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Natural Gums and Carbohydrate-Based Polymers: Potential Encapsulants

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ABSTRACT: Background: Plants possess a wide range of bioactive compounds with established health benefits which are highly susceptible to degradation. The environmental dynamics such as high temperature, light, oxygen limits the shelf life and bioavailability of these compounds in food and drug formulations. Encapsulation serves as an effective way of preserving these sensitive compounds by enclosing them within a coating/wall material and hence improves their bioavailability and functional properties. **Scope and Approach**: The wall materials used for encapsulation also known as encapsulants act as physical barriers between core compound and external stimuli. There are different edible protein, lipid and carbohydrate based encapsulants used for coating of bioactive compounds. However, this review gives a detailed insight on composition, functional properties, and applications of carbohydrate based polymers in food, and pharmaceutical industries while emphasizing on the advantages and limitations of these polymers in encapsulation process. So, we explored recent expansion in the area of natural polysaccharides and their derivatives as carriers for the targeted and sustained delivery of active compounds. **Key Findings and Conclusions:** Polysaccharides, natural gums (Carrageenan, Alginate, Gum arabic, Guar gum, Gellan gum, Xanthan gum) and their derivatives are biodegradable polymers being used as sustained release carriers. They are more advantageous over lipid based and protein based carriers by virtue of their unique features such as thermo stability and versatility of interacting with a range of hydrophilic and hydrophobic compounds. Tailor-made carriers made by structural modifications of the polysaccharides using physical, chemical and enzymatic reactions result in improved functional properties and hence widen their area of applications.

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INTRODUCTION

Bioactive compounds are secondary plant metabolites which are obtained from fruits, vegetables and other plant sources like nuts and legumes. These phytochemicals play a crucial therapeutic role in prevention of diseases like urinary tract infections, coronary heart diseases, stomach ulcers and cancers attributing to their active participation in physiological and cellular activities. Despite being an essential required nutrient to be included in diet, these are found in very small quantities in their sources and hence focus is to achieve the maximum retention from the farm to fork to ascertain health benefits. Moreover, their sensitive nature towards environmental dynamics like heat, oxygen etc., degradation during processing and storage, unpleasant taste and off colour limits their direct application in food industry. [1, 2] Therefore, to ease out their successful application in food industries as a source of antioxidants, dietary fiber etc. by protecting against all the described degradation factors, these compounds needs to be surrounded or coated with an edible and suitable coating agent. The process of enclosing or coating the small particles embedded in a homogeneous or heterogeneous matrix by a suitable wall material is known as “encapsulation”. [3, 4] The major advantages of encapsulating phenolic compounds in an enclosure is improved stability by protection against heat, light, oxygen, easy handling by converting liquid extracts into dried powders and direct incorporation into food systems without being thermally degraded. It has been found that

anthocyanin-rich bilberry extract encapsulated in whey protein gels resulted in stronger stabilisation in extremely high conditions when stored for 28 days at 20° C. [5] Similarly, ethanol extract of tea encapsulated in β-cyclodextrin resulted in enhanced pharmacological activities of tea. [6]

However, the major concern associated with this technique is selection of suitable wall material to encapsulate the core compound which act as an obstacle or physical barrier around the core to prevent its direct exposure with external environment. However, the characteristics that need to be considered to choose the suitable coating agent depends on number of factors like size of required microparticles, aqueous solubility and stability, surface permeability, interaction with the core compound, extracting solvent and desired drug release profile. [7, 8, 9] The stability and release profile of microcapsules is highly dependent on composition of encapsulants. There are variety of encapsulating materials being used in different fields of food and pharmaceuticals such as protein based (gelatin, casein, milk serum, soy and wheat), polysaccharides (starches, maltodextrin, corn syrups and gum Arabic), lipids (stearic acid, mono- and triglycerides) and synthetic polymers (Polyvinyl amine etc.). [10, 11] The prime characteristics of an acceptable wall material are: (a) non-toxic and food grade quality, (b) high encapsulation efficiency and high loading content, (c) biocompatible and biodegradable, (d) economically and environmentally feasible with good nutritional value, (e) high solubility, good emulsifying, film forming and drying properties, (f) ability to release core material on hydration, (g) low viscosity at high solid concentrations and low hygroscopicity, (h) should improve the stability and bioavailability of the compound while ensuring the timely and target release, (i) should remain stable and active within food matrix during processing, storage and consumption without impacting its organoleptic and physicochemical properties. Nevertheless, a single wall material may not have all the properties, hence can be used as a mixture with other polymers to improve the encapsulation properties**.** [11-13]

In this review paper an effort has been done to provide an inclusive knowledge of different natural polysaccharides and some natural/modified gums being used as an efficient wall material in microencapsulation of bioactive compounds and drugs in diverse fields of food, pharmaceutical and biomedical industries (**Figure 1**).

CARBOHYDRATE-BASED POLYMERS AS ENCAPSULANTS

Polysaccharides are defined as complex carbohydrate molecules consisting of long chains of simple mono-saccharides linked by glycosidic linkages. They have diverse functional properties due to varied chemical composition, molecular weight and presence of reactive functional groups. Natural polysaccharides can survive the transit through stomach and small intestine without being digested. The network like structures of polysaccharides facilitate the controlled release effect and can even be utilised as compost in the fields after degradation**.** [14] Therefore, this assorted nature of the polysaccharides accounts for their use in food and pharmaceutical industry as building blocks of the delivery systems. They are amorphous, eco-friendly, biocompatible, biodegradable, low-cost polymers which can be physically, chemically or biologically modified for their effective use as promising vehicle for entrapment of bioactive compound. Also, their ability to survive high temperatures unlike lipid or protein-based delivery systems which gets melted or denatured during transit in GIT or processing, make them versatile carriers for encapsulation of bioactive molecules**.** [11, 13, 15, 16]

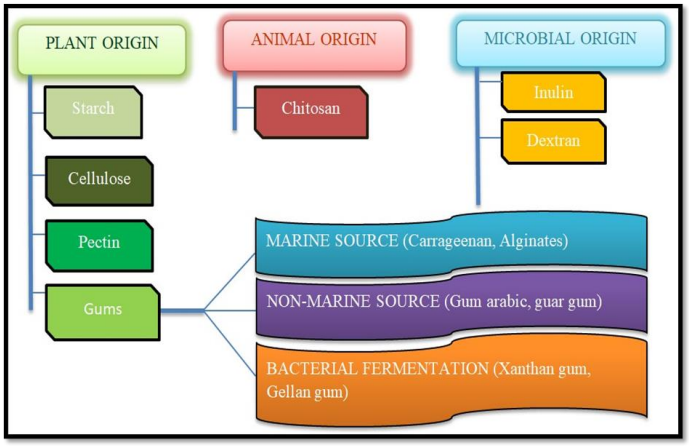
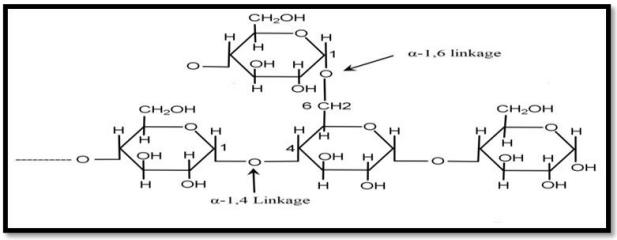


Figure 1: Classification of polysaccharides based biopolymers

1. Plant based delivery Agents

(A) Starch



Starch is a natural carbohydrate-based polymer found in roots of plants, seeds, tubers, cereals, legume and vegetables. It is a non-allergic, inexpensive, bland taste, GRAS polymer complex polysaccharide comprising of two major types of biopolymers i.e. linear amylose composed of glucose units linked by α-1, 4 glycoside bonds and branched amylopectin containing α-1, 6 linkages**.** [11, 17] The molecular and physical form of starch molecules, granule size, amylose-to-amylopectin ratio, pore presence and size governs its digestibility in GIT tract. [8] Commercially available starches being used as wall material are maize, potato, wheat, rice and cassava starch.

Applications: - Native corn starch has been successfully used for target delivery of catechin in GIT. [18] It is also used for

the controlled and targeted delivery of functional compounds such as vitamins, lipids, essential oils, flavors, drugs, pigments, proteins, microorganisms, probiotics, and fragrant compounds. [19, 20]

Limitations of native starch:-

1. The long chain structure makes it susceptible to hydrolysis by gastric acid and enzymes in upper human GIT. [8, 21]
2. Its hydrophilic nature limits its use as delivery system for hydrophobic bioactive compounds.

