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Alginates: Properties, Alginates Based New Materials use in Biopharmaceutical Applications and Future Prospectives

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ABSTRACT

Over the last decades, alginates, natural multifunctional polymers, have increasingly drawn attention as attractive compounds in the biomedical and pharmaceutical fields due to their unique physicochemical properties and versatile biological activities. There is a growing trend in pharmaceutical in food industry to avoid the harsh condition in the preparation for administration to the body or for the storage purpose as it induce the side effects, instability or loss of therapeutic effect of the medicament. The sodium alginate is a versatile functional biomaterial for viscosity enhancement, stabilizer, matrixing agent, encapsulation polymer, bio-adhesive and film former in transdermal and transmucosal drug delivery.

The focus of the paper is to discuss the present use and future possibilities of alginates as a tool for Alginate based new materials.

Keywords: Alginic Acid, β-D Mannuronic acid, *Laminaria hyperborea*, seaweeds,

Alginates

Introduction:

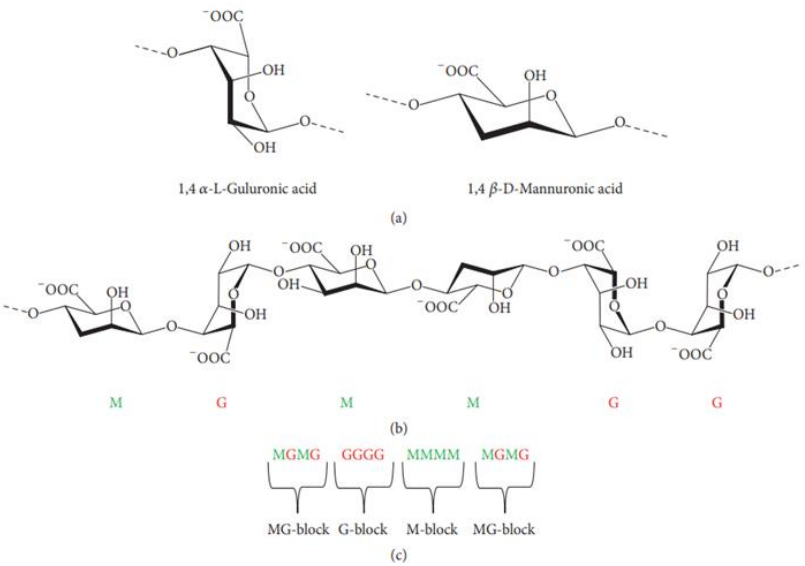
Alginic acid or Algin is a naturally obtained complex carbohydrate i.e. polysaccharides. Alginic acid is edible Polyanionic polysaccharide found in brown Algae [1-2]. Brown algae is a carbohydrate polymer that is an insoluble component of a salt form of alginic acid of calcium, sodium, magnesium, Ammonium and potassium. From these alginates, Sodium, Potassium, and ammonium alginates are water soluble but they are soluble at low pH levels. Calcium alginate and alginic acid are water-insoluble polymers. Calcium and aluminum alginates are monovalent salts of alginic acid. It is the structural component of Brown seaweeds cell walls including *Macrocystis pyrifera*, *Laminaria hyperborean*, *Laminaria japonica*, *Ascophyllum nodosum*, and several bacterial strains like *Azotobacters, and Pseudomonas [4]*. Class- *Phaeophyceae.* It is hydrophilic in nature and when they get hydrated, it forms a viscous gum that is used by the food industry to increase viscosity, as a food thickener and stabilizer, and as an emulsifier [5].

Alginate was first invented in 1881 by British Chemist, E.C.C. Stanford [5,17]. Alginate is a conjugate base of alginic acid. It is a polyelectrolyte that is considered to be Non-Toxic, biocompatible, non-immunogenic, and biodegradable. Alginate takes 40% of the dry weight of algae [2]. It was obtained from 3 different seaweeds [12,13]. Fucans and Alginates are obtained from Brown seaweeds, Carrageenan and agar are obtained from red seaweeds (*Rhodophyceae*) and, Xylan; cellulose; mannan is derived from green seaweeds*(clorophyceae*).The main cell wall components of brown seaweeds are alginates.

