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RECENT TRENDS IN ALGINATE BASED BIOPOLYMER FOR ADVANCED DRUG DELIVERY

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ABSTRACT

Alginate, a naturally occurring biopolymer derived from brown algae (kelp), has many specific properties that have allowed it to be used as a matrix for the trapping and/or release of a variety of biological agents. Alginate is a linear unbranched polysaccharide family that comprises different amounts of 1,4-linked β-D-mannuronic acid and α-L-guluronic acid residues. Alginate is a biomaterial that has found ample applications in drug delivery due to its favorable properties, including thickening, gel forming, stabilizing and biocompatibility properties and biodegradability. In addition, the low price, easy availability, natural origin, versatility and transitional properties of sol-gel make alginate the ideal candidate for producing particles with different applications. The oral route is preferred for drug administration by the most patients. The presence of a mucus layer covering the entire gastrointestinal tract was exploited to extend the use of the oral route by creating a method for the delivery of mucoadhesive drugs that demonstrated extended residence time. Nanoparticles composed of alginate have emerged as one of the most extensively characterized biomaterials used for drug delivery and targeting a set of administration routes. Therefore, the development of synthetic derivatives has the ability to motivate the next generation of alginate applications. This review article gives a comprehensive overview on its present use in various fields of controlled drug delivery, biomedical applications and future possibilities.

Keywords: Alginate, Extraction process, Drug delivery and targeting, Cancer, Wound healing, 3D bio printing

1. INTRODUCTION

The common name for salts of alginic acid or any of its derivatives is alginate, also called **algin.** Alginate consists of 1 to 4 β-D-mannuronic acid (M) and its C-5 epimer α-L-guluronic acid (G). Alginate is an unbranched polysaccharide. The natural copolymer is an important component of algae like kelp and also a bacterial exopolysaccharide, Pseudomonas aeruginosa included. It consists of sequences of M (M blocks) and G (G-blocks) residues interspersed with MG sequences (MG-blocks).

Alginates were discovered by a British pharmacist, E.C.C. Stanford; commercial production began in 1929. Industrial alginate production is approximately 38,000 metric tons per year and is estimated to comprise less than 10% of biosynthesized alginate material **[1]** and 30% of this is used by the food industry, the remainder being used in industrial, dental and pharmaceutical applications **[2, 4]**. Commercial alginates are derived exclusively from algal sources, but recent investigations have been underway to provide more defined physicochemical characteristics of alginate **[3]** for alternative production using microbial fermentation.

Mucus is a complex combination of glycoproteins that cover different segments of the gastrointestinal tract with varying thicknesses and compositions, thus conferring a well-defined mucus rheology, film capacity and adhesiveness **[6]**. A broad variety of pharmaceutical products have been produced in this context combining natural, synthetic and semi-synthetic molecular excipients. Such excipients are required to communicate closely with gastrointestinal mucus and monitor the efficiency of the drug delivery system after administration, as well as to be pharmacologically inert. Breakthroughs in novel mucoadhesive immunization, diagnostic and treatment products have been made ever since micro-technology and nanotechnology emerged **[7]**.

As a result of its extremely good cytocompatibility and biocompatibility, biodegradation **[8]**, transient sol-gel properties and a variety of chemical properties which allow it to be modified are the alginic acid, sodium and potassium alginates have emerged as one of the most widely studied mucoadhesive biomaterials **[9]**.

2. GENERAL PROPERTIES OF ALGINATES

Alginate is available commercially under various structure, molecular weight and M-block and G-block distribution patterns which are responsible for their physical-chemical properties such as viscosity, sol/gel transformation and water absorption. The alginate viscosity depends on the pH of the solution. Decreasing the pH value causes an increase in viscosity due to the protonation of the carboxylate groups in

the alginate backbone, which leads to the formation of the hydrogen bond.

In commercial Alginate, the molecular weight which is the average number of molecules in the sample, varies between 33,000 and 4,000,000g / mol. Increasing the molecular weight of the alginate may affect the physical properties of the resulting gels. In contrast to the water solubility of alginate monovalent salts and alginate esters, alginic acid is insoluble in water and organic solvents **[10]**. Alginate with poly-M or poly-G structures precipitates at low pH, whereas those with alternative MG blocks are soluble at the same condition. Alginate is used in the food and pharmaceutical industries as shown in the **Table 1 [11]**.

Alginate has good mucoadhesive properties, due to the fact that free carboxyl groups are available, which allow the polymer to interact with electrostatic bonding and mucin. Alginate solubility and thus, mucoadhesive properties are greatly influenced by environmental pH, as only ionized carboxylic groups are capable of interacting with mucosal tissue.

