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Review Article

Alginate: Current Use and Future Perspectives in Pharmaceutical and Biomedical Applications

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Over the last decades, alginates, natural multifunctional polymers, have increasingly drawn attention as attractive compounds in the biomedical and pharmaceutical fields due to their unique physicochemical properties and versatile biological activities. The focus of the paper is to describe biological and pharmacological activity of alginates and to discuss the present use and future possibilities of alginates as a tool in drug formulation. The recent technological advancements with using alginates, issues related to alginates suitability as matrix for three-dimensional tissue cultures, adjuvants of antibiotics, and antiviral agents in cell transplantation in diabetes or neurodegenerative diseases treatment, and an update on the antimicrobial and antiviral therapy of the alginate based drugs are also highlighted.

1. Introduction

Alginates (ALG) are a group of naturally occurring anionic polysaccharides derived from brown algae cell walls, including *Macrocystis pyrifera*, *Laminaria hyperborea*, *Ascophyllum nodosum* [1, 2], and several bacteria strains (*Azotobacter*, *Pseudomonas*) [3]. This term usually referred to alginic acid and its salts, but it can also be used for all derivatives of alginic acid. ALG are linear biopolymers consisting of 1,4-linked β-D-mannuronic acid (M) and 1,4 α-L-guluronic acid (G) residues (Figure 1) arranged in homogenous (poly-G, poly-M) or heterogenous (MG) block-like patterns [1–4]. With regard to the initial source material, commercial ALG may differ in composition and the sequence of G- and M-blocks.

ALG extraction process from seaweeds is uncomplicated but multistage procedure, which usually starts with treating the dried raw material using diluted mineral acid. After further purification, the obtained alginic acid is converted into water-soluble sodium salt in the presence of calcium carbonate, which is next transformed back into acid or its expected salt (Figure 2) [2, 4].

Commercial ALG are exclusively possessed from algal sources, although alternative production by microbial fermentation has been recently explored in order to provide ALG with more defined physicochemical properties [3].

Among various ALG, sodium alginate is one of the most widely investigated ones in the pharmaceutical and biomedical field and its monograph is included into both the European Pharmacopeia and the United States Pharmacopeia [5, 6]. The current pharmacopoeial requirements regarding sodium alginate are presented in Table 1.

2. General Properties of ALG

Currently used ALG possess a high degree of physicochemical heterogeneity which influences their quality and determines potential applicability. ALG are commercially available in various grades of molecular weight, composition, and distribution pattern of M-block and G-block, the factors responsible for their physicochemical properties such as viscosity, sol/gel transition, and water-uptake ability. The molecular weight, expressed as an average of all the molecules present in the sample, of commercial ALG varies between 33 000 and 400 000 g/mol. ALG extracted from different sources differ in M and G residues as well as the length of

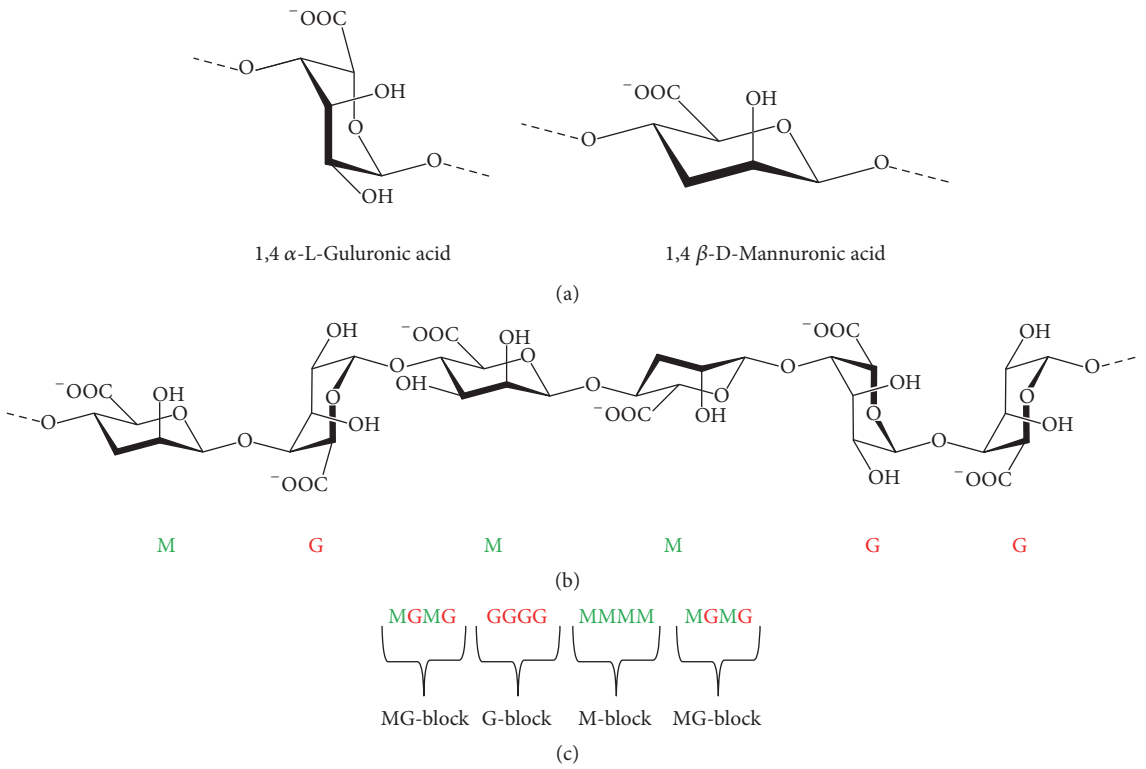


Figure 1: The structure of ALG: monomers (a), chain conformation (b), and blocks distribution (c).

