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REVIEW ARTICLE

Oxidized Polysaccharides as Green and Sustainable Biomaterials

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Abstract: Polysaccharide-based materials have been widely used as the first-choice candidates for various applications, especially in the field of biomaterials. The primary reasons for this are the sustainable nature of these materials and their high bioavailability. Their ability to be easily chemically modified enables them to be utilized in various avenues, with oxidation of the backbone being one of the most common chemical modifications. Additionally, these materials degrade *via* different pathways (enzymatically and chemically) and are hence ideal candidates for biomedical applications. This review summarizes the recent progress made with different oxidized polysaccharides and their potential applications to the field of biomaterials.

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Keywords: Polysaccharides, biodegradation, carbohydrate polymers, schiff base, sustainable, biomaterials.

1. INTRODUCTION

The establishment of a novel degradable *in vitro* model that is applicable in the preclinical phase of drug development has been the most sought-after goal of researchers in the field of materials science. Polysaccharides are promising materials that offer advantages such as abundance, biocompatibility, and biodegradability. They are one of the most abundant and widely used polymers and are composed of monosaccharide units linked together with glycosidic bonds. Polysaccharides are classified as green materials, which are naturally derived and biodegradable, and are hence employed as green alternatives for various applications [1-3]. They are widely utilized for biomedical applications because of their safety, non-toxicity, and bioavailability [4]. An important property of these molecules that is widely exploited is the ease with which their chemical structures can be modified to introduce different functionalities for various applications. The biodegradability of these molecules is another important property that is frequently utilized to develop drug delivery systems (DDSs) and tissue engineering scaffolds.

Hydroxyl groups in the backbones of polysaccharides can be chemically modified to immobilize drugs for the development of pre-drugs and cross-linkable functional groups for hydrogel formation. Many hydrophobic drugs such as paclitaxel, classified as an anticancer agent, are difficult to inject into the human body, and toxic solvents are required for this purpose. Conjugation of hydrophobic drugs onto polysaccharides has been intensively studied as a possible solution, because of the high water solubility of the latter. *In situ* cross-linked compounds are also promising biomaterials for cell therapy and DDSs as implantable injectable hydrogels, whose mechanical properties, gelation time, and biodegradability can be optimized [5]. Many researchers have focused on developing modified polysaccharides by tuning their functionality. For example, ester bonds have been introduced in dextran hydrogels for cross-link points *via* click chemistry to control the degradability [6]. Enzymatic cross-linking *via* tyramine-modified polysaccharides has been used to enhance mechanical properties [7]. These well-tuned conjugations enhance control over the sustained release of drugs as well as their pharmacokinetics, bioavailability, metabolism, and elimination [8, 9]. In addition, polysaccharides are being used as surgical biomaterials such as bioadhesives, wound healing materials, and anticlotting materials after optimized functionalization. Polysaccharides can be enzymatically degraded using different enzymes such as hydrolases, lyases, and phosphorolases, as they can all cleave glyosidic linkages [10]. Chemical degradation offers interesting alternatives, and the potential to control the degradation rate.

2. OXIDATION OF POLYSACCHARIDES AND ITS ADVANTAGE

The targets of functionalization of polysaccharides are generally the abundant hydroxyl groups in their main chains. Oxidation of hydroxyl groups directly introduces carbonyl or carboxyl groups into polysaccharides. For instance, hydroxyl groups at the C2, C3, and C6 positions in pyranosides are the target of various oxidants. Full oxidation has been carried out using strong acids such as nitric acid to produce aldaric acid compounds. On the other hand, selective oxidation has been attempted using mild oxidants such as nitrogen dioxide, the stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), periodates, and hypochlorite. Using nitrogen dioxide, the hydroxyl groups at the C6 position can be selectively oxidized to yield 6-carboxy cellulose or 6-carboxy starch from cellulose and starch, respectively. 6-Carboxy cellulose finds clinical application as a hemostat material [11]. TEMPO-mediated oxidation has been recently reported, and it is one of the most promising methods for the production of polyuronic acids. The advantages of TEMPO-mediated oxidation are a high reaction rate, high selectivity, and moderate molecular degradation; however, there are some drawbacks such as high cost and environmental impact due to the use of halide-based reagents. Many re-

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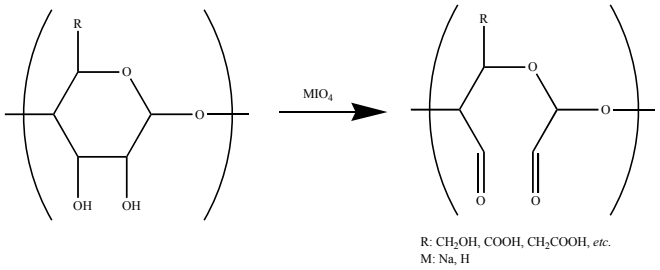
views on TEMPO oxidation provide more detailed information [12, 13].

Periodates selectively oxidize vicinal hydroxyl groups to cleave and form dialdehydes or diketones *via* a process called Malaprade oxidation. This reaction has been utilized for the functionalization of polysaccharides because they have many 1,2-diol moieties in their main chains [14]. Owing to the high reactivity of the introduced aldehyde groups, oxidized polysaccharides can react with amino-group-containing materials to form Schiff bases. This reaction has been widely used to synthesize versatile building blocks for the fabrication of functional materials *via* hydrogel formation and drug conjugation for biomedical applications. Scheme **1** illustrates the general oxidation of polysaccharides by periodates. Table **1** shows a brief summary of the biomedical applications of various oxidized polysaccharide materials.



Scheme 1. Polysaccharide oxidation by periodates.

The side products of the periodate oxidation are generally iodine compounds, especially sodium iodate, which are potentially hazardous. Although sodium iodate has been approved by the European Union for use as a preservative in rinse-off personal care products at low concentrations, safety concerns such as fire risk, effects on the retina, and other pharmacological effects remain (for further details, refer to the final report [15].) in addition to various environmental effects such as the difficulty in elimination from wastewater. To circumvent this problem, an ideal strategy would be to minimize the use of periodates, and this can be achieved by recycling and reusing them. From the viewpoint of sustainability, sodium periodate is recyclable and regenerative *via* electrochemical oxidation production. Using such a green system, more than 93% of periodate has been regenerated during dialdehyde cellulose production [16]. In this review, we provide an overview and summarize the recent advances in the biomedical applications of many periodate-oxidized polysaccharides. In addition, we provide a perspective on the future directions of oxidized polysaccharide materials for clinical applications.

3. STARCH AND DEXTRAN

Starch and dextran are water-soluble polysaccharides with glucose units joined by glycosidic bonds. Starch consists of two major components: poly(1,4-α-D-glucopyranose) (amylose) and branched poly(1,4-α-D-glucopyranose) with approximately 5% branches of(1,6-α-D-glucopyranose) (amylopectin). Starch is widely utilized for chemical modification in biomedical applications owing to its non-toxicity, biodegradability, and sustainability. However, poor processability due to its relatively high solution viscosity and poor thermal and mechanical properties limit its widespread application [70]. Generally, starch should be chemically modified by graft polymerization of the hydroxyl groups, or blended with other materials such as poly(vinyl alcohol), cellulose acetate, and poly(lactic acid) to enhance its thermal and mechanical properties for appropriate biomedical applications. Graft polymerization can be initiated from the aldehyde obtained in periodate oxidation without using harsh conditions. Periodate oxidation and subsequent reductive amination with propargylamine introduces a clickable alkyne moiety to react with azide-functionalized initiators for graft polymerization and thus produce amylose-methacrylate [71]. A similar click chemistry strategy to prepare amphiphilic amylose-*g*-butyl methacrylate for self-assembled nanomaterials has also been reported [72]. Oxidized starch can be utilized for hydrogel precursors that can be reacted with polyamine compounds such as chitosan for bioadhesive applications [61]. The molar ratio of amine and aldehyde and the pH are important parameters to control the gelation time and adhesion strength. Hydrogel formation has been rigorously studied for wound healing, DDS, and tissue engineering applications. The heat-induced self-contracting properties of the hydrogel formed by oxidized starch and gelatin enable its use as a wound closure material [57]. Fig. (**1**) shows a schematic illustration of wound closure and healing by an oxidized starch hydrogel, and the *in vivo* results. An oxidized starch hydrogel with chitosan has been tested as a bone tissue engineering material. A porous nanofiber mat prepared by combination with calcium-phosphate-coated polycaprolactone nanofibers showed spread and anchored osteoblasts on the scaffold [26].

