperature rises into a certain range, that bonding weakens. Hydrophobic interactions start to take over, and the polymer chains either contract or get tangled up. As a result, the hydrogel changes its volume, its pores get smaller, or it even goes through a solution–gel transition. All of this affects how hard it is for drugs to diffuse through the network and how long they hang around inside it, which gives you temperature-controlled release. What materials are often used for this? Methyl cellulose (MC) and its blends with poly(N-isopropylacrylamide) (PNIPAm) show up a lot in temperature-responsive hydrogel designs. In these systems, temperature-induced in situ gelation helps the material stay longer at the local tissue or the drug delivery site. Meanwhile, temperature-induced network contraction gives you another way to fine-tune how fast the drug is released. One example: CNF–PNIPAm composite hydrogel microspheres. They can change their swelling behavior and drug release rate in response to temperature changes [9].

In contrast, light-responsive hydrogels can regulate drug release through molecular structural changes, the generation of reactive oxygen species, or photothermal effects when exposed to

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ultraviolet, visible or near-infrared (NIR) light. The underlying principles mainly comprise three categories: firstly, photosensitive groups undergo isomerisation, cleavage or conformational changes upon exposure to light, leading to alterations in the network structure or cross-linking state; secondly, photosensitisers generate reactive oxygen species upon illumination, which in turn trigger localised chemical reactions, network degradation, or antibacterial/antitumour effects; and thirdly, photothermal components absorb light energy and convert it into thermal energy, causing a localised rise in temperature, thereby inducing hydrogel contraction, changes in pore size, or accelerated drug diffusion. Compared with endogenous stimuli such as pH and temperature, light stimulation offers greater spatiotemporal controllability and can be precisely triggered externally by adjusting the wavelength, intensity and duration of illumination. For example, alginate/2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-oxidized CNFs/polyacrylamide interpenetrating network hydrogels can promote drug release under UV irradiation [10].

Multi-stimulus-responsive systems can further combine signals such as pH, temperature, light and redox potential to enable multidimensional recognition of complex physiological environments and more precise control of drug release. The design approach typically involves incorporating multiple responsive units—such as ionisable groups, thermosensitive segments, photosensitive components or dynamic chemical bonds—into a single hydrogel network, enabling the material to respond synergistically to multiple stimuli. Compared to single-responsive systems, multi-responsive hydrogels are better suited to complex microenvironments such as tumours, infected wounds or the gastrointestinal tract, and enhance release selectivity by combining endogenous and exogenous stimuli. During drug release, the responsive behaviour may alter the hydrogel's pore size and swelling degree, or induce the cleavage of dynamic bonds or network degradation; consequently, the release profile is typically influenced by a combination of material composition, cross-linking density, stimulus intensity and the properties of the drug molecule.

5. The application of stimulus-responsive cellulose hydrogels in drug delivery

Stimulus-responsive cellulose hydrogels have been applied in various fields, including anticancer drug delivery, wound dressings, ophthalmic drug delivery, oral-intestinal drug delivery, and tissue engineering. Because different applications come with their own physiological environments and treatment needs, the design of hydrogels should pay close attention to a few key things. These include how they respond to stimuli (response mechanisms), how strong or flexible they are (mechanical properties), how they break down over time (degradation behaviour), and how they release drugs (drug release profiles). Table 1 gives you a summary of representative cellulose hydrogel systems for each of these application areas. Then, in the discussion that follows, we'll take a closer look at how these systems work when it comes to drug delivery.

Table 1. Representative applications of stimulus-responsive cellulose-based hydrogels in drug delivery

Drug Delivery Applications	Types of cellulose hydrogels	Stimulus-response type	References
Anti-tumour drug delivery	CMC-CHO hydrogel	pH/light response	[11]
Wound dressings and antimicrobial drug delivery	CMC/HEC-PDA hydrogel	pH response	[12]
Ophthalmic drug delivery	HA/MC/PEO-b-PLA hydrogel	Temperature response	[13]
Oral and intestinal drug delivery	CCS/CMC-Na hydrogel	pH response	[14]
Tissue Engineering and Regenerative Medicine	CS/CNFs-CNC hydrogel	pH/temperature response	[15]

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5.1. Anti-tumour drug delivery

When it comes to delivering anticancer drugs, pH/light-responsive cellulose hydrogels can take advantage of two things at once: the slightly acidic microenvironment inside tumours, and external light stimulation. Together, they help control how the drug gets released. Here's the trick—NIR light has good tissue penetration and can be controlled from outside the body. It warms up the hydrogel through a photothermal effect, which speeds up drug release. Meanwhile, the pH response uses the tumour's natural weak acidity to keep a baseline level of release going. Let's look at an example. Researchers built a pH/light-responsive composite cellulose hydrogel using aldehyde-functionalized CMC (CMC-CHO) and a thermosensitive copolymer. This system can load up doxorubicin (DOX) and let it go in the tumour's weakly acidic environment. Then, when you hit it with NIR irradiation, the photothermal effect not only pushes DOX out faster but also causes local thermal ablation. The result? A combined punch of chemotherapy and photothermal therapy that works better together [11]. So, bottom line: pH/light-responsive cellulose hydrogels can link the tumour's own internal environment with external light control. That makes them a pretty promising option for making drug delivery more precise and boosting the effectiveness of local treatment.