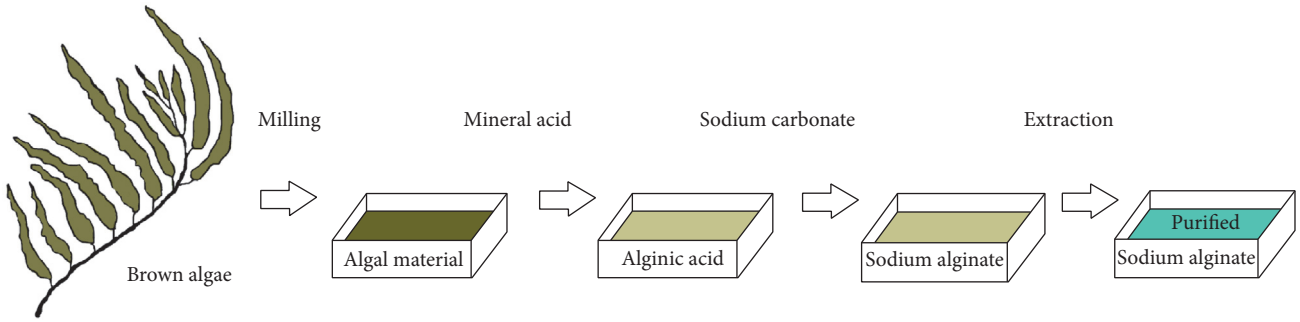


Figure 2: The procedure of sodium alginate extraction from brown algae [2].

each block. Generally, by raising the ALG G-block content or molecular weight, more stronger and brittle ALG gels may be achieved [67]. Alginic acid is insoluble in water and organic solvents, whereas ALG monovalent salts and ALG esters are water-soluble forming stable, viscous solutions [1–4]. The 1% *w/v* aqueous solution of sodium alginate has a dynamic viscosity 20–400 mPa·s at 20°C. ALG solubility is limited by the solvent pH (a decrease in pH below pKa 3.38–3.65 may lead to polymer precipitation), ionic strength, and the content of "gelling ions" [2, 68]. ALG with more heterogeneous structure (MG-blocks) are soluble at low pH compared to poly-M or poly-G ALG molecules, which precipitate under these conditions [69, 70]. Apart from molecular weight, the ALG capability of creating viscous solutions may vary according to their concentration, solvent pH (a maximum pH is reached around 3.0–3.5), temperature, and the presence of divalent ions [1–3, 68].

ALG can be easily formed into diverse semisolid or solid structures under mild conditions because of their unique ability of sol/gel transition. Therefore, ALG are commonly used as viscosity increasing agents, thickeners, and suspension and emulsion stabilizers in food and pharmaceutical industry (Table 2).

ALG gelation can be induced in the presence of divalent ions, which cross-link the polymer chains through the "egg-box" model [68, 71, 72] or by lowering the pH value below the pKa of ALG monomers using lactones like d-glucono-δ-lactone [2, 4]. It should be noted that calcium chloride, most frequently used source of Ca^{2+} ions, is responsible for rapid and uncontrollable ALG gelation. The gelation rate is a critical

Table 1: Sodium alginate characteristic recommended by the European Pharmacopeia (Eur. Ph.) and United States Pharmacopeia (USP) [5, 6].

Parameter	Eur. Ph. 8.0	USP 32-NF 27
Appearance of solid product	White or pale yellowish-brown powder	n.d.
Content	n.d.	90.8%–106.0% of dried basis
Packaging and storage	n.d.	preserved in tight containers
Solubility	Slowly soluble in water, practically insoluble in ethanol 96%	n.d.
Appearance of solution	Not more opalescent than reference formazin suspension in water and not more intensely coloured than intensity 6 of the range of reference solutions of the most appropriate colour	n.d.
Heavy metals	≤20 ppm	≤0.004%
Chlorides	≤1.0%	n.d.
Calcium	≤1.5%	n.d.
Arsenic	n.d.	≤1.5 ppm
Loss on drying	≤15.0%	≤15.0%
Total ash	n.d.	18.0%–27.0%
Sulfated ash	30.0%–36.0%	n.d.
Microbial limits	TAMC: ≤1000 cfu/g TYMC: ≤100 cfu/g	≤200 cfu/g
Absence of specified microorganisms	*Salmonella sp., Escherichia coli*	*Salmonella* sp., *Escherichia coli*

n.d.: not determined, TAMC: total aerobic microbial count, and TYMC: total yeast/moulds count.

Table 2: The use of alginic acid and its salts in food and pharmaceutical industry.

Code	Ingredient	Application in food industry	Application in pharmaceutical industry
E400	Alginic acid [1]	Emulsifier, formulation aid, stabilizer, thickener	Tablet binder and disintegrant, sustained release and release-modifying agent, taste masking agent, thickener, suspending and viscosity increasing agent, stabilizer
E401	Sodium alginate [4]	Texturizer, stabilizer, thickener, formulation aid, firming agent, flavour adjuvant, emulsifier, surface active agent	Suspending and viscosity increasing agent, tablet and capsule disintegrant, tablet binder, stabilizer, sustained release agent, diluent in capsule formulation, thickener
E403	Ammonium alginate [7]	Stabilizer, thickener, humectant	Color diluent, emulsifier, film former, humectant
E404	Calcium alginate [8]	Stabilizer, thickener	Tablet disintegrant
E405	Propylene glycol alginate [9]	Emulsifier, flavoring adjuvant, formulation aid, stabilizer, surfactant, thickener	Stabilizer, emulsifier, suspending and viscosity increasing agent

parameter in controlling gelation process. Slow gelation provides creating uniform gel structures with mechanical integrity [67]. One approach to reducing the rate of gel forming process is to apply to phosphate buffers (e.g., sodium hexametaphosphate). In the reaction with ALG carboxylate groups, phosphate groups present in the buffer compete with calcium ions and as a result ALG gelation process is retarded [73]. Additionally, calcium sulfate and calcium carbonate with lower solubility also prolong the gel formation. The gelation rate is also dependent on temperature; at lower temperatures, the reactivity of Ca^{2+} is reduced [74]. Recently, a freeze-thaw technique has been examined as an advanced controlled method for ALG hydrogels formation [75]. Gelling properties are strongly associated with ALG structure and proportions of M-, G-, and MG-blocks [67, 71, 76]. In addition, ALG gels with an increased amount of repeating G-block units are regarded as stiffer, brittle, and mechanically more stable [71, 72]. In contrast, ALG characterized by high proportion of M-blocks form gradually soft and more elastic gels. However, MG-blocks in ALG gel determine its shrinkage and higher flexibility [77]. Nevertheless, ALG with predominated M-block content, as a result of high water absorption, exchange ions more easily in comparison to ALG with higher amount of G-block residues [68, 71, 72, 78]. It should be noted that a number of studies revealed that ALG solution/gel transition occurred under physiological conditions, for example, in the presence of divalent ions and under acidic environment of body fluids [72]. For instance, nonwoven dressings of calcium alginate capable of exchange ions with the wound fluid have been commonly utilized

