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Review

Research progress on chemical modification of alginate: A review

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ABSTRACT

This review summarizes results of the recent research on chemical modifications of alginate that are as yet relatively unexploited commercially. Alginate is a linear, anionic polysaccharide consisting of two kinds of 1,4-linked hexuronic acid residues, namely β-D-mannuronopyranosyl (M) and α-L-guluronopyranosyl (G) residues, arranged in blocks of repeating M residues (MM blocks), blocks of repeating G residues (GG blocks), and blocks of mixed M and G residues (MG blocks). Alginate has an abundance of free hydroxyl and carboxyl groups distributed along the polymer chain backbone, and it, therefore, unlike neutral polysaccharides has two types of functional groups that can be modified to alter the characteristics in comparison to the parent compounds. Methods used for modification of hydroxyl groups of alginate include oxidation, reductive-amination, sulfation, copolymerization and coupling of cyclodextrin units. Methods used for modification of carboxyl groups include esterification, use of the Ugi reaction, and amidation. Furthermore, the characteristics and applications of some alginate derivatives are also summarized.

Contents

1. Introduction

Alginate is both a biopolymer and a polyelectrolyte that are considered to be biocompatible, non-toxic, non-immunogenic and biodegradable (Klöck, Pfeffermann, Ryser, Gröhn, Kuttler, & Hahn, 1997; Mi, Sung, & Shyu, 2002). It can be characterized as an anionic copolymer comprised of mannuronic acid (M block) and guluronic acid (G block) units arranged in an irregular blockwise pattern of varying proportions of GG, MG, and MM blocks (Matsumoto, Kawai, & Masuda, 1992). The mannuronic acid forms β (1→4) linkages, so that M block segments show linear and flexible conformation; the guluronic acid, differently, gives rise to α (1→4) linkages, which serves to introduce a steric hindrance around the carboxyl groups. For this reason the G block segments provide folded and rigid structural conformations that are responsible for a pronounced stiffness of the molecular chains. In Scheme 1 the M and G blocks of the alginates with their representative sequence are reported. The microstructural features of alginate are biocompatible unbranched binary copolymers that have been widely used as a type of desired biomaterials in many fields such as cell immo-

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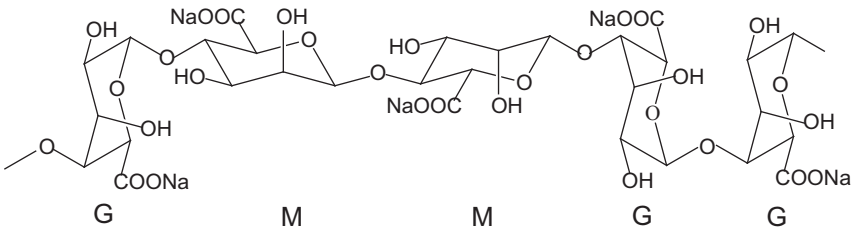


Scheme 1. Molecular structure of sodium alginate.

bilization (Orive et al., 2002), tissue engineering (Drury & Mooney, 2003), drug delivery (Lai, AbuKhalil, & Craig Duncan, 2003), controlled release (Ramesh Babu, Sairam, Hosamani, & Aminabhavi, 2007), immobilization of micro-organisms (Yakup Arıca, Çigdem, Ergene, Gülay, & Ömer, 2003), as well as in food applications (Moe, Dragel, Skjåk-Bræk, & Smidsrød, 1995).

Alginate is known to form a hydrogel in the presence of divalent cations, such as calcium (Ca^{2+}), which act as crosslinkers between the functional groups of alginate chains. Besides hydrogels induced by divalent cations, alginate can form acid gels at pH below the pK_a value of the uronic acid residues (Bu, Kjøniksen, Knudsen, & Nyström, 2004). These gels have been proposed to be stabilized by intermolecular hydrogen bonds. Just as we know, alginates have $–COO^-$ and –COOH groups along the chain conferring different charge densities depending on the pH. The hydrophilic and hydrophobic groups along a molecule chain can be altered by the protonation and deprotonation of carboxyl groups in the backbone chain (Yang, Chen, & Fang, 2009; Yang, Zhao, & Fang, 2008).

