



Review Article

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Advanced Applications of Biomaterials Based on Alginate

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Abstract

Alginate acid, also known as alginate or alginate, is a natural carbohydrate, which is derived from marine brown algae, as well as some microorganisms. It can be used in various applications. In particular, alginate has shown great potential in the areas of wound healing, drug delivery, in vitro cell culture, and tissue engineering, allowing the categorization of it as a promising biomaterial, or a basic component of other biomaterials. The unique characteristics of alginate acid, such as the biocompatibility, the mild required gelation conditions, the low toxicity, the relative low cost and the simple modifications, allow the development of alginate hydrogels, and alginate derivatives with enhanced properties. The aim of this review, is to present an overview of the properties of alginate, shedding light on the current and potential applications and suggesting new perspectives for future studies.

Introduction

Innovative biomaterials made of various constituents seems to be very attractive for biomedical and pharmaceutical applications [1]. Recently, the increasing needs for raw materials, in order to be used for the development of various biomaterials and applications, lead to the use of materials, derived from the nature [2]. Nature materials were utilized in biomedical application, such as in wound healing or in prosthetics, but eventually there were replaced by synthetic polymers and ceramics in the previous century [2]. The new trend in the design of biomaterials focuses on biomimetic approach [3]. Thus, natural materials have currently regained the attention of material science and engineering [4]. Since, a significant part of the earth's surface is covered by water, it is reasonable that marine flora and fauna are characterized by a great biodiversity [5]. Thus, marine life provides a variety of choices, depending on the desirable properties [6]. It has been reported that many aquatic organisms possess antibacterial, anti-fungal, anti-inflammatory, anticancer neuroprotective, analgesic and immunomodulator properties [6].

In the surface of brown seaweeds, it is usual to find novel bacteria containing alginate lyase(s), which is the target

microorganism, for extracting alginate [7]. Thus, marine algae are considered as a significant source of natural polysaccharides and various nutrients, such as vitamins, sterols, salts, with original physical properties [8,9].

Alginate acid, also known as alginate or alginate, is a natural anionic carbohydrate. Actually, alginate is a linear polysaccharide [10]. It is derived from marine brown algae, as well as some microorganisms [11] (Figure 1). The properties of alginate, including biocompatibility, low toxicity, relative low cost and ease of gelation, make it an ideal biomaterial for various applications, related to the food, chemical, medical, and agricultural industries [12]. Particularly, the structural similarity of alginate acid to extracellular matrices of living tissues, allow wide applications in wound healing, drug delivery systems, tissue engineering and cell transplantation [13,10].

This is an extensive review of the general properties of alginate acid and the related suggesting new perspectives for future studies. current and potential applications in biomedical science and engineering.



