1 Natural Polymers for Drug Delivery: An Introduction

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Abstract
Natural polymers are macromolecules composed of repeating structural units joined by covalent bonds. Carbohydrates, proteins and muscle fibres are known examples and have potential as drug delivery systems. A typical delivery system aims at slow and tissue-specific release, and as natural polymers exhibit biodegradability and biocompatibility they are well suited for this purpose. Natural polymers are also utilized as excipients and over the years, new advances in the treatment of diseases using the approach of site specific drug delivery by the utilization of polymers have emerged with several promises. This chapter highlights some available examples with an emphasis on their potent applications and properties in the drug domain.

Introduction

A polymer is a macromolecule with repeating monomeric structural units joined covalently. Carbohydrates, proteins and muscle fibres are common types of polymers. Carbohydrates are polyhydroxy aldehydes or ketones, and could be further classified as monosaccharides, disaccharides and polysaccharides. A polysaccharide consists of more than 20 repeating monomeric units. Polysaccharides can be homopolysaccharides if they contain only one repeating monomeric unit (e.g. cellulose, glycogen, starch and chitin), or heteropolysaccharides if two or more different kinds of monomers are present (e.g. peptidoglycan bacterial cell walls and glycosaminoglycans) (Pérez and Mulloy, 2005). These natural systems can be modified chemically to create biocompatible and biodegradable non-toxic entities, and have readily gained popularity in the pharmaceutical industry as drug delivery agents (Harborne, 1987). Plant-based polymers have also been investigated for this purpose. In addition, various liquid ophthalmic suspensions, buccal films, film-coating agents and microspheres have been proven to be effective (Pandey and Khuller, 2004; Chamarthy and Pinal, 2008; Alonso-Sande *et al*., 2009).

The history of using silicone rubber as a carrier (Folkman and Long, 1964) set the stage for the design and development of prolonged drug delivery systems, and since then the use of polymers in drug therapy has advanced significantly. Several scientific journals highlight the use of polymers as drug vehicles, and Table 1.1 gives an historical perspective with citations of published

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Table 1.1. Top polymer related reviews cited in 'Advanced Drug Delivery Reviews' according to Web of Science core collection in 2014. (Adapted, with permission, from Merkle, 2015.)

Subject	Year	Rank	Citations	Reference
Block copolymer micelles	2001	3	1620	Kataoka *et al*., 2001
Biodegradable nanoparticles	2003	4	1230	Panyam and Labhasetwar, 2003
Environment-sensitive hydrogels	2001	5	1221	Qiu and Park, 2001
Nanoparticles	2002	6	1213	Brigger *et al*., 2002
Hydrogels	2002	7	1083	Hoffman, 2002
Peptide and protein PEGylation	2002	9	803	Roberts *et al*., 2002
Dendrimers	2005	10	788	Svenson and Tomalia, 2005
Drug release from HPMC delivery systems	2001	11	772	Siepmann, 2001
Thermo- and pH-responsive polymers	2006	12	771	Schmaljohann, 2006
Nanoparticle targeting	2004	13	712	Brannon-Peppas and Blanchette, 2004
Thermosensitive hydrogels	2002	14	695	Jeong *et al*., 2002

HPMC, hydroxypropyl methylcellulose; PEG, polyethyleneglycol.

articles in *Advanced Drug Delivery Reviews*, according to the Web of Science core collection in 2014.

The need for natural polymers

Research has focused on the beneficial properties of natural polymers, especially towards delivering toxic therapeutic agents to the target tissue. The use of natural polymers and their derivatives not only enhances the drug availability at the target tissues, but is also regarded as a safe means of delivery. Some of the special characteristics of natural polymers that are attractive are their:

- Biodegradability – they pose no harmful environmental effect and are 100% biodegradable.
- Lack of toxicity – they are non-toxic.
- Economy – they are inexpensive and large quantities can easily be obtained.
- Safety – their natural availability bestows the required safety without any harmful side effects.
- Availability – they are widely distributed globally; for example, cellulose can easily be extracted in large quantities (Prajapati *et al*., 2013).

Some of the disadvantages include the chances of microbial contamination when exposed to the external environment, uncontrolled hydration rate because of differences in availability and the presence of different species.

Classification of Natural Polymers

Natural polymers, mainly polysaccharides, are obtained from various sources including plants, microbes, algae and fungae. Some are neutral and others, such as the carboxylate or sulfate groups, possess a negative charge. Chitosan is the only cationic polysaccharide currently known (Fig. 1.1).

