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Review

A Critical Review on the Synthesis of Natural Sodium Alginate Based Composite Materials: An Innovative Biological Polymer for Biomedical Delivery Applications

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Abstract: Sodium alginate (Na-Alg) is water-soluble, neutral, and linear polysaccharide. It is the derivative of alginic acid which comprises 1,4-β-d-mannuronic (M) and α-l-guluronic (G) acids and has the chemical formula ($NaC_6H_7O_6$). It shows water-soluble, non-toxic, biocompatible, biodegradable, and non-immunogenic properties. It had been used for various biomedical applications, among which the most promising are drug delivery, gene delivery, wound dressing, and wound healing. For different biomedical applications, it is used in different forms with the help of new techniques. That is the reason it had been blended with different polymers. In this review article, we present a comprehensive overview of the combinations of sodium alginate with natural and synthetic polymers and their biomedical applications involving delivery systems. All the scientific/technical issues have been addressed, and we have highlighted the recent advancements.

Keywords: sodium alginate; natural polymer; biomedical delivery; gene delivery; biomedical application

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1. Introduction

1.1. Structure of Sodium Alginate

Alginate is a linear polysaccharide which is anionic in nature and is made up of 1,4-linked d-mannuronate residues and 1, 4-linked l-guluronates in different degrees having the linkage of α (1-4) [1–3]. Alginate is hydrophilic in nature, biocompatible [4], and eco-friendly to some extent. Its chemical formula is $(C_6H_7NaO_6)_n$ with the average molecular weight of 216.121 g/mol, and this weight variation depends upon strains and conditions which are adopted.

In the 1880s a patent was released by Stanford, which had discovered alginic acid [5], and after it, a modification was done and sodium alginate was derived from that alginic acid in 1895 whose linkage was α(1-4) of glucuronic acid.

1.2. Sources of Sodium Alginate

Sodium alginate ($NaC_6H_7O_6$) is a linear polysaccharide, a derivative of alginic acid comprised of 1,4-β-d-mannuronic (M) and α-l-guluronic (G) acids [6–10]. Sodium alginate is a cell wall component of marine brown algae and contains approximately 30 to 60% alginic acid. The conversion of alginic acid to sodium alginate allows its solubility in water, which assists its extraction. Sodium alginate a typical polysaccharide, allowing it to be very extensively used in every field which requires having a linkage of 1-4 linked b-D-mannuronic acid (M), and at its C-5 epimer, there is a group present named L-guluronic acid (G). Sodium alginate has been extracted from different sources of algae and in different compositions. E.g., it was extracted from sargassum with the composition of 30–35% [11]. That is rich source of sodium alginate. The other sources of sodium alginate are *Ascophyllum nodosum* (22–30%) [11], *Laminaria Digitata* (25–44%) [11], *S. baccularia* (23.9%), *S. binderi* (28.7%), *S. siliquosum* (38.9%), *T. conoides* (40.5%) [12], *Sargassum muticum* (13.57 ± 0.13%) [13], *Durvillaea Antarctica* (30–55%), *Durvillaea willana* (30–55%) [14], *Turbinaria* sp (22.69 + 2.12%), *Sargassum* sp (24.56 + 0.56%) [15], *Laminaria Digitata* (51.8%) [16], *C. implexa* (29.15%), and *L. variegate* (27.57%) [17].

1.3. Properties

Sodium alginate is a linear [11], pH-sensitive [12], water-soluble [13], non-toxic, biodegradable [14], hydrophilic [15], biocompatible [5], safe, perishable, non-immunogenic [16,17], cost-effective bioadhering, poly-anionic copolymer [18,19] polysaccharide. Na-Alg has chelating ability, low-cost transparency [20], ease of gelation [21], mucoadhesion [22], thickening ability, and film making ability. It has the properties of a stabilizing nature, high viscosity in water, and a gelling negotiator. In the presence of a gastric environment, the hydrogels that contain sodium alginate have a property of very slow delivery of drug discharge. Na-Alg is thermally stable.

1.4. Application of Sodium Alginate

This novel polysaccharide has potential applications in all aspects of food, drug delivery [23], gene delivery, tissue engineering [24], and wound dressing [25–27] and for wastewater treatment [28]. Na-Alg has novel applications in the field of drug delivery; for instance, it has been used for the delivery of 5 FU [29], Cur [30], anticancer agents (microcapsules) [31], ibuprofen [32], and RIF. The drug delivery technology of sodium alginate plays a key role in the field of biotechnology. It is used for slow drug release. Na-Alg is used for intestinal drugs [2], leukemia [33], immunotherapy, NRT, and hepatocarcinoma cells as a drug delivery agent. This polysaccharide also has some great applications in the field of gene delivery concerning the identification of protease cancer, theophylline sensing, topical chemotherapy [34], probiotic bacterial growth, anti-viral drug delivery—HIV/AIDS, treatment of MDR gastric cancer, anti-tumor chemotherapy, and others [35]. Wound dressing and wound healing applications can be more achievable by using this polymer [36]. Na-Alg can be used in wound dressing and wound healing applications, including the transplantation of OE-MSCs cells [37]; multifunctional scaffolds in tissue engineering [38], soft tissue engineering, and bone tissue engineering [39]; 3D bioprinting [40]; neuro-regenerative applications; mechanical filling in cartilage regeneration [41]; in vivo wound healing; treating numerous irregular and chronic wounds; and alkali burns and other types of serious eye injury.

1.5. Drawbacks

Due to various types of drawbacks, this polymer has limited use in industries. Sodium alginate is used in various medicines, but after use it tends to cause gastrointestinal side

effects, such as bloating, diarrhea, and nausea. As it is derived from alginic acid, it has an acidic character that is not good for healthy foods. Its properties include low mechanical strength and cell adhesion [5], a low level of drug loading, hydrophilicity, microbial degradation, and burst release [42,43]. To overcome such problems, sodium alginate has been blended with different types of synthetic and natural polymers, and they enhance its properties.

2. Blends and Composite of Na-Alg

Na-Alg has been reported to blend with various types of synthetic and natural polymers to enhance its mechanical strength and improve its adhesion properties. It is blended with different types of cheaper materials to give them mechanical strength. It can be used to make blends, hydrogels, micelles, nano-carriers, nano-gels, nano-composites, nanoparticles, tubes, cationic systems, aerogels, etc., which all exhibit its excellent properties when used in drug delivery and in gene delivery, bone and tissue engineering, and food technology. This polymer has promising blends and composites for the wastewater treatment—hydrogels, composites, and blends have been made to remove different types of pollutants, especially organic and inorganic and dyes. Na-Alg coating also becomes more impressive by adding different sorts of antimicrobial agents. The different sorts of sodium alginate composites exhibit much functionality in a different type of cancer and diabetic management. This polymer displays many applications in drug carrying and chemotherapeutic and stem cell treatments. For food, this polysaccharide helps with gelling and food packing. This polymer blends and forms composites with different types of materials to remove the organic pollutants and to confiscate metallic and organic dyes from aqueous solutions that have been listed in Table 1 [44–127].

Table 1. Main applications in medicine for sodium alginate composites

Composite	Characterization Techniques	Properties/Applications	Ref.
Na-Alg/cisplatin	UV, SEM, TEM, Zeta Potential, DLS, ICP-MS	Use for chemo/radiotherapy of proliferating macrophages	[44]
Na-Alg/Graphene oxide/poly(*N*-isopropyl acrylamide)	TEM, FTIR, XRD, DSC, SEM	used as a drug carrier for controlled delivery of bioactive agents to a specific target.	[45]
Na-Alg/PVA	FTIR, TGA	implantable drug-releasing scaffolds in tissue engineering, and as wound dressings in biomedical engineering applications	[46]
Na-Alg/Psyllium-fenugreek	PCR, EE, OM	Use for enhancement of probiotic bacterial growth in the gastrointestinal environment.	[47]
Na-Alg/CS/DOX	SEM, CI	BSA-gel-capsules for the treatment of drug-resistant breast cancer.	[48]
Na-Alg/g-allylamine-mannose/Zn	FTIR, XRD, DLS, SEM, TEM, CU, Zeta Potential	new way for TB treatment with micronutrient Zinc supplementation.	[49]
Na-Alg/Glycol Chitosan Stearate/Amphotericin B	SEM, TEM, CU	therapeutically applicable AmB delivery approach for safer and cost-effective chemotherapy of visceral leishmaniasis.	[50]
Na-Alg/cellulose nanofibres	SEM, AFM, DSC, TGA, FTIR	Use as scaffolds for tissue engineering applications, as drug carriers, or for wound dressing applications	[51]
Na-Alg/bioapatite/ZnO microparticles	XRD, SEM, TEM, FTIR	Gene delivery composites	[52]
Na-Alg/casein/ silver	XRD, TGA, SEM,	Use for antioxidant activity and make bilayer edible films	[53]
Na-Alg/MWCNTs	SEM, LSV, DSV, CV	Use theophylline sensing	[54]