These drawbacks can be overcome by physical, chemical, and/or enzymatic structural modifications for desired properties such as increased hydrophobicity in modified starches like octenyl succinic anhydride, cyclodextrin, maltodextrin which are. [11, 14]

Modified starches: The major objective of starch modification is to improve its functional properties i.e. water holding capacity, heat resistance, binding capacity, viscosity, solubility, gelatinization extent and starch syneresis during processing for expanding its area of applications in food, pharmaceutical and other industries. [13, 17, 22] The non-toxic thermally modified starches produced at low cost are of prominent use for formulation of controlled release tablets. [23] These modifications delay the release of bioactive compounds in microcapsule formulations. Thus, it was inferred that in humans also, this combination would lengthen the GIT transit time hence facilitating the maximum intestinal absorption. [24] The most common structural modifications incorporated are crosslinking, oxidation, hydrolysis and acetylation. [25] Table 1 summarizes some of the modified starches used for the controlled release of ingredients.

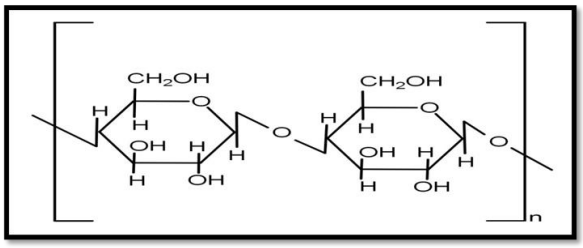
Limitations of modified starches: high cost, time and unit operations required in processing, and increased use of enzymes and reagents required for each, modification. [20]

Table 1: Modified starches used in food and pharmaceutical industries

Modified starch	Method of modification	Properties	Applications	Reference
Capsul ™	*Chemical modification:* Incorporation of lipophilic groups	Excellent film forming properties and low viscosity in high soluble solid concentration	Anthocyanin retention	13
Acetyl salicylic acid and pre-gelatinized starch	*Chemical modification*: acetylation *Physical modification*: gelatinization	Prolong dissolution profiles, improved hydrophobicity and resistance to enzymatic hydrolysis, reduced swelling ability	Compressed into tablets	17, 26
Dialdehyde starch and propyl starch	*Chemical modification*	Better swelling ability and hydrophobicity	Delivery of lipophilic pharmaceutical agents	11, 14
Linear amylose	*Chemical modification*: cross-linking	Higher heat and shear stability, co-crystallize with lipophilic molecules	Aromatic compounds, long chain alcohols, lipids and surfactants	11
Octenyl succinate anhydride (OSA) starch **Sodium octenyl succinate modified starch (SOSMS)**	*Chemical modification*: Incorporation of hydrophobic alkenyl and hydrophilic carboxyl groups. Physic-chemical modification by inserting hydrophobic octenyl side chains	Improve bioavailability of lipophilic bioactive components; excellent emulsifier Higher solubility in simulated gastric fluid (SGF).	Encapsulation of hydrophobic food ingredients such as b-carotene, curcumin and coenzyme Q10;	11, 20, 27-30
Resistant starch	*Enzymatic modification:* Fraction of starch produced by intestinal bacterial action	Resistant to digestion by enzymes in stomach and duodenum	Promising material for designing colon specific delivery system	31

Hydrolyzed starch	Enzyme hydrolysis	High water solubility and bland flavor	Encapsulation of vitamins and oils	30, 32
Cyclodextrin	*Enzymatic modification*: Cyclization of glucopyranose by cyclodextrin-glucosyl transferase enzyme.	Low glycemic index and prebiotics in the GIT of the human.	Encapsulation of kenaf seed oil using CD enhanced its bioaccessibility in human GIT.	16, 33, 34, 35
Glutathione responsive β-CD	Crosslinking β-CD, pyromellitic dianhydride and 2-hydroxyethyl disulfide	Drug release profile was accelerated in the presence of increasing amounts of GSH	For encapsulation of drug doxorubicin	
Oxidized and cross-linked starch	Oxidation using catalyst followed by crosslinking	Enhanced film formation ability and adhesivity, and improved drug release functionality.	Suitable for delivery of pH sensitive ingredients in intestine such as lysozyme, β-carotene, anthocyanins.	25, 30, 36

(B) Cellulose



Cellulose is an abundantly found natural polysaccharide biosynthesized from living organisms such as marine animals (e.g., tunicates), plant sources (e.g., wood, cotton, wheat straw), bacteria and fungi. It is a linear biopolymer comprising of anhydro-D-glucopyranose linked together by β-(1-4)-glycosidic linkages. [16, 37, 38]

Limitations: Long dimensions and low solubility in water and other common solvents has restricted its application for encapsulation in food and pharmaceutical industries. However, physically, chemically or biochemically induced structural modification makes it more suitable to be used as encapsulating shell by decreasing inter- and intramolecular hydrogen bonding. [11, 16, 26, 39, 40]

Cellulose Derivatives: are obtained by esterification or etherification of hydroxyl group rich cellulose backbone. These are biocompatible, non-toxic and easily compressible polymers which can hydrate rapidly at body temperature.

Applications: The ability to accommodate large percentage of drugs without affecting the drug release rates expanded their scope of applications in various fields i.e. cosmetics, pharmaceutical industries, veterinary foods, textile industries and biomedical fields etc. [15, 16, 38]

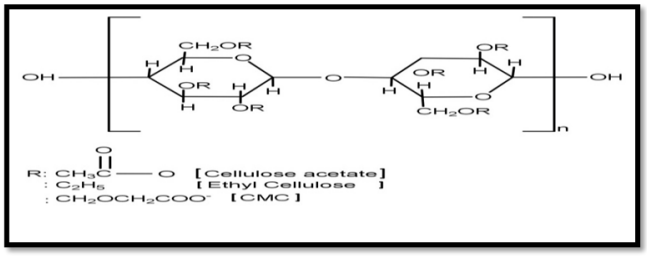
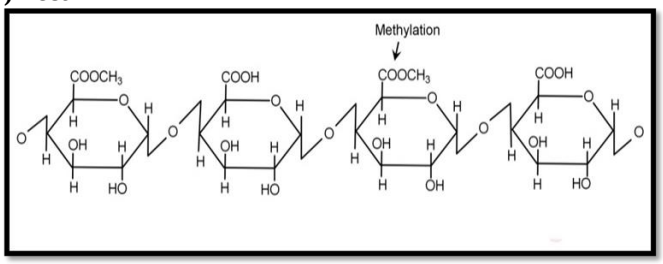


Table 2: Cellulose derivatives used in food and pharmaceuticals industries

CELLULOSE DERIVATIVE	MODIFICATIONS	PROPERTIES	APPLICATIONS
Carboxy methyl cellulose (CMC)	Synthesised by reverse micelle polymerization of cellulose using divinyl sulfone as crosslinking agent. [41]	Biocompatible, non-toxic biodegradable, low cost, water soluble, chemically reactive polymer with excellent film forming and effective oxygen and lipid barrier properties [41, 44, 45]	CMC and carrageenan/ chitosan blends are used as protective vehicle for nutraceuticals. Aluminium CMC-rice bran composite microcapsule are used for delivery of probiotics. [8, 42]
Methacrylated carboxymethyl cellulose and disulfide containing cystamine bis acrylamide (MACMC-CBA)	Electrostatic interactions between the carboxyl groups of MACMC and the protonated amino groups of drug DOX	High encapsulation efficiency (83%) and high drug loading content (36%), improved drug coupling efficiency and colloidal stability. [16, 43]	Used as binder, stabilizer, thickener, tableting as filler with active compounds, and drug formulation to enhance stability and bioavailability of active compounds. [25, 44, 45]
Acylated CMC			
Cellulose Acetate (CA)	Obtained by acetylation with acetic anhydride and acetic acid in the presence of sulphuric acid.	Insoluble in acidic solution but gets readily dissolved in alkaline environment of small intestine	Used as enteric coating of tablets, film and pallate coating sustained and delayed release of drugs .[11, 46] CAPh-dye beads were used as visually readable labels in lateral flow immune-assays. [47]
Cellulose phthalate acetate (CAP)			
Hydroxy propyl cellulose (HPC)		Water soluble, form viscous and non-ionic colloidal solution, good film-forming ability. [36, 39]	HPC phthalate nanoparticles produced were found to have a successful loading % of 10.76% to 16.04% with an encapsulation efficiency of ~100%. [25, 48]
Amphiphilic methyl cellulose (AMC)	Hydrophobic segments, like poly (L-lactic acid), are grafted onto the cellulose backbone. [16]	Non- toxic, inert, compressible , biocompatible hydrophobic thermoplast with good chemical stability and non- biodegradable, [49]	MC in combination with maltodextrin has been used for preparation of fish oil microcapsules. [50]
Ethyl cellulose (EC)			Used for coating and controlled release of bayberry polyphenols [30] and various drugs such as aspirin, theophylline. [36, 51]
Cellulose nanocrystals (CNC)	Formed by acid hydrolysis of cellulose	Enhance encapsulation efficiency and stability of bioactive compounds.	β-CD encapsulated curcumin loaded into CNCs were 3 to 4 times more effective against PC-3, DU-145, and HT-29 cancer cell lines than the curcumin alone.[25, 52]
Nano-fibrillar cellulose (NFC)		immobilization of drug nanoparticles in suspension, stabilization of emulsion systems and sustained drug release. [35]	Drug loaded NFC microspheres produced by spray drying were found to have limited/or slow drug diffusion from the system due to the tight fiber network of NFC. [53]