- Plant origin – starch, hemicellulose, cellulose, agar, glucomannan, pectin, guar gum, locust bean gum, gum acacia, gum tragacanth and psyllium
- Microbial origin – curdlan, gellan, xanthan
- Algal origin – alginate, carrageenan
- Fungal origin – chitin, pullulan, scleroglucan

Drug Delivery Applications of Polysaccharides

Polysaccharides are used as coating agents, polymer matrices, tablets formulations, and emulsifying and gelling agents (Prajapati *et al*., 2013).

Tablet adjuvant formulations

Polysaccharides have been used in tablet formulation due to their inherent adhesive nature.

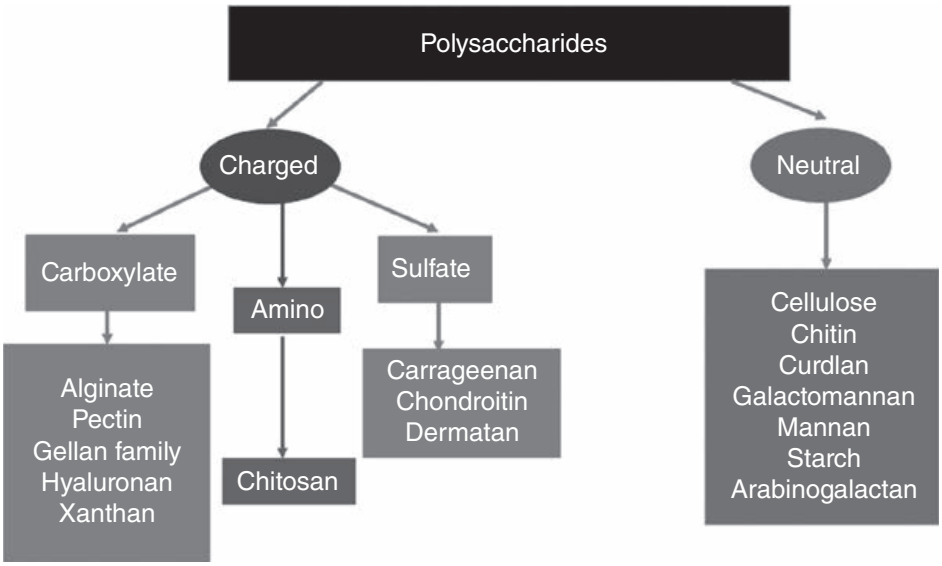

Fig. 1.1. Classification of polysaccharides used in drug delivery.

They adsorb large amount of water and swell, so acting as disintegrants. They also provide cohesiveness to the powder formulations and can easily be incorporated into tablets or granules (e.g. guar gum and acacia).

Mucoadhesive agents

Their main purpose is to control release of the drugs over a stipulated time. Furthermore, they can be retained in the intestinal lining and stomach for longer durations, enhancing drug absorption (e.g. karaya gum and sodium alginate).

Emulsifying and suspending agents

Natural polymers provide stability to emulsions because of their interfacial absorption. They can also form films with high tensile strength and resist coalescence among the droplets (e.g. xanthan gum and acacia gum).

Gelling agents

Mucilage and gums form gels either alone or in combinations with other gums. The gelation is due to inter- and intra-molecular associations among the chains leading to three-dimensional networks that can, in turn, trap large amounts of water. These formulations can be prepared through physical methods, for example changing pH and temperature, as well as by chemical treatments through adding suitable reagents. Examples include carrageenan and locust bean gum.

Coating agents

Certain natural polymers have the intrinsic ability to act as coating agents that protect the drugs from degradation and allow release in a controlled manner (e.g. pectin and sodium alginate).

Sustaining agents in dosage form

Matrix tablets are the most prominent oral drug delivery systems because of their sustained release and easy formulation properties (e.g. locust bean gum and karaya gum).

The main purpose of developing drug delivery systems casting polymers is to abolish any toxic product accumulation inside the body. This is quite feasible as natural polysaccharides do not generate any unusual products inside the body. Instead, they are eliminated easily as carbohydrate units during the regular metabolic processes, and so the polysaccharide disappears after serving its purpose. The biodegradation proceeds with bond breakage within the monomers leading to erosion of the bulk polymer

(Peppas, 1984). Various routes cause polymer degradation:

- hydrolysis;
- photolysis;
- its solubilising nature;
- brittleness;
- biodegradation;
- thermo-degradation; and
- structural weakening.

Polymer Drug Release Mechanism

The therapeutic agents attached to the polymers can be released at a controlled rate from the polymeric matrices via different mechanisms. The delivery of a drug over a specified time period to the tissues exploits various properties of polymers. One prominent example is that of stimuli-sensitive polymers releasing the drug only when there is a change in pH or temperature (Kaur *et al.*, 2014).

