

## Review

# Chemically Modified Alginate-Based Hydrogel-Matrices in Drug Delivery

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## Abstract

Alginate is a biomaterial that has demonstrated considerable potential and adaptability in the field of controlled drug delivery due to its unique physicochemical properties. Chemical modification of alginate has significantly enhanced its functionality, allowing the development of matrices with improved characteristics, such as increased affinity for hydrophobic drugs, sustained and controlled release, and improved cell and tissue adhesion. Hydrogels, microspheres, nanoparticles, and porous scaffolds are among the most extensively studied alginate-based drug delivery systems. It is estimated that over 50% of these systems have shown successful outcomes in in vitro testing, particularly in applications such as oral delivery of proteins and peptides, wound healing, tissue regeneration, and cancer therapy. Recent clinical advances involving alginate include the development of wound dressings, growth factor delivery systems, and cell-based therapies for treating degenerative diseases. Chemically modified alginate thus emerges as a highly adaptable and promising candidate for the design of advanced drug delivery systems across a wide range of biomedical applications. This review encompasses more than 100 research articles and aims to provide an updated overview of the current state of knowledge regarding the use of chemically modified alginate-based hydrogel systems in drug delivery.

**Keywords:** alginate; controlled drug delivery; chemical modification; hydrogels; biomedical applications



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## 1. Introduction

Alginates are natural, hydrophilic, anionic polysaccharides derived from brown seaweed and certain bacteria. These linear copolymers consist of (1 → 4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues arranged in homo-polymeric (MM or GG) or hetero-polymeric (MG) blocks [1,2]. The ratio and sequence of M and G residues vary depending on the source and species of algae, leading to a wide range of

physicochemical properties [3,4]. These unique physicochemical properties of alginate allow this biomaterial to serve as a thickening, stabilizing, gel-forming, and biocompatible agent. However, it has some limitations in terms of functionality, like low mechanical behavior and degradation in high pH environments, which restrict its biomedical applications of native alginate. Therefore, there is a trend toward developing “value-added” alginates by modifying the polysaccharide backbone, which contains abundant free hydroxyl and carbonyl groups [5–7].

Physical, enzymatic, and chemical modifications of alginate are powerful methodologies that can solve potential drawbacks, enhance existing features, and introduce completely new properties that were not previously possible. The carboxyl group at C-6 or the secondary hydroxyl groups at C-2 and C-3 of alginates are generally available for chemical modification. Before selecting any modification, two key parameters (solubility and reactivity) must be considered. These changes provide flexibility to the natural form of the polysaccharide and improve some benefits, such as faster loss of molecular weight with specific degradation, controlled reaction for selective modification of G or M residues, and gel formation due to residual carboxyl groups available in ionic gelation. Modifications also allow the user to fine-tune natural biopolymers as needed for specific purposes in various applications. Esterification, amidation, the Ugi reaction, oxidation, cyanogen bromide reaction, and copolymerization are some of the chemical modifications performed on alginates [8].

In contrast, the presence of carboxyl groups on the uronic acid residues provides a negative charge to the alginate molecules, making them capable of forming stable hydrogels in the presence of divalent cations, such as calcium ( $\text{Ca}^{2+}$ ) [9]. The gelation mechanism involves the formation of an “egg-box” structure, where the divalent cations interact with the G-blocks of adjacent alginate chains, creating crosslinks and leading to the formation of a three-dimensional network [10]. The strength and stability of the resulting hydrogels depend on the content and distribution of G-blocks and the concentration of crosslinking cations [11].

Chemically modified alginates are malleable and can form various types of matrices, such as hydrogels, microparticles, nanoparticles (NPs), and fibers [3]. These matrices can be designed to manipulate the release kinetics of encapsulated drugs, allowing for prolonged or precise administration. Chemically modified alginate hydrogels can be engineered to selectively react to stimuli, such as alterations in pH or temperature, which then initiate the liberation of encapsulated drugs [12]. Furthermore, the porous composition of the alginate matrix facilitates the effective incorporation of drugs with varying solubilities and molecular weights [10].

Thus, the versatility of chemically modified alginate hydrogels allows for a wide range of applications as drug delivery agents (Figure 1). They have been investigated for oral delivery of proteins and peptides, as they can protect these labile molecules from the harsh gastric environment and provide controlled release in the intestine [13,14]. Chemically modified alginate hydrogels have also been employed in wound dressings and tissue engineering scaffolds, where they promote tissue regeneration and accelerate the healing process [5,15,16]. Alginate-based nanoparticles have demonstrated potential in cancer therapy for delivering chemotherapeutic drugs directly to tumor locations, thereby minimizing systemic toxicity and improving therapeutic effectiveness [1,16–18]. Therefore, the aim of this review is to present a complete picture of the most current alginate chemical modification methods and their applications in hydrogel matrices for drug delivery and other biomedical applications.

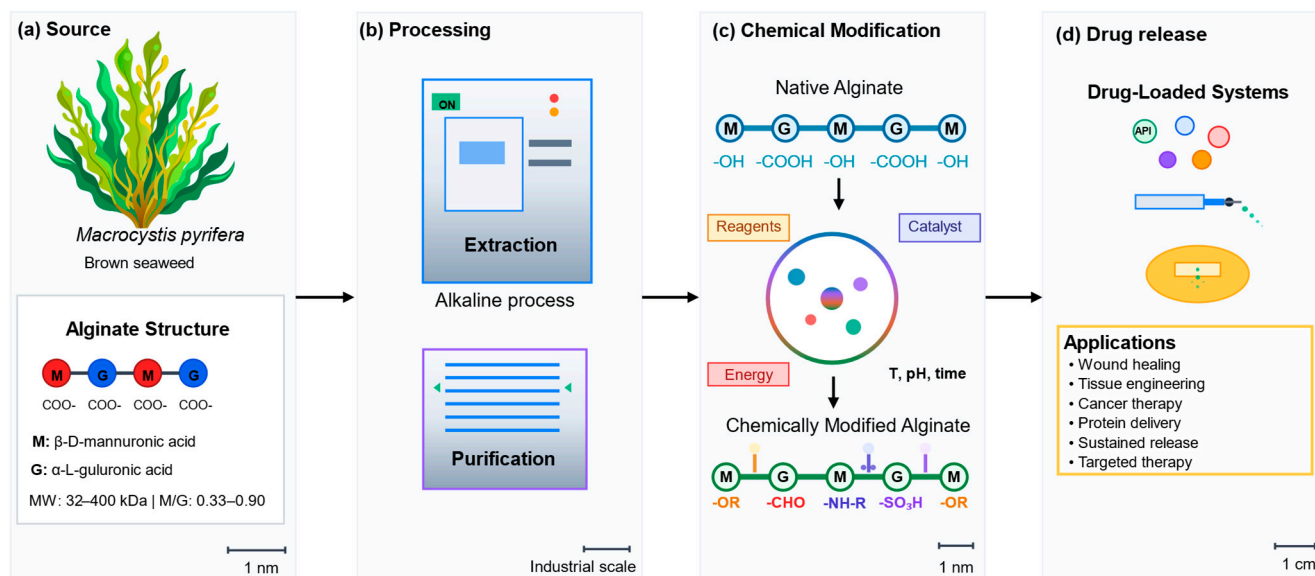


**Figure 1.** Chemically modified alginate-based hydrogel matrices for drug delivery. (a) Marine source and molecular structure. (b) Processing methods on an industrial scale. (c) Chemical modification. (d) Drug-loaded delivery systems. Scale bars indicate dimensional ranges from the molecular (1 nm) to macroscopic (1 cm) levels.

In this review, four databases were used: SCOPUS, Google Scholar, PubMed, and Web of Science. The keywords used for searching the databases included “Sodium Alginate, Hydrogels, Chemical modification, controlled drug delivery, biomedical applications, alginate physicochemical properties, alginate functional properties, and alginate extraction”. The search was limited to the 2000–2025 period, but three citations were taken from 1999, 1998, and 1968, respectively. Publications whose scope was related to alginate applied to Food, Environmental, and Agrochemicals were discarded, and all remaining citations were checked for duplication. After screening, the publications retained for this review were 58 from SCOPUS, 42 from Google Scholar, 27 from PubMed, and 12 from Web of Science.

## 2. Alginates

Alginate is a polysaccharide derived from brown seaweed. This biopolymer has garnered significant attention in the scientific community due to its unique properties and diverse applications, particularly in drug delivery. The sources, compositional variability, and influence of factors such as seaweed species and environmental conditions on the properties are discussed.