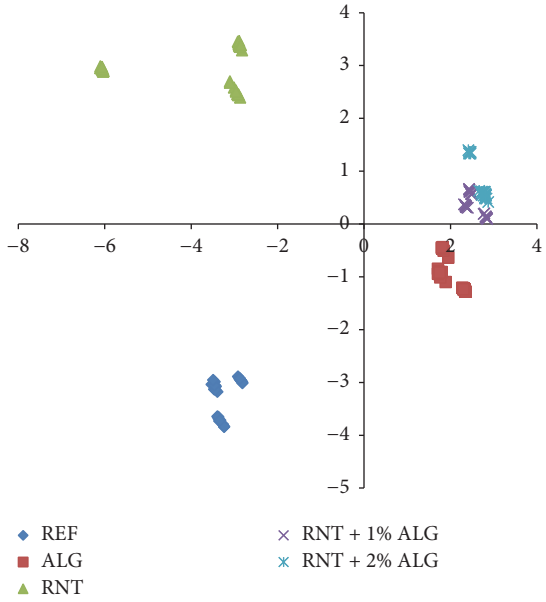


Figure 3: Potentiometric electronic tongue plot showing taste clusters of reference solution (0.0001 M $Ca(NO_3)_2$, 0.0001 M NaCl) (REF), pure ranitidine hydrochloride (RNT), microspheres placebo (ALG), and microspheres prepared with using 1% and 2% ALG solution (RNT + ALG 1% and RNT + ALG 2%, resp.). Samples were placed in 100 mL of deionized water; measurement time was 7 min with signal acquisition every 5 s. The data were processed using Principal Component Analysis (PCA) with autoscaling (author's original unpublished data).

for the treatment of exuding injuries or infected surgical wounds [79–81]. Formation of a highly absorbent soluble gel effectively maintains a physiologically moist environment and aids healing process through facilitating growth of fresh epidermis [75, 79]. Due to mechanical stability and proper viscoelastic behavior, ALG are also applied as structural supporting biomaterials for tissue (teeth, bone, and cartilage) reconstruction [79].

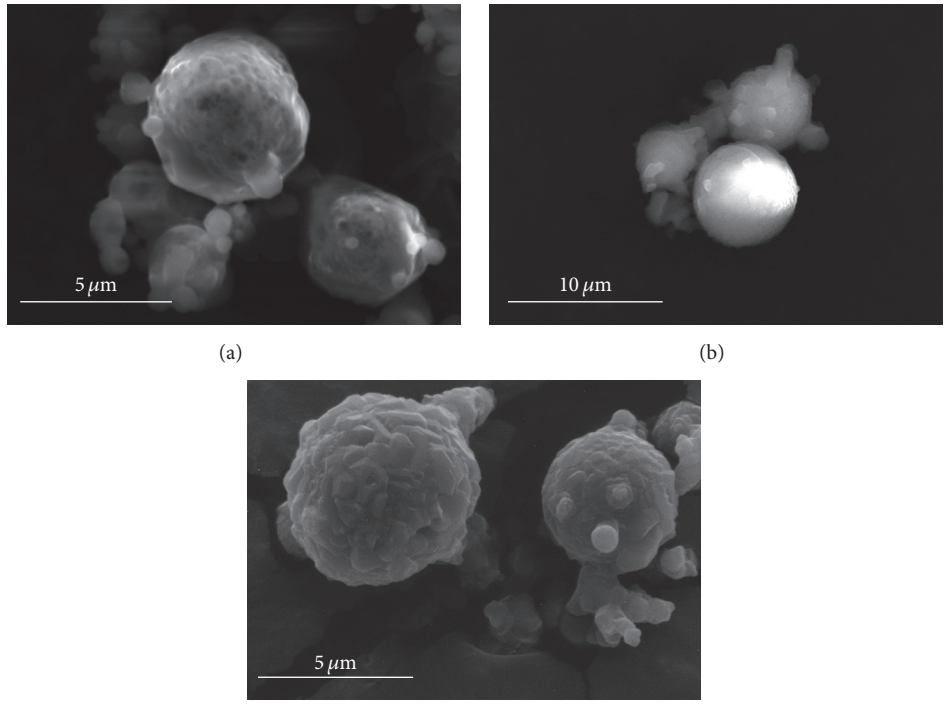
The fact that ALG may undergo in situ gelation makes ALG materials promising tools for a wide range of applications, including injectable vehicles for tissue engineering or topical drug delivery systems [41, 79, 82]. Moreover, due to gelling properties, ALG have been investigated as taste masking agents [83, 84]. Studies performed with using potentiometric electronic tongue [85] have proved that spray-dried microspheres with sodium alginate hid the bitter taste of ranitidine hydrochloride through physical gel-barrier formation (Figure 3). Figure 3 presents final chemical image, which shows that for all samples distinctive clusters are easily observable. They are formed by chemical images of samples of various types, where ALG microspheres with ranitidine hydrochloride are easily discernable from pure drug, which indicates masking effect obtained with the use of sodium alginate.