Degradation

Certain biodegradable polymers degrade inside the body under normal physiological and biological processes. They can also be designed to break under hydrolysing conditions, which results in smaller and manageable chain lengths without any side effects.

Diffusion

A reservoir device is often used, where the drug is located in the core of the tablet, capsule or polymeric network with a shell surrounding it. The shell might be composed of some type of polymer that will dictate the rate of diffusion of the drug from the core. With this mechanism, water will diffuse into the core and dissolve the drug inside, which will then diffuse out. Swelling or degradation of the shell can occur, depending on the polymer. Two different types of diffusion systems exist:

1. Only dissolved drug within the core. The drug load decreases over time as it diffuses out of the core.

2. Initial drug concentration within the core is higher than the aqueous solubility concentration. As the dissolved drug diffuses out more, an amount of drug is dissolved within the core, and the drug load will be constant for a longer period of time.

Swelling

Swelling is another type of controlling phenomenon involved in drug delivery. The matrix former has the capacity to swell and control the drug release rate. When polymer swelling leads to an increase in the length of diffusion pathways, the system volume increases, lowering the drug concentration gradient. This results in a slower release of the drug into the bulk system. In contrast, swelling of the polymer can enhance the molecular mobility, leading to faster release.

Overall, immense progress has been made in diffusion-controlled systems and solvent-activated formulations of drug release. Also, through the use of hydrogels and various other polymeric carrier systems, it is now possible to establish a very safe passage for the therapeutic drug to the target regions, and more importantly to inhospitable physiological regions. Polymeric substances having a controlled molecular architecture can be specifically engineered to provide response to the external stimulus. It has been shown that the therapeutic agents conjugated to the polymer show relatively improved drug release kinetics by preventing carrier accumulation. Polymer drug conjugates also help to improve the circulatory half-life for the cytoplasmic delivery of therapeutics.

Natural Polymers in Drug Delivery

Hierarchical evolution of present-day drug delivery systems began with the use of polymeric carriers that evoked spatiotemporal release of drugs in the implanted reservoir systems. Undoubtedly, conventional drug delivery systems have made great contributions towards treating disease. However, the growing need for special, accurate and potent biological therapeutic delivery procedures that target specific drug delivery

protocols demands novel delivery systems and mechanisms. Recent advances also highlight the need for feedback control of the drug delivery systems (Heller, 2005). There are a number of hurdles to overcome in targeting specific delivery and so implementing intelligent delivery systems is a feasible approach. These may allow not only the development of proper routes for intracellular drug transport but also specific targeting and recognition through feedback control systems (Langer and Peppas, 2003). Many natural and synthetic systems are being examined, and some are described below.

Collagen

Collagen is the most abundant protein of the animal kingdom, and is found in the extracellular matrix of connective tissue. It has a characteristic triple helical structure of repeating glycine–proline–hydroxyproline repeats. As we write, around 19 different collagen systems have been employed in pharmaceutical and medical applications, of which 80–90% belong to type I, type II and type III. Collagen possesses outstanding biocompatibility, few immunity problems and good biodegradability (Harkness, 1961). Collagen formulations are made with the combination of liposomes, in which therapeutic agents are encapsulated in the liposomes and then fused with collagen, making a scaffold or gel that not only prolongs the drug release rate but also increases its therapeutic efficiency. Collagen pellets and tablets used in Japan are known as monolithic devices, and are specialized rods approximately 1 mm diameter and 15 mm length. These are injected using a syringe in plunger for the local delivery of minocycline and lysozyme to treat periodontitis. These pellets have also been used to deliver IL-2 in vivo via a mini-pellet subcutaneous injection (Alonso-Sande *et al.*, 2009).

Another example of the use of collagen in the pharmaceutical industry is the development of the collagen corneal shield, a type of ophthalmic lens. Collagen, being a structural protein, provides support and protection to the eye and treats a variety of eye conditions after corneal transplantation and surgery. Collagen shields are made from procaine and bovine collagen with different dissolving times. For example, Bausch & Lomb Pharmaceuticals has developed collagen contact lenses called BioCora collagen shields. These have potential in delivering corticosteroid and other conjunctivital antibiotics to the eye. Certain water soluble antibiotics and steroids like Vancomycin, Gentamycin, pilocarpine and Amphotericin-B are being used along with shields of collagen to minimize the rubbing of eyelids. Collagen shields marketed preparations include: MediLenso, Biocora, Irvine, ProshieldO and Chiron. They provide a structural scaffold and behave as short-term bandage protections, permitting the oxygen transfer required for metabolism of the eye. These shields dissolve in the cornea, providing good lubrication to the eye.