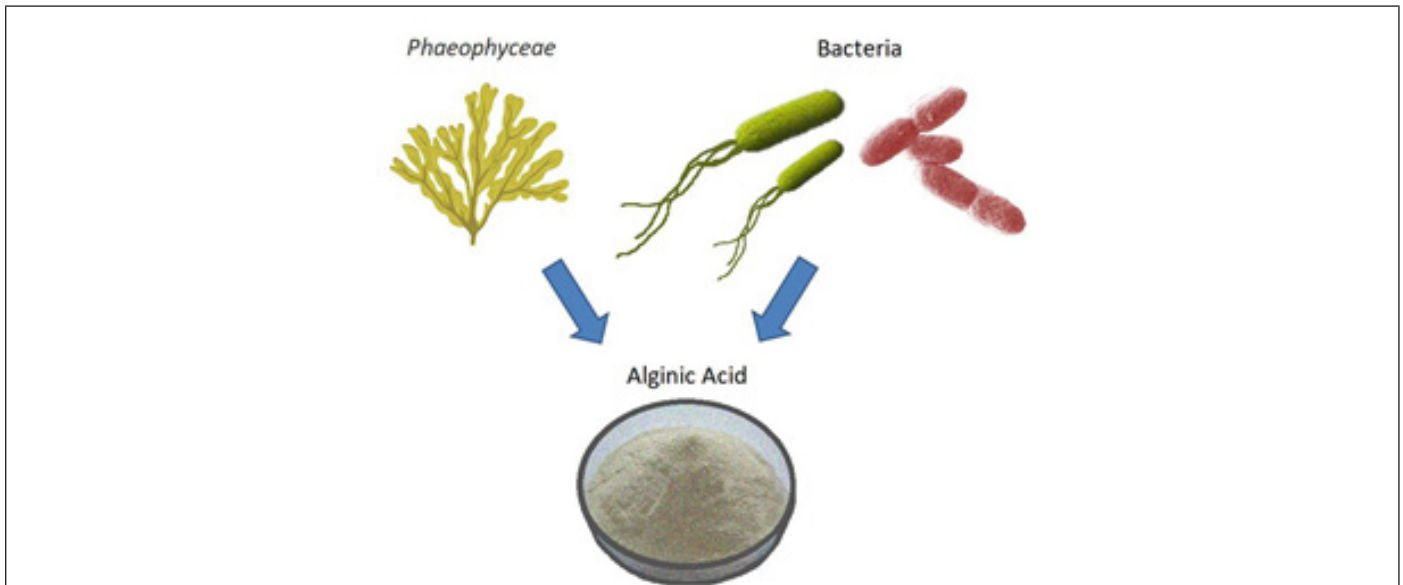


Figure 1: Alginic Acid is derived from marine brown algae, known as *Phaeophyceae*, as well as some micro-organisms, such as bacterial genera *Pseudomonas* and *Azotobacter*.

Alginic Acid structure and properties

Origins and extraction of Alginic Acid

Alginic acid is one of the most popular and intensely studied natural biopolymers [1]. The alginate is typically originated from brown algae, known as *Phaeophyceae*, including *Laminaria hyperborea*, *Laminaria digitata*, *Laminaria japonica*, *Ascophyllum nodosum*, and *Macrocystis pyrifera* [10]. The extraction employs aqueous alkali solutions, such as NaOH [13], the extract is filtered and sodium or alternatively calcium chloride is utilized to precipitate the alginic salt, which can be transformed to alginic acid by dilution of HCl [14]. The final alginate acid is produced by further purification and conversion [10].

Alginic acid is also derived from bacterial genera *Pseudomonas* and *Azotobacter*. In fact, this kind of biosynthesis provides alginate with more defined physical properties compared to that obtained from algae-derived alginate [15].

Four common biogenic synthesis of alginic acid have been reported:

- Precursor substrate synthesis,
- Polymerization and cytoplasmic membrane transfer,
- Periplasmic transfer and modification and
- Export through the outer membrane [16].

Structure and properties of Alginate

Depending on the algae species, the age, the type and the condition of the tissues, as well as the process of extraction, the quantity and quality of the alginates varies [17]. Alginates are actually linear copolymers with blocks of (1→4)- α -L-guluronic acid (G), (1→4)- β -D-mannuronic acid blocks (M) and heteropolymeric sequences of M and G (MG blocks) [18](Figure 2). The M/G ratio as well as the length of each block can be estimated through proton NMR depends on the natural source [19]. The different combinations between M and G blocks, lead to the manufacture of at least 200 different alginates [10]. Purified alginates have the potential to form fibers, beads, hydrogels, or films particularly in presence of calcium. However, it must be mentioned that MM and MG blocks can interact with calcium counterions.

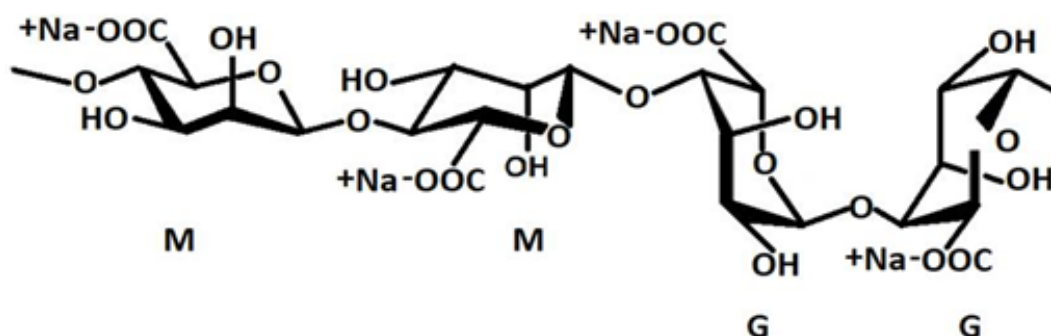


Figure 2: Chemical structures of guluronic (G) and mannuronic (M) acid blocks involved in alginic acid.

