Organic Modification of the Polysaccharide Alginate

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Abstract: The polysaccharide alginate is a linear chain binary copolymer made of guluronic acid and mannuronic acid subunits. Alginate is a natural polymer material produced by a number of organisms, including brown algae and bacteria. It has found application in a variety of areas, including food, cosmetics, pharmaceutical and biomedical industries. In recent years, a number of studies have been published on covalent modification of alginate, often through carbodiimide-mediated reactions at the carboxyl moieties. These modifications have imparted a wide range of different chemical and physical material properties, including altered reactivity, hydrophilicity, viscosity and sorption characteristics. This mini-review focuses on the methods and applications of organically modified alginates from recent publications.

Keywords: Alginate, modification, biopolymer, polysaccharide.

1. INTRODUCTION

Alginate (alginic acid) is an unbranched polymer composed of (1–4) linked *β*-D-mannuronic acid (M) and α-L-guluronic acid (G) subunits in various sequences (Fig. **1a**) [1]. Alginate is produced naturally as a cell wall constituent in several varieties of brown algae, including *Macrocystis pyrifera* and *Ascophyllum nodosum*, and is also found in a number of bacterial species, such as *Azotobacter vinelandii* and *Pseudomonas aeruginosa* [2]. In aqueous solution at neutral pH, alginate salts dissociate into anionic polymer chains to form viscous syrups. These solutions readily gel in the presence of divalent metal cations through multi-dentate ionotropic interactions, which occur preferentially in G-rich blocks of the polymer chain (Fig. **1b**).

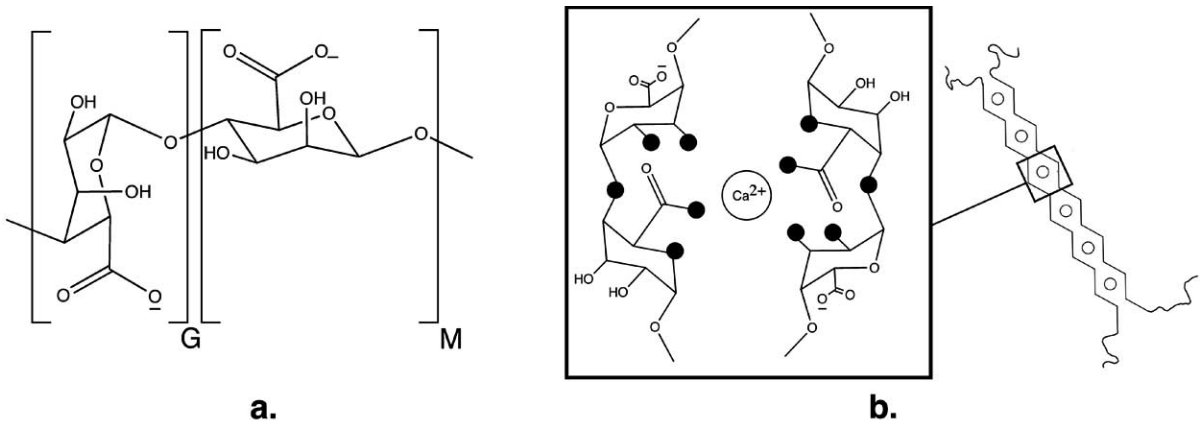

Fig. (1). a.) Alginate consists of subunits of mannuronic acid (M) and guluronic acid (G). **b.)** Alginate is commonly gelled with divalent metal cations, particularly Ca^{2+}, which act preferentially on blocks of repeated G subunits. Oxygen atoms participating in the crosslinking coordination sphere are shown as dark circles [13].

Alginate has proven a versatile material for application in a variety of industries, and is frequently employed for viscosity control, gelation, and emulsification. Alginate is biocompatible, biodegradable, non-toxic, and is classified as "generally regarded as safe" (GRAS) by the U.S. FDA [3]. In the medical and pharmaceutical arenas, alginate is used for cell immobilization and drug delivery, as well as wound dressings and dental impression materials [4, 5]. Alginate is found in food and cosmetic products as a thickener and stabilizer, and is used as a binding agent in reconstructed seafood, meat and other consumables [6-9]. Several industrial applications for alginate have also been developed: dyed alginate pastes are frequently used for textile printing, alginate-derived paper treatments give oil- and flame-resistance, alginate is used as a lubricant and binder agent in coatings for extruded welding rods, and ammonium alginate is used as a can sealant [10-12]. Alginate has also proven an effective binder of metal ions, leading to applications in wastewater remediation and metal recovery [13-17]. Magnetic alginates, created by coprecipitation with ferric and ferrous ions or entrapment/coating of magnetic particles [18-21], have demonstrated strong affinity for lead, cadmium and arsenic species [22]. Alginate precipitated with ferric and divalent cobalt ions has also demonstrate capacity for isolating microbial DNA of lactic acid bacteria, a common test model for food safety industries [18]. Alginate has been used to stabilize iron oxide nanoparticles with unique paramagnetic properties, enhancing use of the particles as contrast agents in medical imaging [19].

