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A Review on Seaweeds Polysaccharides based on Nonoparticles: Preparation and Application for Drug Delivery

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***Abstract*: In recent years, there have been major advances and increasing amounts of research on the utilization of natural polymeric materials as drug delivery vehicles due to their biocompatibility and biodegradability. Seaweed polysaccharides are abundant resources and have been extensively studied for several biological, biomedical, and functional food applications. The exploration of seaweed polysaccharides for drug delivery applications is still in its infancy. Alginate, carrageenan, fucoidan, ulvan, and laminarin are polysaccharides commonly isolated from seaweed. These natural polymers can be converted into nanoparticles (NPs) by different types of methods, such as ionic gelation, emulsion, and polyelectrolyte complexing. Ionic gelation and polyelectrolyte complexing are commonly employed by adding cationic molecules to these anionic polymers to produce NPs of a desired shape, size, and charge. In the present review, we have discussed the preparation of seaweed polysaccharide-based NPs using different types of methods as well as their usage as carriers for the delivery of various therapeutic molecules (e.g., proteins, peptides, anti-cancer drugs, and antibiotics). Seaweed polysaccharide-based NPs exhibit suitable particle size, high drug encapsulation, and sustained drug release with high biocompatibility, thereby demonstrating their high potential for safe and efficient drug delivery.**

***Keywords*: Alginate; carrageenan; fucoidan; drug delivery.**

1. Introduction

Seaweed is an important marine resource for human kind, and in particular, for the multi-billion-dollar companies that have been operating based on seaweed-derived polysaccharides for approximately the last six decades [1–4]. The cell walls of seaweed are mainly composed of polysaccharides. These polysaccharides are generally small sugar units linked with glycosidic bonds. In recent years, significant research has been conducted on seaweed for the production of bioenergy and the development of food applications due to the abundance of thisresource.

Recently, particular attention has been directed toward developing drug delivery systems using seaweed polysaccharides, which is an important field of biomedical research. Among the various synthetic can natural polymers that have been extensively studied for biomedical applications, particularly for drug delivery [15–20], natural sea weed polysaccharides that have been formulated into nano particles (NPs) for drug delivery systems (DDS) will be discussed in this review. Natural polysaccharides for DDS have main advantages their biocompatibility and charge properties [21]. They are also inexpensive materials due to their abundance [22–24] in their biocompatibility and charge properties [21]. They are also inexpensive materials due to their abundance [22–24].

EX: alginate, carrageenan, ulvan, andlaminarin

2. Seaweed polysaccharides based nanoparticles for drug delivery

Seaweed can be classified as red, green, or blue. The cell walls of seaweed are often composed of polysaccharides. For approximately four decades, research has been conducted on the structures and applications of seaweed polysaccharides, especially on their functional food applications [46]. Some seaweed-derived polysaccharides have anionic sulfate groups, which are not present in polysaccharides of terrestrial and animal origin [49]. These seaweed polysaccharide-based NPs avoid aggregation during blood circulation by reduced interaction with serum proteins.

Polysaccharides including agar, alginate, fucoidan, carrageenan, and laminarin have been isolated from seaweed [6, 25, 47]. Seaweed polysaccharides have hydrophilic surface groups, such as hydroxyl, carboxyl, and sulfate groups, which interact with biological tissues easily [48]. Owing to these properties of seaweed polysaccharides, the usage of seaweed polysaccharides in DDS is increasing. The main difference between the sulfated polysaccharides and other polysaccharides is surface charge. Most of the algae-derived polysaccharides are anionic in nature.

3. Polysaccharide based nanoparticles for drug delivery

Generally, polysaccharides are considered safe, biocompatible, stable, hydrophilic, and biodegradable, and they

can be modified into different forms, such as chemically modified polysaccharides, hydrogels, scaffolds, fibers, and NPs. NPs have many advantages for drug delivery purposes compared with larger (micro-sized) particles because they easily penetrate into targeted areas [29–39].

Polysaccharide-based NPs can be obtained using different types of methods. In particular, the most widely studied methods are ionic linking, covalent cross-linking, self-assembly, and polyelectrolyte systems. Research on polysaccharide-based NPs (e.g., alginate, carrageenan, and fucoidan) for DDS has been increasing dramatically over the last decade.

(C6H5O10) n is the general formula for typical polysaccharides. The number of units (n) can vary from 40to3000 [25]. Natural polysaccharides are commonly obtained from several resources, including algae, animals, plants, and microbes. Cellulose, chitin, chitosan, alginate, heparin, hyaluronic acid, chondroitin sulfate, pectin, pullulan, amylose, dextran, ulvan, carrageenan, and their derivatives have been widely studied for several biological and biomedical applications, including those in the fields of tissue engineering, wound management, drug delivery, and biosensors [26–28]. Furthermore, polysaccharides can be divided into two groups according to their charge.

