Chapter

Alginates - A Seaweed Product: Its Properties and Applications

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Abstract

Alginates are natural polysaccharides available as seaweed products. They possess several properties due to their molecular structure made of bipolymeric \( \alpha \)-L-Guluronic acid and \( \beta \)-D-Mannuronic acid polymers. Alginates have several properties such as film-forming ability, pH responsiveness, and gelling, hydrophilicity, biocompatibility, biodegradability, non-toxic, processability and ionic crosslinking. They’re commonly used in several industries, including food, pharmaceuticals, dental applications, welding rods and scaffolding. Due to their gelling and non-toxic properties, as well as their abundance in nature, the cosmetics and healthcare industries have shown a great deal of interest in biodegradable polymers in general and alginates particularly over the last few decades.

Keywords: Alginates, hydrogels, biodegradable polymers, controlled drug delivery, seaweeds

1. Introduction

Polymers are the chemical compounds that play a significant role in the development of medicine and engineering with day-to-day life. Polymers are made of several repeating units of monomers, which decide the structure and properties. In the field of medicine, a range of polymeric materials is being used, however, biodegradable polymers gaining more attention.

Brown algae are composed primarily of alginates, a carbohydrate polymer found in the form of an insoluble combination of potassium, sodium, magnesium, and calcium salts of alginic acid that are structural components of brown seaweed cell walls. They are unbranched binary polymers made up of 1, 4 linkages between \( \beta \)-d-Mannuronic (M) and \( \alpha \)-l-Guluronic (G) acids [1]. The composition of alginates i.e. G: M ratio varies based on the source [2]. They can also be tailored or resized in many varieties by varying molecular weight, cation content, particle form, volume fraction and, G: M ratio.

Alginates were first used in 1883 by a researcher named Edward Stanford, and commercial development commenced in 1927. The global production of alginates has now risen to about 40,000 tonnes per year. Alginates are used extensively in the food, pharmaceutical, cosmetic, and dental industries [3]. Perhaps, in recent years, the medical and pharmaceutical industries have become incredibly influential in biopolymers, specifically alginates.

Alginates are particularly known for their applications in pharmaceutical industries for controlled drug delivery [4], wound healing [5], dermatology [6],...
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and scaffolds [7] because of their properties such as natural disintegration, gel formation, biocompatibility, and non-toxicity. Alginates are a natural gum that has an advantage over synthetic polymers because they form hydrogels, are less expensive, and are readily accessible. Alginate gels may also be orally administered into the body in a minimally invasive manner, enabling a wide range of pharmaceutical applications. Alginate gels are promising biomaterials for tissue engineering and cell transplantation, to replace organs in patients that have lost or failed organs or tissues (Figure 1) [8, 9].

2. Properties of alginates

Brown algae obtained from seaweeds such as Laminaria hyperborea, Laminaria digitata, Laminaria japonica, Ascophyllum nodosum, and Macrocystis pyrifera are used to make commercially available alginates [10]. In general, alginates are insoluble compounds; they are washed, crushed, dried, powdered, and treated with a basic solution especially NaOH or KOH to form sodium/potassium salt of alginic acid which is water-soluble (Figure 2).

Alginates are generally available in the market as Alginic acid of sodium salt or Sodium alginate [12]. Alginates due to their acidic nature make them a favorable biopolymeric biodegradable product in biomedical applications. Because of high acid content, alginates form gels due to the presence of Guluronic acid (G) monomer in alginates within a short period especially in the presence of Ca$^{2+}$ ions. This property of gelling allows the alginate to possess multiple applications such as encapsulation of varied fragments or even cells interior of the alginate matrix with very low side effects [13]. The carboxylic group in alginates are very effective i.e. reason find many applications and can be modified based on the need [14].

Bacteria such as Pseudomonas and Azotobacter can develop bacterial alginate as an exopolysaccharide. These bacterial alginate producers may be able to produce alginates with particular monomer formulations and might be capable of producing ‘tailor made’ bacterial alginates using genetic and protein engineering [15].