Dextran is another type of glucopyranose polymer derived from fermentation that is mainly connected *via* (α1-6) glycol bonds. This polysaccharide has unique properties in that it can be dissolved in cold water and has a lower solution viscosity than starch. In addition, it can be dissolved in polar organic solvents such as dimethyl sulfoxide. These properties make dextran a good candidate for chemical modifications for many kinds of applications, including biomaterials. Dextran has been utilized as a plasma expander owing to its non-toxicity and biodegradability. Periodate-oxidized dextran has versatile applications, especially in the biomedical field, as a bioadhesive, a DDS carrier, a cell scaffold, and nanoparticles. Chan-Park group used oxidized dextran for a cell scaffold hydrogel [17, 18]. In their experiments, methacrylate and aldehyde were introduced into one dextran molecule, and firstly reacted with gelatin to form a hydrogel *via* Schiff base formation, and then crosslinked at the methacrylate part using UV rays for interpenetrating network formation. The oxidized dextran methacrylate formed a hydrogel with methacrylate-introduced gelatin upon UV irradiation, and aldehyde was used for conjugation of some other molecules. The mechanical properties and swelling ratio were well controlled by changing the rate of introduction of methacrylate into both oxidized dextran and gelatin. Chan-Park *et al.* successfully performed 3D smooth muscle cell culture and vascular tissue engineering using these hydrogels.

Historically, fibrin glue has been used for hemostasis in surgery, even though there is a risk of infectious transmission due to its biological origin. Therefore, the development of synthetic or safe bioadhesives is a pressing need. Oxidized dextran and polyamine combinations are good candidates for safe bioadhesives. Hyon *et al.* have reported oxidized dextran and epsilon poly-L-lysine combination bioadhesives for articular cartilage [58] ocular surface [59] and lung surgery [60] applications. These in situ forming hydrogel-based adhesives showed higher adhesion strength than fibrin glue, and interestingly, their biodegradation could be controlled by modifying the amount of amine and aldehyde. For DDS applications, glucose-responsive insulin release has been demonstrated using oxidized starch and dextran. In addition, an oxidized dextran and poly-L-lysine combination has been tested as a gene delivery material by utilizing the cationic nature of poly-L-lysine [52]. Owing to

Table 1. Various applications of oxidized polysaccharides in biomedical engineering.

Application		Oxidized Polysaccharide	Technology Used	Refs.
Tissue engineering	Vascular	Dextran CMC Alginate	Hydrogel with methacrylate gelatin Hydrogel with gelatin Cross-linked decellularized aorta	[17-20]
	Bone	Alginate Alginate Alginate Alginate Bacterial cellulose Starch	Hydrogel with gelatin +Bioglass, Bone tendon interface Oxidized methacrylate alginate MG63 for bone regeneration +Hydroxyapatite PCL nanofibers with chitosan	[21-26]
	Cartilage	Chondroitin sulfate Alginate Alginate hyaluronan	Hydrogel with chitosan Hydrogel with gelatin Hydrogel with hyaluronan Chondrocyte encapsulation	[27-30]
	Heart	Hyaluronan	Coronary artery angiogenesis	[31]
	Nucleus pulposus	Hyaluronan	Injectable hydrogel with ADH	[32]
	Cornea	Hyaluronan Alginate Alginate	Gelatin nanoparticles Hydrogel with hydroxyl propyl chitosan Porous hydrogel with calcium ions	[33-35]
	Meniscus	Alginate Alginate	Hydrogel with gelatin Hydrogel with chitosan / CPP	[36-37]
	Peripheral nerve	Bacterial cellulose	Lyophilized oxidized bacterial cellulose scaffold	[38]
	Bladder	CMC	Cross-linked bladder acellular matrix	[39]
	Cell scaffolds	Galactomannan Cellulose CMC	Hydrogel with chitosan Porous biodegradable cellulose Reinforcement of sericin film	[40-42]
DDS	Anti-cancer drug Insulin	Alginate Alginate Citrus pectin Dextran Starch	Encapsulation of Dox pH-responsive docetaxel release Dox release from hydrogel with ADH Glucose-responsive release Glucose-responsive release	[43-47]
	Phenolphthalein (model drug)	Cyclodextrin	Hydrogel with CMC	[48]
	Photothermal therapy	Alginate Dextran	Combination with Dox Combination with Dox	[49-50]
	Acyclovir (antiviral)	Chitosan	Transdermal delivery from nanofibers	[51]
	Gene	Dextran	Hydrogel with polylysine	[52]
Wound healing		Alginate Alginate Cellulose Chitosan Starch	Hydrogel Hydrogel with gelatin Hydrogel with chitosan Crosslinking with porcine acellular dermal matrix for antibacterial Hydrogel with gelatin	[53-57]
Bioadhesive		Dextran Dextran Dextran Starch Pullulan	Articular cartilage adhesion Ocular surface adhesion Prevention of air leakage from lung Hydrogel with chitosan Mucoadhesive	[58-62]
Antimicrobial		Alginate+gelatin Cellulose Xanthan	Hydrogel Nanofibrillated cellulose for MRSA Film with gelatin	[63-65]
3D printing		Alginate Alginate Cellulose Dextran	Hydrogel with gelatin Hydrogel with gelatin microparticles Hydrogel with gelatin Hydrogel with gelatin	[66-69]

