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Biopolymers in Drug Delivery: A Review

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Summary

Pharmaceutical formulation development involves various components in addition to the active pharmaceutical ingredients. In recent years, excipient development is become core area of research in pharmaceutical drug delivery because it influences the formulation development and drug delivery process in various ways. Biopolymers are choice of research as excipient because of its low toxicity, biodegrability, stability and renewable nature. This review discusses, some of the most common used biopolymers as excipient in pharmaceutical drug delivery systems.

Introduction

Polysaccharides are among the most widespread organic compounds in the plant kingdom. They are typically complex carbohydrate biopolymers composed of monosaccharide units linked together by glycosidic bonds into linear or branched chains of different length, and are classified on the basis of their main building units, i.e. monosaccharide components, type of linkages and the anomeric configuration of glycosidic linkages. Polysaccharides play crucial roles in life processes of all plants. They can be divided into several broad groups according their functions i.e. structural polymers (cellulose), protective polysaccharides (pectin and hemicelluloses) and reserve polysaccharides (starch). Further, polysaccharides can form glycoconjugates with proteins and lipids resulting in biological macromolecules in the cell wall and cell wall membranes, and play important roles in many physiological and biochemical processes. From an industrial point of view, one of the most important polysaccharides is starch. Native starch and its derivatives are used mainly in the food industry (as a main nutrient for humans), in pharmaceutical, medicinal, paper and pulp industries, printing and textile industries, etc. Starch is attractive as a raw material due to its low cost, biodegradability and simple chemical modification.

Biopolymers in Drug Development

Biopolymers may be naturally occurring materials: most materials formed in nature during the life cycles of green plants, animals, bacteria and fungi are polymers or polymer matrix composites. Biopolymers include the polysaccharides such as cellulose, starch, the carbohydrate polymers produced by bacteria and fungi and animal protein-based biopolymers such as wool, silk, gelatin and collagen: biopolymers, especially the carbohydrate origin, have been found very promising industrial application in various forms. The polysaccharides listed below gives a brief layout on its biological source, pharmaceutical use etc.

Cellulose and its derivatives:

Cellulose, discovered in 1838 by Payen, Is the principle structural constituent of the cell walls of many plants (hence the name). Cellulose is found in most plants (albeit not in pure form) in the leaves and stalks, with cotton fiber (95% cellulose) and wood (about 50%) being the principle industrial sources of cellulose. Because of its ubiquity in the plant kingdom, cellulose is arguably the most abundant polymer on earth, with billions of tons produced annually through photosynthesis. Structurally, cellulose is a linear homopolymer consisting of D-anhydroglucopyranose units linked by β(1 4)-glycosidic bonds (Figure 1). Despite being a homopolymer of glucose, cellulose itself is not water-soluble because of extensive intra and inter-molecular hydrogen bonding, and cellulose itself is a highly crystalline polymer. However, disruption of this hydrogen bonding either by chemical modification to the cellulosic backbone or by the use of suitable solvents can render-cellulose or the cellulose derivative soluble. Large scale commercial cellulose ethers include carboxymethyl cellulose (CMC), methyl cellulose (MC),→hydroxyethyl cellulose (HEC), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HFC), ethyl hydroxyethyl cellulose (EHEC), and methyl hydroxyethyl cellulose (MHEC).

