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Sodium alginate: the wonder polymer for controlled drug delivery

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ABSTRACT

The objective of this paper is to discuss the potential of sodium alginate as a biopolymer in the formulation development and its allied applications. There is a growing trend in pharmaceutical in food industry to avoid the harsh condition in the preparation for administration to the body or for the storage purpose as it induce the side effects, instability or loss of therapeutic effect of the medicament. The sodium alginate is a versatile functional biomaterial for viscosity enhancement, stabilizer, matrixing agent, encapsulation polymer, bioadhesive and film former in transdermal and transmucosal drug delivery. The present article reviews sources, preparation, properties, crosslinking methodology, compendial standards, methods utilized for preparation of drug delivery systems using sodium alginate and its potential applications.

Keywords: Sodium alginates, drug delivery, biopolymer, microbeads.

INTRODUCTION

The design and interest in controlled release dosage forms, has been increasing steadily during the last 50 years. In most works the purpose is to make a formulation that keeps a prolonged therapeutic effect at a reduced dosing frequency.It is worthless to mention that the drugs are almost never administered in an unformulated state. Generally a dosage form consists of one or more active principles together with a varying number of other substances (excipients). These excipients enormously influence the physicochemical characteristics of the final products. It is now recognized that excipients can potentially influence the rate and/or extent of absorption of a drug (e.g. by complex formation). Therefore a well-established formulation depends on the careful selection of excipients. By reviewing the present and past scenario it is never worthless to mention, the use of polymers as a formulation aid in controlled drug delivery systems become an important area of research and development (1).

The current trend points to an increasing interest in the use of natural substances in food, drugs and cosmetics. The naturally occurring alginate polymers have a great potential in drug formulation due to their extensive application as food additives and their recognized lack of toxicity. Alginate is a nostalgic term for dietetic, biotechnology, cosmetic and pharmaceutical industries. As this group of polymers possesses a number of characteristics that makes it useful as a formulation aid, both as a conventional excipients and more specifically as a tool in polymeric-controlled drug delivery (1).

The alginates were discovered by a British Pharmacist, E.C.C. Stanford; commercial production started in 1929. The annual production of alginates in the world is about 30,000 tones; 30% of this is utilized by the food industry, the rest being used in industrial, pharmaceutical and dental applications (2,3).

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2. RAW SOURCES OF ALGINATES:

Alginic acid and it's salts [Ca, Mg, Na & K] are abundantly present in brown algae (pheophyta) of the genera "*Macrocystis, Laminaria, Ascophyllum, Alario, Ecklonia, Eisenia, Nercocystis, Sargassum, Cystoseira,* and *Fucus.* The most important are species of *Laminaria* known as kelps or sea tangles and specimens of Fucus known as Wracks (4). However, it is two species, *Macrocystis porifera* and *Ascophyllum nodosum,* that provide the bulk of alginates production in the world (5). In the algal thalus, Phycocolloids are the primary components of both the cell wall and the extra cellular matrix; their function as a "skeleton" increasing the mechanical strength and the flexibility of the tissue probably due to their ability to accumulate divalent metal ions and form gels of the required mechanical strength with these ions. Acetylated alginates are also isolated from some bacteria genera *pseudomonas* and *Acetobacter* (6,7,8,9). Red algae belonging to the family coralenacease also contain these substances (10,11).

2.1. **Extraction and Preparation:** Since alginates occur in the form of insoluble calcium, magnesium, sodium and potassium salts contained in the algal cell walls and the extra cellular matrix, their extraction and purification generally involve ion exchange techniques; the details of the extraction methods are usually protected by patents. Generally to prepare alginates for commercial use, the algae is mechanically harvested and dried before further processing except for *M. Pyrifera* which is processed in wet. Alginates are then extracted from dried and milled algal material after treatment with dilute mineral acid to remove or degrade associated neutral homopolysaccharides such as laminarin and fucoidin. Cuncurrently the alkaline earth cations are exchanged for H^+. The alginate is then converted from the insoluble protonated form to the soluble sodium salt by addition of sodium carbonate at a P^H below 10. After extraction, the alginate can be further purified and then converted to either a salt or acid (12).

The alginates being obtained from a natural source are likely to have a variety of impurities potentially be present. These include heavy metals, endotoxin, proteins, other carbohydrates and polyphenols. For applications in the food and beverage industry, low levels of these impurities do not pose a problem, but for pharmaceutical applications; particularly when alginates will be administered via the parenteral route, these impurities should be removed (13). In view of this limits of these impurities are recommended in pharmacopoeia for alginate (Table.1) (13-18). Alginates of a pharmaceutical grade can now be obtained from several manufacturers including Kelco (surrey, UK) Pronova biopolymer (Drammen, Norway), Chemical MFG Corp. (Gordena, CA, USA), Junsei (Tokyo, Japan), Loba Chemie (India).