### 2.1. Sources of Alginates and Compositional Variability

It is well known that alginates are derived from brown seaweeds, which are marine macroalgae belonging to the class *Phaeophyceae*. Among the various genera of brown algae, *Laminaria* and *Macrocyctis* are the most important commercial sources of alginates [11]. These seaweeds are widely distributed in the coastal regions of the world, with *Laminaria* species being more prevalent in the Northern Hemisphere and *Macrocyctis* species in the Southern Hemisphere [19]. *Laminaria* species, such as *Laminaria digitata*, *Laminaria hyperborea*, and *Laminaria japonica*, are the principal sources of alginates in Europe and Asia [4,20]. These species are characterized by their large, leaf-like blades (laminae) and thick, cylindrical stipes that anchor them to the seabed. *Laminaria* species are known to produce high-quality alginates with a high content of guluronic acid (G) residues, which impart excellent gel-forming properties. G-rich alginates derived from *Laminaria* species

are particularly suitable for applications that require strong and stable hydrogels, such as the formulation of controlled-release drug delivery systems [21].

On the other hand, the *Macrocystis* species, particularly *Macrocystis pyrifera*, are the primary sources of alginates in the Southern Hemisphere, with extensive harvesting and processing operations in countries like Chile, Australia, and South Africa [22]. Nowadays, Chile is the major global producer of alginates, owing to its extensive coastline and the abundance of *Macrocystis pyrifera*, also known as giant kelp [22]. The country's unique geographical and environmental conditions, characterized by cold, nutrient-rich waters and strong ocean currents, provide an ideal habitat for the growth of *Macrocystis pyrifera*. *Macrocystis pyrifera*, commonly known as giant kelp, is the largest seaweed species, reaching lengths of up to 60 m. It forms dense underwater forests that provide habitats for a wide range of marine organisms. Alginates extracted from *Macrocystis pyrifera* typically have a higher content of mannuronic acid (M) residues than those from *Laminaria* species [16].

The composition and properties of alginates extracted from brown seaweeds are influenced by several factors, including the species of algae, geographical location, seasonal variations, and environmental conditions [22]. However, there are additional environmental elements, such as water pollution and ocean acidification, that can potentially influence the composition and characteristics of alginate [23]. The ratio of M to G residues, as well as their sequence and block structure, can vary significantly depending on these factors, leading to alginates with diverse physicochemical properties [4]. To select appropriate seaweed species for medical applications, it is crucial to understand the factors that influence the characteristics and composition of alginates.

## 2.2. Conventional Methods of Alginate Extraction and Purification

The process of obtaining alginates from brown seaweed consists of several stages, with traditional techniques involving acid and alkaline extraction procedures. The objective of these methods is to convert the insoluble alginate salts found in the cell walls of seaweed into soluble sodium alginate. Sodium alginate may then be isolated from the remaining biomass and processed further to synthesize pure alginates [24]. The selection of the extraction technique depends on multiple factors, including the type of seaweed, the necessary amount and quality of alginate, and the financial and environmental factors to be considered [21].

The acid extraction process requires subjecting the seaweed biomass to weak mineral acids, such as hydrochloric acid (HCl) or sulfuric acid (H<sub>2</sub>SO<sub>4</sub>), to transform insoluble alginate salts, mainly calcium and magnesium alginates, into alginic acid [25]. The procedure generally entails immersing seaweed in an acidic solution with a pH range of 2–4 for a particular period, which varies based on the type of seaweed and the required level of extraction effectiveness. Acidic treatment causes the carboxylate groups of alginate to undergo protonation, resulting in the release of the attached cations and the conversion of alginate into its insoluble acid form [26,27]. Alginic acid is then separated from the residual biomass through filtration or centrifugation and subsequently converted into sodium alginate by neutralization with sodium carbonate (Na<sub>2</sub>CO<sub>3</sub>) or sodium hydroxide (NaOH) [9]. One of the main advantages of the acid extraction method is its simplicity and relatively low cost compared with the alkaline extraction process. The use of inexpensive mineral acids and the ability to recover and reuse the acids make this method economically attractive [24].

In contrast, the alkaline extraction procedure involves subjecting seaweed biomass to sodium carbonate (Na<sub>2</sub>CO<sub>3</sub>) or NaOH solutions at temperatures between 60 and 80 °C [24]. Alkaline treatment changes the alginate ions that cannot be dissolved into soluble sodium alginate. The soluble sodium alginate is subsequently extracted from the

residual biomass using both filtration and centrifugation [19]. The alkaline extraction method offers several advantages over acid extraction. Firstly, it yields alginates with higher molecular weights and viscosities, as alkaline conditions are less prone to causing degradation of the alginate chains [28]. Second, the alkaline extraction method is more selective towards alginates, resulting in a higher purity of the extracted product than the acid extraction process [19]. However, the alkaline extraction process has some limitations and disadvantages, such as high production costs associated with the use of sodium carbonate or sodium hydroxide [24] and a high energy input because of the high temperatures required for the extraction process [27], and low selectivity due to the potential for co-extraction of impurities, such as residual alkali and polyphenols, which affect the quality and functionality of the extracted alginates.

After alginates are extracted from brown seaweeds, the resulting alginate solution contains various impurities that must be removed to obtain high-quality alginates suitable for pharmaceutical applications [19]. Therefore, many purification methods have been developed to eliminate these contaminants and obtain alginates with the appropriate properties (Table 1). Precipitation is one of the most common purification techniques used in the alginate industry. This method involves the addition of a solvent or chemical agent to the crude alginate solution to induce the formation of insoluble alginate particles, which can then be separated from impurities through filtration or centrifugation [20]. For example, ethanol is commonly employed to precipitate sodium alginate due to its ability to mix well with water and efficiently remove moisture from alginate molecules [24]. Another commonly used precipitation agent is  $\text{CaCl}_2$ , which is employed to produce calcium alginate, a water-insoluble form of alginate that is widely used in the preparation of gel beads and matrices for drug delivery applications [3].

**Table 1.** Characteristics of alginates extracted from various seaweed sources using different extraction and purification methods.

| Source of Alginate          | Extraction Method    | Purification Method                                    | Characteristics of Alginate                                                            | Reference |
|-----------------------------|----------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------|-----------|
| <i>Laminaria digitata</i>   | Alkaline extraction  | Precipitation with ethanol, dialysis                   | M/G ratio: 0.45, Molecular weight: 200–400 kDa, Viscosity: 200–400 mPa·s (1% solution) | [29]      |
| <i>Macrocystis pyrifera</i> | Acid extraction      | Precipitation with $\text{CaCl}_2$ , ultrafiltration   | M/G ratio: 1.2, Molecular weight: 100–200 kDa, Viscosity: 100–200 mPa·s (1% solution)  | [30]      |
| <i>Ascophyllum nodosum</i>  | Alkaline extraction  | Precipitation with ethanol, activated carbon treatment | M/G ratio: 0.6, Molecular weight: 150–250 kDa, Viscosity: 150–250 mPa·s (1% solution)  | [31]      |
| <i>Lessonia trabeculata</i> | Alkaline extraction  | Membrane filtration, dialysis                          | M/G ratio: 0.8, Molecular weight: 300–500 kDa, Viscosity: 500–700 mPa·s (1% solution)  | [26]      |
| <i>Sargassum muticum</i>    | Enzymatic extraction | Precipitation with isopropanol, ion exchange           | M/G ratio: 0.9, Molecular weight: 80–120 kDa, Viscosity: 50–100 mPa·s (1% solution)    | [32]      |
| <i>Ecklonia cava</i>        | Acid extraction      | Ultrafiltration, diafiltration                         | M/G ratio: 1.1, Molecular weight: 50–100 kDa, Viscosity: 20–50 mPa·s (1% solution)     | [33]      |

Filtration is another purification technique used to remove solid impurities. The crude alginate extract is typically passed through a series of filters with decreasing pore sizes to remove suspended solids such as residual seaweed fibers, sand, and other particulate matter [24]. Therefore, ultrafiltration is an advanced filtration technique that involves the use of semi-permeable membranes with specific molecular weight cut-offs to separate

alginate molecules from lower-molecular-weight impurities, such as salts, sugars, and small peptides [28].

Dialysis is a commonly employed method for purifying alginates, particularly for producing highly pure alginates for hydrogel drug applications. This technique uses a semi-permeable membrane with a defined molecular weight cut-off to exclude small-molecular-weight contaminants, such as salts, from the alginate solution [20]. This process facilitates the diffusion of impurities out of the membrane while preserving the larger alginate molecules [19].

