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A Review on Biomatrix Tablets with Natural Polymers

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ABSTRACT

The creation of controlled release systems enables drugs to be delivered at a specific and expected rate in a programmed manner, thereby regulating the optimal concentration and ensuring a consistent concentration at a particular site or receptor. Matrix tablets represent a widely used type of controlled release drug delivery system, which releases medication through mechanisms of diffusion or dissolution control. The active ingredients are evenly integrated within the material that regulates the release rate, for example, polymers can be hydrophilic, plastic, lipid-based, or composed of minerals, among others. Polymer can be either man-made or naturally-derived, but the appeal of natural polymers in pharmaceutical uses lies in their cost-effectiveness, accessibility, and non-toxic nature. Chitosan, alginate, starch, and collagen are examples of naturally occurring polymers that are used in tissue engineering matrix, regenerative pharmaceuticals, detergents, adhesives, packaging, biodegradable plastics, textiles, and rubber. Because they are relatively safe, biocompatible, and readily metabolized by the body's enzymes. Biopolymers are the organic materials derived from natural sources. Because the biopolymers are biocompatible and biodegradable, they have various uses, including in the food industry. for edible films and emulsions, as well as in the pharmaceutical industry for tissue scaffolds, wound healing, dressing materials, drug transport materials, and medical implants such as organs. Since natural polymers are essentially polysaccharides, they have no negative effects and are biocompatible. The advantages of natural polymers over synthetic ones, as well as their use in creating innovative drug delivery systems, are covered in this paper.

Keywords: *Controlled release, Matrix tablets, Agar, Sodium Alginate, Biopolymer, Natural Polymer*

1. INTRODUCTION

One of the popular and traditional oral solid dose forms is tablets. In 1843, the first tablet was produced using a equipment which is hand operated. Solid dosage form such as tablet are classified into several categories, including buccal tablets, chewable tablets, dispersible tablets, core (uncoated) tablets, modified relaese tablets (which include delayed release, long lasting sustained release, and controlled release formulations), sublingual tablets(under the tongue), effervescent tablets, coated tablets (which in turn encompass both sugar-coated and film-coated varieties).(1,2) There are two kinds of tablets:

immediate-release and extended-release tablets. Extended-release pills are additionally divided into controlled and sustained release tablets, while immediate release tablets release medications immediately after consumption within thirty minutes. Whereas sustained release tablets have no control over the medication release rate, controlled release tablets

release the medicine at a set pace for a predetermined amount of time.(3) The creation of controlled release systems enables drugs to be delivered at a specific and expected rate in a programmed manner, thereby regulating the Curative level and ensuring a constant proportion at a particular binding site or recognition molecule.(4) Controlled release tablet

formulations provide several benefits, including improved adherence to medication schedules, consistent drug levels in the bloodstream, reduced frequency of dosing, fewer complicacies, and a greater margin of safety for powerful medications. By the whole of various controlled release drug delivery systems (CRDDS), matrix-based formulations are most commonly favoured because of straightforward and affordable production system (5)

MATRIX SYSTEM

Matrix tablets represent a widely used type of controlled release drug delivery system, which releases medication through mechanisms of dissolution or diffusion control. The Therapeutic components are evenly incorporated throughout the substance that controls the release rate, including various kinds of polymers such as plastic, hydrophilic, lipid-based, or mineral materials, among others. (6) This polymer material functions as a retardant for release rates. Therefore, it regulates the drug levels in the bloodstream, ensuring a consistent therapeutic range while minimizing fluctuations that could lead to excessively low or toxic concentrations, thereby reducing the risk of local or systemic side effects. Different matrices display varying release patterns, and the unique characteristics of respective matrix have an influence on in total pharmacokinetic release profile. (7)

Positives of oral controlled-release matrix tablets

1. Increase patient adherence

- The oral administration method is considered more dependable and user-friendly
- Decrease the frequency of dosage

2. Benefits of Therapy

- Maintains the therapeutic level over an extended duration
- Lessen medication level fluctuations
- Maintain a steady blood medication level and steer clear of elevated blood levels.
- An increase in bioavailability (8)

3. Diminished Negative Impacts

- Because of poor medication absorption, drug fatalities have decreased.
- Reduce systemic and local medication adverse effects while maintaining a reasonable level of effectiveness.
- Reduce drug build up through long-term dosage (9).

4. Economical

- Simple to produce
- Reduce medical expenses, such as nursing time (10).

5. Enhanced dosage form stability is achieved by safeguarding the active pharmaceutical ingredient from hydration reaction and breakdown (11).
6. Efficiently deliver a large-sized molecule

Negatives of oral controlled release matrix tablets

1. When compared to conventional tablets, these formulations exhibit reduced systemic availability because of heightened pre-systemic metabolism, increased instability, insufficient drug liberation, region-specific absorption, insufficient residence in the stomach and stability that is dependent on pH (12).
2. Meal and stomach emptying time can alter the rate of medication release (13).
3. Tablet breakdown results in the loss of the controlled release feature.
4. The use of costly excipients and specialist equipment raises development costs.
5. It was essential to conduct a thorough assessment of in-vitro/in-vivo correlation (IVIVC) (14)
6. It becomes challenging to modify the dosage of medications administered in varying strengths (15).

Natural Polymer

Macromolecules (which contains large molecules) are known as polymers, made up of persistent structural elements. The chemical bonds present in these components' subunits are covalent bonds. Polymers can originate from either natural sources or be artificially synthesized, although the appeal of natural polymers in pharmaceutical uses lies in their cost-effectiveness, accessibility, and non-toxic nature. They can undergo chemical modifications, possess the capability to be eco-friendly, and aside from a few cases, are generally biologically acceptable. (16)(17) Material derived from plants present several challenges including their production in quantities and as complex mixtures, which may diverge based on the plant's locations and climatic fluctuations. This complexity can lead to lengthy and costly processes for isolation and purification. Additionally, the issue of intellectual property rights has become increasingly significant. (18)(19) The particular use of polymers derived from plants in pharmaceutical formulations encompasses their role in creating nanoparticles, beads, implants, systems that can be inhaled or injected, microparticles, thick liquid formulations films, and solid monolithic matrix systems. (20)(21)(22) In these dosage forms, polymeric substances have served various purposes, including acting as binders, forming matrices or modifying drug release, creating film coatings, enhancing thickness or viscosity, stabilizing, aiding disintegration, promoting solubility, functioning as emulsifiers, serving as dispersing agents, Gel-forming agents, and biocompatible adhesives. (23)

ADVANTAGES OF PLANT-BASED POLYMERS

1. Biocompatible and safe - In chemical terms, most of these plant-based materials primarily consist of carbohydrates made up of repetitive Simple sugar units. Therefore, they are thought to be toxic-free.
2. Biologically degradable- Biodegradable materials are polymers found in nature Generated by all living organisms. They do not cause any harmful effects on the environment or humans.
3. Cost-effective - They are more affordable, and the costs associated with their production are lower than those of artificial materials.
4. Safe and free from complication-They originate from natural sources and are therefore safe and without adverse effects.
5. The widespread accessibility of these products is evident, as many countries manufacture them due to their use across various industries. (24)