3. **CHEMICAL STRUCTURE OF ALGINATES:**

Chemically alginates are linear, unbranched polysaccharide composed of monomers of β-D Mannuronic acid (M) and it's C-5 epimer α –l guluronic acid(G) residues joined together by (1-4) glycoside linkages (Fig.1)

The residues generally vary widely in composition and sequence and are arranged in a pattern of blocks along the chain. These homopolymeric regions of β-D mannuronic acid blocks and α-L guluronic acid blocks are inter-dispersed with regions of alternating structure (β-D-mannuronic acid –α-l-guluronic acid blocks). The composition and extent of the sequences and the molecular weight determine the physical properties of the alginates. The molecular variability is dependent on the organism and tissue from which the alginates are isolated. For example, alginates prepared from the stipes of old *L. hyperborea* kelp contain the highest content of α-L-guluronic acid residues while alginates from *A. Nodosum* and *L. Japonica* have low content of α-L-guluronic acid blocks. As polymunnronic acid was found to dominate tissues of young algae; in older plants it is transformed into polyguluronic acid by the enzyme C_5-epimerase (19). In mature tissues polymannuronic acid is located mainly in the extra- cellular spaces while polyguluronic acid occurs in the cell walls (20).

It has been reported that a seasonal variation is found, especially in *Laminaria* species, where alginates extracted contained a higher proportion of mannuronic acid in summer. Alginates do not have a regular repeating unit and the distribution of monomers along the polymer chain can't be described by Bernoulli statistics (12).

Analytical characterization of alginates is more difficult than for other polysaccharides since acid hydrolysis can lead to destruction of the uronic acids. Circular dichroism spectroscopy has been used to match the linear spectra of the alginate to model samples of well-characterized homopolymeric blocks. NMR spectroscopy has contributed significantly to our understanding of alginate structure. This technique can determine the monomer composition as well as the frequencies of the four possible diad (nearest neighbor) structures F_{GG}, F_{MG}, F_{MM} and F_{GM}. NMR can also provide an estimate of the eight possible triad frequencies and the average block length (12).

The viscosity of alginate solutions depends primarily on the molecular weight of the material. Characterization of purified alginate samples by gel permeation chromatography indicates a polydisperse size distribution. Light scattering has been used to determine the average molecular weights at several alginate samples, which has been shown to range from 80 kilodaltons (kDa) to 290 kDa for *Azobacter Vinelandii* and *pseudomonas aeruginosa* respectively (12).

4. **PROPERTIES OF ALGINATES:**

4.1. **Solubility:** Sodium alginates us slowly soluble in cold water, forming viscous, colloidal solution. It is insoluble in alcohol and hydroalcoholic solutions in which alcohol content is greater than 30% by weight. It is also insoluble in other organic solvents viz. Chloroform and ether, and in acids where the P^H of the resulting solution falls below 3.0. A 1% solution in distilled water has a P^H of approximately 7.2. calcium alginate, is however, practically insoluble in water and organic solvents but soluble in sodium citrate (21).

4.2. **Viscosity:** Various grades of sodium alginates are available, yielding aqueous solutions of varying viscosity within a range of 20-400 centipoises (0.02-0.4 PaS) in 1% solution at 20^0C. Due to distribution of chain lengths, alginate solutions are not clearly Newtonian and behave as pseudoplastic fluid. When dissolved in pure water, their reduced viscosity is expected to increase very rapidly with dilution as observed by **Focus** and **Straues** (22). In the presence of supporting electrolyte rheological behavior of polyelectrolyte solution is known to depend on the ionic structure of the aqueous solvent, e.g. increasing the concentration of a strong electrolyte such as NaCl in the alginate solution up to 100mM was shown to reduce the solution viscosity due to the change in polymer conformation (21).

