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Review Article

Alginate-Based Hydrogels and Particulate Systems: Preparation Techniques, Adaptations, and Utilizations in Pharmaceutical Delivery and Biomedical Research

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Abstract

Alginate, a naturally derived anionic polysaccharide largely extracted from brown algae, has become a versatile biomaterial for pharmaceutical and biomedical applications due to its exceptional biocompatibility, biodegradability, non-toxicity, and gentle gelation qualities. The peculiar block-copolymeric arrangement of alginate, composed of β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues, governs its physicochemical, mechanical, and biological features via modifications in molecular weight, M/G ratio, and block distribution. This review critically analyzes recent developments in alginate-based hydrogels and particulate systems, focusing on extraction methods, structural characterization, and modification strategies designed to address inherent limitations, including inadequate mechanical strength, uncontrolled degradation, and restricted bioactivity. The impacts of ionic and covalent crosslinking techniques, including egg-box gelation, photo-crosslinking, dual-network formation, and thermo-responsive systems, on rheology, stability, swelling, and controlled drug release behavior are discussed. The paper highlights the expanding biological applications of alginate systems in regenerative medicine, tissue engineering, wound healing, controlled and targeted drug delivery, and cell encapsulation. Special emphasis is placed on in vivo efficacy, immunogenicity, toxicity assessments, and regulatory compliance, comprising FDA and EU approvals. We also look at new developments including injectable hydrogels, hybrid scaffolds, and stimuli-responsive alginate composites. Alginate-based platforms comprise a promising category of biomaterials, and continuous developments in molecular modification and crosslinking technologies are projected to boost their translational potential in next-generation pharmacological and biological applications.

Keywords: Alginate hydrogels; Egg-box cross-linking; Bio-polymeric frameworks; Biomedical materials

1. Introduction

Natural polymers derived from living organisms such as bacteria, algae, plants, and animals have been utilized in the field of medicine for a considerable amount of time. These polymers have been utilized for a variety of purposes, including medicines, scaffolds for tissue regeneration, drug delivery, and imaging. Polysaccharides, proteins, and polyesters are all examples of natural polymers. These polymers originate from both plants and wild animals. The human diet contains a number of these polymers, and people have been making use of them for a considerable amount of time. Polymers like this are recognized by the biological environment, which then leads them into the process of metabolic breakdown. Natural polymers are similar to components of the extracellular matrix (ECM), which enables them to avoid the persistent immunological reactions and toxicity that are typically associated with synthetic polymers. [1,2, 3] Natural chemicals are becoming increasingly popular for use in a variety of industries, including food, cosmetics, and pharmaceuticals. The naturally occurring alginate polymers have a great deal of potential for usage in the pharmaceutical industry due to the fact that they are frequently utilized as food additives and are recognized for their safety. Alginate is a word that brings back fond memories for many working in the biotechnology, food, cosmetics, and pharmaceutical industries. An example of a linear copolymer is sodium alginate (SA), which is made up of β-D-mannuronic acid (M) and α-L-guluronic acid (G). This category of polymers possesses numerous characteristics that render it advantageous as an aid in the formulation, serving both as a regular excipient and, more specifically, as a tool for polymeric-controlled drug administration. [4, 5, 3, 6]

Because of its one-of-a-kind egg-box gel structure and properties that are in reliance on the M/G ratio, it has become a prominent focus of research in the field of natural polymer materials since its discovery. Because of its extensive availability, excellent biocompatibility,

and considerable modifiability, SA has garnered a lot of interest in the fields of food engineering, biomedicine, and environmental remediation. This is due to the fact that green chemistry and sustainable development are becoming increasingly significant. Additionally, important regulatory agencies have publicly acknowledged SA as a safe and allowed additive. This is a significant development. The European Union refers to it as food additive E401, and it is included in both Commission Regulation (EU) No 231/2012 and Regulation (EC) No 1333/2008. [7, 8, 9, 10]

In the United States, the Food and Drug Administration (FDA) has determined that sodium alginate is categorized as a chemical that is "Generally Recognized as Safe" (GRAS). This classification is based on the information provided in 21 CFR § 184.1724. [11]

The fact that it can be employed as a thickener, stabilizer, and emulsifier is explained by this explanation. These regulatory approvals provide more evidence that there is potential for usage in the pharmaceutical, food, and biological industries in a manner that is both safe and widespread. It is important to emphasize that the chemical tailoring that is being discussed here is not about promoting the introduction of new food additives; rather, it is about developing materials that can be consumed or come into contact with food. By providing this explanation, the review is ensured to be about food-safe modification techniques and materials that are significant to the field of food science, rather than about the process by which rules are compiled. Despite the fact that SA possesses a number of advantages, it frequently has inherent issues with regard to its environmental stability, bioactivity, mechanical strength, and controlled release. [12] Chemical, physical, and enzymatic approaches are the three primary methods that have been developed to address these issues.