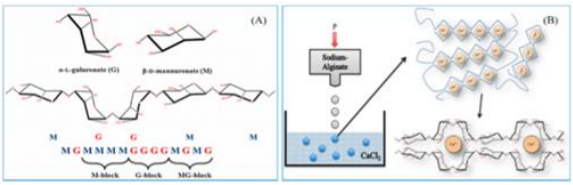
For example, chitosan is a positively charged (cationic) polysaccharide, whereas alginate, carrageenan, and fucoidan are negatively charged (anionic) polysaccharides [21]. Polysaccharide-based NPs can be obtained using different types of methods. In particular, the most widely studied methods are ionic linking, covalent cross-linking, self-assembly, and polyelectrolyte systems.

Research on polysaccharide-based NPs (e.g., alginate, carrageenan, and fucoidan) for DDS has been increasing dramatically over the last decade (Figure 1) [21, 40]. Polysaccharide based NP shave advantages due to abundant availability and biocompatible properties, which make them important candidates for drug delivery system [41–44]. Posoccoetal. (2015) [45] suggested that polysaccharide-based materials exhibit the following advantages:

- They can be useful in stimuli-responsive DDS.
- They can be modified as gels.
- Their sources are abundant and they can be available in a well-characterized state.
- Ionic polysaccharides are mucoadhesive.
- They can give rise to interpenetrated polymeric networks.
- They can be useful in stimuli-responsive DDS.

4. Alginate

Alginate is a water soluble, anionic polymer, commonly produced from marine brown algae. It is mainly composed of α-L-guluronic acid (G) and β-D-mannuronic acid (M) residues linked by 1, 4-glycosidic linkages (Figure 2A). It is nontoxic, biocompatible, biodegradable, and inexpensive, and thus it is extensively used for several biological, biomedical, and functional food applications [8, 50, 51]. Alginate NPs can be prepared by different types of methods, including ionic cross-linking, covalent cross-linking, self-assembly, complexation methods, and emulsion methods [39].



A. *Production of aliginate NPS*

Considerable attention has been directed toward preparative methods to produce the desired properties of alginate NPs for effective drug delivery systems. Different types of methods are explained here.

B. *Polyelectrolyte complexation of alginate NPs*

The production of NPs with polyelectrolyte complex (PEC) systems has gained much attention due to its simple procedure for drug delivery applications. Generally, PECs can be formed by mixing oppositely charged polyelectrolytes and allowing them to interact electrostatically.

Aqueous polycationic solutions (chitosan or poly-L-lysine) were mixed with polyanionic alginate solutions at room temperature to immediately produce alginate-cationic polymeric NPs. pH, temperature, and stirring speed may play major roles in controlling the size of these alginate NPs.

C. *Ionic cross-linked alginate NPs:*

Ionic cross-linked alginate NPs usually form egg box shapes, as illustrated in Figure2B. However, sometimes this method tends to produce micro-sized particles rather than NPs. Therefore, process optimization is important to produce alginate NPs of a desired shape. The optimization can be performed by tailoring calcium ion concentration, alginate concentration, addition speed, pH, temperature, and stirring speed. They can be produced by cross linking alginate with various ions, ca^{2+}, Ba^{2+} and Al^{3+}.

D. *Alginate NPS in drug delivery systems:*

Alginate NPs chemically modified with encapsulation materials may exhibit prolonged periods of material delivery. NP stability is an important parameter in DDS. Azevedo et al. developed alginate-chitosan NPs with high stability. They were stored at 4″C in solution for a period of five months. Their particle size and zeta potential were measured during that period of time. Particle size may change, and they may aggregate over time; this may due to the weak electrostatic interactions between alginate and chitosan. Alginate NPs have been extensively studied for DDS due to their high encapsulation efficiency of highly effective drugs, proteins, and peptides. Alginate NPs usually do not agglomerate in organs while they deliver drugs or proteins.

However, the addition of a stabilizer can overcome this type of issue. For example, the addition of vitamin B2 maintained the stability of alginate–chitosan NPs over a five-month period of time.

E. Preparation of alginate NPS using emulsions:

The size of alginate NPs prepared by emulsions is usually below 250 nm. This size is highly desirable for drug delivery applications due to enhanced cellular uptake. Developed calcium alginate NPs by a water-in-oil (W/O) emulsion. Tetra ethylene glycol Monod decyl ether, as a nonionic surfactant in decane, was mixed with alginate solution at different concentrations to form emulsion.

Then, CaCl2 was added into the W/On an emulsion to form alginate NPs. Finally, alginate NPs were separated from the aqueous phase. The diameter of the developed NPs was approximately 200 nm.

F. Alginate NPS in protein and peptide delivery

Quality of life can be reduced significantly by health problems and common diseases. It was estimated that 9% of adults aged 18+ years and approximately 1.5 million deaths were directly caused by diabetes. The World Health Organization (WHO) predicts that by 2030, diabetes will be the 7th leading cause of death. Insulin is one of the main treatments for diabetes, and the bioavailability of oral insulin is limited by the gastrointestinal tract. As a result, the targeted delivery of insulin is a main objective of NP-based insulin delivery. Polymers play an important role in insulin delivery. Table 1 shows the usage of various alginate NPs for protein delivery, such as insulin delivery.

Table 1. Alginate NPs for protein drug delivery.