4.3. **Chemical stability and degradation:** Degradation of a Ca^{2+} cross-linked alginate gel can occur by removal of the Ca^{2+} ions. This can be accomplished by the use of a chelating agent such as ethylene glycol-bis (b-amino ethyl ether)-*N, N, N', N'*- tetra acetic acid (EGTA), lactate, citrate and phosphate or by a high concentration of ions such as Na^+ or Mg^{2+}. As Ca^{2+} ions are removed, the cross-linking in the gel decreases and the gels are destabilized. This can lead to leakage of entrapped material and solubilization of the high molecular weight alginate polymers. Alginate gels will also degrade and precipitate in a 0.1 M phosphate buffer solution and will completely dissolve in 0.1 M sodium citrate at pH 7.8. If Ca^{2+} is used in the cross-linking solution and phosphate is used as the dissolution medium, the dissolution medium will turn turbid due to the Ca dissociating from the polymer network and forming calcium phosphate precipitate. This phenomenon is more evident when a high guluronic content alginate is used. Low a-L- guluronic acid content alginate and lower molecular weight alginate are known to release encapsulated proteins at a much faster rate .Degradation of the gel can be prevented by storing the gel beads in a medium that contains free Ca^{2+} ions and to keep the Na^+:Ca^{2+} ratio less than 25:1 for high a-L-guluronic acid alginates and 3:1 for low a-L-guluronic acid alginates (12).

Alginates have been reported to undergo proton catalyzed hydrolysis, which is dependent on time, pH, and temperature. A cross-linked alginate matrix delivery system when exposed to low pH can therefore undergo a reduction in alginate molecular weight, which results in faster degradation and release of a molecule when the gel is reequilibrated in a neutral pH solution. Ability of alginate to form two types of gel depend on P^H, i.e. an acid gel and an ionotropic gel, gives the polymer unique properties compared to neutral macromolecules (1). Alginate forms strong complexes with polycations including chitosan, polypeptides such as polylysine and synthetic polymers such as polyethyleneimine. These complexes do not dissolve in the presence of Ca^{2+} chelators and can be used to both

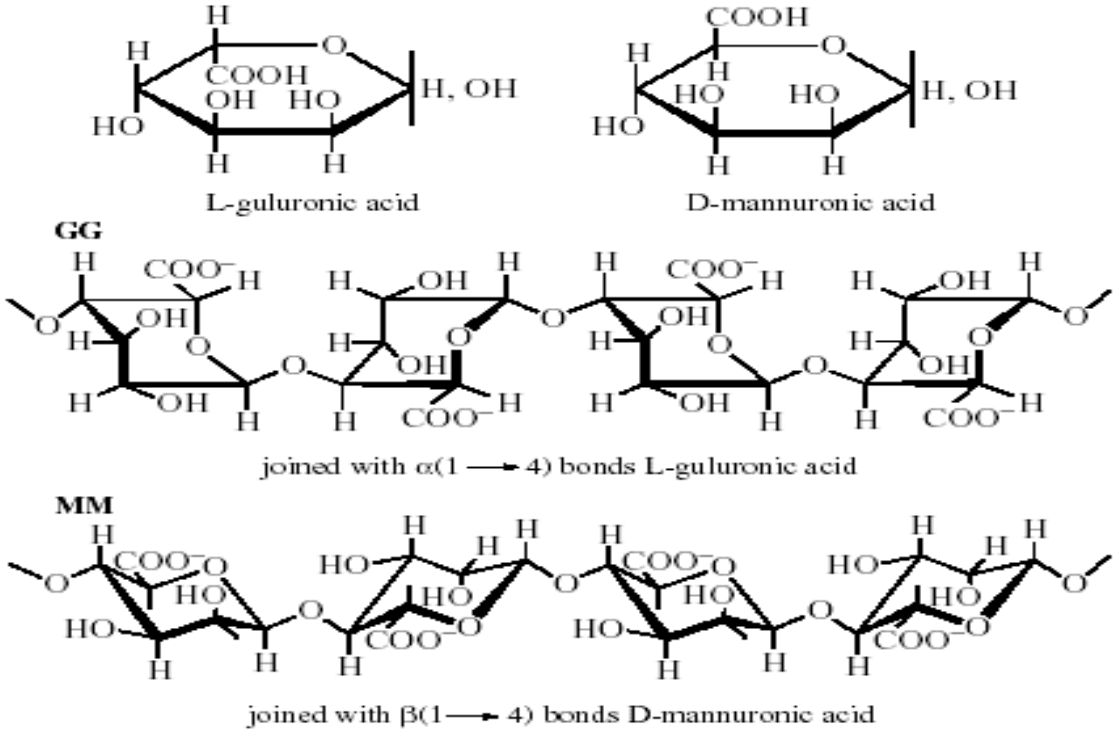

Fig. 1. Structure of polymeric locks of alginic acid. (GG) guluronic sequence, (MM) mannuronic sequence.