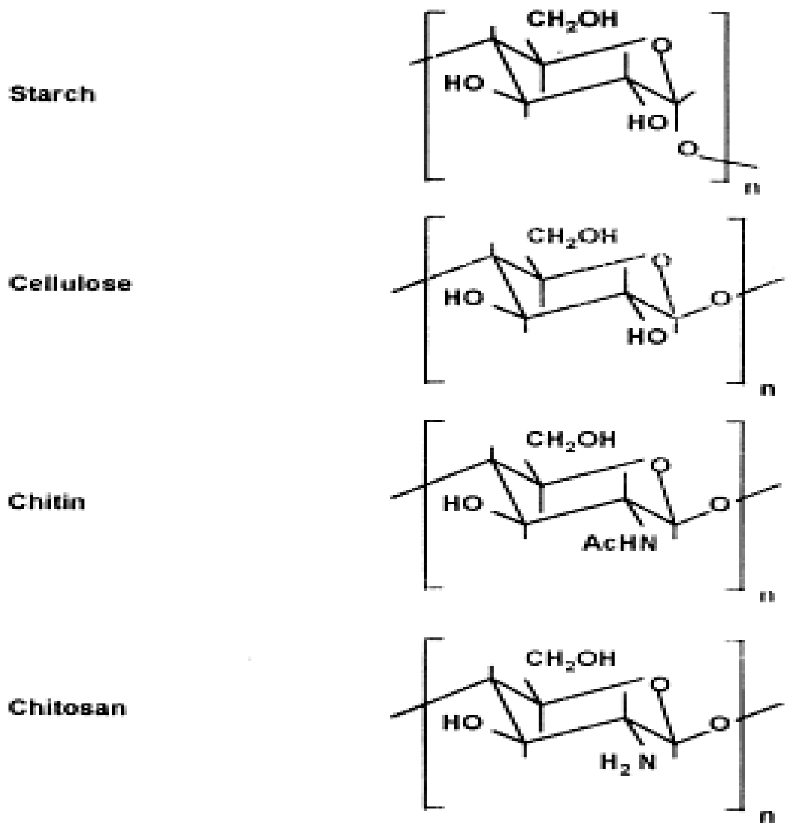

Fig.1. Basic chemical structure of natural biopolymers.

Starch:

Plants synthesize and stored starch in their structure as an energy reserve. It is generally deposited in the form of small granules or cells with diameters between 1-100 μm. After cellulose, starch is the most abundant carbohydrate available from plant kingdom as raw material. The estimated world production of starch amounts to 58 million tonnes, extracted from maize (46 million), wheat (4.6 million), potatoes (3.5 million), and the remainder coming from rice and cassava roots (tapioca). Starch is the main carbohydrate in plants and acts as a reserve food supply for periods of growth, dormancy and germination. Being a biodegradable polymer with well-defined chemical properties, it has a huge potential as a versatile renewable resource for various material applications in food and nonfood areas. The composition and properties of commercial available starches have been studied extensively. The properties of each starch are strongly dependent on their plant source.

Starch is a heterogeneous polymer of α-D-glucose units. The anhydrous glucose units (AGUs) are mainly linked by α-(1,4)-bonds and to some extent by α-(1,6)-linkages. The biopolymer consists of two distinguished structural forms:

amylose and amylopectin. Amylose is mainly found as a long linear polymer containing about several hundred α-(1,4)-linked glucose units (up to 6000 AGUs), with a molecular weight of 105-106 g mol^{-1}. In the solid state, the chains very easily form single or double helices. In contrast, amylopectin is a highly branched molecule with a molecular weight of 107-109 gmol^{-1}. The branched polymer contains α-(1,4)-linked glucose units but has additional α-(1,6)-glucosidic branching points which are believed to occur every 10 to 60 glucose units, i.e. 5% of the glucose moieties are branched.

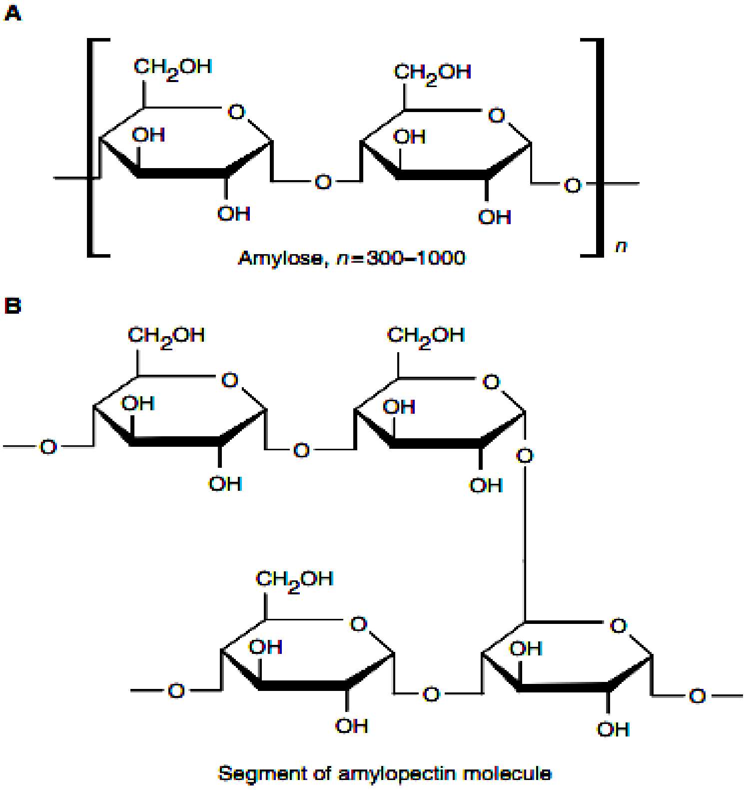

Fig.2. Starch components, A) Linear amylose and, B) Branched amylopectin.