2.1 Molecular weight

Alginates obtained from different locations in a sea bed have different molecular weights ranges between 50,000 to 5lakhs [16]. The viscosity of the alginate solution

Figure 1. Alginate –Brown algae a seaweeds.
is pH-responsive and increase viscosity is reported with the decrease in pH and reaches a pH ~ 3.5 because carboxylate groups in Guluronic acid present in the alginate structure protonated and form hydrogen bonds [17]. Alginates may have different molecular weights depending on whether they need to monitor pre-gel solution viscosity or post-gelling strength distribution separately. To adjust the viscosity of the solution, a mixture of high and low molecular weight alginate polymers is used [18].

2.2 Biocompatibility

The biocompatibility of alginate has been extensively evaluated in-vitro as well as in-vivo at varying levels of purity. It has been reported that alginate containing high M monomers are more immunogenic and 10 times more effective in promoting cytokine synthesis compared to G monomer in alginates [19], but others reported very little response or no immune response across alginate implants [20]. Impurities in the alginates, such as heavy metals, endotoxins, proteins, and polyphenolic compounds, may be causing the variable reaction at the injection or implantation sites. However, not many serious inflammatory results were reported in commercially available or certified or alginates obtained from branded companies [21].

2.3 Alginate derivatives

Alginates are exploited or synthesized for various biomedical applications by introducing different hydrophilic moieties such as alkyl groups or hydrophilic polymers in the alginate matrix. Long-chain alkyl groups such as dodecyl or octadecyl are bonded with alginates matrix via esterification. The various properties such as rheology, gelling and crosslinking characteristics are very useful in bone regeneration and cartilage repair [22]. Sustained or controlled drug delivery vehicles are achieved from alginate derived from Poly (butyl methacrylate) [23].

Alginates are also investigated for their derivatives with cell-adhesive peptides are prepared by adding peptides as side chains and coupled through the carboxylic groups of the sugar residues [24, 25].

2.4 Gelling properties

The ability of aqueous alginate solutions to form gels when treated with divalent ions (Ca$^{2+}$, Sr$^{2+}$, and Ba$^{2+}$) or trivalent ions (Fe$^{3+}$ and Al$^{3+}$) ions has been extensively explored for the fabrication of carriers for sustained or controlled delivery of therapeutic agents. This is due to intramolecular bonding and ionic interactions that exist
within the carboxylic acid groups on the polymer matrix and the cations present as shown in Figure 2 [26, 27].

The calcium or any other divalent or trivalent ions will interact with the G monomer present in the alginate structure to crosslink with another molecule, and the structure is identical to the egg box model (Figure 3) [28].

The complexing forming agents such as EDTA-sodium citrate [29] or monovalent cations, complex anions (phosphate, and citrate) which have a high affinity for Ca\(^{2+}\) ions, which can disrupt calcium alginate gels easily. The presence of high concentrations of non-gelling ions (Na\(^{+}\) and Mg\(^{2+}\)) also contributes to the instability. It was reported that the strength and uniformity of gelling largely depend on the type of crosslinking and temperature [30].

It is also reported that the strength of alginate film with Al\(^{3+}\) ion is very low compared to other divalent ions (Ca\(^{2+}\) and Ba\(^{2+}\)) crosslinking because in the case of Al\(^{3+}\) ions the crosslinking occurs in two different planes of the alginate structure and at the same time it makes the alginate framework more compact [31]. The small size of the Al\(^{3+}\) ion (0.58 Å) facilitates its diffusion into the matrix of the film without crosslinking on the surface and thus results in poor crosslinking [32].

For a variety of uses, including tissue engineering, alginates are being investigated for covalent bonding to enhance the physical properties of gels. In the case of alginates with covalent bonding degradation of chain occurs even with a slight increase in temperature due to breaking of crosslinks ultimately leading to stress relaxation due to water migration. It was reported that covalently bonded alginates are found to be toxic [33]. Furthermore, the Ca\(^{2+}\) ions released out of the gel can boost hemostasis, while the gel acts as a matrix for platelet and erythrocyte aggregation [34].