Due to mucoadhesive properties, alginate is considered to be a proper polymer excipient for the preparation of oral, nasal, ocular and gastrointestinal dosage forms. Several studies have recently shown favorable mucosal adhesion of alginate-based applications in contact with vaginal mucosal tissue. In addition, increased drug residence time on the mucosal surface of the eye and prolonged release of active agents from microparticle delivery systems with alginate were demonstrated. Because of the wide area that can facilitate intimate interaction between polymer and mucin, multiple unit dosage forms of sodium alginate, in particular in the case of substances which are unstable or degraded in alkaline pH **[12]**, are also being explored as gastroretentive medicinal carriers. Alginate has been thoroughly tested as an adjuvant or co-adjuvant vaccine as it has been shown that these polymers improve the bioavailability and immunogenicity of antigens after nasal and oral administration **[13]**.

Table 1: The use of alginic acid and its salts in food and pharmaceutical industry [5]

Ingredient	Application in food industry	Application in pharmaceutical industry
Alginic acid	**Emulsifier, formulation aid, stabilizer, thickener**	**Tablet binder and disintegrant, sustained release and release-modifying agent, taste masking agent, thickener, suspending and viscosity increasing agent, stabilizer**
Sodium alginate	**Texturizer, stabilizer, thickener, formulation aid, firming agent, flavour adjuvant, emulsifier, surface active agent**	**Suspending and viscosity increasing agent, tablet and capsule disintegrant, tablet binder, stabilizer, sustained release agent, diluenting capsule formulation, thickener**
Ammonium alginate	**Stabilizer, thickener, humectant**	**Color diluents, emulsifier, film former, humectants**
Calcium alginate	**Stabilizer, thickener**	**Tablet disintegrant**
Propylene glycol alginate	**Emulsifier, flavoring adjuvant, formulation aid, stabilizer, surfactant, thickener**	**Stabilizer, emulsifier, suspending and viscosity increasing agent**

3. EXTRACTION AND PREPARATION

Generally, the algae are mechanically harvested and dried prior to further processing, except for M. Pyrifera, which is wet-processed. After treatment with dilute mineral acid, alginates are extracted from dried and milled algal material to remove or degrade the associated neutral homopolysaccharides such as laminarin and fucoidin. Simultaneously the alkaline earth cations are exchanged for H^+. The alginate is then converted from the insoluble proton-form to the soluble sodium salt by adding sodium carbonate to the pH below 10. **Figure 1** shows the schematic diagram for the production of sodium alginate. After extraction, the alginate may be further purified and converted into either salt or acid **[14]**.

Alginates obtained from a natural source are likely to have a variety of impurities potentially present. These include heavy metals, endotoxins, proteins, other carbohydrates and polyphenols. Low levels of these impurities do not pose a problem for food and beverage applications, but for pharmaceutical applications; in particular, when alginates are administered via the parenteral route, these impurities should be removed **[15]**.