Serial number	Materials	Method	Particle size	Drug
1	Alginate–chitosan	Ionotropic and polyelectrolyte complex	800 nm	Insulin
2	Alginate–chitosan	Ionotropic pre-gelation	100–200 nm	Insulin
3	Alginate	W/O emulsion	2604 nm	Insulin
4	Alginate–chitosan	Polyelectrolyte complex	700 nm	Insulin
5	Alginate–chitosan	Gelification	750 nm	Insulin
6	Alginate–chitosan–TPP	Ionic gelation	260 to 525 nm	Insulin
7	Alginate–oligochitosan	W/O in microemulsion	136 nm	BSA
8	Alginate NPs	Microemulsion	350 nm	BSA
9	Alginate–chitosan	Gelification	200 nm	BSA

Sarmentoetal. Prepared alginate NPs by ionotropic pre-gelation with CaCl2 followed by a PEC process with chitosan polysaccharides. The pH and mass ratio of the polymers and calcium ions play crucial roles influencing the NP formation. Approximately 800-nm particle sizes were produced by this method at pH 4.7 with a 6:1 mass ratio of alginate to chitosan. Fourier transform infrared spectroscopy results revealed the efficient encapsulation of insulin in the NPs. In work by the same group, alginate NPs were formed by ionic gelation and used for insulin delivery. In vivo results of alginate–chitosan NPs loaded with insulin were obtained from diabetic rats. Orally administered NPs lowered glucose levels by more than 40% at dosages of 50 and 100 IU/kg.

A schematic showing the preparation of chitosan-alginate NPs incorporating insulin.

Developed chitosan–alginate NPs with Penta sodium tri polyphosphate (TPP) using ionic gelation and PEC. The particle size was dependent on the molecular weight of alginate. The particle size increased from 260 to 525 nm with increased alginate molecular weight. Insulin was used as a model drug, and the encapsulation efficiency was found range from 41% to 52%. Insulin-loaded chitosan–alginate–TPP NPs showed efficient systemic absorption in rabbits.

Reis et al. developed alginate NPs using a W/O emulsion method and physical cross-linking with calcium ions; it was demonstrated that calcium ions play an important role in controlling particle size. The mass ratio of calcium ions to alginate was 7% (w/w). The encapsulation efficiency of insulin in the alginate NPs was more than 71%. The smaller particle size was achieved by adjusting the calcium and alginate solution concentrations; higher encapsulation efficiency and lower insulin release at pH 1.2 were also attained in this way. At higher calcium ion concentrations, there are more calcium ions free to react with the M and G alginate monomers, forming more rigid alginate polymer chains and ultimately allowing sustainable insulin release from the alginate.

The size of the alginate–chitosan NPs was further decreased to less than 250 nm using the same ionotropic pre-gelation method by controlling the polymer mass ratio (Figure 3). The average size of the NPs obtained by this method was approximately 100–200 nm. The encapsulation efficiency of the insulin in the alginate-chitosan NPs was approximately 85%, and sustained release and nontoxicity were observed when the NPs were used as a peroral treatment.

Alginate-chitosan NPs have been used for the effective delivery of bovine serum albumin (BSA). Wang et al. developed NPs based on low molecular weight alginate and chito–oligosaccharides using a micro emulsion method. The size of the NPs was approximately 136 nm. The encapsulation efficiency reached approximately 88.4%. The developed NPs were nontoxic, biocompatible, and uniform in size, which suggested that they could be used as vehicles for other drugs. Using the same micro emulsion method, alginate NPs were developed using aqueous $CaCl_2$, dioctyl sodium sulfosuccinate, and isopropyl myristate. The particle size of the alginate NPs was approximately 350 nm, as measured by DLS. The sustained release of BSA from the alginate NPs was observed. The loading efficiency of BSA was approximately 40%. Lietal. Developed chitosan–alginate NPs for BSA delivery. TheparticlesizeoftheNPswasapproximately200nm. There lease

of BSA from the NPs was pH dependent.

G. Alginate NPS for cancer drug delivery:

Cancer has a major impact on society across the world. The number of new cancer cases will rise to 22 million within the next two decades. Currently, surgery, chemotherapy, and radiation are the main therapies for cancer; however, it has been several years since chemotherapy has been used as the primary treatment for cancer because of the extent to which it can kill normal healthy cells. To overcome this issue, DDS with NPs have become alternative methods of targeting only cancer cell, increasing the availability of drugs to cancer cells and leaving normal cells unaffected.

Different types of NPs have been extensively studied for cancer drug delivery. Over the last five decades, liposome-, polymer-, dendrimer-, and protein-based NPs and inorganic NPs have been utilizedasdrug carriers to treat cancer. NPs based on both synthetic polymers (e.g., poly (lactic-co-glycolic acid), polylactic acid, and polycaprolactone) and natural polymers (e.g., alginate, chitosan, carrageenan, and fucoidan) have been used as drug carriers to deliver several cancer drugs, such as doxorubicin and 5-fluorouracil (5-Fu).

Table 2. Alginate NPs for cancer drug delivery.

