

**NATURAL POLYSACCHARIDES AS NOVEL EXCIPIENTS FOR
MODIFIED DRUG DELIVERY SYSTEMS: A REVIEW****Srijita Dutta***

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srijitadutta1991@gmail.com,**ABSTRACT**

The use of natural excipients to deliver the bioactive agents has been hampered by the synthetic materials. However advantages offered by these natural excipients are their being non-toxic, less expensive and freely available. The performance of the excipients partly determines the quality of the medicines. Excipients are any component other than the active substance intentionally added to formulation of a dosage form. The traditional view that excipients are inert and do not exert any therapeutic or biological action or modify the biological action of the drug substance has changed and it is now recognized that excipients can potentially influence the rate and/or extent of absorption of a drug. As herbal excipients are non toxic and compatible, they have a major

role to play in pharmaceutical formulation. The use of natural excipients to deliver the bioactive agents has been hampered by the synthetic materials. Novel drug delivery systems are developed to address the challenges of drug development such as bioavailability, permeability, and poor solubility. Global excipient markets are expected to grow rapidly with the emerging trends in the pharmaceutical industry. This article gives an overview of natural excipients which are used in conventional dosage forms as well as novel drug delivery systems. This review discusses majority of the natural excipients, their sources, chemical constituents, uses and some recent investigations in novel drug delivery systems.

KEYWORDS: Natural, excipients, functional activities, recent advances, formulation, novel drug delivery systems, synthetic excipients.

INTRODUCTION

Drugs are hardly administered as such but are almost always formulated into a suitable dosage form with the aid of excipients, which serve various functions such as binding, lubricating, gelling, suspending, flavoring, sweetening and bulking agent among others ^[1]. The International Pharmaceutical Excipients Council defines excipients as substances, other than the active drug substances of finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture; protect, support or enhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use ^[2]. Excipients play a critical role in the creation of medicines, helping to preserve the efficacy, safety, and stability of active pharmaceutical ingredients (APIs) and ensuring that they deliver their promised benefits to the patients. Optimal use of excipients can provide pharmaceutical manufacturers with cost-savings in drug development, enhanced functionality and help in drug formulations innovation.

Excipients were defined as 'the substance used as a medium for giving a medicament', that is to say with simply the functions of an inert support of the active principle or principles. ^[3] These are used as a medium for giving a medicament with simply the functions of an inert support of the active principles ^[4]. The variability of active compounds, excipients and process are obvious components for the product variability. Nature has provided us a wide variety of materials to improve the drug delivery systems. In recent years, plant derived polymers have evoked tremendous interest due to their diverse pharmaceutical applications such as diluent, binder, disintegrant in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels and bases in suppositories, stabilizers, and coating materials.

Their growing role and application in the pharmaceutical industry may be attributable not only to the fact that they are biodegradable and toxicologically harmless raw materials of low cost and relative abundance compared to their synthetic counterparts ^[5,6], but also because natural resources are renewable and if cultivated or harvested in a sustainable manner, they can provide a constant supply of raw material ^[7]. Furthermore, their extensive applications in drug delivery have been realized because as polymers, they offer unique properties which so far have not been attained by any other materials ^[8]. They can be tailored

for many applications based on the very large chains and functional groups which can be blended with other low- and high-molecular-weight materials to achieve new materials with various physicochemical properties. Consequently, many of the widely used excipients today are chemical modifications of the natural excipients to overcome some of their disadvantages. The advantages of natural excipients over the synthetic one can be listed as:

- Biodegradable
- Non-toxic
- Having low cost
- Environmental friendly
- Local availability
- Better patient acceptance
- Mostly they are from edible sources.

On the other hand there are some disadvantages like microbial contamination, batch to batch variation. ^[9,10]

Excipients are also derived from natural sources, synthesized chemically, or prepared semi-synthetically starting from natural sourced materials. They range from simple, usually well-characterized, organic or inorganic molecules to highly complex materials that are difficult to fully characterize. Classification of excipients is based on their role in the pharmaceutical formulation, their interactions influencing drug delivery, or their chemical and physico-chemical properties.^[11] Excipients are also sometimes used to bulk up formulations that contain very potent active ingredients, to allow for convenient and accurate dosage. Depending on the route of administration, and form of medication, different excipients may be used. To stabilize the active ingredient, excipients are added, ensuring that the active ingredient stays "active", and, just as importantly, stable for a sufficiently long period of time that the shelf-life of the product makes it competitive with other products. Excipients also can serve to mask an unpleasant taste or texture and help ensure that the right amount of the API makes it to the right spot in the body at the right time.^[12]

NEED FOR NEW EXCIPIENTS

Even though there are a large number of excipients available for formulation development, there are still some lacunae in the range of presently available excipients. Some drugs show incompatibilities with many of the current range of excipients. Also there are not many excipients that allow faster manufacturing of formulations, particularly in case of tablets,

there is a need for new materials possessing better compressibility at very high compression speeds ^[13]. There is a need for new excipients to overcome the obvious disadvantages with the currently available materials, like magnesium stearate is a most commonly used excellent lubricant, but renders the tablet hydrophobic; hence a readily soluble lubricant as effective as magnesium stearate is cheerfully welcomed by the pharmaceutical industry.

CHARACTERISTICS OF PHARMACEUTICAL EXCIPIENTS:^[14]

Ideal quality of pharmaceutical excipients are as follows:

- Must be physiological inert.
- Must be acceptably Low.
- Must be physically & chemically stable by themselves & in combination with the drug & other dosage components.
- Must be non-toxic & acceptable to the regulatory agencies in all countries where the product is to be marketed.
- Must be commercially available in an acceptable grade in all countries where the product is to be manufactured.
- Must be color – compatible Must have no deleterious effect on the bioavailability of the drug(s) in the product.
- Must be free from any unacceptable microbiologic load.
- Must not in any group of population for example sucrose in diabetic patients & sodium in hypertensive patients.

Reasons for developing new excipients: For a number of reasons there has been an increase in interest in the development of new excipients/diluents.

Some drugs show incompatibilities with many of the current range of excipients. For example, atenolol PVP, atenolol-mg-stearate ^[15]. One of the more common drug-excipient incompatibilities is the reaction between aldehydic sugars, such as lactose and primary and secondary amines, leading to the formation of Schiff bases. These complex series of reactions lead to browning and discoloration of the dosage form. Despite being a carrier of choice for dry powder aerosol formulations, lactose may need to be replaced with a different carrier, such as mannitol or sucrose, when formulating primary and secondary amines.

Mg-stearate is incompatible with aspirin, some vitamins and most alkaloidal salts ^[16].