Table 1. *Cont.*

Composite	Characterization Techniques	Properties/Applications	Ref.
Na-Alg/Hidrox-6	DSC	Use for topical chemotherapy, anti-aging, and prevention of ultraviolet light-induced skin diseases.	[55]
Na-Alg/MaterBi®	SEM, TGA, FTIR, AFM	potential wound care materials or in the area of hygienic packaging of certain pharmaceutical products.	[56]
Na-Alg/hyaluronic acid	PCR	promising modality of treatment for cartilage tissue regeneration and repair	[57]
Na-Alg/GMSCs/hBMMSCs	SEM	used as a novel treatment modality for biofilm-mediated peri-implant bone loss.	[58]
Na-Alg/PVP	NMR, CLSM, TEM, DLS	optimize IPN hydrogels devoted to the release of active agents.	[59]
Na-Alg/Fenugreek seeds/Psyllium Seed	PCR, OM	enhancement of probiotic bacterial growth in the gastrointestinal environment.	[60]
Na-Alg/methylcellulose	Hmsc, SEM, CLSM	improve the functionality of the plotted cell-matrix constructs.	[61]
Na-Alg/marine collagen/agarose	PCR, CLSM, FTIR, SEM	effective 3D cell culture of various normal and pathological cells, drug screening, and regenerative medicine applications.	[62]
Na-Alg/SO_3HCl	FTIR, CLSM, SEM	broad implications for regenerative medicine.	[63]
Na-Alg/clay	FTIR, SEM, TGA	applications in the medical field such as in controlled-release medications could be further expanded.	[64]
Na-Alg/N-Hydroxy succinimide/MTT	FTRI, TEM, CFM, Zeta Potential	promising candidates for anti-viral drug delivery system for HIV/AIDS therapy.	[65]
Na-Alg/Fe_3O_4/Chitosan	TEM, NMR, CLSM	useful as therapeutic agents to treat MDR gastric cancer by reversing chemosensitization	[66]
Na-Alg/g-Poly(N-isopropylacrylamide)/Doxorubicin	SEM, CLSM,^{1}H-NMR	useful means for the development of various delivery vehicles suitable for cancer therapy.	[67]
Na-Alg/Lactate oxidase/lactic dehydrogenase	PCR, UV, HPLC	potentially useful for different biomedical applications	[68]
Na-Alg/zataria essential oil/Agar	FTIR, AFM, ABTS, Zeta Potential, TGA, DTA	Use as a medicinal food for the treatment of oxidative stress or as a bioactive food packaging materials.	[69]
Na-Alg/PEG	FTIR, SEM, CLSM	Use as large-scale stem cell culture for tissue engineering and cell transplantation.	[70]
Na-Alg /$FeCl_2{\cdot}4H_2O$/ $FeCl_3{\cdot}6H_2O$	FCM, FTIR, TGA, SEM, CLSM	great potential for clinical application in anti-tumor chemotherapy.	[71]
Na-Alg/5-Fu	SEM, EDX, XRD	excellent MR-visuality and multi-drug chemoembolization.	[72]
Na-Alg/PLGA	SEM	Use as Controlled and Sequential Delivery of Fluorophores	[73]

2.1. Gene Delivery

2.1.1. Aerogels

i. Cisplatin-Based Na-Alg

Atherosclerosis is a disease in which the arteries become rubbery and the lipid elements collect in the arteries, and it is the fundamental reason for 50% of death in the Western world. The sub-endothelial accretion of the saturated fat by distended macrophages is how the initial phase of the atherosclerosis is marked; it advances through suave muscles cells and the creation of plaque with necrotic debris [74]. In addition to atherosclerosis, the macro phase plays an important role, which compounds the difficulties of thrombo-occlusive conditions that will cause myocardial infarction and stroke, and so might be a precise appreciated therapeutic target. The scheme used for the cure of atherosclerosis involves macrophages [74]. For the curing of cancer, cisplatin is extensively used, as it is a drug founded on platinum whose treatment system comprises mainly ordinary regimens, sometimes with radioactive treatment. Through the cross-linking of the deoxyribonucleic acid, cisplatin has action on the cell, and as a result, deoxyribonucleic acid is impaired. Radio-sensitizing also gets used alongside cisplatin. Cisplatin has an affinity to produce cross-linking with sulfhydryl and carboxyl groups via the nitrogen atom, which is precise for deoxyribonucleic acid and proteins; their combination in polymers provides control [75], and another transporter is used to overcome the special effects of the drug, for instance, nephron-toxicity, and to overcome the resistance to the drug [76]. Alginic acid is acquired from seaweed, which is recognized for being in-expensive, biocompatible, and non-toxic; alginic acid is a polymer [77]. Alginate gelatinates in the presence of cations—for example, Ca^{2+} [77]. Choi et al., 2018 [44] synthesized the cisplatin base Na-Alg nano-gels for chemotherapy. These nano-gels are pH-responsive. Cisplatin has been used as an antiproliferation agent and acts as a crosslinker between the matrix of sodium alginate. These nano-gels had been used to treat the proliferating macrophages. When cisplatin was mixed with Na-Alg, it formed the TANgel. IDA has been mixed with the alginate base cisplatin—cisplatin acts as a crosslinker and forms TAN gel, and these gels are a promising material with which to release drugs and to use for chemotherapy. Drugs have been loaded onto that nanogel to target other diseases.

2.1.2. Beads

i. PNIPAM-Based Na-Alg

The polymer that is based on graphene oxide (GO) is greatly superior to the polymer that is based on a nanofiller polymer, owing to GO's compatibility with the polymer and advantages in the thermal, electrical, and mechanical properties of these polymeric matrices. Polymer matrixes that were founded on GO have been used in countless biomedical applications—for instance, gene and drug delivery, bioimaging, nano-medicine, and the treatment of cancer [78]. It was exposed through gossip that in the applications of tissue engineering drops of GO calcium alginate and the hydrogels are used [79]. The nanocomposite material which is based on GO is also used in the medication delivery application of 5-FU.

This nanocomposite material, which has excellent features and novel applications, is mostly used for biomedical applications. That material will lessen a medicine's dosage, and this material also decreases the poisonousness of medicine [80]. Consequently, for the controlled drug application the investigation is accompanied by the development of PH and temperature-receptive polymeric nanocarriers [81]. The mono responsive polymeric nanocarriers have fewer applications than the dual responsive polymeric nanocarriers, and they are also given more intensive attention and consideration owing to their extensive probable uses [82]. Rao et al., 2017 [45] synthesized the PNIPAM-based Na-Alg beads in which GO mixed with them, and these biocomposite beads are dual responsive in nature. These beads had been prepared by using the ionotropic gelation technique. The calcium chloride acts as a cross-linker in these composite beads. These beads are very compatible with the HeLa cancer cell line and use for target drug delivery. The dispersion of PNIPAM

with Na-Alg was done with various concentrations, 2, 4 and 6%, which had been taken by weight percentage, and Ca^{2+} act as a cross linker in it.

2.1.3. Blends

i. PVA-Based Na-Alg

In the field of tissue engineering, three-dimensional scaffolds must be industrialized as a possible candidate for curing injuries to organs and tissue. The scaffold will deliver support to the tissue and they are used as templates to improve the communication of cells [83,84]. It is regulated by the mechanical and chemical properties of the scaffold, which it must improve to restore the functionality of the organ and tissue. These blends have been designed with engineering procedures [85]. This constructs the scaffold, which is three dimensional, and the bioprinting method has been used for the tissue engineer's control of the construction of the scaffold at a small scale. For CAM (computer-aided manufacturing) and CAD (conventional computer-aided design) programs, the three-dimensional scanner system has been used for the construction of the scaffold [86]. Additionally, three-dimensional printing bio-inks are used for numerous biomaterials. Seok et al. [46] synthesized the PVA base Na-Alg blends and used them for the fabrication of a 3D scaffold. These blends were prepared by using the post crosslinking method. This scaffold was observed at different intervals of time before post crosslinking and after post crosslinking for 12 h. These blends are very useful for the fabrication of 3D scaffolds and for tissue engineering applications.

ii. Fenugreek-Based Na-Alg

Some microorganisms provide advantageous consequences to health; they are probiotics. Some probiotics belong to the Lactobacillus group. In the protection of the food, this group of microorganisms has been utilized for thousands of years. These microorganisms have some interesting characteristics—for instance, the broadmindedness in the direction of the excretory enzymes' dilapidation and confrontation with the intestines' acidic and bile-containing environments [87]. The matrix which is summarized does not act as a defense, in contradiction to the punitive circumstances of the stomach; nonetheless, there is an upsurge of probiotic microorganisms in the numerous circumstances of dampness and heat throughout the storing and the dispensation time [88]. Psyllium was removed from the *Plantago* genus, and its physiological use is as a herbal gel. Psyllium has a constitution like arabinoxylan, which contains a side chain of arabinose and a backbone of xylose. In numerous cultures, the probiotic benefits of psyllium are known very well—after the ingesting of psyllium to extravagance, one decreases the risk of certain complaints regarding the gut, for example, diarrhea, chronic diseases of the kidney, constipation, irritable bowel syndrome, and ulcerative colitis [89]. For the medium of probiotic encapsulation, psyllium is a good candidate because of its effects on the human gastrointestinal tract's health and probiotic nature. Temporarily, fenugreek is removed from the kernels of Fenugreek, and it is a biopolymer. The fenugreek polymer has a side chain of D-galactopyranosyl and a backbone structure made of D-mannan. Comparably to psyllium, some prebiotic factors were also demonstrated with the fenugreek polymer and have been utilized in nutritious complements and in animal husbandry. Fenugreek secretions have been used for the diabetes treatment and regulation of the level of cholesterol by many practitioners. Moreover, due to the robust activity of the blending and the strong aptitude [90], for the manufacturing of food this gel acts as a stabilizer. Haghshenas et al. [47] synthesized the psyllium–fenugreek based Na-Alg blended for the microencapsulation of probiotic bacteria *Lactobacillus plantarum*. It is used to enhance oral delivery and for colonic release. To produce these blends the agr diffusion method had been adopted. It is used to check for 16S rDNA genes. These blends are used to grow the probiotic bacteria.

