Original Article

Alginate based Nanoparticles and Its Application in Drug Delivery Systems

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Abstract

Nanoparticulate systems made of biopolymers encompass promising properties as carriers and adjuvant for drug delivery. Alginate is one of the most widely investigated biomaterials in the field of nanoparticulate drug delivery due to its biodegradability, biocompatibility, and bioadhesivity. Alginate nanoparticles for drug delivery can be prepared through spray drying, ionic gelation, emulsification, covalent cross-linking, polyelectrolyte complexation, self-assembling, etc. Alginate is an extensively utilized biopolymer in multiple applications due to its gelling property and chemical structure with hydroxyl and carboxylate moieties. The biocompatibility, biodegradability of alginate, and solubility in water have broadened up research perspectives in material, and biomedical sciences. Study of alginate-based nanoparticles, nanoaggregates, and nanofibers initiated recently. In the present review, the physicochemical properties of alginate, which enabled its use as a pharmaceutical excipient and as nanocarriers in drug delivery, have been reviewed. A special insight has been given on the modern advances of alginate nanoparticles in drug delivery and drug targeting applications. Besides this, limitations of alginate as nanocarriers in drug delivery and the future perspectives on how to augment utilization in the pharmaceutical nanotechnology have also been reviewed.

Keywords: Nanotechnology, Alginate, Nanoencapsulation, nanoparticles, drug delivery, Nanoaggregates.

INTRODUCTION

Nanotechnology refers to the research field dedicated to the production and characterization structures and devices at the nanometer size range, namely, nanoparticles. Physicochemical properties of nanoparticles (size, charge, hydrophobicity and targeting molecules) affect the absorption, distribution, metabolism, and excretion (ADME) of nano delivery systems. The fate of the loaded drug depends thus on its physicochemical properties and the location of its release. Therefore, nanoparticles have distinct advantages for the delivery of drugs, ranging from enhancing stability to controlling the release and targeting of the bioactive for improved functionality [1].

Following its first discovery in 1980, alginate-based microencapsulation particles have extensively studied for developing nanomaterials and other functional materials [2]. Hydrogelling ability of alginates has expanded its uses and research perspectives in biomedicine and multiple disciplines, including the food industry, sewage treatment, and as an adsorptive material for heavy metal removal from contaminated water [3]. Biocompatible and biodegradable polymers are extensively explored, targeting their potential biomedical and pharmaceutical applications. Chemical structures of biopolymers closely resemble macromolecules of the native extracellular environment. Hence, the majority of biopolymers are compatible with living systems compared to synthetic polymers [4]. Alginate polymers are biodegradable, biocompatible mucoadhesive, hemocompatible and have not been found to accumulate in biological systems [5].

Thus, alginates could be utilized in multiple applications due to its inert nature. With the rapid advancements in nanotechnology, many inorganic and organic nonmaterial are synthesized through the control of matter and investigated for desirable functional properties [6]. Currently, a vast number of nanomaterials are available with different sizes, shapes, textures, and compositions.

Alginate-based nanomaterials have become one of the major interests in modern-day scientific research. Different types of alginate-based nanomaterials with different sizes, shapes, and compositions have now been synthesized [7].

The desired pharmacological influence is maximized by the nanocarriers that cater the drug directly to the sites. This actually helps to overcome the drawbacks arising from the drugs [8]. The properties of nanocarriers can be modified based on their preparation techniques that enable the maximum entrapment efficiency. Apart from the drugs, nanocarriers can efficiently deliver enzymes by entrapping or dissolving or attaching the moieties to these. Polysaccharides of natural origin such as dextran, chitosan, or alginates have also been extensively investigated for the formulation of nanocarriers [9]. Their uses have comprehensively been evaluated for drug delivery and medical devices areas.

Apart from biodegradability, polysaccharides offer great flexibility in terms of controlling size and surface charge via chemical modifications [10]. Nanoparticles prepared using polysaccharides are proven effective in protecting small as well as large biological macromolecules (e.g., proteins, DNA, vaccines) against the cellular degradation as well as environmental hazards. Their reactive functional groups help to adhere to the cell surfaces enabling better residence time and enhanced drug uptake [11]. Alginate is extracted from algae and commonly used as thickener and additive in foods. Its applications are quite high due to their low price, biocompatibility, and mucoadhesivity. Alginate acts as a promising biopolymeric material in designing controlled release devices, immobilizations of cells, and tissue engineering. Alginate has several reactive groups within its structure making it flexible and easy for chemical modifications. The occurrence of both carboxyl and hydroxylic groups in the chemical structure of alginate helps in better bioadhesion to the mucous membrane due to the formation of noncovalent bonds that can aid the better bioavailability for the problematic drugs [12].