There is a need for excipients that will allow faster manufacturing of formulations. For example, at the present time, in tablet dosage forms, new excipients having better compressibility at very high compression speeds are needed. Today, it is not unheard of to have tableting equipment compressing 8000 to 10000 tablets per min. It is critical under these conditions to have an exceptionally efficient flowing granulation/powder blend. Many sugar-based excipients, such as maltose, mannitol, and sorbitol are not compressible in their natural state and need to be modified for use in direct compression tableting.^[17]

Some future developments may require new delivery systems. For example, new drug delivery systems for oral administration of biotechnology products need new excipients which will avoid the inconvenience of multiple daily injections. Progress in the development of peptides as therapeutic drugs has been impeded in part by their rapid excretion, resulting in short circulating lifetimes. This has generated considerable interest in improving the duration of action of drugs through conjugation with the water-soluble, biocompatible excipient, poly (ethylene glycol). Such conjugates have reduced enzymatic degradation rates and lengthened circulating lifetimes compared with the native compounds. There are six FDA-approved PEGylated products on the market, vouching for the safety and commercial viability of this technology. Other novel lipophilic carbohydrate excipients, termed oligosaccharide ester derivatives (OEDs), have been used to modify the pharmacokinetic profiles of drugs. This technology is quite flexible, offering the ability to formulate drug molecules with modified release characteristics and improved bioavailability.^[18] In other areas of technology, selected carbohydrate excipient, such as trehalose and sucrose to stabilize molecules in the dry state, thereby preventing their physical and chemical degradation at ambient temperatures and above. These patent-protected drug delivery technologies are suited to the delivery of macromolecules, such as proteins and peptides by the pulmonary, oral, and injectable routes.

Classification of Excipients

Excipients are commonly classified according to their application and function in the drug products:^[19]

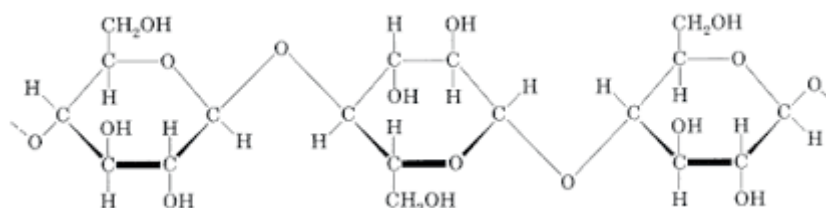
- Binders, Diluents
- Lubricants, Glidants, Disintegrants
- Polishing agents, Film formers and coatings agents
- Plasticizers, Colorings
- Suspending agents Preservatives, antioxidants

- Flavorings, Sweeteners, Taste improving agents
- Printing inks, Dispersing agents^[19]

Polysaccharides in pharmaceuticals: Natural polysaccharides are extensively used for the development of solid dosage forms. These polymers of monosaccharide's (sugars) are inexpensive and available in a variety of structures with a variety of properties. They are highly stable, safe, non-toxic, and hydrophilic and gel forming in nature. Pectin's, starch and amylose are a few polysaccharides commonly used in controlled release dosage forms. Non-starch, linear polysaccharides remain intact in the physiological environment of the stomach and the small intestine, but are degraded by the bacterial inhabitants of the human colon which make them potentially useful in targeted delivery systems to the colon.^[20]

Polysaccharides of the plant cell wall: Natural polymers which have their origin from the plant cell wall mainly include cellulose, hemicelluloses and pectin.

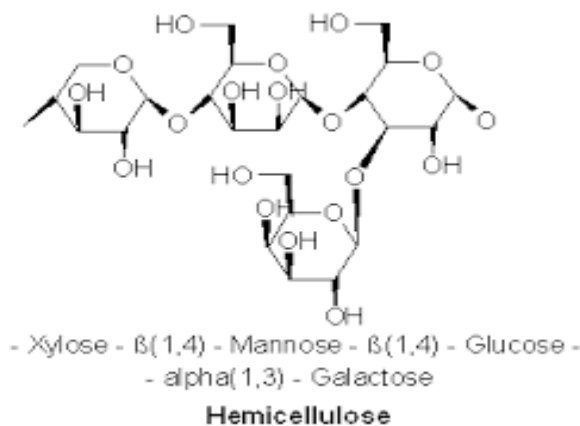
Cellulose: In higher plants, cellulose is an essential structural component and represents the most abundant organic polymer^[21]. Cellulose is a linear unbranched polysaccharide consisting of β -1, 4-linked D-glucose units and many parallel cellulose molecules which form crystalline micro fibrils. The crystalline micro fibrils are mechanically strong and highly resistant to enzymatic attack and are aligned with each other to provide structure to the cell wall^[22]. Cellulose is insoluble in water and indigestible by the human body. It is however digested by herbivores and termites. Cellulose obtained from fibrous materials such as wood and cotton can be mechanically disintegrated to produce powdered cellulose which has been used in the pharmaceutical industry as filler in tablets. High quality powdered cellulose when treated with hydrochloric acid produces microcrystalline cellulose which is preferred over powdered cellulose because it is more free-flowing containing non-fibrous particles. It is consequently employed as diluents or filler/binder in tablets for both granulation and direct compression processes^[23].



Cellulose is a polysaccharide produced by linking additional sugars in exactly the same way.(figure 1)^[23]

The formation of derivatives of cellulose is made possible by the hydroxyl moieties on the D-glucopyranose units of the cellulose polymer to give a variety of derivatives. Cellulose derivatives can be made by etherification, esterification, cross-linking or graft copolymerization ^[24]. Etherification yields derivatives such as hydroxyl-propyl-methylcellulose and carboxyl-methyl-cellulose, while esterification results in derivatives which include cellulose nitrate, cellulose acetate and cellulose acetate phthalate. These derivatives have found application in membrane controlled release systems such as enteric coating and the use of semi-permeable membranes in osmotic pump delivery systems. They have also enjoyed wide use and application in monolithic matrix systems. Extensive studies conducted on these derivatives have proven their ability to sustain the release of medicaments and most of these derivatives have been employed for this purpose ^[25,26].

Hemicellulose: Bound to the surface of cellulose microfibrils are complex polysaccharides which themselves do not form micro fibrils. These bound polysaccharides are called hemicelluloses and include xyloglycans, xylans, mannans and glucomannans, and β -(1 \rightarrow 3, 1 \rightarrow 4)-glucans ^[27]. They can be extracted from the plant cell wall with the aid of strong alkali.