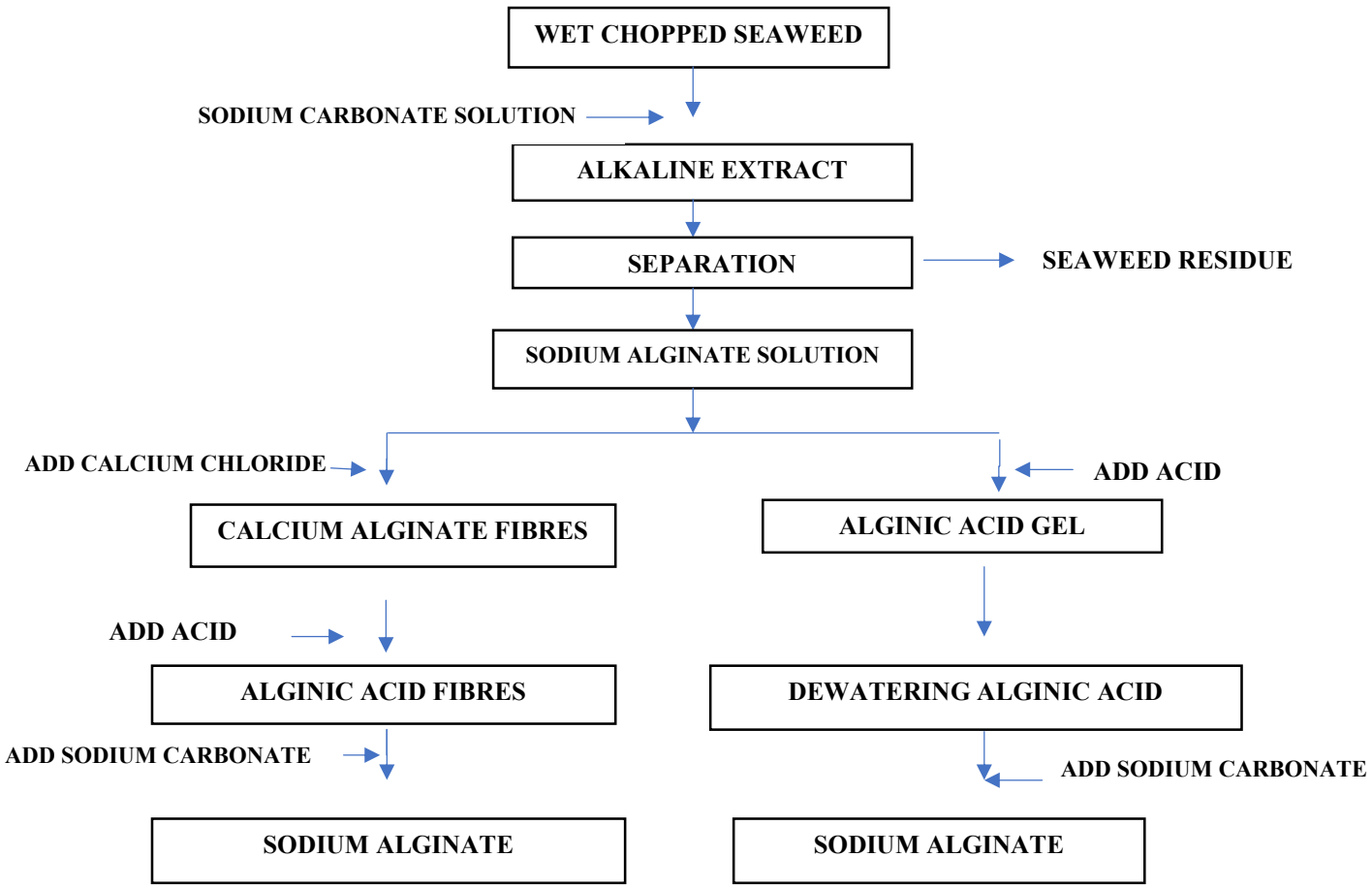

Figure 1: Flow chart for the production of sodium alginate

4. DERIVATIVES OF ALGINATE

Many of the alginate derivatives used in a number of biomedical applications have been reported over time.

4.1 Amphiphilic Alginate:

Amphiphilic alginate derivatives are synthesized by introducing hydrophobic moieties in the alginate spine, such as alkyl chains and hydrophobic polymers. These alginate derivatives may form self-assembled structures (particles and gels in aqueous media) and may be used in a number of drug delivery applications **[8]**. Amphiphilic derivatives of sodium alginate have been developed through the conjugation of long alkyl chains (dodecyl, octadecyl) to the alginate backbone via ester bonding. The aqueous solutions of these derivatives have shown the typical rheological properties of physically interlinked, gel-like networks in the semi-dilute regime, which may be advantageous for cartilage repair and regeneration **[16]**.

In the study, microparticles were constructed by dispersion in sodium chloride solution through these derivatives, once the encapsulation and subsequent release of proteins by the addition of either surfactants, it disrupting intermolecular hydrophobic junctions or esterase that hydrolyze the ester bond between the alkyl chains and the alginate backbone **[17]**.

In another study, dodecyl amine was also prepared using 2-chloro-1-methylpyridinium iodide as a coupling reagent with the alginate backbone via the amide linkage formation. Hydrogels developed from this derivative showed long-term stability in aqueous media compared to those developed from alginate derivatives with dodecyl ester labile to hydrolysis **[18]**. In addition, it synthesized the use of N, N-dicyclohexylcarbodiimide as a coupling agent and 4-(N, N-dimethylamine) pyridine as a room temperature catalyst for water soluble and amphiphilic alginate derivatives grafted with cholesterol groups. Where the derivatives formed self-aggregates with a diameter of approximately 136 nm in aqueous sodium chloride solution **[19]**. Alginate grafted with poly(-caprolactone) (PCL) in aqueous sodium chloride solution has an associative behavior that depends on the length of the PCL chain, which is different from the behavior of the derivatives in water **[20]**.