Serial number	Materials	Method	Particle size	Drug
1	Alginate	Gelification with $CaCl_2$ and poly-L-lysine	250–850 nm	Doxorubicin
2	Alginate	$CaCl_2$ cross-linking	214 ± 11 nm	Doxorubicin
3	Glycyrrhetinic acid–Alginate NPs	Chemical modification	80 and 100 nm	Doxorubicin
4	Alginate NPs	Chemical modification	241 nm	Doxorubicin
5	Aerosol OT-alginate NPs	Emulsification cross-linking method	39 ± 7 nm	Doxorubicin and methylene blue
6	Alginate–$CaCO_3$ NPs	Coprecipitation method	100–400 nm	Doxorubicin and p53
7	Chitosan–alginate NPs	Emulsion method	200 nm	5-Fluorouracil
8	Alginate–chitosan	Ionic gelation	329–505 nm	5-Fluorouracil
9	Alginate-chitosan-Pluronic F127	Ionotropic pre gelation	100 ± 20 nm	Curcumin
10	Alginate NPs	Oligonucleotide/Poly lysine	NA	Antisense oligonucleotide
11	Alginate–chitosan	Ionotropic gelation method	230 to 627 nm	Gemcitabine
12	Bovine serum albumin and thiolated alginate	Coacervation	350 to 500 nm	Tamoxifen

Developed alginate NPs with calcium ions and poly-L-lysine by a gelification method. The particle size of the alginate NPs was approximately 250–850 nm, and they were used for doxorubicin delivery. From this study, significant research has been performed to develop alginate NPs for various drug delivery purposes using a similar type of method.

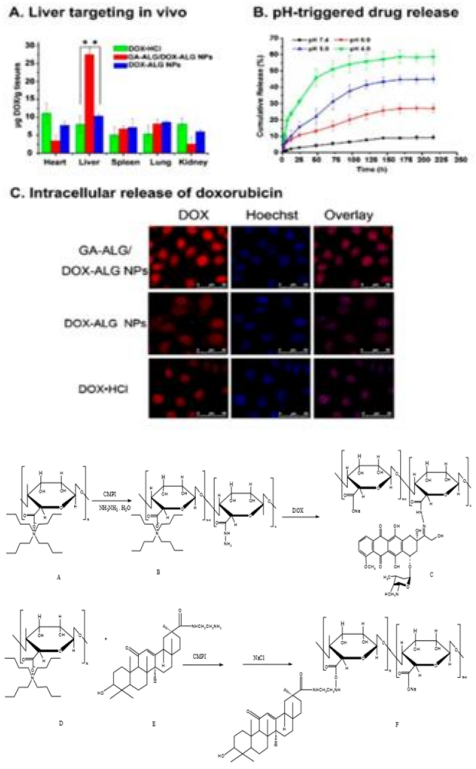
Zhang et al. developed alginate NPs with a CaCl2 cross-linking method. Alginate was modified with a liver targeting molecule (i.e., glycyrrhetinic acid) and chemically characterized. The doxorubicin-loaded glycyrrhetinic acid-alginate NPs exhibited a size of approximately 214 ˘ 11 nm.

Doxorubicin reached 67.8˘4.9 μg/g in the liver after intravenous administration, which was significantly higher compared with the results of both non-glycyrrhetinic acid-modified NPs and the drug only. By the continuous research on complexing NPs, glycyrrhetinic acid-modified alginate (GA–ALG) and doxorubicin-modified alginate (DOX–ALG) were prepared by self-assembly.

pH-Sensitive glycyrrhetinic acid–alginate/doxorubicin–alginate NPs (GA-ALG/DOX-ALG NPs) demonstrated efficient treatment of liver cancer.

DOX concentration in the liver of the GA-ALG/DOX-ALG NPs group reached 27.6 μg/g, which was higher than that of the DOX HCl (8.1 μg/g). Further, DOX release from GA-ALG/DOX-ALGNPs showed pH-sensitivity; less than 10% of the drugs was released at pH7.4with in 9 days while 58.7% of drug was released at pH4.0.Confocal laser scanning microscopy images of HepG2 cells incubated with GA-ALG/DOX-ALG NPs and DOX-ALG NPs at the same DOX concentration (10 μg DOX/mL) showed that GA-ALG/DOX-ALG NPs were efficiently taken up by the cells.

H22 tumor tissue treated with GA-ALG/DOX-ALG NPs showed more effective inhibition of tumor growth compared with bare DOX and DOX-ALG NPs.



The synthesis route of Doxorubicine modified alginate (Dox-ALG) (top)and glycyrrhetinic acid modified alginate(GA-ALG) (bottom).

Surfactant-polymer hybrid NPs using alginate and an anionic surfactant, aerosol-OT (AOT), were prepared for combined chemotherapy and photodynamic therapy. The NPs were able to deliver both doxorubicin and methylene blue. Increased nuclear and cellular accumulation of doxorubicin and methylene blue enhanced the production of reactive oxygen species that contributed to the superior toxicity.