With the wide variety of established and potential uses of alginate, there is heightened interest in tailoring properties through chemical modification. Fig. (**2**). shows the increasing frequency of journal publications and patents related to modified alginates. This review highlights a number of these advancements, published since 2000, on the topic of organically modified alginate.

2. MODIFICATION REACTIONS

The most frequently employed synthesis technique for organically modifying alginate is a carbodiimide-mediated condensation

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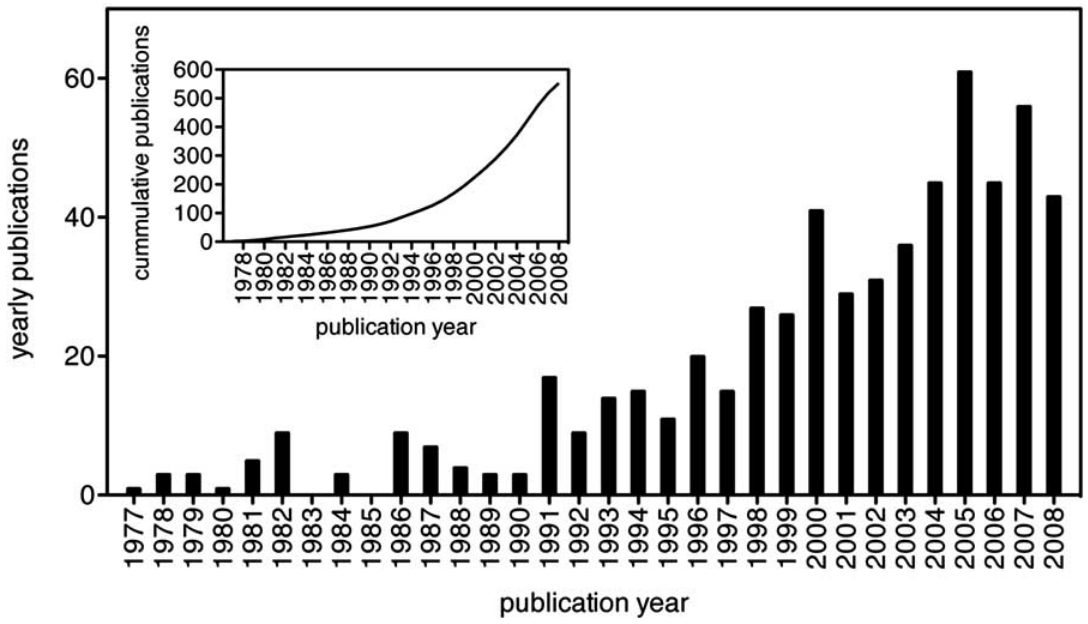

Fig. (2). Publications on modified alginates have steadily risen over the past 20 years. Data were compiled in June 2009 using SciFinder Scholar database search engine (American Chemical Society, Washington, DC). Searched keywords, in combination with *alginate*, were: *modification of*, *covalently modified*, *covalently crosslinked*, *grafted*, and *carbodiimide*.

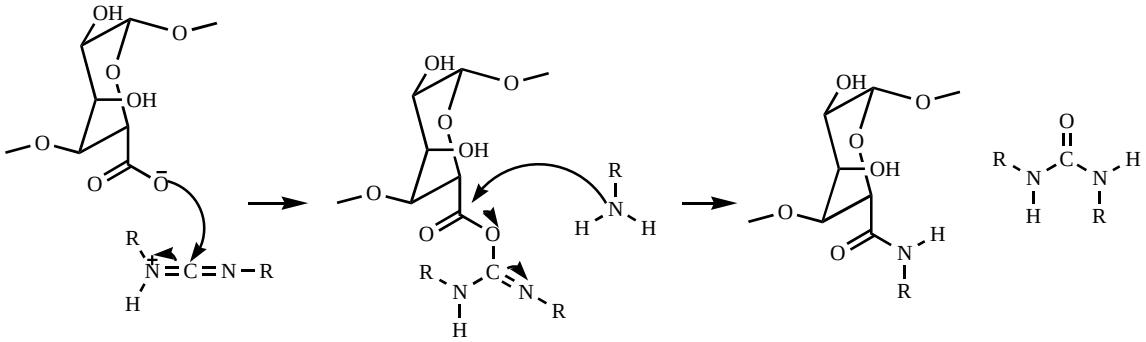

Fig. (3). The deprotonated carboxylate oxygen of an alginate subunit attacks a carbodiimide molecule. The carboxylate carbon is left open for subsequent attack by the primary amine nitrogen, which displaces a urea molecule and forms an amide bond to the alginate backbone.