2. Sources of Alginate and the Process of Extraction

In brown algae, the cell walls and the space between the cells are primarily composed of alginate. Since of this, they are able to withstand the force of the ocean since they have the strength and flexibility necessary. A mixture of salts that are insoluble composed of alginic acid and a wide variety of cations, including Na^+, Ca^{2+}, K^+, Mg^{2+}, and some other ions that are naturally present in saltwater, alginate can be found. Brown algae contain varying amounts of this polymer, which fluctuates depending on the species, the time of year, and the section of the thallus. In point of fact, the portion of the thallus known as the holdfast, which is responsible for securing the algae in place on the substrate, has a greater guluronic acid quantity than the rest thallus portion. This makes it more effective in adhering to the substrate you are using. Additionally, it has been observed that algae that are subjected to waves contain a greater mannuronic acid quantity than those are grown in the habitat that is protected from waves. This enables the algae to be more adaptable and capable of withstanding wave action. Algae such as Ecklonia maxima, Ascophyllum nodosum, Macrocystis pyrifera, Eisenia bicyclis, Lessonia nigrecans, Sargassum spp, and Laminaria spp. are the most common forms of algae that are utilized in the production of industrial alginates. On the other hand, the quality and quantity of alginate are highly dependent on a variety of factors, including the species, age, type, part of the tissues, ambient circumstances, the time of year it is collected, and the method that is used to obtain it. [13, 14, 15]

The removal of alginate from cells and the enhancement of its functionality can be accomplished in a variety of well-documented ways. Some examples of these are pre-treatments, processes for cell disruption, and extraction methods that are both traditional and innovative. Therefore, a significant amount of effort has been put into eliminating or reducing the amount of time and energy required, reducing the amount of toxic chemical solvents, and improving the quality of the alginate that is produced in terms of both yield and quality. The fact that these parameters can change from one species of algae to another and even within the tissues of the same type of algae is something that should be kept in mind. It is also essential to keep in mind that the chemical and physical properties of alginates are significantly influenced by their molecular characteristics. These characteristics include the ratio of uronic acid (M/G), the molecular weight, the block structure of the alginate chain, and the degree of polymerization. Nevertheless, these aspects need to be investigated further in a variety of studies. [16, 15, 17]

The first stage in the procedure of obtaining alginate from brown seaweed is to wash the macro-algal biomass with distilled water. This is done in order to takeout any sand, salt, pollutants, and epiphytes that may be present. Immediately following the washing process, the algae may be subjected to two different kinds of pre-treatments. The first method involves the breakdown of the cell wall, which facilitates mass transfer. The second method, on the other hand, prevents the extraction of bioactive substances that have a similar solubility at many times. An example of the first kind of pretreatment is a mechanical procedure that involves drying the particles and then breaking them down into smaller pieces. Another kind of pretreatment involves removal of additional compounds from the cell matrix that might be attached to the alginate. This is the second kind of pretreatment. Formaldehyde is the pre-treatment method that has been published in the literature and tested in the commercial world. It is the most used method. In order to prevent enzymatic or microbiological reactions from occurring, as well as coloring the alginate, it is utilized. Formaldehyde interacts with phenolic chemicals, leading to polymerization and the insolubility of pigmenting molecules. Researchers stated that in order to separate alginate and prevent polyphenols from being extracted simultaneously, the industry utilizes 0.2% (w/v) formaldehyde. However, this did not assist in extracting more alginate from the mixture. Furthermore, formaldehyde is considered to be exceedingly toxic, allergenic, and carcinogenic, all of which contribute to a decrease in the quality of alginate. [18, 15, 19, 20]

When it comes to the alginate extraction technique, inventors advocated employing the Fenton reaction (7.4 mM FeSO4 for 90 minutes) as an alternative to formaldehyde and heating (60–90 °C). Both the yield of alginate extraction and the amount of water used were reduced by forty percent as a result of the Fenton reaction. Additionally, in comparison to the samples that were treated with formaldehyde, it reduced the amount of d-mannurate by around thirty percent and the viscosity by approximately eighty-four percent. As a result of this, the Fenton pre-treatment has the potential to serve as an alternative to formaldehyde, which is a pollutant that is released into the environment through wastewater. The process of extraction of alginate only requires five steps. In the beginning, a mineral acid (such as HCl, 0.1 M) was utilized in order to extract the brown seaweeds that had been dried and crushed. Insoluble alginic acids were produced as a result of this process, and they are easily distinguished from other contaminated glycans such as sulfated fucoidans and laminarans by the use of centrifugation or filtration. The insoluble alginic acid is then transformed into sodium alginate using an alkaline solution with a pH of 6.0 or higher, which can be sodium hydroxide, sodium carbonate, or aluminum hydroxide. In order to make the sodium alginate soluble, calcium chloride or cold alcohol is utilized after another technique has been performed to separate the two substances. Following that, alginates are cleaned up by adding Ca^{+2} ions, which results in the formation of calcium alginate, or ethanol, which results in the stabilization of the dielectric. [21, 22]

3. Alginate's Chemical Structure

The molecular weight and chemical structure of alginates indicates that they are made of two monomeric units: β-(1,4)-linked d-mannuronic acid (Man Ap or M) with a 4C1 ring shape and α-(1,4)-linked l-guluronic acid (Gul Ap or G) with a 1C4 ring shape.