To prepare gels with a wide spectrum of mechanical properties, covalent crosslinking of alginate with Poly (ethylene glycol)-diamines of different molecular weights was first investigated. The elastic modulus showed improvement in gel with crosslinking density or weight fraction of Polyethylene glycol (PEG), but then decreased as the molecular weight between cross-links increased became less compared to the original PEG [35]. Using various types of cross-linking molecules and regulating cross-linking densities, it was later investigated that the mechanical properties, as well as swelling of alginate strength, are tightly regulated. As most would imagine, the chemistry of the cross-linking molecules has a major impact on hydrogel swelling. While shaping hydrogels, multi-functional

Figure 3.
The divalent calcium cation binds in the cavities of alginates like eggs in an egg box.
cross-linking entities have a greater scope of degradation efficiency and mechanical strength performance than bi-functional cross-linking molecules. Physical properties and degradation behavior of Poly-aldehyde guluronate (PAG) gels are prepared with either Poly-acrylamide-co-hydrazide (PAH) or Adipic acid dihydrazide (AAD) as a cross-linking agent were investigated in-vitro. PAG/PAH gels had higher mechanical stiffness and very low degradation is observed compared to PAG/AAD gels [36].

Photo crosslinking is used for crosslinking in alginates structures under mild conditions either direct or indirect sunlight or in the presence of suitable initiators. For example, the mechanical properties of Polyallylamine and alginate were significantly improved from this technique [37].

2.5 Solubility

The alginates with divalent or trivalent cations are not soluble in water because the alginates contain a terminal carboxylic ion (–COO–), so these cations bond to this and yield an insoluble product. As a consequence, the alternative is the absorption of as much as 200–300 times their weight in water, thus swelling to a hydrogel of paste-like consistency. However, alginates with monovalent cations (Na+, K+, and NH4+) are soluble in hot and cold water. Alginates have a wide range of solubilities due to their different molecular weights.

Alginates derived from Ascophyllum, for example, have aqueous solubility in the range of 22–30% weight percent, whereas those of two Laminaria groups are 17–33% weight percent and 25–44% weight percent, respectively [38, 39].

2.6 Effect of pH on alginates

The solubility of alginates was influenced by parameters such as pH and ionic strength. Alginates have very low solubility in lower pH values due to the deprotonation of carboxylic groups (–COO–). The viscosity of alginates is unaffected above pH > 5, whereas solution having pH < 5, the COO- group present in alginates gets protonated to –COOH, and the electrostatic repulsion between chains decreases, they can move closer together to form hydrogen bonds, whereby the viscosity decreases [40]. It has been reported pH > 11 alginates viscosity is reduced due to de-polymerization [41].

The concentration of ionic solution influences the crosslinking, which increases the viscosity and molecular weight of alginates [39, 42]. Furthermore, the cross-linking depends on the confirmation of monomers G and M groups present in the alginate matrix.

2.7 Sterilization

It is reported that the viscosity of alginates decreases with autoclave sterilization because the heating randomly breaks alginate chains. The degree to which this loss occurs is determined by the presence of other kinds of stuff in the solution. Alginate solutions have also been sterilized using γ-radiation and ethylene oxide [43].

2.8 Immunogenicity

Control drug delivery is the latest trend in the presence of pharmaceutical dosage requirements for successful application in drug carriers; alginates play an important role because of their biocompatibility and immunogenicity [44].
The two key factors responsible for alginate immunogenicity are its chemical composition and the mitogenic pollutants present in alginates [45]. When alginate comes into contact with blood, it is believed to have mild cytotoxic effects and decreased hemolysis.

2.9 Biocompatibility

The biocompatibility and strength of alginic acid are determined by the quantity and quality of the acid. Furthermore, the impacts of the quantity of G monomer on alginate biocompatibility are still under investigation. Experts find different opinions on the G content of extremely purified alginate rich in G monomer residues, while others have emphasized the importance of high purity while ignoring the effects of chemical composition [46]. Animals such as rats are injected in their kidney parts with calcium alginate for biocompatibility studies and the results obtained are very promising [45].

Alginates are also experimented on in mammals and observed that they could not digest because they lack the enzyme ‘Alginase’ that can break the polymer chains. Whereas ionically cross-linked alginate gels undergo dissolution by replacing the divalent crosslinked gel with monovalent cations into the surrounding media. Even alginites dissolve in the body they cannot be expelled from the body because of its high molecular weight are higher than renal clearance [47]. It is reported, alginates were obtained from Undaria pinnatifida, a brown seaweed invasive in the Argentinean coast are found to be toxic, but its purification using commercial techniques improves its biocompatibility and eliminates cytotoxicity in an alginate matrix for bone tissue engineering [48].