Greatly porous three-dimensional ALG hydrogel structure displays favorable swelling properties arising from the presence of hydrophilic functional groups [86]. ALG ability of hydration and gel formation gives the opportunity to prolong release of the active substance at the administration site. Hence, these polymers have been extensively studied for prolonged or controlled release drug delivery systems [87, 88].

In addition, owing to the mild conditions during gel formation, ALG (especially calcium alginate) appear to be favorable tools for cell entrapment used in tissue engineering or regeneration [89–91]. ALG barrier protects immobilized material toward physical stress (maintaining its viability during long-term culture) and enables avoiding immunological reactions with the host. Currently, ALG microparticulate systems are also being developed for the treatment of a variety of diseases, including cancer, diabetes, or Parkinson's disease [92, 93].

ALG possess good mucoadhesive properties resulting from the presence of free carboxyl groups allowing the polymer to interact with mucin by hydrogen and electrostatic bonding. Environmental pH has a strong impact on ALG solubility and consequently on their mucoadhesive character as only ionized carboxyl groups are capable of interacting with mucosal tissue. In addition, soluble ALG facilitate solvent penetration through polymer matrix resulting in formation of more viscous and cohesive gel structure responsible for strengthening the mucoadhesive bonds. In contrary, too excessive hydration of ALG matrix in physiological fluids might weaken mucoadhesiveness as a result of attenuation of ALG functional groups available for interactions with mucosal tissue [94–96].

Owing to mucoadhesive properties, ALG are regarded as proper polymer excipients to prepare buccal [97–99], nasal [100, 101], ocular [102, 103], and gastrointestinal dosage forms [104–108]. Recently, several studies have shown favourable mucoadhesiveness of ALG-based applications in contact with vaginal mucosa tissue [108, 109]. Furthermore, an increased drug residence time at the ocular mucosal surface and prolonged release of active agents from microparticulate



(a) (b)

(c)

Figure 4: SEM images of alginate microspheres obtained by the spray drying method with metronidazole under magnification ×20 000 (a), ranitidine hydrochloride under magnification ×10 000 (b), and metformin hydrochloride under magnification ×20 000 (c) (author's unpublished images).

delivery systems with ALG were displayed [110]. Due to large surface area, which may favour an intimate contact between the polymer and mucin, multiunit dosage forms with sodium alginate are also explored as gastroretentive drug carriers (Figure 4), especially for substances, which are unstable or degraded in the alkaline pH [111, 112].

ALG have been extensively evaluated as vaccine adjuvants or coadjuvants as these polymers were displayed to enhance bioavailability and immunogenicity of antigens after nasal and oral administration [101, 113, 114].

3. ALG Modification for Drug Delivery Systems and Biomedical Devices

ALG can be easily modified through chemical or physical cross-linking in order to form ALG hydrogels and improve physicochemical properties and/or biological activity. Many methods have been described for ALG cross-linking, which includes ionic cross-linking, covalent cross-linking, cell cross-linking, phase transition (thermal gelation), "click" reaction, and free radical polymerization [89]. An alteration of the M- to G-block proportion or an enrichment of polymer backbone in M-, G-, or MG-blocks is being practiced by modification through enzymatic epimerisation catalysed by mannuronan C-5 epimerases. This enzyme, isolated from the soil bacterium *Azotobacter vinelandii* and expressed in *Escherichia coli*, converts mannuronic acid residues into guluronic acid residues in the polymer backbone without breaking of the glycosidic bond [87, 115, 116]. Additionally, from ALG backbone, oligosaccharides might be isolated, which are polymer fragments containing three to ten of simple monosaccharides. There are two methods, which might be used to prepare ALG oligosaccharides: enzymatic depolymerization and acid hydrolysis [56]. The common chemical modification of ALG hydroxyl groups includes oxidation, sulfation, graft copolymerization, acetylation, and phosphorylation process [117, 118]. Modification of the carboxyl groups may be achieved by esterification and amidation [89, 117, 118]. A list of the commonly used chemical changes of ALG structure for biomedical and pharmaceutical application is presented in Table 3. ALG solubility might be changed by modification of hydroxyl groups (in positions C2 and C3) or the carboxyl groups (in C6 position) through covalent attachment of long alkyl chains or aromatic groups to the polymer backbone. Increasing ALG hydrophobicity provides decreasing polymer dissolution and erosion. Additionally, there are many studies, which include production of ALG derivatives by grafting with different substances such as polyacrylamide, methacrylate, galactose, lectin, sulfate, cysteine, cyclodextrins, propylene glycol, and dodecylamine [117–119].

4. ALG Biological Activity and Application in Pharmaceutical Products

ALG are regarded as biocompatible, nonimmunogenic, and nontoxic materials [2]. Although ALG gel is not degradable in mammalian digestive tract (alginase/lyase enzyme involved in depolymerization of ALG is present only in prokaryotic

Table 3: Examples of chemically modified-alginate based drug delivery systems and biomedical devices.

Type of modification	Material	Active substance	Biomedical or pharmaceutical application	Dosage form	Reference
Oxidation	Oxidized-NaALG	Limbal epithelial stem cells	Improvement of corneal wound healing therapy	Hydrogel	Wright et al. [10]
		Flurbiprofen	Sustained oral delivery	Beads	Maiti et al. [11]
Reductive-amination of oxidized alginate	ALG-g-poly(ethylene glycol)	Human foreskin fibroblasts	Specific cell microencapsulation	Microspheres	Mahou et al. [12]
Sulfation	Sulfated ALG	—	Reduction of secretion inflammatory cytokines, improvement of the biocompatibility	Microspheres	Arlov et al. [13]
Phosphorylation	Phosphorylated ALG	—	Mineralization of hydroxyapatite and participation in the chelation process for tissue engineering	Gel	Coleman et al. [14]
Graft copolymerization	NaALG-co-polyacrylamide	Famotidine	Sustained release gastroretentive carrier	Hydrogel	Tripathi and Mishra [15]
	Starch-*g*-poly(acrylic acid)-NaALG	Diclofenac sodium	pH-sensitive matrices for the oral drug delivery	Hydrogel beads	Chang [16]
	ALG-glycidyl methacrylate	Human endothelial cell lines HUVEC and L929	Thermal polymerizable injectable hydrogel for tissue engineering, especially for myocardial repair	Hydrogel	Wang et al. [17]
	Galactosylated ALG	Hepatocytes	Cell carrier with mechanical stability and selective permeability	Microcapsules	Tian et al. [18]
	α-Cyclodextrin-ALG conjugate	*Sphingomonas cloacae*	Immobilization of bacteria	Beads	Pluemsab et al. [19]
	β-Cyclodextrin-ALG conjugate	Ondansetron	Controlled drug delivery systems	Gel	Izawa et al. [20]
Esterification	Propylene glycol ALG	Lysozyme	Protein encapsulation with a sustained release	Microparticles	Hurteaux et al. [21]