Alginate has a number of free hydroxyl and carboxyl groups distributed along the backbone, therefore it is an ideal candidate for chemical functionalization. By forming alginate derivatives through functionalizing available hydroxyl and carboxyl groups, the properties such as solubility, hydrophobicity and physicochemical and biological characteristics may be modified. Thanks to the efforts from many research groups, the chemical modification of alginate has been achieved using techniques such as oxidation, sulfation, esterification, amidation, or grafting methods. The alginate derivatives have been proved to be a lot of potential applications. In this paper, the synthetic methods of alginate derivatives are summarized. Furthermore, the characteristics and applications of some alginate derivatives are also discussed.

2. Chemical modification of the hydroxyl groups

2.1. Oxidation

In recent years, oxidation of alginate has received much attention because oxidized alginates present more reactive groups and a faster degradation when these ones are used in supports for drug controlled delivery (Boontheekul, Kong, & Mooney, 2005; Kong, Kaigler, & Mooney, 2004).

Oxidation reactions on –OH groups at C-2 and C-3 positions of the uronic units of sodium alginate are performed with sodium periodate (Scheme 2), which leads, by rupture of carbon–carbon bond, to the formation of two aldehyde groups in each oxidized monomeric unit. Therefore, larger rotational freedom and new reactive groups along the backbone are obtained. Exclusion of light during oxidation is essential for the limitation of side reaction. It is possible to control the alginate degree of oxidation by varying the concentration of the oxidant.

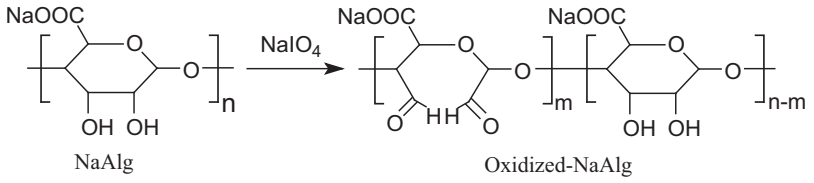
Gomez, Rinaudo, and Villar (2007) synthesized oxidized alginates at room temperature during 24 h, in aqueous solution of sodium alginate, using sodium periodate in the dark. Oxidation of alginate chain produced a decrease in the stiffness of the polymer by breaking C2–C3 bond with a chain scission as a simultaneous reaction. It was observed that over 10 mol.% oxidation no more gels were formed in excess of calcium even over their respective overlap concentration.

In order to improve the biodegradability of alginate, He, Zhang, Geng, Yin, and Yao (2005) performed the oxidation reaction using commercially available high molecular weight alginate with sodium periodate. Oxidized alginate fully degraded at physiological condition (37 °C, pH 7.4 PBS) after 100 h incubation and the molecular weight reduced from 11.2×10^4 g/mol to 3.6×10^4 g/mol.

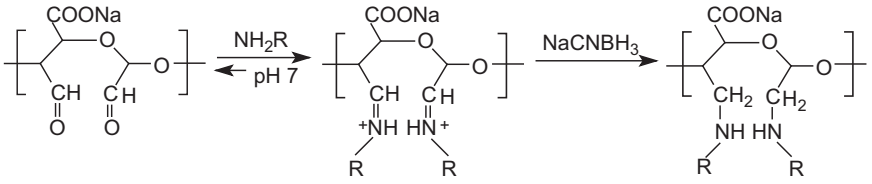
2.2. Reductive-amination of oxidized alginate