2.10 Bioadhesion

The binding or contact between two surfaces, one among being a biological substrate, is known as bioadhesion [49]. Mucoadhesion is an example in which the mucosal layer is used. The carboxyl group in alginates represents a mucoadhesive anionic polymeric layer. It was reported polyanion polymers are more efficient bioadhesives compared to polycation or non-ionic polymers [50]. Alginate has better mucoadhesive strength as compared to polymers like Polystyrene, Chitosan, Carboxymethyl cellulose, and Poly (lactic acid). The bioadhesive properties of alginate would be advantageous as a mucosal drug delivery vehicle to the GI tract and nasopharynx by extending drug residence time at the site of action making them more effective [44, 51, 52].

2.11 Toxicity

Plenty of studies are reported that alginates especially crosslinked sodium/calcium alginates are non-toxic to cells, even not shown any irritation to eyes and skin [53]. Because of the nontoxicity, they found various applications in drug delivery, cosmetics, and food industries.

3. Applications of Alginates

Alginites are available in plenty in oceans and because of their diverse properties such as biodegradation, biodegradable, non-toxic, etc., as mentioned above; they have plenty of applications in the food industry, pharmaceuticals, cosmetics, textile industry, welding, and animal feeds, etc.
3.1 Food industry

FAO/WHO approves that alginates are the safest food additives because of its unique properties in food applications [54]. Over decades, alginates are used in a variety of food items, such as ice cream toppings, fruit jams, jelly, milk products, food packing, instant noodles, beer, etc., because of their unique properties such as thickening, gelling, emulsification, stabilization, texture functionality.

3.2 Pharmaceuticals

In the present medical field, many medicines or drugs administered to patients are causing a lot of side effects. Hence, there’s a lot of demand created in the world for drug loading carriers which increase drug resident time in-vitro or in-vivo, especially in the gastrointestinal tract and on the exterior part of the human body should be safe and non-toxic. The developments of alginates and alginate derivatives are discussed about controlled drug delivery, sustained drug delivery, and targeted drug delivery, etc.

3.2.1 Controlled drug delivery

In general, the structure of alginates gels shows it possesses porous size (~5 nm) helps to fill this gap with small molecular weight drugs through either physical or chemical bonding. When a drug-loaded/embedded drug comes in contact with an aqueous medium, the drug release is controlled. Furthermore, the drug-loaded carriers are water-soluble and may undergo degradation in an aqueous medium, hence crosslinking the alginates with bivalent or trivalent cation will enhance the stability of the gels or films. These properties help us to study the kinetics of drug release. The Sodium salt of alginic acid (SA) and Polyethylene oxide blends are investigated for controlled release of Valganciclovir hydrochloride in-vitro, as an anti-HIV drug [55]. Floating microbeads made of SA and modified Chinese yam starch investigated for controlled delivery of Metformin hydrochloride drug [56]. SA and Chitosan blend with different wt% of Montmorillonite (Cloisite 30B) solution studied for controlled release [57]. An anti-cancer drug such as Paclitaxel was loaded and investigated for release in-vitro in variable pH medium, time, and drug concentrations. SA and Xanthum gum blends crosslinked with zinc acetate loading Ranitidine hydrochloric acid drug in vitro release investigated in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (pH 1.2) [58]. Oral delivery of protein drug is explored for Bovine serum albumin (BSA) using composite microparticles made of Chitosan, SA, and Pectin crosslinked by tripolyphosphate [59]. A pH-responsive Tamarind seed polysaccharide and alginate blends are studied for controlled release of Diclofenac sodium. Swelling and degradation studies were also investigated in different pH mediums [60].

An anti-inflammatory drug such as Nifedipine is investigated for microspheres made of SA and Methylcellulose using Glutaraldehyde as crosslinking agent [61].

The Acrylamide and Poly(vinyl alcohol) beads with SA are grafted on exposure to UV radiation and further crosslinked with glutaraldehyde. The crosslinked beads are used to study the controlled release of Diclofenac sodium drug [62].

The transdermal films are synthesized using SA and Xanthum gum. The films loaded with Ketoprofen drug is studied in vitro for skin permeation [63].