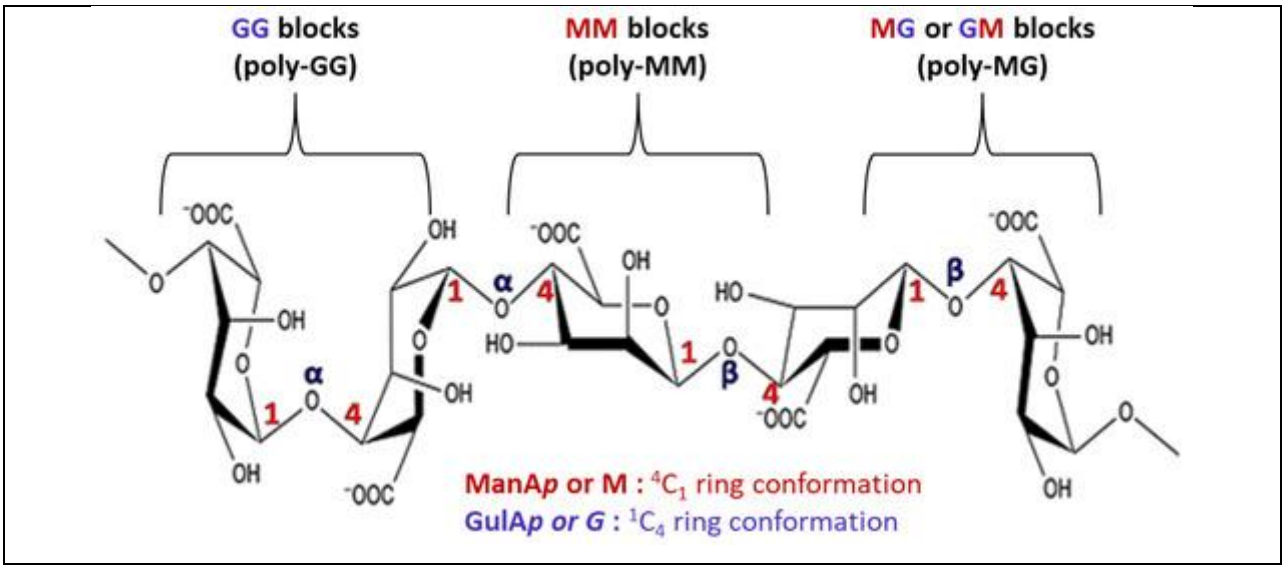

Figure 1: Chemical Structure of Alginates [14]

The structural characterization of alginate comprises fundamental biochemical procedures as well as more intricate investigations, such as spectroscopy and chromatography, which facilitate fine structure identification. For example, spectroscopy and chromatography are examples of these types of investigations. Chemical tests should be able to assess not only the sugar content (neutral sugar, total sugar, and uronic acids), but also the non-sugar pollutants that are also extracted with seaweed alginates. Proteins, sulfated groups, and phenolic chemicals are some of these contaminants. Gas chromatography coupled with mass spectrometry and electron ionization (GC/MS-EI) and high-performance anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD) have been widely used to determine the M/G ratios of alginates after their complete acid hydrolysis using formic acid (90% v/v) and trifluoroacetic acid (2 M, 90 min, 120 °C), respectively. [14, 23]

4. Types and Properties of Alginates

There are many various forms of alginates, and each one serves a specific purpose. Some examples of alginates include sodium alginate, calcium alginate, and potassium alginate. Every one of them possesses a unique collection of characteristics. Consideration ought to be given to the degree to which it is compatible with the formulation as well as the function that it will fulfill. Because of its ability to gel and heal wounds, calcium alginate is utilized in controlled-release formulations, although sodium alginate is frequently utilized in these formulations. [24] For instance, ultrapure alginate, high-G alginate, high-M alginate, high-MG alginate, and alginate derivatives such as furfuryl conjugate alginate and sodium alginate. [25] Alginates copolymers have pieces of β-D-mannuronate (M) and α-L-guluronate (G) that are joined by (1,4)-bonds. The composition and sequential organization of these G and M blocks provide distinct alginates a variety of diverse physical and chemical

properties, which enables them to be used for a variety of applications. [26]

Alginates with a high G content have a greater number of G blocks that are next to one another. The formation of hard, brittle gels is a consequence of the interaction of G blocks with divalent cations (e.g. calcium|). This interaction causes the G blocks to bend into the characteristic egg-box junctions. High-G alginates are excellent for the production of highly durable gels that can be used for a variety of applications, including scaffolds for tissue engineering, dental impressions, and 3D bio-printing. [27]

High-M alginates are characterized by having a greater proportion of flexible M blocks and a lower number of rigid G-block junction zones. The gels become more pliable and flexible as a result of this. On a regular basis, high-M alginates are employed in the food industry as thickeners and stabilizers, as well as in the pharmaceutical and biomedical engineering industries as hydrogel matrix. High-MG alginates are characterized by the presence of G blocks and M blocks that are arranged in a pattern. Additionally, they produce gels that have a medium level of strength and stiffness, as well as the ability to alter shape and cling together. Because of their ability to thicken and encapsulate substances, high-MG alginates are an excellent choice for salad dressings, sauces, and probiotic encapsulation. [28] Alginates that have been altered chemically or enzymatically exhibit a variety of functions, including changes in their molecular weight, hydrophobicity, adhesion, and breakdown. When presented with calcium chelators and acids, propylene glycol alginate demonstrates a greater degree of stability. The usage of modified alginates in coatings, cosmetics, and particular drug delivery systems is enhanced by the use of modified alginates. [29]

5. Merits and demerits of Alginates

The distinctive arrangement and composition of guluronate (G) and mannuronate (M) blocks in various forms of alginate equip them with certain benefits and downsides for use in industry and medicine. [14, 28] Examples of the types of alginate, their applications, and the advantages and disadvantages of using them are included in the following table.