Polysaccharides derived from seaweeds.[12]

Seaweeds type	**Cell-wall polysaccharides**	**Storage polysaccharides**
Brown seaweeds (Phaeophyceae)	Alginate (guluronic acid, Mannuronic acid); Fucans (sulfated fucose)	Laminarin (glucose)
Red seaweeds (Rhodophyceae)	Carrageenan (Galactose, sulfate); Cellulose; Xylan	Floridean starch (glucose)
Green seaweeds (Chlorophyceae)	Cellulose; Xylan; Mannan; Glucuronoxylorhamnan (sulfated)	Starch

Properties of alginates [10]



Alginates are polysaccharides in structure and they are composed of linear binary copolymers of (M) β-D Mannuronic acid and (G) α-L guluronic acid units which connect with glycosidic bonds (1-4) [10]. It forms alternate sequences of M and G block units composed by homogeneously and heterogeneously. The structure of alginate is organized by its sources of M and G acid units. for example, *Laminaria Hyperborea* leaves contains high content of mannuronic acid and the outer cortex and stip region contains high content of guluronic acid [16]. The difference between bacterial alginate and algal alginate is the O-acetyl groups which are not present in the algal alginates [14]. As compared to algal alginates, bacterial alginates have higher molecular weight. Alginic acid, potassium, and sodium alginate have good biocompatibility and cytocompatibility, biodegradation [10].

Advantages of Alginates [15]

i. Less toxicity in encapsulated cells.
ii. Bio-inert in nature.
iii. Available in natural and Marine sources.
iv. Biodegradable
v. Low cost
vi. Biocompatible
vii. Ease of Gelation
viii. Easy to regenerate

Disadvantages of Alginates [15]

i. Incompatible with heavy metals
ii. Limitation on control of mechanical properties
iii. Instable during the Ion-Leaching process
iv. Because of poor tear strength, it should be given in combination with biopolymers.

Alginate based new materials [17]

Alginates in solution:

Future alginate-based products will not be limited to the solid state. The alginate molecule itself is anticipated to have a variety of effects on biological systems and give unique technical aspects in the liquid phase due to its large range of chemical possibilities, different compositions, and molecular

weights. A biological effect of alginate was in fact hypothesized in the early animal transplantation trials of encapsulated Langerhans islets for diabetes control. It's crucial to keep in mind that microbially produced alginates have a great potential for use as industrial polymers when looking for new alginate-based products. Their structural diversity, which ranges from pure mannuronan to polymers with more than 80% guluronate residues in terms of chemical composition, and sequence (from alginates with a conventional block structure in A. 6inelandii to poly-alternating polymers in Pseudomonas species), is undoubtedly one of their advantages. Furthermore, the recent genetic discovery in bacteria that produce alginate makes it possible to create polysaccharides, either by altering the producing organism or by using recombinant enzymes in vitro.

Chemical modified alginates

Today, the only commercially valuable alginate derivative is propylene glycol alginate (PGA). This substance is made by esterifying alginate with propylene oxide. Because of its increased solubility at low pH, PGA is used in beers and salad dressings. Recently, two new derivative families have formed. By using alkylating compounds in an organic aprotic medium like DMSO to transform the quaternary ammonium salt of alginic acid, a variety of alginate esters can be produced. Because the changed polymer functions as a vehicle for drug release, esters with pharmacologically active alcohols are particularly relevant.

Super swelling alginate materials

Pre-formed Ca-alginate gels can also be covalently crosslinked with epichlorohydrin and the Ca2 ions removed using EDTA. These Na-alginate gels can be dried and rehydrated to exhibit distinct swelling properties. A polymer network can swell under three different types of pressure. 'Swelling pressure' can be used to describe two of these phrases that encourage swelling: (A) the term for mixing (Dp mix is the osmotic pressure produced by mixing polymer and solvent); and (b) the ionic term (the Donnan equilibrium; Dp ion is the osmotic impact of an unequal distribution of polymer counterions inside and outside the gel).

Diffusional setting (e.g. beads, fibres and films)

In contrast to internal setting, diffusional setting is essentially the alginate gelling procedure in which the crosslinking ions, such as Ca2, are allowed to diffuse into a solution of soluble alginate. This technique can be used to create beads, fibres, and films. When alginate is utilised as an immobilization matrix, the diffusional setting is always used. This is due to the biocatalyst being entrapped by a quick and mild gel formation when droplets of soluble alginate (containing a biologically active ingredient) strike the gelling liquid. Diffusional setting is also used in a number of applications involving food reformation.

Applications of Alginate

1. Alginate uses in food industry (19)

Because they are entirely organic, they are regarded as safe materials for use in culinary applications (20). Alginates are therefore frequently employed in jams and jellies as food additives to enhance and stabilise the dish's structural integrity. When they are dissolved in water, they can thicken a solution, and when they are added to a solution of calcium salts, sodium, calcium alginate films, or calcium alginate fibres, they can either create gels or fibres or films (21).

2. Alginate uses in Biomedical (22)

Alginates' primary functions in biomedical applications are related to controlled medication release, cells encapsulation, scaffolds in ligament and tendon tissue engineering, and the creation of dental moulds.