4.2 Cell-Interactive Alginate:

Recently, alginate derivatives have been produced containing cell adhesive peptides. These alginate derivatives were developed by chemically introducing peptides as side chains through the use of carbodiimide chemistry to couple sugar residues through carboxylic groups. Appropriate ligands are important in the promotion and regulation of cellular interactions, especially for cell culture and tissue engineering applications, as alginate is inherently lacking in mammalian cell adhesivity **[8]**. Peptides have been widely

used as model adhesion ligands, such as arginine-glycine aspartic acid (RGD) sequence, due to the widespread presence of integrin receptors for this ligand on various cell types **[21]**.

The use of water-soluble carbodiimide chemistry can also be chemically coupled to RGD containing peptides to the alginate backbone **[22]**. The minimum concentration of RGD peptides in alginate gels is essential for cell adhesion and growth and is cell-specific. The minimum concentration for significant adhesion of MC3T3-E1 cells to alginate gels in vitro has been reported to be 12.5 g / mg of alginate, while the minimum concentration for significant adhesion of C2C12cells is 10.0 g / mg of alginate **[23]**. The affinity of RGD peptide also plays a key role, and cyclic RGD peptides have been shown to be more potent and are needed at lower concentrations compared to linear RGD peptides **[24]**. Other peptides have also been used to alter alginate gels and strengthen adhesive interactions with other cell types, including peptides containing DGEA (Asp-Gly-Glu Ala) and YIGSR (Tyr-Ile-Gly-Ser-Arg) derived from other extracellular matrix proteins.

Alginate has been updated with YIGSR peptides by the use of water-soluble carbodiimide chemistry to facilitate neural cell adhesion **[23]**. Nevertheless, most of the innovations to date have been with RGD-alginate. Cell-interactive alginates were used as substrates for cell culture in the 2-D and 3-D cultures as well as scaffolds in tissue engineering applications **[8]**.

5 ALGINATE NANOPARTICLES FOR DRUG DELIVERY AND TARGETING

Drug delivery systems with controlled release (CR) provide different advantages compared to regular dosages such as increased effectiveness, reduced toxicity, greater patient compliance and convenience. As a result, these systems can improve the efficacy of drug therapy **[25]**. Alginate biodegradability is the most significant benefit of its use as a matrix for control release preparations since it is absorbed and processed by the body without any adverse effects during or after drug release. It may therefore be a suitable matrix for the sustained release of various drugs **[26]**. In addition, CR is possible for conventional low-molecular weight drugs as well as macromolecular drugs, including peptide hormones (insulin and growth hormone), polysaccharides (heparin), antibiotics, antigens and enzymes **[27]**. Many drugs have been incorporated in various alginate matrices. Forms for CR therapies such as beads, microspheres, films and tablets **[28]**.

Alginate has many properties which allow it to be used as a controlled drug delivery matrix:

1) It is readily available, cheap and also biodegradable in nature

2) It has a protective effect on the mucous membranes of the upper gastrointestinal tract and is also non-toxic when taken orally

3) It is hemo-compatible and does not accumulate in any organ of the body.

4) Hydrogels can be formed under mild conditions.

5) Water soluble, reducing the use of noxious solvents during manufacturing and thus the stability, toxicological as well as environmental impacts associated with solvents that can be reduced.

6) It forms gel at room temperature, which decreases the chances of damaging the operation of sensitive drugs at high temperatures.

7) Soluble sodium alginate, cross-linked with a number of cross-linking agents, forms an insoluble gel which can be used to prolong the release of some drugs.

8) Flow properties of drugs with needle-like crystals (Sulfadiazine) may be improved by incorporation into alginate beads. If the agglomerates are formed from the dispersion of drugs, this method of agglomeration often avoids polymorphic transformations.

9) The formed beads are mechanically strong, and it can be coated with enteric polymers to produce enteric delivery systems for drugs **[26]**.

Since non-coating nanoparticles can be absorbed by the immune system, surface modification with hydrophilic polymers or surface coating with cell-specific receptors facilitates targeting and enhances drug bioavailability shown in **Figure 2**. Alginate nanoparticles have been used for many routes of treatment, e.g. pulmonary, oral, nasal, intravenous, vaginal and ocular. These particles have also been used to transport a variety of drugs, such as metformin, doxorubicin, ethionamide, and many other biotechnological drugs. Cross-linking of alginate can be accomplished by the use of cationic polyelectrolytes during the processing of nanoparticles or between alginate with cationic drugs to be loaded **[29]**.