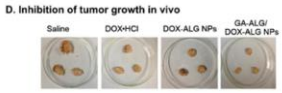


Figure 5. (A) The results of an *in vivo* liver targeting study; (B) the release results at different pH levels; and (C) the cellular uptake of doxorubicin using glycyrrhetinic acid–alginate (GA–ALG)/doxorubicin–alginate (DOX–ALG) NP complexes and doxorubicin–alginate (DOX–ALG) NPs; (D) H22 tumor tissue slices from mice treated with saline, doxorubicin, doxorubicin-alginate (DOX–ALG) NPs, and glycyrrhetinic acid-alginate (GA–ALG)/doxorubicin-alginate (DOX–ALG) NP

On the other hand, wt. p53 protein is positive in response to a variety of stress signals including DNA damage caused by antitumor drugs". Thus, the combination of p53 and doxorubicin may increase the efficacy of the cancer treatment. The developed particle size, approximately 100 to 400 nm, depended on the polymer content. The NPs showed a high drug encapsulation efficiency and completely inhibited the growth of the HeLa cells. These NPs were used for both gene and drug delivery purposes. Xing et al. developed chitosan–alginate NPs by an emulsion method to incorporate 5-Fu. 5-Fu is a pyrimidine analog drug that has been used to treat cancer for several decades.

Antioxidant and antimicrobial activity and the inhibition of different types of tumor cells. Das et al. developed alginate–chitosan–Pluronic F127 NPs for curcumin drug delivery. The encapsulation efficiency of the NPs was improved by the addition of Pluronic F127. The size of the NPs was found to be approximately 100 nm.

H. Alginate NPS for antibiotic and antimicrobial drug delivery

Several antimicrobial drugs are available on the market to kill bacteria, viruses, and fungi. Zahoor et al. developed alginate NPs as antitubercular drug carriers. Isoniazid, rifampicin, and pyrazinamide were encapsulated by the alginate NPs. The encapsulation efficiency of these drugs was approximately 70%–90%. The size of the alginate NPs was approximately 235.5 nm with a polydispersity index of 0.439.

Choonara et al. developed alginate NPs with an ionic cross-linking and reverse emulsion method. Ghaffari et al. developed alginate–chitosan NPs encapsulating ciprofloxacin with a particle size of approximately 520 ± 16 nm. The loading efficiency of ciprofloxacin was 88%.

A sustained release of ciprofloxacin was observed over 45 h. Bi-specific and biodegradable chitosan alginate polyelectrolyte NPs were developed by Arora et al. for amoxicillin delivery.

The particle size of the developed NPs was 264 nm. By increasing the chitosan concentration in the polyelectrolyte system, the particle size was increased. Chopra et al. developed chitosan–alginate NPs for streptomycin delivery. The size of the developed NPs was 328 nm, and the encapsulation efficiency of the drug was 93.32%. Other alginate-chitosan NPs encapsulating antimicrobial drugs have also been developed.

Table 3. Alginate NPs for antibiotic drug delivery.

Serial number	Materials	Method	Particle Size	Drug
1	Alginate NPs	Cation-induced gelification	NA	Rifampicin, isoniazid, pyrazinamide and ethambutol
2	Alginate–chitosan	Polyelectrolyte complex	264–638 nm	Amoxicillin
3	Alginate NPs	Cation-induced gelification	235.5 ± 0 nm	Rifampicin
4	Alginate NPs	Cation-induced gelification	235.5 ± 0 nm	Isoniazid, rifampicin, pyrazinamide, and ethambutol
5	Alginate	Reverse emulsion	240 ± 8.7 nm	Rifampicin and isoniazid
6	Calcium alginate	Polyelectrolyte complex	520 nm	Ciprofloxacin
7	Alginate–chitosan	Ionotropic pre-gelation	328 nm	Streptomycin
8	Alginate–chitosan–silica	Polyelectrolyte complex	NA	Piperacillin-tazobactam, cefepime, piperacillin, imipenem, gentamicin, ceftazidime
9	Alginate–chitosan	Gelification	50–250 nm	Nisin

I. Alginate NPS for other drug delivery

Alginate NPs are excellent for encapsulating various drugs. Methylene blue, fluorescein sodium salt, nifedipine, gatifloxacin, rhodamine 6G, EGFR phosphorothioated 21-mer antisense 50, turmeric oil, epidermal growth factor, Bupivacaine, vitamin D3, 5-aminolevulinic acid, tuftsin, candida rugosa lipase, ibuprofen, ivermectin, enoxaparin, nitric oxide, benzoyl peroxide, and quinapyramine have all been encapsulated in alginate NPs for drug delivery.

Table 4. Alginate NPs for other drug delivery.