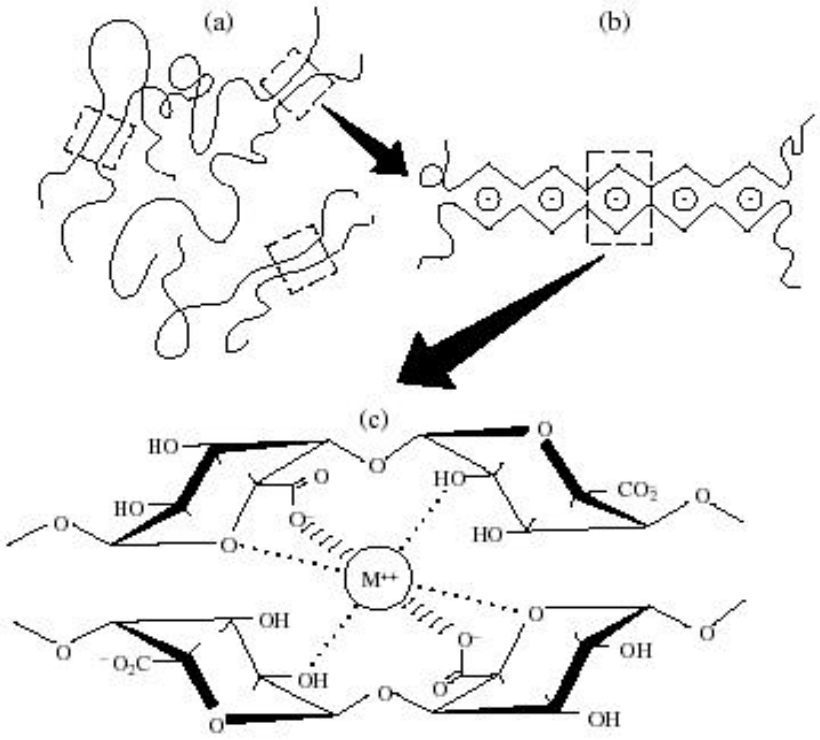

Fig. 2. Schematic representation of the "egg-box" model of alginate gel. (a, b) Binding zones between polymeric alginate molecules; (c) an elementary cell of the binding zone. The dotted line indicates hydrogen bonds between the oxygen atoms of the pyranosic cycles and the metallic ion; the dashed line indicates ionic bonds between carboxyl groups and the metallic ion.

Table 1: Pharmacopoeial standards of Sodium alginate

Test	NationalFormulary/ United States Pharmacopoeia	British Pharmacopoeia & British Pharmaceutical Codex	Indian Pharmacopoeia
Identification	+	+	+
Microbial limits	Total bacterial count <200/g *Salmonella* species and *E. coli* absent	Total viable aerobic count $<10^3$/g complies with *E. coli* and *Salmonella* test	1.0 g free from *E. coli*, 10.0 g free from *Salmonellae*
Loss on drying	≤15% by weight	≤15% by weight	≤15% by weight
Ash	18.0–24.0%	—	—
Lead	≤0.001%	≤10 ppm	—
Arsenic	≤1.5 ppm	≤3 ppm	—
Heavy metals	≤0.004%	≤20 ppm	≤40.0 ppm
Sulfated ash	—	30.0–36.0%	30.0–36.0%
Chloride	—	≤1.0 %	≤1.0%
Calcium	—	≤1.5%	—
Iron	—	≤400 ppm	—

Table 2. Toxicity data for alginate (14,21,26).

Compound	Animal used	Route of administration	LD_{50} (g/kg)
Alginic acid	Mouse	i.v.[a]	1.0
Alginic acid	Rat	i.p.[a]	1.6
Sodium alginate	Mouse	i.v.	<0.2
Sodium alginate	Rabbit	i.v.	0.1
Sodium alginate	Cat	i.p.	0.25
Sodium alginate	Rat	Oral	>5.0
Sodium alginate	Rat	i.v.	1.0
Calcium alginate	Rat	i.p.	1.407
Calcium alginate	Rat	i.v.	0.064

[a]i.v.: intravenous; i.p.: intraperitonial.

Table 3. Methods of Preparation of Alginate beads:

S. No.	Method ofpreparation	Characteristics	References
1.	Air atomization	Requires an extrusion device with a small orifice through which alginate solutions containing drug are forced. Beads of 5- to 200-µm particles can be produced. The size of beads can be controlled by either adjusting gas and liquid flow and operating pressure or distance between the orifice and the surface of the crosslinking solution	(34)
2.	Coaxial bead generator	Coaxial air stream pulls droplets from a needle tip into gelling bath Can produce spherical beads ranging in size down to around 400 µm.	(32, 35)
3.	Dropping method	It is a Simple method Involves use of syringe with a needle or pipette. It is a most extensively utilized method for preparing the >500 µm particles. The size of beads formed is dependent on the size of needle used and viscosity of the alginate solution.	(36-40)
4.	Electrostatic bead generator	Electrostatic force pulls droplets from needle tip into gelling bath. By this method150- to 1000-µm particles can be produced. Bead size depends on the voltage and distance between the needle tip and the gelling bath, solution viscosity, flow rate of the solution as well as on needle diameter	(35, 21)
5.	Emulsification	Used only for stable drugs because it involves use of harsh chemical reagents to remove oil at the end of the process. Particles of size range 1- to 150-µm can be produced By this method. Size of microbeads produced depends on stirring speed and the rate of the addition of the cross-linking solution	(21, 41, 42, 43)
6.	Laminar jet break up technique	A device based on laminar jet breaks up induced by applying a sinusoidal frequency with defined amplitude to the nozzle. Normally 300-to 600 mm particles can be produced.	(21)
7.	Mechanical cutting	Bead formation is achieved by means of a rotating cutting tool which cuts jet into uniform cylindrical segments, which form spherical beads due to surface tension while falling down into a gelling bath. 150-µm to 3-mm particles can be produced.	(21)
8.	Spinning disk atomization	Bead formation is achieved by specially designed spinning disk atomizer. It is suitable for 300- to 600-µm size particles.	(21)
9.	Vibrating nozzle technique	The encapsulation technique is based on a harmonically vibrating nozzle. By this method >200-µm particles can be produced	(21)
10.	Complex coacervation	Under specific conditions of polyion concentration, PH and ionic strength, the polyelectrolyte mixture can separate into two distinct phases; a dense coacervate phase which contains the microbeads and a dilute equilibrium phase. Oppositely charged complex poly-electrolytes have been commonly used. Optimum condition for maximum coacervate yield are pH of 3.9, an ionic strength of 1 mM and a 0.15% w/v total polyion concentration	(12)

stabilize the gel and reduce its porosity (12).

4.4. **Sterilization:** Filtration is the simplest and least detrimental means of aseptization but mostly alginate solutions are sterilized by autoclaving rather than filtration. It is reported that some decrease in viscosity occurs following sterilization by autoclaving, as the thermal process randomly cleaves alginate chains. The extent of this loss depends on the presence of other substances added to the solution(15).γ-Radiation and ethylene oxide have also been used to sterilize alginate solutions (21).

4.5. **Biological properties:**

4.5.1. ***Immunogenecity and Biocompatibility****:* Biocompatibility and Immunogenecity of polymer materials are two cardinal issues for successful application in carriers for drug delivery. Most authors agree that the chemical composition and the mitogenic contaminants found in alginates are two main contributors to alginates Immunogenecity (12, 21). Alginates can be readily purchased in several different grades namely, ultra pure, food or research grade. Commercial research grade alginate and ultrapure alginate have been tested for their endotoxin levels and their ability to activate lymphocytes. The study showed that mitogenic impurities which are found in commercial alginate but not in purified alginate are solely responsible for the side effects observed (21). Side effects include cytokine release and inflammatory reactions. Other groups have also shown that alginate rich in mannuronic acid seem to activate cytokine production more than guluronic-rich alginate. It is therefore strongly recommended by these investigators that ultra pure alginate with low β-D-mannuronic acid and high α-1-guluronic acid contents should be considered for any in vivo research if inflammatory reactions are to be avoided (12).

Alginate biocompatibility has been studied by injecting calcium alginate into kidney capsules of rats, and it has been reported that calcium alginate is biocompatible (21). It is very conceivable that with all the contradictory reports, more than one factor can be attributed to alginate immunogenecity. Cappai et. al. have summarized this concern very well by stating that factors such as sphericity, strength and volume of the implanted beads, smoothness of the membrane, viscosity, composition and purity of the alginate solution, are all contributing factors in preventing cell over growth (12).

4.5.2. ***Bioadhesion****:* Bioadhesion is generally defined as the adhesion or contact between two surfaces with one being a biological substratum. If one of the surfaces involved is a mucosal layer; the term mucoadhesion is used (23). Alginate possesses a bioadhesive property which could serve as a potential advantage in mucosal drug delivery. Alginate with its carboxyl end groups is classified as anionic mucoadhesive polymer, and studies have shown that alginate has the highest mucoadhesive strength compared with polymers such as polystyrene, chitosan, CMC, and poly (lactic acid), because it has been reported that polyanion polymers are more effective bioadhesive than polycation polymers or non-ionic polymers. This bioadhesive property of alginate serves as a potential advantage in mucosal drug delivery such as to the gastrointestinal tract and nasopharynx (12, 21). These mucoadhesive drug delivery systems work by increasing the drug residence time at the site of activity or resorption and hence aid in its utility as a potential delivery vehicle for drugs to mucosal tissues. It also improves the overall drugs effectiveness and bioavailability (12, 21, 24, 25).