(C) Pectin



Pectin is a complex plant based anionic linear polysaccharide found primarily in cell walls of terrestrial plants and produced commercially from apple pomace and 25–30% dry weight citrus. Chemically, it comprises of at least 17 different kinds of monosaccharides connected linearly such as rhamnogalacturonan, homogalacturonan, substituted galacturonan, and xylogalacturonan with α-(1-4)-d-galacturonic acid as main component followed by the D-galactose and L-arabinose. It remains chemically intact in upper human GIT but gets degraded by pectinolytic enzymes produced by colonic micro flora, hence considered as a suitable carrier for target delivery of acid sensitive bioactives. [25, 26, 54-57]

Modified Pectin: Pectin structures undergo modification by methoxylation i.e. the functional group carboxylic acid (COOH) on the galacturonic chain is substituted by methyl group. Based on the percentage of carboxyl group esterified with methanol i.e. degree of esterification (DE) it is classified into two types: Low methoxyl (LM) pectin (25-50% methoxylation) and High methoxyl (HM) pectin (50-80% methoxylation). [11, 14, 57] The degree of esterification varies with the source of pectin and influences pectin structure, interaction and properties. The arrangement of methyl groups and DE accounts for gel forming and structural characteristics of pectin. LM pectin form gels in presence of divalent cations (e.g. calcium ions), whereas HM can form gels at low pH and high sugar concentration. [8, 58] The size of nanoparticles ranges from large (r > 1000 nm) when used as single biopolymer to smaller one when used as a blend with other biopolymers such as chitosan, gellan gum etc. [59, 60]

Limitations:, The major drawback associated with its use is rapid in-vitro release. The relatively porous structure of calcium pectinate beads causes hasty release of incorporated bioactives and hence accounting for low encapsulation efficiency. However, this drawback can be overcome by increasing rate of dissolution of encapsulants in pectin by high intensity ultrasound. This property of gelation leads to its application in food and pharmaceutical industry. [5, 11, 61]

Table 3: Pectin uses in food and pharmaceutical industries

Indomethacin, a drug encapsulated in LM pectin and charged modified HMP nano-hydrogel beads were found to have high encapsulation efficiency with minimal release. [62]
Mangiferin, a drug encapsulated using different pectin formulations found to exhibit higher retention rate. [63]
Pectin coating on protein nanoparticles results in improved physicochemical stability, loading capacity and sustained release of lipophilic compounds (e.g. curcumin) under GIT conditions. [25, 64]
As a *stabilizer, gelling agent and fat replacer* in jams, marmalades and acidic milks etc. [57, 60]
As an *additive* for sustained release of non-steroidal anti-inflammatory drugs (NSAIDs) and for colon specific controlled release of folic acid. [26, 65]
Probiotic encapsulated in pectin starch based food-grade hydrogel particle was found to be resistant against adverse conditions of the GIT and bile salt solution compared to non-encapsulated cells. [42]
Curcumin loaded chitosan-pectinate nanoparticle used for treatment of colorectal cancer was able to retain its integrity in SGF and had about 64% encapsulation efficiency. [66]
It was found that 78.28% of citrus peel flavonoids encapsulated in pectin nanoparticles were released in simulated gastro-intestinal fluid unlike 73% of flavonoids from naked citrus peel extracts after just 2 h, thus indicating exhibiting the improved bioaccessibility of these pectin nano-particles. [67]
HMP interaction with hydrophobic molecules such as antibiotics of the fluoroquinolone's family results in an improved incorporation to matrix and controlled release profile. [68]

(D) Gums

Gums are defined as group of organic, natural hydrophilic polysaccharides obtained as plant exudates and form viscous dispersions or colloidal solutions. [40, 69, 70]

Advantages over synthetic biodegradable excipients:- they are non-toxic, less expensive, and biocompatible and can be modified into tailor made polymers to overcome problems such as uncontrolled rate of hydration, thickening, decrease in viscosity on storage, microbial contamination etc.

Applications:- Owing to their unique properties, availability of reactive sites for molecular interactions and easiness of use, these gums and their derivatives have widespread applications in food and pharmaceutical sector. Some of the broadly explored uses of this edible polysaccharide are:

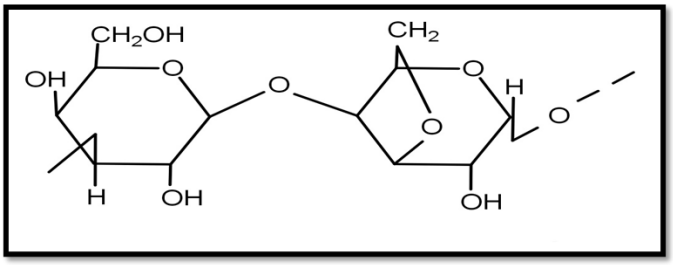
1. Used as wall materials for a variety of nano encapsulated food ingredients such as flavouring agents, vitamins, minerals, and essential fatty acids etc. [71]
2. Used as gelling agents, thickening agents, stabilizers and emulsifiers etc. in food industry.
3. Restricted digestion and absorption in body, makes them suitable carrier to improve the controlled drug release function of targeted drug delivery system. [72]

There are several classifications of these natural polysaccharides but are generally classified on the basis of origin into three categories These are agar, sodium alginate and carrageenan (marine source), gum arabic, guar gum, glucomannan etc. (non-marine botanical sources) and xanthan gum and Gellan gum (bacterial fermentation). Commercial

gums commonly used in foods are locust bean gum, carrageenan, xanthan, Ghatti, Karaya, and Tragacanth and gum Arabic. Some lesser known gums from non-traditional sources identified as native gums are Cress seed, Angumgum, Balangu, Basil, and Qodume Shirazi. [25, 26, 40] Some of the recent studies have explored the use of gums as delivery agents for microencapsulation of drugs and antioxidants. Quercetin encapsulated in gum nanoparticles resulted in higher antioxidant activity and physical stability. [71] However, these gums are generally used as a blend with other polysaccharides e.g. modified starches, chitosan. Bioactive compounds of golden berry juice encapsulated using different blend i.e. maltodextrin and Arabic gum, maltodextrin and alginate; maltodextrin and pectin were found to have 75% retention of phenolic compounds and maximum encapsulation efficiency. [73, 74] Similarly Tan et al. [75] has proved that curcumin encapsulated in chitosan-arabic gum nanoparticles resulted in enhanced stability and controlled release in SGI conditions.