and eukaryotic microorganisms) [120], it simply dissolves as a result of elution of cross-linking calcium ions. It should be noted that only small ALG molecules are excreted by renal clearance threshold. To enable complete elimination of ALG from the body, partial oxidation of polymer backbone is necessary [121]. ALG biocompatibility was confirmed in vivo after ocular [122], nasal [114], topical [123], local [124, 125], and oral administration [126]. Food and Drug Administration has recently affirmed several ALG salts (calcium, sodium, ammonium, and potassium) as well as propylene glycol ALG derivative as GRAS (generally regarded as safe) ingredients for oral administration [127]. Nevertheless, several data reported that chemical composition of ALG may affect polymers' immunogenicity. For instance, Otterlei et al. described that ALG with high M-block were much more potent in inducing cytokine production compared with ALG with high G constituents [128]. In addition, various impurities such as heavy metals, endotoxins, proteins, and polyphenol compounds present in ALG material could potentially exert immunogenic response [129, 130]. Therefore, to assure high purity of ALG, proper decontamination methods should be applied concomitantly with extraction procedure [130].

ALG have been extensively studied for a wide range of applications. They include in situ gel formation, controlled release, targeted drug delivery, and medical purposes [2, 87, 88]. List of the pharmaceutical products based on ALG is presented in Table 4.

ALG are known to act as a physical barrier in order to reduce reflux episodes [131, 132]. A number of available ALG-based pharmaceutical products used for the symptomatic treatment of heartburn and oesophagitis exist [132]. As ALG formulations generally contain bicarbonate salt, it converted to carbon dioxide (entrapped within the gel matrix) enabling polymer to float on the surface of the gastric fluid. ALG-based products may retain in the stomach for several hours providing long-lasting relief [132–134]. Several studies revealed that sodium alginate is able to move to the oesophagus ahead of gastric contents and hence might be helpful in decreasing the number of acid esophageal episodes. Additionally, owing to mucoadhesive properties, ALG was demonstrated to protect

Table 4: List of the pharmaceutical products based on ALG.

Product	Main ingredients	Description	Indications
		Oral administration	
Gastrotuss® baby syrup [22, 23]	Magnesium alginate, simethicone, fructose, xanthan gum, honey, D-panthenol, fluid extracts of *Althaea officinalis, Papaver rhoeas*, zinc oxide, sodium bicarbonate, sodium hydroxide	Creates a mechanical barrier between the stomach and the esophagus which prevents the reflux, recurrent symptoms of respiratory, choking, dysphagia, heartburn, belching, irritability; accelerates gastric movement, regenerates mucous membranes of the esophagus and ensures its protection	Children and infants from the first days of life reflux treatment
Algicid® suspension/tablets [24]	500 mg sodium alginate, 100 mg potassium bicarbonate per 5 ml/per 1 tablet		Adult reflux treatment
Gaviscon Double Action Liquid® [25]	250 mg sodium alginate, 106.5 mg sodium bicarbonate, and 162.5 mg calcium carbonate per 5 ml		
Gaviscon Double Action tablets® [26]	250 mg sodium alginate, 106.5 mg sodium bicarbonate, and 187.5 mg calcium carbonate per tablet		
		Dermal application	
Flaminal Forte® gel [27]	Hydrated alginates polymers in a polyethylene glycol (PEG) matrix with a biologic enzyme system based on glucose oxidase and lactoperoxidase stabilized by guaiacol	Dissolution of dry scab and necrotic material, absorption of lysed material and bacteria by alginates in hydrated form	Leg and diabetic ulcers, pressure sores, complex grazes, burns, oncology and wounds dermatosurgery
Purilon Gel® gel [28]	Carboxymethylcellulose, calcium alginate	Provides moist environment at wound surface	Dry and sloughy necrotic wounds, pressure and venous ulcers, second-degree burns, cuts, abrasions and skin tear, noninfected diabetic foot ulcers
Saf-Gel® gel [29]	Carbomer, propylene glycol sodium/calcium alginate		
Hyalogran® dressing [30]	Ester of hyaluronic acid (HA) and sodium alginate	Exudate absorbs and transforms to soft gel; removes necrotic tissue	Variety of exuding wounds including leg ulcers, pressure sores, ischemic and diabetic wounds, particularly those which are covered with slough and necrotic tissue or areas that are difficult to dress
SeaSorb® dressing [31]	Calcium alginate	Creates moist environment at wound surface, conversion soft fibres to wet gel	Heavily exuding wounds including leg and pressure ulcers, diabetic ulcers and second-degree burns, cavity wounds
Tromboguard® dressing [32]	Two-layer dressing built from hydrophilic polyurethane sponges and biologically active layer containing chitosan, sodium alginate, calcium alginate, and silver cations	Strong haemostatic and antibacterial activity	Control of bleeding traumatic and postoperative wounds
Fibracol Plus® dressing [32]	90% collagen and 10% calcium alginate	Provides moist environment at wound surface, tissue granulation, epithelialisation, and healing	Exuding wounds including: full-thickness and partial-thickness wounds; pressure ulcers; venous ulcers; ulcers caused by mixed vascular etiologies; diabetic ulcers; second-degree burns
Algivon® dressing [33]	Calcium alginate dressing impregnated with Manuka honey	Binds of exudate, regeneration	Sloughy, necrotic, and malodorous wounds
Guardix-SG® [34, 35]	Sodium alginate, poloxamer, calcium chloride	Creates thermosensitive viscous gel in contact with body temperature and forms mechanical barrier separates injured tissues	In spine and thyroid surgeries to reduction of the incidence postoperative adhesions

Table 4: Continued.