reaction. Carbodiimide coupling agents such as the water-soluble 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) are used to form amide bonds between alginate carboxyl groups and amine moieties. The key feature of the carbodiimide is its N=C=N chemistry, which activates carboxyl groups by forming an *O*-acylurea structure. The carboxyl carbon atom is left open to nucleophilic attack by the amine. Salient stages of this dehydration mechanism are shown in Fig. (**3**). Although several alternative reaction pathways are possible, the procession of undesired side reactions can be significantly minimized with the addition of *N*-hydroxysuccinimide (NHS) [23].

While many organically modified alginates have been synthesized using carbodiimide reactions at the carboxyl groups, other mechanistic pathways have been employed as well. Hydroxyl groups on C-2 and C-3 have been functionalized by reagents such as cyanogen bromide and succinyl anhydride, and have also been oxidized into dialdehyde groups for further reaction [24-28]. Hydrogen abstraction has been used to initiate covalent bonding directly to alginate ring carbon atoms [29]. A number of modification strategies found in recent literature are summarized in Fig. (**4**).

3. GELATION AND CROSSLINKING

Ionic Crosslinking. Alginate is often ionotropically crosslinked by chelation with metal cations, particularly divalent calcium. The reported pK_a of alginate ranges from 3.38 to 3.65, depending upon the ratio of M and G residues [30]. An alginate chain of typical composition will feature deprotonated carboxyl groups at pH levels greater than 6.0 [31]. These deprotonated carboxyl groups, along with hydroxyl groups and oxygen atoms within the chain rings and glycosidic linkages, participate in multi-dentate cation coordination [32-35]. The polymer–cation interactions are frequently referred to as the "egg-box" model, because cations are packed into segments of the alginate chain like eggs in a carton. Blocks of repeated G subunits, with their axial O-1 structures, provide a more favorable cation binding geometry than do M subunits, with their equatorial O-1 configurations.

Covalent Crosslinking. There are a number of reasons for pursuing covalent crosslinking strategies for alginate. Ca^{2+} crosslinks are easily reversed by addition of cation chelators such as EDTA, citrate and lactate, or by ion exchange with high concentrations of Na^+ or other cations [36]; covalent crosslinks can be designed to be more resistant to such environmental effects. Covalently crosslinked alginates also offer the potential for enhanced swelling properties. The expansion of cation-crosslinked alginates is limited by the long and inflexible G-block "junction zones" that form in response to treatment with Ca^{2+} and other gel-inducing cations [37]. Individual covalent crosslinks, on the other hand, can be more homogeneous scattered throughout the gel to allow for larger dimensional changes. Covalently crosslinking strategies also offer the