(i) Marine based gums

(A) Carrageenan

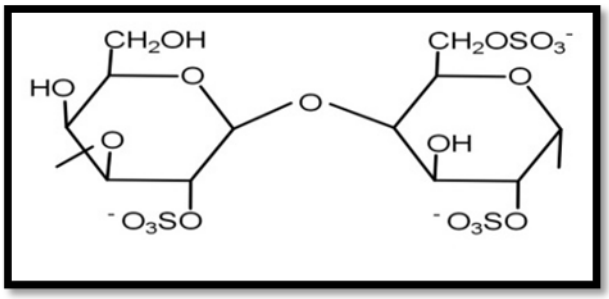


Carrageenan is a hydrophilic biodegradable, edible biopolymer extracted from some species of marine red algae (Rhodophyceae) such as *Chondrus crispus* and *Gigartina stellata*. [26] It comprises of β-(1, 3) sulphated ɒ-galactose and α-(1, 4)-3, 6-anhydro-ɒ-galactose residues extracted from the extracellular matrix of red edible seaweeds. [70, 76]

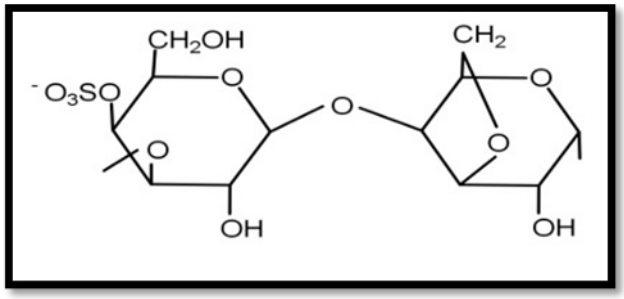
Applications:-This polymer has gained varied applications in experimental medicine, pharmaceutical formulations, biomedical field, cosmetics and industries. It's an extremely versatile ingredient with no nutritional value, being useful in tissue engineering, preparation of drug vehicles for controlled release, as a potential material for hydrogels. It is also used as a stabilizer, gelling agent, thickening agent, and emulsifier and as a fat substitute in meat. [77, 78] It is considered as a suitable wall material for encapsulation by spray drying attributing to its pseudo plastic properties, which enhances the force of adhesion between the core material and wall material resulting in the formation of spherical and smooth surfaced microcapsules. [79]

There are three types of carrageenan commonly used in foods having different gelation properties. These are κ- (kappa), ι- (iota) and λ-(lambda) depending on the number and position of the sulfate groups per repeated disaccharide units**.** These comprises mainly of sulfated esters of d-galactose and 3, 6-anhydro-d-galactose copolymers, linked by α-1, 3 and β-1, 4 linkages. [26, 38, 45] These are soluble in hot water to form gels. The Carrageenan microgels are prepared by non-covalent interactions (as hydrophobic or ionic interactions) or by covalent linking (chemical cross-linking of polymer chains with cross linker). The gelling properties of non-covalent binding are influenced by coil-to-helix transition in the presence of cations such as K^+, $Ca^{2+,}$ and Na^+ and types, valencies, and concentrations of cations in the salts. However, viscosity and the gel strength of carrageenan drop in acidic pH (<4.3). [22, 54]

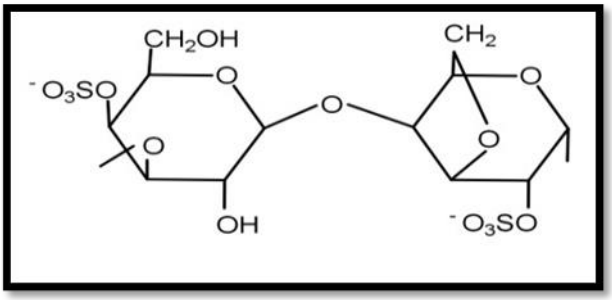
Lambda *(λ)-carrageenan* is highly sulphated (three sulfate ester groups) and doesn't contain 3,6-anhydro galactose, therefore doesn't form gel and is used as thickening agent primarily.



Kappa *(κ)-carrageenan* (one sulfate ester group) form strong, rigid, and brittle gels with poor freeze–thaw stability in the presence of K^+ or Ca^{2+} salts. [80]



Iota *(ι)-carrageenan*: (two sulfate ester groups) form soft and elastic gels in the presence of calcium ions with good freeze–thaw stability. The gels formed are thixotropic in nature and yields fragments of greater molecular weight upon hydrolysis in the GIT. [70, 78]



The polymer has been explored for target delivery in food and pharmaceutical applications. κ-Carmacrogels formed by chemical cross-linking of the polymer chains with epichlorohydrine (ECH) resulted in high salt responsiveness

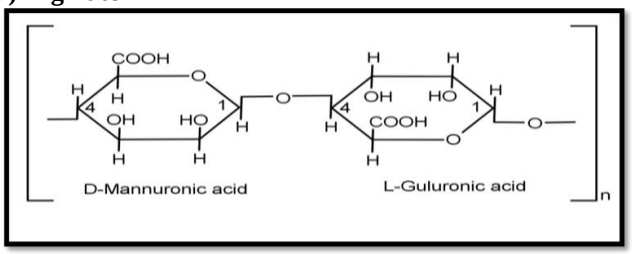
and a targeted release of their content in the GIT. [81] Sagbas et al. [82] also reported carrageenan microgels/nanogels prepared by using DVS as cross-linkers (100 nm to 10 μm in size) as potential targeted drug delivery agent.

Structural modifications: Although carrageenan is used as potential delivery agents for encapsulation, certain modifications can be introduced in their chemical structure to ensure the target release of encapsulated drug/ active compounds in the intestinal region without getting degraded in the stomach.

(i) *Carboxymethylation*: i.e. attaching pH sensitive carboxylic acid groups (–COOH) groups to the carrageenan polymeric structure, best suited for site-specific drug delivery to the intestine due to the change in pH from acidic (pH ~ 1.2) in the stomach to slightly alkaline (pH ~ 7.4) in the intestine as the drug carrier passes through GIT. [83] Leong et al. [84] synthesised pH-responsive carboxymethylated κ-Car microparticles through ionotropic gelation with KCl for target delivery of drug fluorescein isothiocyanate-labeled dextran. The drug release rate was found to be different in acidic (about 23% at pH 1.2) and alkaline conditions (about 90% at pH 7.4) in simulated intestinal fluid. It is therefore, considered as a suitable carrier for encapsulation of bioactive molecules such as peptides, hormones, or gene fragments.

(ii) *NaOH treatment*: Carrageenan microgels were treated with NaOH to generate deprotonated O–groups, which directly interacted with epichlorohydrine (ECH) bounding agent with the amine sources. The negatively charged Car microgels become positively charge modified Car microgels by chemical bonding with the NH_2 groups of diethylenetriamine (DETA). This alteration resulted in 250 fold increase drug loading capacity of microgels from 0.18 mg/g for bare gels to 43.7 mg/g loading for modified Car microgels. The three types of carrageenan microgels along with modified forms were found to have high hemocompatibility properties i.e. low haemolysis ratio and high blood clotting index suggesting them to be suitable and safe for in the vascular system for biomedical applications. Thus these modifications make carrageenan microgels and its modified forms potential and sustainable drug carriers, antimicrobial agents, and can also be used in the cancer therapy against different cancer cells. [45]

(B) Alginate



Alginate is a natural anionic unbranched polymer extracted from brown seaweed algae (Fucophyceae). It is a linear polysaccharide comprising of β-(1, 4)-linked α-L-guluronic (G) and β-D-mannuronic (M) acids. [16, 32] The physiochemical properties and structure of alginates depends on their polymer sequence and M/G ratio. It is also secreted by bacteria Pseudomonas aeruginosa, Azotobactersp as an exopolysaccharide (EPS) with more defined chemical structure and physical properties compared to seaweed derived polymer. Presence of O-acetylase unit on the second and/or third positions of the D-mannuronic acid residues of alginates synthesized by bacteria increases their water binding capacity. [40, 37]

Advantages:

1) It's a non-toxic, biocompatible, biodegradable, easy to use, low-cost polymer with chelating ability and hence extensive uses in pharmaceutical, cosmetic, chemical, and food industries. [11, 85]
2) It can form strong hydrogels and hence considered as an excellent delivery agent for target delivery of drugs and nutraceuticals in human body attributing to block like structural arrangement of its monomers residues. [86, 87]
3) The polymer has several advantages owing to its excellent swelling property, non-toxicity and hydrophilic nature.
4) It facilitates slow and reproducible degradation rates can be used to encapsulate both hydrophilic and hydrophobic materials, effective transportation of drug/biomolecule against enzymatic degradation, high oral bioavailability of encapsulated drugs and can be administered orally, thus preserving cellular metabolism. [37, 90]

Applications:

1) The hydrophilic nature and ability of the polymer to form three-dimensional networks in the presence of multivalent metal cations such as Cu^{2+}, Zn^{2+}, Ca^{2+}, Ba^{2+}, Al^{3+} etc. i.e. ionotropic gelation makes it the most favourable and widely used material for encapsulation of bioactive compounds. [56, 85, 88, 89]
2) The polymer hydrogels are thermally stable, biocompatible, pH sensitive, insoluble at low pH and swells in a high-pH environment. Therefore it is used for delivery of acid sensitive bioactive ingredients in the intestine by concurrently delaying its release in acidic environment. [14]
3) The versatile nature of the polymer accounts for its extensive applications in food, pharmaceutical and agricultural industries in the form of hydrogels, films, fibers, beads, oral tablets, microcapsules, implants, and topical delivery systems. [86]
4) Alginates and its derivatives have been used for encapsulation of agrochemicals (herbicide, insecticide and bactericide), bioactive compounds, drugs, lipophilic compounds, enzymes (lipase) and oils etc.. [26, 32, 37, 56]
5) Polymer beads produced by modified emulsification or gelation are used as a matrix for immobilization of thermally stable materials such as microbial cells [50, 58. 19, 87]