Over the past few decades, biodegradable polymers have been studied for the fabrication of drug delivery systems. There was extensive development of biodegradable polymeric nanoparticles for drug delivery and tissue engineering, in view of their applications in controlling the release of drugs, stabilizing labile molecules from degradation and site-specific drug targeting. In the last year, scientific research has witnessed the increased interest in innovative controlled release dosage forms. The primary aim was to reduce the dosing frequency and prolong the therapeutic outcomes. For this purpose, inert excipients should be selected, being biopolymers (e.g. chitosan, sodium alginate and starch) commonly used in controlled drug delivery [13]. Biodegradable polymeric nanoparticles are being used as novel drug delivery systems, due to their versatility and wide range of properties, mainly in the areas of cancer therapy and controlled delivery of vaccines [14]. Polysaccharides are monosaccharides linked together by glycoside bonds and have long straight or branched chains. It is estimated that, in nature, 90 % of all carbohydrate mass is in the form of polysaccharides, exhibiting a complexity of functions. Biopolymers degrade in the body, are of low cost and are considered innocuous i.e. not interfering with the cellular osmotic balance. In general, they have been widely used in several scientific areas, especially in pharmaceutics and cosmetics. Biomaterials have traditionally been designed to be inert and not to interact with biological systems in the host. These materials derived from natural sources have often been used to replace tissues lost to disease or trauma, such as prosthetics. Since the early twentieth century, synthetic polymers, ceramics and metal alloys came to replace these materials, because when compared to naturally derived materials, they have better performance and more reproducible properties. A biomaterial is now defined as a material intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ or function of the body [15]. Boundaries for the use of biomaterials are still expanding, the design of new biomaterials is now focused on mimicking many functions of the extracellular matrices of body tissues, regulating host responses in a well-defined manner. Naturallyderived materials have been regaining much attention owing to their inherent biocompatibility [9]. Polymers obtained from natural sources have been used in pharmaceutical technology. Incorporation of the therapeutic agent into a polymeric matrix or capsule may improve the protection of the biologically active compound from degradation, control the release profile, enhance its absorption, thereby increasing the therapeutic effect and decreasing the dosage frequency. The association of two or more polymeric materials has allowed significant advances in the development of modifiedrelease drug delivery systems. The use of blends is a rational approach to get materials with adequate biopharmaceutical properties to be used for drug delivery and targeting, avoiding the high costs involved in the synthesis and characterization of new materials [16].

In this review, different aspects related to the use of alginate nanoparticles for drug delivery and targeting and how their toxicological profile determines the therapeutic outcome of the drug delivery system will be discussed.

ALGINATE

Commercially available alginate is extracted from the cell wall of brown marine algae (Phaeophyceae) in the form of alginic acid or bacterial source, such as Laminaria hyperborea, Laminaria digitata, Laminaria japonica, Ascophyllum nodosum and also Macrocystis pyrifera through treatment with aqueous alkali solutions (NaOH). The extract is filtered and sodium or calcium chloride is added to the filtrate to precipitate alginate. Through the treatment with dilute HCl, this alginate salt can be

transformed into alginic acid. After purification and conversion, water-soluble sodium alginate powder is produced [17]. On a dry weight basis, the alginate contents are between 22 to 3% for A. nodosum and be- 1314 Current Pharmaceutical Design, 2019, Vol. 25, No. 11 Severino et al. tween 25 to 44 % for L. digitate. Alginic acid is recognized as the most abundant naturally derived biopolymer from the marine source and second most abundantly available biopolymer in the world. Alginate is extracted from the brown seaweeds (including Laminaria hyperborea, Laminaria digitata, Laminaria japonica, Ascophyllum nodosum, and Macrocystis pyrifera). The extracts are further treated with alkali and can be converted into alginic acid by means of mineral acids (dilute). Depending upon the percentage of its monomers, alginate and its salt form are available in 200 different grades. Alginate is available in neutral/charged form and ultrapure form making it compatible with wide range of materials [18].