In addition to these conventional purification techniques, other methods, such as ion exchange and electrodialysis, have been explored for the purification of alginates. Ion exchange involves the use of resins with charged functional groups to selectively remove ionic impurities such as heavy metals and residual calcium ions from the alginate solution [26]. Electrodialysis, on the other hand, employs an electrical potential to drive the migration of ionic impurities across ion-selective membranes, resulting in the purification of alginate solution [25].

### 2.3. Challenges and Future Perspectives of Alginate Extraction and Purification

Although alginate purification and extraction techniques have witnessed significant progress, they continue to present obstacles and opportunities for improvement. An important issue that arises is the environmentally friendly acquisition of algal waste products, given that the increased demand for alginates could potentially result in a decrease in natural seaweed ecosystems. To address this issue, researchers have explored alternative sources of alginates, such as microalgae and genetically engineered bacteria [21]. Another challenge is the optimization of extraction and purification processes to improve the yield, purity, and functionality of the extracted alginates, while minimizing environmental impact and production costs [9]. The development of novel extraction techniques, such as ultrasound-assisted extraction, microwave-assisted extraction, and enzymatic treatment, has shown promise in enhancing the efficiency and selectivity of alginate extraction [34]. These techniques reduce process times and energy consumption, and sometimes improve extraction yields. Table 2 shows some comparative studies in terms of extraction performance between conventional and non-conventional (eco-friendly) methods. As can be seen from this table, the yield percentages do not show a clear trend favoring conventional or non-conventional methods. This is because the extraction method is not the only factor to consider; the type of algae used and the purification process must also be taken into account.

**Table 2.** Eco-friendly and conventional extraction methods for alginates from different macroalgae species.

| Source of Alginate              | Extraction Method                     | Purification Method                                   | Yield (%)/(M/G) ratio | Reference |
|---------------------------------|---------------------------------------|-------------------------------------------------------|-----------------------|-----------|
| <i>Sargassum angustifolium</i>  | Ultrasound                            | Precipitation with ethanol                            | 45.0/2.99             | [34]      |
| <i>Nizamuddinina zanardinii</i> | Ultrasound<br>Microwave<br>extraction | Precipitation with<br>Na <sub>2</sub> CO <sub>3</sub> | 11.88–15.36           | [35]      |
| <i>Undaria pinnatifida</i>      | Microwave<br>extraction               | NA                                                    | 37.79                 | [36]      |
| <i>Sargassum Algae</i>          | Microwave<br>extraction               | Precipitation with ethanol                            | 36.0                  | [37]      |
| <i>Nizamuddinina zanardinii</i> | Microwave<br>extraction               | Precipitation with ethanol                            | 31.39                 | [38]      |

Table 2. Cont.

| Source of Alginate             | Extraction Method                        | Purification Method                                | Yield (%)/(M/G) ratio | Reference |
|--------------------------------|------------------------------------------|----------------------------------------------------|-----------------------|-----------|
| <i>Ascophyllum nodosum</i>     | Hydrostatic pressure-assisted extraction | 0.2 M HCl, 12 h at room temperature                | 14.0                  | [39]      |
| <i>Laminaria digitata</i>      | Acid extraction                          | Precipitation with Na <sub>2</sub> CO <sub>3</sub> | 51.8/1.12             | [19]      |
| <i>Macrocystis pyrifera</i>    | Acid extraction                          | Precipitation with Na <sub>2</sub> CO <sub>3</sub> | 23.2                  | [40]      |
| <i>Ascophyllum nodosum</i>     | Alkaline extraction                      | Precipitation with NaHCO <sub>3</sub>              | 13.8                  | [41]      |
| <i>Sargassum vulgare</i>       | Acid extraction                          | Precipitation with Na <sub>2</sub> CO <sub>3</sub> | 40.0                  | [42]      |
| <i>Nizimuddinina zanardini</i> | Acid extraction                          | Precipitation with Na <sub>2</sub> CO <sub>3</sub> | 24.0/1.1              | [43]      |
| <i>Sargassum natans</i>        | Acid extraction                          | Precipitation with Na <sub>2</sub> CO <sub>3</sub> | 23.0/0.6              | [44]      |

### 3. Physicochemical Properties of Alginate

Alginate is a biopolymer extensively utilized in the food, pharmaceutical, cosmetic, textile, drug delivery, and biomedical engineering industries, among others. Its recognition is attributed to its functional properties, versatility, biocompatibility, low toxicity, non-immunogenicity, biodegradability, hydrophilicity, and surface activity, which are related to its structure and composition [45]. The main physicochemical characteristics of alginates include their chemical structure, functional group type, and morphology. Alginate is an anionic polysaccharide found as a salt of alginic acid in the intercellular matrix and cell wall of brown seaweeds and the capsules of *Azotobacter* sp. and *Pseudomonas* sp. bacteria [46].

The chemical formulas for alginic acid and sodium alginate are (C<sub>6</sub>H<sub>8</sub>O<sub>6</sub>)<sub>n</sub> and (C<sub>6</sub>H<sub>7</sub>O<sub>6</sub>Na)<sub>n</sub>, respectively, where the hydrogen ions in alginic acid are replaced by cations (Na<sup>+</sup>, Ca<sup>2+</sup>, and Mg<sup>+</sup>) to form the respective salt of alginate by means of acid/alkaline conversion [47]. Chemically, alginates are linear hydrophilic polysaccharides composed of blocks of (1,4)-linked-β-D-mannuronic (M) and α-L-guluronic acid (G) residues with diverse patterns for their M-block or G-block sub-units (homopolymer, GGG or MMM-blocks, or heteropolymer, GMG or MGM-blocks, structures), with the M/G ratio usually found between 0.33 and 0.90 [48]. Their distribution and abundance in macromolecules not only influence the rigidity (G-blocks) and flexibility (M-blocks) of the polysaccharide macromolecule but also contribute to determining the mechanical strength, performance, stability, and functionality of alginate-based systems [3,49–51].

The main functional groups are hydroxyl (-OH) and carboxyl (-COOH) groups present in the molecular chains of the M or G units, which allow alginates to form hydrogen bonds or electrostatic interactions [46,52]. The Fourier-transform infrared—attenuated total reflectance (FTIR-ATR) spectra obtained from alginates exhibited broad signals at 3430 cm<sup>-1</sup> associated with the stretching vibration of the -OH groups and signals at 2939 cm<sup>-1</sup> attributed to the stretching vibration of CH. Additionally, signals at 1618 cm<sup>-1</sup> are associated with COO-asymmetric stretching vibrations of -COOH groups of alginates, while COO-stretching vibrations of uronic acids for mannuronic acid and guluronic acid are located at 1419 and 1093 cm<sup>-1</sup>, respectively [53–55].

Molecular weight (MW) is a crucial property that influences the functional properties of alginates, including (i) the viscosity of aqueous dispersions, where higher MW produces more viscous materials that are suitable for applications as thickeners or stabilizers [56]; (ii) gelling capability by forming stronger gel systems as the MW increases; (iii) film-

forming properties through the modification of the mechanical properties, thickness, and permeability of the films; (iv) encapsulation performance by influencing the long-term stability and controlled release of the core material; and (v) biocompatibility through resistance to enzymatic degradation [3,57].

Alginates are generally characterized by their molecular mass through properties like viscosity-average molecular weight ( $M_v$ ), weight-average molecular mass ( $M_w$ ), number-average molecular mass ( $M_n = 4.8 \times 10^4 - 6.5 \times 10^5$  Da), polydispersity index ( $PI = M_w/M_n$  of 1.5–3.97), weight-average degree of polymerization ( $DP_w$ ), number-average degree of polymerization ( $DP_n$  ranging from 50–3000) [57,58], macromolecular parameters like intrinsic viscosity ( $\eta_{int} = 400 \text{ mL.g}^{-1}$ ), critical concentration ( $C^* = 0.006 - 0.001 \text{ g.mL}^{-1}$ ) [59], and hydrodynamic properties ( $R_h = 17.7 \text{ nm}$ ) [60,61].