Serial number	Materials	Method	Particle size	Drug
1	Sodium alginate–chitosan	Ionic gelation, polyelectrolyte	205 to 572 nm	Gatifloxacin
2	Sodium alginate: $CaCl_2$-(poly-L-lysine or chitosan)	Ionic gelation	544 ± 53 nm	Methylene blue
3	Silica/alginate	NA	50–200 nm	
4	Alginate–chitosan	Ionotropic gelation	600 nm	Fluorescein sodium salt
5	Alginate–chitosan	Polyelectrolyte	20–50 nm	Nifedipine
6	OT-alginate hydrogel loaded with Fe_3O_4	emulsification-cross-linking process	25 and 50 nm	Rhodamine 6G
7	Alginate–chitosan	Precipitation method	194 nm	EGFR Phosphorothioated 21-mer antisense 50
8	Alginate–chitosan	Gelification	522 ± 15 nm	Turmeric oil
9	Alginate–chitosan	NA	NA	Epidermal growth factor receptor
10	Alginate–chitosan	Polyelectrolyte	NA	Bupivacaine
11	Alginate–chitosan	NA	600–650 nm	pAcGFP1-C1 plasmid
12	Hydrophobic alginate derivative	Chemical modification	200–400 nm,	Vitamin D_3
13	Alginate folic acid chitosan	Ionic gelation	115 nm	5-aminolevulinic acid
14	Alginate NPs	Gelation method	200 nm	Tuftsin
15	Superparamagnetic sodium alginate NPs	W/O emulsion method	25–30 nm	Candida rugosa lipase
16	superparamagnetic alginate NPs	Coprecipitation	200 nm	Ibuprofen
17	Thiolated chitosan alginate	NA	265.7 ± 7.4 to 471.0 ± 6.4 nm	Ocular drug
18	Chitosan–alginate NPs	Coacervation	155 nm	Ivermectin
19	Chitosan–alginate NPs	Ionic gelation	213 nm	Enoxaparin
20	Chitosan–alginate NPs	NA	NA	Nitric oxide
21	Chitosan–alginate NPs	Polyelectrolyte complex	50 nm	Benzoyl peroxide
22	Alginate beads	W/O emulsion	200 to 1000 nm	NA
23	Alginate	NA	NA	Pesticide
24	Sodium alginate NPs	Emulsion-cross-linking technology	60 nm	Quinapyramine

J. Alginate np patents

There are several patents regarding alginate-based NPs with different types of preparative methods. The methods of W/O emulsion and ionic cross-linking with calcium ions are patented. Aerosol alginate NPs with doxorubicin, verapamil, and clonidine are also patented.

5. Carrageenan NPS

Carrageenan is an anionic, sulfated polysaccharide and is commonly isolated from red seaweed. It is mainly composed of D-galactose and 3,6-anhydro-D-galactose with glyosidic units. Carrageenan has been widely used for functional food applications and cancer treatments. Recently, carrageenan has also been used for several biomedical applications, which were intensively reviewed by Li et al.

The extraction procedure, structure, and subsequent product applications have also been discussed by Prajapati et al. (2014) in detail. Three different types of carrageenan are available, depending on the extraction procedure: kappa (κ), iota (ι), and lamda (λ) carrageenan.

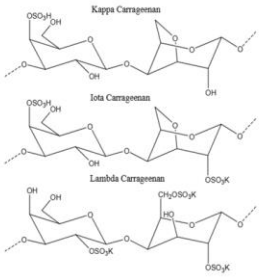


Figure 6. The structure of κ carrageenan, ι carrageenan, and λ carrageenan. The figures were adopted

A. Production of carrageenan NPs:

NPs formed by chitosan-carrageenan complexing have been studied for drug delivery purposes. These NPs can be prepared by the ionic gelation or polyelectrolyte complexing methods by mixing carrageenan with cationic polymers such as chitosan.

The developed NPs were stored at 4″C in an aqueous solution, and their size and zeta potential were measured. No statistically significant changes were observed in the size and zeta potential. This indicated that the stability of the NPs was not dependent on the mass ratio of polymers. In work from the same group, the addition of TPP to the chitosan-carrageenan mixture was observed to increase the stability of the NPs for over 250 days, suggesting that TPP can act as an effective stabilizer.

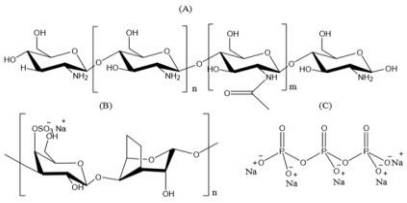


Figure 7. Structure of (A) chitosan; (B) carrageenan; and (C) tripolyphosphate (TPP). The figures

B. Carrageenan NPS as drug delivery vehicles:

The most widely used method to prepare carrageenan NPs is the polyelectrolyte method, which is very simple and requires mild conditions. In recent years, particular attention has been directed toward carrageenan-chitosan NPs for the delivery of drug molecules (Table 5). A very mild, feasible, and convenient polyelectrolyte method for the production of carrageenan–chitosan NPs was investigated.

Bulger et al. developed chitosan-carrageenan NPs by ionotropic gelation for the controlled release of recombinant human erythropoietin (rHu-EPO). The size of the developed NPs ranged from 200 to 1000 nm.

It has been reported that the prepared NPs were nontoxic to L929 cells. Moreover, ovalbumin was used as a model protein, and the loading efficiency of the ovalbumin varied from 4% to 17%. Cross-linked carrageenan nanogels were prepared using a microemulsion method. The size of the NPs was smaller than 100 nm. Chitosan–carrageen–TPP NPs by ionic gelation were developed. The size of the NPs was approximately 150–300 nm. Other carrageenan-based NPs for DDS have also been reported.

6. Fucoidan NPs

Fucoidan is an anionic, sulfated polysaccharide found in brown seaweed (e.g: Laminariajaponica, Macrocystis pyrifera, Fucus vesiculosus, and Ascophyllum nodosum). It is mainly composed of α-(1-3)-linked fucose units or repeating disaccharide units of α-(1-3)- and α-(1-4)-linked fucose residues with O-2 branches (Figure 8). It has excellent bioactivity, including antivirus, antitumor, antithrombotic, anticoagulant, anti-inflammatory, and antioxidant activity. Research on fucoidan for biomedical applications is still at the early stage of determining its exact function. Some studies have been conducted regarding fucoidan-based NPs for the delivery of curcumin, doxorubicin, and growth factors.