Structure, extraction and composition of alginate

Alginate is anionic linear polysaccharide (unbranched) containing linear blocks of (1-4)-linked-β-D-mannuronic acid (M) and its C-5 epimer, α-L-guluronic acid (G) monomers. All the linear units are linked by 1,4-glycosidic linkages. The presence of monomer units in alginate greatly affects the drug release properties. High M and G contents contribute for better thickening and gelation properties, respectively. In addition, molecular weight, G-block length, composition (i.e., M/G ratio), and sequences are the critical factors affecting the physical properties of alginate and its resultant hydrogels [19]. Alginate chains are composed of mannuronic and guluronic acid units whose pK values are published as 3.38 and 3.65, respectively. Alginic acid forms a precipitate generally below pH 3.6 at ambient temperature. Hence alginates are purified from the powdered brown algae under alkaline extraction conditions using sodium carbonate, sodium hydroxide, or gelatinous aluminum hydroxide (above pH 6.0). Subsequently, alginates are precipitated out from the filtrate by techniques such as acidification, the addition of Ca2+ ions (forms calcium alginate), or by adding ethanol (lowering dielectric constant) [20]. Depigmentation of algae powder prior extraction is essential to reduce brown discoloration of the final product. Another impurity, which alters the purity and rheological properties of alginate is polyphenols. Phenolic compounds form strong dipolar forces with polysaccharides. Hence, algae powder after depigmentation is soaked in formaldehyde or formaldehyde in ethanol to facilitate formaldehyde crosslinking of phenolic compounds, making them insoluble in the extraction solvent [21]. Fluorescence spectroscopy at an emission wavelength of 450 nm could be generally used to estimate the polyphenolic levels in the final product isolated during the extraction process. Diluted acid pretreatment before the alkaline extraction seems to increase the yield of alginate and reduce phenolic content. Diluted mineral acids could convert calcium alginate into alginic acid which could increase the extraction efficiency with alkali than using the original calcium alginate [22]. Further, it has shown to remove any soluble phenolic compound after the formalin treatment.

Molecular Weight and Solubility Alginate is a hydrophilic and anionic polymer, soluble in water and insoluble in ethanol and organic solvents [9]. Alginic acid is soluble in alkaline solutions, which results in viscous solutions. It is capable of absorbing 200 to 300 times its weight in water and dissolves in solutions of sodium carbonate, sodium hydroxide and also trisodium phosphate. It reacts to give salts (alginates) with compounds incorporating ions of alkali metals, aluminium or magnesium and these salts are water soluble and from various solutions typical of hydrophilic colloids. However, the salts of most other metals are water insoluble. The presence of anionic groups in the polysaccharide makes the solubility sensitive to the presence of ions. Sodium alginate is slowly soluble in cold water, which leads to forming viscous and colloidal solution. However, it is insoluble in alcohol, in hydroalcoholic solutions where the alcohol content is above 30 % by weight and is also insoluble in other organic solvents, such as, chloroform, ether and in acids where the pH of the resulting solution falls below 3.0. While calcium alginate is practically insoluble in water and organic solvents, but it is soluble in sodium citrate. It is known that the solubility of the alginate is influenced by the pH of the medium. The pKa values of the acid mannuronic acid and guluronic acid of the alginate are 3.38 and 3.65, respectively. When the pH is lower than the pKa of the alginate, it undergoes precipitation, leading to the formation of alginic acid, which is insoluble in water. When the pH value is above this value, the alginate becomes negatively charged. It is chemically stable at pH values between 5.0 and 10 causing its decarboxylation. The polymer is chemically versatile, varying its viscosity according to the pH values. The viscosity increases as the pH decreases, i.e., carboxylate groups in the alginate backbone get protonated and form hydrogen bonds, reaching a maximum range of pH 3 – 3.5 [23]. The molar mass of the commercial alginate is around 32, 000 and 400, 000 g/mol. In the Mark–Houwink relationship ([] = KMva) for sodium alginate in 0.1 M NaCl solution at 25◦ C, the parameters are K=2×10−3 and a=0.97, where [] represents intrinsic viscosity (mL/g) and in its turn Mv represents the viscosity-average molecular weight (g/mol). It is known that enhancing the molecular weight of an alginate can increase the physical properties of the resultant gels, but an alginate solution with high molecular weight polymer is extremely viscous, being undesirable for processing. Cells or proteins mixed with an alginate solution of high viscosity can be damaged due to the high shear forces that are generated during mixing and injection into the body. The pregel solution viscosity and post-gelling stiffness be controlled independently by manipulation of the molecular weight and its distribution. Through the use of a combination of high and low molecular weight alginate polymers, the elastic modulus of gels can be enhanced whereas the viscosity of the solution can be minimally increased [24].