Limitations: There are two major limitations associated with this complex bead system.
1) Low encapsulation efficiency: alginate beads may collapse on exposure to intestinal fluid due to presence of acids and Na^+ ions thus resulting in leaching out of encapsulants and

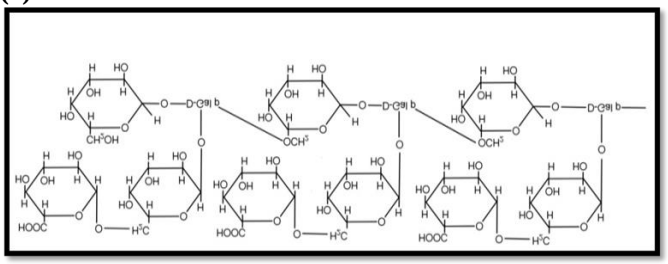
henceforth accounting for low encapsulation efficiency of the matrix. Therefore, it is considered a suitable carrier for low molecular weight drugs. [8]

2) Rapid Dissolution (Burst release): The ability of sodium alginate to swell up in aqueous media may result in microcapsules rupture under certain environmental conditions i.e. pH or presence of ions etc. [91]

Structural modifications: Nevertheless, these drawbacks can be overcome by introducing some structural modifications in the polymer such as covalent crosslinking, copolymerization and blending with other polymers like pectin, chitosan etc. The modifications results in a biopolymer with improved and markedly different properties such as enhanced encapsulation efficiency, swelling capacity, mucoadhesive property and sustained release profile with enhanced stability of sensitive compounds (i.e. vitamins, antioxidants) thus up surging its demand in different fields of tissue engineering, drug delivery, environment, and others. [90, 92]The effective combination of alginate-pectin copolymer has been shown to have high encapsulation efficiency. Similarly, alginate was combined with guar gum using a crosslinking agent glutaraldehyde to attenuate these limitations. Numbers of studies have been done on uses of modified alginate derivatives in food and pharmaceutical industries. An ionotropically cross-linked mixture of sodium alginate and chemically modified carboxymethyl chitosan grafted with poly (ethylene glycol) hydrogel microspheres showed an improved in-vitro delivery and higher percentage of drug release for protein drugs in simulated intestinal fluid (SIF) than in simulated gastric fluid (SGF). [93] Similarly, Clitoria ternatea petal flower extract (CT) encapsulated in calcium alginate microspheres has shown increased biological activity, antioxidant activity, pancreatic α-amylase inhibitory activity and bile acid binding capacity suggesting it to be a potential delivery system to impede the carbohydrate and lipid digestion in GI tract. [94]

(ii) Non-marine (botanical sources) based gums

(a) Gum Arabic/Gum Acacia



Gum arabic is a highly water-soluble polymer obtained as a dry exudate from trunks and branches of Acacia Senegal and Acacia seyal trees. It is an edible heteropolysaccharide which is found as a complex salt of calcium, magnesium, and potassium. The polymer is an amalgam of 90–99% of arabinogalactan oligosaccharides (d-galactose, l-arabinose, l-rhamnose, d-glucuronic acid), and 1-2% glycoprotein which differentiates its functional properties with other gums. [95] The backbone is made up of 1, 3-linked β-d-galactopyranosyl units. [16, 19, 96]

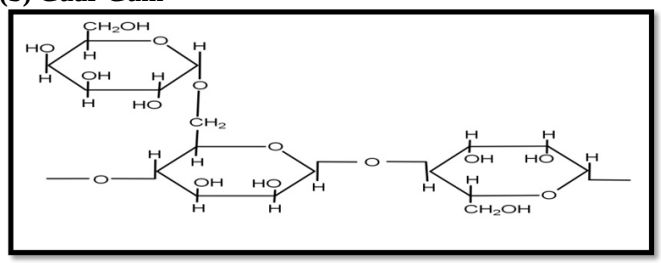
Advantages: It is soluble in cold water and stable in acidic environment. It shows antimicrobial, anti-inflammatory, and anticoagulant activity. Owing to its versatile functional characteristics i.e. good emulsifying capacity, film forming ability, high solubility and compatibility with high sugar concentrations, delicate taste, and low viscosity at high solid concentrations, high oxidative stability and good retention rate of volatile compounds encapsulated; it is treated as the most desirable wall material for microencapsulation by spray drying in food industries.

Applications: It is being used as an emulsifier for oils and flavors attributing to the presence of protein and polysaccharide fractions, texturizing agent, foam stabilizer, coating agent and encapsulating agent (especially for flavors). [14, 26, 97, 98]

Limitations: However, despite having resourceful applications and properties, there are some factors which confines its application as a wholesome single polymer such as low protein content (2%) as 15-25% required for emulsification [99], high cost, inconsistency in quality, limited supply as it is only produced in regions with unpredictable climate variations i.e. Sudan and Africa. [96, 97, 100] Therefore, complete or partial substitution of gum arabic by low cost materials such as modified starch, maltodextrin and inulin has been stimulated. [23, 89, 101]

The different blends used are pullulan combined with gum arabic and maltodextrin used to stabilize turmeric oleoresin emulsion without using stabilizers and diluents. [102]The blend of gum arabic and Maltodextrin has better level of water solubility, encapsulation efficiency and stability and hence being used as encapsulating material to overcome hindrances such as stickiness and high hygroscopicity, occurring during spray drying process. [103, 104] Currently, modified gum arabic derivatives are also being explored for encapsulation of antioxidants, oils and flavours and as an additive in food industries. Some of the modified gums being used are octenyl succinic anhydride gum arabic as food additive [14], acetylated gum arabic for preparing iodine complexes. [105] Similarly, Hu et al. [106] reported that citrus flavonoids encapsulated in gum Arabic-whey protein complex resulted in high powder yield (72.74%) and encapsulation efficiency (97.60 ± 0.99%) with better retention of antioxidant activity.

(b) Guar Gum



Guar gum is an inexpensive and flexible carrier obtained from seeds or endosperm of legumes *Cyamopsis tetragonolobus.* It's a high molecular weight biodegradable functional

polysaccharide consisting of linear chain of d- mannose units linked by β (1→4) glycosidic linkages and branches of d-galactopyranosyl units linked by α (1→6) glycosidic linkage. [26]

Advantages: It is non-toxic, biocompatible, inexpensive water-soluble polysaccharide.

Applications:-

1) It is being used for target delivery and prolonged release of active compounds and drugs in food and pharmaceutical applications.

2) It is also used in textile and paper industries as sizing and finishing agents; as a thickening agent for lotions and creams, as a binding agent for tablet making, as an emulsion stabilizer in cosmetics and food industries,; and in mining industry as a fracturing fluid additive in hydraulic fracturing processes. [88, 107]

3) The high water swellabilty and non-toxicity makes it a suitable polymer for making hydrophilic matrix tablets.

Limitations:

1) Uncontrolled hydration rate and decreased viscosity on storage limits its application in pharmaceuticals for controlled drug delivery resulting in premature release of loaded drugs. This drawback can be overcome by conjugating the gum with other polymers i.e. blends, forming an interpenetrating polymer networks (IPN).

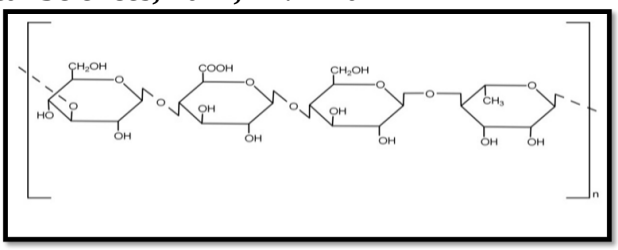
2) Another limitation associated with this gum is its susceptibility to microbial degradation in GIT and hence guar gum succinate-sodium alginate beads can be prepared for colon specific drug delivery. [109]

Gum derivatives: guar succinate, guar benzoate, guar phthalate, oxidized guar and sodium carboxymethyl guar, guar gum hydrolysate (GGH) etc. are modified gums. [1,15, 26, 108] Studies have shown that formulations having 5 % guar gum gave an appropriate release pattern over a certain period of time of 12 hrs.