In both cases, the controlled release profile of the loaded drugs can be achieved, with the enhanced long-term stability of nanoparticles. **Table 2** shows the overview of alginate nanoparticle for drug delivery.

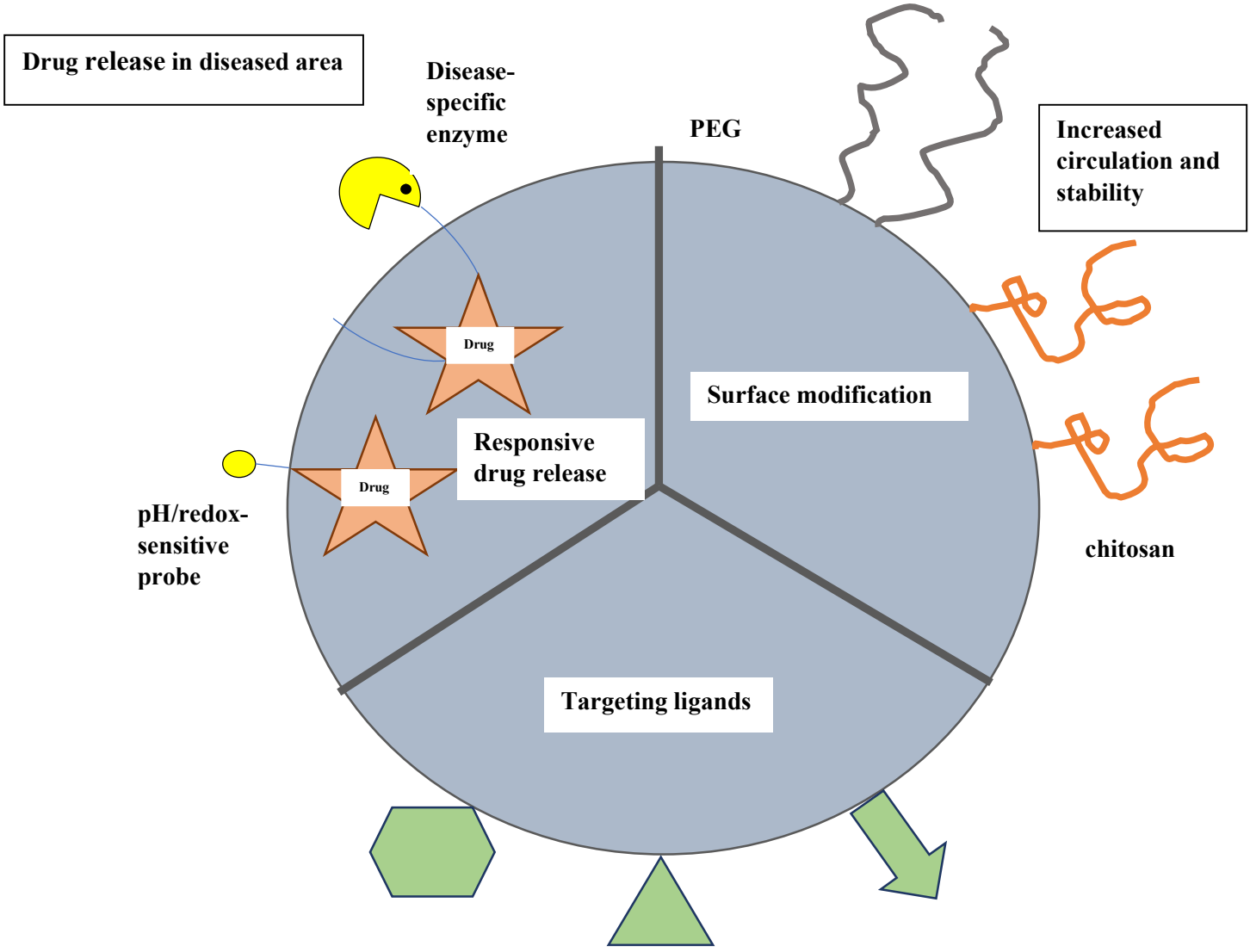

Figure 2: Schematic diagram summarizing the different properties of alginate nanoparticles for drug delivery and targeting

Table 2: Overview of alginate nanoparticles for drug delivery

Nanoparticles	Drug	Administration Route	Application
Polyurethane–alginate/Chitosan	A model antigen	Subcutaneous	Enhance immune response
Chitosan-alginate	Crocin	-	Antioxidant and anticancer
Chitosan-alginate	Naringenin	Oral	Diabetes
Chitosan/alginate	Quercetin	-	Antioxidant
Lipid/alginate	Dexamethasone	Nasal	Anti-inflammatory
Chitosan-alginate	Insulin	Oral	Diabetes
Chitosan-alginate	Doxorubicin	-	Cancer
Polyurethane–alginate	Insulin	Oral	Diabetes
Poly vinyl alcohol-alginate	Metformin	Oral	Diabetes