Applications of Alginate

Due to its special properties, alginate is one of the most used polymers in microparticle's formation [25]. However, currently, alginate is less commonly used in the formation of alginate nanoparticles. Alginates have some common applications, such as in food and beverage industry, drinks stabilizers, icecream stabilizers, jelly Stabilizers, ethanol production, pharmaceutical industry, cell culture and transplantation, dental impression material, tablets, and in wound dressing and can also be used in other industries, including fabrics, papers, paints as well as toothpastes [26]. Since the first clinical use by Major George Blaine in the 1940s, various useful applications of alginates are included in pharmaceutics. Alginate has been used for encapsulation of islet cells, for cell delivery and transplantation, for oral delivery of peptide or protein drugs, for sustained/controlled drug release and for immobilization of active cells and enzymes. It has the conventional role of a thickening, gel-forming and stabilizing agent. Alginates can play an important role in controlled release drug products. The most frequent use of alginates in pharmaceutical applications is in the oral dosage forms, however, there has been a growing use of alginate hydrogels as depots for tissue localized drug delivery. They can be used to develop a formulation in beads, matrix block, foams, fibers, sponges, microparticles as well as nanoparticles. Among these, nanoparticles have been exploited for drug delivery because they improve bioavailability and reduce the toxicity of drugs [9]. Alginates can be used in dosage forms designed for any type of drug release. Sodium alginate has been used as a tablet binding agent, whereas alginic acid is used as a tablet disintegrating in compressed tablets designed for immediate drug release [4]. Therefore, alginates can be used as ratecontrolling excipients in drug delivery systems, as a matrix for biomolecules and as an excipient in pharmaceutical preparations for local administration. It is known that a new approach in the field is the development of systems that can adjust drug release according to physiological needs, such as pH-responsive systems based on polymer swelling or magnetically triggered delivery systems, and alginates have physicochemical properties that are required to make them a crucial contributor to this area of future research [27].

Drug encapsulation and targeted delivery

Nanoencapsulation is a developing field of research in drug delivery. Nanoencapsulation is proven to increase the bioavailability of drugs and deliver them to the right place, with the right dosage. Studies regarding alginate nanomaterials initiated during the past few years. At present, an increasing demand is placed towards the use of alginate-based nanoencapsulation for controlled delivery of drugs. Compared with other particulate carrier systems such as liposomes, microparticles, and some nanoparticles, which are rapidly taken up and degraded by mononuclear phagocytes such as the Kupffer cells, alginate nanomaterials have shown better ability to withstand. They are desirable for encapsulating proteins, enzymes, and some other drugs while enhancing their stability and oral bioavailability [28]. A matrix with an aqueous environment, a higher gel porosity, and biocompatibility are some of the major properties in the majority of alginate nanoparticles. Oral administration of drugs, such as proteins, remains challenging due to their gastric digestibility. Encapsulation in alginate-based nanoparticles could offer a solution to this problem due to their indigestible nature and sustained drug release rate.

Gene therapy

Gene therapy is seen as a promising approach for the treatment of cancer and genetic disorders. Alginate/CaCO3 hybrid nanoparticles (145.0 ± 7.8 nm) have shown higher encapsulation efficiency and delivery capabilities for tumor suppressor gene (p53) expression plasmid and doxorubicin hydrochloride (an anticancer drug). Apart from effective delivery into targeted cells, they have shown advantages concerning the biocompatibility and cost 23 over the conventional methods of using viral vectors. Surface-modified alginate nanoparticles have been used as a method of gene transfer to targeted macrophages, a potential approach for anti-inflammatory therapy. Tuftsin (a peptide sequence) has been used as targeting ligands that bind with specific receptors on polymorphonuclear leukocytes and macrophages [29].