DISADVANTAGES OF PLANT-BASED POLYMERS

1. Unintentional introduction of microbial agents occurs when products are produced and thus come into contact with the external environment, increasing the risk of exposure to harmful microbes.
2. Water uptake speed can be unpredictable - Variations in the procurement of natural substances over different periods, combined with factors such as location, species, and climatic conditions, can lead to differences in the chemical composition found in a particular material.
3. Batch-to-batch variations occur because synthetic manufacturing involves a regulated process utilizing fixed amounts of ingredients. In contrast, the production of natural polymers relies on environmental conditions and various physical factors.
4. The production of natural polymers occurs at a slow pace due to its dependence on environmental conditions and various other factors, which cannot be altered. Therefore, the rate of production for these materials is inherently low.
5. Metallic impurity presence - The presence of metallic impurity presence is a potential concern frequently linked to herbal excipients. (25)

THE CLASSIFICATION OF POLYMERS THAT ARE NATURAL

1. Sources from plants include substances such as aloe vera gel, karaya gum, locust bean gum, rosin, pectin, glucomannan, cellulose, tragacanth, acacia, guar gum, inulin, starch as well as hemicellulose also.
2. Sources from animals encompass xanthan gum, carrageenans, chitin, psyllium, and alginates.

NATURAL POLYMERS FROM PLANT ORIGIN

Cellulose

Cellulose is a naturally abundant biopolymer, readily available due to its renewable nature, decomposable and safe. The chemical formula $(C_6H_{10}O_5)n$, where n indicate the total count of glucose units, represents the extent of polymerization. It is an extended linear polymeric carbohydrate composed of repeating units of β-(1-4)-linked D-anhydro-glucopyranose (AGU). (30, 31) It is found in higher concentrations in plants and in trace levels in the cell walls of some organisms. (32) The commercial sectors of pharmaceuticals, cosmetics, food production, paper manufacturing, textiles, and engineering all make extensive use of Cellulose derivatives, which include cellulose acetate, carboxy methyl cellulose, methylcellulose, hydroxyl propyl methyl cellulose, ethyl cellulose, and microcrystalline cellulose. (33, 34, 35, 36, 37) Cellulose exists in four distinct polymorphic forms: cellulose I, cellulose II, cellulose III, and cellulose IV. The natural form of cellulose is called cellulose I, or native cellulose (NC). And is the most prevalent form found in nature. Through procedures like regeneration (where solubilization is followed by recrystallization) or mercerization (which involves alkali treatment), this form can be changed

into Cellulose II, also referred to as alpha cellulose.[38]. Compared to cellulose I, cellulose II has greater thermodynamic stability. Amorphous cellulose III is obtained by treating cellulose I or II with amines, while cellulose IV is formed by treating cellulose III with glycerol. (39) The odourless, tasteless, and white powder known as alpha cellulose is insoluble in water. It is a common raw material used to make cellulose derivatives, electrical cable insulators, paper, paperboards, textiles, and propellants, among other products. (40).

Alpha cellulose is the source of microcrystalline cellulose (MCC), a refined, partially depolymerized cellulose derivative. Fibrous material made from wood pulp is the most widely used commercial source of microcrystalline cellulose. MCC highest prevalent kind of cellulose. In the food processing, it acts as an emulgents, stabilizing material and free-flow agent; in the pharmaceutical and cosmetics sectors, it acts as an emulsion stabilizer, disintegrant, adhesive, abrasive, bulking, binding, adsorbent, and anti-caking. (41, 42, 43, 44).

Hydroxy propyl methyl cellulose is a cellulose ether derivative that is moderately modified with O-methyl and O-(2-hydroxypropyl) groups. Because of its gelling ability, As an additive in systems intended for controlled-release drug administration, it has been the focus of a great deal of research. To control how much of the soluble drug diltiazem is released, two cellulose ethers that is carboxy methylcellulose and hydroxyl propyl methylcellulose. They were used in matrix type tablets as a polymeric carrier material. It was found that in these systems, drug release may be sustained for a significant period of time by each polymer alone. More significantly, the combination of two cellulose ethers within matrix-type tablets enabled drug release kinetics to follow a zero-order rate at two distinct pH levels, namely pH 6.8 and pH 4.5. (45) The dissolving characteristics of hydroxyl propyl methylcellulose monolithic matrix systems were comparable to those of a Commercialized osmotic drug delivery system for the poorly soluble medication glipizide. Furthermore, it was demonstrated that the gel structure of hydroxyl propyl methylcellulose matrix systems is stronger than that of polyethylene oxide ones, "which might offer enhanced in vivo performance regarding the matrix's ability to withstand the disruptive forces present in the digestive tract (46)

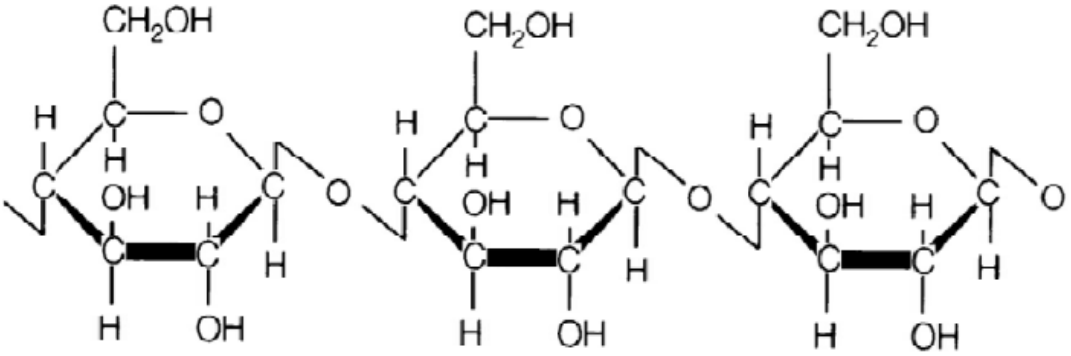


Fig .1: Structure of cellulose

Hemicellulose

Hemicelluloses, which are heteropolymers (matrix polysaccharides) like arabinoxylans, found alongside cellulose in nearly all plant cell walls. The structure of hemicellulose is amorphous and irregular and is weak, whereas cellulose is resistant to hydrolysis, crystalline, and robust. Hemicellulose, another polysaccharide, i.e, composed of 500–3,000 sugar units, less than cellulose's length. Furthermore, cellulose is an unbranched polymer, whereas hemicellulose is a branched one. Hemicellulose polysaccharides, such as xylans, xyloglucans, and mannans, can be procured from cell walls of plant using a strongly alkaline compound. Their backbones consist of dglycans that are β-1,4-linked. With the exception of three out of every four glucose monomers having xylose branches, the backbone of xyloglucan is comparable to that of cellulose. The structure of arabinoxylan features a backbone of D-xylan connected by β-1,4 linkages, with branches of arabinose. (47,48)