iii. CS-Based Na-Alg

Cancer is the most widely recognized disease in women; breast cancer affects 1.38 million women overall every year [91]. Over the last 20 years, the usage of screening programs and the advancements of new treatments have essentially diminished the mortality rates of

women in the Western world. However, the protection provided from these treatments is a developing and major problem [92]. They provide resistance, yet the cancer might still be procured. Certainly, at least 30% of women are influenced by breast cancer in early stages (sickness), and protection from helpful operations can in 25% of all situations [93,94]. The frequency of protection from therapeutics is enhanced with aliment progression. A high refractivity index associates with the greatest mortality rate. In 2008, after lung cancer, the incidence of breast cancer was 12.9/100,000 [95]. Breast cancer is a heterogeneous disease. It is divided into three main subtypes clinically. First, it is determined by the expression of hormone receptors, in particular, progesterone and estrogen; secondly, by "human epidermal growth factor receptor 2 (HER2); and thirdly is triple-negative breast cancer. They express none of all above mentioned receptors [96]. The subtypes of breast cancer are further subdivided—for instance, basal-like, enriched by "human epidermal growth factor receptor 2," luminal A, and luminal B. Very recently, breast cancer was classified into different 10 subdivisions [97]. In this way, they only considered three main clinical sub-divisions to clarify their treatment. Every subdivision has a different treatment strategy from other subdivisions. The best treatment for the hormone receptor-positive breast cancer is endocrine therapy, and the best method for the treatment of "human epidermal growth factor receptor 2-poisitive" cancer is "trastuzumab" (Herceptin; Roche, Basel, Switzerland). The best method for the triple negative breast cancer is the conjunction of all above-mentioned therapeutics with ordinary cytotoxic chemotherapeutics. These cytotoxic chemotherapeutics include taxanes and anthracyclines [94]. In this way, there is an outline of chosen instruments and mechanisms of the basic drug resistance in every one of these various groups. It highlights the basic and main mechanisms that particularly concentrate on the role of the pathway of the "phosphatidylinositide 3-kinase (PI3K)/Akt," an epigenetic alternation in resistance of drug and miRNAs in breast cancer. They also provide information related to the interactions that contribute to a multidrug-resistant phenotype. The identification of potential targets for new adjuvants and new methods of therapeutics will be emphasized to restore each subtype's sensitivity to current treatment.

The molecule of BSA is made up of 583 amino acids that bind in a single long chain cross-linked with residues of 17 cystines (such as one free thiol group and eight disulfide bonds); 66,400 Da is the molecular mass of BSA [91]. The chain of amino acids consists of three structurally discrete domains (I, II, and III) but they are homologous. These are divided into nine different loops that are connected with disulfide bonds. They arranged in a heart shaped molecule. Every discrete domain is made up of two sub-domains A and B. The secondary structure of protein is mainly α-helical (that makes up the 74% of the whole molecule) and combines with the residues of the polypeptide chain that occur in turns and in flexible and extended regions present between the sub-domains [91]. The characteristic structural properties of BSA are important. Their characteristic structural properties are low glycine, tryptophan, methionine, and isoleucine. On the other hand, BSA is abundant in ionic amino acids, for example, lysine and glutamic acid. Due to these ionic residues, the protein has a greater total charge; i.e., at neutral pH its molecular weight is 185 ions per molecule. This molecular weight contributes to its solubility [91]. It is one of few proteins with a deficiency of carbohydrate groups, because it is manufactured or synthesized in the liver without combining any other additives or prosthetic groups. In this way, BSA is a globular non-glycosylated protein. Drugs, hormones, fatty acids, and xenobiotics are some examples of endogenous and exogenous compounds [97]. If numerous endogenous and exogenous compounds enter the bloodstream at once, they are transported and discharged, which is of significance for the formation of a complex with serum albumins. The function of this class of proteins is to maintain the pH of the blood and also to contribute to the colloid blood osmotic pressure. However, the most important property of albumins is that they combined with different compounds in a revocable manner. In the plasma, this protein often enhances the ostensible solubility of hydrophobic drugs and effects the circulation, efficacy, and metabolism of the drugs. In mammals, the serum albumins are also involved. They are utilized to control the ionized and biologically active concentrations of Mg^{2+} and

the concentration of Ca^{2+}. It has already been demonstrated that the affinity of drugs for plasma proteins is directly affect the concentrations of said drugs in the bloodstream and their biological effects. Usually, the effect of weak protein binding has a short lifetime and poor distribution, and on the other hand, the effect of strong protein bindings leads to reducing the concentration of drugs. They demonstrated the pharmacological activity because it was the unbound fraction of the drug. BSA demonstrates different binding sites with discrete specificities. The most important binding sites are represented as site-I and site-II. They are located in the cavities of hydrophobic subdomains, i.e., IIA and IIIA respectively.

Doxorubicin is represented as one of the most important and potent drugs that has been approved by the Food and Drug Administration among chemotherapeutic drugs. In its unaltered form, it demonstrates great potential for treatment [97]. Its functions of quickly separating cells and moderating disease progression have been widely recognized for quite a few years. It is only restricted due to its poisonous quality for non-cancerous cells in the human body. It is a drug from class I; it is a non-selective anthracycline that possess sugar moieties and aglycone. The sugar component is also known as daunosamine. The sugar component is attached to one of the rings with the help of a glycosidic bond. The sugar component is mainly composed of a "3-amino-2,3,4-trideoxy-L-fucosyl moiety." On the other hand, aglycone is mainly composed of a tetracyclic ring with the help of adjacent group of "quinine-hydroquinone" and the substituent of methoxy as a short side chain that is followed by the carbonyl group. Shen et al., 2018 [48] synthesized the CS-based Na-Alg that is used for the treatment of breast cancer. It was used to treat the MCF-7 breast cancer cell line and to treat ADR cells. The BSA capsules were loaded at an optimum pH of 6.5 and they released at pH 5. In the capsule shell, the CS/Na-Alg blend is present; it then disperses. They had been loaded in mice to check their effects.

The treatments of the MCF breast cancer line were done by taking different parts of mouse breasts and checking them out for 24 days with saline, without DOX and with DOX capsule-loaded blend.

2.1.4. Cationic System

i. Allylamine-Mannose-Based Na-Alg

MTb (bacillus *Mycobacterium tuberculosis*) resides in humanoid alveolar macrophages [98]. Bacillus *Mycobacterium tuberculosis* is homicidal; according to the World Health Organization, the most severe communicable disease is tuberculosis [99]. There are four main medicines, RF (rifampicin), pyraz-inamide, iso-niazid, and isoniazid, in use in the treatment of tuberculosis, and they are used over an extended timeframe. Rifampicin is described as a potential drug amongst these medicines. Rifampicin's mechanism is to constrain the transcription of the genes by inhibiting the β-subunit of the microbial ribonucleic acid polymerase [100]. If an adequate quantity of rifampicin is not transported into the cell, it is not operational. In accumulated, rifampicin has an enormous number of disadvantages, such as poor bioavailability and poor solubility. To overcome the disease, some new treatment still needs to be industrialized. To cure tuberculosis via expanding the anti-tuberculosis medications, alveolar macrophages' rifampicin has been measured with a new method, medication carriage. This method also makes possible a reduction in the resistance to the medicine and reduces the opposing consequences connected to the rifampicin—for instance, hepatotoxicity. The distribution of the medicine is done through an outstanding primarily absorbed system on the measured medicine distribution, which takes the drug to that organ which is preferred to exploit beneficial effectiveness and to diminish the opposing outcome. Fabrication of the system of the medicine distribution is absorbed upon skillful delivery of the medicine to the board site. The investigators in the last insufficient periods tied the robust importance of the distribution of the medicine to the method of distribution of the medicine and the precise distribution of the medicine. For the rheostat distribution of medicine, particles in minor amounts stick to the well-ordered distribution of medicine; this is applicable to the action of cardiovascular illness, the distribution of

a healing protein, in the expansion of a vaccine, chemo-therapy, and hormone treatment. Conjugation of that polymer which is small with that ligand which is targeted must be stimulated. The solubility of a hydrophobic medicine is recovered by the conjugates of a polymeric ligand; it defends the medicine and the bioavailability will be shrunk [101]. Rajan et al. [49] synthesized the allylamine-mannose base Na-Alg by using zinc as a cross linker, which acts as the Zn^{2+} for the nanotheraphy of tuborcolusis. This copolymer was synthesized by atom transfer free radical polymerization, and coupling was done with conjugates. This copolymerization was done in the presence of a catalyst named sodium acetate with the pH of 4.0.

