Biodegradable Polysaccharides

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Abstract

Biodegradable polymers are polymers which break down after its planned use. Their backbone could possess ester, amide, and other functional groups. The manner of their degradation as well as their properties is determined by their structure. Biodegradable polymers could be polyesters, polyamides, polyanhydrides, polycarbonates, polysaccharides, etc. Polysaccharides are biodegradable polymers of a kind of monosaccharide or combination of more than one kind of monosaccharide. They are commonly found in living organisms such as plants and animals. The plant origin polysaccharides are such as starch, cellulose, hemi cellulose, hyaluronic, alginate, guar gums and etc, and the animal origin polysaccharides are chitin and chondroitin.

Polysaccharides play various types of roles in nature. The roles range from food storage, structural support for plants, interphase adhesion in cell wall of plants, structural role for aggregation assembly and extracellular component, structural support in arthropods, cell wall constituents, a component in plant cell wall and middle lamellar, anionic extracellular cell wall and seed husk. Polysaccharides are mostly considered to be amorphous polymers. Research interests are focused on these green polysaccharides for their abundance renewability, good biocompatibility, non-toxicity, biodegradability, good photo-stability, and capability of enhancing the absorption capacity.

Keywords

Biodegradable; Biomedical; Drug delivery; Polysaccharides
Biodegradable Polysaccharides

Biodegradable polymers are polymers which break down after its planned use. The degradation of the polymer results in the formation of natural byproducts such as oxygen, nitrogen, carbon dioxide, water, biomass, and inorganic salts. Typically studied biodegradable polymers could be naturally and synthetically derived. Their backbone could possess ester, amide, and other functional groups. The manner of their degradation as well as their properties is determined by their structure. There are vast examples and applications of biodegradable polymers. Biodegradable polymers could be polyesters, polyamides, polyhydridides, polycarbonates, polysaccharides, etc. Polysaccharides are biodegradable polymers of a kind of monosaccharide or combination of more than one kind of monosaccharide. They are commonly found in living organisms such as plants and animals. The plant origin polysaccharides are such as starch, cellulose, hemicellulose, hyaluronic, alginate, guar gum and etc and the animal origin polysaccharides are chitin and chondroitin. Polysaccharides play various types of roles in nature. The roles range from food storage (starch) (B. Zhang et al., 2015), structural support for plants (cellulose) (Bao et al., 2015), interface adhesion in cell wall of plants (hemicellulose) (Yang et al., 2011), structural role for aggregation assembly and extracellular component (hyaluronic acid) (Lin et al., 2015), structural support in arthropods (chitin) (Reijnold et al., 2012), cell wall constituents (alginate) (Saarai et al., 2012; Khong et al., 2013), a component in plant cell wall and middle lamellar (pectin) (Srivastava and Malviya, 2011), anionic extracellular cell wall (gelatin gum) (De Silva et al., 2013), and seed husk (psyllium husk) (Mishra et al., 2014).

The slight variation in the microstructure of the polysaccharides gives a significant difference in the properties for example starch and cellulose which differs only in the stereochemistry plays a different role in nature. These polysaccharides are rich in functional groups such as carboxyl, hydroxyl, amide (-CONH2) or other hydrophilic functional groups that can be used to modify the properties of resulting polymers that suit the desired applications. Polysaccharides are mostly considered to be amorphous polymers. Research interests are focused on these green polysaccharides for their abundance renewability, good biocompatibility, non-toxicity, biodegradability, good photo-stability, and capability of enhancing the absorption capacity. In aspects of biodegradability, polysaccharides are useful for ingestion and subsequently elimination from the body. For example, the intestine possesses at least 500 bacterial species, making up an extraordinary microbial ecology in this organ. The microbiota needs to maintain its capacity to carry out a basic set of biochemical reactions, including degradation of carbohydrates, synthesis of vitamins, and fermentation. In particular, the degradation of polysaccharides takes place in the intestines.