Alginate hydrogels

Alginate can be used in a hydrogel form in biomedicine, for wound healing, drug delivery and tissue engineering applications [20]. Hydrogels are 3-D cross-linked networks synthesized mainly by hydrophilic polymers [21]. They are typically biocompatible, due to the similarity of their structure with various biomolecules [12].

Alginate hydrogels can be prepared by various cross-linking methods, such as chemical or physical cross-linking of hydrophilic polymers, via gelation process [22]. George M et al. support the idea that only the G-blocks participate in intermolecular cross-linking with divalent cations, forming hydrogels [23]. The existence of GG block content in an alginate hydrogel has a direct impact on the stiffness of the final product [24]. Particularly the sodium alginate, as a typical example of the monovalent salt form of alginate, presents a high water-solubility, increasing the solvent viscosity upon dissolution and allowing the use in interesting applications [25]. The average molar mass, and the distribution of the molar masses also controls the viscosity of the solution as well as the stiffness of the hydrogels [10]. Actually, increasing the molecular weight of an alginate, the physical properties of the resultant hydrogel are improved [10]. In alginic medium, alginate may provide gels based in H-bond network [18]. The ion-exchange properties of alginic acid are very important, since they allow strong interactions with Ba, Sr and Ca, resulting to a hydrogel with reversibility in the presence of large excess of monovalent salts or other complex compounds [8].

It is important to be mentioned that the physical properties control the stability of the gels and the rate of drug release from the alginate hydrogels [10]. Alginic acid is non-degradable in mammals, since they lack the enzyme "alginase", which is responsible for the cleavage of the polymer chains [26]. The ionically cross-linked alginate gels can be dissolved, under specific conditions, such as when creating partial oxidation of alginate chains [27]. However, even in this case, the alginates cannot be completely removed from the body, because the average molecular weight is higher than the renal clearance threshold of the kidneys [10].

Derivatives of Alginic acid

Amphiphilic alginate: Various alginate derivatives are utilized in a wide range of biomedical applications. Perhaps the most common type of alginate derivatives is the amphiphilic alginate which is synthesized by introducing hydrophobic moieties [11]. Among the main advantages of the amphiphilic alginates is that they can form self-assembled structures in aqueous media, and that they have the potential to be used in various drug delivery systems [28].

Amphiphilic derivatives of sodium alginate can be produced through the conjugation of long alkyl chains, via ester bond formation [29]. Aqueous solutions of these alginate derivatives could be exploited in cartilage repair and regeneration approaches

[20]. Additionally, microparticles can be prepared from these amphiphilic derivatives by dispersion in a sodium chloride solution, allowing the encapsulation of proteins and their release, in the presence of surfactants that disrupt intermolecular hydrophobic junctions or esterases which hydrolyze the ester bonds between alkyl chains and the alginate backbone [10]. Furthermore, hydrogels can be prepared from this alginate derivatives, providing long-term stability in aqueous media [30].

Cell-interactive alginate: Recently another category of alginate derivatives, containing cell-adhesive peptides, has been gained attraction [31]. These compounds can be prepared through the addition of peptides, such as side-chains [32]. Appropriate ligands are of crucial importance to regulate cellular interactions, particularly for tissue engineering applications, since alginate lacks mammalian cell-adhesivity [33]. Peptides including the triplet (RGD) are widely used as model adhesion ligands, due to the wide-spread existence of integrin receptors for this ligand on various cell types [34]. These peptides can be chemically coupled to the alginate backbone [10]. A minimum concentration of RGD peptides in alginate gels is needed for the adhesion and growth of cells, and this ratio is perhaps cell type – dependent [35]. The affinity of the RGD peptide is another important parameter. Cyclic RGD peptides are considered to be more potent and are needed at lower concentrations than linear RGD peptides [34]. Also, various peptides, containing either the DGEA (Asp-Gly-Glu-Ala) or the YIGSR (Tyr-Ile-Gly-Ser-Arg) sequences have also been utilized for the modification of alginate gels [10].