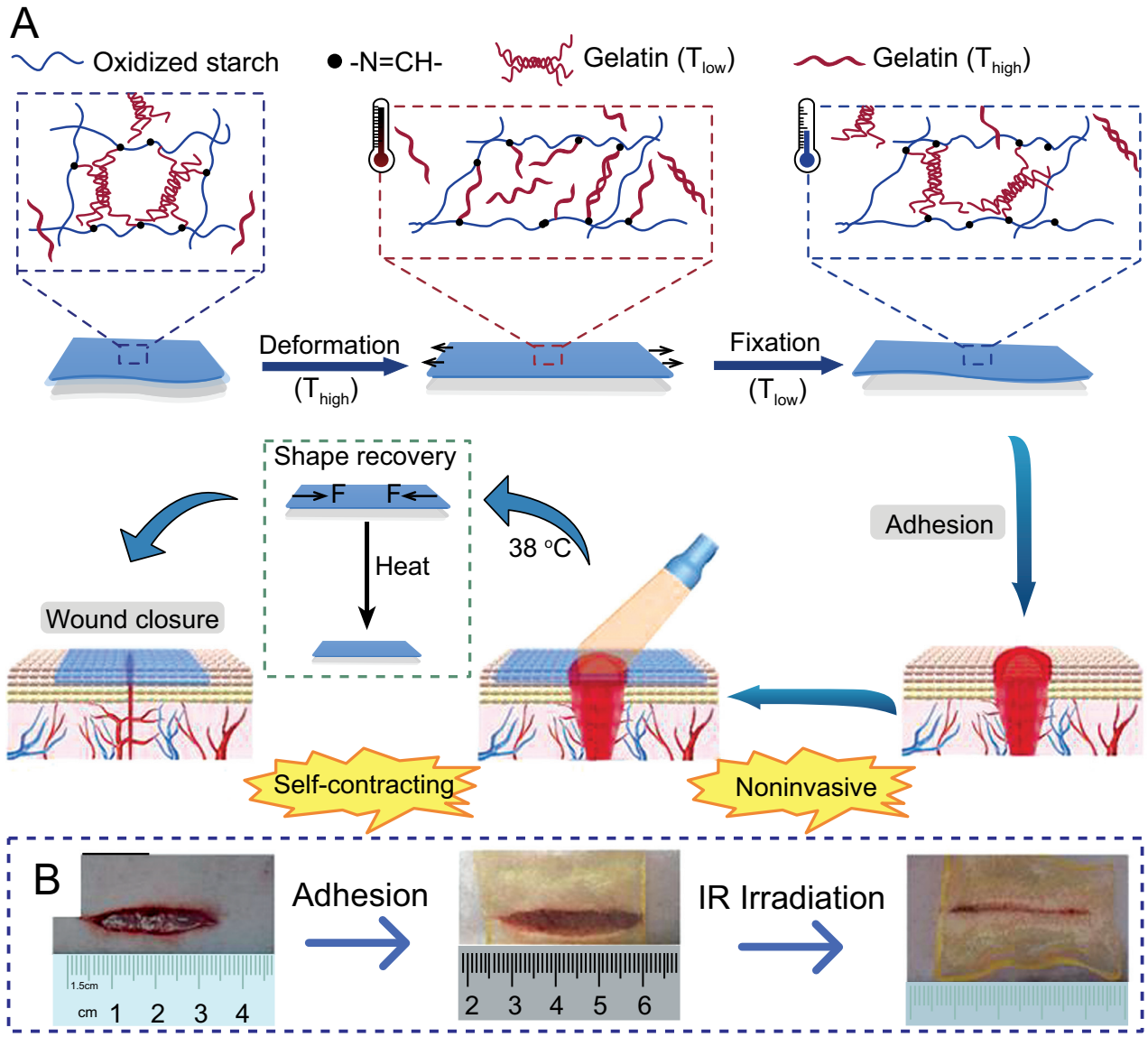


Fig. (1). (**A**) Schematic representation of self-contracting oxidized starch gelatin (OSG) for noninvasive wound closure and healing. (**B**) Noninvasive wound closure effect of self-contracting OSG applied on a dorsal full-thickness incision model with infrared (IR) irradiation for heating. Reproduced with permission from Ref. [57], under Creative Commons CC-BY-NC-ND license. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

the ease of its preparation and characterization, the molecular structure of oxidized dextran has been reported by many researchers [73]. Its degradation is related to its structure before and after reaction with amine compounds. The degradation mechanisms and applications are presented in detail in the following section.

4. CELLULOSE

Cellulose is one of the most abundant polysaccharides in the world. However, crystal formation *via* hydrogen bonding between hydroxyl groups, because of its linear and highly regular structure, makes cellulose difficult to dissolve in general solvents. This has limited its application as a biomaterial. Recently, cellulose nanofibers have attracted much attention in the field of biomaterials because of their easy dispersibility in water, eco-friendliness, and reinforcing effects when incorporated into composite materials [74, 75]. Facile production of cellulose nanocrystals (CNCs) using periodate oxidation of lignocellulose has been reported [76]. This oxidation method has various advantages over current systems to produce CNC, including the direct use of biowaste, mild stirring conditions, lack of requirement for pre/post treatments, and scalable production. Larsson *et al.* first synthesized nanocellulose using periodate oxidation and a reduction by $NaBH_4$ to prepare a shell-core modification of nanopaper with a breaking strength of 175 MPa and a breaking strain of 15% [77]. This protocol can be a powerful tool in biomedical applications for the preparation of strong biodegradable, biocompatible nanocellulose sheets. Nanocellulose-based antibacterial materials are one of the most advanced biomedical applications [78]. There are many types of surface modifications to

convert nanocellulose into antimicrobial materials, such as the introduction of quaternary ammonium functional groups, and conjugation of various antibiotics and silver/gold nanoparticles. Periodate oxidation of nanofibrillated cellulose enhanced its antibacterial properties against *Staphylococcus aureus* and multidrug-resistant *S. aureus* (MRSA) with good wound healing ability (Fig. **2**), and this activity increased with the aldehyde content [64]. Oxidized nanofibrillated cellulose also displayed good biocompatibility and blood compatibility.

Oxidized cellulose is also utilized as a crosslinker for film formation with chitosan [79] or hydrogel formation with poly(vinyl alcohol) [80]. The crosslinking reaction occurs between aldehyde and amine or hydroxyl groups; therefore, the ratio of these functional groups in the system affects the mechanical properties and stability of the composite materials.

Cellulose has been reported to dissolve in ionic liquids, although it does not dissolve in water. After dissolution in an ionic liquid, it can form porous scaffold materials *via* salt leaching. It has been reported that periodate oxidation of these cellulose porous scaffolds produced biodegradable cytocompatible scaffolds [41]. According to the report, aldehyde groups introduced into cellulose react with amino groups of protein and undergo degradation. In addition, protein binding *via* a Schiff base onto the surface of oxidized cellulose may enhance cell adhesion. This can support the easy production of tissue engineering scaffolds from bio-resources. In addition, bacterial cellulose has been extensively studied for biomedical applications because of its high biocompatibility and mechanical properties, which resemble those of soft tissue. Therefore, to introduce functionality and degradability, oxidation has been proposed for various tissue engineering applications. For bone tissue engineering, oxidized bacterial cellulose was combined with hydroxyapatite *in vitro*, and it showed good biodegradability [25]. Oxidized bacterial cellulose has also been studied as a peripheral nerve scaffold, and the results showed that suitable degradation could be achieved while maintaining mechanical properties by optimizing the oxidation degree [38].

Methyl cellulose and carboxymethyl cellulose (CMC) are water-soluble cellulose ester derivatives with an amphiphilic character and a range of substitution degrees from 1.4 to 2.5. Methyl cellulose is used in the cosmetic and food industries and exhibits a unique thermoresponsive sol-gel transition. Oxidized methyl cellulose has been studied for decreasing the molecular weight and enhancing the flexibility of the cellulose backbone *via* periodate oxidation [81]. It forms biocompatible hydrogels with chitosan and adipo-dihydride-introduced hyaluronan. CMC has COOH groups in the backbone, and can hence be easily modified with esterification, amidation, *etc.* For example, tyramine-introduced CMC that underwent enzymatic hydrogelation with peroxide was used for 3D cell culture [82]. In addition, oxidized CMC has been applied as a cross-linking agent of silk sericin to reinforce the sericin film [42]. Sericin is a protein produced by the silkworm and it behaves like an amorphous material due to its 63% random coil structure. It shows low toxicity and immunogenicity, and promotes cell adhesion and proliferation [83]. Owing to its amorphous structure, sericin exhibits low mechanical properties and water solubility, and hence faces difficulties in industrial applications. Oxidized CMC crosslinks sericin *via* Schiff base formation and successfully produces a film with good stability and blood compatibility, promoting cell proliferation for wound healing materials. Oxidized CMC has been employed for bladder regeneration by cross-linking with a bladder acellular matrix [39]. In the study, oxidized CMC was developed to replace glutaraldehyde, which is a highly toxic cross-linker for the bladder acellular matrix.