- **Drug delivery**

A well-known technique for delivering medications and managing their rate of release is microencapsulation. Drug-encapsulated microspheres can be utilised to offer delayed or controlled drug release, target the pharmaceuticals to certain areas in the body, and improve bioavailability and stability of the drugs.

Alginate gels can be used to microencapsulate a variety of medications for oraldelivery that are encapsulated.GI tract inflammation is less. In the highly acidic stomach fluid, the outer coating of AMS is hydrated and transformed into an insoluble form of alginic acid, shrinking and safeguarding the medications (23).

For instance, green tea polyphenol was added to AMS to treat osteomyelitis with the least amount of invasiveness possible (24).

- **Cell delivery**

Immobilizing bioactive cells inside of microparticles is known as microencapsulation of cells A polymeric membrane that encloses the cells enables oxygen, nutrients, and therapeutic protein products to pass through unhindered. Additionally, AMS can serve as a barrier against physical stress and

prevent host immunologic reactions. So much research is being done on using sodium alginate to encapsulate cells to create therapeutic products that can be used to treat a variety of ailments (25).

According to one research, the arginylglycylaspartic acid (RGD) peptide modified AMS contains human mesenchymal stem cells (hMSCs), which support cardiac repair. This in vitro study showed that the RGD modified AMS increased cell adhesion, proliferation, and the generation of angiogenic growth factors (26).

- **Vaccine delivery**

Non-parenteral delivery of vaccines is only seldom used; parenteral injection is preferable (27). But science is starting to recognize the benefits of oral or intranasal immunisation. Due to its high mucoadhesive properties and capacity to shield the vaccine from the acidic environment of the GIT, AMS can be used to effectively administer vaccines via non-parenteral routes (28). In a study, the contagious hematopoietic necrosis virus DNA vaccine (pIRF1A-G) was first packaged in AMS and then administered orally in sodium citrate at room temperature. The outcomes demonstrated that fish oral administration of the AMS containing DNA vaccine significantly enhanced fish immune responses and tolerance to the contagious hematopoietic necrosis virus.

Additionally, it was discovered that AMS shields DNA vaccination from the digestive system's acidic and degrading environment (29,30).

- **Proteins delivery**

Enzymes, growth factors, hormones, and interleukins are a few examples of proteins used in biomedicine for tissue regrowth or as therapeutic agents (31). The therapeutic properties of proteins can, however, be readily lost due to denaturement or alteration of the protein structure in harsh environmental circumstances, such as variations in pH and temperature (31,32). Hence, AMS can be utilised to encapsulate these proteins in order to stop their deterioration and provide controlled, site-specific release (32). Comparing AMS-prepared formulations to those made with alternative biomaterials, they show better protein loading. Because of their natural characteristics, such as isoelectric points and hydrophilicity, some proteins are often difficult for the body to absorb.

In one experiment, chymotrypsin and lysozyme were encapsulated to see if proteins with high isoelectric points could be loaded quickly and released over an extended period of time. Proteins with extraordinarily high isoelectric points crosslink with alginate, which results in sustained releasing behaviour in the system (32,33).

- **Microbes and vectors delivery**

Probiotics and bacteriophages are two examples of microorganisms that can be given therapeutically. These aims include treating diarrhoea and balancing the microbiota in the intestines. Particularly in the body's GIT, microbes play an important role. By preventing dangerous diseases and bacteria from colonising and infecting the GIT, the microbiota in the GIT lumen contributes to the maintenance of optimum GIT conditions.AMS that combine bacteriophages and vectors enable improved acid stability, defence against GIT acid hydrolysis of the enclosed contents, and controlled, prolonged release of the contents.Alginate works in GIT settings as a pH buffering agent and prevents extreme temperature swings, protecting the therapeutic medication from the GI acidic environment even though the viscosity of the alginates rises at lower pH. At lower pH values, alginates' carboxylate groups are protonated and create hydrogen bonds, which raises viscosity. AMS also work to stop encapsulated microorganisms from being destroyed by bile and digestive enzymes in the GIT (34,35).

In one experiment, AMS was used to encapsulate both viable Bacillus subtilis cells and fungus spores. As a result of alginate's biocompatibility, the outcomes showed that both categories of enclosed materials were media-protected. The spores and cells that were enclosed grew significantly more slowly than the control. The growth of encapsulated cells was on pace with the expansion of free cells even after the lag-time after encapsulation (36).