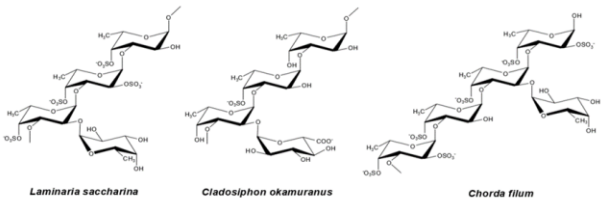


Fig. Structure of fucoidan.

A. Production of fucoidan NPs:

Chitosan/fucoidan-based NPs were synthesized using different types of methods, such as self-assembly, coacervation, polyelectrolyte complexing, ionic cross-linking, chemical modification, and emulsion. Pinheiro et al. developed chitosan-fucoidan NPs using self-assembly for the delivery of bioactive compounds. Lee and Lim et al. discussed the formation of chitosan-fucoidan NPs in two papers in detail. The size of the developed chitosan–fucoidan NPs ranged from approximately 365–900 nm. A 1:1 ratio of chitosan to fucoidan was the optimum condition to produce NPs with a small size, high yield, and good stability. They also found that pH5 was optimum to produce the polyelectrolyte NPs. Kimuraetal. developed fucoidan-based NPs and assessed their activity against osteosarcoma. The experimental results suggested that the fucoidan NPs were more effective than native fucoidan.

The particles were stable for a period of eight days. O-carboxy methyl chitosan/fucoidan NPs were prepared by ionic crosslinking and used for curcumin delivery (Figure9). The synthesized curcumin-loaded chitosan/fucoidan NPs dramatically increased the cellular uptake of curcumin. Fucolidan NPs by coacervation process and anionic emulsion polymerization were also developed.

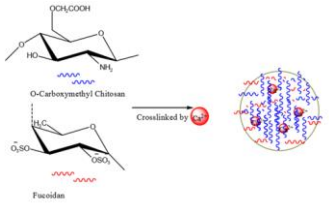


Fig. The formation of fucoidan NPs.

B. Fucoidan NPS for growth factor delivery:

A diverse set of fucoidan NPs for the delivery of growth factors has been reported (Table 7). Huang et al. developed chitosan fucoidan-based NPs as vehicles for stromal cell-derived factor-1 (SDF-1). In work from the same group, chitosan-fucoidan NPs were produced by a PEC process and used for nerve tissue engineering. The size of the NPs was approximately 200 nm. The developed chitosan-fucoidan NPs were nontoxic to PC12 cells at a concentration of 125 ng/mL. Fucoidan-chitosan NPs were also prepared by a PEC processs with sonication. BSA-loaded fucoidan-chitosan NPs showed a sustained release of BSA.

Table 7. Fucoidan NPs for growth factor delivery.

Serial number	Materials	Method	Size	Drug
1	Chitosan–fucoidan NPs	Polyelectrolyte complexing	200 nm	bFGF
2	Chitosan–TPP–fucoidan	Ionic gelation and polyelectrolyte complexing	173–403 nm	SDF-1
3	Fucoidan–chitosan NPs	Polyelectrolyte complexing	860 nm	BSA

C. Fucoidan NPs for Cancer Drug Delivery

A number of studies have reported that fucoidan itself has the capability of eliminating cancer cells by inducing apoptosis. Curcumin can be used as a natural anticancer drug, but its application has been hindered due to low bioavailability. To improve bioavailability, curcumin-loaded NPs have been attempted. The release of curcumin increases with increasing pH; while the release of curcumin from the chitosan-fucoidan NPs was inhibited at pH 1.2, its release was increased at pH 6.0 and 7.0. The encapsulation efficiency increased significantly to 92.8%. Curcumin was efficiently released from the chitosan-fucoidan NPs in a pH-dependent manner. In HCT-8 cells (MDR model cells) exposed to DOX-loaded AcFu NPs, a time-dependent cellular internalization of the drugs was observed. Over 99% of the total DOX load was internalized by the HCT-8 cells after 2 h, whereas 1.99% and 1.79% of a fucoidan–DOX mixture and free DOX were internalized, respectively (Figure 10A–D). Only the DOX-loaded AcFu NPs could be clearly identified in confocal images (Figure10E). However, these researchers mentioned that the mechanism behind this result was unclear mechanism.

Table 8. Fucoidan NPs for cancer drug delivery.