Alginate nanoparticles have also been tested as potential carriers for chemotherapeutic drugs. Sodium alginate was complexed with doxorubicin and stabilized by the surfactant Aerosol OT to develop polymer-surfactant nanoparticles. Doxorubicin is a water-soluble drug and has high molecular weight. The size, zeta potential, and drug loading of the developed nanoparticles were ~150 nm, ~-16 nm, and ~4 %, respectively. These nanoparticles were shown to improve doxorubicin transport across the cells overexpressing P-gp in Transwell® studies, attributed to the inhibitory effect of the surfactant of P-gp activity. Doxorubicin-loaded in alginate-surfactant nanoparticles had a higher oral bioavailability in mice than free drug formulations. Alginate nanoparticles can also be used to loading biotech molecules, such as DNA, peptides and proteins, antigens, and cells [30]. As alginate is positively charged, it can crosslink with proteins resulting in the reduction of the diffusion rate or protein inactivation. On the other hand, as alginate nanoparticles are mucoadhesive, they may improve the oral, nasal or intranasal bioavailability drugs [4]. Bakhshi et al. studied the encapsulation of IgY in alginate nanoparticles as a vaccine against E. coli O157: H7, for oral administration. The the in vitro release profile was shown to be dependent on the pH of the medium, i.e. 10

% and 99.84 % of IgY released in simulated gastric fluid (pH 1.2) and simulated intestine fluid (pH 6.8), respectively. The released IgY sustained its biological activity while particles did not show cytotoxic effects on tested Vero cells. Alginate nanoparticles have been exploited for several administration routes e.g. pulmonary, oral, nasal, intravenous, vaginal and ocular. These particles have also been exploited for the transport of several drugs, such as metformin, doxorubicin, ethionamide, and several other biotech drugs. The cross-linking of alginate may be achieved by the use of cationic polyelectrolytes during the production of nanoparticles or between alginate with cationic drugs to be loaded. In both cases, the controlled release profile of the loaded drugs can be achieved, with the enhanced long-term stability of nanoparticles. Table 1 gives an overview of different types of alginate nanoparticles applied in drug delivery. Alginate nanoparticles have been widely used to load antibiotics against Staphylococcus aureus and Pseudomonas aeruginosa [31] infections. Polymyxins are polypeptide antibiotics with a potent action on various gram-negative bacteria. Their use was practically abandoned between 1970 and 1980, due to the appearance of drugs with lower toxicity. With the increase of multiresistant gram-negative bacteria, mainly in patients in intensive care units, and the absence of new antimicrobials against these pathogens, interest in polymyxins has been renewed in recent years. Polymyxin B sulfate (PLX) has been firstly formulated in solid lipid nanoparticles, which were then cross-linked with sodium alginate. The challenge of loading the hydrophilic drug in lipid matrices was overcome by combining alginate and PLX in the proportion of 1:1. The formulation exhibiting a gel-like dynamic behavior, was shown to be non-toxic in HaCat and NIH/3T3 cell lines, while the polymer-drug complex enhanced the minimal inhibitory concentrations in Pseudomonas aeruginosa strains.

Limitations for use of alginate in pharmaceutical nanotechnology

Although alginate has been widely investigated as a nanocarrier, its use is limited by its batch-to-batch variability as well as extensive distributions of molecular weight which makes it less striking in comparison to that of synthetic polymers that have superior reproducibility and versatility. In addition, the hydrophilicity of alginate resulted in nanoparticle instability at biological pH and low drug encapsulation due to drug leakage [32]. In numerous cases, the hydrophilicity of alginate directs to swelling and swifter release (burst effect) in comparison to synthetic polymers (predominantly for water-soluble drugs) because of ample leaching of drug from alginate nanoparticles to the surrounding media during preparation. Some alginate nanoparticles fabrication conditions like utilization of organic solvents, high temperature of processing, lengthy fabrication time, reduced yield, as well as complicated purification conditions have also limited the use of alginate nanoparticles as nanocarrier [33]. To overcome these limitations, several approaches have been implemented. The most successful approach used was to enhance the hydrophobic character of alginate through chemical modifications resulting in enhanced encapsulation efficiency of these nanoparticles. The use of chemical cross-linking may augment the mechanical strength of alginate nanoparticles in spite of the safety apprehensions. Approach of covalent cross-linking includes chemical conjugation of alginates (within calcium alginate matrices) with the cross-linking reagents like aldehydes. Actually, this process entails difficult synthetic steps with respect to the ionic cross-linking technique besides the utilization of chemical reagents which are toxic in nature that demands extensive cleaning processes prior to any medical uses. Moreover, the reactions of covalent crosslinking may need anhydrous conditions (organic solvents), which would badly influence labile active drugs like proteins or genes. The use of bridging cross-linking aid agent such as tannic acid enhanced the encapsulation and release of alginate-based nanoparticles. The method is based on strengthening the coordinate bonds in calcium alginate by tannic acid within the nanoparticles leading to more stable particles with higher resistance to attack by adjoining water molecules and reduced burst effect. Consequently, calcium alginate tannic acid nanoparticles showed inferior drug leakage upon formulation leading to superior drug encapsulations. It should be noted that these nanoparticles can congregate within the cells and lead to intracellular alterations, like disruption of organelle integrity or gene modifications, which causes severe toxicity. This factor combined with the unexpected release behavior of alginate (and other natural polymers) and their high fabrication costs contributed to the vague clinical future of alginate nanoparticles vis-a`-vis achieving regulatory approvals [34].