Applications of gum derivatives: The ability of guar gum to combine with high polymeric groups and other materials has extended its applications in water purification treatments. Guar gum grafted onto multiwall carbon nanotube (MWCNT) and iron oxide nanoparticles (GG–MWCNT– Fe3O4) have been used as adsorbents for the removal of industrial dyes such as neutral red and methylene blue dye from the wastewater or other aqueous systems. [110] Similarly, Sharma et al.[111] made nanohydrogel sheets adsorbent by crosslinking guar gum with soy-lecithin for removal of fungicide, thiophanate methyl.

(iii) Bacterial fermentation based gums

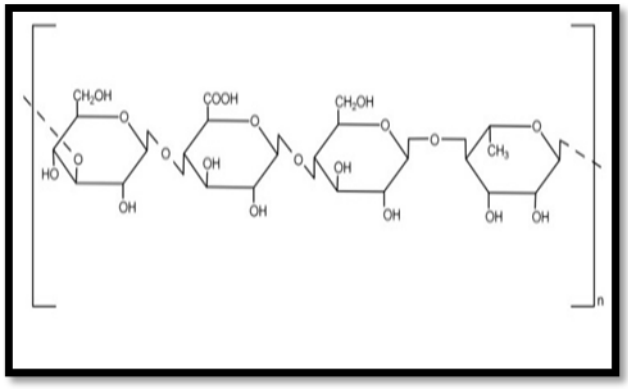
(a) Gellan Gum



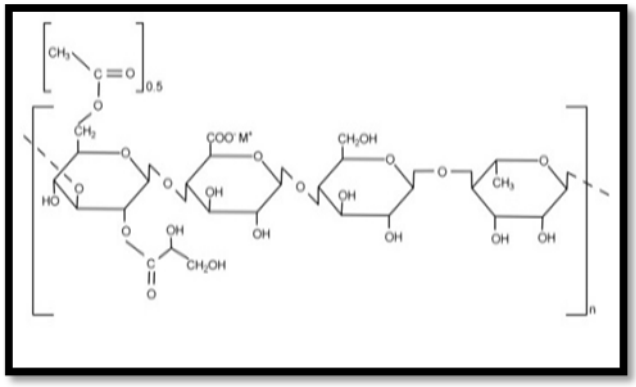
Gellan is an anionic exopolysaccharide produced as a secretion of bacteria *Sphingomonas elodea* or *Pseudomonas elodea* by fermentation. Chemically it is composed of repeating tetra saccharide units (1, 3-β-D-glucose; 1, 4-β-D-glucuronic acid; 1, 4 β-D-glucose; and 1, 4-α-L-rhamnose). [16, 88, 112]

Advantages: It is a thermostable, biocompatible, biodegradable, ductile, non-toxic hetero-polysaccharide with stability over a wide range of pH. It's resistant to enzymatic action and acidic pH with an exception of being susceptible to degradation by enzyme galactomannanases in colonic fluids. This resistance makes it suitable carrier for targeted colon delivery of active compounds. [8]

Commercially it is found in two forms i.e. high acyl GG (HAG) or acylated Gellan gum (Gelrite TM) and low acyl GG (LAG) or deacylated Gellan gum (Kelcogel TM). Structurally, it's found as random coils at high temperature and as double helices at low temperature. [88, 113, 114] The polymer hydrogels formed by cross-linking with monovalent/divalent cations are more thermostable and acid resistant as compared to other polysaccharide hydrogels, hence making it a suitable carrier for acid sensitive compounds. [115] However, gel strength is affected by number of factors such as gellan concentration, pH, temperature, valency, concentration and type of cations resulting in the formation of gels with variable textural properties. LAG gum forms strong, hard and transparent gels while HAG forms soft and elastic gels. [10, 116]



Low acyl gellan gum



High acyl gellan gum

Applications: The widely explored fields for usage of gellan gum are:

1) Biomedical applications: gene therapy and gene transfection, protein carrier, diabetic wound healing, cell adhesion, biological signalling, guided bone-regeneration material biocides in the prevention of spreading of microbial infections etc. [74]

2) Pharmaceutical applications: drug formulations, controlled drug release, injectable nanoparticles, ionotropically gelled beads, in situ gel etc. [16]

3) Tissue engineering: as substrates for bone and fibroblast tissue engineering and tissue-mimicking materials.

4) Food industry: as FDA approved potential stabilizer, emulsifier, binder, gelling agent, coagulant, lubricant, film former and thickening agent in confectionery, dairy products, acidic foods etc. [116]

5) Used as a wet cleaning agent in Textile industry.

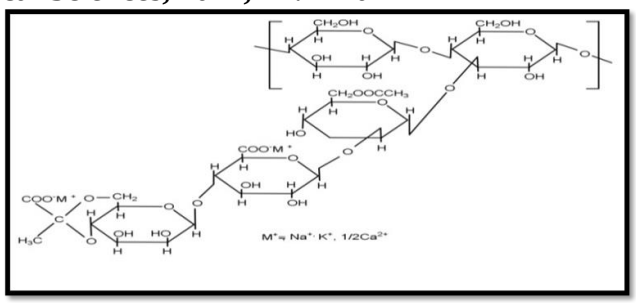
6) Biotechnology: preserving the viability of LAB (Lactic acid bacteria) useful for production of many fermented foods such as cheese, wine etc. [114]

Limitations: With the numerous applications of the polymer, there are certain drawbacks associated:

1) Rapid in-vitro release: The relatively porous structure of calcium pectinate beads causes hasty release of incorporated bioactives and hence accounting for low encapsulation efficiency. However, this drawback can be overcome by increasing rate of dissolution of encapsulants in pectin by high intensity ultrasound. [11, 59, 61]

2) Poor mechanical strength of gel and disordered coiled formation due to temperature dependent structural changes resulting in thermally reversible weak gels. However, these downsides can be overcome by blending it with other polysaccharides such as chitosan pectin, pullulan, cellulose etc. Gellan gum grafted pectin was used for aroma retention. [116]

(b) Xanthan Gum



Xanthan gum is a non-toxic high molecular weight exopolysaccharide produced by fermenting action of bacteria *xanthomonas campestris*. It is primarily composed of linearly linked repeated pentasaccharide units i.e. a cellulose backbone (1, 4-linked β-d-glucose residues) and a trisaccharide side chain of β-d-mannose-β-d glucuronic acid-α-d-mannose attached with alternate glucose residues of the main chain. [48, 88, 117]

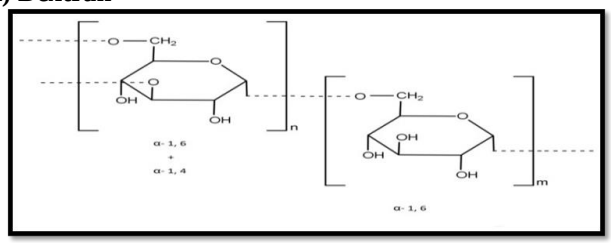
Advantages: It is a colourless, tasteless, and odourless gum with smooth texture. The gum is highly stable in terms of its resistant to heat, acid and alkali conditions and ability to form clear weak gel-like liquid.