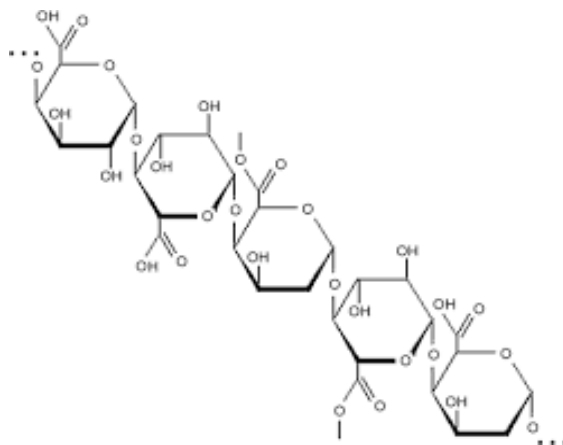


Hemicellulose(figure 2)^[27]

Hemicelluloses have β -(1 \rightarrow 4)-linked backbones with an equatorial configuration. In contrast to cellulose which is crystalline and unbranched, hemicellulose is amorphous and branched. Although the xyloglycans have similar backbone as cellulose, they contain xylose branches on 3 out of every 4 glucose monomers, while the β -1,4-linked D-xylan backbone of arabinoxylan contains arabinose branches. ^[28]

Pectin: Pectins are non-starch, linear polysaccharides extracted from the plant cell walls. ^[29] In the food industry, folic acid incorporated microcapsules were prepared using alginate and combinations of alginate and pectin polymers so as to improve stability of folic acid. The

blended alginate and pectin polymer matrix increased the folic acid encapsulation efficiency and reduced leakage from the capsules as compared to those made with alginate alone, they showed higher folic acid retention after freeze drying and storage. ^[30]



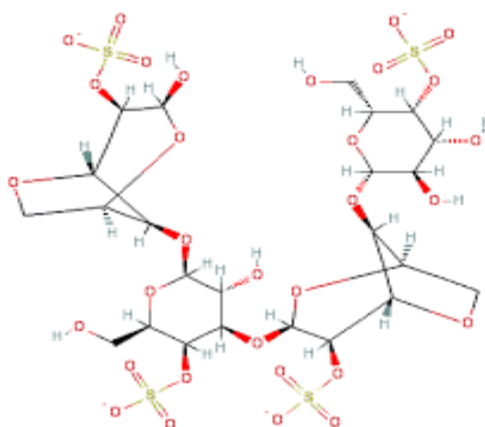
Pectin (figure 3) ^[30]

Polymeric hydrogels are widely used as controlled-release matrix tablets. Some researchers ^[31] investigated the high-methoxy-pectin for its potential value in controlled-release matrix formulations. The effects of compression force, ratio of drug to pectin, and type of pectin on drug release from matrix tablets were also investigated. The results of the *in vitro* release studies showed that the drug release from compressed matrix tablets prepared from pectin can be modified by changing the amount and type of pectin in the matrix tablets. A very low solubility pectin-derivative (pectinic acid, degree of methoxylation 4%) was found to be well suited as an excipient for pelletisation by extrusion/spheronisation. The capacity as an extrusion aid was found to be high. Formulations containing only 20% pectinic acid resulted in nearly spherical pellets. All pectinic acid pellets were mechanically stable. They possessed an aspect ratio of approximately 1.15–1.20 and released 30–60% of a low solubility model drug within 15 min in simulated gastric fluid (0.1M HCl) and intestinal fluid (phosphate buffer pH 6.8). ^[32]

Micro particulate polymeric delivery systems have been reported as a possible approach to improve the low bioavailability characteristics observed in standard ophthalmic vehicles (collyria) ^[33]. In this context pectin microspheres of piroxicam were prepared by the spray drying technique. *In vivo* tests in rabbits with dispersions of piroxicam-loaded microspheres also indicated a significant improvement of piroxicam bioavailability in the aqueous humour (2.5–fold) when compared with commercial piroxicameye drops.

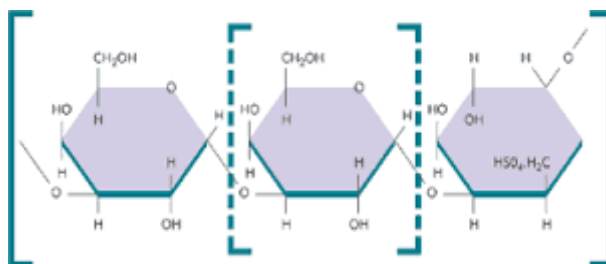
Seaweed polysaccharides: Seaweed gums are typified by the carrageenans, agar and the alginates.

Carageenans: The carrageenans are sulphated marine hydrocolloids obtained by extraction from seaweeds of the class Rhodophyceae, represented by *Chondrus crispus*, *Euchemaspinosum*, *Gigartinaskottsbergi*, *Gigartinastellata*, *Iradaealaminarioides*. These are red seaweeds growing abundantly along the Atlantic coasts of North America, Europe and the western Pacific coast of Korea and Japan.^[34-36] Carrageenan is not assimilated by the human body. It provides only bulk but no nutrition. Carrageenan has been categorized into 3: kappa (κ), iota (ι) and lambda (λ). Lambda (λ -type) carrageenan produces viscous solutions but does not form gels. While the Kappa (κ -type) carrageenan forms a brittle gel, the iota (ι -type) carrageenan produces elastic gels^[37]. Studies have shown that the carrageenans are suitable in the formulation of controlled release tablets^[38-40].



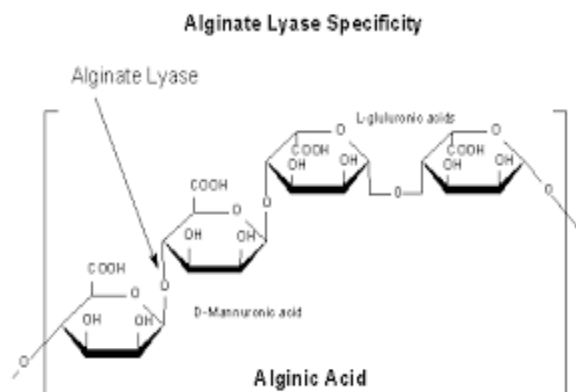
Carrageenan (figure 4)^[39]

Gum agar: Gum agar is extracted from the red-purple marine algae of the Rhodophyceae class. The species include *Gelidium cartilagineum* and *Gracilaria confervoides* which grow abundantly in the waters along the coast of Japan, New Zealand, South Africa, Southern California, Mexico, Chile, Morocco, and Portugal^[40,41,42].



Agar-agar is insoluble in cold water, but it swells considerably, absorbing as much as twenty times its own weight of water. (figure 5)^[41]

Alginates: Alginates are natural polysaccharide polymers isolated from the brown sea weed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used. Alginates offer various applications in drug de-livery, such as in matrix type alginate gel beads, in liposomes, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications. ^[43] Bio-adhesive sodium alginate microspheres of metoprolol tartarate for intranasal systemic delivery were prepared to avoid the first-pass effect, as an alternative therapy to injection, and to obtain improved therapeutic efficacy in the treatment of hypertension and angina pectoris. The microspheres were prepared using emulsification-cross linking method. *In vivo* studies indicated significantly improved therapeutic efficacy of metoprolol from microspheres. There was sustained and controlled inhibition of isoprenaline-induced tachycardia as compared with oral and nasal administration of drug solution ^[44].