The colloidal behavior of alginates is associated with and influenced by the molecular structure of the biopolymer. Alginates are hydrophilic polysaccharides that exhibit solubility in polar solvents, including aqueous ethanol solutions, while organic solvents like chloroform and ether are insoluble. Based on water solubility, alginates can absorb more than 300 times their weight of water. Environmental factors that affect solubility include the pH of the solvent, ionic strength, and the presence of cations that lead to gelling processes. Although the chemical stability of alginates is set at pH 5–10, the best solubility is found at pH 3–3.5, where the carboxyl groups of alginates are protonated and better water dispersibility can be achieved due to hydrogen bond formation. Higher pH values render insoluble alginate material due to the deprotonation of carboxyl groups [3,62]. Regarding the heterogeneity in the alginate structure, alginates rich in MG content exhibit high solubility at low pH rather than Poly-M or Poly-G content alginate molecules, which tend to precipitate under these conditions [63].

The viscosity of alginate solutions is another property intrinsically related to the molecular structure, length, and number of M or G monomers in the alginate segments. Longer chains in the backbone structure (higher MW) exhibit greater viscosity behavior. Alginates usually behave as non-Newtonian pseudoplastic fluids, diminishing the apparent viscosity as the shear rate increases, although some alginates with low MW exhibit Newtonian fluid behavior. The concentration of alginate in the aqueous solution also influences its rheological performance, with solutions below 5% wt. alginate usually exhibits fluid-like behavior, while higher contents display more substantial viscoelastic behavior [64]. From rheological characteristics, alginate solutions in the absence of ions (mono- or divalent cations) display typical viscoelastic behavior with a viscous modulus ( $G'$ ) predominantly higher than its elastic modulus ( $G''$ ) within a frequency range of  $0.1\text{--}100 \text{ s}^{-1}$  [59], whereas in the presence of  $\text{Ca}^{2+}$  ions, a gel point can be defined when  $G' > G''$ , indicating the formation of a viscoelastic gel-like material [65,66].

## 4. Functional Properties of Alginates

Alginates for their chemical structure and composition related to (1,4)  $\beta$ -D mannuronic and  $\alpha$ -L-guluronic acids, which are organized in blocks (MM or GG, MG, GM) and present functional properties that enhance their uses and applications in several areas [39,60]. These functional properties are described as follows:

### 4.1. Gelling Properties

Alginates can form gels in response to temperature changes and cations (ionic gels) or acid sedimentation (acidic gels). The gelling process depends on the type of alginate used, degree of conversion to calcium alginate, calcium chloride, phosphate, lactate, or acetate ions used, algal sources, origin, molecular mass, and obtaining methods. This property depends on the affinity between alginates and divalent and trivalent metal cations, which

form a three-dimensional matrix (Egg-Box). Therefore, this property has been used to create alginate-based hydrogels with small pores to provide elasticity and function [3,60,67,68]. In addition, gelled alginate-based hydrogel particulates in the form of beads, microparticles, and nanoparticles have been created to evaluate their functionality in the encapsulation and release of drugs, bioactive compounds, and herbal extracts [39,69–73].

#### 4.2. Rheological Properties

Rheological properties are important for measuring the viscous and elastic behavior of alginate viscoelastic systems [74]. The particle size affects the rheology of the alginate gel because tiny particles with a larger surface area with respect to the particle mass enhance gel formation over time. Temperature influences gel formation and elasticity. Furthermore, the presence of NaCl promotes higher thickness in alginate systems [39,73,75].

#### 4.3. Water Retention, Syneresis, and Swelling Properties

In alginate gel formation, water linked to the internal gel is confined in the system, and when a force is applied, syneresis occurs. Higher syneresis is perceived in alginate gels when particles with low molecular weight tend to create a fixed gel structure, preventing water molecules from diffusing out of the geloid matrix. In contrast, when alginates present particles with high molecular weight, they tend to create gels with greater syneresis, and the addition of  $\text{Ca}^{2+}$  ions makes the syneresis insignificant. In addition, the rate of swelling of alginate gels is influenced by the amount of calcium ions because the distension function of alginate systems declines with an increase in  $\text{Ca}^{2+}$ , and swelling decreases at pH = 6.6. The swelling behavior and water retention capacity of alginate are important properties for several applications, including its ability to retain bioactive compounds, ions, and drugs through ionic, covalent, and physical crosslinking mechanisms [76].

#### 4.4. Release, Biodegradability, and Biocompatibility Properties

Diffusion is the principal mechanism involved in the delivery of components from alginate gels. Generally, water-soluble compounds with low molecular weights can be instantly diffused in the gel, developing an efficient encapsulation process and smart delivery of the compounds. Instead, alginate gel separates the components at elevated pH values in the presence of ethylenediaminetetraacetic acid (EDTA), affecting the relief of compounds. Interior gelation produces a uniform gel that permits an elevated rate of diffusion, whereas exterior gelation creates a non-homogeneous gel that interrupts the exit of compounds. Consequently, these factors influence the free diffusion of alginate matrix components and their final applications in drug delivery systems [68].

Alginate systems are biodegradable and biocompatible materials that undergo degradation by enzymes, microorganisms, humus, and water molecules. It has also been effectively utilized as a biomaterial. Alginate hydrogels have been applied to make biomaterials compatible with biological systems owing to their water-binding capability [77].

### 5. Alginate Modification Methods

Alginate stands out as one of the most versatile biopolymers in drug delivery [51] owing to its favorable characteristics, such as thickening capacity, gel formation, soothing application, and biocompatibility. However, alginate has some intrinsic disadvantages, such as low mechanical behavior, limited stability in aqueous environments, difficulty in controlling the degradation rate, and low solubility in some solvents, which restrict its biomedical applications [78]. However, to improve its performance in specific applications, its properties can be modified through physical, chemical, or enzymatic methods.

### 5.1. Physical Modification

The physical modification of alginate involves changes in its structure using physical methods. For example, nanoparticles can be added. In this process, nanoparticles are added to improve the mechanical and barrier properties of alginate. For example, Nyoo Putro et al. [79] achieved physical modification of alginate through an ionotropic gelation process with cellulose nanocrystals (CNC) using calcium ions ( $\text{Ca}^{2+}$ ) to form a hydrogel that allowed the delivery of doripenem. This hydrogel exhibited a higher swelling capacity than sodium alginate alone. The higher swelling capacity of the composite hydrogel was attributed to the  $-\text{OH}$  functional group of CNC, which has a high water-binding capacity. Furthermore, the CNC alginate hydrogel exhibited a different XRD diffractogram compared to sodium alginate, indicating changes in the crystal structure after modification. The resulting hydrogel was then used in doripenem delivery experiments.

### 5.2. Chemical Modification

In chemical modification, various functional groups are added to alginate to improve its solubility, biodegradability, and biocompatibility. This includes the synthesis of sodium alginate grafted with polyacrylamide using microwave irradiation, which resulted in a higher degree of substitution and reproducibility. Generally, the two secondary hydroxyl groups (at C-2 and C-3) or the carboxyl group (at C-6) of the alginate structure can be chemically modified. Hydroxyl group modification is mainly carried out through oxidation, reductive amination, and copolymerization reactions (Figure 2). Chemical modification of the carboxyl group comprises esterification, Ugi, and amide reactions [80].

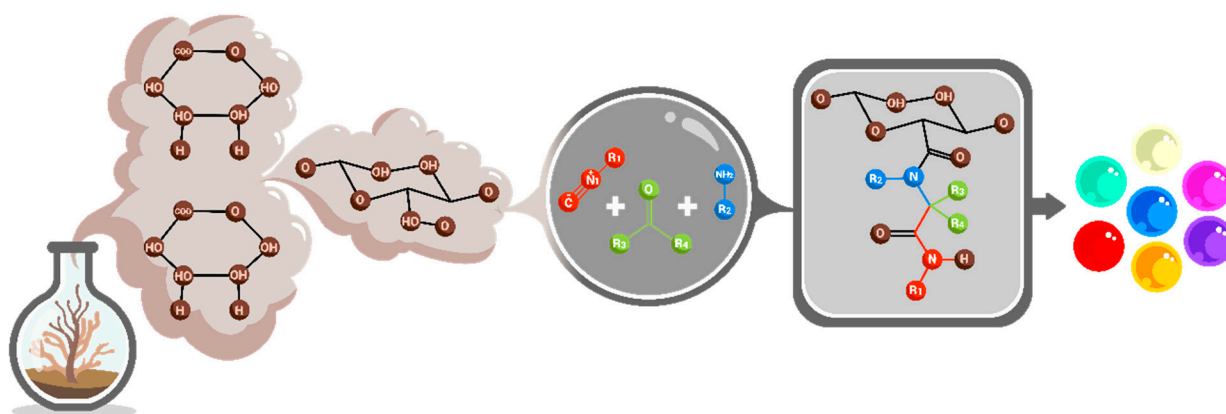


**Figure 2.** Schematic illustration of the chemical modification of alginate.

Regardless of the modification process used, the aim is for said modification to improve the functional properties of alginate, thereby increasing its applications in different industries, mainly as a drug release material. In esterification reactions, an ester group is introduced into the alginate structure to improve its water resistance and biodegradability. In acylation reactions, an acyl group is introduced to improve the hydrophobicity of alginate, and in graft copolymers, other polymers are grafted onto the alginate structure to improve its mechanical and barrier properties. Modification using organic compounds, where polymers such as chitosan or polyethylene glycol are added, helps improve their bioadhesive properties [81].