Crosslinking for Single Polysaccharide

In polysaccharides, the presence of the hydrophilic functional groups and in amorphous states allows for crosslinking reaction to take place by various crosslinking methods such as shown in Figure 1. The chemical crosslinking methods are by using chemical or natural crosslinker (Figure 1(a)), radiation (Figure 1(b)), complex coacervation (Figure 1(d)) and ionic crosslinking (Figure 1(f)). The crosslinking could be taking place with the single type of polysaccharide. Chemical crosslinking achieved by using crosslinker such as epichlorohydrin (ECH) for cellulose and carboxymethyl cellulose (Iriebeish et al., 2013; Chang et al., 2010) for starch (Cole et al., 2011), itaconic acid, triplyphosphosphate and ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) for chitosan (Trluković et al., 2014; Shukla and Tiwari, 2012; Frata and Grosso, 2015; Kim et al., 2015; Palma et al., 2012), glutaraldehyde and 1,2,3,4-butanetetraacryloyl diisocyanate (BTDA) for guar gum (Shukla and Tiwari, 2012; Kono et al., 2014). Ionic crosslinking are carried out by using cation solutions such as Al3+, Fe3+, or Ca2+ that crosslink the anionic polymers and stabilized by electrostatic interactions. Ionic crosslinking of single type of polysaccharide are such as carboxymethyl cellulose with Al3+ (Thirupakkam et al., 2013), gellan gum, alginate, and pectin with Ca2+ (De Silva et al., 2013; Iriebeish et al., 2014; Shukla and Tiwari, 2012; Venner et al., 2013). The radiation crosslinking are carried out by using electron beam or gamma radiation for carboxymethyl cellulose (Pushpamalar et al., 2013a), bacterial cellulose (Mold Amin et al., 2012), starch (Jain et al., 2013), chitosan (Jain et al., 2015), modified psyllium mucilage (Thakur and Thakur, 2014), xanthan (Bhattacharya et al., 2012), and alginate (Qian et al., 2015). All these crosslinking methods for single type of polysaccharide are producing a crosslinked polymer with improved physical and chemical properties such as solubility, crosslinking density, swelling behavior, mechanical strength, thermal stability, and sensitivity to the environment such as pH and temperature that widen the applicability to many areas (Pushpamalar, 2010; Pushpamalar et al., 2013b).
Figure 1 Crosslinking by using (a) chemical or natural crosslinker, (b) radiation, (c) complex coacervation, and (d) ionic.

Crosslinking for Polysaccharides Mixture

These crosslinking methods were also used for polysaccharides mixtures to enhance and to achieve desired properties. Polysaccharides obtained from various sources and by various chemical modifications leads to polysaccharides with different chemical compositions, molecular weights and structures. The polysaccharides possess various physicochemical properties including gelation, solubility, low osmotic effect, and surface properties depending on their composition and architecture (Zong et al., 2012).
Chemical crosslinking of two polymers obtained using crosslinker such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) for carbosulphoxyethyl cellulose/chitosan (Zhar et al., 2012) and for chitosan/hyaluranesan (Huang and Hsu, 2014), sodium tripolyphosphate for chitosan/gelatin (Basu et al., 2011) and genipin for leppo carrageenan/carboxymethyl cellulose (Muhammad et al., 2011). Ironic crosslinking of two polymers are such as alginate/chitosan with Ca²⁺ (Ahou-Taleb et al., 2015).

Radiation crosslinking of the two polymers with gamma, electron beam or ultra-visible radiation are such as CMC/chitosan (Ninan et al., 2013), chitosan/alginate (Ahou-Taleb et al., 2015), pectin (Wang et al., 2011), chitosan/dextran (Valente et al., 2013), and alginate (Hu et al., 2012).

Another crosslinking method for polysaccharides mixture is called complex coacervation. Complex coacervaction is achieved by adding two oppositely charged polymers crosslinking forms due to the attraction of the opposite charges. For example, the anionic modified saccharides chitosan (Saboktaiek et al., 2012; Namiki et al., 2012) and pectin/chitosan (Mohamed Al-Azli et al., 2014), carboxymethyl agarose/gelatin are mixed and stirred to form micro/nanoparticles.

These crosslinking methods for single polysaccharide or polysaccharides mixtures lead to formation of hydrogel (Pushpamalar et al., 2013a,b), microcapsules, microgels (Dhawan et al., 2012), nanocomposites (Ahou-Taleb et al., 2015), nanoparticles (Saboktaiek et al., 2011; Hadinoto and Yang, 2014), and nanogels (Reinholdt et al., 2012; Fujars et al., 2013) via crosslinking that are being exploited in many areas such as in pharmaceutical, medical, cosmetics and food industries (Gonzalez and Smirnova, 2011). The combination of various polysaccharides with different properties and different crosslinking methods are important and interesting because it has opened a new research area to producing polymers with tailored properties of the single polymers such as with enhanced mechanical strength, thermal stability, miscibility, absorption, and swelling capacity.