Product	Main ingredients	Description	Indications
		Rectal administration	
Natalsid® suppositories [36]	Sodium alginate	Anti-inflammatory local action	Chronic haemorrhoids, proctosigmoiditis, and chronic anal fissures after surgical interventions in the area of the rectum
		Periodontal application	
Progenix putty®, Progenix plus® injection [37]	Demineralised bone matrix in type-1 bovine collagen and sodium alginate	Regeneration, complementation of bone losses; periodontal diseases	Bony voids or gaps of the skeletal system
Emdogain® gel [38–40]	Enamel matrix derivative (EMD), propylene glycol alginate	Regeneration, periodontal diseases, paradontosis	1-, 2-, and 3-wall intrabony defects, class II mandibular furcation defects with minimal interproximal bone loss, recession defects
		Arthroscopic application	
ChondroArt 3D™ injection [41]	Autologous chondrocytes situated on a hydrogel scaffold built from connection of alginate and agarose	Increase production and growth of cartilage	Degenerative diseases of joints and backbones (osteoarthrosis, osteochondrosis)

gastric mucosa from harmful activity of gastric fluid [131, 132, 134]. Antacid ALG products are generally regarded as safe and may be used in children and pregnant women [134].

ALG are also considered as promising candidates in obesity and type 2 diabetes treatment as they are able to attenuate the postprandial glycemic response by modulation of gastric emptying [135–138] or inhibition of glucose transporters and glucose intestinal absorption rate [137]. Additionally, there are studies which have also revealed that ALG mode of hypoglycemic action might be associated with the reduced activity of α-amylase, intestinal enzyme responsible for hydrolyzing the bonds between glucose residues in carbohydrate polymers [106, 139].

Superior anti(hyper)lipidemic efficacy of ALG was also displayed. ALG were found to combine bile acids in the digestive tract and to reduce their intestinal reabsorption [140], which in consequence enhance their excretion [141–143]. Furthermore, Houghton et al. suggested that ALG are capable of reducing pancreatic lipase activity by protonating active sites in enzyme's structure [144]. Calcium alginate was also reported to show hypocholesterolemic activity after oral administration as it was found to reduce plasma cholesterol level effectively in the rat model [140].

Numerous data have drawn attention to the use of ALG derivatives as antibacterial, antiviral, and antifungal agents [145, 146]. Several mechanisms have been proposed to explain ALG antimicrobial activity. Negatively charged ALG were found to interact with the outer bacterial cellular surface, leading to its disruption and leakage of intracellular substances [147, 148]. A decrease in membrane function by formation a viscous ALG layer around the cell preventing nutrient transport was also demonstrated [147]. In addition, antibacterial efficacy could be related to ALG chelation capacity responsible for modulating the production of toxins, microbial growth, and factors crucial for microorganisms stability. Bacteriostatic activity of ALG was proved against a wide variety of species, including *Pseudomonas, Escherichia, Proteus,* and *Acinetobacter* [42, 43]. Nonetheless, it ought to be point out that the antimicrobial activity of ALG differs substantially according to a number of factors, namely, molecular weight, M/G-block ratio, modification of their structure, environmental pH, and the state of applied formulation [145].

Sulfated polysaccharides and alginic acid-containing fractions extracted from algae were found to exert antiviral efficacy against a number of viruses families, including *Flaviviridae*, *Togaviridae*, *Rhabdoviridae,* and *Herpesviridae* and might be helpful in treatment of virus infections [146, 149–151]. The mode of action may be related to the strong anionic charge of sulfated ALG capable of interacting with the positively charged host cell and, as a result, virus contact with the host cell is prevented and the viral material could not enter in the cells [61, 152–154]. In contrary, Meiyu et al. indicated that virus penetration was inhibited by physical barrier created by ALG around the cell [154]. Furthermore, studies performed by Son et al. revealed that ALG with high M-block content possessed immunostimulating properties by activating macrophages responsible for excreting cytokines and cytotoxic factors [155].

Haemostatic efficacy of calcium alginate through platelets activation and thrombin generation was also displayed [156–159] enabling polymer application in wound dressings [30–33]. Furthermore, sulfated ALG derivative propylene glycol alginate sodium sulfate (PSS) is the first oral heparinoid approved by Chinese Food and Drug Administration and has been used as an anticoagulant drug for over 30 years [160].

Sodium alginate oligosaccharides have been reported to lower blood pressure [64]. The hypotensive mechanism appeared to be associated with calcium antagonist activity, especially toward voltage-operated calcium channels [65]. Sodium alginate oligosaccharides in dose 60 mg/day were found to decrease blood pressure and to eliminate hypertension after 14 days of treatment, whereas Moriya et al. displayed polymers facility to prevent early-stage of kidney injury by decreasing the rate of glomerular filtration [66]. In addition, alginate potassium might be considered as promising agent for preventing cardiovascular complications associated with

hypertension, including cardiac, renal hypertrophy in the risk of stroke occurrence [161].