Many examples of chemical modifications can be listed, such as the case of Matsuura et al. [82], who synthesized hydrogels based on grafted alginate with grafted sodium alginate-poly(N-isopropylacrylamide) due to its characteristics: unique rapid hydration and dehydration at a low critical solution temperature of 32 °C. The sodium alginate (N-isopropylacrylamide)-grafted polymer-based synthetic comb-shaped hydrogels were

shown to compress quickly. A small-angle X-ray scattering analysis technique was used to examine the hydrogel contraction mechanism during the phase separation phase.

In another case, alginate-based derivatives with polymer grafts developed rapid gelation between the active aldehyde groups of oxidized sodium alginate and the amino groups present in carboxymethylated chitosan molecules. The swelling properties and rapid gelation of this type of cross-linked hydrogel make it useful in the biomedical industry. Nanosilver was added to carboxymethylated chitosan hydrogels grafted with oxidized sodium alginate as an antibacterial agent [83].

It is worth mentioning the amazing results of Goh et al. [84] who manufactured alginate ferrogels with iron oxide nanoparticles for the controlled administration of transforming growth factor beta 1 (TGF- $\beta$ 1) in response to magnetic stimulation. These ferrogels were fabricated by ionic cross-linking of an alginate solution and iron oxide nanoparticles using calcium sulfate. It was discovered that the content of polymers, calcium, iron oxide nanoparticles, and the intensity of the applied magnetic field all affected the deformation of the ferrogels. This strategy for controlling the distribution behavior of bioactive molecules, including growth factors, from hydrogels under external stimulation may benefit drug delivery and tissue regeneration.

Finally, Sarker et al. [85] modified alginate by functionalizing it with gelatin using two different methods: mixing and covalent cross-linking. The mixing method involved combining an aqueous solution of gelatin with alginate at a specific volume ratio. In contrast, the covalent cross-linking method involved the synthesis of di-aldehyde alginate (ADA) by controlling the oxidation of sodium alginate in a mixture of ethanol and water, followed by covalent cross-linking of ADA and gelatin to create the ADA-GEL hydrogel. -x, resulting in final concentrations of 2.5% (*w/v*) ADA and gelatin. These modifications aimed to confer cellular adhesive functionality to alginate hydrogels, thereby improving cell adhesion, spreading, and proliferation within the hydrogel matrix. The three distinct alginate-based hydrogels initially exhibited comparable mechanical qualities; however, their rates of breakdown and biological responses varied. After prolonged incubation periods, both pure alginate and alginate combined with gelatin demonstrated reduced metabolic activity and failed to promote cell adhesion and migration. Alginate hydrogel functionalized with gelatin via covalent cross-linking (ADA-GEL-x) showed better cell adhesion, expansion, and migration, as well as greater mitochondrial activity after longer incubation times. Additionally, this study demonstrated that the gelatin cross-linking strategy is a viable method to maximize the stiffness and degradation behavior of alginate-based materials for cell encapsulation in tissue engineering applications.

### 5.3. Enzymatic Modification

The modification of alginate can also be carried out through enzymatic reactions, which is a form of chemical modification where the enzymes chitinase and chitosanase are mainly used. These enzymes play crucial roles in the degradation of chitin and chitosan. Chitinase catalyzes the hydrolysis of glycosidic bonds in chitin, while chitosanase catalyzes the hydrolysis of glycosidic bonds in chitosan. The two enzymes differ in their substrate specificity, with chitinase acting on chitin and chitosanase acting on chitosan.

Enzymatic epimerization is typically used to improve the structure of the polymer into M, G, or MG blocks and to change the ratio of mannuronate (M) to guluronate (G) units or vice versa. Mannuronan C5-epimerases, which are identified from soil bacteria like *Escherichia coli* and *Azotobacter vinelandii*, catalyze the kind of reactions [86]. These enzymes disrupt the glycosidic link of the primary alginate structure but leave mannuronic acid residues in the guluronic acid residues. Furthermore, it is possible to separate

oligosaccharides—polymeric fragments made up of three to ten simple monosaccharides—from the alginate structure.

Kaczmarek et al. [87] analyzed the enzymatic modifications of chitin, chitosan, and chito-oligosaccharides. The properties of the modified polymers include their solubility, degree of acetylation, molecular weight, degree of polymerization, acetylation fraction, and acetylation pattern. These modifications are important for tailoring the properties of chitin and chitosan for various industrial and medical applications. Chitosan possesses several properties that make it suitable for the development of drug delivery systems. These properties include its polycationic nature, which allows it to interact with mucous membranes, increasing adhesion to the mucosa and improving the contact time for the penetration of drug molecules. In addition, chitosan acts as a permeation enhancer for hydrophilic drugs with low oral bioavailability, as it can open the tight junctions in the cell membrane. It is also metabolically degraded in the body, which facilitates its elimination after drug administration [88].

Alginates and their synthetically modified derivatives are of great importance in drug delivery due to their unique properties. These materials can regulate and control the delivery of encapsulated drugs, allowing for an increased drug concentration at the site of infection while reducing unwanted side effects. In addition, modified alginates can encapsulate both hydrophilic and hydrophobic drugs, making them versatile for use with different types of drugs. Their ability to form gels allows them to be used in a wide variety of drug delivery systems, including gels, microspheres, membranes, and other devices [79]. In conclusion, alginate can be modified using different methods, and Table 3 shows some relevant publications where alginate has been modified to improve the release of drugs, nutraceuticals, and other substances in different applications.

**Table 3.** Alginate modification method.

| Method   | Description                                                                                                                        | Results                                                                                                                                                                                                                                        | Reference |
|----------|------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Chemical | Mixture of sodium alginate and chemically modified chitosan for the oral delivery of protein drugs                                 | Development of hydrogel microspheres with protein-trapping capacity, sustained drug delivery profiles, and controlled biodegradation.                                                                                                          | [89]      |
| Chemical | Hyaluronic acid-pNIPAM and alginate-chitosan thermo-sensitive hydrogels as phage delivery systems for the treatment of infections. | Modified alginate showed the most consistent and sustained delivery of bacteriophages over a 21-day period, highlighting the potential of these materials for both rapid, controlled, and extended local delivery of bacteriophages.           | [90]      |
| Chemical | Sodium alginate hydrogel/Cur-PLA microspheres for the encapsulation of curcumin.                                                   | The new material is hemocompatible, cytocompatible, and antimicrobial, with improved swelling capacity and prolonged curcumin delivery time. It proved to be an option for improving curcumin bioavailability and its effective oral delivery. | [91]      |
| Chemical | Alginate modified by a sulfhydryl bond for oral administration in aphthous stomatitis                                              | The formation of the sulfhydryl bond between the carboxylic group of alginates and the cysteine thiol groups of the drug ambroxol allowed improvement of the release profile and its adhesiveness in the mouth.                                | [92]      |
| Chemical | Modified sodium alginate hydrogels with dopamine graft for diabetic wound treatment                                                | Dopamine was grafted onto sodium alginate oxidized by a Schiff base reduction reaction, improving the hydrogel's adhesion and biocompatibility. Its application in wound healing reduced inflammation and promoted collagen deposition.        | [93]      |

Table 3. Cont.