Composed of blocks of β -D-(1-4) mannuronic acid homopolymeric regions (MMMM...), α -L-(1-4)guluronic acid (GGGG...) homopolymeric regions (figure 6) ^[44]

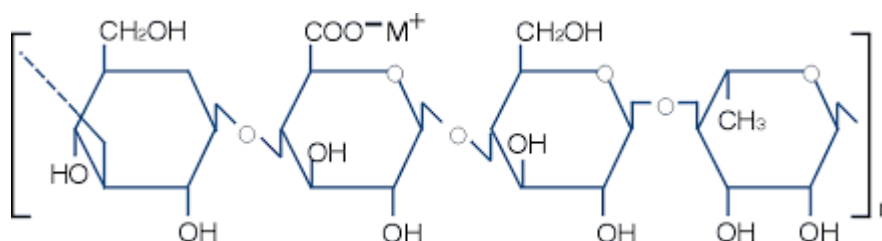
Uses of alginates

- Alginates have proven to be effective for the symptoms of malignant wounds. ^[45]
- Bleeding in malignant wounds is caused by the absence of platelets and the abundance of friable capillaries. Because bleeding occurs easily, it is essential that dressings do not adhere or cause trauma. Alginates are ideal for bleeding wounds as they have haemostatic properties. ^[46]
- Alginates are thin, self-adhesive and conform well to contours. This increases the freedom to carry out normal daily activities. ^[47]

Microbial polysaccharides: Natural polysaccharide gums have also been obtained as carbohydrate fermentation products including Xanthan gum, produced in pure culture

fermentation by the bacteria *Xanthomonas campestris*. It was originally obtained from the rutabaga plant ^[48]. Gellan gum is a microbial polysaccharide obtained by fermentation by *Pseudomonas elodea* ^[49,50]. Pullulan is an extracellular homo-polysaccharide of glucose produced by many species of the fungus *Aureobasidium*, specifically *A. pullulans*.

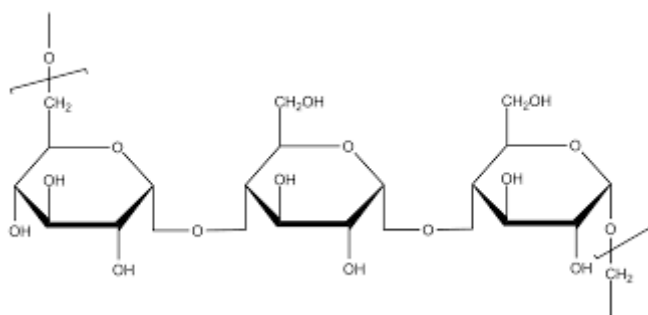
Gellan gum: Deacylated Gellan gum (Gellan) is an anionic microbial polysaccharide, secreted from *Sphingomonas elodea*, consisting of repeating tetrasaccharide units of glucose, glucuronic acid and rhamnose residues in a 2:1:1 ratio: $[\rightarrow 3)\text{-}\beta\text{-D-glucose-(1}\rightarrow 4)\text{-}\beta\text{-D-glucuronic acid-(1}\rightarrow 4)\text{-}\beta\text{-D-glucose-(1}\rightarrow 4)\text{-}\alpha\text{-L-rhamnose-(1}\rightarrow]_n$. In the native polymer two acyl substituents, L-glyceryl at O(2) and acetyl at O(6), are present on the 3-linked glucose. On average, there is one glyceryl per repeating unit and one acetyl for every two repeating units. Deacylated Gellan gum is obtained by alkali treatment of the native polysaccharide. Both native and deacylated Gellan gum are capable of physical gelation ^[51]. To induce Gellan gelation it is necessary to warm up preliminarily a concentrated water solution of the polysaccharide: when the temperature is decreased, the chains undergo a conformational transition from random coils to double helices (Coil-Helix Transition). Then a rearrangement of the double helices occurs leading to the formation of ordered junction zones (Sol- Gel Transition) ^[52] thus giving a thermo-reversible hydrogel [64]. Much stronger physical thermo-reversible hydrogels are also obtained by addition of mono and divalent ions to Gellan solutions ^[53], or in acidic conditions ^[54].



Structure of Gellan Gum.(figure 7)^[52]

Pullulan: Insulin (Ins) spontaneously and easily complexed with the hydrogel nanoparticle of hydrophobized cholesterol-bearing pullulan (CHP) in water. The complexed nanoparticles (diameter 20–30 nm) thus obtained formed a very stable colloid. The thermal denaturation and subsequent aggregation of Ins were effectively suppressed upon complexation. The complexed Insulin was significantly protected from enzymatic degradation. Spontaneous dissociation of Insulin from the complex was barely observed, except in the presence of

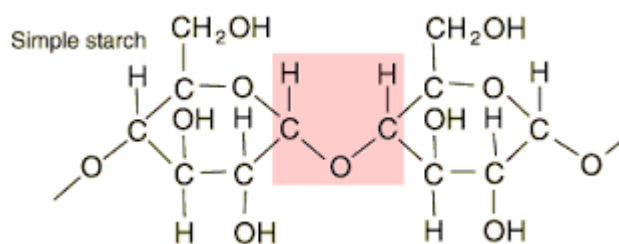
bovine serum albumin. The original physiological activity of complexed Insulin was preserved in vivo after i.v. injection ^[55]



Pullulan (figure 8) ^[55]

Animal polysaccharides: Natural gums have also been obtained from animal sources. Examples include chitin and chitosan. Chitin is a structural polysaccharide which takes the place of cellulose in any species of lower plants and animals. It therefore occurs in fungi, yeast, green, brown and red algae and form the main component of the exoskeleton of insects and shells of crustaceans ^[56]. Chitin is insoluble in water but when treated with strong alkali, it forms the water-soluble polysaccharide chitosan which is the only polysaccharide carrying a positive charge ^[56].

Starch: Starch that is a natural polysaccharide polymeric material widely exists in fruit, root, pedicle, and leaf of plants.



Foods such as potatoes, rice, corn and wheat contain starch granules which are important energy sources for humans (figure 9) ^[57]

Starch is classified into:- I. Raw starch

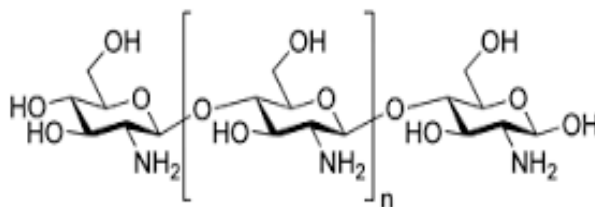
II. Physical-modified starch or chemical-modified starch. ^[41]

Modified starch was tested for general applicability of a new pregelatinized starch product in directly compressible controlled-release matrix systems. ^[57]

Use of starch: The two major components of starch are amylose and amylopectin. Amylose consists of long linear chains of α -1,4 linked glucose residues with relatively few α -1,6 linked branches whereas amylopectin is a highly branched molecule of shorter α -1,4 linked glucose molecules and more frequent α -1,6 branches. ^[58]

Amphoteric Starch: Amphoteric starches have been used as wet-end and size-press papermaking additives by aid in retention, drainage and strength properties. They can also be used as ceiling tile additives drilling fluid additives, viscosity modifiers and agents in ore recovery operations. ^[59]

Chitosan: Chitosan is a natural positively charged (cationic) biopolymer derived from the hydrolysis of the polysaccharide chitin. ^[60] Chitin is an amino polysaccharide (combination of sugar and protein) abundantly available natural biopolymer found in the exoskeletons of crustacean like shrimp, crab, lobster and other shellfish. ^[61]



Chitosan chemical structural formula (figure 10) ^[60]

Properties of Chitosan: - CS is a linear randomly distributed, hetero polysaccharide consisting of S (1-4) linked -acetamido-2-deoxy-S-D-glucopyranose and 2-amino-2-deoxy-S-D-glycopyranose units. ^[61]

Physicochemical Properties: - Chitosan is highly basic polysaccharides due to presence of primary amino group in its structure. The main factors which may affect the CS properties are its molecular weight and degree of deacetylation (DD). These factors enable the researcher to formulate different grades of CS which differ primarily in molecular weight and degree of deacetylation. ^[62]

Biological Properties: During the last two decades, chitosan has been used as a safe excipient in drug formulations.