Rosin

Rosin, obtained from *Pinus palustris* Miller and *Pinus linnae*, is a non-volatile natural polymer with phenomenal biocompatibilities and biodegradation capabilities (Berkland *et al.*, 2002). It is a tricyclic diterpene containing carboxylic acids and non-acidic components. Rosin has applications in printing inks, paper-sizing agents and chewing gum, to name a few. It is also a renewable chemical for polymer synthesis and a good film-forming agent, along with its derivatives, and thus is used for prolonged release of drugs as well as for enteric coating and transdermal drug delivery (Sheorey and Dorle, 1991a). Resin displays high compatibility with a variety of drugs having varied molecular weights and water solubility (Felder *et al.*, 2003). Rosin has also been evaluated for its encapsulating properties in different pharamaceutical preparations (Sheorey and Dorle, 1991b). Microspheres of rosin with glycerol esters could be developed for controlled drug release. The release rate is found to depend on the size and morphology and the polymer degradation rate. Resin polymers maintain the drug concentration in the target tissue within the permissible therapeutic range, and implants can be prepared from them as they are completely degradable inside the body and do not require removal.

Rosin also has some special properties and behaves as an anti-tumour agent. It possesses similar actions of inflammation to Poly (DL-lactic-co-glycolic acid) (PLGA) (Liu *et al.*, 2003). Rosin polymers show enhanced emulsifying ability and good skin permeability with homogeneity

and spreadability for transdermal drug delivery. Transdermal patches with enhanced pharmacodynamic performance and pharmacokinetics could be accomplished by combining rosin with polyvinyl pyrrolidone (Bohme, 2002).

Chitosan

Chitosan, a polymer of glucosamine and N-acetyl glucosamine, is obtained by deacetylation of chitin from the exoskeleton of crustaceans. It is a cationic polymer, biocompatible, biodegradable and non-toxic. It is used extensively in powder formulations, gels, emulsions and tablets. It is not only a good excipient but also an exceptional platform for parenteral delivery. Chitosan is also a good antimicrobial agent and could mask flavours. Low molecular weight chitosan exhibits reduced toxicity on Caco-2 cells. In association with ovalbumin gels, chitosan is used for cosmetic and pharmaceutical applications, and along with non-ionic surfactants is a good bioadhesive agent at different physiological pH regimes. Another important application of chitosan is as a vaginal delivery system for metronidazole. Introduction of thiol groups in the preparation certainly improves its mucoadhesion properties, which in turn enhance bioadhesion by increasing the residence time of drugs in the mucosal lining of the vagina (Uhrich *et al.*, 1999).

Starch

Starch is synthesized by plants and stored as an energy reserve. After cellulose, it is the second most abundant carbohydrate in the plant kingdom. World starch production in the year 2000, based on estimates from the European Union (EU) Commission and the United States Department of Agriculture (USDA), was 48.5 million tons (www.starch.dk/ISI/market/index.asp), of which, 39.4 million tons were from maize, 4.1 million tons from wheat and 2.6 million tons from potatoes. The rest is comprised of cassava, rice and other sources. It is a heterogeneous polymer of α-D-glucose units linked by α-(1, 4)-bonds and α-(1, 6)-linkages. Starch is found in two forms: amylose and amylopectin. Amylose is a linear polymer of several hundred α-(1,4)-linked glucose moieties and amylopectin a branched molecule composed of α-(1,4)-linked glucose moieties along with branching through α-(1,6) linkages. Starch and its derivatives have gained a niche in the pharmaceutical applications as a filler, diluent, glidant, disintegrant, and binder. It is economical and readily available. Also, starch is being used as an excipient in the extended release preparations due to its ease of enzymatic degradation and low compactibility. Enzymatic hydrolysis further improves its excipient potential (Hong *et al.*, 2014). Pregelatinized starch is routinely used as a controlled release matrix. Starch tablet formulations follow zero-order kinetics, but the release rates can be fine-tuned, for example by altering compaction force and tablet geometry. Important research has been carried out into developing synthetic derivatives of starch for various drug delivery systems, and these have been formulated.

Gelatin

Gelatin is a water-soluble polymer produced as a denaturation of collagen. It possesses good biodegradability and low antigenicity and could be used effectively in pharmaceutical applications. It is a protein and can be manipulated by appropriate changes in the isoelectric point for drug delivery applications. Its charge changes from positive to negative in the normal body physiological pH range. Gelatin is not only a good material for cell culture but is also used in tissue engineering. Gelatin-based systems are also used in controlled-release tablet formulations carrying appropriate therapeutic agents. Liposome-loaded active compounds are also made using PEG-gelatin gel systems which act as good scaffolds for prolonged drug release profiles (Foox and Zilberman, 2015).