5.2. Wound dressings and antimicrobial drug delivery

The processes of wound healing and antimicrobial drug delivery can be facilitated by pH-responsive cellulose hydrogels, which enable the controlled release of antimicrobial agents. When a wound happens or gets infected, the local pH changes—it shifts depending on how far along the healing process is and how bad the infection is. And that makes pH a pretty useful internal trigger. If you design the hydrogel with ionisable structures or dynamic bonds, it can adjust its network structure, how it swells, and how drugs move through it under specific pH conditions. For wound treatment, the value of this design lies not only in drug loading, but also in whether the dressing can maintain an effective antimicrobial level over time. In a reported pH-responsive CMC/HEC-polydopamine (CMC/HEC-PDA) composite hydrogel, the dual-network structure enabled a drug-loading capacity of approximately 80%. More importantly, the hydrogel retained antimicrobial activity for about five days, suggesting that it may help reduce repeated dosing and provide more continuous anti-infective protection at the wound site [12].

5.3 Ophthalmic drug delivery

Temperature-responsive cellulose-based hydrogels can be applied as a solution and then form a gel on the ocular surface. Compared with conventional eye drops, this in situ gelation process can prolong the residence time of drugs on the corneal and conjunctival surfaces, which helps maintain local drug concentration and reduce repeated dosing. In the HA/MC temperature-responsive hydrogel combined with PEO-b-PLA nanoparticles, the two components play different roles. The HA/MC matrix allows in situ gel formation after administration, whereas the nanoparticles support sustained drug release. This formulation released the drug for about 24 h and enhanced corneal permeability and tissue uptake, indicating that the combination of a responsive hydrogel matrix and nanocarriers can improve the overall efficiency of ophthalmic drug delivery [13].

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5.4. Oral and intestinal drug delivery

In oral and intestinal drug delivery, the marked pH differences along the gastrointestinal tract are not only a challenge for drug stability, but also a useful trigger for site-selective release from pH-responsive cellulose-based hydrogels. Here's how it usually works. These systems stay fairly stable in the acidic environment of the stomach—that's to keep the drug from being released too early. Then once they reach the intestine, conditions change. The hydrogels start to swell, break apart, or shift their network structure, which helps the drug get released right where it's needed. That makes the treatment more effective at the target site. Take carboxylated chitosan/sodium CMC (CCS/CMC-Na) composite hydrogels as an example. They can form a stable structure in stomach acid, but then gradually fall apart and release the drug once they get into intestinal conditions. On top of that, they also show targeted adhesion to inflamed colonic tissue. All of this points to their potential for use in targeted intestinal drug delivery [14].

5.5. Tissue engineering and regenerative medicine

Tissue engineering and regenerative medicine place high demands on scaffold materials in terms of mechanical support, cell compatibility and the ability to deliver bioactive molecules. Stimulus-responsive cellulose hydrogels possess high water content and a porous network structure, enabling them to mimic the natural extracellular matrix and provide a suitable microenvironment for cell adhesion and proliferation; simultaneously, their responsiveness to factors such as temperature and pH helps to regulate the gelation process, mechanical properties and the cellular microenvironment. Here's one example: an injectable composite hydrogel made from chitosan (CS) and CNFs-CNC. At body temperature, it goes through a solution–gel transition. Then, when you combine that with pH regulation, you can get in situ gelation and also fine-tune its mechanical properties. That makes it a good fit for things like loading cells and regenerating bone tissue. Adding CNC into the mix speeds up how fast the gel forms and improves its mechanical strength, all while keeping good compatibility with cells. So it really shows promise for use in bone tissue engineering Here's one example: an injectable composite hydrogel made from chitosan (CS) and CNFs-CNC. At body temperature, it goes through a solution–gel transition. Then, when you combine that with pH regulation, you can get in situ gelation and also fine-tune its mechanical properties. That makes it a good fit for things like loading cells and regenerating bone tissue. Adding CNC into the mix speeds up how fast the gel forms and improves its mechanical strength, all while keeping good compatibility with cells. So it really shows promise for use in bone tissue engineering [15].

6. Conclusion

Stimulus-responsive cellulose hydrogels combine the advantages of cellulose, including its wide availability, renewability, good biocompatibility and biodegradability. Their three-dimensional porous network and high water content not only facilitate drug loading and diffusion, but also provide a suitable environment for cell adhesion, growth and nutrient exchange. Through chemical modification or composite design, functional groups such as hydroxyl and carboxyl groups in the cellulose molecular chains can be further utilised for cross-linking or responsive structure formation, enabling the hydrogels to respond to stimuli such as pH, temperature, light and redox conditions, thereby allowing for the regulation of drug release rates and release sites. Consequently, these materials demonstrate significant application potential in fields such as anticancer therapy, wound repair, ophthalmic drug delivery, oral-intestinal delivery and tissue engineering.

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However, stimulus-responsive cellulose hydrogels still face a number of challenges before they can be put into practical use. Firstly, some hydrogels have inadequate mechanical properties, which may lead to structural deformation or reduced stability during long-term implantation, tissue repair, or in dynamic physiological environments. Secondly, the drug release behaviour and the hydrogel degradation process still need to be better aligned; if degradation occurs too rapidly, it may result in a sudden surge in drug release, whilst if it is too slow, it may impair effective drug delivery. Furthermore, the in vivo environment is complex, and factors such as pH, enzymes, ionic strength and metabolic processes may all affect the responsiveness and release efficiency of the hydrogels. In the future, mechanical strength and structural stability could be enhanced by developing dual-network, multi-crosslinked or physico-chemical synergistic crosslinking systems; the drug release process could be optimised by regulating crosslinking density, pore structure, degradation rate and stimulus response thresholds; and research into in vivo safety, long-term degradation behaviour and clinical suitability could be intensified, thereby facilitating the transition of stimulus-responsive cellulose hydrogels from laboratory research to practical drug delivery applications.

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