Applications: It is widely used in food, pharmaceutical, cosmetics and petroleum industry. [21, 48]

Limitations: Its hygroscopic nature can cause the agglomeration of pre-blended powder mixtures during storage thus causing deformation in shape of powder particles i.e. 'fish-eye' shape as reported. However, these deformations can be corrected by some physical or chemical modifications of the polymer or by blending it with other polysaccharides such as chitosan, maltodextrin etc. [118] Reportedly, a mixture of XG and chitosan has been used for controlled release of ambroxol HCl. [119]

2. Microorganism based delivery agents

(A) Dextran

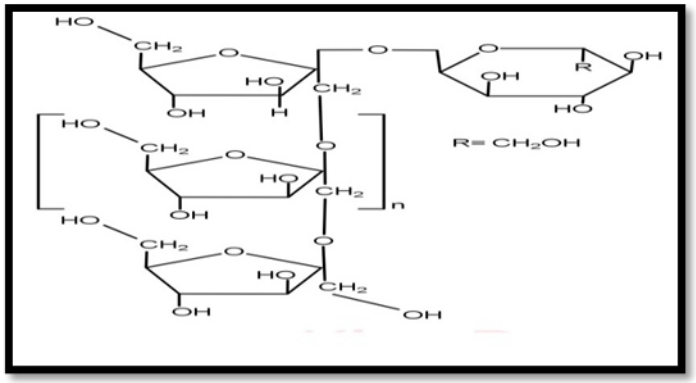


Dextran is a hydrophilic neutral polysaccharide produced by enzymatic action on cell surface of Lactic acid bacteria such as leuconostoc mesentroides. The glucose homopolysaccharide consist of d-anhydro glucosyl units linked by α (1 → 6) linkages in the main chain and α (1 → 3) linkage in side chain. It's biodegradable, biocompatible but susceptible to degradation by enzyme dextranases produced by gram-negative intestinal anaerobic bacteria. [8, 16, 37] The hydroxyl groups present facilitate the covalent bonding with hydrophobic compounds, thus making it a suitable drug delivery agent in pharmaceutical industry. [14]

Applications: Predominantly it is used for colon specific delivery of drugs attributing to its stability in the stomach and small intestine. It is also used as molecular sieve to separate and purify bio-macromolecules due to its good compatibility with the human body. [37, 45] In 2011, Varshosaz et al. [120] encapsulated the drug budesonide in dextran in a core: polymer ratio of 1:10 for colon specific target delivery to treat acetic acid-induced colitis.

Modifications: Moreover, some physicochemical modifications in the structure of the polymer further widen its field of applications. The hydrophilic polysaccharide can be easily modified owing to its high content of –OH groups by blending with other natural biopolymers such as chitosan or with artificial polymer such as polyvinyl amine, or by incorporation of functional groups such as acetyl which can improve its stability at low pH and hence enable the release of both hydrophobic or hydrophilic compounds at mild acidic conditions (pH 5). [121] Dextran derivatives can be either water soluble or insoluble depending on varying degree of substitution. A dramatic decline in biodegradability of dextran was reported by Aumelas et al. [122] on substitution with hydrophobic group. Similarly, hydrophilic modification of dextran can also be done by negatively charged carboxylic or sulfuric acids or positively charged amino groups. Zou et al. [123] prepared dextran sulfate coated amphiphilic chitosan derivatives nano liposomes and found to have high zeta potential and high encapsulation efficiency. Fan et al. [124] reported Dextran - Bovine serum albumin conjugate nanoparticles as an effective carrier for curcumin by retaining its stability and antioxidant activity. TSPO-Dex conjugate, a cancer targeted drug delivery system was also made by combining dextran with translocator protein (TSPO) ligand. [125] Pramod et al. [126] made a dextran based multidrug carrier by incorporating 3-pentadecylphenol to the dextran side chains which can carry both hydrophobic drug camptothecin (CPT) and the hydrophilic drug doxorubicin together thus enhancing their synergistic action to kill breast and colon cancer cells**.** However, these dextran based conjugates show pH-activated release which makes them suitable carrier for biomedical applications. [16, 45]

(B) Inulin



Inulin is a fructo-oligosaccharide found as a storage carbohydrate in fruits and vegetables such as onion, garlic, banana, and chicory roots. It's a polymer comprising of fructose units linked by β (2-1) linkages with a chain length of 2 to 60 units and an average degree of polymerisation (DP) of 12**.** [45, 96, 127] Variation in DP may influence the functional properties of polymer such as solubility, thermal stability, sweetness power, and prebiotic activity. Chicory (*Cichorium intybus)*, one of the natural sources of inulin has an average DP of about 10 to 12 and long chain chicory has an average DP of 25**.** [128] The polymer can also be synthesized enzymatically by transfer of the gene fructosyltransferase of *Streptococcus mutans* into *Escherichia coli*. The other natural sources of inulin are *Dahlia pinuata* (dahlia), and *Helianthus tuberosus* (Jerusalem artichoke).

Advantages: It is also considered as a dietary fibre with established functional activities such as prebiotic effects (owing to its ability to surpass digestion in the small intestine and only being degraded by certain colon bacteria like bifidobacteria), enhancement in calcium bioavailability, supports the cardiovascular system by decreasing cholesterol levels, anticancer, and immunomodulatory properties . [127, 129]

Applications: Attributing its biological role in human body and thermal resistance inulin has offered numerous applications as a substitute for partial replacement of biopolymer particle matrices such as modified starches, gum arabic wall material for encapsulation of drugs and functional compounds in food and pharmaceutical industries. [130]

1) It is used as a substitute for sugars and fats in dressings, ice cream, spreads, baked goods, dairy products and low-calorie foods, as a thickener, emulsifier, and gelling agent in food industry and as an ingredient in diabetic food supplements owing to its prebiotic action resulting in low glycemic index. [8, 128]

2) Its low hydrolysis capacity and pH resistance in GIT makes it a suitable polymer for colon specific delivery of bioactive compounds, essential oils etc.[96]

3) It is also used as excipient, stabilizer and a drug delivery medium with slow release in pharmaceutical industry.

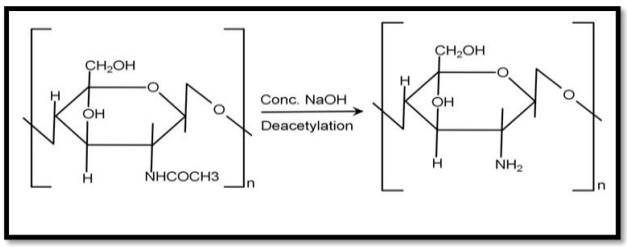
4) Its outstanding ability to survive through GIT and encouraging the propagation of healthy gut micro flora such as lactobacillus, consequently causing a reduction in count of harmful bacteria such as Escherichia coli and Clostridium spp., proves it to be most suitable carrier for microencapsulation of probiotics. L. acidophilus microencapsulated along with inulin results in an increase in viable count as compared to when encapsulated alone. [114] Similarly, Darjani et al. [131] have reported the highest survival rate of 2.7 log reduction for L. casei, against gastric and bile salt exposure by encapsulating in a blend of inulin and chitosan-coating.

Modifications: Moreover inulin derivatives produced by certain modifications in inulin structure results in improved functional properties. Acetylation of inulin results in delayed gallic acid release owing to its decreased hydrophilic properties and swelling power. [132] A blend of modified starch and inulin was found to be a worthwhile substitute for

gum arabic. The blend results in better oil retention and high glass transition temperature, an important parameter for better storage. [101, 133] Likewise, Castel et al. [129] evaluated the potential of blend of Brea gum (BG) and inulin for encapsulation of corn oil and reported significantly high encapsulation efficiency.

3. Animal based delivery agents

(A) Chitosan



Chitosan is the second most abundant natural, non-toxic, poly-cationic biopolymer after cellulose. The linear polysaccharide is obtained by alkaline *N*-deacetylation of polymer chitin found in exoskeleton of crustaceans, cuticles of insects and cell walls of fungi. Chemically it is composed of β-(1-4)-linked 2-amino-deoxy- β -D-glucan, a deacetylated derivative of chitin. [11, 32, 25, 134] The conversion reaction is reversible depending on the degree of deacetylation (DD) i.e. glucosamine/N-acetyl glucosamine ratio. Polymer having high percentage of N-acetyl glucosamine is chitin and with higher degree of glucosamine is called chitosan. [17] The solubility of polymer also varies with DD; at more than 50% deacetylation (Chitosan) it becomes soluble in aqueous acidic conditions i.e. and becomes hydrophobic in nature at less than 40% DD (Chitin) due to strong inter- and intramolecular hydrogen bonding between alcohol, amide and ether functionalities attached on repeating glucan units. [37, 99, 135] However, these H-bonds in chitin can be broken down by treating with complex mixture solvents such as $CaCl_2$-H_2O saturated methanol, lithium chloride/N, N-dimethylacetamide, NaOH/urea, hexafluoroisopropylalcohol (HFIP) etc. [136] The variation in solubility with the change in pH accounts for its applications in different forms such as films, nanofibers, hydrogels or pastes. [11] Therefore, chitin deacetylation is required to overcome its hydrophobic nature which limits its use in biomedical applications.

Applications: Owing to its biodegradable and biocompatible nature with no allergic and toxic dose dependent effect on human body, chitosan has been used in food, pharmaceutical and cosmetic industries.