**Crosslinking for Polysaccharides and Synthetic Biodegradable Polymer**

Polysaccharides are added to other synthetic biodegradable polymer to gain better desired altered properties such as improved mechanical strength, swelling capability with intact in shape, pH sensitive, biodegradability, absorption capacity and others. Superabsorbent hydrogels with better swelling and mechanical properties were obtained by crosslinking various polysaccharides and polysaccharides/synthetic mixtures such as tan gum/acyric acid (Abd Allah et al., 2012), bacterial cellulose/acylic acid (Mohamed et al., 2014), dextran/poly(e-caprolactone) (Li et al., 2013a). chitosan/polyethylene glycol (Zhang et al., 2011; Liu et al., 2012), chitosan/alcogel (Tian et al., 2013), modified hemimicellar/N-isopropylacrylamide (NIPAm) (Yang et al., 2011), carboxymethyl cellulose/poly(acylic acid) (Cao et al., 2014), modified chitosan/carbon (Gujarathi et al., 2012), alginate/poly (N-vinyl-2-pyrrolidone) (Inai and Eudragan, 2015), alginate/polyacrylic acid (Xin et al., 2015), chitosan/chondroitin-6-sulfate (Kuo et al., 2015), pyrllinium/acylamide (AAm) and 2-acrylamido-2-methylpropanesulfonic acid (AMPSA) (Singh and Bala, 2013), pyrllinium/acylic acid (Kumar et al., 2012), xantham/poly(acylic acid)/poly(vinyl alcohol) (Bhattacharya et al., 2012) and chitosan/gelatin (Prata and Cossa, 2015). chitosan/poly vinyl alcohol (Zhang et al., 2015b). These semisynthetic hydrogels provide a wide variety of biomedical application such as in controlled release drug delivery (Singh and Bala, 2014; Li et al., 2013a; Mohamad et al., 2015; Zhang et al., 2011; Shubia and Tiwari, 2012; Lautenschlager et al., 2014; Sun et al., 2013), wound dressing (Saras et al., 2012; Tran et al., 2011; Zhang et al., 2015a; Huang et al., 2015), tissue engineering (Zang et al., 2014; Ninan et al., 2013) and gene therapy (Li et al., 2013b; Zhou et al., 2012). The polysaccharides mixtures or chemically modified form of polysaccharides have eradicated the weaknesses associated with the use of single natural polysaccharide.

**Biodegradable Polymers for Controlled Drug Delivery**

Research interest on using biodegradable polymers as a drug carrier for drug delivery system are becoming increasingly important. These natural biodegradable polymers are being used as binders in tablets, viscosity enhancer in liquids or emulsions, etc. Polymers are also being used as a coating agent to eliminate the unpleasant taste of a drug and to improve drug stability and to modify the amount and release rate of the drug. The consequence of short half-life of the drugs leads to multiple dosing. Multiple dosages has tendency to increase the side effects and cost of the medication. To overcome these problems, biodegradable polymers are anticipated to improve method of providing drug to the patients. The drug encapsulated in the crosslinked biodegradable polymers could release the drug in sustained or controlled manner as shown in Figure 2.

The rate of drug release is dependent upon the cross-linking extent of the polymer which is turn is dependent on the concentration of the cross-linking polymer where the higher concentrations resulting in greater cross-linking and therefore slower drug release (Boppamalar et al., 2010). The drug can be loaded into hydrogel such as carboxymethyl cellulose (CMC) hydrogels which consists of many pores and shaped into beads/tablets that disintegrates by biodegradation to release the drug (Pushpamalar, 2010; Thenapakiam et al., 2013). Recently, many kinds of polysaccharides are being used as a carrier for drug delivery in the biomedical. Intensive researches are focused on connecting the polysaccharides and drugs in order to reduce the side effects of the commonly used synthetic polymers as well as over dosage of the administered drugs. The formulation of the drug carrier and loading of the drug are carried out in four
different methods. The four methods are polysaccharide drug conjugates, encapsulation of drug in the hydrogels and aerogels matrix, polysaccharide drug loaded nanoparticles by self-assembly, and polysaccharide-supported drug loaded nanoparticles.

**Polysaccharide Drug Conjugates**

The concept of polymer drug conjugates was invented more than three decades ago. Many natural and synthetic water-soluble polymers have been conjugated directly or indirectly using a chemical linkage, to develop a prodrug (Pang et al., 2014) as shown in Figure 3. The pharmacokinetics studies of drug conjugated polysaccharides exhibited the advantage of natural polymers. Even though synthetic water-soluble polymers were widely utilized, natural polymers such as chitosan, dextran, cellulose, and hyaluronic acid are also used because of their remarkable potential as drug carriers (Yang et al., 2011).