The oxidized alginate with aldehyde groups on the polymer chain gives new reactive groups for chemical modification especially by reductive-amination. The subsequent reductive amination is performed with alkyl amine by using $NaCNBH_3$ as reducing agent, as it is more reactive and selective than the frequently employed sodium hydroborate ($NaBH_4$). The advantage of $NaCNBH_3$ is that the reduction of imine intermediate groups by $CNBH_3^-$ anion is rapid at pH values of 6–7 and the reduction of aldehyde or ketone is negligible in this pH range (Scheme 3). The reaction was carried out as already described (Andresen, Painter, & Smidsrød, 1977; Carré, Delestre, Hubert, & Dellacherie, 1991; Kang, Jeon, Lee, & Yang, 2002). Kang, Shin, and Yang (2002) prepared new alginate-derived polymeric surfactants using this method. The addition of long alkyl chains to the alginates endowed them with amphiphilic characteristics, such as lower surface tension, solubilizing of solid azobenzene and adsorption of heavy metal in practical application.

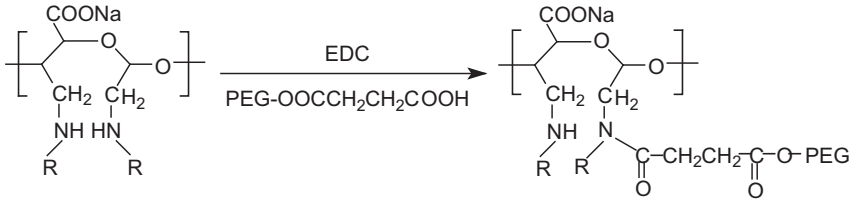
Li, Ni, Xiong, and Li (2009) made microsphere beads with the alginate-derived polymeric surfactants in aqueous solution of sodium chloride and calcium chloride. A hydrophobic drug of ibuprofen was loaded on the modified alginate for controlling release in vitro. It was found that the loading level of drug was obviously increased and the release rate was well controlled.



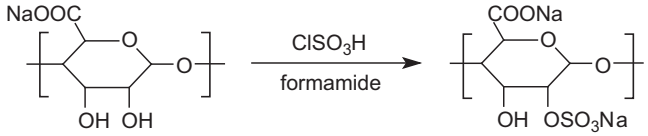
Scheme 2. Oxidation of sodium alginate.



Scheme 3. Reductive-amination of oxidized alginate.



Scheme 4. Synthesis of alginate-g-PEG copolymer.



Scheme 5. Sulfation of sodium alginate.

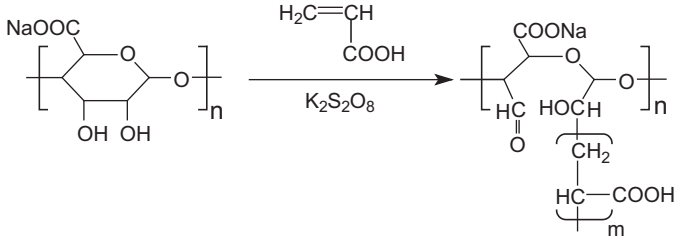
Laurienzo, Malinconico, Motta, and Vicinanza (2005) synthesized a novel alginate–polyethylene glycol (PEG) graft copolymer by reacting a mono-carboxyl terminated PEG with a sodium alginate modified by inserting a given amount of amine functionalities (Scheme 4). The coupling between PEG and alginate was carried out using carbodiimide chemistry in aqueous solutions. The alginate-g-PEG copolymers retain the gelation characteristics of alginate since the PEG chemical grafting does not consume the carboxyl groups. The presence of grafted PEG molecules inside alginate gels will increase the pore dimensions and, concurrently, will induce improved cell anchorage. The alginate–PEG copolymers are promising candidates for any application in which alginate gels with higher biocompatibility and pore dimensions are required, as for gel entrapment devices and microencapsulation techniques.