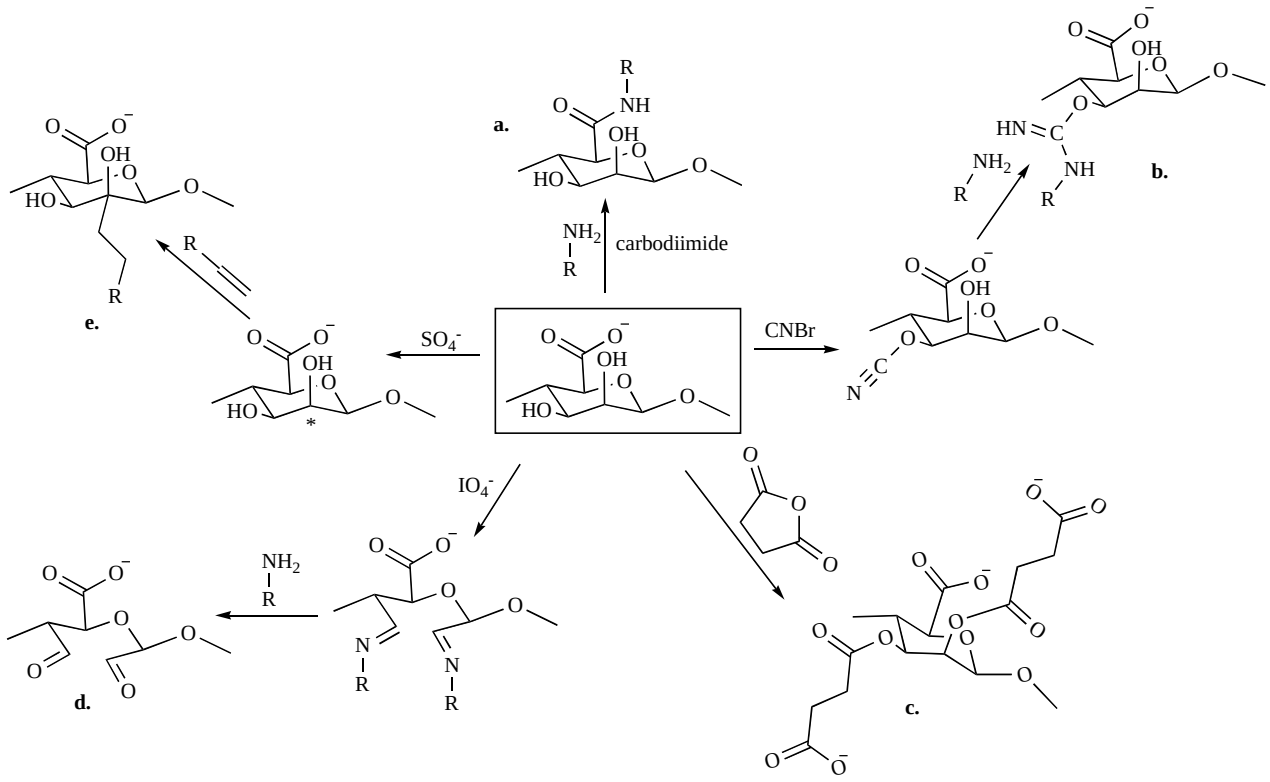

Fig. (4). This figure illustrates general reactions for alginate derivatives that have appeared in recent literature (for clarity and brevity, only the mannuronic acid subunit is shown). **a.**) Reactions of amine groups at the alginate carboxyl are most common. Other alginate modification strategies include: **b.**) amine reactions at functionalized hydroxyl groups; **c.**) succinylation; **d.**) ring-opening and subsequent amine reactions; and **e.**) radical initiation and reactions on in-ring carbon atom.

potential for controlled initiation by external stimuli, such as photo- or thermal-activation.

Carbodiimide chemistry has commonly been used to covalently crosslink alginate with bi-functional amine molecules, such as ethylenediamine. A study published in 2000 focused on three crosslinking agents with reactive nitrogen terminals: adipic acid dihydrazide (AAD), methyl ester L-lysine and poly(ethylene glycol)-diamine (PEG-diamine) [38]. A key finding of this research was the covalently-crosslinked gels all exhibited decreased shear moduli above a critical crosslinker concentration, which depended upon crosslink chain length. This tunable mechanical property was not observed in control gels made with Ca^{2+}, which can be regarded as having zero-length crosslinks and which showed no reduction in moduli over the studied concentration range.

In subsequent publications, adipic dihydrazide crosslinks were formed in aldehyde-functionalized polyguluronate (PAG), which had been isolated from sodium alginate by acid hydrolysis [28, 39]. The polyguluronate was partially oxidized with sodium periodate to generate dialdehyde groups, which were crosslinked with adipic acid dihydrazide without need for a coupling agent or other catalyst. This study further illustrated the importance of crosslink density for obtained desirable gel properties. PAG gels made with 100 mM AAD were prone to complete degradation in tissue culture medium at 5 days, while gels made with 200 mM showed no statistically significant weight loss in the same time period. Osteoblast cells injected with the 200 mM PAG-AAD gels resulted in bone tissue formation after 9 weeks (the 100 mM PAG-AAD gel degraded before bone formation could occur).

A photo-crosslinking alginate was synthesized by reacting the polysaccharide with methyacrylic anhydride [40]. The authors of the study identified a number of potential *in vivo* applications for this material including sutureless wound seals, cell immobilization and encapsulation, and soft tissue reconstruction. The temporal control offered by photo-initiated crosslinking allowed the gel to be formed into complex shapes, making the material an attractive candidate for use in areas of the body with limited accessibility such as the ear and eye.

Past research has indicated successful crosslinking of alginate hydroxyl groups with glutaraldehyde (GA) [41]. In a more recent publication, glutaraldehyde was used to crosslink alginate gel spheres containing the pesticide neem seed oil (NSO) [42]. By varying the duration of exposure to GA, changes in gel behavior (e.g. percent NSO loading, NSO release rate, drying time, water uptake) were observed. In another study, Ca–alginate beads were covalently reinforced by conversion of alginate hydroxyl groups to cyanato groups with cyanogen bromide, followed by crosslinking with 1,6-diaminohexane chains [27]. It was determined that the desirable Cu(II)- and Mn(II)-sorbing capacity of these beads was not diminished compared with a non-covalent alginate control. However, the covalently linked beads had improved mechanical properties and resistance to degradation compared with their ionically crosslinked counterparts.