4.5.3. ***Toxicity:*** Calcium alginate gels are found to be non-toxic to cells and hence are suitable for drug delivery. Alginate-polylysine capsules are, however, found to be pyrogenic (21). The toxicity data for alginate as prepared by the Joint FAO/WHO Expert Committee on Food Additives (26) are described in Table 2. Numerous studies have tested the high level of safety of sodium alginate in foods. Allergy tests conducted with sodium alginate have shown that the material is not allergic. Sodium alginate has not been shown to possess any eye or skin irritation properties (15).

4.6. **Gel Properties:**

4.6.1. ***Mechanism of formation:*** This polysaccharide has many anionic or cationic groups in the structure; therefore, it exhibits a unique physical property by electrostatic interaction. A property of aqueous solutions of alginate, which has been widely exploited for fabrication of vehicles for sustained delivery of bioactive molecules, is their ability to form firm gels on addition of di- and trivalent metal ions such as bivalent alkaline earth metals (Ca^{++}, Sr^{++}, and Ba^{++}) or trivalent Fe^{+++} and Al^{+++} ions. This is a result of ionic interaction and intramolecular bonding between the carboxylic acid groups located on the polymer backbone and the cations that are present (27, 28). Regions of guluronate monomers in one alginate molecule can be linked to a similar region in another molecule by means of calcium or other divalent cations. In the presence of divalent calcium ions, the calcium is ionically substituted at the carboxylic site. A second alginate strand can also connect at the calcium ion, forming a link in which the Ca^{2+} ion attaches two alginate strands together (21). The result is a chain of calcium-linked alginate strands that form solid gel. The divalent calcium cation fits into electronegative cavities like eggs in an egg-box; from this similitude arises the term "Egg Box" model (29).This binds the alginate polymer together by forming junction zones, thus leading to gelation of solution (30) as shown in Fig.2. The cross-linking sites that occur when a polyvalent cation causes interpolysaccharide binding are called junction zones. The junction zone is an alignment of helices with two anhydroguluronic acid units per turn, the helices being held together by chelate bound Ca^{++}, which looks like the eggs in the pocket of an egg carton. As evident from Fig. 2 (12, 29, 21, 31), only half of the carboxylate groups engage in chelate binding of calcium if the egg box is a dimerization of molecules. The rest of the Ca^{++} is ordinary bound. A multimeric junction zone is also possible with this model. The interpretation is that the dimeric junction zone binds the Ca^{++} strongly, which is inside the egg box, whereas the Ca^{++} outside the egg box is less strongly bound. Furthermore, it may be interpreted that the multimeric junction zones are less stable than dimeric zones (21). Ca^{++} and Ba^{++} bonding to alginate is expected to occur in a planer two-dimensional manner; on the other hand, trivalent aluminium cation is expected to form a three-dimensional valent bonding structure with alginate (31).

4.6.2. ***Different Methods of preparation of gel beads:*** The methods for preparation of alginate beads or microparticles should be such that it allows for production of beads with a narrow size distribution and should have a high production rate. Alginate beads are conventionally prepared by extrusion through needles into calcium solutions.

Air-jet, electrical potential, vibration units etc have been added to increase the droplet output of syringe-based systems.

Table 4. **Cross-linking agents used for preparation of alginate gel.**

S. No.	Cross-linking agent	Characteristics	References
(A) Inorganic			
1	Ca^{++}	Most widely used cross-linking agent leads to production of calcium alginate gel. Beads obtained are compact, but the pore dimensions and volume change after drying and subsequent reswelling.	(21, 39, 45, 46)
2.	Ba^{++}	More stronger microcapsules than that cross-linked with calcium	(21, 37)
3.	Sr^{++}	Release is faster as compared to calcium alginate beads as shown in case of Nicardipine HCl.	(21)
4.	Al^{+++}	Affects release profile as well as morphology of beads.	(46, 47)
5.	Fe^{+++}	Useful in prolonging release of drugs	(21)
6.	Zn^{++}	Release slowly as compared to calcium beads	(21)
(B) Organic			
1.	Epichlorhydrin	Beads produced are reported to be more elastic than calcium alginate beads. Also after drying and subsequent reswelling, their pore size and dimensions remain the same.	(21)
2.	*N,N*-(3-Dimethyl -amino propyl)-*N*-ethylcarbodi- imide (EDC)	Improvement in mechanical properties	(21)
3.	Glutaraldehyde	Enhances mechanical stability but not recommended due to its toxicity	(41, 48, 49, 50)
(C)Simultaneous organic and inorganic			
1.	Calcium sulfate with calcium carbonate-d- gluconic acid lactone	Gelation can be controlled Useful for a variety of biomedical applications	(21)

However these improvements still don't make it very practical to use a syringe-based unit for large scale production because of the large number of needles required and operational problems such as needle blockage, cleaning, and sanitation. Various methods used are shown in Table 3. The materials to be encapsulated are usually mixed with an alginate solution, and the mixture is dropped into a solution of calcium ions, resulting in the instantaneous formation of micro particles that entrap cells or drug within a tridimentional lattice (21).