5. ALGINATE

Alginate is a natural polysaccharide that consists of guluronate and mannuronate units, and is extracted from seaweed. The unique property of divalent cations that are ionically cross-linked *via* polyguluronate blocks has been widely utilized in the food industry and biomedical field. Cell encapsulation to avoid immune rejection of alginate hydrogels has been utilized for islet transplantation [84-86]. In addition, alginate hydrogels can protect encapsulated cells from ice crystal formation during cryopreservation [87]. Mooney *et al.* investigated alginate [88, 89] and oxidized alginate [90] hydrogels as tissue engineering scaffolds. Even when 4.9% of the uronate groups were oxidized by periodate, the oxidized alginate aqueous solution maintained hydrogel formability in the presence of calcium ions [90]. The oxidized alginate hydrogel cross-linked by calcium ions showed poorer mechanical properties compared with normal

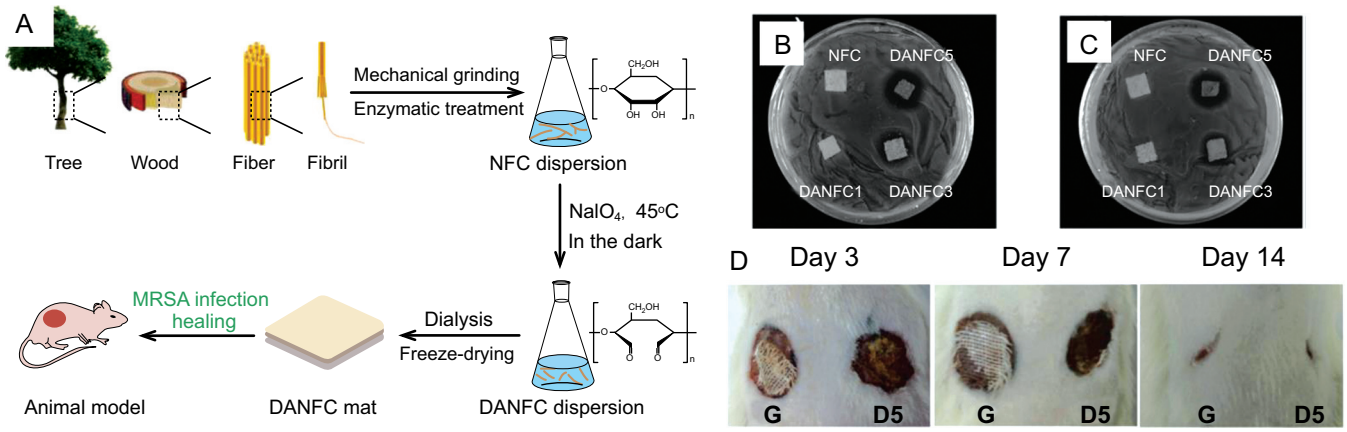


Fig. (2). Scheme of the experimental process and wound healing of the rat model (**A**). Inhibition zone of nanofibrillated cellulose (NFC) and dialdehyde nanofibrillated cellulose (DANFC) against (**B**) *S. aureus* and (**C**) against MRSA, (**D**) the recovery process of wound, with G and D5 on behalf of gauze and DANFC5 mat. DANFC1, DANFC3 and DANFC5 are respectively 2,3-dialdehyde nanofibrillated cellulose with reaction time of 1h, 3h and 5h. Reproduced with permission from Ref. [64], Royal Society of Chemistry, 2017. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

alginate hydrogels, but showed good biodegradability in the main chain, leading to the degradation of the hydrogel, which showed improved cartilage-like tissue formation[90] and was utilized for tissue engineering materials [91, 92]. Oxidized alginate also formed a hydrogel with gelatin in the presence of borax *via* Schiff base formation [93]. Owing to the relatively poor cell adhesion on the ionic cross-linked alginate hydrogel, gelatin was utilized as the gelation agent against oxidized alginate with cell adhesion sequences. In this experiment, the gelling time could be controlled within 1 min by varying the aldehyde and borax concentrations for hepatocyte encapsulation. Similarly, it has been reported that attachment, proliferation, spreading, and viability of human dermal fibroblasts are enhanced on gelatin-oxidized alginate hydrogels as the drawbacks of poor cell adhesion and uncontrolled degradation are overcome [94]. Oxidized alginate has been intensively studied as a bone and cartilage tissue engineering material. Sarker *et al.* revealed that human adipose-derived cells show osteogenic differentiation in oxidized alginate hydrogels with gelatin that have a highly interconnected porous morphology [21]. Furthermore, an application of oxidized alginate-based microparticles for bone tissue engineering has been reported by Alsberg and co-workers [23]. Methacrylate-introduced oxidized alginate was mixed with methacrylated gelatin to form coacervate microparticles. The osteogenic differentiation of human mesenchymal stem cells was enhanced upon the incorporation of BMP-2 into the microparticles. For cartilage tissue engineering, Balakrishnan *et al.* enhanced glycosaminoglycan deposition of chondrocytes by incorporating differentiation factors in the hydrogel [28]. Corneal tissue engineering has also been attempted using oxidized alginate hydrogels. Liang *et al.* investigated in situ hydrogel formation with hydroxypropyl chitosan for *in vivo* corneal endothelium regeneration [34]. After 120 days of transplantation of encapsulated corneal endothelial cells on Desemet's membrane, the recovery of corneas to a normal state was observed. Wound healing applications that utilize the non-toxicity and relatively tough hydrogel formation ability of oxidized alginate have been reported. Chen *et al.* developed a self-healing tough hydrogel with superior cell affinity *via* hydrogen bonding and Schiff base cross-linking between dopamine-grafted oxidized alginate and polyacrylamide chains. The hydrogel showed efficient self-healing mechanical properties (80% recovery after 6 h) with good tissue adhesiveness as a wound dressing material *in vitro* and *in vivo* [53].

The aldehyde in oxidized alginate can be the target site of drug conjugation for a DDS substrate hydrogel [43]. In the case of oxidized alginate, there are two different reactive groups in one molecule; therefore, a more complicated and precise design of functionalization can be obtained using 3D printing [66]. Heo *et al.* developed 3D bioprinted cell scaffolds with carbohydrazide-modified gelatin (Gel-CDH) and oxidized alginate (O-Alg) [67]; Figs. (**3A** and **3B**) show the scheme of cross-linking between Gel-CDH and O-Alg and the 3D printing process, respectively. They successfully synthesized 3D complex-shaped constructs of a mesh tube (Fig. **3C**), mesh sphere (D), ball-in-a-cage (E), and humerus model (F); Figs. **3G**, **3H**, and **3I** show 3D bioprinted constructs laden with fluorescent labeled human mesenchymal stem cells (green) and human umbilical vein endothelial cells (HUVECs) (red).