Applications of alginic acid

Application of alginic acid in industry

Alginates in Food Industry: The most common applications of alginates are based on their gel-forming ability. Their properties make them quite suitable in the field of food and beverages [36]. They are completely organic and for this reason they are considered as safe substances for food applications [36]. Thus, alginates are widely used as food additives in jams and jellies, to improve and stabilize the structure of food [37]. They are capable of thickening a solution, whenever they are dissolved in water and they have the ability to form either gels whenever they are added to a calcium salt solution or sodium or calcium alginate films and calcium alginate fibers [10]. For the aforementioned reasons, alginates are used as enhancers of viscosity, stability and for emulsifying solutions, to enhance food preservation, improve flavor, taste, and appearance of the food [36]. For safety reasons, in Europe, regulations assign each additive a unique number, the well-known "E numbers," for each and every approved additive [38]. The regulatory status of alginic acid products, which are widely known as E 401, E 402, E 403, E 404, and E 405, in dietary supplements, is summarized in Table 1.

Table 1: Regulatory status for alginate products.

Product	Regulatory Status	
	European Union	United States of America
Sodium alginate	E 401	GRAS, 21 CFR 184.1724
Potassium alginate	E 402	GRAS, 21 CFR 184.1610
Ammonium alginate	E 403	GRAS, 21 CFR 184.1133
Calcium alginate	E 404	GRAS, 21 CFR 184.1187
Propylene glycol alginate	E 405	21 CFR 172.858

Alginates in packaging

Nowadays, it is well established that packaging is very crucial for the containment and preservation of food products [39]. The materials that are widely used, are typically based on polymers from non-renewable sources, associated with environmental

concerns [40]. Hence, several studies carried out in recent years have focused on the development of food packaging, based on natural polymers [41]. Alginate is perhaps the most widely studied essential biopolymer and it is considered as the preferred film-forming material [36].

Table 2: Alginate in food packaging [5].

Alginate form	Additional compounds	Advantage
Sodium alginate	Silver nanoparticles	Increase in shelf life of some fruits and vegetables (carrots, pears, etc.)
	Polyethyleneimine, poly(lactic acid)	Increase in oxygen barrier properties
	a. Montmorillonite/cellulose nanoparticles and b. Montmorillonite clay	a. Reduction in the water vapor permeability, b. Reduction in the water permeability and increase in the water solubility.
	CaCl ₂	Improved mechanical properties, water resistance, Decrease water vapor permeability
	Lemongrass oil and glycerol	Flexibility, Increased antimicrobial properties, mechanical strength
	Natamycin	Increase water solubility, water vapor permeability and opacity; Decreased tensile strength
	Lysozyme, nisin, ethylenediaminetetraacetic acid	Antimicrobial effect
Food-grade alginate	-	Preserves quality of mushrooms and increases the shelf life
Alginate cast film	Glycerol and sorbitol	Positive influence on the mechanical properties.
	Enterocins and high-pressure processing	Delayed growth of <i>L. monocytogenes</i>
	Potassium sorbate	Potential use for release of active substances
Calcium alginate	Silver-montmorillonite nanoparticles	Prevents dehydration, Antimicrobial effect, Increased shelf life
	Nisin	Suppression of bacterial growth
	-	Lowered shrinkage loss
Biocomposite film of cellulose and alginate	Microfibrillated cellulose, nanofibrillated cellulose, nanofibrillated anionic dicarboxylic acid cellulose	Increased mechanical properties, increased grease barrier properties, decreased water vapor permeability
Gelatine/sodium alginate blend	Corn oil, olive oil	Minimizes water loss
Propylene glycol alginate	Soy protein isolate films	Tensile strength increased, decreased water vapor permeability and solubility

Active packaging is currently the key technology, preserving food quality via the controlled release of active agents from the packaging [42]. For instance, in order to avoid lack of crunchiness, during cooking or warming breaded foods in a microwave oven, new products based in the active packaging, are proposed, usually including alginate gel film of alginate gel [8]. Thus, antimicrobial packaging with lactic acid bacteria, embedded in alginate film matrix allows to control the growth of food-borne pathogens [43]. Also, antiradical properties are obtained in the presence of

oregano-based film made of polycaprolactone/alginate-calcium film [44]. Table 2 summarizes the applications of alginate in food packaging, gathering the advantages of them [45].

