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

Marta Szekalska,1 Agata Puciłowska,1 Emilia Szymańska,1 Patrycja Ciosek,2 and Katarzyna Winnicka1

1Department of Pharmaceutical Technology, Medical University of Białystok, Mickiewicza 2c, 15-222 Białystok, Poland
2Department of Microbioanalytics, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland

Correspondence should be addressed to Marta Szekalska; marta.szekalska@umb.edu.pl

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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
Alginites (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 I.

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
1,4α-L-Guluronic acid 1,4β-D-Mannuronic acid

(a)

(b)

(c)

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]. Alginate 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].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Eur. Ph. 8.0</th>
<th>USP 32-NF 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of solid product</td>
<td>White or pale yellowish-brown powder</td>
<td>n.d.</td>
</tr>
<tr>
<td>Content</td>
<td>n.d.</td>
<td>90.8%–106.0% of dried basis</td>
</tr>
<tr>
<td>Packaging and storage</td>
<td>n.d.</td>
<td>preserved in tight containers</td>
</tr>
<tr>
<td>Solubility</td>
<td>Slowly soluble in water, practically insoluble in ethanol 96%</td>
<td>n.d.</td>
</tr>
<tr>
<td>Appearance of solution</td>
<td>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</td>
<td>n.d.</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>≤20 ppm</td>
<td>≤0.004%</td>
</tr>
<tr>
<td>Chlorides</td>
<td>≤1.0%</td>
<td>n.d.</td>
</tr>
<tr>
<td>Calcium</td>
<td>≤1.5%</td>
<td>n.d.</td>
</tr>
<tr>
<td>Arsenic</td>
<td>n.d.</td>
<td>≤1.5 ppm</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>≤15.0%</td>
<td>≤15.0%</td>
</tr>
<tr>
<td>Total ash</td>
<td>n.d.</td>
<td>18.0%–27.0%</td>
</tr>
<tr>
<td>Sulfated ash</td>
<td>30.0%–36.0%</td>
<td>n.d.</td>
</tr>
<tr>
<td>Microbial limits</td>
<td>TAMC: ≤1000 cfu/g</td>
<td>TYMC: ≤100 cfu/g</td>
</tr>
<tr>
<td>Total ash</td>
<td>n.d.</td>
<td>≤200 cfu/g</td>
</tr>
<tr>
<td>Absence of specified microorganisms</td>
<td><em>Salmonella sp., Escherichia coli</em></td>
<td><em>Salmonella sp., Escherichia coli</em></td>
</tr>
</tbody>
</table>

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.

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

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...
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

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).
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 (alginate/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.

<table>
<thead>
<tr>
<th>Type of modification</th>
<th>Material</th>
<th>Active substance</th>
<th>Biomedical or pharmaceutical application</th>
<th>Dosage form</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation</td>
<td>Oxidized-NaALG</td>
<td>Limbal epithelial stem cells&lt;br&gt;Flurbiprofen</td>
<td>Improvement of corneal wound healing therapy&lt;br&gt;Sustained oral delivery</td>
<td>Hydrogel&lt;br&gt;Beads</td>
<td>Wright et al. [10]&lt;br&gt;Maiti et al. [11]</td>
</tr>
<tr>
<td>Reductive-amination of oxidized alginate</td>
<td>ALG-g-poly(ethylene glycol)</td>
<td>Human foreskin fibroblasts</td>
<td>Reduction of secretion inflammatory cytokines, improvement of the biocompatibility</td>
<td>Microspheres</td>
<td>Mahou et al. [12]</td>
</tr>
<tr>
<td>Sulfation</td>
<td>Sulfated ALG</td>
<td>—</td>
<td>Mineralization of hydroxyapatite and participation in the chelation process for tissue engineering</td>
<td>Gel</td>
<td>Coleman et al. [14]</td>
</tr>
<tr>
<td>Phosphorylation</td>
<td>Phosphorylated ALG</td>
<td>—</td>
<td>Cell carrier with mechanical stability and selective permeability</td>
<td>Microcapsules</td>
<td>Tian et al. [18]</td>
</tr>
<tr>
<td>Graft copolymerization</td>
<td>NaALG-co-polyacrylamide&lt;br&gt;Starch-g-poly(acrylic acid)-NaALG&lt;br&gt;ALG-glycidyl methacrylate</td>
<td>Famotidine&lt;br&gt;Diclofenac sodium&lt;br&gt;Human endothelial cell lines HUVEC and L929</td>
<td>Sustained release gastroretentive carrier&lt;br&gt;pH-sensitive matrices for the oral drug delivery&lt;br&gt;Thermal polymerizable injectable hydrogel for tissue engineering, especially for myocardial repair</td>
<td>Hydrogel&lt;br&gt;Hydrogel beads&lt;br&gt;Hydrogel</td>
<td>Tripathi and Mishra [15]&lt;br&gt;Chang [16]&lt;br&gt;Wang et al. [17]</td>
</tr>
<tr>
<td>Esterification</td>
<td>Propylene glycol ALG</td>
<td>Lysozyme</td>
<td>Protein encapsulation with a sustained release</td>
<td>Microparticles</td>
<td>Hurteaux et al. [21]</td>
</tr>
</tbody>
</table>