6. HYALURONAN

Hyaluronic acid (hyaluronan) is a glycosaminoglycan found in the extracellular tissues of the animal body, and is composed of alternating N-acetylglucosamine and D-glucuronic acid units attached by β (1-4) and β (1-3) linkages, with molecular weights in the range of 6500 to 10,900 kDa [95]. One important characteristic of hyaluronan is its high water-holding capacity, owing to which it plays a role in various cellular and tissue functions, *e.g.*, as a lubri-

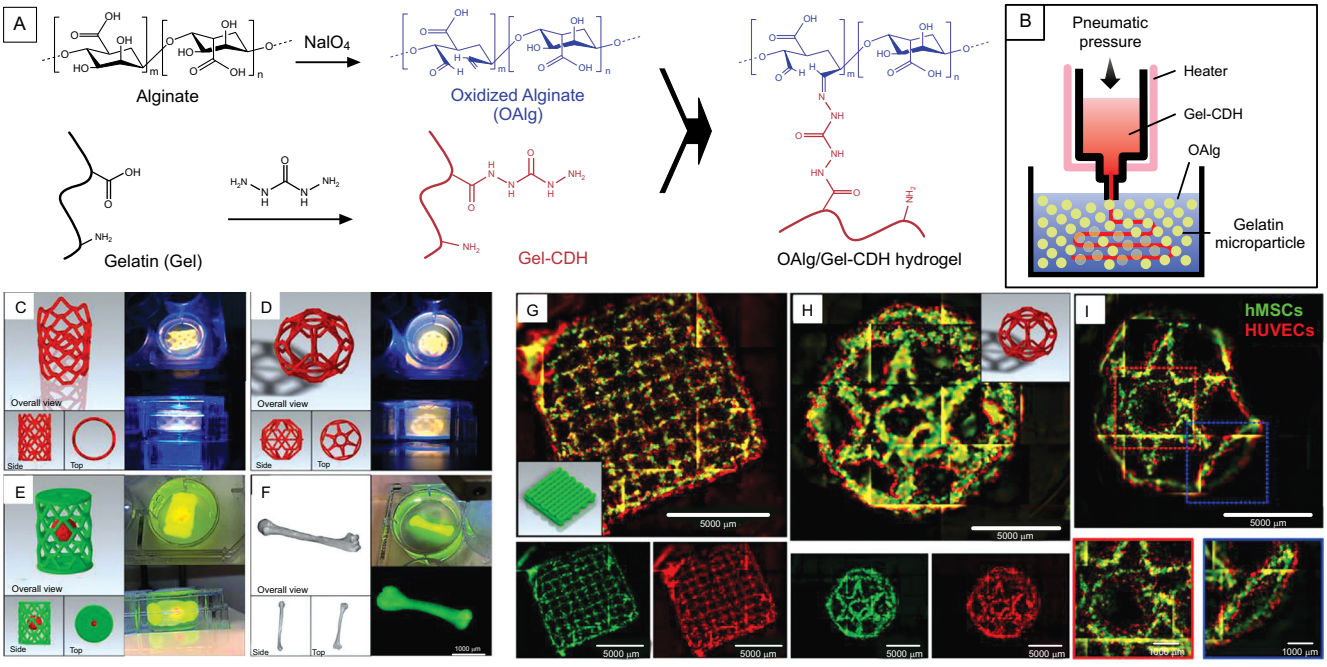


Fig. (3). (**A**) Chemical structure of OAlg and Gel-CDH. (**B**) Schematic illustration of 3D printing process. (**C–F**) 3D printed complex-shaped constructs with their 3D computer-aided design models: (**C**) meshed tube, (**D**) meshed sphere, (**E**) ball-in-a-cage construct, and (**F**) humerus model. (**G–I**) 3D bioprinted constructs laden with fluorescent hMSCs (CMFDA-labeled, green color) and HUVECs (tdTomato+, red color): (**G**) crosshatched grid and **(H**, **I**) meshed sphere models. Reproduced with permission from Ref. [67], ACS, 2020. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

cating fluid molecule, in the human body [96]. Periodate-oxidized hyaluronan can couple with peptides and immobilize cell-containing materials. Hyaluronan-based hydrogels have been extensively studied for biomedical applications of tissue engineering, DDSs, and wound dressings because of the ease of modification of the carboxyl groups in the hyaluronan backbone. Hydrazide derivatives of hyaluronan have been used to synthesize hydrogels using 1-ethyl-3-[3-(dimethyl amino)-propyl] carbodiimide (EDC) as a crosslinker [97]. Alternatively, divinyl sulfone can connect two hydroxyl groups of hyaluronan to yield a hydrogel [98]. However, because excess cross-linkers should be removed after hydrogel formation, such hydrogels are not injectable. Thiol-conjugated hyaluronan and PEG-diacrylic acid crosslinking have been reported to exhibit in situ hydrogel formation [99]. In such a reaction, owing to the instability of bifunctional PEG and thiolated hyaluronan, various steps that require careful control are used to prevent inactivation. For such in situ hydrogel formation, oxidized polysaccharide and amine compound reactions have been widely utilized. Chondrocyte encapsulation into an oxidized hyaluronan injectable hydrogel with glycol chitosan has been reported [30]. The oxidation degree and polymer concentration was used to control the gel properties and cytocompatibility. Moreover, an injectable hydrogel with adipodihydrazide for nucleus pulposus regeneration has been synthesized [32]. Oxidized hyaluronan hydrogels can assist in nucleus pulposus cell synthesis of type II collagen and aggrecan mRNA gene expression, and show good biocompatibility based on cell viability and cytotoxicity assays. Since hyaluronan has carboxyl groups in the main chain, aldehyde and COOH groups can independently react with different molecules. Khorshidi *et al.* developed tricomponent hydrogels consisting of oxidized hyaluronan, oxidized alginate, and gelatin for tissue engineering [100]. Aldehydes in two different polysaccharides and amino groups in gelatin reacted to form Schiff bases as crosslinking points, and the swelling and mechanical properties could be controlled using the hydrogel composition; these hydrogels are promising for stem cell residence and cartilage formation.

7. CHITOSAN

Chitosan is a derivative of chitin, an unbranched polysaccharide consisting of (1-4)-linked N-acetyl-β-D-glucosamine and b-D-glucosamine units. Although chitosan does not have vicinal hydroxyl groups, periodate oxidation occurs in β-D-glucosamine residues, yielding dialdehyde chitosan [14]. Nitrogen is released as ammonia, which serves as a quantitative measure of the degree of oxidation. The controlled release of anti-viral drugs from oxidized-chitosan-modified scaffolds has been reported by Zhu and coworkers [51]. In their study, oxidized chitosan was immobilized *via* a Schiff base on ethylene diamine-introduced polyacrylonitrile nanofibers. Then, acyclovir (an anti-viral drug) was immobilized on the nanofibers using the Schiff base reaction and hydrogen bonding. The modified nanofibers controlled the release of anti-viral drugs while maintaining cytocompatibility. Although the applications of oxidized chitosan are limited by extensive depolymerization accompanying the oxidation [101] utilization of the flexible structures of oxidized chitosan while maintaining the complex formation ability with anionic molecules such as DNA has potential in biomedical applications.

8. OTHERS

Many types of polysaccharides are oxidized using periodate for various applications, *e.g.*, as biomaterials. Pullulan is a natural linear polysaccharide obtained from fungi, and is mainly composed of a continuous maltotriose unit linked by (1-6)-α-glycosydic bonds [102]. An oxidized pullulan and collagen mixture has been used to prepare hydrogels for skin reconstruction. In addition, oxidized pullulan has been used as a stabilizing agent for gelatin hydrogels with 5.80 MPa compressive stress, which is 153 times higher than that of pure gelatin hydrogel [103]. Konjac glucomannan made up of β-1,4-linked D-mannose and D-glucose[104] has been utilized in food chemistry, and engineered *via* oxidization by periodate to synthesize dialdehyde Konjac glucomannan. There have been attempts to prepare hydrogels with collagen and chitosan for hemostatic materials [105] and with gelatin for application in food packaging with anti-oxidant immobilization [106]. Varghese *et al.* introduced pendant diol groups into the side chain of glycosaminoglycans, and prepared aldehyde-grafted glycosaminoglycans without any oxidation of the backbone, using periodate oxidation (Fig. **4A**, **B**). Such injectable hydrogels mimic the extracellular matrix without modification of the backbone of the naturally derived polysaccharides and control the release of proteins by changing the composition of hydrogels (Fig. **4C**, **D**) [107]. There are many kinds of polysaccharides, and the combination of their unique properties as well as those of reactive aldehydes prepared through oxidation will open up new degradable biomedical applications. To this end, it is important to understand the mechanisms of biodegradation.