Monosaccharides of simple sugars like dextran are widely used for drug conjugation (Paili et al., 2014). Dextran is bacterial origin polysaccharide produced by bacteria from strains such as Leuconostoc or Streptococcus (Sidhu et al., 2014). The primary and secondary hydroxyl in the dextran provides a potential site for drug conjugation using different methods. Initially dextran was used as plasma expanders (Sidharth et al., 2015) and further developed to conjugate drugs to dextran that have entered clinical trials. This dextran has been an attractive biopolymer for drug delivery due to its physicochemical characteristics and low cost (Stay et al., 2014).

Hyaluronan (HA) is a disaccharide of anionic biopolymer, composed of repeating d-glucuronic acid and d-N-acetylgalactosamine, linked with β-1,4 and β-1,3 glycosidic bonds (Longinotti, 2014). Biocompatibility, biodegradability, non-immunogenicity of HA have paved way for various drug delivery applications. The hyaluronate backbone comprises of hydroxyl and carboxylic groups that are involved in drug conjugation. Both direct and indirect conjugation of the drug can be achieved. The direct conjugation may be less reactive because of steric hindrance and low reactivity of carboxylic group (Bierko et al., 2013). HA derivatives that provide reactive functional groups (NH₂–NH₂) will make it more reactive and increase the efficiency to form drug conjugates. HA-derivatives that allow degree of substitution (DS) of carboxylic acid have exhibited more drug loading with minimal polymer modification (Branjalova et al., 2014). Paclitaxel (PTX) conjugates with hyaluronic acid–deoxycholic acid. When linked with bio reducible cysteamin excised high loading limits the toxicity of the drug when compared to free PTX (Li et al., 2012).
It was also observed that high degree of substitution did not affect the targeting property of the drug. In order to address the poor solubility of HA which hinders conjugation reaction with cytotoxic drugs has been improved by various methods (Fatelah et al., 2014). The improved methods are such as using combination of polar solvents and water, nano-complexation by dimethoxy polyethylene glycol and ion pair complex with long aliphatic chain cationic salts (Goodarzi et al., 2013). Since 1996, study on using HA-drug conjugate designed to specifically target over-expressed CD44 was performed (Coomens et al., 2014). The drug conjugation with HA are well studied such as HA-conjugated mitomycin C (MMC), HA-conjugated epirubicin, HA-butyrate, and HA-paclitaxel (Arpegio et al., 2014). The HA-butyrate, a histone deacetylase inhibitor (Arpegio et al., 2014) has shown increased in apoptosis activity, resulted in a decreased tumor burden in in vivo and inhibited cell growth in in vitro.

Polymeric nanoparticles were produced by modifying the sucrose molecules for bio-mimetic model to intervene in carbohydrate-mediated biological processes that will assist in drug delivery. The modification of sucrose and poly(ε-lactic-co-glycolic acid) (PLGA) was made by crosslinking using N,N’-dicyclohexylcarboimidide (DCC) and cholic acid derivatives was conjugated by esterification. It is a promising work for controlled drug delivery system for poorly water soluble drugs (Hurcho and Barros, 2015). The chitin polymer was made into nanogel in spherical shape and conjugated with rhodamine-123 dye that could be useful for drug delivery and tissue engineering (Rejinold et al., 2012). Carboxymethyl cellulose was conjugated with folate and fluorescence molecules in order to increase the drug loading and release in sustained manner to the specifically targeted site such as cancer cells and also could be used for gene therapy (Nowak et al., 2012).

In recent years, pectin was combined with cellulose and micro-fibrillated cellulose for wound healing. It was used as to create a scaffold for wound healing on rats to study the skin regeneration. The results was promising on rats but further animal study needed to be carried out before undergoing clinical trial (Ninan et al., 2014). Pectin is also used as a drug carrier in nasal spray for drug delivery. The nasal spray drug is Fentanyl that relieves cancer pain (Bosil et al., 2014; Mercadante et al., 2014).