6. APPLICATION

Alginate-based particles are a useful tool for a wide range of applications, taking into account that alginate is one of the most versatile polysaccharides. Alginate microparticles and nanoparticles have become very attractive for a variety of reasons, particularly when compared to many synthetic organic polymers. Its mucoadhesive properties increase the time of interaction between the particles and the absorptive epithelium and the mucosa-associated lymphoid tissue M cells, facilitating better uptake **[30]**.

6.1 Alginate-Based Drug Delivery Vehicles For Cancer Treatment:

In the world, cancer is a major public health problem. It includes a wide range of diseases caused by the uncontrolled growth of malignant cells that have metastatic ability in the body. With more than 10 million new cases every year, the World Health Organization has predicted cancer-related deaths about 13 million by the year 2030. Advanced modes of diagnosis and medical devices; mortality has declined over the past 5 years of life **[31]**.

Chemotherapy, radiation therapy or a combination of these are popular approaches commonly used in the treatment of cancer. Chemotherapy can mainly affect DNA synthesis and mitosis, resulting in rapid death in the growth and division of cancer cells. Chemotherapy agents are non-selective and cause significant systemic toxicity, which leads to undesired side effects in healthy tissues, such as loss of appetite and vomiting. On the other hand, due to the poor bioavailability of these drugs at the tumor site, high doses of these drugs are required, resulting in increased toxicity to normal cells and increased resistance to multiple drugs. It is therefore desirable to develop different delivery systems that can target cancer cells either actively or passively, thereby reducing adverse side effects on normal tissues **[32]**.

A number of delivery mechanisms with enhanced therapeutic efficacy have recently evolved due to the understanding of tumor biology and the development of flexible materials with increased bioavailability such as polymers, lipids, polymeric hydrogels, inorganic carriers and biomacromolecular scaffolds. In contrast to conventional chemotherapeutic agents, nanoscale delivery systems have the potential to improve the efficacy of treatment while avoiding Systemic toxicity through increased permeability and retention (EPR) and active cell uptake **[33]**.

Table 3: Various alginate-based drug delivery vehicles used in cancer therapy

Description of Carrier	Type	Overcomes multi-drug resistance	Drug	Specify	Reference
Alginate- Cyclodextrin	Nanogel	Enhance chemotherapeutic efficacy by pressure controlled drug release	5-FU	Colon cancer (HT-29)	[34]
Magnetic Alginate/Chitosan	Nanoparticles	Sustained release profiles, enhanced uptake efficiency, strong cytotoxicity to cancer cells, potential for targeted drug	Cur	Human breast cancer (MDA-MB-231)	[35]
Alginate nanogel platform	Nanogels	Inhibit tumor growth, reduce the adverse side effects, improve the quality of life of cancer patients	Cisplatin/ Gold	Breast cancer (MCF-7)	[36]
Alginate – PAMAM(GS)hybrid nanogel	Dendrimer	Sustained release. targeted and sufficient tumor an accumulation, increased efficiency and decreased toxicity	EPI	Human breast cancer (MCF-7)	[39]

Alginate hydrogels have outstanding properties, such as high-water content, non-toxicity, soft consistency as well as biocompatibility and biodegradability, which make them ideal candidates for the delivery of low molecular weight drugs and macromolecules, including proteins and genes, either sustained or localized **[37]**. The cargo may be immobilized or encapsulated in the pores of the carrier. Depending on the pH of the surrounding medium, alginate may form two types of gels. It shrinks at low pH (gastric environment) and produces a viscous acidic gel that does not release its encapsulated drugs.

When it has gone through the gastrointestinal tract with a higher pH, the skin looks like Structure of alginic acid converted to soluble viscose gel, which induces drug degradation and release by disrupting the polymeric network. So, in case of delivering drugs to the target tissue, controlling release over a prolonged period of time prevents systemic toxicity. Drug releases from hydrogel pores are carried out by a variety of mechanisms, including diffusion-controlled, swelling-controlled, chemically-controlled and environmentally-responsive releases **[38]**.