Antioxidant and anti-inflammatory activity of alginate oligosaccharides was also observed. Alginate oligosaccharides were found to attenuate the production of nitric oxide, reactive oxygen species (ROS), prostaglandin E2, and cyclooxygenase COX-2 [57, 162–166]. Yamamoto et al. demonstrated that the mechanism underlying antioxidant effect of high mannuronic alginate was based on stimulating monocytes to secrete anti-inflammatory cytokines [164]. Additionally, because of chelating capacity, ALG are capable of binding toxins and heavy metals in the intestine, protecting cells from the carcinogenesis process [57, 60, 163–166]. Furthermore, Jeong et al. indicated that alginic acid exerted antianaphylactic activity relating to inhibition of histamine release from mast cells followed with downregulation of histidine decarboxylase and proinflammatory cytokines expression [167]. Moreover, studies performed by Uno et al. showed that alginic acid reduced IgE production in the serum of mice immunized with β lactoglobulin [168]. Additionally, alginic acid at concentration of 0.01 μg/ml was found to reduce histamine release from rat peritoneal mast cells up to 60% [167].

5. Future Perspectives

5.1. ALG-Based Three-Dimensional (3D) Cell Culture Systems. 3D culture systems, macroporous structures prepared from using natural, synthetic polymers or their composites, with ability to reflect the native extracellular matrix and natural physiological conditions have been regarded as advanced technology for complex cellular physiology investigations, drug evaluation, and tissue engineering [169–171]. Among natural polymers, ALG, with regard to gel formation ability, mechanical strength, and interactions with cell via bioadhesive bonds, are considered to be promising material for cell and tissue culture and have been employed as 3D systems [89]. 3D material based on ionically gelled and dried ALG macroporous scaffolds creates favorable conditions for cellular attachment, proliferation, and differentiation. ALG scaffolds are able to turn into hydrogels upon rehydration following cell seeding. At present, two ALG-based 3D products for cell culture AlgiMatrix® (Thermo Fisher Scientific/Life Technologies, USA) and NovaMatrix® 3D (NovaMatrix, Norway) are commercially available in different formats of standard cell culture well plates [172, 173]. AlgiMatrix is a lyophilized sponge prepared of pharmaceutical-grade ALG extracted from brown seaweed. After application of the cell suspension on the top surface of porous ALG-platform, the lyophilisate becomes hydrated and entraps cells inside its porous structure [174]. Unopened product is stable at room temperature up to 12 months. In contrary, NovaMatrix 3D comprises sterile ALG foam structure, a source of gel forming ions to initiate polymer gelation, and a vial of lyophilized ALG to be dissolved in a culture medium. Once the pores are filled with the ALG solution, in situ hydrogel is formed which enables fast and gentle cell immobilization under physiological conditions [170, 173].

5.2. Cell-Based Microparticles for Therapeutic Applications. Immobilization of living cells or cell inducing factors in ALG matrix is commonly used technique in tissue and cartilage engineering. Over the last ten years, an advanced research has been conducted on the development of cell transplantation therapy in long-term diabetes and neurodegenerative diseases treatment with using ALG-encapsulation technology Immupel™ (LCT, Living Cell Technologies Limited, Australia). This selectively permeable system with ability to protect the encapsulated living cells from host immune system manages them to function and differentiate accurately [175–177]. Currently, two ALG-based products, DIABECELL® and NTCELL®, are in advanced stage of clinical investigations.

DIABECELL implant consists of microencapsulated neonatal porcine islets capable of secreting insulin. The single system is designed to be delivered into the patients abdomen during laparoscopy procedure. Each multilayer microcapsule comprises the inner core of ALG (M/G ratio 60 : 40) cross-linked with calcium chloride and coated with poly-L-ornithine- (PLO-) polycationic polymer responsible for strengthening the capsule wall. To reduce the risk of immunogenicity arisen from the presence of PLO, the additional outer layer prepared of ALG is present [178, 179]. Recently additional modification of microcapsules shell by cross-linking the PLO surface with genipin has been employed in order to improve microcapsules biocompatibility. The clinical data displayed a statistically significant efficacy of DIABECELL in reduction of hypoglycemic episodes in patients with type 1 diabetes after transplantation [179]. Another example of porcine pancreatic islet cells encapsulation is monolayer cellular device (MCD) technology. A single capsule contains collagen matrix base and monolayer of porcine islet cells (monolayer allows for a faster kinetic diffusion relative to the cluster of islands) and then coated by gelled layer built of 3% (*w/v*) ALG. The capsules are formatted to a 1–32 cm sheet for subcutaneous implantation. The MCD was histologically examined after a resection. Surrounded tissues graft fibrosis or ALG degradation has not been observed. In comparison to nonencapsulated porcine islets, less level of lymphocytes and macrophages has been noted [180, 181].

NTCELL with choroid plexus cells encapsulated within Immupel platform has been displayed to regenerate damaged tissue and significantly restore function in humans with Parkinson's disease. Following implantation into an impaired site within the brain of model animals, NTCELL was found to promote the production of cerebrospinal fluid as well as nerve growth factors. In addition to Parkinson's disease, the product may have the potential to be utilized in a number of other neurodegenerative disorders, including Huntington's, Alzheimer's or motor neuronal diseases [182, 183].

5.3. Biological Activity of ALG Oligosaccharides. In recent years, ALG oligosaccharides, low molecular polymer fragments obtained by enzymatic depolymerization or acid hydrolysis at elevated temperatures, have received much attention because of their unique opportunity for combination treatment in which the polymer acts as the drug vehicle and concomitantly as an active part of the therapy [116].

Table 5: Examples of ALG oligosaccharides with biological activity and pharmaceutical application.