This copolymer was attacked by a cross linker named Zn^{2+}; then a drug RF was loaded on this cross-linker polymer; and then the drug was released in the body with macrophages. It showed potential defense against *M. tuberculosis* and a promising material for TB treatment.

ii. Amphotericin B-Based Na-Alg

Leishmania spp. are compulsory intracellular vermin of macrophages which cause a wide range of diseases in humans, such as CL (localized cutaneous leishmaniasis), VL (visceral leishmaniasis), ML (mucosal leishmaniasis), self-healing skin lesions, and cutaneous leishmaniasis. On the T cell, all types of disease control and resistance depend [102]. GC (glycol chitosan) is obtainable commercially for the distribution of the medicine that is a derivate of usual polymer, biodegradable, biocompatible, soluble in water, and has been used as a scaffold. Stearic acid has a long acyl group that delivers the communication from the amphotericin to the copolymer; it is accountable for the more continuous release for AmB (amphotericin B) [103]. The co-polymer of GCS (glycol chitosanstearate) was synthesized; it is recognized to form self-assemblies. Gupta et al., 2015 [50] synthesized the amphotericin B-based Na-Alg cationic polymer in which glycogen chitosan had been encapsulated by using strong electrostatic interaction, and it was used to treat the cell line J774A. Sodium alginate was mixed with the glycogen chitosan acetate by inotropic gelation and by hydrophobic interaction; they mixed that with amphotericin B. These are very useful for treatment in visceral leishmaniasis and for better chemotherapy.

2.1.5. Composites

i. Cellulose Nanofiber-Based Na-Alg

Cellulose is mainly isolated from plants [104] and it is also released from several microorganisms. Cellulose has been converted into numerous nanostructures, for example, nanoparticles, films, nanofibers, hydrogels, aerogels, nanocrystals, nanowhiskers, and so on [105]. As we know, among the numerous nanostructures derived from cellulose, the cellulosic nanofibers have been most broadly utilized because of their excellent properties. They demonstrate the properties of having flexibility, the possibility of blending, chirality, low thermal expansion, excellent mechanical strength, the possibility of functionalization, thermo-stability, and biodegradability. For numerous applications, the cellulose nanofiber (CNF) has been used as a potential matrix. It has many biomedical applications, such as those in drug delivery, biomedical materials, protective coatings, antimicrobial activity, transparent films, filtration media, nanofillers, energy storage, optoelectronic packaging, barrier membranes, pharmaceuticals, and bioimaging [106]. The cellulose nanofibers (CNFs) show the properties of low cost, having low density material, being renewable, and being less rough. They also demonstrate the properties, for example, of biocompatibility, wettability, purity, crystallinity, and tunable surface structure, and have powerful consequences in numerous environmental applications. The most important property of cellulose nanofibers (CNFs) is biocompatibility, which makes them extremely suitable for countless biomedical applications, particularly in scaffolds for tissue engineering. This property is also helpful and very much important for its environmental applications. If we study the membranes for water purification and filtration systems, the cellulose nanofibers (CNFs) discharge the toxic materials but do not eliminate that toxicity. In this way, the treated water becomes unsuitable for the consumption of human beings. According to

environmental aspects, highly pure cellulose nanofibers (CNFs) are the most important components. This fact is most important because if the purity of cellulose nanofibers increases, they increase the thermal stability of the fibers [107].

Rw (rice water), a decoction of rice, is described as an antique normal drug, as a refrigerant and demulcent in inflammatory and febrile sickness in folklore practice [108]. It is described that rice water comprises numerous metals—iron, sodium, potassium, zinc, manganese, calcium, etc. Yadav and Maji, 2019 [51] synthesized the cellulose nanofiber-based Na-Alg biocomposite. Sodium alginate had been taken from an egg box and had a suitable interaction with the CNFs and starch, and a honeycomb structure formed due to this interaction. These are used to treat bacterial infections, i.e., those of *E. coli* and *P. aeruginosa*, and for potential wound dressing applications.

ii. Bioapatite-Based Na-Alg

BT (bone tissue) is a compound of unusual material that has a constituent which is organic collagen, type I, where the crystals of minor size of nonstoichiometric hydroxylapatite biological apatite are entrenched [109]. Having said organic constituent, this construction (bone) us strong in tautness, and due to the inorganic constituent, it is strong in density. An amount of inorganic ions is in the biological apatite—for instance, Mg^{2+}, Zn^{2+}, Na^{+}, K^{+}, Ba^{2+}, Fe^{3+}, Sr^{2+}, and Ca^{2+}. It should be noted that the presence of an insufficient amount of such ions, specifically, ions of Mg, Cu, Zn, and silver, has an important effect on bioapatite's construction [110]. The ion of zinc is donated to raise the density of the BT and stop loss of mass from the bone; the antibacterial activity will rise, as will the recovery of the bonds of proteins [111].

Drugs that have antimicrobial actions are used very widely, leading to the formation of microorganisms resistant to an extensive variety of antibiotics. There is active exploration to resolve this problem with the constituents of the inorganic antimicrobials or to provide antimicrobial activity ions and to induct a skillful reaction in tissues by the inorganic ions, which constitutes bioactive usage for the alteration of biomaterials [112]. Pogrebnjak et al. [52] synthesized the bioapatite-based Na-Alg biocomposite by using microwave irradiation and by reactionary suspension using ultrasonic treatment. Zinc oxide powder was mixed with Na-Alg/HA solution; then cross linking was done; and they formed the beads. The zinc oxide nanoparticles were formed using a co-precipitation method.

The antibacterial mechanism of zinc oxide nanoparticles is very beneficial in terms of release of drug by wrinkling the cell wall. This biocomposite was used to treat the NIH-3T3 cell line and showed an excellent antimicrobial effect against S. *aureus.*

2.1.6. Conjugates

i. Casein-Based Na-Alg

Bora et al. [53] synthesized bilayer edible conjugate films of casein-based Na-Alg with silver. At a temperature of 80 °C, these edible films were formed. These films are very useful for loading antioxidants and help in sensitive product packing.

2.1.7. Films

i. Polyarginine-Based Na-Alg

1, 3-dimethyl-3,7-dihydro-1H-purin-2,6-dion (Theophylline) is recognized as a class of byproducts of methyl xanthine; it is obtainable extensively in the landscape. The ophylline is the adherent of usual alkaloids; in cocoa beans and tea it is present in large quantities [113]. In A1, A2, and A3 receptors the ophylline antagonizes as a nonspecific adenosine antagonist. For adults, one breathing sickness is known as COPD (asthma and chronic obstructive pulmonary disorder). In addition, for asthmatic severe-stage treatment and baby apnea treatment, breathing stimulators are used. In order to be effective as a born chodilator, the level of the ophylline in plasma is taken. In the serum, the extraordinary amount of 20 g/mL will be problematic, which can be present with, for example, coma, anorexia, heartburn, and breathing or cardiac arrest. Theophylline, through a simple,

precise, rapid, and luxurious method, is significant in medicinal affairs. The method of molecular imprinting is recycled in the molecular recognition stage, through self-assembly of that monomer which is useful around a template particle over the communication among their useful assemblies. In the devices, this equipment has been industrialized for usage, and it delivers improved understanding and discrimination. MIP (molecularly imprinted polymers) benefit from the comfort of training along with the decent constancy in mechanical and physiochemical properties. Additionally, through the groundwork of molecularly engraved polymers by the electro-polymerization, for the alterations resulting from disorders, it is conceivable to enhance the breadth of polymers and the morphology of the polymer, which is very final upon the final device's creation. Poly-arginine enjoys exclusive properties as a conductive polymer, such as biocompatibility, non-toxicity, conductivity, and biodegradability [114]. Kazemipour et al., 2019 [54] synthesized the MWCNTs-based sodium alginate films for the reason of sensing theophylline. Polyarginine was also mixed in to accomplish these films. These films were invented by a mathematical modeling process. MWCNTs are mixed with Na-Alg, and then in the presence of polyarginine form GCE, and their electropolymerization occurs after that. At last, rebinding extraction happens, and these films are complete. These films are promising for targeted drug delivery.

ii. Hydroxytyrosol-Based Na-Alg

Up-to-date chemotherapy can involve the request of a drug applied to the skin. This is accepted through the FDA (Food and Drug and Administration): binary creams for basal cell carcinoma: imiquimod and 5-fluorouracil creams in 1970 and 2004, correspondingly. It was found by the revisions that the ointments which are anti-cancer decrease the universal side effects that are related to the conservative chemo-treatment and can allow possibly for the evasion of aggressive medical events [115]. At-home patients are self-treated; nonetheless, the recurrent solicitation provides clues to the cross consequence which is opposing, for example, superficial erosions and erythema at the affected site [115]. Certain patients' annoyance from pruritus means that they need close follow-up throughout the course of the cure to screen for the response to the prescription. As proven by the consequences in patients with skin cancer, for the management of the blood cancer up-to-date chemotherapy is practical [116]. The breast is not a difficult to access organ; consequently, the authorization for the skin of the breast in the zone which is beleaguered is a means for the distribution of the medications. Alongside breast cancer chemotherapy comes radiation, conservative chemo-treatment, and surgery.