Serial number	Materials	Method	Particle size	Drug
1	Chitosan–fucoidan NPs	Self-assembled	Approximately 100 nm	PLL
2	O-carboxymethyl chitosan/fucoidan	Ionic cross-linking	270 nm	Curcumin
3	Chitosan–fucoidan	Ionic gelation	173 nm	Curcumin
4	Fucoidan NPs	Self-assembly	140 nm	Doxorubicin

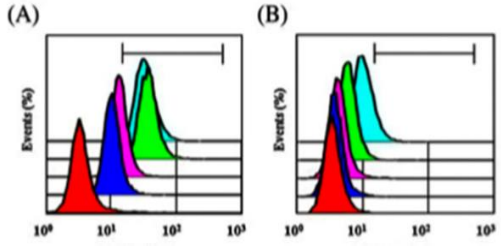
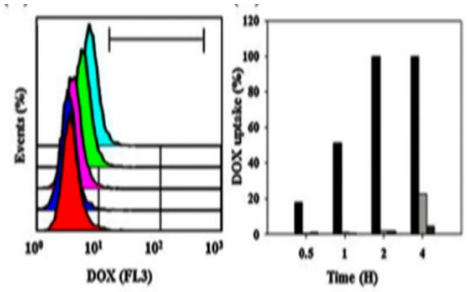
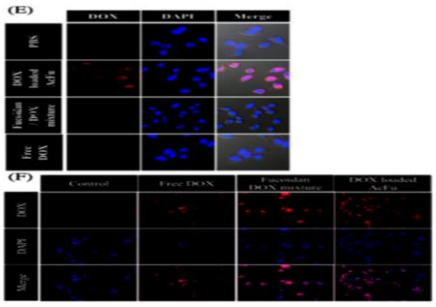


Fig. DOX (FL3) DOX (FL3)





(Black: doxorubicin-loaded AcFu NPs; gray: natural fucoidan–doxorubicin mixture; dark gray

The time-dependent cellular uptake efficiency of doxorubicin was estimated by FACS analysis. Flow cytometry analysis of cell streated with (A) doxorubicin loaded acetylated fucoidan NPs (AcFu NP); (B) natural fucoidan–doxorubicin mixtures; and (C) free doxorubicin. The colors in these graphs indicate the time after sample treatment: red—control; blue—30 min; pink—1 h; green—2 h; and sky blue—4 h. The uptake efficiencies at each time point are indicated by the bar graph in (D); (Black: doxorubicin-loaded AcFu NPs; gray: natural fucoidan–doxorubicin mixture; dark gray: free doxorubicin.); (E) Confocal images of doxorubicin uptake 4 h after treatment; (F) Confocal images of doxorubicin uptake in HCT-116 cells 4 h after sample treatment.

7. Future Research in Seaweed Polysaccharide NPs

Ionic gelation and PEC methods provide excellent

opportunities to produce large amounts of natural polymer-based NPs. There is a need for more in vivo research on carrageenan NPs and fucoidan NPs for further commercialization and use in clinical settings. However, there a several factors to be considered for developing natural polymer-based NPs, including the molecular weight of the polymers, addition time, pH, stirring speed, and temperature. To date, few in vitro, in vivo studies, and particle formation studies have been performed using alginate, carrageenan, and fucoidan NPs for drug delivery.

A. Active Targeting Molecules

Proper NP charge, size, and shape can improve drug delivery efficacy. In addition to those factors, engineering NPs with targeting moieties can significantly enhance drug delivery efficacy through the high accumulation of drugs in the targeted disease areas. In recent years, various targeting moieties, including peptides, small molecules, and polysaccharides themselves, have been incorporated into polysaccharide-based NPs to obtain targeted delivery. Somatostatin receptors, A54 hepato carcinoma binding peptide, RGD peptide, and small molecules (e.g., glycyrrhetinic acid and vitamin E succinate) have also been used as targeting moieties [40]. Polysaccharides such as chitosan have also been known to have a capacity to promote drug absorption in the small intestine due to muco adhesion.

B. Other Seaweed Polysaccharides

The seaweed polysaccharide NP preparations in this review were mainly based on combinations of chitosan and polyanions (e.g., alginate, carrageenan and fucoidan). The main reason to combine the chitosan and polyanions is to produce stable polymeric NPs, which can be achieved by the opposite charge interactions of chitosan and alginate. Developed NPs have been shown to protect the encapsulated materials and release drugs sustainably and effectively. Further advantages of the chitosan-polyanionic system include nontoxicity, biocompatibility and biodegradability.

Future research can be focused on the formation of NPs from other sea weed polysaccharide-based biomaterials, such as ulvan and laminarin. Different seaweed polysaccharides have their own merits and applications. Ulvan is an anionic polysaccharide and thus easily forms NPs with cationic polymers such as chitosan, which indicates its potential as a biocompatible drug delivery carrier.

8. Conclusion

The introduction of targeting moieties to polysaccharide-based NPs will improve their therapeutic efficacy while also reducing undesired side effects. In this review, we have discussed the production of various NPs using seaweed-based poly saccharides and their applications in drug delivery. The formation of seaweed polysaccharide-based NPs can easily be achieved by means of ionic gelation and PEC; these materials have the capacity to hold drug molecules and release them in specific locations. We believe that these methods will be increasingly utilized for the production of polysaccharide-based NPs in the future. Seaweed polysaccharide-based NPs have shown promising results in delivering proteins, peptides, anti-cancer drugs, and other drugs with increased bioavailability and sustained release properties. In particular, alginate-based NPs have extensively been studied for the delivery of anti-cancer drugs. In the last three decades, several studies have been conducted on seaweed polysaccharides both in vitro and in vivo; these studies have demonstrated the high stability and biocompatibility as well as sustained drug release achievable by these systems, which will support their future use in clinical settings.

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