9. DEGRADATION CONTROL

The control of degradation is an important issue in biomedical applications of polymeric materials. An appropriate degradation time of biomaterials in the human body can control tissue regeneration, enhance the functionality of the regenerated tissue, and maintain drug release from such materials. For chemically cross-linked polysaccharide hydrogels, degradation depends on the type of chemical bonds of the cross-links and the stability of the backbone of the polysaccharides. Some polysaccharides are degraded by enzymes in the human body, such as amylase for starch, dextranase for dextran, chitinase for chitin, and hyaluronidase for hyaluronan. Other polysaccharides, including alginate, cellulose, and chitosan, are relatively stable in the body because of the lack of degrading enzymes; therefore, appropriate degradability is required, and oxidation is a facile solution. The kinetics of the degradation of oxidized alginate have been studied [108, 109]. Biodegradability of alginate is enhanced by partial oxidation by periodate. Merely 1-8% oxidation made the alginate backbone easily degradable in alkaline conditions by β-elimination while maintaining gelation ability (Fig. **5**) [108]. Interestingly, not all the introduced aldehydes were equally degradable, resulting in the levelling off of the molecular weight reduction [108]. Controlled biodegradation of oxidized alginate hydrogels has been studied for multi-functional biomaterials [110] meniscal repair [36], osteogenesis [111, 112], and 3D printable biomaterials [67].

Biodegradation of oxidized cellulose has been well discussed in the literature [113-115]. The major drawback of cellulose for biomedical applications, despite its non-toxicity and functionality, is its poor biodegradability. Solubility in water can be conferred onto cellulose by acetylation, carboxymethylation, and other reactions to reduce the crystallinity. However, these modified celluloses still show molecular stability in the human body because of the lack of cellulase. Similar to the oxidization of alginate, ring-opening aldehyde introduction by periodate causes not only reactivity but also instability of the backbone of cellulose. It is known that oxidized cellulose is hydrolyzed in alkaline media *via* main chain scission by elimination of alkoxy-type grouping in the position with respect to carbonyl groups, leading to degradation into 2,4-dihydroxybutyric

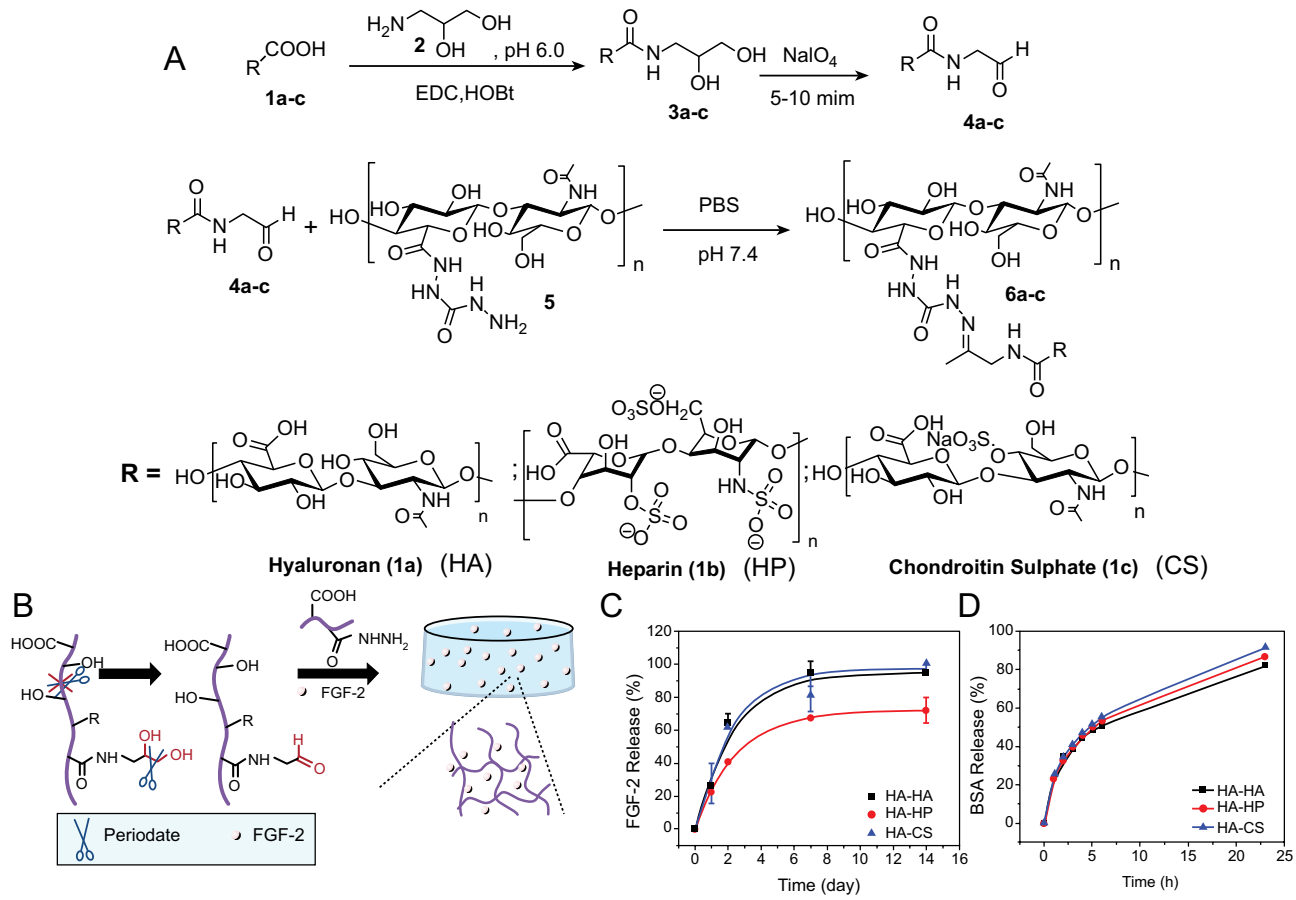


Fig. (4). Protein release from side chain oxidized GAGs. (**A**) Synthetic strategy for designing aldehyde modified GAGs and hydrazone crosslinking strategy to obtain injectable hydrogels. (**B**) Schematic illustration of fibroblast growth factor-2 (FGF-2) delivery from the injectable gels. Release profile of (**C**) FGF-2 and (**D**) bovine serum albumin (BSA) in different gels. Reproduced with permission from Ref. [107], ACS, 2013. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