Future perceptive in using alginate particles as nanocarriers

Nanocarriers made of natural polymers will continue to magnetize the investigators researching in the domain of drug delivery. These nanoparticles can be tailored to convene the explicit necessities like diminishing immune system detections. Alginate as natural polymer offers great possibility as nanocarriers owing to its aptitude toward chemical modification, its inherent characteristics of being harmless, biocompatibility, as well as biodegradability. Alginate has been assessed for numerous drugs including antibiotics, anticancers, vaccines, and genes, though none was evaluated in clinical trials. Investigating endeavors should advance in the direction of understanding further regarding cellular uptake mechanisms of alginate nanoparticles. The majority of targeted delivery system mechanisms excel the in vitro studies; however, these fail the in vivo studies. For this reason, more extensive in vivo evaluation is warranted to understand this apparent discrepancy. Targeted delivery has been attained prolifically by means of stimuli-triggered release from alginatecontaining nanoparticles as in the case of cancer. However, more exertion is required on other diseases together with immune and genetic diseases. As per chemical viewpoint, alginate alteration or tailoring will continuously expand the domain of nanoparticles fabrication by producing novel derivatives

with best physicochemical characteristics. Furthermore, domains of stimuli-triggered release from nanoparticles may have brilliant effect on attaining targeted delivery of numerous drugs. This might also augment the localized effect of a number of drugs [35].

Conclusion

Nowadays, alginate is being employed as nanocarriers for drugs and genes. The drug delivery and release efficiency of biologically active molecules from alginate-based nanoparticles are prejudiced by factors like alginate chemical modifications, cross-linking agent, drug loading, particle size, drugpolymer interactions and quite a few other technical and pharmacotechnical factors. The joint use of nanoparticles in drug delivery technologies in a preformulation work accelerates the improvement of new therapeutic moieties, as well as helps in the reduction of attrition of new molecular entities, which is caused by unwanted biopharmaceutical and pharmacokinetic properties. Nanodelivery systems have many physical and chemical advantages in order to enhance bioavailability and stability of bioactives. Each type of nano delivery system contributes to distinct benefits and the properties of the bioactive as well as the purpose of delivery decide which nanoparticle type should be applied. The nano-bio interaction and ADME profile will be determined by the system's chemical, physical and also morphological properties. Size, charge, hydrophobicity and also targeting molecules are the properties important for cellular and immunological interaction. Uptake of the nano delivery system and bioactive absorption are hindered due to the degradation in the stomach, i.e. low pH and presence of enzymes, the presence of the firmly adherent mucosal lining, selectively permeable epithelial and M-cell membranes and also enzymatic degradation in the intestines. The nano delivery system must evade the MPS after the absorption, which will remove nanoparticles from systemic circulation. Once nanoparticles enter the systemic circulation by the lymph or caudal vena cava, the distribution of the nano delivery system begins. Further studies are required for increasing current understanding of how the monomer composition of alginate, monomer attachment sequence and alginate molecular weight would affect the physicochemical properties of nanomaterials and biocompatibility. In this manor studying structural properties of alginate in major seaweeds, which is used for industrial alginate production, is an immense requirement. Further verification of functional properties in proper animal models would endure the future advancements of this research area in clinical trials. The continuing advancements in exploring alginate-based nanomaterials will revolutionize the future progresses in nanotechnology, biotechnology, medicine, and numerous scientific disciplines.

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