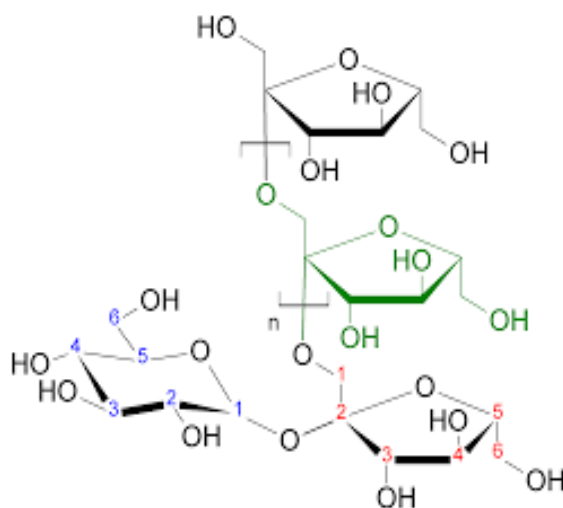
- Due to its bioadhesive property, it can adhere to hard and soft tissues and has been used in dentistry, orthopedics and ophthalmology and in surgical procedures.
- It also has a fungistatic or bacteriostatic, anticancerogen and anticholestermic action. ^[63]

Applications of chitosan in Pharmaceuticals

- It is good diluents in direct compression of tablets, use binder for wet granulation, slow release of drugs from tablets and granules, film controlling drug release. ^[64]
- It increases viscosity in solutions preparing hydrogels, improves the dissolution of poorly soluble drugs, absorption enhancer for nasal and oral drugs, biodegradable polymer for implants and carrier to vaccine delivery and gene therapy. ^[65]

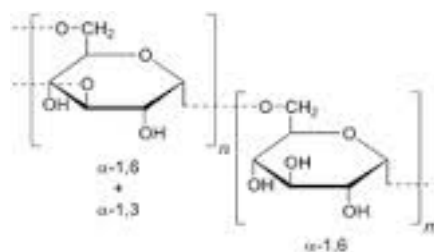
Inulin: Inulin is a naturally occurring storage polysaccharide found in many plants such as onion, garlic, artichoke, and chicory. Chemically, it belongs to the gluco-fructans and consists of a mixture of oligomers and polymers containing 2 to 60 (or more) β -2-1 linked D-fructose molecules. Most of these fructose chains have a glucose unit as the initial moiety. The inulin has been incorporated into Eudragit RS films for preparation of mixed films that resisted degradation in the upper GIT but digested in human fecal medium by the action of Bifidobacteria and Bacteroids. ^[66]

Various inulin hydrogels have been developed that serve as potential carriers for the introduction of drugs into the colon ^[67]. Vinyl groups were introduced in inulin chains to form hydrogels by free radical polymerization. Inulin was reacted with glycidylmethacrylated in N,N-dimethylformamide in the presence of 4-dimethylaminopyridine as catalyst. ¹H and ¹³C NMR spectroscopy were used for the characterization of the obtained reaction product and revealed the conversion of the incorporated vinyl groups into covalent crosslink's upon free radical polymerization of aqueous solutions of the derivatized inulin ^[67].



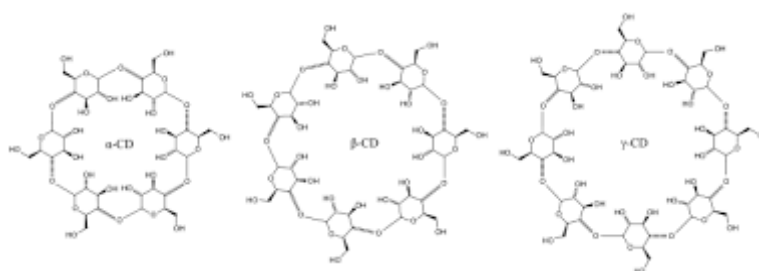
Inulin (figure 11) ^[67]

Dextran: Dextran hydrogels have been shown to be the promising carrier for the delivery of drugs to colon. [68-70]



Dextran (figure 12) [68]

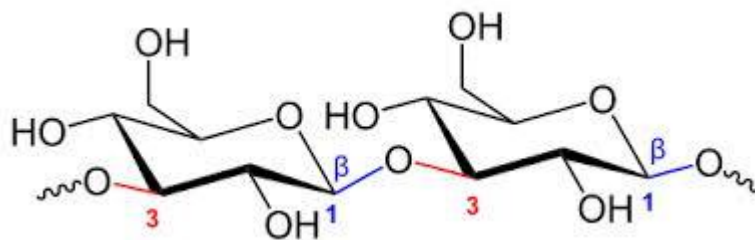
Cyclo dextrins: Cyclo dextrins (CyDs) are cyclic oligosaccharides consisting of six to eight glucose units joined through α -1,4 glucosidic bonds. CyDs remain intact during their passage through stomach and small intestine. However, in the colon, they undergo fermentation from the presence of vast colonic micro flora into small saccharides and thus absorbed from these regions [71,72]. CyDs form inclusion complexes with drug molecules because the interior of the molecule is relatively lipophilic while the exterior is hydrophilic [72]. It has been investigated through a study in healthy human volunteers that β CyDs are degraded to a very small extent in the small intestine but are completely digested in large intestine. Most bacterial strains that are isolated from human beings are capable of degrading CyDs. This has been proved by their ability to grow on cyclo dextrins by utilizing them as the sole carbon source and by the stimulation of cyclo dextrinase activity as low as 2–4 hr of exposure to CyDs.



Chemical structure of the three main types of cyclodextrins (figure 13) [72]

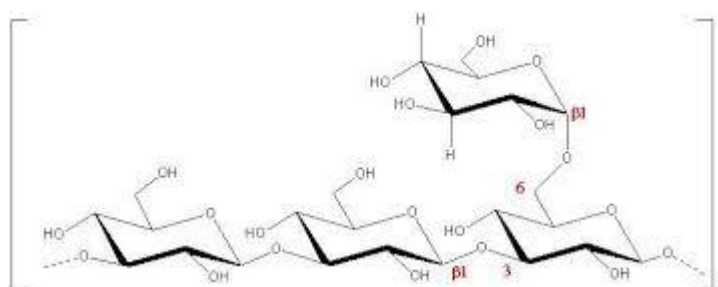
Curdlan: Curdlan is a neutral, essentially linear (1 \rightarrow 3)- β -glucan which may have a few intra- or inter-chain (1 \rightarrow 6) linkages. Curdlan's unusual rheological properties among natural and synthetic polymers underlie its use as a thickening and gelling agent in foods. Apart from being tasteless, colourless and odourless, the main advantages are that in contrast to cold-set gels and heat-set gels, the heating process alone produces different forms of curdlan gel with different textural qualities, physical stabilities and water-holding capacities [73]. Gels of

variable strength are formed depending on the heating temperature, time of heat-treatment and curdlan concentration. The safety of curdlan has been assessed in animal studies and *in vitro* tests and it is approved in food use in Korea, Taiwan and Japan as an inert dietary fibre. It is registered in the USA as a food additive.