SA mixture with Sodium Carboxymethylcellulose, Carbopol-934, and Polyvinyl pyrrolidin e backing membrane (Ethylcellulose), and Glycerol as plasticizer give promising results for control of drugs [64].
Hypertension drugs such as Felodipine were investigated for control release from alginate microspheres in combination with a mixture of Hydroxypropyl methylcellulose, Eudragit RS 30D, and Chitosan in simulated intestinal media [65]. Bioadhesive ocular insert of Ciprofloxacin hydrochloride using SA as gel and Chitosan as bioadhesive agent, Glycerin as a plasticizing agent are used in vitro release studies were carried [66].

3.2.2 Protein delivery

The proteins drugs are in high demand and thanks to advances in recombinant DNA technology, a diverse variety of protein drugs are now available. Alginates are an ideal candidate for protein drug delivery because they can load into the alginate matrix at different formulations at relatively mild conditions which can avoid denaturation as well as degradation. A variety of techniques are explored for the controlled release of protein from alginate gels. Alginates are known for minute pores due to the presence of G and M blocks because of their bi-polymeric structural arrangements. The vascular endothelial growth factor binding to alginate hydrogels is successful in sustained and localized release [67, 68]. It is reported that alginate microspheres are efficiently loaded with lysozyme and chymotrypsin for sustained release [69]. Oral delivery of proteins such as Amino group-terminated Poly[(2-dimethylamino) ethyl methacrylate) with alginate gel beads was prepared [70]. Alginates are explored for stimuli-responsive gels in the synthesis of tetra-functional acetal-linked polymer networks with adjustable pore sizes.

Bovine serum albumin is used as a model protein using blends made of alginate, chitosan, and pectin composite mixture [71]. In another work, hemoglobin as a model protein loaded in poly (L-histidine)-chitosan/alginate microcapsules are reported [72, 73].

3.2.3 Wound dressing

Any injury, burns, torn, muscle pains, cuts occurring on the human body may take a longer duration for curing for even applying any ointments such as antiseptic, antimicrobial, anti-inflammatory, antipruritic, pain-relieving gels, anti-mycotic with fungal action may cause skin irritation or side effects. Hence alginates due to their appreciable properties and due to their non-toxic are extensively used in wound healing to load appropriate drugs in alginate gels and which increases the retention time of the drug, so that the drug release in small dosages on the specific site. Alginates also have hemostatic properties, making them useful in the treatment of bleeding wounds. Several investigations are reported which initially experimented on animals such as mice, pigs, and rabbits. Alginates are employed to make hydrogels, films, wafers, foams, nanofibers, including therapeutic formulations for wound dressings. Alginate wound dressings readily absorb wound fluid, maintain a physiologically moist atmosphere, and protect against bacterial infections at the wound site. Since alginates are poor in mechanical strength are blended with other polymers or composites to improve film strength. The amount of M-block presents in alginate influences the immunogenic effect and M-block induces cytokine production (Table 1; Figure 4) [81].

3.3 Alginates in cosmetics

Scientists have been researching alginates for decades to create high-quality cosmetic products that provide all benefits to the skin. Alginates, being marine
plants known to absorb UV rays, repair the sun’s harmful effects, moisturize the epidermis, skin smoothening, and ensure the small cells renewal [83]. Alginates, in general, are known for gel formation can thicken and maintain moisture, are used in a variety of cosmetics. By forming a gel network, alginate assists in the retention of lipstick color on the lips and face creams as well as body lotion moisturizers. To make stable all-around lotions, alginate a natural thickener is incorporated in sunflower wax. Polysorbate-20 is the best commercial product is manufactured which is a smooth lotion in which instant cold emission products are combined with an emulsifier [84]. Alginates are a natural polysaccharide that possesses a very high viscosity and has a strong potential for water absorption. Perhaps, alginate’s viscosity can be optimized to ensure maximum viscosity. Alginates are explored for anti-aging masks and face masks which slow down the aging process, even wrinkles and lift the skin. Also, alginates are explored in Dentures which removable set of replacement teeth and gum tissue that can provide you with the complete backing and attractive appearance you need, even as you age.