2.3. Sulfation

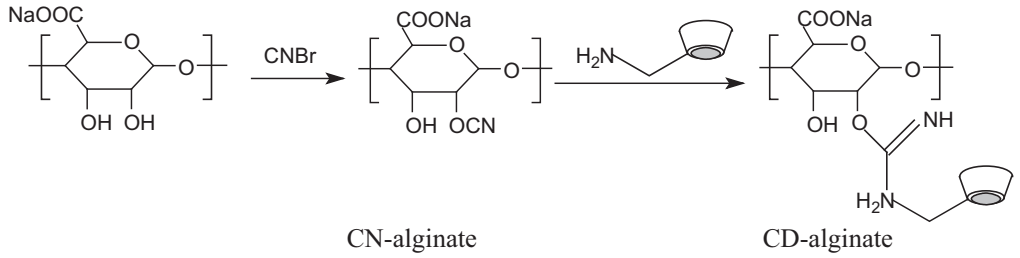
When alginate is sulfated it will show high blood compatibility because the structural similarity to that of heparin, which has been widely used for anticoagulant therapy for more than 60 years (Alban, Schauerte, & Franz, 2002). Huang, Du, and Yang (2003) reported the alginate sulfates prepared from sodium alginate through reaction with $ClSO_3H$ in formamide (Scheme 5). A simple procedure is summarized as follows: 10 g sodium alginate is added to the sulfating reagent containing 80 mL formamide and 20 mL $ClSO_3H$, and the mixture is preserved at 60 °C for 4 h to give a brown solution. 200 mL acetone is added to precipitate the solution, and the precipitate is redissolved in distilled water and its pH is adjusted to 10–11 by 0.1 mol/L NaOH, then the solution is dialyzed for 72 h and concentrated to give alginate sulfates. The in vitro coagulation assay of human plasma containing the sulfates indicated that alginate sulfates had considerably high anticoagulant activity especially to the intrinsic coagulation pathway.

2.4. Copolymerization

Liu and Cao (2002) reported a superabsorbent resistant to saline solution prepared from copolymer of sodium acrylate with sodium alginate (Scheme 6). Their research showed that if the superabsorbent was allowed to swell in distilled water and 0.9% (mass fraction) aqueous NaCl at room temperature for 30 min water absorbency of the superabsorbent was about 1000 and 85 times its own mass respectively. Meanwhile, the superabsorbent also had excellent hydrogel modulus. In addition, grafting reaction can take place at hydroxyl group. Sen, Singh, and Pal (2010) reported the synthesis of various grades of graft copolymers based on acrylamide and sodium alginate via microwave irradiation. Their experiment showed that the copolymer having higher percentage grafting and molecular weight is a better flocculant in coal suspension compared with other grades of the grafted polymer and sodium alginate. Sand, Yadav, and Behari (2010) reported an alginate-g-vinyl sulfonic acid prepared by employing potassium



Scheme 6. Copolymerization of sodium acrylate with sodium alginate.



Scheme 7. Synthesis of CD–alginate.

peroxydiphosphate/thiourea redox system. The synthesized graft copolymer shows better results for swelling, metal ion uptake, flocculating and resistance to biodegradability properties in comparison to alginate.

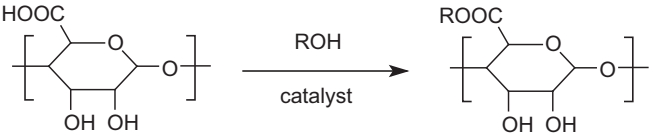
2.5. Cyclodextrin-linked alginate

The research of Pluemsab, Sakairi, and Furuike (2005) showed that the inclusion ability on alginate was introduced by covalently linking α-cyclodextrin (α-CD). The coupling reaction (Scheme 7) between α-CD and alginate was designed at the hydroxyl groups of alginate via CNBr method in order not to affect the carboxyl groups, which was necessary to form the calcium–alginate beads. A simple procedure is summarized as follows: sodium alginate (0.1 g) is dissolved in water (100 mL) and then reacts with CNBr (60 mg). The pH of reaction mixture is controlled to between 10 and 11 by dropping aqueous NaOH solution for 1 h. The CN-treated alginate is subjected to ultrafiltration through a membrane with molecular weight cut-off 10,000. The product is washed with water for 2 days. Subsequently, 6-amino-α-CD is added to the resulting solution, allowed to stir for 2 days and then washed by ultrafiltration to give the products. Using p-nitrophenol as a model compound the modified CD–alginate showed an ability to form a host–guest complex. Stable and spherical beads were also obtained simply by dropping an aqueous solution of modified CD–alginate into a calcium chloride solution. This novel synthesis may provide a useful combination between inclusion ability and gel-bead formation, which are in the field of environmental remediation as for bacterial encapsulation.