Curdlan colored (figure 14)^[74]

Scleroglucan: Among these macromolecules, scleroglucan (Sclg) also seems to be potentially useful for the formulation of modified release dosage forms and numerous studies have been devoted to this specific topic^[75]. Scleroglucan (Sclg) is a branched homo polysaccharide consisting of a main chain of (1-3)-linked β -D glucopyranosyl units bearing, every third unit, a single β -D-glucopyranosyl unit linked (1-6). This polysaccharide is resistant to hydrolysis and its solutions show an interesting rheological behaviour: viscosity remains practically constant, even at high ionic strength, up to pH-12 and to 90°C.



Scleroglucan (figure 15)^[75]

Rosin: Rosin is a low molecular weight (400 Da) natural polymer obtained from the oleoresin of *Pinus* *resinosa*, *Pinus longifolia* and *Pinus strobus*. It has as components abietic and pimaric acids. Rosin and its derivatives have enjoyed growing roles in Pharmacy. They have been investigated for microencapsulation, film-forming and coating properties, and as matrix materials in tablets for sustained and controlled release.^[76,77]



Dark Rosin (figure 16)^[76]

Studies on the film forming and coating properties of rosin and the glycerol ester of maleic rosin showed that rosin has excellent film forming properties with good to be used as coating materials for pharmaceutical products as well as in sustained-release drug delivery systems. The rosin films were biodegradable and biocompatible^[78]. Derivatives of rosin have been synthesized by reaction with polyethylene glycol 200 and maleic anhydride. The derivative proved suitable for sustaining drug release from matrix tablets and pellets^[78]. Rosin nanoparticles loaded with hydrocortisone retarded the release of the active and demonstrated the potential of rosin production of effective nanoparticulate drug delivery systems.^[79]

Gums and mucilages: Gums are considered to be pathological products formed following injury to the plant or owing to unfavorable conditions, such as drought, by a breakdown of cell walls (extra cellular formation; gummosis). Mucilage's are generally normal products of metabolism, formed within the cell (intracellular formation) and/or are produced without injury to the plant. Gums readily dissolve in water, whereas, mucilage form slimy masses. Mucilage's are physiological products.^[80]

Gums are pathological products, whereas mucilages are physiological products.^[80] Acacia, tragacanth, and guar gum are examples of gums while mucilages are often found in different parts of plants. For example, in the epidermal cells of leaves (senna), in seed coats (linseed, psyllium), roots (marshmallow), barks (slippery elm) and middle lamella (aloe).^[81]

Gums and mucilages have certain similarities—both are plant hydrocolloids. They are also translucent amorphous substances and polymers of a monosaccharide or mixed monosaccharides and many of them are combined with uronic acids. Gums and mucilages have similar constituents and on hydrolysis yield a mixture of sugars and uronic acids. Gums

and mucilages contain hydrophilic molecules, which can combine with water to form viscous solutions or gels. The nature of the compounds involved influences the properties of different gums. Linear polysaccharides occupy more space and are more viscous than highly branched compounds of the same molecular weight. The branched compounds form gels more easily and are more stable because extensive interaction along the chains is not possible.

Isolation and Purification of Gums and Mucilage's: Mucilage can be extracted from plant parts by various methods like heating, solvent precipitation, and microwave assisted extraction. The easiest method is solvent precipitation. In this method the part of the plant containing gum/mucilage is selected followed by drying, grinding, and sieving of that plant part. This is then stirred in distilled water and heated for complete dispersion in distilled water and kept for 6–8 h at room temperature. The supernatant is obtained by centrifugation. The residue is then washed with water and the washings are added to the separated supernatant. Solvent for precipitation is selected and, finally, the supernatant is mixed with twice the volume of precipitating solvent by continuous stirring. The precipitated material is washed with distilled water and dried at 50–60°C under vacuum. Plant material must be treated with petroleum ether and chloroform (to remove pigments and chlorophyll) and then with distilled water. ^[82,83]

Characterization of Gums and Mucilage's

For characterization, analytical techniques can be classified according to the type of information generated.

Structural: Gums and mucilages are polysaccharides and they contain sugars. So, confirmation of different sugars present can be done by chromatography (TLC/HPLC) and structure elucidation can be carried out by FTIR, mass, and NMR spectroscopy.

Purity: To determine the purity of the selected gum and mucilage, tests for alkaloids, glycosides, steroids, carbohydrates, flavonoids, terpenes, amino acids, saponins, oils and fats, and tannins and phenols are carried out.

Impurity Profile: Suitable analytical techniques can be used for testing of impurities.

Physicochemical Properties: Colour, odour, taste, shape, texture, touch, solubility, pH, swelling index, loss on drying, hygroscopic nature, angle of repose, bulk and true densities, porosity, and surface tension can be estimated. The microbial load and presence of specific

pathogens are also determined. Gums and mucilages are highly viscous in nature. So, the rheological properties of excipients are important criteria for deciding their commercial use.

Toxicity: The acute toxicity of gums and mucilages are determined by fixed-dose method as per OECD guideline no. 425. ^[84]

Advantages of natural gums and mucilages in pharmaceutical sciences

The following are a number of the advantages of natural plant-based materials:

Biodegradable—Naturally available biodegradable polymers are produced by all living organisms. They represent truly renewable source and they have no adverse impact on humans or environmental health (e.g., skin and eye irritation).

Biocompatible and non-toxic— Chemically, nearly all of these plant materials are carbohydrates composed of repeating sugar (monosaccharides) units. Hence, they are non-toxic.

Low cost—it is always cheaper to use natural sources. The production cost is also much lower compared with that for synthetic material. India and many developing countries are dependent on agriculture.

Environmental-friendly processing—Gums and mucilages from different sources are easily collected in different seasons in large quantities due to the simple production processes involved.

Local availability (especially in developing countries) —In developing countries, governments promote the production of plant like guar gum and tragacanth because of the wide applications in a variety of industries.

Better patient tolerance as well as public acceptance— There is less chance of side and adverse effects with natural materials compared with synthetic one. For example PMMA, povidone.

Edible sources—Most gums and mucilages are obtained from edible sources.

Disadvantages of natural gums and mucilages ^[85-86]

Microbial contamination—The equilibrium moisture content present in the gums and mucilages is normally 10% or more and, structurally, they are carbohydrates and, during production, they are exposed to the external environment and, so there is a chance of microbial contamination. However, this can be prevented by proper handling and the use of preservatives.