Table 1: Different types of alginate, their applications, advantages, and disadvantages [14, 22, 28]

Type of Alginate	Uses	Merits	Demerits
Alginates (High- G)	Tissue engineering, dental impressions, and three-dimensional printing	Gels that are strong and rigid, have a high stability, and printed very well.	Gels with a low biocompatibility and brittleness
Alginates (High- M)	Food gels and hydrogels used in biomedicine	Gels that are good biocompatibility and soft and elastic	Gels that are feeble and unstable
Alginates (High-MG)	Thickening agents and encapsulation	Gels that exhibit cohesion and viscosity improvement	A level of strength and stability that is adequate
Alginates (Modified)	Personal care products, coatings, and customized delivery	Increased stability, stickiness, and the capacity to retain moisture	It is possible for natural alginate to lose its inherent characteristics.

When divalent cations like calcium and G blocks come together at egg-box junctions, high-G alginates, which have a lot of G blocks, readily create stiff gels that are very stable and robust. This is because high-G alginates have large amounts of G blocks. Dental imprints retain a high degree of shape integrity as a result, and 3D-printed structures have a high degree of dimensional stability. On the other hand, high-M alginates with primarily flexible M blocks produce gels that are soft and stretchy. This is because High-G gels' rigidity can make it more difficult for cells to remain alive and for tissues to collaborate in more delicate biological applications. [22]

Gels with a high molecular weight are useful for gently wrapping around medications, proteins, or probiotics; but, they are not stable enough for other uses, such as scaffolds and food gels. [28]

High-MG alginates provide a gel matrix that is somewhat pliable but still maintains its structure. The utilization of microbeads for the delivery of medications and the thickening of foods both benefit from this balance. However, high-MG alginates do neither offer the robust stiffness of high-G gels or the flexible biocompatibility of high-M gels. [30] Chemical or enzymatic modifications can make alginate more stable, improve its ability to hold moisture, and improve its ability to stick. However, this may result in the loss of some of the beneficial natural qualities that alginates possess. Choosing the right type of alginate lets you use their strengths while minimizing their weaknesses for a specific use. [28] Aligning the distinct mechanical and rheological properties of alginate types with the particular needs of many applications, such as food, medicines, coatings, 3D printing, and biomedical engineering, requires an understanding of the structure-function relationship of alginate types. [31]

The flow properties of alginate are significant elements impacting its application in industrial and biological contexts, especially in drug administration formulations.

Native alginates that are formed from brown algae produce viscous polymer solutions that exhibit non-Newtonian and pseudoplastic flow properties. When the shear rate is increased, the viscosity of the substance appears to decrease. The molecular weight of an alginate solution is the primary factor that determines the viscosity of the solution. Alginates with a higher molecular weight have features that are more viscous, yet there is less solubility in them. When necessary, controlled breakdown by hydrolytic or oxidative procedures can reduce the molecular weight and viscosity of the substance. [28]

Calcium and other divalent cations that bind to alginate can have a significant impact on the way the substance flows. At sufficiently enough concentrations, ionic crosslinking results in gelation, which contributes to the preservation of the shape. Within the range of temperatures below the gel point, ionic interactions cause the liquid to become more viscous, which makes it simpler to shear. Because of this, it is possible to adapt the flow characteristics of liquid formulations. [24]

Carboxylation and amidation are two chemical alterations that alter the viscosity of alginate by altering the structure of the molecules, the way in which they adhere to one another, and the way in which they interact with hydrogen. It is because the interactions between the polymer and the solvent are not as strong that propylene glycol alginate has a lower viscosity than other types of alginate. The hydrophobically modified alginates have a viscosity that is suited for regulated medicine release since it is shear-thinning. [32]

6. Physical and Chemical Properties

Numerous factors affect the physicochemical characteristics of alginates, including mechanical qualities, swelling capacity, and diffusion capacity. These criteria include the composition and arrangement of the two groups of uronic acid in the structure, the molecular weight of the polymer, the type of functional groups that are present, and the concentration of the reticular agent that is employed. [33] It is possible for the quality of alginates to differ depending on the natural source from which they are derived, the time of year, and the geographical location of the plant harvest

6.1. Molecular Weight

The molecular weight of sodium alginate that is sold commercially ranges from 32,000 to 400,000. In addition to possessing lengthy G and M chains, the structure also has a polydispersion index that ranges somewhere between 1.5 and 3 (Mw/Mn). The pH of the reaction and mass molecular mass are two factors that have been shown to influence alginate solution's viscosity, according to studies. As the pH decreases, the viscosity increases, and it achieves its maximum value somewhere between 3 and 3.5 points on the pH scale. The carboxyl groups in the structure undergo protonation, which enables them to form hydrogen bonds with other groups in the structure. This is the reason why this occurs. When the molecular weight of alginate is increased, it causes gels to gel more quickly and alters the physical properties of the gels, including their viscosity, elasticity, and tensile strength. It is possible that an excessive increase in molecular weight could cause the alginate solution to become extremely thick, which is undesirable in certain circumstances. [7, 34] However, this cannot be said for all instances. As an illustration, when it comes to the production of alginate hydrogels that are utilized as a matrix for cell immobilization (for example, in vaccines), if the alginate solutions are excessively thick, it is possible that the cells will not be able to withstand the strong shear forces that are utilized to mix them with alginate. In certain cases, cell membranes are extremely sensitive to mixing, and strong mixing can occasionally result in the death of cells. [33]