1) It is used for drug delivery, gene delivery (due to their ability to complex with negatively charged DNA) [137] tissue engineering, in agricultural industry for its plant growth promoting activity , as nano-fertilizers and as pharmaceutical ingredient due to its biological properties such as antitumor, immune enhancing, antimicrobial activity, antioxidant activity and hypocholesterolemic properties.[19, 37, 99]

2) Primarily, it is used as a delivery agent for nano/micro encapsulation of active ingredients, drugs, herbicides, insecticides etc. [32] Resveratrol nano-encapsulated in chitosan showed an increased antioxidant capacity and bioavailability over the free resveratrol. [138] Similarly, curcumin encapsulated in a chitosan-gum arabic blend resulted in higher retention rate during storage, enhanced antioxidant capacity, stability and delayed release. [75]

Advantages: Chitosan-based nano materials have excellent physico-chemical properties and advantages over other delivery systems i.e. slow and controlled bioactive/drug release, *in situ* gelling to form beads, mucoadhesion, hydrophilic behavior, transfection and permeation enhancing, requirement of less amount of core material, efflux pump inhibitory characteristic, compatibility with living cells (for encapsulation of probiotics), improved drug absorption and enhanced bioavailability of the targeted compound. Thus, chitosan facilitates the development of numerous drug delivery systems for different application routes, i.e. oral, ocular, nasal, vaginal, buccal, parenteral, and intravesical. [19, 32, 134] The oral administration of chitosan-based curcumin nanocapsules with an improved encapsulation efficiency of 64-76%, loading capacity of 20-26% and yield of 50-72% caused a significant decrease in hyperglycaemia within 7 days. [139] Similarly, Roy et al. [140] developed chitosan based nanoparticles for delivery of a gene therapy-based vaccine against peanut allergy. Fareez et al. [141] encapsulated the Lactobacillus plantarum (LAB12) strain using chitosan coated alginate–XG beads. The beads so formed had an improved pH resistance, temperature tolerance, storage durability and in-vitro targeted release of the strain. In a study by Zou et al. [142], a comparison was done between pectin/starch coated and chitosan coated B. bifidum F-35 alginate microspheres. The chitosan coated alginate microspheres showed up the highest protection for microencapsulated bacteria under in vitro GI conditions during 1 month of storage at 4°C, hence considered as an effective approach for intestinal colonization of bifidobacteria. These results of probiotic encapsulation studies have shown that chitosan can serve the purpose of achieving a well perceived future trend of probiotic–prebiotic synergy for target release of bioactive molecules and probiotics in intestine.

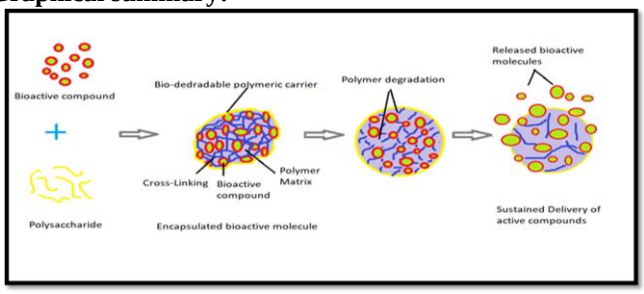
Chitosan derivatives: The cationic nature of chitosan due to presence of reactive functional groups (hydroxyl and amino groups) makes it a desired biopolymer for encapsulation. However, it may cause pre-systematic metabolism of bioactive compounds in GIT due to its poor solubility at physiological pH. Therefore, chitosan derivatives have been reported as potential alternatives e.g. carboxylated, acylated, thiolated and conjugates. [143] **A** range of chitosan derivatives can be made by crosslinking amino groups with other anionic crosslinking agents into a stable complex matrix. [17, 144]Wang et al. [145] reported an enhancement in encapsulation efficiency and stability of anthocyanins encapsulated in chitosan-cellulose crosslinked nanocrystals. The polymer can also be blended other anionic biopolymers, e.g. pectin, carrageenan, and alginate. Lin et al. [146] prepared a novel water-soluble chitosan derivative [N-(2-carboxybenzyl) chitosan] by crosslinking chitosan with GA (CBCSG) hydrogel and

reported a faster release of a poorly water-soluble drug fluorouracil (5-FU), in both simulated gastric and intestinal pH conditions. These derivatives are also derived from partial deacetylation of chitin. The three major chemical reactions involved in chitosan modifications are: sulfaltion/sulfonation, amine quaternization, and carboxymethylation.

Table 4: Applications of chitosan and its derivatives

Chitosan derivative	Modification	Properties and Uses	Reference study
N-octyl-N-trimethyl chitosan (OTMCH)	Derivative with N-quaternized sites	Mucoadhesive properties, used for encapsulation of hydrophobic compounds	A TMCS nano emulsion with dextran sulfate delivered a Parkinson's disease drug through the nasal mucosa. [147]
Carboxymethyl chitosan (CMC) and Chitosan hydrochloride (CHC)	Carboxylation (Possess both amine and carboxyl groups)	Most promising water soluble, biocompatible, biodegradable and non-toxic biomedical material	Anthocyanin loaded in CMC/CHC derivatives resulted in an improved stability and controlled release. [148]
Sulfated and/or sulfonated chitosan (SCS)	Sulfation	Used for vascularization and bone tissue regeneration, As a coating material for better blood circulation and for constructing hierarchical structure with PLGA microsphere	[149] [159]
Glycol chitosan (GCH)	Conjugate of chitosan and ethyl glycol	Improved water solubility over a wide range of pH values. Used for colon delivery of acid sensitive bioactive and for hydrophobic compounds to improve water solubility.	[11, 134]
Chitosan tripolyphosphate (CS-TPP)	Cross-linking with sodium tripolyphosphate	Non -toxic, organic solvent free, convenient and controlled release. Used to encapsulate proteins, genes, drugs vitamins and different phenolic compounds	CCS-TPP microcapsules containing galactagogue herbs extract were reported to have sustained release in simulated GIT conditions and were stable for a period of 150 days during storage. [151]
Chitooligomers	Chemical/ enzymatic modification: Shorter chain length	Readily soluble in water, low viscosity and were reported to have 100% absorption rate in human body. Possess antibacterial, antifungal, antitumor, radical scavenging, antimicrobial, wound healing effect and immunomodulatory activity.	[14] Chatterjee et al. [152] also reported the application of ferulic acid grafted chitosan for microencapsulation and controlled release of vitamins.

Graphical summary:



CONCLUSION

The purpose of writing this review was to compile and provide an organized outline regarding wall materials (particularly natural gums and carbohydrate based coating agents), which are actually the “soul section” of an encapsulation process. The summarized information has clearly demonstrated the advantages and limitations of using carbohydrate based polymer over lipid and protein based coating agents. Carbohydrate based biopolymers are evidenced to be great delivery vehicles for controlled and target release of drugs, bioactive compounds, vitamins and minerals in biomedical applications, food and pharmaceutical industry owing to their innate characteristics including biocompatibility, biodegradability, physicochemical and biological properties. These complex carbohydrates carriers have been found to be

superior over lipid and protein-based carriers owing to their functional attributes of being thermo-stable and reactivity to a wide range of bioactive compounds. In addition, these polymers can be modified by physical, chemical or enzymatic reactions like carboxylation, acetylation, and methoxylation etc. to develop appropriate materials for delivery systems. Blends of carbohydrate based polymers with protein or lipid based coating agents can be used for specific applications with the objective of improving functional and mechanical properties like sustained release profile with enhanced stability of sensitive compounds, better encapsulation efficiency and shelf life stability of microcapsules. These modified delivery systems have discovered potential applications, thus assuring future researches with the aim of producing improved materials for drug delivery systems with scientifically established benefits and applications. However, the applications of these carbohydrate based polysaccharides and their blends summarized in this study are largely studied at laboratory scale. Therefore, industrial and practical implications of these carbohydrates based encapsulating agents should be done for commercial applications.

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ETHICS STATEMENT

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CONFLICT OF INTEREST

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ABBREVIATIONS

CAP: Cellulose phthalate acetate	**CD: Cyclodextrin**
CE: Cellulose Ethers	CMC: Carboxymethylcellulose
DE: Degree of esterification	EC: Ethyl cellulose
EOR: Enhanced oil recovery	FDA: Food and Drug Administration
GG: Guar gum	GIT: Gastrointestinal Tract
GRAS: Generally recognised as safe	HM: High methoxyl
HPMCP: Hydroxy propyl methyl cellulose phthalate	LM: Low methoxyl
LAB: Lactic acid bacteria	MC: Methylcellulose
DD: Degree of Deacetylation	DVS: Divinyl sulfone

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