Batch to batch variation—Synthetic manufacturing is a controlled procedure with fixed quantities of ingredients, while the production of gums and mucilages is dependent on environmental and seasonal factors.

Uncontrolled rate of hydration—Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary. There is a need to develop suitable monographs on available gums and mucilages.

Reduced viscosity on storage—Normally, when gums and mucilages come into contact with water there is an increase in the viscosity of the formulations. Due to the complex nature of gums and mucilages (monosaccharides to polysaccharides and their derivatives), it has been found that after storage there is reduced in viscosity.

Classification of gums and mucilages ^[87-90]

Gums and mucilages are present in high quantities in a varieties of plants, animals, seaweeds, fungi and other microbial sources, where they perform a number of structural and metabolic functions; plant sources provide the largest amounts. The different available gums and mucilages can be classified as follows:

According to the charge

Non-ionic seed gums: guar, locust bean, tamarind, xanthan, amylose, arabinans, cellulose, galactomannans.

Anionic gums: arabic, karaya, tragacant, gellan, agar, algin, carrageenans, pectic acid.

According to the source

(a)marine origin/algal (seaweed) gums: agar, carrageenans, alginic acid, and laminarin;

(b)plant origin: (i)shrubs/tree exudates: gum arabic, gum ghatti, gum karaya, gum tragacanth, and khaya and albizia gums;

(ii)seed gums: guar gum, locust bean gum, starch, amylose, and cellulose;

(iii)extracts: pectin, larch gum;(iv)tuber and roots: potato starch;

(c)animal origin: chitin and chitosan, chondroitin sulfate, and hyaluronic acid;

(d)microbial origin (bacterial and fungal): xanthan, dextran, curdian, pullulan, zanflo, emulsan, Baker's yeast glycan, schizophyllan, lentinan, krestin, and scleroglucan.

Semi-synthetic

Starch derivatives—hetastarch, starch acetate, starch phosphates.

Cellulose derivatives— carboxy methyl cellulose (CMC), hydroxy ethylcellulose, hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), microcrystalline cellulose (MCC).

According to shape

Linear: algins, amylose, cellulose, pectins.

Branched: (1) **short branches**—xanthan, xylan, galactomanan;

(2) **branch-on-branch**—amylopectin, gum arabic, tragacanth.

According to monomeric units in chemical structure:

Homoglycans— amylose, arabinanas, cellulose;

Diheteroglycans— algins, carragennans, galactomannans;

Tri-heteroglycans—arabinoxylans, gellan, xanthan;

Tetra-heteroglycans—gum arabic, psyllium seed gum;

Penta-heteroglycans—ghatti gum, tragacanth.

Gum acacia: Gum acacia or gum arabic is the dried gummy exudate obtained from the stem and branches of *Acacia senegal* (Linne) Willdenow and other related species of acacia (Family Leguminosae). The gum has been recognized as an acidic polysaccharide containing D-galactose, L-arabinose, L-rhamnose, and D-glucuronic acid. Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of pastilles and lozenges and as a tablet binder.^[91]

Sustained release of ferrous sulfate was achieved for 7 h by preparing gum arabic pellets. Release was further sustained for more than 12 h by coating the pellets with polyvinyl acetate and ethylene vinyl acetate, respectively. An increase in the amount of gum arabic in the pellets decreased the rate of release due to the gelling property of gum arabic. The gel layer acts as a barrier and retards the rate of diffusion of FeSO₄ through the pellet.^[92]

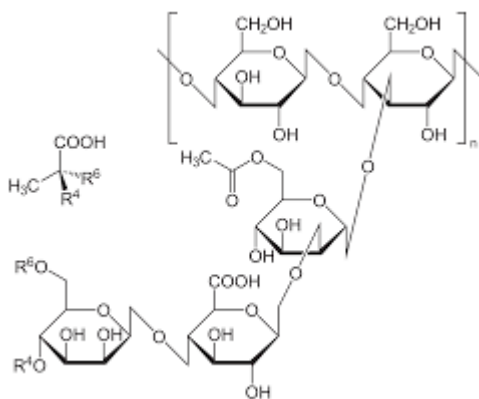
Gum arabic was used as an osmotic, suspending and expanding agent in the preparation of a monolithic osmotic tablet system (MOTS) with two orifices on both side surfaces. Water-insoluble naproxen was selected as the model drug. The optimal MOTS was found to be able to deliver naproxen at a rate of approximately zero order up to 12 h in pH 6.8. Cumulative release at 12 h is 81%, and is independent of environment media and stirring rate. Therefore, these MOTS can be used in the oral drug-controlled delivery field, especially for water-insoluble drugs.^[93]

Karaya gum: Karaya gum is obtained from *Sterculia urens* (Family sterculiaceae) is a partially acetylated polymer of galactose, rhamnose, and glucuronic acid.^[91] Swellable hydrophilic natural gums like xanthan gum and karaya gum were used as release-controlling agents in producing directly compressed matrices. Caffeine and diclofenac sodium, which are having different solubilities in aqueous medium were selected as model drugs. Gum erosion, hydration and drug release studies were carried out using a dissolution apparatus (basket method) at two agitation speeds. In case of xanthan gum neither agitation speed nor drug solubility had any significant effect on water uptake, but matrices with the lower proportion of gum produced a lesser degree of hydration. In contrast, karaya gum displayed a much lower hydration capacity and a higher rate of erosion, both markedly affected by agitation speed. Hence it was concluded that drug release from xanthan and karaya gum matrices depended on agitation speed, solubility and proportion of drug.

Both xanthan and karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in karaya gum matrices^[94]. Park *et al.* showed that mucoadhesive tablets prepared by karaya gum for buccal delivery, had superior adhesive properties as compared to guar gum and was able to provide zero-order drug release, but concentrations greater than 50% w/w may be required to provide suitable sustained release.

Xanthan gum: Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris*. The

primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β -D-glucose residues) and a trisaccharide side chain of β -D-mannose- β -D-glucuronicacid- α -D-mannose attached with alternate glucose residues of the main chain. The terminal D-mannose residue may carry a pyruvate function, the distribution of which is dependent on the bacterial strain and the fermentation conditions. The non-terminal D-mannose unit in the side chain contains an acetyl function. The anionic character of this polymer is due to the presence of both glucuronicacid and pyruvic acid groups in the side chain^[93].