Alginates in paper and textiles

Alginic acid enriched with calcium and mixed with starch presents high water retention in paper coating (Rinaudo M., 2014). This property is very important for size press coating formulation, improving coating rheology, controlling migration

and increasing coat weight uniformity [46]. Alginate fibers are widely used as wound management materials [47]. The common process to produce highly absorbent wound dressing materials is wet-spinning [1]. The mixture of alginate with sodium and calcium fibers result to a final product with high wet integrity, due to calcium and enhanced absorbency, due to sodium [10]. Alginate fibers and silver fibers can improve the anti-microbial properties, while zinc fibers can act as immune modulators [48]. Alginate calcium fibers, prepared via wet-spinning process, possess high tensile strength, desirable property for cloth materials [49]. The combination of yarns and textile of alginate calcium fibers lead to a nice feeling and strength [8].

Biomedical applications of alginic acid

Alginate hydrogels are quite attractive in wound healing, drug delivery, and tissue engineering applications [10]. This fact is related to the structural similarity of the hydrogels to the extracellular matrices in tissues and for this reason they can be manipulated, playing several critical roles [12]. In pharmaceutical industry, purified alginates are utilized as stabilizer in solution and dispersion of solid substances [8]. The main uses of alginates in biomedical applications are associated with controlled drug release, cells encapsulation, scaffolds in ligament, tendon tissue engineering and preparation of moulds in dentistry [20].

Alginic acid is also used in certain medications, such as Gaviscon liquid, creating a foam barrier for coating the stomach [50]. It is often combined with aluminum hydroxide and magnesium carbonate to form antacids. This combination of alginic acid, aluminum hydroxide, and magnesium carbonate can help to treat symptoms of stomach ulcers, gastroesophageal reflux disease and other conditions caused by excess stomach acid [51]. This medicine can be used for the treatment of heartburn, upset stomach, sour stomach, or acid indigestion. Alginate seems not to be absorbed or metabolized after ingestion [52].

New technology of medical textiles is an important field, showing great expansion, in the design and development of wound management products [53]. Fibers and dressings, which are fabricated to be used as wound care products ought to have hemostatic, anti-bacterial, anti-viral, fungistatic, non-toxic, high absorbent, non-allergic, breathable, biocompatible, and good mechanical properties [54]. Various materials are used for textile structures in modern wound dressings, such as sliver, yarn, crochet, braided, woven, non-woven, knitted and composite materials [55]. The addition of specialized additives can enhance the properties of advanced wound dressings [56]. Alginates can be used in hemostatic material and wound dressing [47]. Alginate wound dressings can maintain the normal moist microenvironment, minimizing bacterial infection at the wound, and facilitating wound healing [57].

Nanofibers are also used in wound care, since they gather unique properties, such as high surface area to volume ratio, nanoscale fiber diameter, porosity and light weight [58]. Alginate nanofibers, produced by electrospinning technique in presence of various synthetic polymers, can improve the processability [59].

Alginate wound dressings can absorb a large quantity of liquid inside the fiber structure, due to their unique gel blocking properties [60]. Furthermore, these wound dressings possess novel hemostatic and antimicrobial potential, promoting wound healing [47]. Thus, they are now widely used in the management of highly exuding wounds such as surgical wounds, leg ulcers and pressure sores [61]. Calcium alginate in wound dressing can provide hemostasis and tissue repair, since in contact with blood, Ca^{+2} ions can activate platelet aggregation, reducing the coagulation time [62]. Enhanced alginate with hydrolyzed chitosan shows improved antibacterial properties [63].

Alginate gels allow the controlled release of drug molecules, from small chemical drugs to macromolecular proteins, depending on the cross-linker types and cross-linking methods [64]. Additionally, alginate hydrogels can be orally administrated or injected into the body allowing extensive pharmaceutical applications [65]. Furthermore, they are considered as promising candidates for cell transplantation in tissue engineering, by delivering cells to the target-area, providing space for new tissue formation, and controlling the structure and function of the engineered tissue [66-68].

Conclusion

It is clear that alginates are natural polysaccharides which may be used in various applications. Biomedical and pharmaceutical applications of purified alginates seem certainly the most promising field of their applications. Particularly, alginate has shown great potential in the areas of wound healing, drug delivery, *in vitro* cell culture, and tissue engineering. Its biocompatibility, the mild required gelation conditions and the simple modifications, allow the development of alginate hydrogels, and alginate derivatives with enhanced properties. It is expected that in the future, the alginate-based materials which are designated to be used in medicine are likely to evolve considerably, particularly in active applications, like active packaging, active wound dressing and other smart systems. The production of new alginate polymer derivatives, with distinct properties, employing the use of genetic engineering, to control the biogenetic synthesis of alginate through bacteria, remains a great challenge.

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