| Method          | Description                                                                                                                                             | Results                                                                                                                                                                                                     | Reference |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Chemical        | Alginate-modified graphene oxide anchored with lactoperoxidase for the treatment of colorectal cancer.                                                  | LPO is a protein that, when coated with alginate-modified graphene oxide (GO-SA), provides stability and anticancer selectivity, enhancing the immune response.                                             | [94]      |
| Physicochemical | PEG-modified calcium alginate microspheres for encapsulation of probiotic bacteria                                                                      | Greater protection of probiotic bacteria under extreme conditions and greater bioavailability that improves their survival, transport, and controlled release.                                              | [95]      |
| Physicochemical | Addition of Aloe vera to a hydrogel composed of sodium alginate/polyvinyl alcohol                                                                       | The composite hydrogel improves the release properties of active substances because it forms a rigid three-dimensional structure, is thermally stable, and can be applied in wound dressings.               | [96]      |
| Physical        | Injectable borax-loaded alginate hydrogels for activation of borate transporter NaBC1 and fibronectin-binding integrins for in vivo muscle regeneration | Increased formation of focal adhesions, increased area of cell expansion, and improved myofiber fusion; enhanced and accelerated muscle regeneration was promoted.                                          | [97]      |
| Physical        | Sodium alginate/gelatin/poly(vinyl alcohol) blend films added with polyphenols                                                                          | Alginate films with polyphenols added as multifunctional crosslinkers improve the mechanical properties and antioxidant activity of the film, which can be useful in edible packaging.                      | [98]      |
| Enzymatic       | Enzymatic modification of alginate from marine biomass                                                                                                  | <i>Sphingomonas</i> sp. A1 has been genetically modified to convert alginate, derived from algae, into ethanol using enzymes such as lyases, sulfatases, and glycoside hydrolases.                          | [99]      |
| Enzymatic       | Enzymatic modification of alginate for the production of oligosaccharides                                                                               | <i>Serratia marcescens</i> NJ-07 was used to isolate polyM-specific alginate lyase, AlgNJ-07, with high degradation efficiency to produce mannuronic acid oligosaccharides used as humectants in cosmetics. | [100]     |

## 6. Application of Chemically Modified Alginate in Drug Release

The chemical modification of alginate allows its physicochemical and mechanical properties to be varied, which is of great importance in medical and pharmaceutical applications, as it tends to improve the affinity characteristics with the drug and allows a controlled release of these. In addition, alginate has applications as a support and adhesion in tissue engineering. Chemically modified alginate is used in drug delivery through various systems, such as nanoparticles, microspheres, hydrogels, and alginate complexes. These systems have demonstrated significant efficacy in drug encapsulation, improved bioavailability, decreased drug degradation, and prolonged amplification of therapeutic effects [81]. Below is a review of some chemically modified alginates used for drug release and biomedical applications.

Alginate forms an ester in acid with methanol, which reacts with hydrazide to form alginic acid hydrazide. This compound then reacts with furoyl chloride or maleimidopropionic acid to obtain alginate-functionalized furan or alginate-functionalized maleimide, respectively, with varying degrees of furan functionalization. These derivatives were mixed stoichiometrically at 5% *w/v* and gelled after 5 h at 60 °C via the Diels-Alder (DA) reaction. As a result, the crystalline structure of alginate was disrupted, and the hydrogel matrices displayed an uneven microstructure with well-mixed porous and compact zones. The hydrogel exhibited pronounced elastic behavior at low frequencies during dynamic rheological experiments. Gliclazide did not affect the formation of alginate hydrogels for encapsulation, and its release was correlated with furan functionalization. These hydrogels

are biocompatible, pH-sensitive, and candidates for controlled release of gliclazide for insulin-independent diabetic patients [101].

Polyelectrolyte complexes were formed using a mixture of chitosan, sodium alginate, and polyethylene glycol (PEG) with 1,4-diaminobutane as a cross-linking agent to release ceftriaxone sodium. These gels swell more in acidic media, have bacteriostatic effects, are chemically stable, and are cytocompatible with fibroblasts. These gels allowed a linear release of ceftriaxone in different media that simulate the digestive system; however, in acidic medium, the release was faster (more than 10% in 30 min) [102]. Another example of cross-linking is a hybrid hydrogel of chitosan with hydroxyapatite and sodium tripolyphosphate as ionic crosslinkers. The formed hydrogels are spherical beads of about 2 mm in diameter that release dexamethasone. The pH for the formation of the hydrogel slowed the dexamethasone rate at pH 9 compared with pH 6, extended the *in vivo* retention of the hydrogel injected subcutaneously, and improved the bioavailability of the steroid drug [103].

The chemical modification of alginate by graft copolymerization has recently been proposed and has interesting applications as a drug carrier. It modifies drug release, promotes drug targeting, avoids unwanted side effects, and improves the binding, solubilization, stabilization, and transport of drugs. Examples of grafting copolymerization of alginate have been carried out with raw materials such as lectin, poly(acrylamide), and cholesterol, which have managed to release the drug at a specific target, improve its sensitivity to pH, and self-assemble [78]. The reactivity of alginate esters depends on the type of ester. Hydroxyalkyl alginate esters readily react with human serum albumin (HSA) to form microparticles via transacylation. In contrast, alkyl alginate esters do not react with proteins to form microparticles because they lack hydrophobic domains. The increase in the degree of esterification ( $DE > 50$ ) and chain length is an important factor in the formation of hydrophobic microdomains that promote interaction with HSA [104].

Oxidation is a common reaction in the chemical modification of alginate. In this sense, sodium alginate was oxidized to obtain different molecular weights, which varied from 275,057 to 24,614  $\text{g}\cdot\text{mol}^{-1}$ , and aldehyde group contents (3.15–8.37  $\text{mmol}\cdot\text{g}^{-1}$ ) using different dosages of sodium periodate and fractional precipitation to form reticules with collagen fiber. The thermal stability and dispersion degree of the cross-linked fiber were significantly improved with decreasing molecular weight of oxidized sodium alginate. In this case, the final molecular weight is very important for the properties of the material and, therefore, for its biomedical applications [105].

In another study, alginate was oxidized with sodium periodate in its main chain, so that the aldehyde groups combined with other aldehydes of the same chain or adjacent chains to form diacetals, and cross-linked gelatin hydrogels were formed. To form the hydrogel, it is necessary to have an oxidized alginate with a molecular weight  $<40,000 \text{ g}\cdot\text{mol}^{-1}$ . By increasing the alginate concentration (1–5%) and the ratio of sodium periodate (40, 60, and 80 %mol) to the number of alginate repeating units, more aldehyde groups were generated, and the chain scission rate was improved. Control of alginate oxidation and degree of oxidation produces chains with different molecular weights and variations in the number of terminal aldehyde groups that interact with other gels, producing a wide variation in the way drugs are delivered [106]. Another example of alginate oxidation is that of dialdehyde alginate (ADA), which was used as a naturally derived crosslinker with collagen and chitosan (COL-CS) to obtain reticulated films with better mechanical properties and thermal stability. COL-CS-ADA films with different degrees of oxidation modification (10, 17.5, 25, and 50%) have medical applications, such as wound healing. COL-CS-25% yielded better results owing to the formation of wound granulation tissue, good cellular biocompatibility, and absence of cytotoxicity [107]. The partial oxidation of

alginate leads to its biodegradation; therefore, it can be safely used for drug administration because it degrades upon contact with an aqueous medium [62].

On the other hand, alginate has been sulfated through a reaction with sulfuric acid in formamide, given its functionality as an anticoagulant and its biocompatibility with blood, and it has immune-modulatory, antioxidant, and anti-inflammatory properties. This chemical modification has enabled its application in drug delivery and tissue engineering [103]. An example is the sulfated alginate synthesized using the sulfuric acid/DCC method to form ionic complexes enriched with mannuronate, which is used as a vehicle for the cationic drug tetracycline hydrochloride (TCH). Chemical modification of alginate with sulfate groups resulted in drug-polymer complexes with remarkable TCH entrapment efficiency (%EE). The highest %EE of 35.5 was achieved in the TCH-AlgS complex using a drug concentration of 0.90% *w/v*. Therefore, sulfated alginate can be used for the release of small cationic drugs [108,109]. Laffleur and Kuppessa [87] modified the main chain of alginate through an anchor with a sulfhydryl bond between the carboxylic group of the alginate and the thiol group of the cysteine, resulting in greater stability (3.5 times more than control), an increase in buccal adhesion time (11.6 times more), a more controlled release of ambroxol (1.4 times more), and an increase in the permeation profile of sulfhydryl-anchored alginate (1.9 times more) compared to conventional alginate, which is favorable for application in the treatment of oral apthae.