3. Chemical modification of the carboxyl groups

3.1. Esterification

Esterification often used as a simple method whereby alkyl groups are attached to molecules. This method was successfully used by researchers to modify native alginate, increasing its hydrophobic nature by the addition of alkyl groups to the backbone of the native alginate (Fischer et al., 1998; Leonard, Rastello De Boisseson, Hubert, Dalencon, & Dellacherie, 2004; Pelletier, Hubert, Payan, Choplin, Marchal, & Dellacherie, 2001; Sinquin, Dellacherie, & Hubert, 1993). Native alginate can be modified by direct esterification with several alcohols in the presence of catalyst and the alcohol is present in excess to ensure that the equilibrium is in favour of product formation (Scheme 8). Over the past few decades, in the esterified derivatives of alginate the only derivative having a commercial value was the propene glycol esters of alginate (PGA) that was obtained by esterification of alginate with propyleneoxide (Carré et al., 1991).

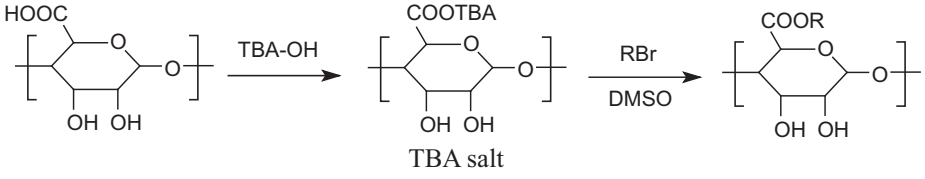


Scheme 8. Esterification of alginate and alcohol.

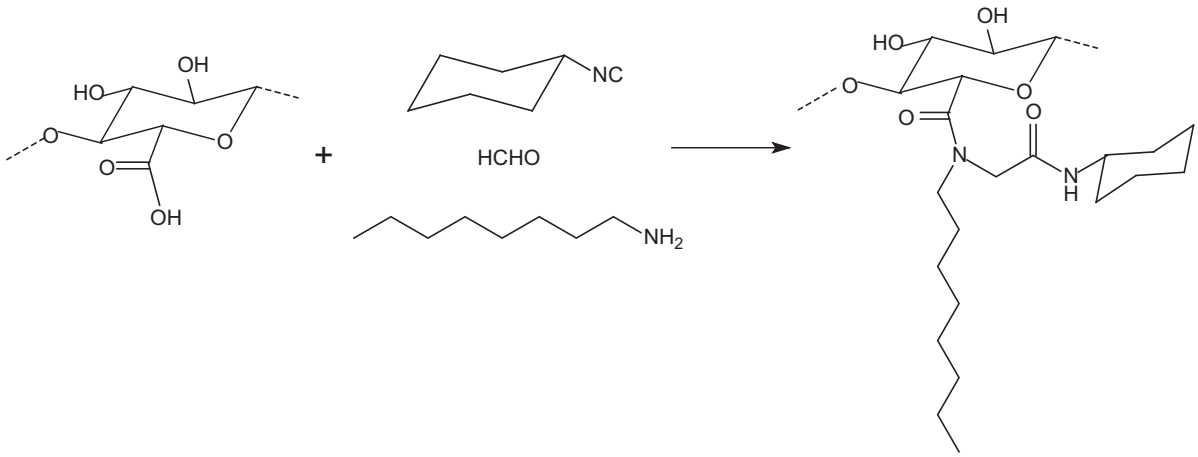
Yang, Zhang, and Wen (2007) synthesized a novel water soluble amphiphilic cholesteryl ester of alginate. The reaction between the carboxylic acid groups of protonated sodium alginate and the hydroxyl of cholesterol was carried out at room temperature for 24 h, after adding N,N′-dicyclohexylcarbodiimide (DCC) as a coupling agent and 4-(N,N′-dimethylamino) pyridine (DMAP) as a catalyst. Their research showed that the amphiphilic cholesteryl ester of alginate can self-assemble into the more stable and compact nano-aggregates through the intra- and intermolecular hydrophobic interactions between cholesteryl grafts in aqueous NaCl solution, compared with the parent sodium alginate.