Alginate-PAMAM was introduced by a group of researchers in 2015.Dendrimer (AG-G5) hybrid nanogel as an effective platform for enhanced delivery of anti-cancer drugs. For the embedding of Polyamidoamine (PAMAM) into the alginate backbone, 1-ethyl-3-(3-dimethylamino propyl) carbodiimide hydrochloride (EDC) was used for the activation of alginate carboxylate groups to form an amide bond with PAMAM amine groups. Finally, the remaining carboxylate groups of the alginate networks were cross-linked in the presence of calcium chloride ($CaCl_2$). Therefore, the combination of ion and covalent bonds in the alginate-

PAMAM dendrimer network has increased structural stability and drug encapsulation effectiveness. They used Epirubicin (EPI) as a model drug for encapsulation in AG-G5 nanogel and examined the anti-cancer efficacy of the resultant EPI & AG-G5 nanogel in MCF-7 human breast cancer cells. The penetration of the G5 PAMAM inside the AG network decreased the size of the nanogel and gave the nanocarrier superior responsiveness. EPI & AG-G5 was also in a position to release its Payload in a safe and regulated manner. In addition, In vitro cytotoxicity analysis of EPI & AG-G5 nanogels suggested that they could induce cell death by apoptosis shown in **Table 3 [39]**.

6.2 Wound Dressing

Wound dressings have been used for the treatment of serious skin burns and accidents for decades. The primary benefits of conventional gauze-based dressings have been simple. Nonetheless, secondary injury to the gauze can occur. At present, high-quality wound dressings are considered as an integral part of the healing cycle. It is designed to prevent infection, avoid bleeding, and remove it. Exudates, permeable to the transformation of water and gas and Provide a dry, moist atmosphere for easy and productive use for the phase of recovery. Among the different dressing materials, Hydrogels are promising candidates used in the treatment of burns and chronic wounds **[40]**.

Alginate dressings are constructed by gel formation by ionic cross-linking of its solution with Ca, Mg, Ba, Zn, etc., as well as by freeze-drying of porous sheets in the shape of foam or fibrous clothing **[41]**. They could absorb both gel and dry wound excaudate while providing a physiologically moist environment and minimizing bacterial infection. The amount of M block in the alginate structure affected the immunogenic properties by favoring the production of cytokines. The healing cycle is carried out by stimulating the monocytes to generate high levels of cytokines, such as interleukin-6 and factor-ш tumor necrosis, resulting in releases high levels of cytokines Stimulating anti-inflammatory factors **[42]**.

Biocompatibility, porosity, high water content and gas permeability are some of the significant factors properties that make a good candidate for alginate hydrogel for the cleaning of wound. Given these outstanding properties, it nevertheless suffers from a deficiency such as low mechanical stability in swollen form and fast dehydration when it is not covered by a secondary dressing **[43]**. The composition of alginate with certain synthetic or natural polymers can improve its mechanical stability.

In the treatment of chronic injuries caused by exudate or contaminated surgical wounds, a dressing containing calcium alginate is capable of transmitting ions to the wound fluid in order to help blood clot and act

as a hemostat **[44]**. The resulting soluble and absorbent gel provides a moist environment and helps the healing process by helping the fresh epidermis to grow.

6.3 Alginate Based Bio Ink In 3d Bioprinting

Millions of patients with incurable illnesses have been suffering since the 1950s but it has succeeded through organ transplantation. They had immune shortcomings response and rejection of the organ. As an alternative, 3D bioprinting processing significantly established after the first U.S. patent award in order to have realistic and innovative solutions outcome in the field of regenerative medicine. Several attempts have been made in this area, from the bioprinting of cells and biological molecules to the biomanufacturing of tissues and organs. 3D bioprinting tissue engineering technology offers layer-by - layer printing of bio ink in a scaffold-free manner to replicate the structure of living tissue.

This technique makes it possible to produce 3D, scalable and complex geometry with a spatial heterogeneity. A 3D bio printed tissue or organ formed either in vitro that has been incubated in the bioreactor for maturation prior to implantation by surgery or in situ in which the human body functions as a bioreactor. A variety of bioprinting experiments have been performed for tissues such as bone, cartilage, skin, vascular and human ear cartilage. Many of the traditional 3D bioprinting techniques include extrusion, inkjet, layer assisted and the electrospinning cell.

Hydrogels are promising candidates as a bio ink matrix among several biopolymers. Bio ink is commonly referred to as biomaterials that could be used encapsulate cells and can be assembled into three-dimensional scaffolds and tissue-like structures. They are allowed to replicate or remove the target tissue on the basis of their resemblance and their tunable degradation to the native extracellular matrix (ECM) and physical properties. Their viscosity and the process transform the sol/ gel that defined the structure and shape of the resulting three-dimensional bio printed hydrogels. Several biocompatible hydrogels are used as bio inks for cell proliferation in 3D bioprinting techniques such as gelatin, agarose, hyaluronic acid, and alginate **[45]**.