4. ALGINATE MODIFICATIONS

Graft Copolymers. Graft copolymers are nonlinear macromolecules comprised of a polymeric backbone with covalently attached pendant chains of a second, chemically distinct polymer species. Numerous graft copolymers featuring an alginate backbone have been discussed in the literature. These copolymers have been used to tune the characteristic properties of alginate for improved

performance in a variety of applications, particularly in the biomedical field.

Modulation of hydrogel swelling by environmental factors of pH and temperature are of obvious pertinence for controlled release applications. Alginate gels intrinsically exhibit pH-sensitive swelling/deswelling behavior tied to the dissociation of protons from carboxyl moieties along the polymer chain with increased pH. The gels swell in response to electrostatic repulsion between the ionized carboxylate groups as pH rises [36, 43]. A complementary temperature-dependent behavior has been observed in alginate gels graft copolymerized with poly(*N*-isopropylacrylamide) (PNIPAAm) [44]. PNIPAAm gels exist in an extended hydrated conformation below 32 °C, but dehydrate to a smaller volume at higher temperatures. The alginate–PNIPAAm hydrogels retained sensitivity to pH and also exhibited dimensional changes in response to temperature. These swelling behaviors were accentuated in highly porous gels, which had void spacings that acted as water reservoirs.

The porosity of gels is an important factor for drug delivery systems; encapsulated pharmaceutics can diffuse through highly porous alginate at an undesirable rate. In the past, control over gel porosity has been demonstrated with mixtures of alginate and varying amounts of poly(ethylene glycol) (PEG) [45]. A more recent investigation focused on a conjugate material made from an amine-functionalized alginate and PEG [26]. A ring-opening oxidation reaction was employed to generate dialdehyde moieties at the C-2 and C-3 positions in a fraction of the alginate G and M subunits. These reactive aldehyde groups were functionalized with octyl amine. Carbodiimide chemistry was used to covalently couple acid-functionalized PEG chains to the amine groups. The usefulness of this strategy is that a high degree of modification can be achieved without consuming carboxyl groups, which are important for ionic gelation.

Graft copolymerization has also been used to introduce specific biological characteristics to alginate. Both alginate and the cationic polysaccharide chitosan share properties of biocompatibility and low toxicity, but chitosan is also a known antimicrobial agent, with efficacy against fungal, algal and bacterial organisms [46, 47]. Mixtures of alginate and chitosan typically form insoluble gels as a result of electrostatic interactions between the alginate carboxyl groups and chitosan amine groups. While such gels have demonstrated potential for drug-delivery applications, their insolubility presents challenges for shape molding. A study of covalent attachment of chitosan to the alginate backbone was conducted to address this issue [29]. Chitosan olligomers were functionalized with *N*-methyl acrylamide (NMA) and subsequently bonded directly to an alginate ring carbon via a redox reaction using potassium peroxodisulfate initiator. Antimicrobial properties of these alginate–chitosan conjugates increased with chitosan concentration; addition of 1.8 wt. % chitosan was sufficient to achieve a 99.9% reduction in *Staphylococcus aureus* activity compared with the pure alginate control.

Graft copolymers has also been used to create core multi shell microspheres for the encapsulation and *in vivo* dispensation of parathyroid tissue [48]. Calcium crosslinked microspheres of parathyroid tissue and alginate were formed and coated with poly(L-lysine). The spheres were photo-crosslinked and coated with a copolymer of alginate and methoxy-polyethylene glycol (MPEG). The alginate-co-MPEG was formed via Schiff base formation between the amino-capped MPEG and alginate carboxyl. The resulting multilayered microspheres were placed in sodium citrate to liquefy the alginate parathyroid core and facilitate permeation through the shells. The microspheres were shown to be biologically stable when implanted into the abdominal cavity of rat hosts. Furthermore, the permeability of the membrane of tissue-encapsulated microspheres was identical to the tissue-free control.

Amino Acids and Peptides. As previously noted, alginate's carboxyl functionality is readily coupled to the amine terminus of amino acid residues or peptide chains via carbodiimide reactions. Amino acid and peptide modifications can be used to impart a variety of physical, chemical and biological effects. Perhaps the most common application of peptide-modified alginates is the mediation of cellular attachment to polysaccharide surfaces.

Work has been published describing the attachment of the Tyr-Ile-Gly-Ser-Arg (YIGSR) peptide to an alginate backbone for the purpose of encouraging neuroblastoma cell attachment and growth [49]. Cell attachment increased from 1.5% on an unmodified alginate surface to 66% on a surface of alginate treated with a 2 mg/g concentration of YIGSR. The binding of YIGSR to alginate was more effective than a surface coating of alginate with the glycoprotein laminin. The attachment of neuroblastoma cells and subsequent neurite growth was determined to be a function of peptide density on the alginate gel.