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 esophagitis 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 esophagus 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.

<table>
<thead>
<tr>
<th>Product</th>
<th>Main ingredients</th>
<th>Description</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrotuss® baby syrup [22, 23]</td>
<td>Magnesium alginate, simethicone, fructose, xanthan gum, honey, D-panthenol, fluid extracts of Althaea officinalis, Papaver rhoeas, zinc oxide, sodium bicarbonate, sodium hydroxide</td>
<td>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</td>
<td>Children and infants from the first days of life reflux treatment</td>
</tr>
<tr>
<td>Algicid® suspension/tablets [24]</td>
<td>500 mg sodium alginate, 100 mg potassium bicarbonate per 5 ml per 1 tablet</td>
<td>250 mg sodium alginate, 106.5 mg sodium bicarbonate, and 162.5 mg calcium carbonate per 5 ml</td>
<td>Adult reflux treatment</td>
</tr>
<tr>
<td>Gaviscon Double Action Liquid® [25]</td>
<td>250 mg sodium alginate, 106.5 mg sodium bicarbonate, and 187.5 mg calcium carbonate per tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gaviscon Double Action tablets® [26]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dermal application</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flaminal Forte® gel [27]</td>
<td>Hydrated alginites polymers in a polyethylene glycol (PEG) matrix with a biologic enzyme system based on glucose oxidase and lactoperoxidase stabilized by guaiaol</td>
<td>Dissolution of dry scab and necrotic material, absorption of lysed material and bacteria by alginites in hydrated form</td>
<td>Leg and diabetic ulcers, pressure sores, complex grazes, burns, oncology and wounds dermatosurgery</td>
</tr>
<tr>
<td>Purilon Gel® gel [28]</td>
<td>Carboxymethylcellulose, calcium alginate</td>
<td>Provides moist environment at wound surface</td>
<td>Dry and sloughy necrotic wounds, pressure and venous ulcers, second-degree burns, cuts, abrasions and skin tear, noninfected diabetic foot ulcers</td>
</tr>
<tr>
<td>Saf-Gel® gel [29]</td>
<td>Carboxymethylcellulose, calcium alginate</td>
<td>Carboxymethylcellulose, propylene glycol sodium/calcium alginate</td>
<td>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</td>
</tr>
<tr>
<td>Hyalogran® dressing [30]</td>
<td>Ester of hyaluronic acid (HA) and sodium alginate</td>
<td>Exudate absorbs and transforms to soft gel; removes necrotic tissue</td>
<td>Heavily exuding wounds including leg and pressure ulcers, diabetic ulcers and second-degree burns, cavity wounds</td>
</tr>
<tr>
<td>SeaSorb® dressing [31]</td>
<td>Calcium alginate</td>
<td>Creates moist environment at wound surface, conversion soft fibres to wet gel</td>
<td></td>
</tr>
<tr>
<td>Tromboguard® dressing [32]</td>
<td>Two-layer dressing built from hydrophilic polyurethane sponges and biologically active layer containing chitosan, sodium alginate, calcium alginate, and silver cations</td>
<td>Strong haemostatic and antibacterial activity</td>
<td>Control of bleeding traumatic and postoperative wounds</td>
</tr>
<tr>
<td>Fibracol Plus® dressing [32]</td>
<td>90% collagen and 10% calcium alginate</td>
<td>Provides moist environment at wound surface, tissue granulation, epithelialisation, and healing</td>
<td>Exuding wounds including: full-thickness and partial-thickness wounds; pressure ulcers; venous ulcers; ulcers caused by mixed vascular etiologies; diabetic ulcers; second-degree burns</td>
</tr>
<tr>
<td>Algivon® dressing [33]</td>
<td>Calcium alginate dressing impregnated with Manuka honey</td>
<td>Binds of exudate, regeneration</td>
<td>Sloughy, necrotic, and malodorous wounds</td>
</tr>
<tr>
<td>Guardix-SG® [34, 35]</td>
<td>Sodium alginate, poloxamer, calcium chloride</td>
<td>Creates thermosensitive viscous gel in contact with body temperature and forms mechanical barrier separates injured tissues</td>
<td>In spine and thyroid surgeries to reduction of the incidence postoperative adhesions</td>
</tr>
</tbody>
</table>
Table 4: Continued.