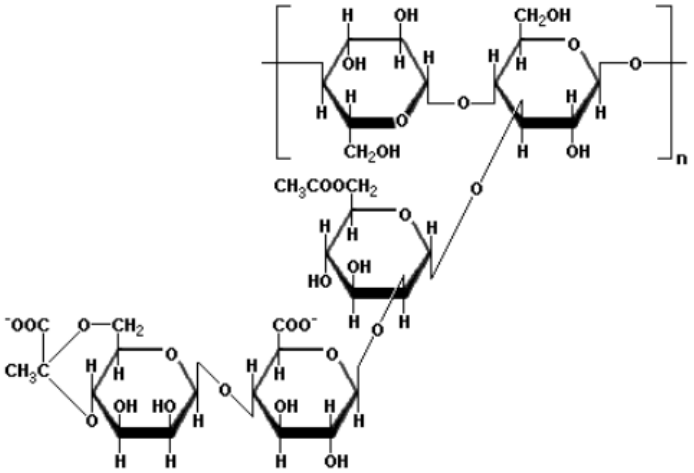


Fig. 2: Structure of Hemicellulose

Glucomannan

It is considered that glucomannan is a dietary fiber.(49). Although the Source-dependent variations exist in the mannose:glucose ratio, Glucomannan is a polysaccharide belonging to the mannan family, characterized as a hydrocolloid. It consists of monomers of D-mannose and D-glucose linked together by β-1,4 bonds, with some backbone units featuring acetyl side chains. The acetyl groups help make it a natural polymer which is soluble, with the maximum viscosity and water retention ability, as well as contributing to its swelling and solubility. Plant bulbs, roots softwood, tubers, and are the specific sources of this polysaccharide, which is found in great abundance in nature. The type of glucomannan that is most frequently used is konjac glucomannan, a polysaccharide that shows great promise for application in drug delivery systems. It is extracted from Amorphophallus konjac tubers. Konjac glucomannan has been studied as a beneficial element in controlled-release drug delivery systems when paired with different polymers or altered at the molecular level, since on its own it creates relatively weak gels. Additionally, it is a soluble fiber that has been explored for its potential role in alleviating constipation. In order to alleviate constipation, glucomannan can reduce the transit time of bowel movements. (22,50,51) For eight hours, Konjac glucomannan gel systems have been demonstrated to preserve the stability of theophylline and diltiazem while regulating their release. However, this response differed according to the region of origin—whether America, Japan, or Europe attributed to variations in the acetylation levels of konjac glucomannan. The availability of β-mannanase in the colon notablyexpedited the release of cimetidine, yet matrix tablets made solely of konjac glucomannan exhibited the capability to maintain drug release under typical physiological conditions found in the stomach and small intestine. The tablet's gel structure is strengthened through a network of hydrogen bonds formed between the two polymers, which significantly restricts the diffusion of the drug. For that reason, combinations of xanthan gum and konjac glucomannan in matrix type tablets showed great promise for controlling and maintaining drug release. (52) Hydrophilic cylinders and particles were created using konjac glucomannan to allow for the controlled release of DNA. (53) Trisodium tri metaphosphate-cross linked konjac glucomannan produced hydrogel systems that, depending on the polymer network density and enzyme-catalyzed degradation, might maintain the release of hydrocortisone. (54)

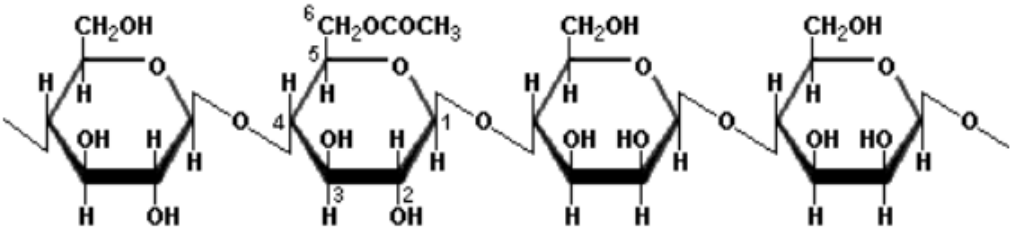


Fig. 3: Structure of Glucomannan

Agar

Agar, commonly referred to as agar-agar, is a desiccated gelatinous material obtained from the red algae species *Gelidium amansii* (Gelidaceae) as well as a number of others varieties of rhodophyta, such as Gracilaria (Gracilariaceae) and Pterocladia (Gelidaceae). (58) Depending on the form, it can be yellowish grey, white, or almost colorless. It is available in sheets, flakes, strips, and coarse powder, among other forms. It does not dissolve in cold water, but when boiled and refrigerated, it turns into a gooey mass. It is also insoluble in organic solvents. (55) Agrose and agaropectin are two distinct polysaccharides that make up agar. Agaros, which is made up of D-galactose and three to six anhydro Lgalactose units, gives agar its gel strength. About 3.5% of it is cellulose, while 6% is made up of materials that include nitrogen. Agaropectin is what gives the agar solution its viscosity. Galactose and uronic acid units undergo partial esterification with sulfuric acid,

leading to the creation of this sulfonated polymer. On account of its strong gel strength, agar serves as an effective disintegrant. (56, 57, 58) Pankaj Bhardwaj et al. utilized this polymer as a naturally derived super disintegrant to formulate an ODT of metformin hydrochloride, aiming to enhance bioavailability, disintegration time, dissolution efficiency, and patient compliance. When compared to other formulations, it was discovered that the one containing 6% super disintegrant produced superior outcomes. 11.03 seconds was the disintegration time, and 98.5% of the medication was released in less than 30 minutes. (59). Agar serves as a gelling agent in suppositories, an emulsifier, a surgical lubricant, a laxative, a pill disintegrant, a bacterial culture medium, and a suspension or gel-forming agent.

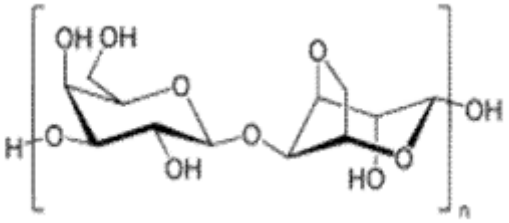
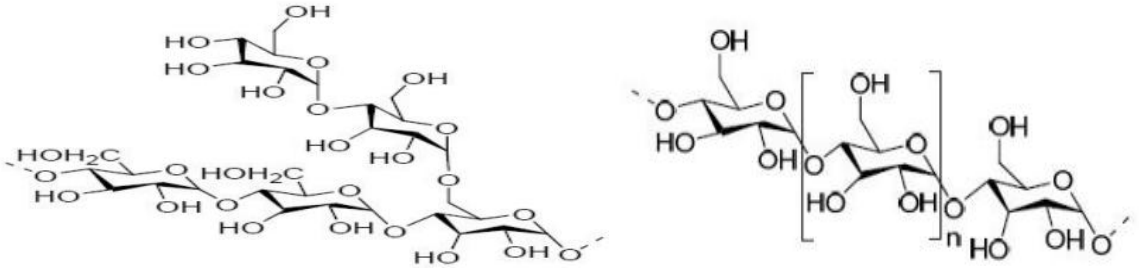


Fig. 4: Structure of Agar

Starches

Amylum, commonly referred to as starch. It is a carbohydrate made up of several glucose units linked together by glycosidic bonds. This type of polysaccharide is synthesized through every autotrophic plant as a means of storing energy. It acts as the main carbohydrate source in green plants and is mainly located in underground parts and seeds. Granules, or starch grains, are a type of starch. Several starches are known to have medicinal use. These consist of rice (Oryza sativa), potatoes (Solanum tuberosum), maize maize (Zea mays) (Zea mays), and wheat (Triticum aestivum). (60) It is composed of 2 polymers: amylopectin, which is extensively branched and comprises both alpha-1,4 and alpha-1,6 linked D-glucose monomers, along with amylose, a linear helical polymer formed of alpha-1,4 linked D-glucose basic units.