Other publications report binding Arg-Gly-Asp (RGD) peptides to alginate, with resulting enhanced affinity for myoblast and chondrocyte attachment, as well as enhancement in cell proliferation and growth. The ability for C2C12 mouse skeletal myoblasts to proliferate and differentiate was found to be dependent upon the peptide density of the alginate gel [50]. Chondrocytes attachment to RGD-modified alginate was 10-20 times higher on RGD–alginate compared to unmodified alginate [51]. It was also determined that cell behavior was impacted by the degree of Ca^{2+}-crosslinking. The crosslink density, correlating with the stiffness of the substrate, affected the equilibrium level and rate of chrondrocyte attachment, and also impacted the morphology of the attached cells (stretched versus rounded).

A hydrogel made from alginate bonded to an oligopeptide derived from bone morphogenic protein demonstrated ability to incite ectopic bone growth [52]. In past studies, BPM encapsulated in biodegradable materials has undergone rapid *in vivo* release in a manner not conducive for calcifying bones. Covalently linked alginate–BMP permitted a slower and controlled release of the peptide, aiding in bone formation.

Alginate is an established mucoadhesive agent, a class of material that aids in drug delivery by increasing retention time at mucosal tissues [3]. Improvement in alginate's intrinsic mucoadhesive properties was achieved by the addition of thiol functionality in an alginate–cysteine complex [53]. The added thiol groups, which form disulfide bridges with cysteine domains of mucus glycoproteins, enhanced the thiolated alginate's mucoadhesive properties compared with an unmodified alginate control. Increases in swelling, viscosity, tensile strength, work of adhesion, and internal crosslinking were indicative of a higher degree of interaction between mucus and polymer.

Amphiphilic Groups. Alginate provides a suitable structural framework for engineering a type of molecule known as a hydrophobically modified water-soluble polymer (HMWSP). HMWSP materials feature hydrophilic polymer backbones with attached hydrophobic side groups [54]. In dilute aqueous solutions (generally <0.1%), HMWSPs organize into nanoscale domains with hydrophobic cores surrounded by hydrophilic interfaces. These micelles behave as individual units that are governed by intramolecular interactions. As HMWSP concentration increases into the semidilute regime (typically >0.5%), the polymer chains are increasingly influenced by intermolecular interactions and form transitory three-dimensional polymer networks, held together with relatively weak physical crosslinks [55]. This network-forming behavior manifests itself in noteworthy rheological properties. An HMWSP solution has dramatically higher viscosity than its unmodified polymer antecedent at low shear; this enhanced viscosity is lost as shear is increased and physical crosslinks are broken [54, 56].

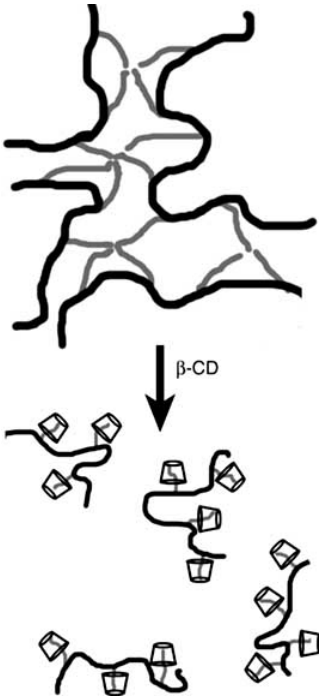

Fig. (5). Hydrophobically modified alginate chains form physically-crosslinked networks at low shear conditions. These networks can be modulated with addition of *β*-cyclodextran, which solubilizes amphiphilic side chains and disrupts intermolecular binding interactions.

Alginate-based HMWSPs have been investigated in a number of recent publications. The micelle and network structures of these molecules are of great interest for encapsulation of a variety of species, from medicinal compounds to dyes. Amphiphilic alginate derivatives can form gels without need for chemical (ionic/coordination or covalent) crosslinking. HMWSPs are resistant to cation scavengers such as EDTA, which dissolve Ca–alginate gels, but can also undergo controlled dissolution, which can be problematic with covalently-crosslinked alginates.

Alginate–alkyl conjugates made with dodecyl and octadecyl chains formed viscous solutions and hydrogels in pure water and NaCl solution [57]. The solution/hydrogel properties were dependent on polymer concentration, the degree of alkyl modification, the alkyl chain length and interactions with co-dissolved salt species. Most notably, these stable gel structures were formed without need of additional chemical crosslinking agents like divalent calcium (although the authors noted that Ca^{2+} ions could be used to reinforce gel integrity). This system was subsequently studied for use in protein encapsulation [58].