Xanthan gum (figure 17)^[94]

Tragacanth: This gum is obtained from the branches of *Astragalus gummifer*, Family Leguminosae. Tragacanth when used as the carrier in the formulation of 1- and 3-layer matrices produced satisfactory release prolongation either alone or in combination with other polymers.^[92]



Gum Tragacanth (figure 18)^[92]

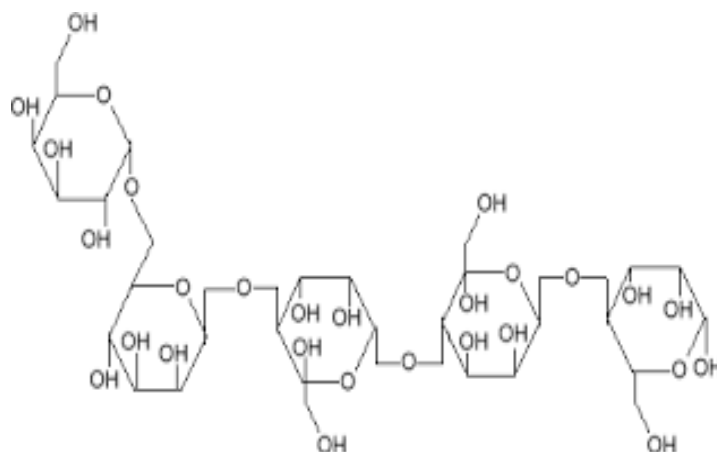
Hakeagibbosa gum: The muco adhesive and sustained-release properties of the water-soluble gum obtained from Hakeagibbosa (hakea), for the formulation of buccal tablets. The mechanism by which CPM release was sustained was more likely due to slow relaxation of the hydrated hakea.

Moringaoleifer gum: A natural gum obtained from plant *Moringaoleifera* gum was extracted by using water as solvent and precipitated using acetone as non-solvent. Physical characteristics such as, solubility, swelling index, loss on drying, and pH were studied. Diclofenac sodium was used as model drug for the formulation of gels. The gels prepared with 8.0% of mucilage were found to be ideal and comparable with a commercial preparation.^[95]

Kyaha gum: Khaya gum is obtained by extraction from *Khayasenegalensis* and *Khayagrandidifoliola*(Fam. Meliaceae). The comparative binding effects of khaya gum obtained from *Khayasenegalensis* and *Khayagrandidifoliola* in paracetamol tablet formulation were evaluated.^[96]

Mucilage gums: Many seeds contain polysaccharide food reserves which produce intracellular seed gums usually obtained by extraction from the seeds. Guar gum is obtained from the ground endosperms or seeds of the plant *Cyamopsistetragonolobus* (Fam. Leguminosae). Locust bean gum is obtained from the endosperms of the hard seeds of the locust bean tree (Carob tree), *Ceratoniasiliqua*(Fam. Caesalpiniaceae).^[97]

Locust bean gum: It is also called carob gum, as it is derived from the seeds of the leguminous plant carob, *Ceratoniasiliqua* Linn (Fam. Caesalpiniaceae). Locust bean gum has an irregularly shaped molecule with branched β -1, 4-D-galactomannan units. This neutral polymer is only slightly soluble in cold water; it requires heat to achieve full hydration and maximum viscosity. *In vitro* drug release studies and *in vivo* studies revealed that the locust bean gum and chitosan as a coating material applied over the core tablet was capable of protecting the drug from being released in the physiological environment of stomach and small intestine and was susceptible to colonic bacterial enzymatic actions with resultant drug release in the colon.



Locust bean gum (figure 19)^[97]

Grewia gum: Grewia genus is today placed by most authors in the Family Malvaceae, in the expanded sense as proposed in the Angiosperm Phylogeny Group (APG). Formerly it was placed in either the linden Family (Tiliaceae) or the Spermamanniaceae. However, these were both not monophyletic with respect to other Malvales. Grewia and similar genera have been merged into the Malvaceae. Together with the bulk of the former spermanniaceae, Grewia is in the Family Grewiodeae and therein the tribe Grewieae, of which it is the type genus^[98].

Applications of gums and mucilages: Gums and mucilages of different sources and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms. Various kinds of gums are used in the food industry and are regarded as safe for human consumption.

However, there is growing concern about the safety of pharmaceutical excipients derived from natural sources. Plant gums and exudates are now screened for their use as pharmaceutical adjuvants. Mucilages of different origins are also used in conventional dosage forms of various drugs for their binding, thickening, stabilizing and humidifying properties in medicine. Newer uses of different gums and mucilages in cosmetics and textiles has increased the demand and screening of gums has become an important pharmaceutical area. However, different gums and mucilages used as pharmaceutical adjuvants have stringent specifications, which few natural agents can fulfill.

Volatile Oil: Volatile oils are very complex mixtures of compounds. The constituents of the oils are mainly monoterpenes and sesquiterpenes which are hydrocarbons with the general formula $(C_5H_8)_n$.^[99]

Menthol: Menthol was tested for improving the bioavailability of poorly water-soluble ibuprofen in the rectum with poloxamer. The effects of menthol and poloxamer 188 on the aqueous solubility of ibuprofen were investigated. ^[100]

Terpenes such as menthol, cineole and propylene glycol (PG) were tested as chemical enhancers to improve the skin penetration of propranolol. ^[101]

Caraway: Caraway seeds technically are half-fruits, the whole fruit being a schizocarp which comprises two distinct halves ('mericarps') which each contain one seed. We will use 'seed' where we refer to the agricultural product (half fruit) and 'fruit' when we refer to the entire schizocarp (containing two seeds).

Caraway essential oil has been used as a flavouring for liquors and toothpaste, while the seeds have been used as a spice and flavouring. ^[102]

Disadvantages of synthetic polymers in pharmaceutical sciences: The synthetic polymers have certain disadvantages such as high cost, toxicity, environmental pollution during synthesis, non-renewable sources, side effects, and poor patient compliance. Acute and chronic adverse effects (skin and eye irritation) have been observed in workers handling the related substances methyl methacrylate and poly- (methyl methacrylate) (PMMA) . Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site produced by povidone. There is also evidence that povidone may accumulate in organs following intramuscular injections ^[103]. Acute oral toxicity studies in animals have indicated that carbomer-934P has a low oral toxicity at a dose of up to 8 g/kg. Carbomer dust is irritating to the eyes, mucous membranes and respiratory tract. So, gloves, eye protection and dust respirator are recommended during handling ^[104]. Studies in rats have shown that 5% polyvinyl alcohol aqueous solution injected subcutaneously can cause anemia and can infiltrate various organs and tissues ^[105]. Some disadvantages of biodegradable polymers used in tissue engineering applications are their poor biocompatibility, release of acidic degradation products, poor processing ability and rapid loss of mechanical properties during degradation. It has been shown that poly glycolides, polylactides and their co-polymers have an acceptable biocompatibility but exhibit systemic or local reactions due to acidic degradation products. An initial mild inflammatory response has been reported when using poly-(propylene fumarate) in rat implant studies. ^[106]

CONCLUSION

The research into and use of excipients from natural sources was reviewed and were discussed according to their classes. Natural polymeric excipients and their modifications have continued to dominate the research efforts of scientists in finding cheap, less expensive, biodegradable, ecofriendly excipients. Some of these excipients have obvious advantages over their synthetic counterparts in some specific delivery systems due to their inherent characteristics. If the current vigorous investigations on the use of natural polymeric materials are sustained and maintained, it is probable that there would be a breakthrough that will overcome some of the disadvantages of this class of potential pharmaceutical excipients that would change the landscape of the preferred pharmaceutical excipients for drug delivery in the future.

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