(A) (B)

Fig.5: Structure of a) Amylopectin and b) Amylose

Modified Starch

The extensive applicability of a newly developed pre-gelatinized starch for incorporation into directly compactable controlled-release matrices have been assessed. This product is produced by the enzymatic breakdown of potato starch, Subsequent to a series of procedures including filtration, precipitation (retrogradation) and ethanol washing. It represents various benefits, such as easier tablet formulation, the potential to provide sustained zero-order drug release over an extended duration, and the capacity to handle high drug concentrations with diverse physicochemical properties. The tablet release rates formulated from retrograded pre-gelatinized starch can be adjusted to meet specific release profiles by manipulating various factors, including compaction force, tablet shapes, and the addition of other additives. (61)

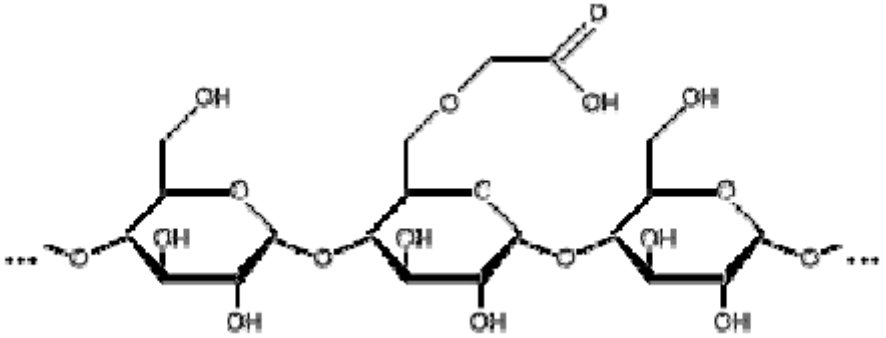


Fig. 6: Structure of Modified Starch

Native Starch

Because of its significant swelling and quick enzymatic breakdown, which causes many medicines to release too quickly, it might not be appropriate for application in drug delivery systems that require controlled release. As a result, starch derivatives that demonstrate greater resistance to enzymatic degradation, along with methods such as crosslinking and co-polymerization, are being considered, are currently being utilized. Acetyl esterified starch acetate has demonstrated delayed enzymatic degradation, suggesting its possible application as a targeted drug delivery system for the colon. (62) In controlled-release, directly compressible matrix systems, Spray-dried high-amylase carboxy methyl starch demonstrated a significant capability for loading the soluble drug acetaminophen. (63) Microcapsules incorporating a protein compound and a protein-degrading enzyme inhibitor were developed to improve the oral delivery of protein or peptide-based drugs. The mixed-walled microcapsules, made from bovine serum albumin and starch, were produced using terephthaloyl chloride to facilitate interfacial cross-linking. Throughout the cross-linking process, protease inhibitors were added to the aqueous phase to encapsulate either native or amino-protected aprotinin. In vitro studies demonstrated that aprotinin-containing microcapsules provided a protective effect on bovine serum albumin. (64)

Pectin

Citrus peels, such as Citrus Aurantium or Citrus Simon, include an inner portion called pectin, which is a refined carbohydrate product that is generated by acid hydrolysis (Rutaceae). The principal element of pectin is a straight-chain polymer made up of 1,2-linked L-rhamnose residues that break up alpha-1,4-linked D-galacturonic acid residues. Because each molecule is made up of hundreds to thousands of building units, its mean molecular mass falls between 50,000 to 1,80,000. (65) Neutral saccharide like glucose, rhamnose, galactose, arabinose, xylose are abundant in galacturonic-containing polysaccharides. On the basis of plant origin, pectin's composition might change. For instance, pectin from citrus has a smaller molecular size and fewer neutral sugars than pectin from apples. (66,67) In a bid to mask the unpleasant flavor of oral chloroquine, the potential of amidated pectin as a matrix patch for transdermal delivery were investigated. The results indicate that the pectin-chloroquine patch formulation may be beneficial for malaria treatment and for administering chloroquine through the skin. (68)

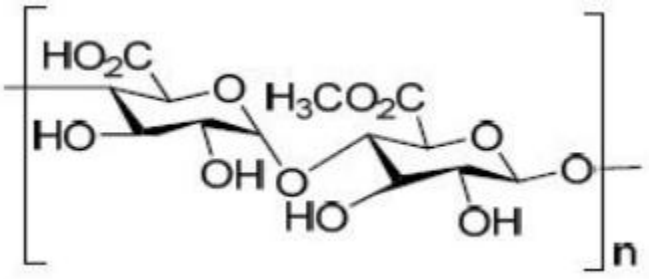


Fig. 7: Structure of Pectin

Inulin

A large number of plants naturally possess inulin, which is a polysaccharide that serves as a carbohydrate for storage, primarily composed of fructose monomeric units with a glucose terminal, unlike starch, the most common glucose storage polymer. It is found in over 30,000 plant species, with its key commercial origins being the tubers of Jerusalem artichokes (Helianthus tuberosus) and dahlias (Dahlia pinnata), as well as the roots of chicory (Cichorium intybus) and yacon (Polymnia sonchifolia). (69, 70) Inulin naturally occurs in plants as a blend of fructose oligosaccharides and polysaccharides, varying from two to hundred units depending on the plant extraction process, age and species. (71) Valentine Rose, a German scientist, identified inulin as a plant carbohydrate from the roots of Inulin helenium in the 1800s, and it was given its name in 1817.Rose discovered this unusual polysaccharide as a water-soluble extract and used boiling water to separate it from plant sources. Julius Sachs, a german plant physiologist and a pioneer in fructans, demonstrated the spherocrystalline structure of inulin from several plant roots later in 1864. For many years, people with diabetes have used inulin as a sweetener. (72) The molecule is typically terminated by an alpha-D-glucosyl group linked via a (1↔2) bond. Inulin belongs to the fructan carbohydrate family (fructose-based polymers) and primarily consists of beta-D-fructosyl subunits connected through (2→1) glycosidic linkages. (73). Fructose chains vary in length; for inulin, they typically range from two to sixty monomers, however they can exceed one hundred. The general formula GF_n,in which G stands for glucose units, F for fructose units, and n for the number of fructose molecules joined to create the entite carbohydrate chain, is frequently used to represent fructans. (74) By changing the inulin's cooling temperature in solutions, two distinct morphologies-obloid and needle-like-can be created from its fivefold helical crystalline structure. (75). While the obloid crystals enhance food lubrication (mouthfeel), the needle-like crystals increase viscosity. The degree of polymerization affects inulin's solubility, much like it does for many other polymers. As the degree of polymerization increases, inulin becomes less soluble. It was also noted that solubility increased with heat. (76)