Hidroxl is acquired from the fresh olives liquids and it is an original restriction preparation of olive polyphenols which is dehydrated; CreAgri was presented to the market. The antioxidant particle hydroxyltyrosol is in the hidroxl, which has action of the antioxidant ORAC (oxygen radical absorbance capacity) of 27,000 mmole TE per gram, or 13 times greater than the ascorbic acid oxygen radical absorbance capacity 2100 mmole TE per gram. 4-(2-hydroxyethyl)-1,2-benzenediol and hydro-xytyrosol are phenolic antioxidant molecules which originate in the olives, and exert numerous pharmacological and biological activities. It has been established that 4-hydroxytyrosol has anti-cancer activity which is reliant on the amount, and it is accomplished by persuading cells of apoptosis and constraining proliferation in humanoids and growth cell lines M14 and MCF-7, cells of hominid breast cancer, and HL60, cells of human myeloid leukemia. To defend from the injury of deoxyribonucleic acid, for the normal breast cancer cells hydroxytyrosol was used to decrease ROS (reactive oxygen species) [117]. Consequently, hydroxyltyrosol may characterize a possible anti-cancer alternative to conventional drugs which are cytotoxic. It is exposed by the preceding article that the films of alginate can act as a system of TCDD [118]. Cho et al., 2015 [55] synthesized the hydroxyl-tyrosol-based Na-Alg films and used them for topical drug delivery. These are bilayer films, and these films are produced by the solution casting method. These films are antioxidants, so they are very useful for the preservation of skin against UV light, and the cell line these films treated is MCF-7.

iii. Mater-Bi-Based Na-Alg

The first family of biopolymers is "Mater-Bi®." It utilizes substances isolated from vegetables—for example, starch, and maize. Their chemical structures are preserved and are generated with the help of photosynthesis. With an extensive range of properties, a diversity of molecular superstructures is generated by complexion of starch with measures of the complexion agents. These complexion agents are gotten from synthetic, mixed, and renewable sources. "Mater-Bi®" is a group of materials planned to adjust to the different levels of execution according to the demands of the market. It is manufactured in a factory; "Mater-Bi®" is obtained in a granular form. It can be handled utilizing the most well-known alternative procedures to make the products whose attributes are similar or far and away superior to those of traditional plastics. However, they are perfectly compostable and biodegradable. After utilization, those products that are manufactured by "Mater-Bi®" are biodegrade in a composting-only cycle [119]. Bayer et al., 2018 [56] synthesized the Mater-Bi-based Na-Alg films by using dry emulsion method and by solution casting method. Na-Alg was mixed with Mater-Bi, and then vortexed and sonicated after the solution had been evaporated, and when the emulsion dried the films produced a stable liquid emulsion. It was checked and different drugs were loaded on this film. These films are promising materials for in vitro hydrophilic and hydrophobic drug release and potential candidates for wound care materials.

2.1.8. Hydrogels

i. HA-Based Na-Alg

As the basic capacity for the repair and regeneration of articular cartilage that has been damaged is very poor, repair and regeneration are very much challenging. The biomechanical features and biological composition of cartilage are not reproduced by the method of grafting of autologous osteochondral tissue. The use of mesenchymal stem cells (MSCs) can regenerate the cartilage tissues that have been lost. Based on the signals from the microenvironment, MSCs can be differentiated into various linages, and they are known to be very multi-potent cells. They can be differentiated into chondrogenic tissues, and a matrix specific to cartilage is deposited if proper signaling molecules are present. In order to carry out studies on the regeneration or repairing of cartilage, there has been wide use of bone marrow MSCs (BMMSCs) as a cell therapy source.

It was shown by those studies that as a molecule which provides good signaling, mesenchymal stalk cells have aptitude in distinguishing them in chondrogenic tissue and provide a matrix which is exact for cartilage. BMMSCs (bone marrow MSCs) have been extensively used for the treatment of cells for cartilage renaissance or overhaul trainings. Orofacial and dental mesenchymal stem cells, periodontal ligament stem cells (PDLSCs), have measurements for differences in chondrogenicity [120]. It was established by Moshaverinia et al. that degradable and injectable vehicle distribution founded on the alginate which is joined with the RGD or the hydrogel participate in the TGF-β1 ligands as a system of mesenchymal stem cell distribution [120].

It is noted that the hydrogel HA is a promising material of the distribution for the regeneration of cartilage and the repair of cartilage. Moreover, there are some disadvantages of the HA hydrogel: including their contribution to the response of hydrolytic acid and their rapid effect. Ansari et al., 2017 [57] synthesized the hyaluronic acid-based Na-Alg hydrogels and used them for delivery of stem cells. Alginate-based hyaluronic acid hydrogels were mixed with chondrogenic differentiation and used for both in vivo and in vitro drug release. This is a promising material for cartilage tissue engineering and use for delivery of stem cells.

ii. Human GMSCs-Based Na-Alg

Peri-implantitis constitutes an inflammatory reaction in the tissues that border the dental implants; it also has very efficient clinical properties that include mainly inflammation of soft tissue (blood loss when suppurated or probed) and greater harm to the

supporting bone beyond the remodeling of bone biologically [121,122]. In craniofacial implant-ology the loss of peri-implanted bone is one of the most common inflammatory complications. It is noted that the microbial species which are related to the peri-implantitis and periodontitis are comparable; they mostly contain the Gram-negative anaerobes aggregatibacter action-mycetemcomitans, prevotella inter-media, and Porp-hyromonas gingivalis [121,123]. In particular, aggregatibacter action-mycetemcomitans, a facultative Gram-negative bacterium, in the definite types of per-iodontal disease, appears to play a significant role. Aggregatibacter action mycetemcomitans or a creature which is like Aggregatibacter action-mycetemcomitans, has been isolated in a number of patients who are young with quickly continuing failure of the alveolar bones [124]. It will be shown that on the titanium grafts, Aggregatibacter action-mycetemcomitans produces a biofilm; in a superficial setting in vivo, it is allowable that there is an inflammatory swarm response and microbial perseverance response. The pro-inflammatory cytokines, for instance, TNF-α, IL-6, IL-1, and IL-8, will be planned for in the peri-implantitis. It was established via the revisions that the developments of the biofilm play a significant role in the development and beginning of the peri-implant sickness, and in the advancement of that infection round a dental implant is dangerous.

As there are a large number of bacterial agents used at a large scale, silver (Ag) can represent them as a member of that group. The antimicrobial spectrum of silver is very broad, and as compared to antibiotics, it has lower chances of bacteria being resistant to it, particularly in the case of quick bactericidal action. Ag is known to be inert, but silver ions are released when Ag comes in contact with moisture, and these ions have very cytotoxic effects on microorganisms. Hence, it is used in much lower concentrations than are necessary for the cell functioning of mammals [125]. Diniz et al., 2016 [58] synthesized the human GMSCs-based Na-Alg hydrogels for the delivery of stem cells. The study concluded that this hydrogel exhibits good antibacterial activity against *S. aureus* and novel material for biofilm-mediated peri-implant bone loss.

iii. PVP-Based Na-Alg

"Polyvinylpyrrolidone (PVP)" is a bulky (several groups are attached), non-toxic (harmless), "non-ionic" polymer with different functional groups, such as C–N, CH_2, and CvO [126]. The molecule of polyvinylpyrrolidone is broadly utilized in the synthesis of NP. The molecule of polyvinylpyrrolidone is composed of a considerable hydrophobic group (such as the alkyl group) and a strongly hydrophilic component (such as the pyrrolidone moiety). The excellent solvents for polyvinylpyrrolidone are non-aqueous liquids and water. In this way, the apolar methine and methylene group in the ring react with non-aqueous liquids, and the highly polar amide group inside the pyrrolidone ring attaches to water and along its backbone [127]. By utilizing the repulsive forces generated from its hydrophobic carbon chain, polyvinylpyrrolidone (PVP) prevents the aggregation of NPs. Therefore, it is known as a great stabilizer. Hydrophobic carbon chains extend into solvents and interact with one another, but in this way, they produce steric hindrance [128]. Polyvinylpyrrolidone can be considered a dispersant, because in some situations, the inter-particle distances are so extended. Fanesi et al., 2018 [59] synthesized the PVP-based Na-Alg hydrogels for an anti-synergistic effect. These hydrogels were prepared by sequential method. These hydrogels were used to release the optimum types of active agents.