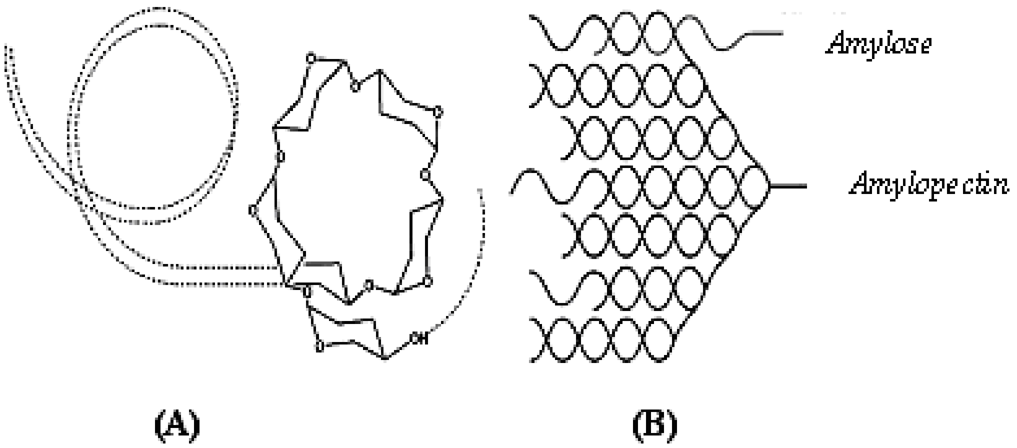

Fig.3. Structure of single helix amylose (A), and cluster model of amylose and amylopectin in double helix structure.

With an average degree of polymerization of about 2 million, this biopolymer is one of the largest molecules in nature. Besides amylose and amylopectin, starch granules contain (very) small amount of protein, lipids and inorganic compounds.

Native starches differ in the amylose/amylopectin ratio depending on their botanic source, e.g. native starches are composed of 20-30% amylose and an additional amount of amylopectin, amylose-enriched starch may contain up to 84% amylose while waxy starches consist of nearly pure amylopectin. Microscopic studies have revealed that starch granules can vary in shape, size and composition depending on the source of starch. In general, the appearance of the starch granules varies from small granules (cereals) to large granules (tuber and root The shape of a granule can be oval, spherical, polygonal or truncated [1,2].

The native starch granule consists of a semi-crystalline structure. The molecules of amylose and amylopectin are organized and packed as single and double helices into small granules. Amylose and the branching points of amylopectin form the amorphous region. Amylopectin in the granule is the main crystalline structure in the granular starch, consisting of double helices. For native starch, the type of crystalline patterns is labeled as A, B- and C-type crystalline pattern. The A-type pattern is characteristic for cereal starches, the B-type for tuber starches. The differences between A- and B-types result from the packing of the double helices in the crystalline structure and the quantity of water molecules stabilized in the unit cell. C-type starches (e.g. pea starch) are a mixture of A- and B-type[3].

Hemi cellulose:

Hemicellulose is the second most abundant polysaccharide after cellulose comprising one-fourth to one-third of most plant materials, and in the past twenty years hemicelluloses have been used as feedstock for the production of sugars. Hemicelluloses are mostly heteropolysaccharides classified according to the sugar residues present, namely xylans, mannans, arabinans and galactans, and they are either linear orbranched polymers. The β-1→4-D-xylan is the most abundant hemicellulose built from β-1→4-linked D-xylopyranosyl residue, which forms the linear backbone of the polymer.

Chitin and its derivatives:

Chitin was discovered in 1811 by Braconnot and was initially termed fungine because it was discovered in mushrooms. It was later in 1823 that Odier gave the name chitin to the same material discovered now in the elytrum of the cock chafer beetle based on the Greek term chitos, meaning coat. Chitin is a naturally occurring polysaccharide that is found widely in nature as a structural constituent in fungi and yeast as well as in the exoskeletons of insects and crustaceans. Next to cellulose, chitin is arguably the most abundant polysaccharide on earth. Structurally, chitin is a polysaccharide consisting of p-(1->4) 2-acetamido-2- deoxy-D-glucose repeat units, some of which are deacetylated. The degree of deacetylation usually varies between 8% and 15%, but depends on the species from which the chitin is obtained and the method used for isolation and purification. In the last two decades, most forms of chitin, chitosan, and their derivatives have found a number of pharmaceutical or biomedical applications. Although chitosan has been mostly used as a diluent in tablet manufacturing, it has been also proposed as a binder, lubricant, or potential disintegrating agent [4-5]. The mucoadhesive properties of chitosan make it an attractive material for the local delivery of drugs in the oral cavity [6].