A number of derivatives of natural polymers have been exploited worldwide for more than two decades. Derivatization not only enhances the physicochemical properties of these polymers but also couples their use with some synthetic polymers in drug delivery strategies. One example is the achievement of resistance by plasmid DNA in cancer treatment, by incorporating micelles into the polyion complex (PIC) micelles, which protect it from nuclease digestion (Kataoka *et al.*, 1999). The use of natural polymers and their derivatives have laid an important platform for modern drug delivery strategies.

Hibiscus mucilage

Hibiscus rosa-sinensis (Family Malvaceae), commonly known as the China rose, is a landscape shrub growing to 7–12 feet (2–4 m). It has glossy dark-green leaves which are medium textured, and produced throughout the year (King, 1999).

Diclofenac sodium formulation has been prepared in the form of tablets using *H. rosa-sinensis* leaves, and subsequently mucilage was developed. Its release retardant activity has been studied in all the sustained release formulations. A number of physicochemical properties of this mucilage have been investigated in diclofenac sodium formulations. The resulting matrix formulated tablets showed a better uniformity of weight, friability and hardness. The swelling of these formulations and their characteristic property of release rate *in vitro* showed that the mucilage from dried leaves of *H. rosa-sinensis* can potentially be used in sustained drug release applications. The mucilage followed zero-order reaction kinetics (Jani and Shah, 2008).

Aloe mucilage

Aloe vera leaves and Burm.f. (*A. barbadensis*) have also been investigated by isolating the exudates of adjacent cells of the vascular bundles and from the central parenchyma leaf tissue of *A. vera*. The exudates are bitter and yellow in colour, and contain glycosides of dihydroxyanthraquinone (Vázquez *et al*., 1996). The *A. vera* parenchyma contains lipids, amino acids, proteins, vitamins, enzymes and various carbohydrates. Arabinan, glucogalactomannan, arabinorhamnogalactan, galactan and glucuronic acids are the main constituents (Choi and Chung, 2003). The combination of povidone and mucilage of dried *A. barbadensis* can be used effectively for sustained release formulations (Hamza and Aburahma, 2010).

Fenugreek mucilage

Fenugreek, *Trigonella foenum-graecum*, is a herb belonging to the Fabaceae family. A high percentage of mucilage is present in the fenugreek seeds along with a natural gummy agent in the seed coatings. It does not dissolve in water and forms a tacky mass upon exposure to fluids and becomes slick with over exposure (Shakuntala *et al*., 2011). The isolation of the husk from the seeds is done by reducing the size and suspending the seeds in chloroform before decanting them. Chloroform extraction removes the oily part which can then be dried (Avachat *et al*., 2007). Fenugreek at 66% w/w was superior in retarding drug release compared to hypomellose (Nokhodchi *et al*., 2008).

Guar gum

Guar gum is obtained from the endosperm of the leguminous plant *Cyamopsis tetragonolobus*. Its extraction is through drying the pods in sunlight and their manual separation from the seeds. The commercial gum extraction involves mechanical roasting, sieving, differential attrition and polishing. The seeds are then broken and the endosperm releases the germ. The seed breaks into the two halves of the endosperm, which are referred to as the guar splits. These refined splits are coated with fine fibrous material layer forming the husk which can be removed from the endosperm by polishing. Different processing techniques are employed to obtain finished powders of refined guar splits. Guar gum consists of 1, 4-linked mannose units with 1, 6-galactose as side groups. It is used as a cosmetic thickener and to prevent ice crystals in ice creams. *In vitro* studies on the tablets made with xanthan gum, pectin and guar gum revealed that furosemide could be released at pH 7.2 in a sustained manner for 15 h (Inpharma Weekly, 1992). More importantly, guar gum tablets show a higher swelling index compared to xanthan gum and pectin.

Conclusions and Future Prospects

Currently, natural polymers have received considerable attention due to their value in environmental protection, as well as in the maintenance of human health. These polymers and their derivatives, coupled with biodegradable polymers, are also used in active packaging, fibre reinforcements and tissue engineering. In addition, they also have applications in

mucosal, colonic and targeted protein/peptide, gene/vaccine, anticancer and drug delivery. In the pharmaceutical and medical arenas, these systems have received considerable interest as intelligent materials such as artificial tissues. Thorough understanding of the relationships between structure, property and performance will contribute significantly to the advancement of modern science and technology, and there is promise in the future of more sophisticated and better understood natural polymer systems.

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