The Ugi reaction with alginate involves the simultaneous addition of functional groups, such as aldehydes, ketones, carboxylic acids, amines, or cyanides, to functionalize alginate. This process produces “peptidomimetic” compounds that are amphiphilic, self-assemble, and tend to form gels, making them suitable for targeted drug delivery applications. Using the Ugi reaction, a pH-sensitive amphiphilic alginate was obtained to encapsulate acetamiprid. The results show an increase in the drug encapsulation efficiency from 55% to 96% by increasing the sodium ion concentration from 0.01 M to 0.3 M and from 55% to 80% by decreasing the pH from 5.3 to 2.0; thus, both variables have an important effect on drug release [110]. The chemical modification of alginates that participate in tissue engineering has improved their mechanical properties, adherence to cells, and drug release. For example, alginate has been adhered to a peptide (Arg-Gly-Asp, RGD) of a cell, which allows ligation of integrins and has been useful in the development of neural retina from human induced pluripotent stem cells (hESC/hiPSC) by three-dimensional (3D) culture in hydrogels. The most relevant results showed that the 0.5% alginate-RGD hydrogel improved the derivation, transport, and transplantation of the neural retina and its epithelial tissue [111].

In reductive amination, a long chain of alkyl molecules is added to the alginate backbone to promote the immediate release of the drug. It also allows the incorporation of small molecules, generates flexibility in the alginate chain, and changes its properties, increasing its solubility and decreasing its surface tension. One of the main applications of reductive amination of alginate is the incorporation of bioactive peptic molecules for cellular interactions [62]. In addition, reductive amination has been used for the synthesis of hybrid alginate hydrogels attached to peptides to mimic neural tissue, allowing the adjustment of gelation parameters such as gel stiffness and degradation. In this case, reductive amination generated softer hydrogels (50–210 Pa) with good degradation, depending on the amount of peptide in the formulation. The biofunctionalization of alginate by adhering it to a peptide has advantages, such as better adaptation of certain materials in a matrix, which favors a biological response [112].

Chemically modified alginates have also served as supports or scaffolds, and these biomaterials allow the controlled release of drugs. For example, alginate was reacted with  $\alpha$ -tricalcium phosphate  $\alpha$ -TCP to form fibrous scaffolds loaded with cytochrome C protein

for controlled release. The direct deposition of the Alg/ $\alpha$ -TCP solution using a designed concentric nozzle in a  $\text{CaCl}_2$  bath allowed the generation of fibrous scaffolds for loading cyt C protein in situ. Cyt C release is dependent on conditions such as crosslinking time and  $\text{CaCl}_2$  concentration, as well as on the change in  $\alpha$ -TCP composition within the scaffold core-shell. The addition of  $\alpha$ -TCP (up to 75%) resulted in more continuous and sustainable release patterns. The scaffolds with the best mechanical properties were those with the highest concentration of  $\alpha$ -TCP, achieving hardening of the alginate and modifying its release rate [113].

3D bioprinting is a novel technique used in tissue engineering and regenerative medicine. Alginate is a material with appropriate characteristics for this purpose, and has been combined with various materials to produce bioinks and bioprint soft living tissues. Alginate has been combined with cellulose nanofibers (CNF) to formulate bioinks, where it is very important to evaluate the viscosity and line width in the print. Alginates show low zero-shear viscosity behavior in flow curves; for example, using 2% alginate, a maximum viscosity value of 1 Pa·s and the highest line width (1.07 mm) were obtained. On the other hand, 2.5% CNF has pseudoplastic behavior and high viscosity (maximum viscosity value: 10,000 Pa·s), which provides fidelity in the print but does not gel and is fragile when mechanical force is applied. The combination of alginate and CNF improved the rheological properties of alginate and achieved high resolution in printing. Human chondrocytes bioprinted with alginate-CNF bioink showed cell viability of  $73 \pm 6\%$  and  $86 \pm 1.9\%$  after 1 and 7 days, respectively, which could have biomedical applications as a wound dressing [114].

Recently, hydrogels composed of cellulose nanofibrillated (CNF) with C8 alkyl-modified alginate (degree of substitution  $\sim 27\%$ ) have been proposed for hydrophobic drug delivery. In this work, bovine serum albumin (BSA) was tested for drug delivery using 3D printing. Hydrophobic modification of alginate (HMAAlg) did not affect the viscosity ( $\sim 20,000$  Pa·s) or mechanical properties of the CNF-alginate composite gels; however, the addition of alginate and modified alginate to the CNF gels produced thinner gels. The addition of the protein BSA to the gel hindered the production of defined filaments and scaffolds. Regarding the release tests, the CNF1.8-Alg1 scaffold with BSA added released 90% of the substance in 6 min, while the CNF1.8 scaffold without alginate took 240 min to release. These tests demonstrate that material combinations can alter the mechanical properties and release rates of drugs used in wound dressings [115].

In cancer treatment, chemically modified alginate has been used as a vehicle to enhance the effectiveness of chemotherapy. An example is the alginate—PAMAM dendrimer hybrid nanogel (AG-G5), which was obtained by adding the PAMAM dendrimer to the alginate main chain so that the carboxylate groups of alginates formed an amide bond with the amine groups of PAMAM, which reduced the nanogel size and provided the nanocarrier with greater responsiveness. The formation of ionic and covalent bonds from this chemical modification of alginate increased the stability of the structure and improved the encapsulation efficiency of Epirubicin (EPI) drug. In addition, these EPI-AG-G5 nanogels induced cell death, which is useful for treating breast cancer. The results demonstrated that the AG-G5 nanogel could release the drug in a controlled manner, and in vitro cytotoxicity studies showed cell death by apoptosis [116].

Tables 4 and 5 summarize the current applications regarding the use of chemically modified alginate using different methodologies for tissue engineering (in scaffolds, bioinks, etc.) and drug administration (anti-cancer, diabetes treatments), respectively.

**Table 4.** Application of chemically modified alginate in tissue engineering.

| Coupled Substance          | Alginate (ALG) Modified Matrix                                                                                            | Main Results                                                                                                                                                           | Application                                                                         | Reference |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------|
| RGD-peptides               | Carboxy coupling of carbodiimide and ALG to introduce peptides as alginate side chains.                                   | Improve cell attachment, survival, and proliferation of fibroblasts, and facilitate the expression of vascular growth factors.                                         | Scaffolds for prosthesis                                                            | [117]     |
| Hyaluronic acid (HA)       | Hyaluronic acid-ALG crosslinked with the aldehyde through a covalent bond.                                                | The HA-ALG hydrogel 5:5 exhibited a more rigid matrix, shear-thinning behavior, constant degradation profile for 35 d, and biological properties.                      | Bioink in a 3D-bioprinter for tissue engineering in cartilage tissue.               | [118]     |
| Gelatine (GEL)             | ALG-dialdehyde was oxidized using (meta)periodate, then was added to a GEL solution for hydrogel formation (ADA-GEL).     | ADA-GEL (3.75%:7.5%) at 80 °C for 3 h reached scaffold heights of over 1 cm.                                                                                           | Bioink in a 3D-bioprinter for tissue engineering in cartilage tissue for scaffolds. | [119]     |
| Tetrabicyclo-nonyne (tBCN) | Azide-ALG crosslinked with tBCN depots using multi-arm cyclooctyne cross-linkers and tBCN by “click” reaction.            | Improvement in mechanical resistance and refillable depot stability (4–10% of doses) of hydrogel for applications at intramuscular sites.                              | Tissue engineering and drug administration through refillable depots.               | [120]     |
| Honey                      | Double cross-linking (ionic and covalent) with CaCl <sub>2</sub> and maleic anhydride and was embedded with honey (HSAG). | In vivo wound contraction in murine models with HSAG-4% was: 94.5% with good re-epithelialization and antimicrobial potential to <i>S. aureus</i> and <i>E. coli</i> . | Cutaneous wound healing (dermal reconstruction) with antimicrobial property.        | [121]     |
| Peptides RGD and YIGSR     | With peptides such as: arginine-glycine-aspartate (RGD) or tyrosine-isoleucine-glycine-serine-arginine (YIGSR).           | Peptides-ALG scaffolds have an initial biofabricated porous structure for 3 weeks and promote superior directional neurite outgrowth.                                  | Scaffolds for support and regeneration of neuronal cells.                           | [122]     |

**Table 5.** Drug release profiles and application of chemically modified alginates.

| Drug                 | Alginate (ALG) Modified Matrix                                                                                                                       | Release Profile                                                                                                       | Application                                                                                    | Reference |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-----------|
| Doxorubicin (DOX)    | By adding glycyrrhethinic acid, a metabolite of glycyrrhic, to obtain nanoparticles (GA-ALG NPs).                                                    | Approximately 35% of DOX was released in 96 h (pH = 7.4).                                                             | Controlled release of the anticancer agent (DOX) in liver tumor using NPs.                     | [123]     |
| Coumarin fluorophore | Coumarin grafted blue-emitting fluorescent ALG by aqueous conjugation through a coupling with carbodiimide and then, an alkyne–azide click reaction. | Hydrogels maintained ~80% of their initial fluorescence upon long periods of incubation under physiologic conditions. | Allows in vitro and in vivo screening since the hydrogel is biocompatible in 3D cell cultures. | [124]     |