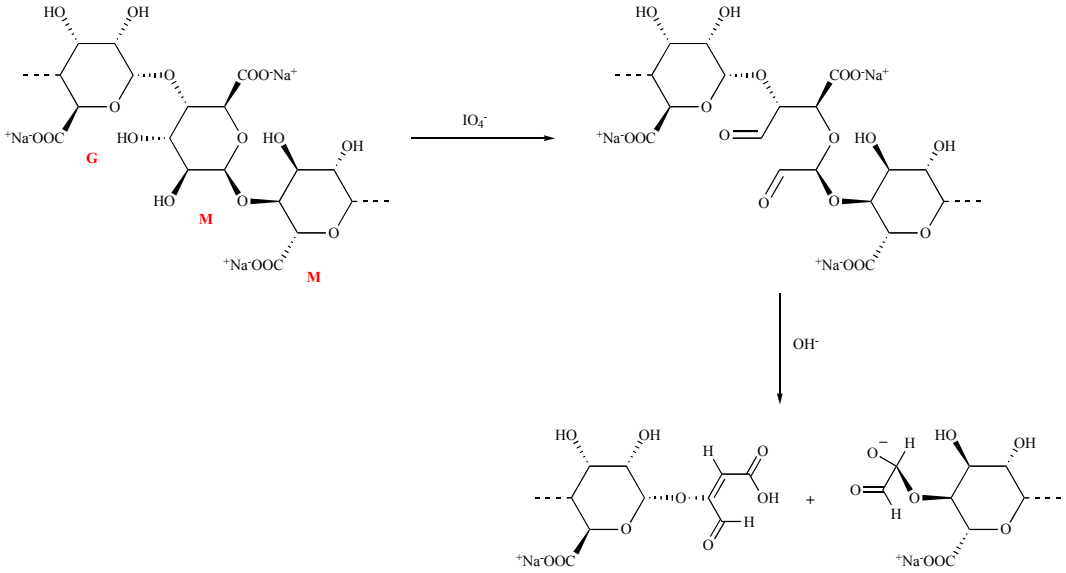


Fig. (5). Chemistry of periodate oxidation and subsequent alkaline elimination of alginate. Both G (1,4-linked L-guluronic acid) and M (1,4-linked D-mannuronic acid) can be oxidized.

acid and glycolic acid [113]. In addition, *in vivo* degradation in rats has been studied using ^{14}C labeling of oxidized cellulose, and it was concluded that degradation occurred faster in the first few days and was sustained for a month. This tendency is similar to that reported by others [41, 115] and agrees well with a kinetic study of oxidized alginate, which showed that the molecular weight decrease satu-

rated [108]. The biodegradable oxidized cellulose was fabricated into a porous sponge-like structure for tissue engineering and wound healing [116-118].

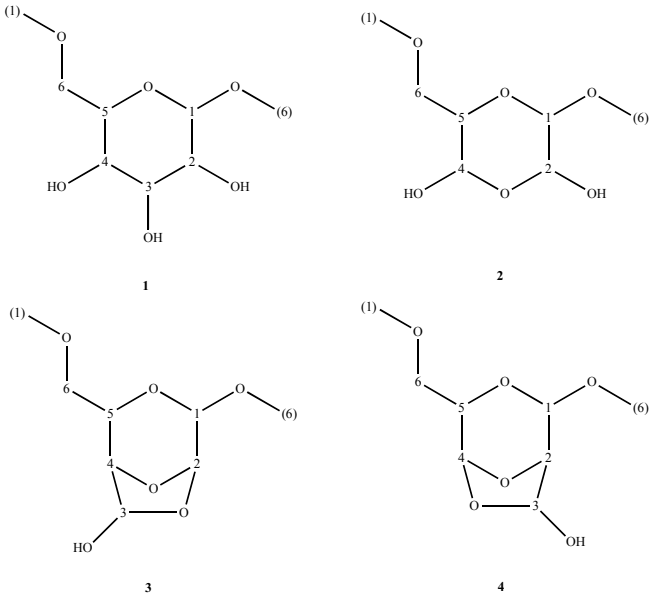


Fig. (6). Substructures identified in oxidized dextran chain. Glucose (**1**); C2–C3 and C3–C4 cleavages, C3 desorption, hemiacetal structure (**2**); C2–C3 cleavage, hemiacetal structure (**3**); C3–C4 cleavage, hemiacetal structure (**4**). Reprinted with permission from Ref. [121], Wiley, 2016.

The general chemical structure of oxidized polysaccharides is shown in Scheme **1**. However, based on the results of both FTIR and NMR spectroscopy, it can be concluded that in various oxidized polysaccharides, the aldehyde groups form several different structures of hemiacetals through reactions with neighboring hydroxyl groups [119-121]. For instance, more than 4 hemiacetal substructures have been identified in oxidized dextran (Fig. **6**) using 2D-NMR [121]. Periodate oxidizes and cleaves the C2-C3 and C3-C4 bonds in the glucose moiety of dextran. When both bonds are cleaved, C3 is removed, and C2 and C4 are converted into aldehydic carbons. Thus, two aldehyde groups and a water molecule are converted into a hemiacetal structure (substructure 2, Fig. **6**). For C2-C3 bond cleavage, oxidized glucose is converted into a hemiacetal structure (substructure 3, Fig. **6**). A hemiacetal structure (substructure 4, Fig. **6**) is also obtained upon C3-C4 bond cleavage. Chimpibul *et al.* reported that the hemiacetal was relatively stable in the buffer, and after a reaction with an amine to form a Schiff base, it initiated rapid degradation in the main chain of dextran [121]. Fig. (**7A**) reveals that the molecular weight of oxidized dextran after reacting with amine rapidly decreases. In addition, the intensity of protons in substructure 2 and the reducing end proton in time-course NMR spectra decrease and increase, respectively, with almost the same time constant. These results clearly suggest that molecular degradation occurred after Schiff base formation. The reaction mechanism is shown in Scheme **2**.

Partial hemiacetal structures produced by periodate oxidation react with amino groups and undergo an Amadori rearrangement in the Maillard reaction, which leads to the scission of the glucose unit ring. This was also confirmed in the *in vitro* degradation of the oxidized dextran hydrogel after Schiff base formation through the Maillard reaction [122, 123]. Based on this mechanism, degradability in the human body can be precisely controlled by external stimuli such as light or heat, using stimuli-responsive release of encap-

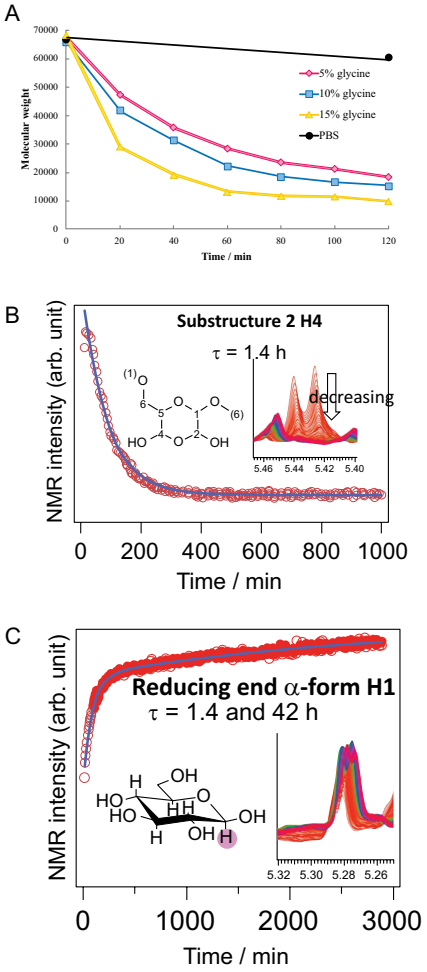
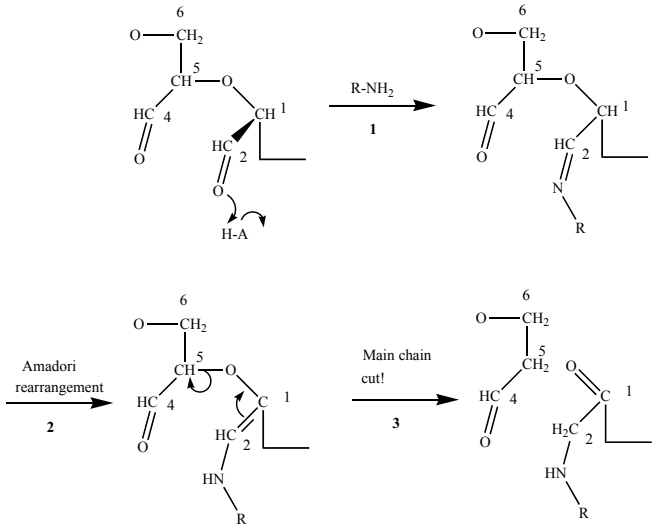


Fig. (7). (**A**) Change in Mw of 21.2% oxidized dextran in glycine solutions of various concentrations, determined by GPC. (**B**) Kinetic analysis of time-course NMR spectra for substructure 2 and (**C**) reducing end α-form H1. Blue solid lines were calculated using single-exponential curve fitting, and the time constants of the exponential function are shown. Reproduced with permission from Ref. [121], Wiley, 2016. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*



Scheme 2. Molecular scission mechanism of oxidized dextran in reaction with amine. Reproduced with permission from preprint of Ref. [124], under Creative Commons CC-BY license.