Alginates application indentures are a removable set of restorative dentistry and gum tissues that can provide us with both the complete backing and beautiful appearance even at older age (Figures 5 and 6) [87].
3.4 Alginates in the textile industry

Color paste substrates are prepared using textile-grade alginates in the application of patterns in print fabrics, shawls, towels, and other products. Alginates are cleaner and easier to decompose substrate for textile printing than other substrates. Alginates application in printing cotton, jute, and rayon allows for easier disposal of wastewater. Sodium alginates are thickeners used in textile printing to thicken the dye paste. Screen or roller printing devices may be used to apply the pastes to the cloth. Alginates became common thickeners with the discovery of reactive dyes. The cellulose in the cloth reacts chemically with these substances. Many popular thickeners, such as starch, react with reactive dyes, resulting in lower color yields and sometimes difficult-to-wash-out by-products. Alginates are the strongest thickeners for reactive dyes because they non-reactive with the dyes and quickly washout from the finished textile.

In older screen printing the alginate of medium to high viscosity is used, whereas in modern high-speed roller printers even low viscosity alginates are giving very attractive printing.

3.5 Welding rods

Welding is the technique finds application building all kind of structures with metals. In the welding, process coating is used as a flux and to monitor conditions.
near the weld, such as temperature, and oxygen, and hydrogen. In this case, sodium silicate (water glass) is mixed with the dry coating ingredients to provide some of the plasticity needed for coating extrusion into the rod and to tie the dried coating to the rod. The silicate, on the other hand, neither binds nor provides enough lubrication to allow for successful and smooth extrusion. A lubricant and a binder are needed to keep the damp mass together before extrusion and to keep the coating on the rod in form throughout drying and baking [88]. To achieve these standards, alginates are used.

3.6 Alginates used in animal feeds

Alginate salts of sodium and potassium are meant to be used as industrial substances as emulsifiers, stabilizers, thickeners, gelling agents, and binders. There is no competent authority that has recommended the usage of sodium alginate in feeding stuffs for dogs, other non-food-producing animals, and fish. Whereas potassium alginate is used in cat and dog food at a speck of 40 g/kg feed [89]. The use of alginates in fish feed has no harmful effect on the consumer. Alginates are said to be slightly irritating to the eyes but not to the skin. The use of these ingredients in fish feed poses no threat to the aquatic environment.

A gel-type livestock feed mixture is formed by mixing feed nutrients, water, alginate, and a water-insoluble calcium component to resist the calcium content from reacting with the alginate. The calcium component is solubilized or the sequestrate affecting the reactivity between the alginate and the calcium component is extracted after the feed mixture is formed, resulting in a gel feed containing a gel matrix containing the feed nutrient ingredients. The livestock can then be fed the gel meal [90].

4. Conclusions

Alginate is a seaweed product which is a polysaccharide or carbohydrate polymer has plenty of applications in day-to-day life due to its potential characters. The Alginate properties such as biocompatibility, biodegradability, hydrogel formations, nontoxic, pH-responsive, and its ability to form a gel with crosslinking agents find their application in controlled, sustained, and targeted drug delivery carriers for a wide range of drugs or any other bioactive agents. Alginates films like any other hydrogels lack physical strength, which can be overcome by crosslinking with different divalent or trivalent cations. A continuous challenge was on researchers to explore the possibility of modification of alginate structure by grafting with other low or high molecular weight polymers to improve its strength based on the need of the application. Biomedical applications, specifically in wound healing in-vitro cell culture, and tissue engineering, look interesting as a potential biomaterial. Acid-responsive drugs and drugs that irritate the gastric mucosa can also be released with alginate. Alginates in combination with other polymer additives or nanoparticles are used in wound healing in diabetic wounds, ulcers, and burns. Alginates are used in an increasing number of food-related applications and have the potential to be used in a growing number of food-related applications. The gelling property of alginates makes them ideal for use as thickeners, stabilizers. Alginate consumption has several physiological effects in the gastrointestinal tract and in the body that are similar to a variety of other viscous polysaccharides. Dentures made of alginates composites are found to be very flexible, removable, and compact with the gum tissues. The high viscosity of alginates finds suitable thickeners in the textile industry as a paste containing a dye that can be applied to the fabric by either screen or roller printing. Potassium alginates and gel-type animal feeds are found to highly nutritious for cats, fishes, and piglets.
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