6.2. Solubility

Dissolvability Sodium alginate makes the solution thicker because it dissolves more slowly in cold water than it does in warm water. It does not dissolve in alcohol, hydroalcoholic solutions that contain more than thirty percent alcohol, chloroform, or ether. [33] According to the findings of research conducted, the solubility of the substance is affected by factors such as pH, ionic strength, molecular weight, the properties of the ions present in the structure, and concentration. [35] At a pKa value of 3.6, guluronic acid is significantly more acidic than manuronic acid, which has a pKa value of 3.3. [34]

6.3. Stability

It is not possible to dissolve calcium alginate in either water or organic solvents. While sodium alginate is effective with the majority of anionic substances, it is only effective with a small number of cationic molecules. When it is in the form of a powder rather than a liquid, it is also more resistant to the effects of external forces than when it is presented in the form of a solution. When sodium alginate is combined with acids that have a low pH level, it gradually transforms into a gel composed of alginic acid. When exposed to high pH levels, alginic acid is able to dissolve and transform back into its original viscosity. Due to the fact that pH levels higher than 11 cause sodium alginate to become less viscous, it can only be stored for a short period of time in alkaline conditions. It is possible to sterilize sodium alginate since it is able to withstand high heat for a brief period of time. A decrease in viscosity may occur over time as a result of the high temperature that is employed in the sterilization process. [36]

7. Mechanical Properties

7.1. Viscosity

The ability of alginate to thicken is determined by the degree of concentration of the polymer as well as its molecular weight, whereas its ability to gel (attract cations) is determined by the quantity of glucuronic acid that is present in the structure. By increasing the quantity of glucuronic acid that is made available within the structure, the amount of soluble alginate that is produced in water increases, and the amount of gel that may be produced increases as well. This results in a gel that is more robust, more stable, and more resistant to breaking down. [33] According to research data, this gel is

also capable of providing controlled release action. [37] It has been demonstrated through research that there is no such thing as a Newtonian fluid; rather, sodium alginate solutions are considered to be pseudoplastic fluids whose viscosity varies greatly depending on the degree to which they are dissolved and diluted in water. [4]

7.2. Mucoadhesion

The presence of free carboxyl and hydroxyl groups within the structure of alginate is responsible for the mucoadhesive qualities that it possesses. The negative charges of sialic acid and sulfate groups in the mucus structure, along with the anionic carboxylic groups of alginates, create electrostatic repulsive forces between alginate and mucin in the physiological environment. These forces are responsible for the formation of the electromagnetic force. This suggests that hydrogen bonding both within and between molecules promotes the bioadhesion that takes place between mucin and alginate. According to research, there are several stages involved in the mechanism of mucoadhesion: the first is close contact with the mucosa, which causes the polymer to wet and swell; the last stage is the creation of hydrogen bonds by the interpenetration of mucin with polymer chains. [38] This characteristic is useful for the delivery of pharmaceuticals to mucosal membranes as it enhances the contact time and adherence of the drug to the target location, while also enhancing the bioavailability of the treatments. [4]

7.3. Biological Characteristics

The Federal Drug Administration (FDA) has given its approval for the use of sodium alginate in the biomedical, food, and pharmaceutical industries because it does not cause an immune response, is compatible with living things, and decomposes naturally. [35]

7.4. Biocompatibility of Sodium Alginate

The biocompatibility of sodium alginate has been thoroughly researched both in vivo and in vitro, and the results have shown that there are noticeable changes depending on the purity of the material. Due to its biocompatibility and mild gelation upon the addition of divalent cations such as Ca^{2+}, alginate, which is a naturally occurring anionic polysaccharide, has been the subject of extensive research and has been exploited in a range of applications. [39] The purity and biocompatibility of alginate are both determined by the composition of the substance. Alginate that contains a high concentration of M monomers has been shown to be more immunogenic and to promote cytokine production by a factor of ten when compared to alginate that contains G monomers. On the other hand, data indicate that alginate implants are associated with a low or nonexistent immunological response. [40] Alginates have the capacity to retain pollutants such as heavy metals, endotoxins, polyphenolic compounds, and proteins, which could possibly provoke a variety of reactions at injection or implantation sites. [41]

8. Behavior of Cross-linking

The most frequent method for producing hydrogels is to mix ionically cross-linking substances, especially divalent cations like Ca^{2+}, with an aqueous ALG solution. This is the most popular method. Because the structure of the guluronate blocks allows for a considerable quantity of divalent ion coordination, researchers believe that divalent cations connect to the guluronate block polymers of the ALG chains in a manner that is distinct from other approaches. A gel structure is created as a result of the guluronate units of one ALG chain creating links with the guluronate blocks of different polymer chains that are placed nearby. Specifically, this method of cross-linking is referred to as the egg-box style. [42] An example of an ionic cross-linking agent that is commonly used for ALG is calcium chloride ($CaCl_2$). The fact that it dissolves easily in water is one of the reasons why it frequently causes gelation to occur rapidly and without much control. The utilization of a buffer that is rich in phosphates, such as sodium hexametaphosphate, is one method that can be utilized to restrict and manage the production of gels. The carboxylate groups of the ALG are in competition with the phosphate molecules in the buffer for the opportunity to bind with calcium cations during the process. The gelation process is slowed down as a result of this. [43] When divalent cations are used, the rate of gelation has a significant impact on the gel's strength and consistency. A higher gelation rate leads in structures that are more uniform and brings about improvements in their mechanical properties. The rate at which gelation takes place and the efficiency with which gels function are both influenced by the temperature at which gelation takes place. At lower temperatures, for instance, ionic cross-linkers such as Ca^{2+} are less reactive, which makes the process of cross-linking more difficult overall. The cross-linked structure that was produced as a result demonstrates improved order, which ultimately leads to an improvement in the mechanical characteristics. [44, 24, 45] It is also possible for the chemical composition of the ALGs to have a considerable impact on the mechanical properties of ionically cross-linked ALG hydrogels. Specifically, ALG hydrogels that contain a greater number of G blocks are more rigid than those that have a smaller number of G blocks. [46]