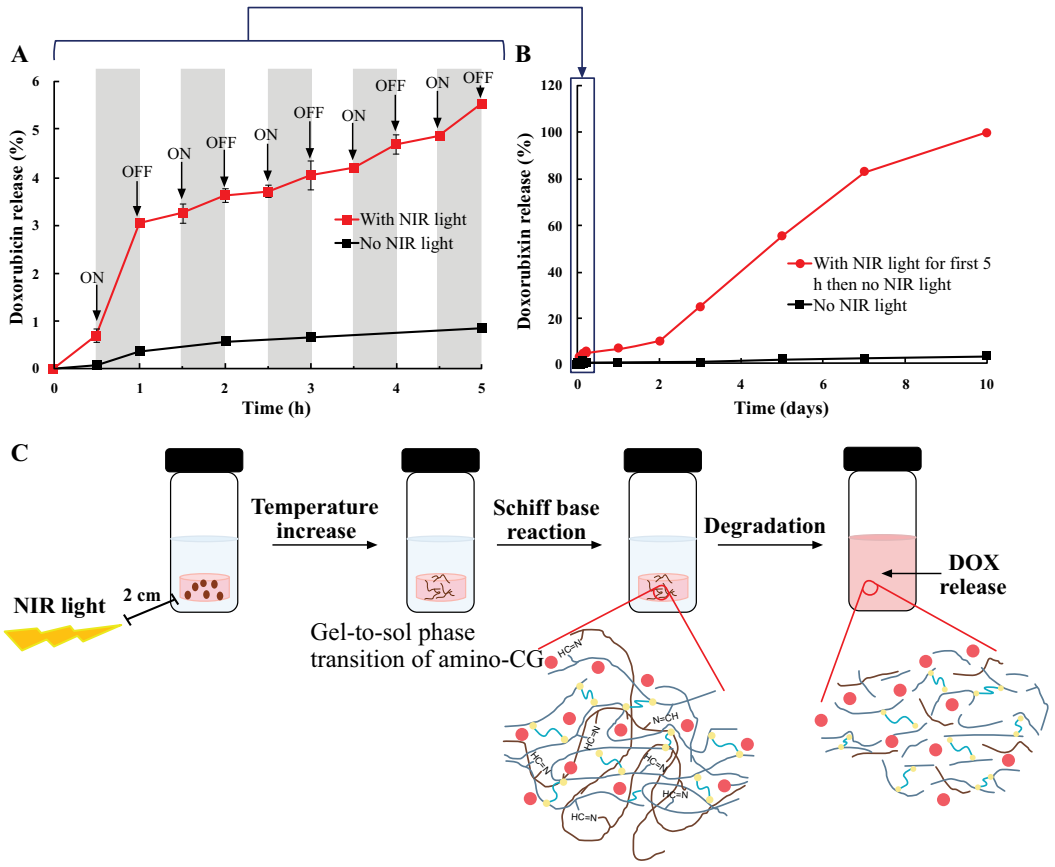


Fig. (8). (**A**) Cumulative release profiles of DOX from hydrogel with and without NIR-light irradiation over 5 h. (**B**) Cumulative release profiles of DOX from hydrogel over 10 days. (**C**) Schematic presentation of drug release under NIR irradiation. Reprinted with permission from Ref. [50], ACS, 2019. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

sulated amino compounds triggered by hydrogel degradation and drug release [50, 124]. In the aforementioned experiments, two different types of cross-linkable moieties (aldehyde and methacrylate) were independently introduced into dextran and showed independent control of the degradation speed and mechanical properties [50, 124]. Using this "self-degradation" property of oxidized polysaccharide-amine hydrogels, Nonsuwan *et al.* demonstrated light-responsive drug release from a hydrogel *via* gel degradation through a Maillard reaction after Schiff base formation (Fig. **8**) [50]. Fig. (**8C**) shows the strategy of light-responsive drug release. Doxorubicin (Dox) was incorporated into the hydrogel to prepare methacrylated oxidized dextran and dithiothreitol (DTT) *via* thiol-en cross-linking. Near infrared (NIR)-responsive amino-carrageenan (CG) beads were incorporated into the hydrogel. Upon NIR irradiation, amino-CG dissolved into the hydrogel, and Schiff base formation between amino-CG and the aldehyde of oxidized dextran triggered the degradation of the hydrogel, initiating the release of Dox. Figs. (**8A** and **8B**) clearly show that the Dox release was well controlled by NIR irradiation. This degradation mechanism agrees well with the biodegradation process of oxidized cellulose, which is an amine-reactive degradation-controllable cellulose scaffold [41]. This mechanism could also explain the *in vivo* or even *in vitro* degradation of oxidized polysaccharides in amine-containing buffers such as Tris buffers [125]. Based on these research reports, it was concluded that oxidation depolymerizes polysaccharide molecules and the Maillard reaction of the introduced aldehydes can cause main chain degradation. Therefore, degradation in the human body is precisely controlled by reaction conditions such as the oxidation ratio and polymer concentration, as well as external stimuli such as pH and temperature.

CONCLUSION AND FUTURE PERSPECTIVE

In summary, oxidized polysaccharides prepared with recyclable periodate using renewable naturally derived materials have expanded biomedical applications owing to their non-toxicity, selective reactivity, and scalability. Over the last few years, progress has been made to further develop the field of polysaccharide-based biomaterials. Although several methods are in use, more research on many aspects is warranted to create universally applicable and reliable materials for various applications. Firstly, easier purification methods can be developed. Further, the structure-function relationship of oxidized polysaccharides needs to be studied in detail. The specific functions of original polysaccharides after oxidation, *e.g.*, those of COOH groups in hyaluronan; ionic crosslinking for alginate; hydrophobicity; crystallinity of cellulose; low viscosity at higher concentration for dextran; *etc.* need to be utilized.

Stimuli-responsive biomaterials are a hot topic in the field; therefore, such functions should be combined with those of oxidized polysaccharides. Another crucial aspect that should be carefully examined is controlling the rate of biodegradation. To this end, Schiff base formation that triggers biodegradation is an interesting phenomenon for controllable degradation, and further research is needed to tune the rate according to specific requirements.

Oxidized polysaccharide composites for smart healthcare materials such as implantable scaffolds, controlled drug release materi-

als, and wearable devices need to be further researched. The next generation of oxidized polysaccharides can open new avenues for a wide range of sustainable bioengineering materials. Owing to the tremendous progress made in the last few decades, it would be interesting and exciting to see the developments and new research coming out over the next few years, which may propel the field to newer heights and solve many of the existing challenges.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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