Broderick et al. (2006) reported that butyl ester of alginate prepared from sodium alginate through esterification with butanol in the presence of concentrated sulphuric acid as catalyst at room temperature for18 h. The study showed that the novel material is capable of encapsulating both hydrophilic and hydrophobic molecules. Crucially, the all-important gelling and non-toxic properties of native alginate have been retained.

Moreover, some literatures (Babak et al., 2000; Boisseson et al., 2004; Pelletier, Hubert, Lapicque, Payan, & Dellacherie, 2000) introduced that ester of alginate prepared from an alkyl halide with the carboxylic groups of alginate, previously transformed into their tetrabutylammonium (TBA) salts, in homogeneous medium (Scheme 9). A simple procedure is summarized as follows: sodium alginate is first transformed into its acidic form, by treatment with ethanolic HCl. After filtration, the resulting acidic polysaccharide is washed with ethanol (70%) until any remnant of chloride ion is removed, then with acetone. After drying at room temperature and reduced pressure, this compound is dispersed in water and neutralized (pH 7.0) by tetrabutylammonium hydroxide (TBA-OH) under



Scheme 9. Esterification of alginate and alkyl halide.



Scheme 10. Ugi four component reaction.

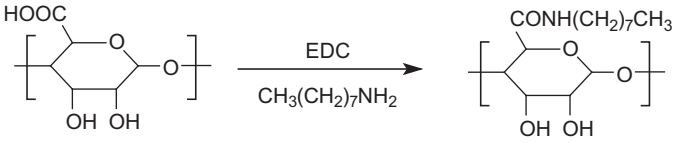
controlled-delivery conditions. The TBA salt of alginic acid is dissolved in dimethylsulfoxide (DMSO). Then an alkyl halide (dodecyl bromide) is introduced at adequate stoichiometry and left to react for 24 h under stirring at room temperature. The long alkyl chains are thus linked to the backbone of alginate chain via ester functions. NaCl is then added to the solution in order to exchange TBA^+ by Na^+. Sodium alginate derivatives are finally recovered after precipitation in 70% ethanol, filtration, and drying at room temperature.

3.2. Ugi reaction

The Ugi reaction is a multi-component reaction in organic chemistry involving a ketone or aldehyde, an amine, an isocyanide and a carboxylic acid to form a bis-amide (Ugi, 1962). It is an important reaction used in combinatorial chemistry (Ma, Li, & Zhao, 2003). Bu, Kjøniksen, and Elgsaeter (2006), Bu, Kjøniksen, Knudsen, and Nyström (2005) and Bu, Nguyen, and Kjøniksen (2006) reported that the hydrophobically modified alginate prepared by the Ugi multicomponent condensation reaction (Scheme 10). The synthesis procedure is summarized as follows: native alginate is dissolved in water at room temperature by weighing the components, and is gently stirred overnight to obtain a homogeneous solution. The solution is then slightly acidified with 0.1 mol/L HCl to obtain the acidity (pH 3.6) necessary for the Ugi reaction to proceed (Ugi, Lohberger, & Karl, 1991). The molar amount (12 mol.%) of the n-octylamine groups is calculated with respect to the molar amount of carbohydrate monomers. The other components are added to the reaction mixture in an excess of about 40%. Formaldehyde, n-octylamine and cyclohexyl isocyanide are added to the solution successively. After the addition of each component, the solution is stirred vigorously to disperse the components homogeneously in the solution at room temperature for 24 h. The diluted reaction mixture is dialyzed against pure water for several days to remove the unreacted monomers as well as other low-molecular weight impurities, and thereafter the solution is freeze-dried.