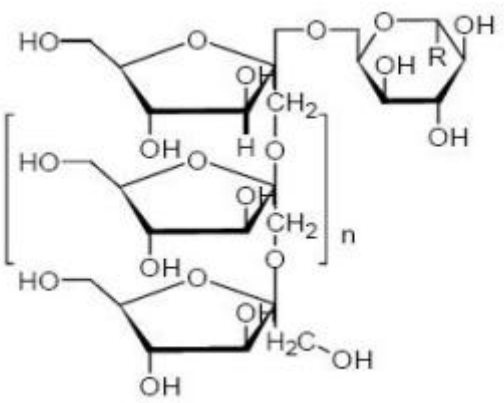


Fig. 8: Structure of Inulin

Guar Gum

Guar gum, which belongs to the Leguminosae family, is obtained from the ground endosperm of the seeds of Cyamopsis tetragonolobus Linn. (58) Other names for guar gum include guaran, clusterbean, Guyarem, Gum cyamposis, Gum lucern, Cyamopsis gum, and Guarina. beta-D-mannose monomers that are (1→4) di-equatorially linked make up galactomannans, a linear polymer, some of these connections involve single glucose side group composed of alpha-D-galactose. (77) The fundamental structure of guar gum is made up of β-1,4-linked D-mannopyranose units, where every other mannose is generally bonded at the 1–6 position to α-D-galactose. (78) The FDA has classified guar gum as generally recognized as safe. (79) Recently, there has been increased interest in guar gum as a cost-effective and versatile system for delivering oral extended-release medications. (80) Guar gum is particularly advantageous for delivering drugs to the colon because it can be broken down by specialized enzymes present there. It shields the medication from the acidic conditions of stomach and small intestine, facilitating its transit to the colon, where it is either degraded by microbial enzymes or absorbed by certain microorganisms. Guar gum itself shows substantial promise as a carries for oral controlled-release matrix systems. Additionally, it was shown that excipients can be added to these matrix systems to regulate the release of drugs. (81) Guar gum, formulated as tri-layered controlled-release tablets can serve as a carrier for the development of oral prolonged-release drug systems, particularly for high-aqueous solubility drugs like trimetazidine dihydrochloride. (82) A model medication with high solubility, metoprolol tartrate, was used in the same investigation. When developing oral controlled drug delivery methods for drugs that are extremely soluble in water, such as metoprolol tartrate, The research results indicated the potential for guar gum to serve as a carrier in the design of three-layer matrix tablets. (83) Diltiazem HCl, another water-soluble drug, the release profile of this formulation is carefully designed to be similar to that of commercially available sustained-release diltiazem hydrochloride tablets (D-SR tablets), which are created using a matrix that incorporates guar gum and are manufactured through the wet granulation method. (84)

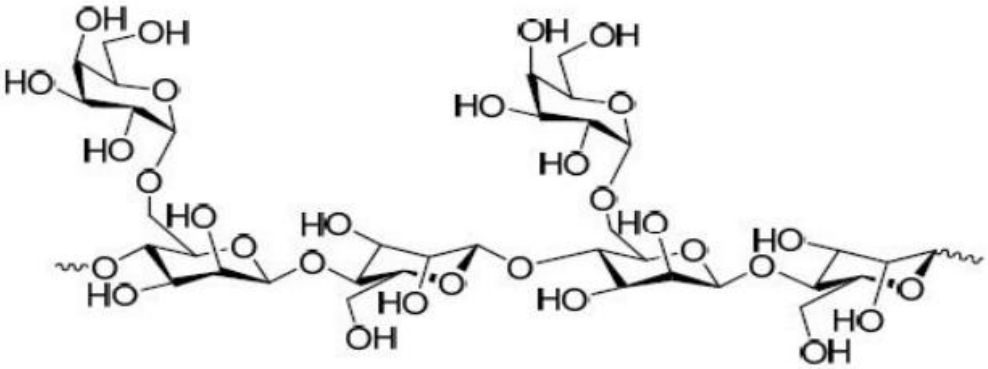


Fig. 9: Structure of Guar Gum

Locust Bean Gum

The seeds from the leguminous plant Ceratonia siliqua Linn (Leguminosae) are processed to produce locust bean gum, also referred to as carob bean gum. Rather than being extracted directly from the plant, it is made by grinding the endosperms that are present in the locust bean tree's brown pods or beans. The primary element of this substance is a neutral galactomannan polymer, which consists of D-mannopyranosyl units joined by 1,4 bonds. Every fourth or fifth unit along the chain is replaced with a D-galactopyranosyl unit at the C_6 position. Due to its neutral nature, locust bean gum maintains stable solubility and viscosity across a pH range of 3 to 11. (85) Matrix tablets formulated with locust bean gum, both with and without glutaraldehyde as a cross-linker, exhibited drug release characteristics comparable to those of scleroglucan and guar gum across various model drugs. (76) A study revealed that minimatrix systems formulated with locust bean gum could enable

the extended release of diclofenac sodium. Additionally, Penwest Pharmaceuticals developed a commercially available tablet formulation (TIMERx®) using a fusion of xanthan gum and locust bean gum, which exhibited prolonged release properties both in vitro and in vivo. (87)

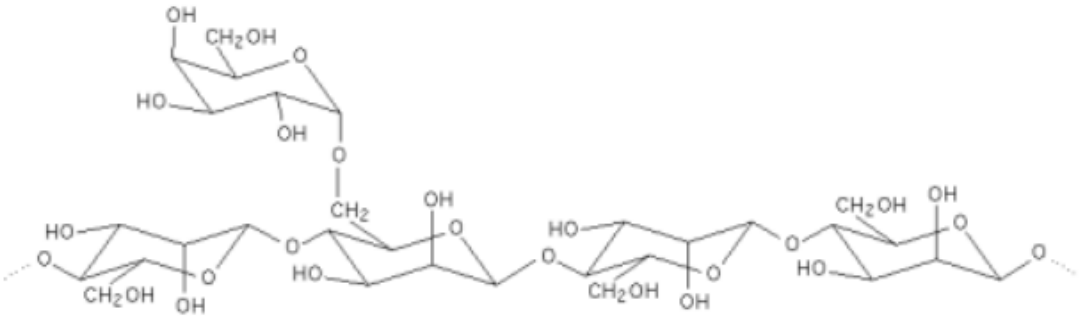


Fig.10: Locust Bean Gum

Gum Arabic

The stem and branches of the wild Acacia Arabica plant, a member of the Leguminosae family, are used to extract the dried sticky material known as gum acacia or gum Arabic. It is known that the gum is an acidic polymer made up of L-arabinose, D-glucuronic acid, L-rhamnose and D-galactose. In oral and topical medication formulations, acacia is mostly used as an emulsifying and suspending component, usually in conjucation with tragacanth. Additionally, it is also utilized as a tablet binder and in the manufacturing of pastilles and lozenges. (88) Gum Arabic proved to be a successful matrix microencapsulating material for the endoglucanase enzyme, increasing its stability and allowing for a gradual release of the encapsulated enzyme. (89) To create a monolithic osmotic tablet method, In monolithic osmotic tablet formulations, gum arabic has been employed as suspending, expanding and osmotic agent. For up to twelve hours at pH 6.8, an optimized system in one research released the hydrophobic medication naproxen at a rate of about zero orders of magnitude. (90) In another investigation, gum arabic pellets were utilized to attain a sustained release of ferrous sulfate over a span of seven hours. When these pellets were coated with polyvinyl acetate or ethylene vinyl acetate, the duration of release was extended to almost 12 hours. The gelling characteristics of gum arabic played a crucial part in this process: a higher concentration of gum arabic in the pellets formed a gel layer that functioned as a Obstacle, thereby reducing thediffusion rate of ferrous sulfate. (91)