8.1. Covalent bonds for crosslinking

The utilization of covalent bonds for crosslinking Researchers are investigating the possibility of employing covalent crosslinking to make ALG hydrogels more stable for a wide variety of various biological applications. One of the most common locations for the formation of covalent bonds is the carboxylate group. In addition to the water being extracted from the hydrogel and the stress that was placed on it being removed, the cross-links disintegrate and move to a new location, which results in the hydrogel undergoing plastic deformation. When it comes to covalently cross-linked gels, the movement of water can help alleviate tension; yet, the fact that these gels cannot dissolve and establish new links again makes them extremely elastic. The use

of covalent cross-linking reagents, on the other hand, may be associated with potential dangers, which calls for the elimination of all unreacted compounds from gels. The covalent cross-linking of ALG with poly(ethylene glycol)-diamines of varying molecular weights was initially studied in order to generate gels that exhibited a variety of mechanical qualities at the beginning of the study. [47]

In a consistent manner, the elastic modulus increased as the crosslinking density or weight percent of PEG in the gel increased. Consequently, the elastic modulus diminished when the molecular weight between cross-links fell below that of the more pliable PEG. [48] Subsequent studies revealed that the mechanical properties and swelling behavior of ALG hydrogels can be meticulously controlled by exploring various cross-linking agents and adjusting cross-linking densities. This was accomplished by controlling the cross-linking densities. There is a significant relationship between the chemical composition of the cross-linking chains and the rate at which the hydrogel can expand. The hydrogel loses its hydrophilicity throughout the cross-linking reaction. This phenomenon can be elaborated by the addition of hydrophilic cross-linking agents, such as polyethylene glycol (PEG), as a supporting macromolecule. In order to circumvent the issue of ionic crosslinked hydrogels degrading when exposed to water, Gao et al. utilized dual cross-linked methacrylated alginate hydrogel. The dual cross-linked chains of the hydrogels were prevented from breaking when they were subjected to ultraviolet light as a result of the covalent cross-links that existed between the methacrylate groups. [49, 48, 50] Through the use of covalent cross-linking, a new method of gelling in place has been developed.

8.2. Photocross-linking

In the presence of adequate chemical precursors and under mild reaction circumstances, photocrosslinking can take place. This phenomenon can even take place in direct contact with drugs and cells. The alginate hydrogels attained transparency and flexibility following treatment with methacrylate and subsequent cross-linking via an argon-ion laser (514 nm) for thirty seconds, utilizing eosin and triethanolamine. [48]

8.3. Gelling with Heat

Due to the fact that thermosensitive hydrogels have the ability to expand in reaction to changes in temperature, they have recently been the subject of research in a wide variety of therapeutic applications. This makes it possible to regulate the dispersion of drugs from gels in a pro re nata manner. There are several different kinds of thermo-sensitive gels, but the most prevalent ones are poly(N-isopropyl acrylamide) (PNIPAAm) hydrogels. They undergo a phase change in water when the temperature is below the critical solution temperature, which is 320 degrees Celsius. Although thermo-responsive hydrogels are extremely important in biological applications, there have been various systems based on ALG that have been reported up until this point. This is due to the fact that alginate is not inherently thermosensitive. To establish the framework for the semi-interpenetrating polymer network (semi-IPN), sodium alginate (SA) was incorporated into N-isopropyl acrylamide (NIPAAm) and poly(ethylene glycol)-copoly(-caprolactone) (PEG-co-PCL) macromer. The gels' capacity to expand had a positive correlation with the amount of SA present, while it had a negative correlation with the temperature. The incorporation of sodium alginate into semi-IPN structures resulted in the hydrogels being more robust and facilitated the release of BSA, indicating that it may have potential applications in the field of drug delivery. [51, 52, 53]

8.4. Cross-linking of cells

The capacity of cells to improve gel synthesis has been largely disregarded, despite the fact that several chemical and physical procedures for the creation of ALG gels have been discovered. Cross-linking of cells nevertheless has been described. It is possible for cells to bind to more than one polymer chain, despite the absence of chemical cross-linkers. This can result in the network becoming longer and more flexible when the alginate is altered with cell adhesion molecules. When cells are placed in a solution that has been functionalized with arginine, glycine, and aspartic acid (Arg–Gly–Asp, RGD), they spread out in an almost uniform manner. Through the use of particular receptor–ligand interactions, this system is able to create cross-linked networks without the requirement of any additional cross-linking chemicals. [45, 24]