<table>
<thead>
<tr>
<th>Product</th>
<th>Main ingredients</th>
<th>Description</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rectal administration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natalsid® suppositories [36]</td>
<td>Sodium alginate</td>
<td>Anti-inflammatory local action</td>
<td>Chronic haemorrhoids, proctosigmoiditis, and chronic anal fissures after surgical interventions in the area of the rectum</td>
</tr>
<tr>
<td>Progenix putty®, Progenix plus® injection [37]</td>
<td>Demineralised bone matrix in type-I bovine collagen and sodium alginate</td>
<td>Regeneration, complementation of bone losses; periodontal diseases</td>
<td>Bony voids or gaps of the skeletal system</td>
</tr>
<tr>
<td>Emdogain® gel [38–40]</td>
<td>Enamel matrix derivative (EMD), propylene glycol alginate</td>
<td>Regeneration, periodontal diseases, paradontosis</td>
<td>1-, 2-, and 3-wall intrabony defects, class II mandibular furcation defects with minimal interproximal bone loss, recession defects</td>
</tr>
<tr>
<td><strong>Periodontal application</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Arthroscopic application</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
hypertension, including cardiac, renal hypertrophy in the risk of stroke occurrence [161].

Antioxidant and anti-inflammatory activity of alginate oligosaccharides was also observed. Alginic acid at the serum of mice immunized with β-lactoglobulin [168]. Additionally, 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 lyophilsate 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 microparticle 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 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.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of action</th>
<th>Biological activity and pharmaceutical application</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>OligoG</strong>&lt;sup&gt;*&lt;/sup&gt; (ALG oligosaccharide)</td>
<td>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</td>
<td>Cystic fibrosis, treatment of chronic obstructive pulmonary disease (COPD), improvement of antibacterial and antifungal therapy, antifungal activity</td>
<td>Khan et al. [42] Pritchard et al. [43] Powell et al. [44]</td>
</tr>
<tr>
<td><strong>Heparinoid 911</strong> (sulfated high mannuronic and guluronic oligosaccharides)</td>
<td>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</td>
<td>HIV/AIDS, hepatitis B virus</td>
<td>Xin et al. [45] Xin et al. [46] Jiang et al. [47] Wu et al. [48]</td>
</tr>
<tr>
<td><strong>ALG oligosaccharides; oligomannuronate (HS971)</strong></td>
<td>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</td>
<td>Alzheimer’s disease and neurodegenerative diseases</td>
<td>Tusi et al. [49] Zhou et al. [50] Manigandan et al. [51] Hu et al. [52] Wang et al. [53]</td>
</tr>
<tr>
<td><strong>Propylene glycol alginate sodium sulfate oligosaccharides (PSS)</strong></td>
<td>Inhibition of thrombin by interfering with the coagulation cascade, prolongation of the activated partial thromboplastin time, clotting time and reduction platelet aggregation</td>
<td>Anticoagulant and antithrombotic activity, blood viscosity reduction</td>
<td>Ronghua et al. [54] Xin et al. [55]</td>
</tr>
<tr>
<td><strong>Guluronate oligosaccharide</strong></td>
<td>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</td>
<td>Antioxidant and anti-inflammatory activity, protection cells from the carcinogenesis process</td>
<td>Falkeborg et al. [56] Zhou et al. [57] An et al. [58] Ji et al. [59] Hu et al. [60]</td>
</tr>
<tr>
<td><strong>Unsaturated guluronate oligosaccharide</strong></td>
<td>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</td>
<td>Immunomodulatory activity</td>
<td>Xu et al. [61] Xu et al. [62]</td>
</tr>
</tbody>
</table>
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Table 5: Continued.

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