Karay Gum

Sterculia urens (Sterculiaceae) is the source of karaya gum, a polymer that is moderately acetylated and includes galactose, glucuronic acid, rhammnose was utilized. Matrices were created through direct compression using hydrophilic swelling natural gums, specifically xanthan gum and karaya gum , which served as agents for controlling release. Caffeine and diclofenac sodium were chosen for studies on drug release, gum erosion and hydration, owing to their varying solubilities in water, utilizing a dissolution testing eqipment with the basket method at 2 different agitation rates. The findings indicate that the release of the drug from matrices containing xanthan and karaya gum is affected by the quantity of the gum present, the solubility of drug and agitation speed. Notably, in karaya gum matrices, the erosion process plays a dominant role in achieving near zero-order drug release. (92) Studies show that mucoadhesive tablets designed for buccal use, which are made with karaya gum, demonstrate better adhesive qualities compared to those produced with guar gum. These karaya gum-based tablets can achieve zero-order drug release; however, to attain an appropriate sustained release profile, concentrations exceeding 50% w/w may be necessary. (93)

Tragacanth

The stems and branches of many trees that grow in Turkey, India, and the northern and western parts of Iran are used to make the natural gum known as tragacanth. Tragacanth gum is available in 2 primary forms: ribbons and flakes. Ribbons, considered the superior grade, exhibit higher viscosity but lower surface activity compared to flakes. (94, 95, 96) In general, TG is regarded as an anionic polysaccharide that is viscous, odorless, and tasteless and that is neither carcinogenic, allergic, or mutagenic.(97) Methoxy content, soluble and insoluble components, and sugar composition make up TG. Seasonal changes, geographic variance, environmental and growth circumstances, and the place of extraction all affect the proportional variances. With several side chains made up of L-fructose, D-xylose, and minute quantity of D-glucuronic acid, D-galactose, single strand chains of 1,4-linked alpha-D-galacturonic acid traces joined to the acidic bakebone from the complex heterogeneous polymer known as TG.(98) With the advantages of superb rheological behavior, remarkable heat stability, biocompatibility, high hydrophilicity, and non-toxicity, Among the natural gums, Tragacanth is the most aggressive vicious. (99,100,101)

Tragacanth, whether used alone or in combinationwith other polymers, effectively extended drug release when employed as a carrier in the formation of single- and triple-layer matrices. (102) Some initial findings also suggest that consuming tragacanth alongside a high sugar intake may help reduce blood sugar levels in diabetic patients. (103), similar to other water-soluble gums. However, this effect has not been consistently demonstrated (104), and more research is required to completely

understand it. While gum tragacanth increases stool bulk and reduces gastrointestinal transit time, similar to other soluble fibers, it seems to have no impact on triglyceride, serum cholesterol or phospholipid levels over a twenty-one day supplementation timeframe. (103,105) Traditionally, tragacanth has been used as a thickening, emulsifying and suspending agent. (106)

Aloe Gel

The interior Aloe vera (L.) Baum. F. (Aloe barbadensis Miller) leaves is made up of parenchyma tissue that contains a gelatinous mucilage(107). In an experiment, diclofenac sodium was utilized as a test drug; the Aloe Vera gel was extracted from the leaves, filtered, and subsequently underwent acetone precipitation. The mucilage obtained was directly compressed into matrix type tablets, which displayed favorable swelling characteristics and sustained drug release. (108)The carbohydrate polymer observed in gel of Aloe vera leaves are linked to numerous health advantages. These biological functions include promoting healing of wounds, demonstrating hypoglycemic or antidiabetic effects, exhibiting antifungal activities, potential anticancer effects, immunomodulatory properties, and gastroprotective benefits. Furthermore, liquid formulations obtained from the entire leaves or the inner fillet gel of A. vera can improve skin penetration, intestinal uptake, and the bioavailability of drugs delivered alongside. An additional important pharmaceutical use involves utilizing dried Aloe Vera gel powder as an additive in sustained-release pharmaceutical formulations. (109)

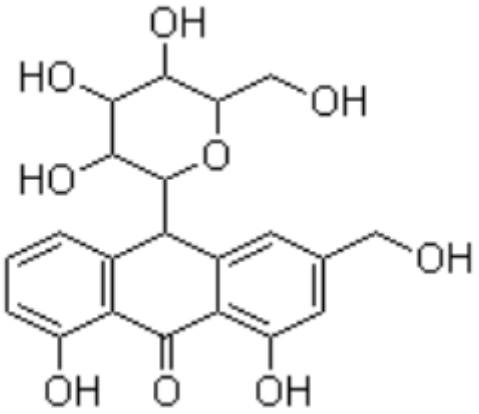


Fig. 11: Structure of Aloin

NATURAL POLYMER FROM ANIMAL ORIGIN

Chitin

Researchers and industry participants are interested in two biopolymers: chitin and chitosan. This is because of their potential applications in textile production, bioengineering, agriculture, papermaking, and the food industry. (110,111). Because of their abundance, no-toxic properties, and high biocompatibility, Chitin and chitosan possess versatile functionalities. (112,113). The isolation of this polymer from variety of sources has been extensively researched and explored in numerous studies over the last 20 years. These sources include crustacean shells, medicinal fungi, colorado potato beetle larvae and adults, spider species (114,115), insect cuticles, Melolonthamelolontha, bat guano (116,117), Orthoptera species (118), Daphnia magna resting eggs (119), and at last green algae and fungal cell walls. Nonetheless, studies have shown that the source selection affects the yield as well as the physiocochemical properties of chitosen and chitin that are extracted. However, this assessment noted that none of these researchers' methods have reached the industrial level. N-trimethyl chitosan and mono-N-carboxymethyl chitosan are two examples of chitosan and its derivatives that are reliable and effective for improving absorption, facilitating the delivery of hydrophilic macromolecules through mucosal routes (nasal and oral). This includes various peptide and protein medications as well as heparins. Chitosan promotes the intercellular pathway of macromolecular medications by means of opening intercellular tight cell junctions, which increase absorption. For regulated drug release, chitosan nanoparticles and microparticles are also appropriate. Vaccines associated with certain particle systems have demonstrated the ability to increase the absorption of antigens by mucosal lymphoid tissues. This enhancement subsequently triggers robust mucosal and systemic immune reactions to the antigens. The formulation type and the level of deacetylation appear to influence the non-specific adjuvant properties of chitosans. This polymer and its derivatives are favorable polymeric additive for the delivery of vaccines and mucosal treatments, according to the reviewed literature. (120)