4.6.3. ***Role of Cross-linking agents:*** It has been shown in different studies that cross-linker type has a pronounced effect on the release behavior of drugs from the cross-linked matrix (31). Cross-linking of alginic acid in general is done with calcium chloride, resulting in formation of calcium alginate hydrogel beads (21). There is a wide variety of physical and chemical methods of cross-linking alginates. In chemically cross-linked gels, covalent bonds are present between different polymer chains, whereas in physically cross-linked gels, a physical interaction exists between different polymeric chains (21). In general, microcapsules prepared from alginate and polycations lack mechanical strength because the interaction between alginate and polycations is ionic, instead of covalent, this represents a much stronger bond. Two functional groups of alginates OH and COOH are mainly being used for the cross-linking. Covalent linkages between polymer chains can be established by the reaction of functional groups with complementary reactivity such as amino-carboxylic acid or an isocyanate-OH/NH_2 reaction. The OH group can also be cross-linked with glutaraldehyde, but because glutaraldehyde is a toxic compound even at low concentration, alternatives have been developed. It has also been reported that alginate forms strong gels with Ba^{++} and Sr^{++}; however, no gelation is observed in the presence of Mg^{++} and monovalent cations Na^{+} and K^{+}. Physical cross-linking is preferred because it avoids use of cross-linking agents, which are often toxic compounds and have to be removed or extracted from gels before use. Physical methods include cross-linking with ionic interaction. These interactions are not only based on electrostatic interactions that neutralize acidic groups but also on the coordinating function of calcium as a chelating center. Cross-linking can be carried out at room temperature at physiological pH and hence is advantageous for encapsulating living cells, proteins, and drugs (44). Cross-linking agents used for formation of alginate gel are listed in Table 4.

5. USEFUL PROPERTIES OF ALGINATE AS MATRIX FOR CONTROLLED DRUG DELIVERY:

Alginates have been widely used as tablet disintegrant, binding agent, viscosity modifying agent, as a stabilizer in disperse system in the production of suspension and emulsion and also as thickening agent in pharmaceutical industries. The most important advantage of using alginate as a matrix for Controlled release (CR) formulations is its biodegradability, because it is degraded and is absorbed by the body during and/or after drug release without any toxic effects. This allows bypass of surgical removal of the device. Hence, it can be a suitable matrix for sustained release of various drugs. Furthermore, because drug delivery can be controlled primarily through properties of polymer devices, CR is possible for conventional low molecular weight drugs as well as macromolecular drugs including peptide hormones (e.g., insulin, growth hormone), polysaccharides (e.g., heparin), antibiotics, antigens, and enzymes (21). The release of drugs from alginate beads occurs mainly by diffusion through matrix and at certain pH due to erosion mechanism (51). Release of drugs can be controlled by coating of matrix beads with sodium alginate. Sodium alginate has also been evaluated as release-controlling diluent in CR capsules. Several drugs have been incorporated into alginate matrices in a variety of forms (e.g., beads, micro spheres, films, and tablets), for CR therapies (52, 53). The following properties of alginates have enabled it to be used as a most acceptable matrix for controlled drug delivery (53, 54).

*(i)*It is readily available and is relatively inexpensive.

*(ii)*It contains ingredients that are accepted food additives.

*(iii)*It is non-toxic when taken orally and also has a protective effect

Table 5: Alginate based drug delivery system.