Table 5. Cont.

| Drug                       | Alginate (ALG) Modified Matrix                                                                                                              | Release Profile                                                                                                                              | Application                                                                 | Reference |
|----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------|
| Paclitaxel                 | Hydrofobically modified ALG using thiol and grafted with amine-terminated poly butyl methacrylate (PBMA-NH <sub>2</sub> ).                  | Nanocomposites coated with modified ALG increased 9% the encapsulation efficiency and ~10% the efficacy against carcinoma cells.             | In photothermal cancer treatments, hyperthermia and in computed tomography. | [125]     |
| Islets of Langerhans cells | Crosslinked ALG microbeads using 2-aminoethyl methacrylate hydrochloride (AEMA) to add groups, when photoactivated, produce covalent bonds. | Alginate methacrylate produced stable microbeads in vivo for 3 weeks (without inflammation) and maintained viable cells after encapsulation. | Treatment of type 1 diabetes.                                               | [126]     |

## 7. Critical Perspectives and Future Directions

In the case of the chemical modification of alginate, a large number of studies have shown that the molecular modification of alginate introduces various new functional groups in its backbone structure, changes its physicochemical properties, improves its biological activity, and endows the polysaccharide with new techno-functional characteristics. Unfortunately, chemical modification methods have some disadvantages to consider, such as the difficulty in controlling the reaction, by-product generation, and large and expensive reagent consumption. To overcome these disadvantages and improve chemical modification methods for industrial applications in the context of a circular economy, it is necessary to conduct studies with a deeper understanding of each existing method and perform a critical analysis of them.

Among the chemical modification methods, acylation stands out. O-acylation modification refers to the process in which the hydroxyl hydrogen in alginate is replaced by an acyl group to form esters. Because the substitution rate and capacity of acylation reactions are also affected by molecular steric hindrance and electronic effects, acylation reactions can be carried out in the presence of suitable bases (such as sodium hydroxide) or catalysts containing heavy metals in order to increase the reaction rate. However, the use of solvents or toxic heavy metal catalysts has long limited their application. In this regard, it has been proposed that this chemical acylation method be performed using natural donors and organic catalysts for modification. However, this area of research is still limited and requires further study [127].

Oxidative modification involves randomly oxidizing the alcohol hydroxyl groups of polysaccharide molecules into carbonyl, aldehyde, and carboxyl groups using an oxidizing agent (sodium hypochlorite, chlorine, sodium peroxide) and simultaneously performing depolymerization. The introduction of carboxylic acids can produce electrostatic repulsion and steric hindrance, which hinder gel formation in oxidized polysaccharides, thereby modifying their viscosity. Unfortunately, these chemical reagents pollute the environment and may pose specific potential safety risks. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) is used as the oxidizing agent, the reaction conditions are milder, and the products and processes are more environmentally friendly than those of traditional oxidation modification. Furthermore, the degree of oxidation of TEMPO oxidation products is accurate and controllable, and the hydrophilicity of polysaccharides is significantly improved [128].

Graft copolymerization refers to the use of alginate as the main chain, and the polymer of another component as a branch chain connected to the main chain. Although graft modification is considered a simple and effective method, it has some limitations. The

grafted molecules may affect steric hindrance and electron density, thus affecting the degree of grafting. Therefore, in the grafting process, active sites for grafting are often formed on the polysaccharide surface using initiators to reduce the influence of steric hindrance [128].

Conversely, chemically modified alginate-based hydrogel matrices are an important innovation in drug delivery systems, considering the multipurpose gel-forming capabilities of alginate, and future directions in the development of these matrices are focused on innovative material design that improves their functionality. However, it is important to consider the key limitations and critical perspectives related to some topics of these matrices that can make their functionality and application difficult.

In the case of calcium alginate hydrogels, complications arise in solutions with a pH higher than the pKa of their substituent groups, constraining their applicability under specific reactions and environmental conditions. During digestion, the system has a basic pH value that preserves the gel structure. This behavior suggests that the formation of this material comes with intrinsic chemical stability weaknesses, which require specific chemical modifications and approaches to achieve wider and more unfailing physiological applicability [129,130].

The mechanical stability for controlled drug release, molecular weight of alginate, and density of crosslinking within the matrix structure are critical factors that influence the mechanical behavior. Higher molecular weight monomers enhance the formation of extended polymer chains and stronger systems, while a higher crosslinking density produces firmness in the structure [130,131].

The influence of crosslinkers on the delivery behavior is another critical feature. The type, concentration, and affinity of crosslinking ions affect the morphology, drug entrapment efficiency, and drug release kinetics. Divalent cations like  $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Sr^{2+}$ , and  $Ba^{2+}$ , can promote differences in particle size and entrapment efficiency, affecting drug release. When particle size growth and entrapment efficiency decline with the increasing size of the divalent ions, a critical relationship is established related to the importance of the selection of the crosslinker, which commands the final physical features of the hydrogel [132].

Despite substantial developments in polymer technology and production procedures using 3D, 4D printing, and microfluidics processes, the transformation of hydrogel-based crops from research laboratories to clinical backgrounds has been particularly slow for their practical application, which requires regulatory compliance, manufacturing approval procedures, and establishing scalable manufacturing protocols in the future design of hydrogel systems, connecting academia, industry, and regulatory agencies [133–136].

Additionally, future directions in the design of alginate matrices require exploring innovative approaches to reduce production costs and facilitate their validation and commercialization. This involves adjusting production conditions to decrease energy inputs, performing scalable green chemistry techniques for alginate sources, product formulations using biomaterial combinations and nanoparticles, optimized modification methods, efficient drug delivery systems, and medical and pharmaceutical approved applications that guarantee the quality properties of these types of matrices and their reliability [70,72,134–139].

## 8. Conclusions

This review highlights the relevance of chemically modified alginate-based hydrogel matrices in drug delivery and their potential applications in various medical treatments, including cancer, diabetes, tissue regeneration scaffolds, and wound healing. Special attention is given to the diverse chemical modification methods used to enhance the functionality of alginate and increase its suitability for biomedical applications. Despite their promise, the large-scale deployment of modified hydrogels faces several challenges. Key

issues include environmental impact, cost, and the complexities of regulatory approval and legal frameworks. Regulatory processes, particularly in the United States, can be especially intricate. Agencies such as the FDA frequently categorize these systems as medical “devices”, and when intended for pharmacological or cell-based therapies, they are defined as “combination products”. As a result, these technologies must undergo the Premarket Notification process, which may span up to a decade, significantly delaying their entry into clinical use and hindering commercial viability. Overcoming these regulatory barriers requires advocacy beyond the research community, especially when safety, efficacy, and biocompatibility have already been validated. Additionally, scaling up production demands careful consideration of multiple factors, including the availability and cost of raw materials, environmental sustainability of modification methods, nature of byproducts generated, product shelf life, and usability in clinical settings. Looking forward, personalized medicine offers a promising direction for further development. The ultimate goal is to engineer hydrogel biomaterials tailored to the unique therapeutic requirements of individual patients. The next major breakthrough in biomaterials engineering is anticipated to involve the design of hydrogels capable of delivering precise, patient-specific therapeutic solutions.

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## Abbreviations

The following abbreviations are used in this manuscript:

|                                 |                                                |
|---------------------------------|------------------------------------------------|
| M                               | $\beta$ -D-mannuronic acid                     |
| G                               | $\alpha$ -L-guluronic acid                     |
| HCl                             | hydrochloric acid                              |
| H <sub>2</sub> SO <sub>4</sub>  | sulfuric acid                                  |
| NaOH                            | sodium hydroxide                               |
| Na <sub>2</sub> CO <sub>3</sub> | sodium carbonate                               |
| CaCl <sub>2</sub>               | calcium chloride                               |
| NMR                             | Nuclear Magnetic Resonance                     |
| FTIR                            | Fourier Transform Infrared Spectroscopy        |
| MW                              | molecular weight                               |
| HPSEC                           | High-Performance Size Exclusion Chromatography |
| G'                              | viscous modulus                                |
| G''                             | elastic modulus                                |
| EDTA                            | ethylenediaminetetraacetic acid                |
| CNC                             | cellulose nanocrystal                          |
| XRD                             | X-ray diffraction                              |
| ADA                             | aldehyde alginate                              |
| PEG                             | polyethylene glycol                            |

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