iv. Fenugreek Seed-Based Na-Alg

Probiotic microorganisms provide valuable benefits to health. There are numerous distinguishing features which are shown through these microorganisms; for example, they show resistance to the abdominal and gastric juices and tolerance to intestinal enzymes [87]. Some challenges can be addressed through the microorganisms which are microencapsulating the gut in a defensive physical matrix [88]. Fenugreek is extracted from the seed of the fenugreek plant, and it is a biopolymer. Through the side chain of the D-galactopyranosyl and the backbone of the D-mannan the polymer, fenugreek is composed. There are numerous prebiotic properties which are exhibited through the gum

of fenugreek, and it is exploited in nutritious complements and animal husbandry [129]. Its combined activity and stability for the nutrition industry make this gel an appropriate preservative. Temporarily, the psyllium in its physiological surroundings is a cationic herbal gel, and it is gone from the *Plantago* genus. Arabinoxylan is the gel structure of psyllium; the construction contains a side chain of arabinose and a back bone of xyliose [130]. Psyllium is the ordinary polysaccharide, which is therapeutically active, if appropriately custom-made to make the hydrogels that show the potential to perform as novel strategies of medicine delivery. Hence, synthesize the poly(AAm) established hydrogels and psyllium by using N,N-MBAAm as the irritated linker and APS (ammonium persulfate). For healing management, psyllium is used, and it is used in the treatment of numerous gut disorders, for example, ulcerative colitis, irritable bowel syndrome, diarrhea, chronic kidney disease, and constipation [131]. Similarly, the probiotic microencapsulation matrix is a better applicant because of its legatee effect on humanoid digestive health and probiotic cultures. Haghshenas et al., 2015 [60] formulated the fenugreek seed-based Na-Alg hydrogels in the form of a polymeric blend. It is used to form probiotics and enhance the probiotic growth of bacteria in the gastrointestinal environment.

v. Methyl Cellulose-Based Na-Alg

For "tissue engineering (TE)," the technology of "rapid prototyping (RP)" has become much important. In order to design 3D scaffolds having porosity and tailored structures in accordance with the datasets of "computer-aided design (CAD)" having layer by layer sequences, a large number of methods and materials are accessible now [132]. As the hydrogels have very attractive features towards biofabrication because of the ability to encapsulate a cell in a 3D medium that is very hydrated, for getting rid of the issue for shaping of hydrogels into various shapes before designing them—they are being investigated to be processed by using the RP techniques.

In order to manufacture a new biomaterial with excellent physicochemical features, those polymers that are chemically modified have been broadly examined. The main classes of modified polymers are cellulose ethers, for example, hydroxypropyl methylcellulose (HPMC), carboxy methylcellulose (CMC), methylcellulose (MC), and hydroxyethylcellulose (HEC). Cellulose is found in nature and it is one of the most abundant polysaccharides. It is a linear and regular polymer comprised of "(1→4) linked β-D-glucopyranosyl" units. The configuration of β-(1→4) organized with intramolecular hydrogen bonds produces a rigid or inflexible structure. When the intermolecular hydrogen bonds are present between the groups of hydroxyls, crystals and aggregates occur. Due to this structure, the insolubility of cellulose in water is assigned between the single molecules. In this way, they manufacture highly ordered regions of crystal [133]. This morphology is related to the origin of cellulose, and it controls its reactivity because this morphology has low availability to reactants. However, under heterogeneous conditions, their derivatives are manufactured. They have often an asymmetrical distribution of their substituents along the cellulosic backbone. The commercially most important cellulose ether is methylcellulose (MC). It has broad applications in several industries [134]. Methylcellulose (MC) is the simplest derivative of cellulose, where hydroxyl groups are substituted by methyl groups (-CH3) at the positions of C-2, C-3, and C-6 of "anhydro-D-glucose" units. This derivative of cellulose has the same original physico-chemical and amphiphilic properties. When the degree of substitution (DS) fluctuates from 0 to 3, the methylcellulose (MC) becomes organo-soluble and water soluble. It illustrates a remarkable thermal behavior: when we increase the temperature above a critical point (i.e., 29 ± 2 °C), the viscosity of the aqueous solution is constant or decreases to some small extent. If we increase the temperature continuously, then the viscosity increases strongly. As a result, a thermo-reversible gel is formed [135]. Due to these features, methylcellulose (MC) is classified as a "lower critical solution temperature polymer (LCST)." Schütz et al., 2017 [61] synthesized the methylcellulose-based Na-Alg hydrogel that is used to improve the strength and compatibility of cell matrixes and in biofabrication. Due to sheer stress and strain, the MC/Na-Alg hydrogel-based matrix

is more efficient than the Na-Alg matrix. It is very efficient and a potential candidate for prototyping.

vi. Agarose-Based Na-Alg

In fields such as biotechnology, biomedicine, and life science, the vital and basic clinical and research tools for in vitro study are the systems of cell culture, yet the cell cultures of the past that have a 2D nature are not the best replacements for the availability of complex natural environments of a 3D nature. Various biological processes, including proliferation, survival of cells, migration, adhesion, differentiation, and development, are more closely represented by 3D culture systems. The cells are supported in uses of tissue engineering and 3D cultures by scaffolding, and hydrogels are known to be very effective matrices among these scaffolds [136]. Hydrogels constitute the polymers that are made up from the crosslinking of the networks of 3D polymers, and that is why they have the ability of holding water and are not dissolved by water. Resultantly, the microenvironment of natural tissue is a copycat of the features of hydrogels, including interstitial flow, features of diffusive transport, and "extracellular matrix (ECM)-like viscoelasticity." Due to these features, hydrogels are finding applications in various biomedical fields, including mainly 3D bioprinting, 3D cell cultures, tissue engineering, cell transplanting, and drug delivery. The suggested hydrogels till now include mainly composite hydrogels comprising nanocomposite hydrogels in order to enhance the functional and mechanical features [137].

Agarose results from numerous species of rhodophyceae (red marine algae). It contains the reiterating units of the β-D-galactose, which are 1–3 linked and 1–4 linked 3,6-anhydro-α-L-galactose, providing the capacity to agarose to produce a gel at a low concentration [138]. Additionally, agarose is a gelling agent which is rescindable; it liquefies or solidifies upon cooling or heating, and thus no specific seasonings or counter ions are necessitated for gelation [139]. In biomedical research, agarose is commonly used, and it is also used in the field of molecular biology because it is non-toxic and inexpensive; additionally, it provides excellent distinguishing of crystals with large pores, with the size of a regular pore scope being 100–300 nm. It is established that the hydrogels of agarose are used to support the proliferation of cells and uphold cellular phenol-types in in vitro three dimensional culture revisions. Shin et al., 2016 [62] synthesized the marine collagen/agarose-based Na-Alg biocomposite hydrogel and used it for 3D bioprinting. Sodium alginate and marine collagen and agarose were mixed with the cells, and then the whole process was done in 3 steps named cooling, aging, and 3D structure arrangement. Gelatin was added at 4 °C, and then the hydrogel was loaded, and finally, the 3D structure was rearranged. These composite hydrogels are used to treat the tumor cell line A2780 cells and 3D cell culture and for the screening of drugs.

vii. Chlorosulphonic Acid-Based Na-Alg

Chlorosulphonic acid is a highly reactive, corrosive, and toxic substance. It exists in liquid form. Whenever this acid is discharged from a containment and simultaneously exposed to the atmosphere, it creates a serious and dangerous atmosphere through the mist of sulfuric acid and clouds of hydrogen chloride. In the presence of aqueous media or water, it decomposes explosively and violently, and discharges a large amount of heat. It generates pools of liquid upon spillage, which can either evaporate or boil. Öztürk et al., 2016 [63] synthesized the sulfated type of hydrogel by mixing sulfonic acid with sodium alginate. By increasing the degree of sulfation there becomes a composite hydrogel.

Through the Na-Alg sulfated hydrogel, cell proliferation happened and it caused an interaction between the growth factor and receptor. These hydrogels have promising applications in regenerative medicine.

2.1.9. Magnetic Nanoparticles

i. Clay Nanocomposite-Based Na-Alg

Clay minerals are made up of silicate and aluminate groups that are tetrahedrality and octahedrally arranged. They have a sheet-like structure that forms platelets, which

are held tightly together by relatively weak polar forces and van der Waals forces. These platelets are made up of cationic metal and have the ability to be compact due to its internal electrostatic forces. Nowadays, hydrogels are very important in some applications in which they modify absorption capacity, and have low toxicity, chemical inertness, and the ability to regulate the release of several different pharmaceuticals [140]. Zeolites minerals are porous and are used as adsorbents and catalysts and in medical applications. They are composed mainly of aluminosilicates. Different studies show that zeolites are highly effective in kidney dialysis, wound dressing, and diarrheal drugs. Zeolites are also utilized in controlling the drug release system. Zeolites also have the properties of antimicrobial activity, antiviral activity, and antitumoral activity [141].

CaP (calcium phosphate) is a communal name of the inorganic family that comprises Ca^{2+} (catains) that are organized with the $PO_3{}^{-4}$ (orthophosphate), PO^{-3} (metaphosphate), $P2O_4{}^{-7}$ (pyrophosphate) amines, and erstwhile the ion of hydroxide and hydrogen. In the blood and bovine milk, calcium phosphate is the major form of calcium. The main one in bone is 60% of the inorganic weight of bone, and the chief component of tooth-enamel calcium 90%. The phosphates of calcium with the atomic ratios of the calcium phosphate of 1.5 and 1.67 are termed apatites—for example, hydroxyl-apatite and fluor-apatite. Via the German geologist Abraham Gottlob Werner, the term apatite was coined in 1786; apatite is from the Greek word "apatao," which means "to mislead." Aouada et al., 2018 [64] synthesized the clay-based Na-Alg magnetic nanoparticles. The cross-linker base Na-Alg has a versatile interaction with the clay, and this interaction is hydrophobic.