9. Alginate-based Systems

9.1. Three-dimensional networks (Hydrogels)

Three-dimensional networks that are composed of hydrophilic polymers and are capable of holding a significant amount of water are known as hydrogels. When cells are put to hydrogels, the hydrogels become very swollen, which makes it simpler for nutrients to enter the cells and for waste to exit the cells? Generally speaking, alginate is hydrophilic, which means that it dissolves in water. In neutral conditions, it thickens, which is a highly significant characteristic for the production of hydrogels in situ environments. On the basis of the manner in which they gel, alginate hydrogels that have the potential to be utilized in tissue engineering can be classified into two distinct groups: physical gels and covalent gels. The production of alginate hydrogels can be accomplished through a variety of methods, including ionic contact, phase change (thermal gelation), free radical polymerization, and cell-crosslinking reactions. Alginate hydrogels are likely to respond to pH variations owing to the presence of carboxyl groups in their structure. The pH-responsive behavior is demonstrated by elevated swelling ratios at higher pH values. This is ascribed to the chain expansion resulting from ionic carboxylate groups on the backbone. It is commonly essential to change synthetically created alginate hydrogels. [54]

9.2 Microspheres

In the field of tissue engineering, delivery systems that are based on microspheres have been utilized to

transfer cells, growth factors, genes, proteins, and other drugs. After the appropriate procedures have been carried out, alginates have the potential to easily produce gel- and solid-microspheres that can be utilized as delivery systems. In a nutshell, ionic crosslinking is the process that is utilized in order to create alginate gel-spheres in water. These gel-spheres are beneficial for the retention of cells, growth factors, and biologic proteins. It is possible to create alginate solid spheres through the use of emulsion solvent evaporation techniques, which are typically employed for loading pharmaceuticals. Both gels based on alginate and solid microspheres are highly biocompatible when used in the domain of regenerative medicine. [54]

10. Biomedical applications

Alginate is a biopolymer that is formed from nature. It has attracted a lot of attention in biomedical applications due to the fact that it is very biocompatible, can gel, and can form hydrogels at low temperatures. Alginate is also used in the delivery of drugs, in tissue engineering, and in the healing of wounds. Utilization of alginate in pharmaceutical delivery systems is one of the most popular applications for this substance. In these systems, alginate may transport and release medicinal compounds to precise locations. Tablets, capsules, gels, patches, emulsions, and suspensions are all examples of examples of solid, semi-solid, and liquid forms that can be produced from alginate respectively. The chemical structure of the gel may be altered to fine-tune the release of the medication, and the nanoscale pore size of the gel, which is approximately 5–6 nm, makes controlled diffusion easier to achieve. Microcapsules made of alginate have been developed for prolonged release. [45, 24] Their advantages include a high drug loading, the fact that they are biodegradable, the fact that they do not cause immunological reactions, and the fact that they are low in toxicity. Whenever they are subjected to magnetic fields, stimuli-responsive microcapsules, particularly those that include magnetic nanoparticles, have the ability to transport medications to specified regions of the body. Furthermore, it has been demonstrated that alginate microcapsules can facilitate the transportation of drugs that do not dissolve well in water, such as glucocorticoids. This is accomplished by making loading more effective and causing less damage to the tissues. It is also possible for alginate hydrogels to function as carriers for protein pharmaceuticals, preventing the medications from degrading and allowing them to be released in a controlled manner. For example, hydrogels that included vascular endothelial growth factor (VEGF) demonstrated extended release over a period of seven days, which made it easier for neovascularization to occur. The use of alginate as a scaffold material in regenerative medicine and tissue engineering has been demonstrated to facilitate cell proliferation, tissue formation, and organ repair. [55] It is frequently combined with other polymers or inorganic materials in order to make it more robust, increase its cell-friendly properties, and improve its ability to form gels. Composites that contain chitosan, collagen, or hydroxyapatite (HA) are used in bone tissue engineering to improve structural stability, induce osteogenesis, and assist in the growth of blood vessels. As an illustration, scaffolds composed of chitosan and alginate are able to make objects more robust when subjected to pressure, whilst hybrids composed of collagen and alginate assist osteoblasts in growing and transforming into various cell kinds. When HA is added to the mixture, the substance becomes more similar to the extracellular matrix of bone, which results in the material becoming more porous, stronger, and beneficial to cells. Scaffolds made of alginate have been extensively researched for their potential applications in the engineering of cartilage, liver, and vascular tissues. Chitosan-alginate scaffolds are known to promote chondrocyte proliferation and cartilage regeneration. On the other hand, hyaluronic acid-alginate hydrogels are known to provide binding sites for chondrocytes. Hepatocyte proliferation, spheroid formation, and functional integration are all improved with the use of galactosylated chitosan-alginate scaffolds or alginate-gelatin-fibrin composites in liver tissue engineering. Microencapsulation techniques offer an additional layer of protection to cells, which enables them to survive for longer periods of time and operate more effectively in both in vitro and in vivo settings. An additional significant application of alginate is in the process of wound healing. [56, 57, 58] As a result of its affinity for water and its ability to retain it, it generates a moist environment that facilitates the healing of tissue. Hydroxygels, films, sponges, and membranes are all examples of dressings that contain alginate. These dressings have the ability to absorb exudates, maintain a steady pH level, and reduce the likelihood of infection. Polymers, whether natural or synthetic, such as chitosan or hyaluronic acid, are added to the substance, which results in the material becoming more robust, more easily degraded, and more active within the body. Dressings made of alginate that are loaded with pharmaceuticals deliver controlled doses of antimicrobials, which assist in the compression of wounds more quickly. Alginate scaffolds also assist in the regeneration of cartilage and liver tissue by promoting the adhesion of cells to one another, the proliferation of cells, and the production of functional tissue. [59, 60]