S. no.	Drug	Dosage form	References
1.	4-Acetamidophenol	Microspheres	(21)
2.	5-Aminosalicylic acid	Beads	(55)
3.	5-Fluorouracil	Beads	(56)
4.	Acetaminophen	a) Beads	(47,21)
		b) Microparticles	(57,58)
5.	Amoxycillin	Floating beads	(59)
6.	Ampicillin	a) Liquid preparation	(21)
		b) Beads	(60)
7.	Bovine serum albumin	Microspheres	(43)
8.	Cefadroxil	Beads	(50)
9.	Chloramphenicol	Minimatrices	(58)
10.	Chlorpheniramine maleate	Beads	(21)
11.	Chlorthiazide	Beads	(21)
12.	Cisapride monohydrate	Matrix film	(31)
13.	Dextran	Beads	(37,61,62)
14.	Diclofenac sodium	a) Cross-linked pellet	(63)
		b) Microspheres	(46,65)
		c) Beads	(30,49)
15.	Diclofenac hydroxyethyl pyrrolidine	Beads	(65)
16.	Dipyridamole	Microspheres	(21)
17.	Doxorubicin	Nanoparticles	(21)
18.	Ganciclovir sodium	Gel	(66)
19.	Guaifenesin	Polymer particles	(21)
20.	Ibuprofen	Beads	(36,67)
21.	Imipramine	Beads	(21)
22.	Indomethacin	Beads	(21,36)
23.	Ketoconazole	Microparticles	(21)
24.	Ketoprofen	Beads	(21)
25.	Lidocaine HCl	Microspheres	(21)
26.	Metoclopramide hydrochloride	Matrix film	(31)
27.	Metronidazole	Floating beads	(68)
28.	Micronized griseofulvin	Beads	(36)
29.	Nicardipine hydrochloride	a) Beads	(69)
		b) Microparticles	(21)
30.	Nicotinic acid	Beads	(70)
31.	Nimesulide	Microspheres	(71)
32	Nifedipine	Beads	(21)
33.	Pindolol	Beads	(21)
34.	Prednisolone	Beads	(72)
35.	Propranolol HCl	Beads	(21)
36.	Pseudoephedrine HCl	Polymer particles	(21)
37.	Salbutamol sulfate	Beads	(73)
38.	Sodium salicylate	a) Microspheres	(21)
		b) Beads	(21)
39.	Sulfadiazine	Beads	(36)
40.	Sulfaguanidine	Microspheres	(21)
41.	Sulfamethoxazole	Beads	(74)
42.	Tetramidine	Microspheres	(42)
43.	Theophylline	a) Beads	(21)
		b) Microspheres	(58,75,76)
44.	Tiaramide	Beads	(21)
45.	Timolol maleate	Beads	(21)
46.	Tolbutamide	Beads	(36)
47.	Vancomycin	Beads	(21)
48.	Vitamin C	Microparticles	(21)

on mucous membranes of upper gastrointestinal tract.

*(iv)*It is haemo-compatible and does not accumulate in any organ of the human body.

*(v)*It is biodegradable so there is no need for surgical removal after the drug is exhausted.

*(vi)*It can form hydro gels under mild conditions.

*(vii)*It is water soluble so it eliminates use of noxious solvents during processing and hence stability, toxicological, and environmental problems associated with solvents can be minimized.

*(viii)*It forms gel at room temperature and hence reduces chances of destroying activity of sensitive drugs at elevated temperatures.

*(ix)*Soluble sodium alginate cross-linked with a variety of cross-linking agents, forms insoluble gel, which is used to delay release of some drugs.

*(x)*Flow properties of drugs with needlelike crystals (e.g., Sulfadiazine) can be improved by incorporating in alginate beads. This method of agglomeration also avoids polymorphic transformations as agglomerates are formed from drug dispersions.

*(xi)*Beads formed are mechanically strong so they could be coated with enteric polymers to prepare enteric drug delivery systems.

*(xii)*Adopted by European Pharmacopoeia.

*(xiii)*The acceptable daily intake (ADI)for alginates are not specified which is the highest possible classification for food additives. The Food and Drug Administration has granted the generally recognized as safe (GRAS) status to alginates. The joint additive committee of the FAO and WHO experts has concluded that the daily permissible dose of sodium alginate 0-50 mg per Kg of human body weight. In 1990, the FAO and WHO removed the limitations for the daily consumption of alginates by man (33).

There have been several investigations for use of alginate gels as carriers for a variety of drugs. Alginate beads can be administered by filling in capsules or by compressing into a tablet (36). The successive sections will throw light on the use of alginate as controlled drug delivery carrier for several drugs of different characteristics (Table 5).

CONCLUSION: In conclusion, the sodium alginate as biopolymer has wide range of applications in the food and pharmaceutical industry. It has versatile pharmaceutical utility starting from thickening agent to polymeric backbone in sustained release dosage forms. Being biopolymer of high biological tolerability, it has a special role to play in the formulations of proteins or peptides and other biological products. Its capability of fabrication in all aqueous systems, cross-linking with variety of agents, miscibility with other polymers of biological or synthetic origin offers the most widely applicable polymeric systems avoiding harsh conditions.

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