Pectin:

Pectin is a family of complex polysaccharides present in the walls that surround growing and dividing plant cells. It is also present in the junctional zone between cells within secondary cell walls including xylem and fiber cells in woody tissue. Pectin is an essential component in the initial growth and ripening process of fruit and is often a waste material from the food and fruit processing industry with a consequent high availability [7]. The main component of pectin is a linear polysaccharide composed of α-1,4-linked D-galacturonic acid units, but the linear structure is interrupted with highly branched regions. Pectin has been investigated as an excipient in many different types of dosage forms such as film coating of colon-specific drug delivery systems when mixed with ethyl cellulose, microparticulate delivery systems for ophthalmic preparations and matrix type transdermal patches. It has high potential as a hydrophilic polymeric material for controlled release matrix drug delivery systems, but its aqueous solubility contributes to premature and fast release of the drug from these matrices[8].

Alginates:

Alginates or alginic acids are linear, unbranched polysaccharides found in brown seaweed and marine algae such as *Laminaria hyperborea*, *Ascophyllum nodosum* and *Macrocystis pyrifera*. These polymers consist of two different monomers in varying proportions, namely β-D-mannuronic acid and α-L-guluronic acid linked in α- or β-1,4 glycosidic bonds as blocks of only β-D-mannuronic acid or α-L-guluronic acid in homopolymers or alternating the two in heteropolymeric blocks[9]. Alginates have high molecular weights of 20 to 600 kDa. Alginates have been used and investigated as stabilizers in emulsions, suspending agents, tablet binders and tablet disintegrants [10].

Carrageenans:

Carrageenans are marine hydrocolloids obtained by extraction from some members of the class Rhodophyceae. The most important members of this class are *Chondrus crispus* and *Gigartina stellata*. Carrageenans were mainly used as gelling and thickening agents. Only a few studies have dealt with carrageenans for controlled-release tablets [11-13]. These studies dealt only with drug delivery from tablets on a hydraulic press or from tablets that contain the carrageenans in a mixture with other excipients.

***Gums and Mucilage:**:*

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) while, mucilages 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. Various gums and mucilages were used in various forms as sustained release excipient, binder, disintegrant etc. Some natural gums are presented below[14-16]:-

Xanthane gum:

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

***Guar gum**:*

Guar gum comes from the endosperm of the seed of the legume plant *Cyamopsis tetragonolobus*. The gum is commercially extracted from the seeds essentially by a mechanical process of roasting, differential attrition, sieving and polishing.

Acacia gum:

Gum acacia or gum arabic is the dried gummy exudates obtained from the stem and branches of *Acacia senegal.*

Locust bean gum:

Locust bean gum is a linear chain of β-d-mannopyranosyl units with nonuniformly spaced side branches. It is known botanically as Gleditsia triacanthos, and belongs to the order Leguminosea. Locust bean gum was evaluated as sustained release matrix former in Theophylline based tablets. Munday et al. [17] evaluated locust bean gum as minimatrix formulations enclosed in a hard gelatin capsule in an attempt to design an oral sustained-release multiple unit dosage formulation.

***Khaya gum**:*

Khaya gum is a polysaccharide obtained from the incised trunk of the tree *Khaya grandifoliola* from family Meliaceae[18]. Khaya gum is a hydrophilic polymer and has been shown to possess direct compressible matrix system in the formulation of controlled release tablets [19].

Sterculia gum:

Sterculia is a genus colloquially termed as tropical chestnuts, obtained from *Sterculia foetida*. It contains a mixture of D-galactose, Lrhamnose and D-galactouronic acid.

Tara gum:

Tara gum is obtained from the endosperm of seed of *Caesalpinia spinosa*, commonly known as tara. It is small tree of the family Leguminosae or Fabaceae. The use of tara gum as a controlled release carrier in the formulation of gastro-retentive controlled release tablets and emulsions for drugs has been claimed in patents.

Conclusion

Polysaccharides based excipients are well explored and used in pharmaceutical formulation development in recent years. Bioploymers are also used for specific purposes like controlled/sustained delivery of drugs from formulations. Now, researchers are engaged in isolating various other resources of biopolymers from natural origins.

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