11. Toxicity, in vivo performance, and regulatory considerations

Biocompatibility of alginates has been demonstrated in vivo following oral, topical, local, ocular, and nasal administration. A number of alginates salts containing sodium, potassium, calcium, and ammonium have been deemed acceptable for consumption by the Food and Drug Administration, which has officially verified that propylene glycol alginates derivatives are safe to consume. [61]Alginate hydrolysate is generated by hydrolyzing alginate and its derivatives, including sodium alginate. This process results in the separation of the components of alginate hydrolysate into molecules that are safe and biocompatible, notably mannuronic and guluronic acids. In order to assess the levels of safety, tolerability, and effectiveness of guluronic acid, a great number of experimental models

have been carried out. In the course of this research, it was discovered that guluronic acid is a substance that may be safely used orally. For the purpose of conducting acute toxicity tests, a total of six groups of mice were utilized, including five treatment groups and one control group. The number of mice in each group was eight, with four males and four females. Two thousand, three thousand, four thousand, five thousand, or six thousand milligrams per kilogram of body weight were administered orally to the guluronic treatment groups. The amount of deionized water that was consumed by the control group was the same. In the fourteen days that followed the administration of the drug, the mice were continuously monitored and examined for any changes in behavior, manifestations of toxicity, and signs of mortality. During the phase of the experiment that focused on acute toxicity, a lethal dosage (LD50) value of 4800 mg/kg was assigned to guluronic acid. In the course of this experiment, the animals that were administered guluronic acid did not exhibit any obvious indicators of disease or death. The average weekly weights of the treatment groups (groups 2 to 5) were almost identical to those of the control group over the course of the study. In addition, the weekly fluctuations in water and food consumption among mice that were treated were not significantly different from those that were in the control group. [62, 63, 64]

12. Concerns, Limitations, and Prospects for the Future

The ionotropic gelation technique was utilized in order to produce sodium alginate beads that contained surfactant particles. An examination of their stability was carried out by observing the changes in their appearance and diameter that occurred after they were placed in solutions with varying pH values. The beads diminished in size when exposed to acidic media, but they grew in size when exposed to neutral phosphate-buffered saline, indicating that they were sensitive to changes in pH levels. However, when exposed to alkaline circumstances, the beads initially grew larger and subsequently disintegrated, indicating that they were not very stable when exposed to basic conditions. According to the findings of compression testing, the beads made of sodium alginate became less rigid as the pH increased. This indicates that they are more rigid in acidic solutions and more pliable in alkaline solutions at the same time. According to the findings of these investigations, sodium alginate beads exhibit a stability that is dependent on pH. This stability is defined by a decreased resistance in alkaline conditions and a vulnerability to structural changes in both acidic and neutral settings. [65, 66, 67]

Alginate-based materials are gaining popularity due to the fact that they are biocompatible, have the ability to gel with cations, and possess physicochemical properties that can be altered. Enzymes such as epimerases are being used to modify alginates in order to produce polymers that are more elastic, compact, and stable within the body. This is a significant scientific advancement. Because of their increased mechanical strength and decreased permeability, these modified alginates are more suitable for use in biomedical and tissue engineering applications. Ionic methods are not the only methods that can be used to gel; other methods include cryogelation, non-solvent phase separation, CO2 induced crosslinking, and photo induced crosslinking. Because of these technologies, it is feasible to carefully regulate the structure, porosity, and mechanical properties of a network. This opens the door for the creation of individualized drug delivery systems, scaffolds, and environmental applications. In the food industry, polymers based on alginate are being manufactured for the purpose of creating intelligent and active packaging. Composites that combine alginate with carnauba wax, calcium ascorbate, or metal-organic nanoparticles have the ability to detect spoilage, possess antibacterial properties, and are more resistant to water. Alginate has the potential to be utilized in packaging that is both functional and environmentally friendly. The cleanup of the environment is yet another significant development. Through the use of chemical, physical, and electrostatic adsorption techniques, composites that are composed of alginate and contain biochar, graphene oxide, titanium dioxide, or other functional additives are able to effectively remove heavy metals, antibiotics, dyes, and pesticides from wastewater. For the purpose of healing wounds, growing new skin and nerves, making bone tissue, and transporting medications, alginate hydrogels are utilized in the field of biomedicine. The efficiency of antibacterial agents, mechanical properties, and release over time are all improved by hybrid systems that contain natural polymers, nanoparticles, or bioactive chemicals. When it comes to cell survival and therapeutic outcomes, injectable and self-crosslinking hydrogels surpass the competition. [24, 68, 69, 70]

Conclusion

Alginate-based hydrogels and particle systems have become significant biomaterials in drug delivery and biomedical sciences owing to their biocompatibility, biodegradability, and gentle gelation characteristics. The molecular weight, the M/G ratio, and the crosslinking process are all structural characteristics that have a significant impact on how they perform mechanically, how stable they are, and how effectively they release pharmaceuticals. Alginate has become more effective for tissue engineering, controlled drug delivery, and wound healing as a result of recent advancements in methods that can change the physical and chemical properties of alginate. There are still issues with mechanical strength, long-term stability, and reproducibility, despite the fact that these advancements have been made. In the future, research that focuses on advanced modification techniques and in vivo validation will serve to improve the translational potential of systems that are based on alginate.

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