Sodium alginate mixed with the crosslinker and with the claycomposite is a nanocomposite; there are different types of hydrogels formed in different conditions, such as without a nanoclay composite or with a clay composite. These hydrogels act as promising materials for the controlled release of medicine.

ii. Succinimide-Based Na-Alg

An antiviral drug accepted or approved for treatment is "3′-azido-3′-deoxythymidine" (it is also known as AZT and zidovudine for "human immunodeficiency virus" (HIV)). It can be utilized alone and it can also be utilized in combination with other specialized antiviral agents. These antiviral agents are utilized for the treatment of "acquired immunodeficiency syndrome" (AIDS) and derivatives of AIDS diseases. In this way, the drug experiences a lot of disadvantages; for example, these drugs have very low biological half-lives and temperately low bioavailability [2]. It can lead to fast-pass metabolism, and most importantly, dose-dependent anemia. After oral ingestion, it is absorbed quickly with a large amount of the concentration in plasma being from the gastrointestinal tract. The process of metabolism is done rapidly in its inactive form known as glucuronide with an average eradication half-life (t1/2) of 60 min. It is necessary to get hold of a high dose, i.e., 200 mg every 4 h on a regular basis. Throughout the course of treatment, it is very difficult to sustain the concentration of a systemic drug on the therapeutic level. To counter those disadvantages, nanoparticles have been accepted as a carrier vector. It is utilized to deliver 3′-azido-3′-deoxythymidine (AZT) and it can be intravenously administrated [142].

In the classic procedure, PEI is used, and it is a cationic polymer used in the manufacture of paper, the manufacture of shampoo, and the refinement of water [143]. Nevertheless, until 1995 PEI was not familiarized as a multi-purpose vector for the distribution of genes. Dissimilar molecular weights, the ionic-strength of the solution, the degree of diverging, the zeta potential, and the dissimilar elemental magnitude of PEI gene treatment matter. PEI is used extensively in the non-viral transfer of genes, and it is a cationic polymer. On the other hand, cytotoxicity is incomplete owing to its extensive usage. It is expected that the PEI will show linear conformation and divided deliberation. Joshy et al., 2018 [65] synthesized the succinimide-based Na-Alg conjugated nanoparticles and used them for HIV drug delivery. These nanoparticles were prepared by using the emulsion solvent evaporation method and coupling with glutamic acid. Sodium alginate become the GAAD in the presence of catalysts named EDC and NHS.

These nanoparticles are very useful candidates for HIV and AIDS treatment, and antiviral drug delivery generally. Zidovudine's in vitro release has been done very efficiently by this nanoparticle. These nanoparticle attacks glioma cells, and drug release happens resultantly.

iii. Quaternized Chitosan-Based Na-Alg

Quarternized CS, which is familiarized with perpetual positively charged quaternary ammonium clusters and improves the solubility of H_2O, as a microscopic antiseptic agent has a significant effect above the usual variety of PHs [144–146]. In recent years, the classification and amalgamation of different quartered CS byproducts were done [147–149]. Li et al., 2016 [66] synthesized magnetic nanoparticles based on quantized CS/Na-Alg. Na-Alg was treated with Fe_3O_4, and calcium chloride was mixed with them; after that, sonication was done, and finally, fabrication was completed. These magnetic nanoparticles have various potential applications, such as treating MDR gastric cancer and multidrug-resistant gastric carcinoma by the process of chemo-sensitization.

2.1.10. Micelles

i. PNIPAAm-Based Na-Alg

Poly(*N*-iso-propylacrylamide), differently abbreviated PNIPAAm, PNIPA, PNIPAA, NIPA, or PNIPAm, is a polymer that is heat receptive, and in 1950 it was first created. *N*-iso-propylacrylamide is obtainable commercially and it is manufactured through this. It is also manufactured through the polymerization of the free radical. It will form a 3-D hydrogel and it is cross linked with the *N,N*′-cystamine-bis-acrylamide (CBAm) or *N,N*′-methylene-bis-acryl-amide (MBAm). Beyond 32 °C when it is active in the H_2O, it will endure a LCST (lower critical solution temperature) transition stage from a stage of distended hydrated to a stage of shrunken dehydrated; 90% of its capacity is lost. At or near the heat of humans, PINPA ejects its liquid contents; it was examined through the investigations showing that the PNIPA for solicitation is promising in tissue engineering, and there was well-ordered distribution of the medication. Lee et al., 2014 [67] synthesized the PNIPAAm-based Na-Alg micelles for the treatment of cancer. Sodium alginate and PNIPAAm had been mixed in presence of EDC and sulfo-NHS.

These micelles are formed by using the radical polymerization technique. These micelles are thermally reversible, and the drug that was loaded on it was DOX, and it was used to treat the mice at different intervals of time. These micelles are a promising material for the treatment of cancer their imaging and therapy.

ii. Lactate Oxidase-Base Na-Alg

For several applications, the controlled release of bimolecular substances, especially the discharge of DNA (deoxyribonucleic acid) [150] has been examined. It is mainly related to drug delivery [151] and many other biomedical applications. The discharge of signal-triggered DNA from those different activated materials that are stimuli-responsive with several chemicals and physical signals has received great attention in the past few years [152]. As modified electrode surfaces have a versatile range of applications and simplicity, they have found much attraction among many assemblies of chemicals that are loaded with DNA molecules and then are released when activating signals are sent to them. On electrode surfaces, the loading or stacking DNA is combined with supplementary components of single-responsive systems. This was usually achieved under some conditions such as electrochemically controlled conditions. On the other hand, the discharge of DNA processes is triggered by utilizing electrochemical means and chemical means. Alternation of electrochemical potential that is applied to the modified electrodes is termed as electrochemical means. When the modified surfaces react with the soluble chemical species, then we obtain some signals which are known as chemical signals [153]. Katz et al., 2017 [68] synthesized the lactate oxidase-based Na-Alg micelles in which a cross-linker was attached named Fe^{3+}. Biocatalytic reactions were performed on logic gates AND, INH,

and OR. The release factor using Na-Alg-based beads of cross-linker first took input signals and then released soluble alginate.

The single triggered DNA was treated with these micelles to form films and DNA-FAM was released. These micelles are very useful materials for signal-control release and are used for different biomedical applications.

iii. Essential Oil-Based Na-Alg

"Essential oils" that are obtained from pharmaceutical plants have a complex mixture of the variability of volatiles and lipophilic molecules. These lipophilic and volatile molecules contain several components, for example, sesquiterpene, phenol, monoterpenes, and aliphatic components [154]. Essential oils have a greater interest in food industries due to having comprehensive medicinal and biological properties. Essential oils are utilized for the manufacturing of food packaging materials that are antioxidative and antibacterial. Fungicidal, parasiticidal, sedatives, anti-inflammatory, bactericidal, virucidal, analgesic, and spasmolytic activities are some examples of biological and medicinal properties. Their applications are limited in food industries and in drug industries because these compounds are volatile and insoluble in water. These compounds can be easily degraded by some environmental factors, such as oxygen, extreme pH, light, and high temperature. The essential oils can be converted into polymeric nanoparticles and lipid carriers by utilizing the process of microencapsulation. This may enhance the property of solubility, the efficacy of formulating essential oils, reduce the volatility, and improve stability. Those polymers that are isolated from seaweed are naturally occurring biopolymers, for example, alginate, carrageenan, and agar.

Agar is composed of two units mainly, alternating the "1,4-linked 3,6-anhydrous-L-galactose" unit and the "1,3-linked D-galactose" unit. The acidic side groups substitute both units, for example, sulfate. Agar is a hydrophilic fibrous polysaccharide. Agar can form a film and gel because it has high mechanical strength along with moderate water resistance. It is utilized as packaging and wound dressing materials [155]. Alginate is composed of residues of α-L-guluronate and β-D-man urinate. It is a linear polymer. It is naturally isolated from brown seaweed. It is an anionic polymer. Alginate has the properties of low toxicity, excellent capacity for the formation of gels, and biocompatibility. Due to these properties, it has been broadly utilized in several biomedical and food applications. "Zataria" multiflora belongs to the family of Lamiaceae. It is a thyme-like plant. It is generally utilized as a flavor ingredient in a broad diversity of fields in its native area. Zataria possesses a broad range of biological features, for example, antioxidative and antimicrobial ones. This was shown by the modern pharmacological examination [156]. The Zataria essential oils (abbreviated as ZEO) have played important roles in the food and pharmaceutical industries. Thymol, p-cymene, γ-terpene, and carvacrol are the main components of Zataria essential oils (ZEO) [157]. Rahmati et al., 2018 [69] synthesized the EO-based Na-Alg micelles using the microencapsulation technique. By applying EO to Na-Alg, one gets medicinal food that is used for the treatment of oxidative stress, and bioactive food packing is also made with it.