Compound	Mechanism of action	Biological activity and pharmaceutical application	Reference
OligoG® (ALG oligosaccharide)	Regulation of mucus viscosity by induction alterations in mucin surface charge, formation porosity of the mucin networks in cystic fibrosis sputum; eradication bacterial and fungal lung infections by modification of biofilm structure together with growth inhibition, improvement the efficiency of conventional antibiotics against multidrug resistant bacteria or fungi	Cystic fibrosis, treatment of chronic obstructive pulmonary disease (COPD), improvement of antibacterial and antifungal therapy, antifungal activity	Khan et al. [42] Pritchard et al. [43] Powell et al. [44]
Heparinoid 911 (sulfated high mannuronic and guluronic oligosaccharides)	Interaction with glycoproteins present on the cell surface, which leads to the counteracting HIV-virus, prevention of viral adsorption and inhibition of viral reverse transcriptase; inhibition of DNA polymerase of hepatitis B virus	HIV/AIDS, hepatitis B virus	Xin et al. [45] Xin et al. [46] Jiang et al. [47] Wu et al. [48]
ALG oligosaccharides; oligomannuronate (HS971)	Inhibition effect on neuroinflammation, promotion effect on microglial phagocytosis, protection neurons from cell death by blocking oxidative stress, inhibition of production of nitric oxide and prostaglandin E2, expression of inducible nitric oxide synthase and cyclooxygenase 2, secretion of proinflammatory cytokines, promotion of the phagocytosis of amyloid β protein through its interaction with toll-like receptor 4 (TLR4) in microglia	Alzheimer's disease and neurodegenerative diseases	Tusi et al. [49] Zhou et al. [50] Manigandan et al. [51] Hu et al. [52] Wang et al. [53]
Propylene glycol alginate sodium sulfate oligosaccharides (PSS)	Inhibition of thrombin by interfering with the coagulation cascade, prolongation of the activated partial thromboplastin time, clotting time and reduction platelet aggregation	Anticoagulant and antithrombotic activity, blood viscosity reduction	Ronghua et al. [54] Xin et al. [55]
Guluronate oligosaccharide	Reduction of the production of nitric oxide, prostaglandin E2, reactive oxygen species, the expression of inducible nitric oxide synthase and cyclooxygenase 2, secretion of proinflammatory cytokines IL-1 and IL-6, reduction of the inflammatory responses through blocking the activation of nuclear factor NF-κB and mitogen-activated protein kinases, inhibition lipid peroxidation	Antioxidant and anti-inflammatory activity, protection cells from the carcinogenesis process	Falkeborg et al. [56] Zhou et al [57] An et al. [58] Ji et al. [59] Hu et al. [60]
Unsaturated guluronate oligosaccharide	Dose and time depend on induction of production of nitric oxide, inducible nitric oxide synthase, reactive oxygen species and TNF-α, induction of macrophage to release nuclear factor NF-κB and mitogen-activated protein kinase signaling pathways	Immunomodulatory activity	Xu et al. [61] Xu et al. [62]

Table 5: Continued.

Compound	Mechanism of action	Biological activity and pharmaceutical application	Reference
ALG oligosaccharides	Stimulation cecal and fecal microflora	Probiotic and prebiotic activity	Wang et al. [63]
Sodium alginate oligosaccharides (including unsaturated 3α-L-guluronate and/or β-D-mannuronate)	Hypothesis mechanism involves blood pressure reduction related to direct action on vascular vessels, by effect on the adrenergic nervous system or endothelial cell function	Hypertension	Terakado et al. [64] Chaki et al. [65] Moriya et al. [66]

Examples of ALG oligosaccharides with biological activity and pharmaceutical application were presented in Table 5.

OligoG®, the highly purified oligomer with a high content of G-blocks and a relatively narrow molecular weight distribution, represents a novel therapeutic approach for treatment of microbial infections [184]. The unique mode of OligoG action is related to mucolytic activity and modification of biofilm formed by bacteria during colonization process. OligoG (at concentration of 10%) is able to alter the biofilm surface charge and porosity, weakening its growth and as a result to damage pathogens cell membranes. OligoG was demonstrated to increase the efficiency of conventional antibiotics against several resistant pathogens, including *Pseudomonas*, *Acinetobacter,* and *Burkholderia* sp. [184, 185]. In addition, Tøndervik et al. indicated that OligoG improved antifungal activity of commonly used polyenes, azoles, and allylamines against *Aspergillus* and *Candida* strains [186]. OligoG is currently being tested as novel inhaled polymer therapy for the treatment of chronic respiratory disease. The advantage of OligoG is its suitability for pulmonary administration after simple dissolution in isotonic solvents followed with effective lung deposition and resistance to enzymatic degradation [43].

It should be noted that ALG oligosaccharides might be also considered as promising probiotic and prebiotic agents due to their beneficial effect on promoting the growth of *Bifidobacterium* sp. with simultaneous inhibition of *Salmonella enteritidis* colonization in the large intestine [187]. The influence on the balance of commensal bacteria could be attributed to immunostimulatory activity of oligosaccharides through ability to upregulate the production of anti-inflammatory factors [61, 62].

Additionally, considerable research effort has been made to explore the usability of heparinoid ALG derivatives to support HIV treatment. At present, drug 911, sulfated high mannuronic and guluronic heterogeneous fragments of ALG, belonging to a group of heparinoid polysaccharides, is in advanced phase of clinical investigations in China as anti-AIDS drug [45–48]. Heparinoid 911 possesses an average molecular weight of 10 kDa and 1.5 sulfates and 1.0 carboxyl groups per sugar residue [48]. Heparinoid 911 was demonstrated to interact with the positively charged regions of glycoproteins present on the cell surface, leading to the shielding effect on these regions, thus counteracting HIV-virus binding to the cell surface [45, 46]. The unique mode of 911 action was found to be related to the inhibition of viral reverse transcriptase and prevention of viral adsorption. Furthermore, a significant inhibitory effect on DNA polymerase of hepatitis B virus was also reported which gives the opportunity to apply 911 in hepatitis B treatment [47].

6. Conclusions

Owing to unique properties, swelling capacity, mucoadhesiveness, and ability of sol/gel transition ALG have gained a preferential place in the development of advanced drug delivery systems. These natural, multifunctional polymers are widely studied in the design of microparticulate systems for controlled release, targeted drug delivery, and biomedical application (as matrix for three-dimensional tissue cultures, adjuvants of antibiotics, and antiviral agents or in cell transplantation in diabetes and neurodegenerative diseases treatment). Additionally, highly absorbent ALG-based hydrogels with mechanical stability and viscoelastic properties are applied as wound dressing. This paper also describes ALG chemical modifications, ALG biological activity, and application in pharmaceutical products.

Competing Interests

The authors declare no conflict of interests.

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