The reversible nature of the physical crosslinks that maintain HMWSP networks has been explored recently using *β*-cyclodextran (*β*-CD) [56]. Alginate chains with grafted hydrophobic ocylamine pendants exhibited shear rate versus viscosity behavior typical of an HMWSP material. When *β*-CD molecules were introduced to the solution and capped the hydrophobic pendant groups, the intermolecular network-forming interactions between chains were disrupted, causing the gels to dissolve (Fig. **5**). This type of controllable dissolution system could be used to control release of drugs or other species encapsulated within HMWSP materials.

In another publication, a branched poly(*β*-CD) polymer was added to solution containing amphiphilic alginate [59]. In this case, the conjoined *β*-CD moieties provided an additional avenue for intermolecular bonding between HMWSP alginate chains, strengthening the physical gel network. Interesting, when the HMWSP alginate concentration reached critical threshold, steric hindrance effects from the entangled HMWSP alginate chains effectively blocked poly(*β*-CD) from establishing network-strengthening intermolecular bonds. At this concentration, poly(*β*-CD) molecules behaved like monomeric *β*-CD, and viscosity dropped as physical networks were disrupted.

Surfactants have also been investigated as potential "switches" for modulating the solubility of amphiphilic alginate networks. Interactions between HMWSP alginate featuring *N*-cyclohexyl-2-(*N*-octylamino)ethanamide pendants and the surfactant sodium dodecyl sulfate (SDS) were investigated [60]. Addition of small concentrations of SDS to dilute (0.05–0.1 wt. %) and semidilute (0.5 wt. %) solutions of HMWSP induced the formation of polymer–surfactant micelles, leading to an initial rise in viscosity and turbidity. As the concentration of SDS was increased relative to the concentration of HMWSP, amphiphilic side groups were solubilized and the HMWSP network structure was disrupted.

Other Small Molecules. Silanated alginate, formed by covalent grafting and subsequent hydrolysis of 3-aminopropyltriethoxysilane, has the ability to nucleate apatite crystals [61]. Apatite deposition correlates to the availability of functional groups on the modified alginate. Gelling mechanisms like diamine crosslinking result in a net loss of functionality in typical alginates, limiting the efficiency for apatite deposition. By contrast, the use of 3-aminopropyltriethoxysilane creates a net gain in functionality, with the loss of one carboxyl and gain of three silanol groups. Silane chemistry has also been used to immobilize alginate layers on stainless steel to improve blood compatibility of the surface [62]. The alginate-treated stainless steel benefited from reduced platelet adhesion, minimizing undesirable blood clotting effects.

Alginates have been designed for protection and transport of microbial organisms. Lactic acid bacteria in yogurt and other dairy products aid in intestinal tract health by participating in a variety of beneficial biological processes. These bacteria are prone to deterioration during food production and storage, as well as during their transit through the gastric system. Alginates modified with succinic anhydride yielded derivatives with carboxyl-containing sidechains in place of hydroxyl groups [24]. This synthesis had the effect of increasing the titratable anionic charge centers in the polymer matrix by a factor of nearly two, further buffering the material and its

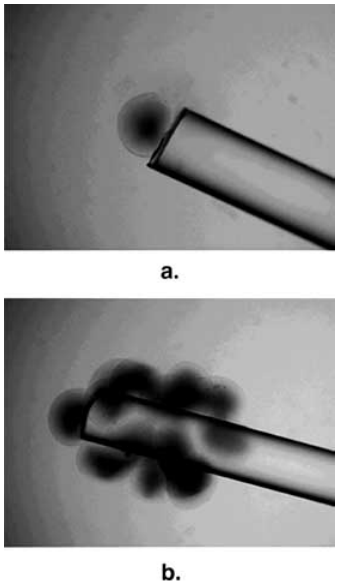

Fig. (6). An alginate–biotin material, which was engineered into Ca^{2+}-crosslinked microspheres with encapsulated bioluminescent cells. As shown in these optical microscope images by Polyak and colleagues, the spheres were attached to streptavidin-coated optical fibers for biosensing applications. Fibers with attachment of single **(a.)** and multiple (**b.**) spheres were produced [63].