2.1.11. Microcarriers

i. PEG-Based Na-Alg

As the "mesenchymal stem cells (MSCs)" can differentiate and self-renew, they have found extensive applications in the engineering of tissues and transplantation of cells [158]. Naturally, the mesenchymal stem cells are isolated from adipose and bone marrow. Due to their characteristic properties, the "human umbilical cord blood-derived MSCs (HUCB-MSCs)" suggest an excellent source. Those characteristic properties are tropism, which reduces the risk of transmission of infection, hypo-immunogenicity, and collection by a non-invasive procedure [159]. Moreover, there are three main kinds of "human umbilical cord blood-derived mesenchymal stem cells (HUCB-MSCs)." The first is adipocytes, the second is osteoblasts, and the last is chondrocytes [160]. For the treatment of human diseases, for example, cardiac diseases, tumors and neurodegenerative ones, they provide

incredible promise [77]. Although they are obtained from the donor, the actual number of "HUCB-MSCs" is high when compared with the clinical requirements. The clinical requirement is about 109–1010 cells [161]. In this modern age, the vast majority of cell expansion methods are based on mainly in vitro cultures of plastic surfaces that are two-dimensional (2D). It is always a time-consuming, labor-intensive, and expensive method because of the two-dimensional method that provides a restricted culture area, and in this way, their expansion efficiency is low. Additionally, the process of passage and frequent sub-culturing lead to difficulties; how should we keep the homogenous state for "HUCB-MSCs"? In different areas of tissue engineering and transplantation of cells, it a great challenge to maintain the homogenous state. Therefore, it is very necessary to develop a suitable method for the scalable harvesting and reproduction of undistinguished "HUCB-MSCs." In 1967, "Van Wezel" was a scientist who first introduced a three-dimensional piece of technology. He introduced three-dimensional stem cell culture technology by utilizing micro-carriers [162]. This technology has the ability to reduce all the above limitations. Li et al., 2016 [70] synthesized the PEG-based Na-Alg micro-carriers. This micro-carrier is used to harvest stem cells. Na-Alg was mixed with PEG and with peanut oil and then stirred afterward by EDC this micro-carrier had been formulated.

The degradation was caused by using PEG, and a degradable micro-carrier was formed. This micro-carrier is a very useful material in the cell culturing of stem cells and for tissue engineering and cell transplantation.

ii. SPION-Based Na-Alg

SPION are superparamagnetic iron oxide nanoparticles. In this examination, the physical and chemical properties of superparamagnetic iron oxide nano elements and their in vivo presentations are considered methodically; we also cover just how surface engineering will extend the time of movement and overcome the biological obstacles at tissue, organ, and cellular levels. The upcoming prospective of the superparamagnetic iron oxide and the medical solicitation constructed on the MRI in the tumor, CVD, and inflammation diseases are addressed. The directing tools of superparamagnetic iron-oxide in individual medical usage and investigations were improved [163]. Peng et al., 2016 [71] synthesized the SPION-based Na-Alg nano-carriers for the treatment of cancer. All schemes were done under an argon atmosphere. SPION was mixed with the Na-Alg in the presence of a cross-linker, and a nano-carrier of modified SPION was formed. This SPION is used to treat the tumor cells and is a promising material for clinical applications.

2.1.12. Microspheres

i. 5-FU-Based Na-Alg

For the treatment of tumor therapy, an effective method has been developing known as transcatheter arterial embolization (TAE). The embolization of the arteries that feed the tumor is helped by embolic agents, which is the basis for the transcatheter arterial embolization (TAE) method and this embolization. In this way, they blocked the supply of nutrition to the tumor that causes a disease known as tumor necrosis [164]. Another improved transcatheter arterial embolization (TAE) method was developed in the last 10 years. That method is known as transcatheter arterial chemoembolization (TACE). In this method, the drugs related to anticancer were loaded inside the embolic agents. In transcatheter arterial chemoembolization (TACE), both the chemotherapy and embolization methods are combined. It is the ability of transcatheter arterial chemoembolization (TACE) that enhances the targeting of the drug and revealed better efficiency, and reduces the side effects when it is compared with conventional chemotherapy. Due to these features, the transcatheter arterial chemoembolization (TACE) has been approved as the most acceptable therapy for those cancers that are not easily removed by surgery, such as unresectable liver cancer [165]. On the other hand, both methods, i.e., transcatheter arterial embolization (TAE) and transcatheter arterial chemoembolization (TACE), have a major drawback. In these methods, we have no idea how to determine the positions of the embolic agents in the blood vessels and how to estimate the impact of embolization. This problem was

solved by utilizing a conventional assessment method based on the flow of blood through angiography. However, their reliability was not improved enough. For instance, for the therapy of uterine fibroids, angiography designated that the blood vessel was completely embolized in the tumor. Actually, the complete blood vessels were not embolized; only a small portion was left—for instance, 20% of the blood vessels were not embolized. This 20% was leading to the regeneration of tumor cells [166]. Though, if a large number of embolic agents were inserted in the blood vessels, they caused uterine damage [167]. Therefore, in the field of embolization therapy, the improvement related to the visibility of the embolic agents yet remains a challenge. "Lipiodol (ethiodized poppyseed oil)" has efficient X-ray radiopacity, and that is why it has found extensive applications as an embolic agent either to be used as a mixture with other embolic agents to be used alone. It exists in the liquid state naturally. This natural liquid state means that it readily dissociates and diffuses from the blood vessel. It was found that two microspheres are encapsulated with in situ nanoparticles; i.e., they synthesized in situ $BaSO_4$ nanoparticles. The two microspheres are poly(N-isopropyl acrylamide) microspheres and alginate microspheres [168]. Under X-rays, these microspheres can demonstrate excellent visuality. However, on the other hand, the drawback of utilizing X-rays is that this technology produces potential radiations that are harmful to human health. Magnetic resonance imaging (MRI) is an alternative technology for X-rays. Recently, it has played a very important role in the area of medical imaging diagnosis. Magnetic resonance imaging (MRI) is not only utilized to determine the locations of embolic agents precisely in less time (in real-time) [169]. It is the property of magnetic resonance imaging (MRI) that it protects the patient from hazardous radiation [170]. Wang et al., 2017 [72] synthesized the 5-FU-based Na-Alg microspheres and used them for encapsulation of the drug. Na-Alg was mixed with 5-FU in the presence of a cross-linker and microsphere was formulated. This micro-carrier has excellent MR-visuality and is a promising material in the chemoembolization of multi-drugs.

2.1.13. Tubes

i. PLGA-Based Na-Alg

Through the unsystematic melt copolymerization of the glycolide and lactide, PLGA should be acquired under the attendance of a catalyst and extraordinary emptiness—for example, octet; however, it must be done while upholding the temperature of the reaction between 160 and 190 °C [171]. Glycolides and lactides are the cyclic dimers from the de-hydration of the glycolic acid and lactic acid. Lactic acid should be fashioned in D and L by the fermentation of corn and other agricultural fonts, and it is a methyl switched glycolic acid or 2-hydroxy-propanoic acid [172]. Through consuming the enzymatic biomedical procedure, glycolic acid is organized; it is also organized through the chemical amalgamation by consuming the chloroacetic acid and sodium hydroxide; it is the 2-hydroxy-ethanoic acid. Do et al., 2017 [73] synthesized the PLGA-based Na-Alg tubes for controlled delivery of drugs named fluorophores. A mechanical pump that contained a blue fluid was extruded from Na-Alg, and its coaxial nozzle was used to formulate the tubes. These tubes are a promising material for drug treatment and for the different releases of fluorescent dyes as well.

3. Conclusions

This potential polymer has novel characteristics, such as non-toxicity, low-cost transparency, non-immunogenicity, biocompatibility, and biodegradability, but it has also some drawbacks and limitations, such as poor cell adhesion, poor mechanical properties, hydrophilicity, microbial degradation, and burst release. Due to these drawbacks, it has been combined with different natural and synthetic or petrochemical-based polymers to improve and overcome these limitations. Hydrogels, microspheres, blends, microparticles, nano-gels, electrospun fibers, films, nanoparticles, nanocomposites, scaffolds, and prodrugs based on sodium alginate/natural or synthetic polymers are used as promising candidates for biomedical applications, among which are drug delivery, gene delivery,

tissue engineering, wound dressing, and wound healing. Due to its vast use in different novel applications, it produces interest in the minds of researchers for making potential blends with inorganic/organic, natural, and synthetic polymers for different promising applications in different fields.

Almost all of the studies listed in this overview have been performed in a laboratory environment. Upgrading in an unregulated environment for large data sets needs more research, as the dynamics and structural strengths of compounds based on alginate can alter. Price and efficacy are the crucial variables to be measured in research to investigate alginate-based composite materials in a wide range of applications. Additionally, it is possible to further investigate the performances of alginate-based nanocomposites within field trials. In tests investigating multiphase solutions and complex effluents in a changing environment to simulate field conditions, such analyses may also be carried out. Although this paper does not concentrate on binding, formulation techniques may be particularly relevant to the development of nano-composites based on alginate to satisfy multiple features. It is possible to perform comparison studies amongst these composite materials under controlled environments. Optimizing current alginate-based composite materials and engineering new ones with unique features and inventive interfaces for future applications are yet more research goals.

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