Sodium alginate, a naturally occurring polyanionic and linear block copolymer, exhibits high biocompatibility due to cell growth support. Due to the shear-thinning properties, the alginate solution is the perfect precursor for 3D bio printed tissue-engineered constructions. To address in-situ cross-linking limitations, an alginate solution optimized for shear thinning in which it could reduce its viscosity by increasing the shear.

6.4 Alginates Microcapsule:

One of the concepts that has shown a high potential to become a viable

therapeutic option for chronic diseases is cell microencapsulation. Cell microencapsulation inside alginate matrices is a promising method for controlling hidden cell dysfunction. Once inserted in the body, the tissues and vasculature that surround the capsule provide cells with oxygen and nutrients that promote cell viability. Immobilized cells are able to generate the therapeutic factor de novo on a sustained basis from weeks to months, which can balance the period of treatment with the longevity of the disease **[46]**. As a result, a single treatment of the medication will significantly increase patient satisfaction and compliance. This can resolve the enormous problem of adherence, especially in diseases where a rigorous regulation of the delivery of drugs is necessary in order to achieve the effectiveness of care.

6.5 DNA Encapsulation

New methods for the efficient delivery of DNA oligonucleotides are being evaluated with recent advances in the field of gene therapy. They are two studies have identified the possible use of alginate as an enteric delivery mechanism for DNA. The encapsulation of DNA and its derivatives that can be used in the enteric targeting of nucleic acids as gene transfer agents, modified oligonucleotides and DNA intercalator carriers. In vitro studies have shown that DNA can be successfully encapsulated and released at pH 6.5 without any denaturation of the DNA molecule. Nevertheless, the DNA depurination is not easily determined by the methodology used by the investigator.

Depurination of the molecule that occurs at low pH is beneficial because it can aid in the release of drugs in the stomach and duodenum. The *in vivo* evaluation of encapsulated calf thymus DNA in chitosan-alginate microbeads through the GI tract is discussed in another study. The aim of this research was to demonstrate the feasibility of using alginate-chitosan encapsulated DNA as a target or carrier for the evaluation of intestinal carcinogens. Fast recovery of intact chitosan – alginate microbeads is obtained from rat feces following gavage and GI transit **[18]**.

7. FUTURE PERSPECTIVE

Biocompatible and biodegradable alginate has lead to the widespread use of alginate-based particles in various fields. Due to very good biocompatibility and US-FDA approval as a food additive, alginate has become a favorite among the developers of pharmaceutical products in advanced drug delivery system for mucosal administration. Alginate latest work as a technology platform to develop micro-particles and nanoparticles for delivery of oral drugs has been reviewed in this review. Mucoadhesiveness and mucopenetration are the most outstanding features that increase the transition to the gastrointestinal epithel of the medicinal product. This could be used to improve local and systemic delivery, increase oral

bioavailability and prolong release. The detailed studies of alginate particle production methods that range from simple ionotropic gelation to more complex approaches and equipment contributed greatly to various processing parameters, particularly in terms of size reduction, drug encapsulation and the reproducibility of methods. These developments have a major positive effect on the industrial expansion potential of some of the mentioned innovative methods.

On the contrary, ALG research was limited to a few payloads and insulin was evaluated most closely. In our perspective, once this task is achieved, the development of innovative alginate systems with applicative and translation potential in the coming years will come to fruition. In many fields of research, nanotechnology could play an important role, such as goal-specific medicines and early diagnosis methods of disease. Alginate-based medicinal materials are expected to evolve Considerable

8. CONCLUSION

Alginate has gained a preferential place among pharmaceutical excipients for the development of advanced drug delivery systems for mucosal administration. This paper also describes alginate properties, preparation and extraction, derivatives, future perspective and application in pharmaceutical products. Being biodegradable and biocompatible, alginate is being widely used in pharmaceutical research as a controlled-release polymer. A chemically modified alginate has been widely used as a carrier to promote the efficacy of the chemotherapeutic agents in cancer treatments. Alternatively, highly absorbent ALG-based hydrogels are used as wound dressing with mechanical stability and viscoelastic properties. Due to the excellent biocompatibility, the alginate hydrogels have also demonstrated good printability. As research and development continues with alginate polymeric delivery systems, we expect to see many innovative and exciting applications in the future.

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