- **Applying a dressing to a wound**

Because of its high water content and exceptional biocompatibility, alginate has shown to be one of these polymers. The presence of water keeps the region moist, preserves the ideal pH, and hastens the healing process. A popular commercial wound dressing is KaltostatR Alginate dressing, which is based on sodium or calcium alginate. It takes the shape of fluid-contacting absorbent gelfibre matrices. Hemostasis, atraumatic removal, and minor haemorrhage control can all be facilitated by maintaining moisture in a wound. Nevertheless, alginate hydrogel alone is insufficient to promote bioactivities and stop bacterial infections, particularly in the case of chronic wound healing. As a result, alginate composite dressings have become more popular recently. The additional ingredients may improve blood coagulation, hemostasis, antimicrobial activity, cell adhesion, and high cell survival (the ability to halt and prevent bleeding). Alginate is largely converted into hydrogels in composites by a cross-linking mechanism with counterions like calcium or other multivalent ions.

Despite the fact that alginate has been electrospun into fibre mats, sponges, and foam sheets, when water and moist exudate come into contact with the alginate dressings, they transform into hydrogels. In an alginate composite, additional components are also added while the hydrogel is being created, including poly (vinyl alcohol), cellulose, chitosan, and gelatin. The inclusion of polyethylene altered the hydrogel dressing's physicochemical properties, including its swelling ratio, tensile strength, and elongation. (vinyl alcohol). The swelling capacity, protein adsorption, hydrolytic breakdown, and heat stability are frequently increased when sodium alginate levels are raised; however, the gel fraction, maximal strength, and break elongation are usually decreased. Several clinical studies have looked at the use of antimicrobial elements like silver ions or silver nanoparticles in alginate composite bandages. Ionic silver alginate/carboxymethylcellulose (SACMC) dressing was applied to 36 individuals with venous or pressure ulcers during a four-week clinical

study. According to the study, silver-containing calcium alginate fibre (AF) dressings are more effective than non-silver AF dressings at preventing the colonisation of microorganisms (biofilm infection) to the wound. The healing process was hastened by this. One negative impact of the SACMC dressing was wound maceration, according to the clinical investigation. The five adverse events (AEs) linked to the AF dressingwhich also included over-granulation, significant wound dressing adhering, and wound infection - were less severe than this one.

Both acute and chronic cutaneous wounds are a substantial clinical concern due to inadequate vascularization, protease sensitivity, and microbial invasion at the wound site (37,38,39).

3. Biological Activity and Pharmaceutical Applications of ALG

ALG are thought to be nonimmunogenic, nontoxic, and biocompatible substances (40,41). ALG gel simply dissolves due to the elution of calcium ions that are cross-linking the gel, despite the fact that ALG gel cannot be broken down in the mammalian digestive system (42).

It should be noted that the renal clearance threshold only excretes tiny ALG molecules. ALG must undergo some polymer backbone oxidation in the body in order to be completely removed (43). Following administration via the ocular (44), nasal (45), topical (46), local (47,48), and oral pathways (49), ALG biocompatibility was shown in vivo. Numerous ALG salts and propylene glycol derivatives have lately received GRAS designation from the Food and Drug Administration for use in oral medications (50).

Conclusion

This paper provides a current review of alginates and alginate based new materials used for drug delivery in various forms like in solution form, chemically modified developed alginates and its super swelling property. Alginates have enormous potential as biomaterials for biomedical uses in human healthcare and for common biotechnology applications including tissue growth, drug delivery, Gene engineering, stem cell research and wound healing Alginates are widely used as food additives in jams and jellies to improve and stabilize the structure of food. Natural multifunctional polymers are extensively researched in the creation of microparticulate systems for targeted drug administration, controlled release and biological applications (for the treatment of diabetes and heart illnesses). Alginate has demonstrated considerable promise for use in tissue engineering, medication delivery, *in-vitro* cell culture, and wound healing. Alginates are gaining attention for creating nano-systems that can deliver a variety of medicinal compounds. They permit the delivery of therapeutic substances like insulin, genes, and medications in a bio-responsive and site-specific manner. By doing this, they become more competent while having less negative impacts and raises patient compliance as well.

Future perspectives

Alginate is the only polysaccharide where each constituent residue has a carboxylgroup by nature. Food films and colloids can be created with it. It also contains a number of beneficial biological actions, opening the door to its development into functional foods and nutraceuticals.CRISPR technology advancements and other contemporary technologies enable professionals to modify or rework genomic sequencing for gene therapy.Finding bacterial resources for alginate production with high viscosity and low capital cost is extremely difficult since alginate-producing seaweed is not readily available in India and its viscosity is unsuitable for the textile sector. Alginate production is based on the demands of diverse businesses, and by genetically modifying recombinant strains of Azotobacter, it is possible to increase the viscosity of alginate synthesis.

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