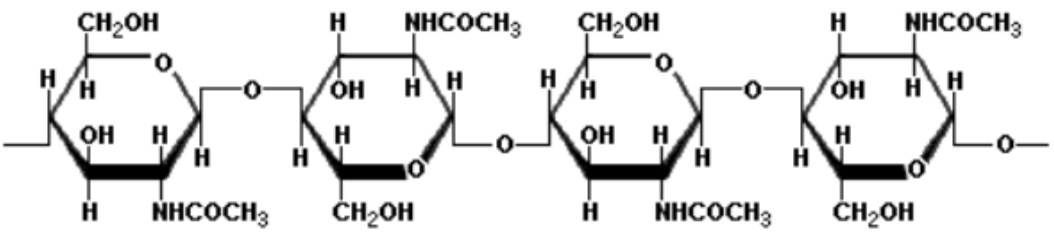


Fig. 12: Structure of Chitin

Alginate

The polymer alginate naturally occurs in the cell walls of algae & bacterial capsules of Azotobacter and Pseudomonas species. Brown algae, sometimes referred to as brown seaweeds, have cell walls that contain alginate, which gives them flexibility and a strong structure while shielding them from potential damage from strong ocean waves. (121) It helps bacteria develop protective capsules, forms biofilms (122) and promotes bacterial colonization and adherence. (123) Since its discovery from kelp by Stanford in 1881, alginate has gained widespread recognition as a stabilizing agent, thickening, gelling agent, and emulsifier (124) due to its propensity to create hydrogel. Following the patent issuance for alginate extraction from algae in the 1930s, alginate was extensively extracted from brown algae (Phaeophyceae sp.), including Macrocystis pyrifera, Laminaria japonica,Laminaria hyperborea, Ascophyllum nodosum, & Laminaria digitata. (124) To evade first-pass metabolism, function as an injectable alternative, and enhance treatment effectiveness for angina pectoris and hypertension, bioadhesive microspheres of sodium alginate incorporating metoprolol tartrate wew developed for intranasal systemic administration. The microspheres were formulated using the emulsification-crosslinking method. Comparing metoprolol from microspheres to oral and nasal drug solution delivery, in vivo trials showed a markedly enhanced therapeutic efficacy, with prolonged and regulated suppression of isoprenaline-induced tachycardia. (125) A comparative analysis indicated that the alginate formulation was more effective than the polylactide-co-glycolide(PLG) preparation in increasing the rate and extent of absorption of the anti-fungal drugs econazole & clotrimazole. Nanoparticles were created using the cation-induced controlled gelification technique for alginate and the emulsion-solvent evaporation method for PLG. (126)

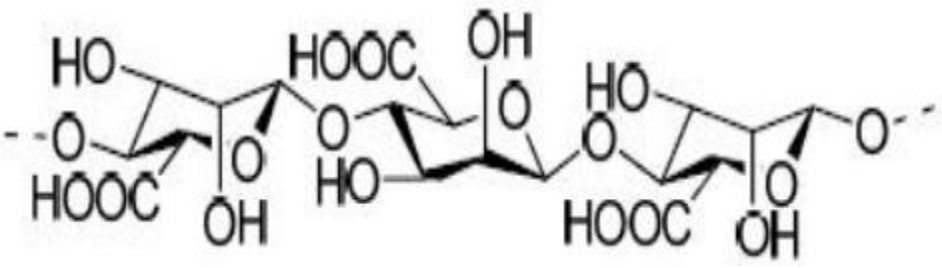
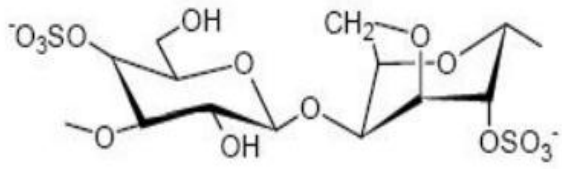


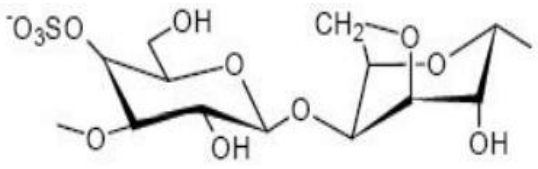
Fig. 13: Structure of Alginates

Carrageenans

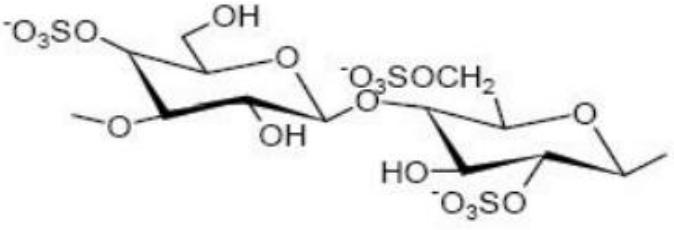
Carrageenan, often known as Irish moss, is a sulphated polysaccharide extract of the seaweed known as carrageen, which is derived from the red algae Chondrus Crispus (Rhodophyceae). (58) The human body cannot absorb seaweed-derived carrageenan, which gives the body weight but no nourishment. Carrageenan comes in three primary varieties: iota (ι), lambda (λ) and kappa (κ) (47) While kappa-type carrageenan produces a delicate gel, lambda-type carrrageenan generate thick solutions that do not solidify into a gel. Elastic gels are produced by iota-type carrageenan. (79) The capacity of compaction of one iota-carrageenan (Gelcarin®GP-379 NF) and two kappa-carrageenan (Gelcarin®GP-911 & GP-812 NF) was assessed, demonstrating their ability to produce robust compacts with significant elastic recovery. According to the study's findings, the studied carrageenans were relevant additives for formulating controlled-release medicine (127) To produce hydrogel beads with a smoother surface morphology than single-polysaccharide network beads, cross-linked alginate and potassium were combined with κ-carrageenan. The hydrogel's carrageenan elements significantly improved the thermal stability of the polymeric framework. Initially, these beads were employed as carriers in advanced drug delivery systems. (128)



(A)



(B)



(C)

Fig. 14: Structure of A) iota-carrageenan, B) lambda-carrageenan and C) kappa-carrageenan

Psyllium

To obtain the psyllium mucilage, the seeds of Plantago ovata are ground to break down their outer layer. Additionally, Its ability to bind tablets and to create hydrogels via radiation-induced cross-linking for the controlled release of 5-Fluorouracil as a prototype medication, as its capacity to bind tablets. (129,130) For the preparation of methacrylamide and psyllium hydrogels a cross-linker N, N'-methylenebisacrylamide is used, which were subsequently loaded with insulin. By relaxing the polymer chain during swelling, these cross-linker containing hydrogels demonstrated a predetermined release of active component via not following the fick's law of diffusion. (131) Using psyllium husk in conjunction with various additives such as HPMC(Hydroxy propyl methylcellulose) for the preparation of unique sustained release, mucoadhesive and swellable gastro-retentive drug delivery system for ofloxacin was developed.(132)

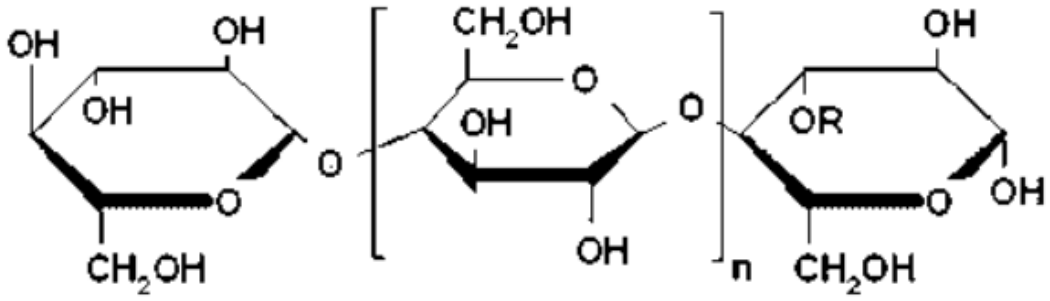


Fig. 15: Structure of Psyllium

Xanthan Gum

The gram-negative bacterium Xanthomonas campestris ferments to yield xanthan gum, an extracellular biopolymer with a macromolecular structure. Its fundamental structure consists of a cellulose backbone composed of beta-D-glucose units and a trisaccharide side chain of beta-D-mannose, beta-D-glucuronic acid and alpha-D-mannose that joins to alternating glucose units in the primary strand. One study indicated that xanthan gum was more effective than the synthetic polymer hydroxyl propyl methylcellulose at slowing down medication release. Hydroxy propyl methylcellulose and xanthan gum were both used as hydrophilic matrixing agents in the production of modified-release diltiazem HCl tablets. The drug release from the tablets made using the direct compression technique was notably affected by the ratio of these two polymers. The study concluded that by optimizing the combination of hydroxyl propyl methylcellulose and xanthan gum, the desired modified drug release profile can be attained. (133)