3.3. Amidation

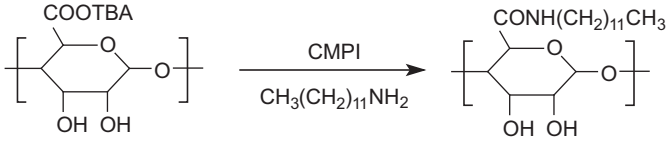
Galant, Kjøniksen, Nguyen, Knudsen, and Nyström, 2006 reported that alginate was hydrophobically modified by use of the coupling agent 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC-HCl) to form amide linkages between amine-containing molecules and the carboxylate moieties on the alginate polymer backbone (Scheme 11). The preparation of alginate derivatives via amide linkage has also been reported in literatures (Gomez, Chambat, Heyraud, Villar, & Auzély-Velt, 2006; Polyak, Geresh, & Marks, 2004; Yang, Goto, Ise, Cho, & Akaike, 2002; Zhu et al., 2002). This type of reaction is described as follows: an aqueous solution of sodium alginate is adjusted to pH 3.4 by addition of HCl, then this solution was added a certain amount of EDC-HCl. After 5 min of reaction, octylamine was added and the mixture was stirred for 24 h at ambient temperature. The product was isolated by precipitation in acetone and the polymer was collected by filtration. To remove low molecular weight impurities, the polymer was thoroughly dialyzed against water and isolated by freeze-drying.



Scheme 11. Amidation of alginate using EDC as coupling agent.

Abu-Rabeah, Polyak, Ionescu, Cosnier, and Marks (2005) reported that coupling of N-(3-aminopropyl) pyrrole to the alginate via amide linkages was achieved using the same method. They found that the pyrrole–alginate conjugate prepared at a degree of 30% of molar modification can be efficiently electropolymerized, providing a biocompatible host matrix that retained enzyme molecules by both gellification and electrochemical cross-linking.

Vallée et al. (2009) reported that new amphiphilic derivatives of sodium alginate were prepared by covalent attachment of dodecylamine onto the polysaccharide via amide linkages at different substitution ratios, using 2-chloro-1-methylpyridinium iodide (CMPI) as coupling reagent (Scheme 12). The derivatives are prepared as follows: Na^+ alginate is transformed into its acidic form, and then neutralized to pH 7 by TBA^+OH^-. The TBA-alginate salt is dissolved in DMF and stirred overnight to allow its complete dissolution. Then CMPI (required amount) and an excess of dodecylamine are added at 0 °C. Triethylamine is added into the solution at a concentration similar to that of dodecylamine. The solution is kept at 0 °C for 45 min, and then left at room temperature for 20 h. Aqueous NaCl is added to the solution in order to exchange TBA^+



Scheme 12. Amidation of alginate using CMPI as coupling agent.

by Na^+ ions. Finally, the polymers are purified by precipitation in 7:1 EtOH–water, washed three times and dried under diminished pressure.

4. Outlook

A significant amount of research has been aimed at modifying alginate chemically, due to free hydroxyl and carboxyl groups distributed along the backbone, to alter the characteristics in comparison to the native alginates. However, only very little of alginate chemically modified derivatives such as propylene glycol alginate have been used for many years in some industries, while others have not yet been employed commercially. Although there has been extensive work on synthesis of alginate derivatives, there are still many potential pathways that have yet to be investigated, and meanwhile, it must be paid greater attention that the applications of alginate derivatives in various fields still holds considerable promise for the future.

Acknowledgements

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