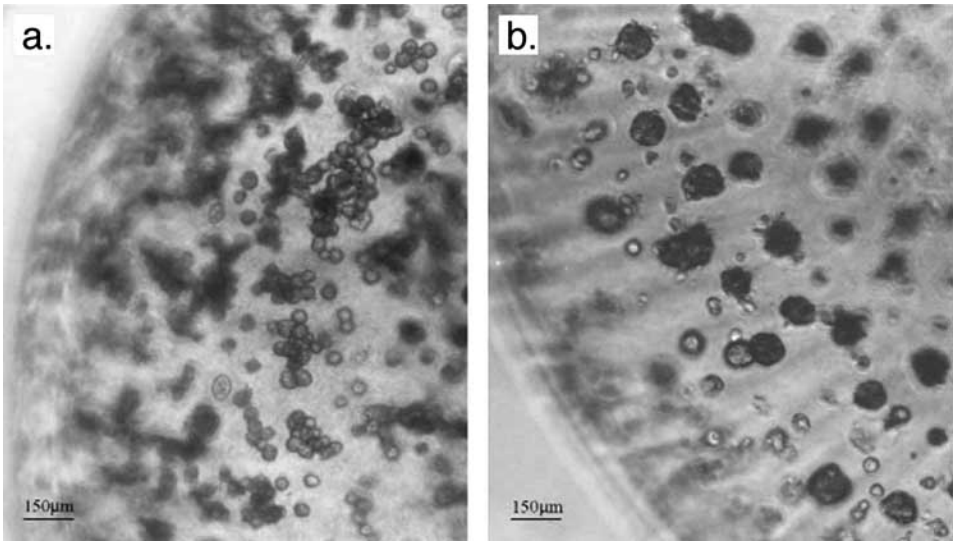

Fig. (7). Phase-contrast micrographs by Yang *et al*. show hepatocyte cells encapsulated in Ca^{2+}-crosslinked gels of alginate (**a.**) and galactosylated alginate (**b.**) In the galactose–alginate conjugate gel, cells were clustered in regularly distributed spheroids because of ligand interactions between the galactose pendants and cellular receptors [65].

encapsulated contents against the low pH of the stomach. Lactic acid bacteria encapsulated in the succinylated alginate matrix had improved survival in a pH 1.5 environment simulating gastric fluid; 22–26% of cells in native alginate gels remained viable, compared with 60% of cells in succinylated alginate gels.

An alginate–biotin conjugate was synthesized for use in biosensor applications [63]. The carbodiimide reaction between alginate and biotin was used to create a 10–13% modified product, which was deemed an appropriate density of biotin molecules while still retaining sufficient alginate gelling. The conjugate was fashioned into Ca^{2+}-crosslinked microspheres (0.9–1.0 μm diameter), which encapsulated genetically engineered bioluminescent reporter bacteria. The spheres were attached to the streptavidin coating of an optical fiber through biotin–avidin interactions. The authors of the study demonstrated control over the attachment for both single- and multi-sphere systems (Fig. **6**). The luminescence of the cells entrapped in the microspheres was transmitted along the fibers and used to detect various concentrations of mitomycin C, a naturally derived compound use as chemotherapy agent.

Small-molecule addition has been used to generate alginates with cell-specific adhesion ligands. Prior research has indicated that galactose acts as a ligand for asialoglycoprotein receptors on hepatocyte cells [64]. Ca^{2+}-crosslinked galactosylated alginate (GAC) gels were produced by carbodiimide coupling of alginate and ethylenediamine-modified lactobionic acid [65]. Hepatocyte cells immobilized in these GACs demonstrated self-organizational behavior, forming spherical aggregates (Fig. **7**). Additionally, hepatocyte adhesion to a galacosylated polystyrene surface was inhibited by addition of galactosylated alginate into the cell suspension fluid.

An important consideration for any carboxyl modification of cation-crosslinked alginate is the potential for undesirable reduction of crosslinking efficacy and corresponding mechanical properties. This problem was recently addressed in another publication on galactosylated alginate, featuring selective modification of uronic subunits [66]. Carbodiimide chemistry was used to couple alginate with 1-amino-1-deoxygalactose. The resulting conjugate product was subsequently modified with an enzymatic strategy; two C-5 epimerases were introduced to effect a change in unmodified M subunits into G subunits, thus increasing the number of Ca^{2+}-binding junction blocks. Rheological properties of the enzymatically treated conjugate were enhanced, compared with a galactose–alginate with addition to both M and G subunits.

5. CONCLUSIONS

Alginate is a versatile material with properties that make it appropriate and attractive for use in a wide variety of applications. Through adjustment of the alginate structure by covalent organic modification, a number of derivative polysaccharides have been produced with a wide gamut of material properties. Potential applications of these modified alginates include use in encapsulation matrices, immobilization and sorption surfaces, sensors, gels with tunable mechanical and other physical properties, and coatings for surfaces and particles. Modified alginates have demonstrated ability for mediating cellular behaviors such as adhesion and proliferation, and have shown potential for anti-fouling coatings. Organic modification is an effective means of tuning the behaviors and modulation effects of alginate-based encapsulation matrices, which are of interest for pharmaceutical and other biological applications. Interesting rheological properties have been achieved with amphiphilic alginate derivatives, which form physically crosslinked networks at low shear and low viscosity solutions at high shear. We expect that alginates modified with a variety of substituents, conferring a diverse assortment of chemical, biological and physical properties, will continue to be the subject of research and will continue to gain prominence in future publications.

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