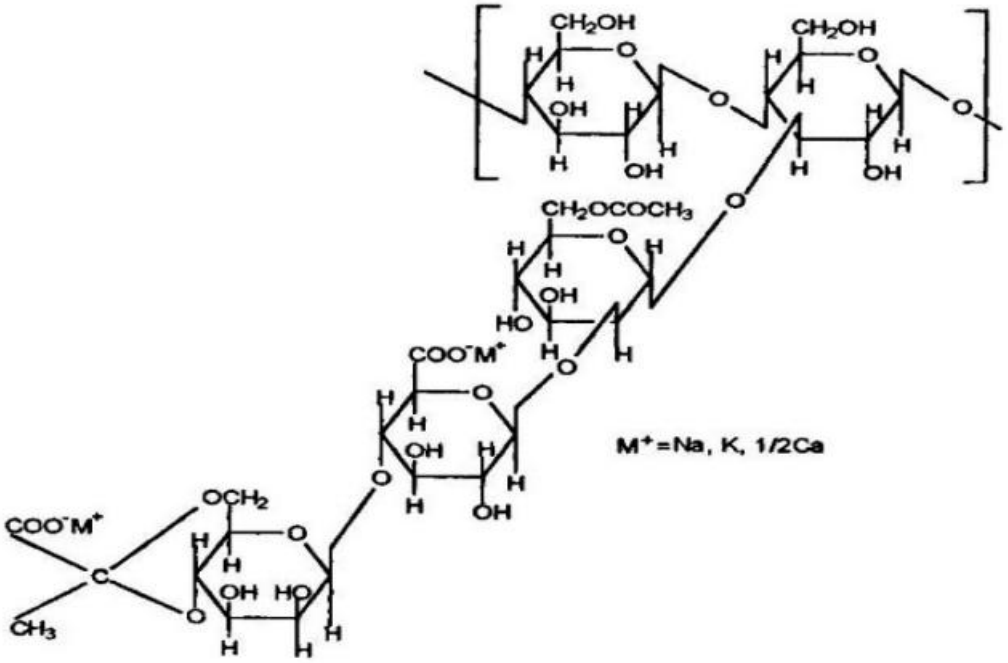


Fig. 16: Structure of Xanthan Gum

Biopolymer

Organic molecules are naturally found in biopolymers. Originating from the 2 Greek terms "bio" & "polymer," which denote

life & natural materials, the term "biopolymer" was created. High molecular weight polymer made up of multiple repeating units are called biopolymers. (134, 135). Biopolymers are used in the pharmaceutical industry for wound healing, tissue scaffolds, dressing materials, drug transport materials & medical implants like organs. They are also used in the food sector for edible films and emulsions. This is due to the biopolymers' biocompatibility and biodegradability. This review aims to provide insight into biopolymers and the uses they have in food and pharmaceutical sectors. Proteins, carbohydrates, lipids, nucleic acids & huge non-polymeric substances such as macrocycles and lipids are examples of biopolymers, which are among the most prevalent macromolecules. (136). In contrast, synthetic high molecular weight polymer embrace materials like plastics, synthetic fibers & experimental substances such as carbon nanotubes. (137)

Need for Biopolymers

Biopolymers have garnered significant interest in applications that demand sustainable and biodegradable solutions. Improvements in this area are crucial, as methods for drug delivery continue to be a fundamental approach in increasing the efficacy of bioactive compounds for disease treatment. In this context, drug delivery methods are frequently developed using natural, synthetic and semi-synthetic polymers (138). Numerous environmental issues are brought up by the food and medical industries' extensive usage of synthetic and chemical-based polymers. The development of packaging materials based on biopolymers is being propelled by growing awareness of sustainability, pollution prevention, and municipal solid waste management. (139) Incorporating biopolymers helps reduce reliance on petroleum-based resources, minimizes municipal solid waste, and lowers carbon dioxide emissions. (140).

Sources of Biopolymers

Natural biological sources of biopolymers include agricultural waste, plants, microbes, and animals. Biopolymers can also be chemically synthesized from monomeric components such as amino acids, oils, & sugars, utilizing plant sources like sorghum (141), maize, rice (142), yams (143), wheat (144), banana (145), cassava (146), tapioca (147), potatoes (148), cotton (149), corn (150), and barley (151). Cats are the most prevalent animal source, but the most common marine sources include fish, shrimp, corals, lobsters, and sponges. The most frequent microbiological sources are algae, fungus and yeasts. Agricultural waste, paper trash, crops, green garbage, and wood waste are eaxmples of biomass sources that are high in carbohydrates. Triglycerides are found in vegetable oils such as castor, rapeseed, safflower, jojoba, sunflower, soyabean and meadowfoam oil. (152) Vegetable oils purchased from food producers are great substitutes for the manufacturing of natural polymers. These biopolymers can be melted and shaped similarly to synthetic and chemical thermoplastics, they are naturally synthesized and degraded through microbial metabolism. (153)

Properties of various Biopolymers

Biopolymer	Properties	Reference
Agar	Swelling Agent	(154)
Guar gum	Thickening agent	(155)
Pullulan	Film Formation	(156)
Xanthan gum	Foam stabilizer	(157)
Pectins	Adhesive	(158)
Carboxymethyl cellulose	Coating, Emulsifying agent	(159) (160)
Gellan	Inhibitor	(161)
Gum karaya	Syneresis inhibitor	(162)
Alginate	Gelling agent	(163)
Starch	Stabilizer	(164)
Hemicellulose	Binding agent	(165)

CONCLUSION

With a number of benefits, including biocompatibility, biodegradability, and adjustable drug release profiles, matrix tablets made with biopolymeric components have become a viable method for controlled drug release. The potential of both natural and synthetic biopolymers, including chitosan, alginate, cellulose derivatives, and xanthan gum, to alter drug dissolving rates and improve patient compliance has been extensively studied. Achieving the intended release kinetics and enhancing drug stability depend heavily on the choice of biopolymer, either alone or in combination. Apart from their potential, issues with scalability, batch-to-batch consistency, and polymer variability continue to be major difficulties in pharmaceutical formulation. To improve accuracy in matrix tablet design, future studies should concentrate on refining polymer blends, investigating new biopolymer modifications, and incorporating cutting-edge technologies like 3D printing. All things considered, biopolymeric matrix tablets have a lot of potential to further regulated drug delivery and enhance therapeutic results.

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