Entrapment of Drug in the Hydrogels and Aerogels Matrix

Three-dimensional, hydrophilic, polymeric networks that can retain large volumes of water or biological fluids are called hydrogels (Martino et al., 2015). Whereas aerogels are high porous and has large internal surface area and exhibit outstanding performances in drug delivery (Song et al., 2015). These are mostly rigid and brittle but hydrogels are incorporated to form aerogels, it has a tendency to form transparent hydrogel and randomly interpenetrated polymeric network (Toivonen et al., 2015). The structural and physical characteristics depend solely on the density of the aerogel formed. Hydrophilic polysaccharides and their precursors are used evidently to synthesis hydrogels and aerogels for drug delivery that are chemically stable (Veronovski et al., 2013). ‘emotropic’ hydrogels formed by interaction between a polyelectrolyte and an oppositely charged multivalent ion using a technique called complex coacervates (Pastel et al., 2012). Hydrogels can be sensitive to various environmental influences like ionic strength, pH, and temperature affecting their properties and morphology (Kulmanovich et al., 2012). Permanent changes can be made my forming covalent cross-linking to these hydrogels which are also called as smart hydrogels (Tong and Yang 2014). Single network within the hydrogels decreases the mechanical strength and in order to enhance the mechanical strength and swelling-deswelling properties of the polymer, the interpenetrating polymer networks (IPNs) have been designed. The IPNs are formed by crosslinking two different polyaccharides to form interpenetrating polymer network that are shown in Figure 4. These natural polysaccharides are often used alone or with synthetic polymers with hydrophilic functional groups like –COOH, –OH, –CONH₂.

![Figure 4](image-url)  Two polysaccharides are crosslinked to form interpenetrating polymer network.
SO₂H, amines, and others (Dragan, 2014). These IPNs are also called as alloys of hydrogels, it could be made of a synthetic polymer or a cross linker. Advanced multicomponent polymeric IPNs system can be designed and generally classified as simultaneous IPNs and sequential IPNs. This classification of IPNs is based on the synthesis method of the IPNs (Dragan, 2014) (Pilay et al., 2013) on how these two polymers are cross-linked within the hydrogel.

Alginate is refined from brown seaweed, it is polyacrylamide of repeating disaccharide units composed of 1-4-linked β-L-mannuronic acid and α-L-guluronic acid (Khong et al., 2013), arranged in an individual blocks or alternating blocks with different ratios. The ability of forming a gel rapidly using ionic and covalent conjugation methods makes the polymer to undergo extensive research toward developing improved delivery systems for chemotherapy drugs. Hydrogels and nanogels are formed using this rheo-responsive alginate by SDC crosslinked polymers (Naciri et al., 2013). These gels formed using cross-degradable polymer networks degrade to release the therapeutic drug. Temperature and pH sensitive hydrogels are synthesized using poly(diallyldimethylammonium chloride) (PDADMAC) and alginate (Guexzuthe et al., 2012). The pH-responsiveness of these hydrogels show maximum swelling at pH 4 (Aalst et al., 2013) which is caused by electrostatic repulsion due to ionization of COOH groups on alginate. On the contrary, PDADMAC co-existing along with ionized COOH forms polyelectrolyte complexes resulting in decreasing the swelling ratio (Wijeratne et al., 2013). Along with the swelling property, other properties like super-porous, electrical sensitivity help researchers to create a system for drug controlled release. Another attempt has been made by using ionic crosslinking for α-carboxymethyl chitosan and carbox methyl cellulose sodium to colonic area where the usage of the biodegradable polymers has prolonged the release time due to muco-adhesive property (Cuguralu et al., 2011).

A hydrogel from bacterial cellulose and acrylic acid was irradated with electron beam radiation and loaded bovine serum albumin via diffusion method. The hydrogel was thermo-sensitive and could be exploited for temperature controlled protein based drug (Mohi Armin et al., 2012). Another temperature sensitive hydrogel obtained via ultra-visible radiation from modified hemcellulose and N-isopropylacrylamide (NIPAAm) could be useful materials for biomedical (Yang et al., 2011).

Carboxymethyl sago pulp (CMSP) hydrogel was prepared via ionic (A⁺) crosslinking for colon targeted delivery. The 5-aminosalicylic acid (5-ASA) loaded CMSP hydrogel released very low amount of 5-ASA in the stomach pH and sustained drug release in the colon pH. This formulation is produced from industrial waste that would reduce the pollution and the cost of formulation (Thennapalam et al., 2013). Locust bean gum was crosslinked with poly(vinyl alcohol) using glutaraldehyde to control release buflomellic hydrochloride. It was found that this formulation was suitable for controlling the release rate for short half-life and high water solubility drugs (Kany et al., 2013). Recently, alginate was used as a medium to add the hydrophilic fluorescent in (FIT) (chemotherapeutic agent) loaded gelatin microbeads into the alginate solution and crosslinked to enter the FL loaded gelatin into the crosslinked matrices of alginate (Qian et al., 2015).

Another modified polysaccharides are commonly used in the pyrillum based polymers. Pyrillum/polyvinyl alcohol loaded with sulfonacrylate sodium and the drug release was found to be more in pH 7.4 buffer. Thermobimetality study and hemolysis index confirmed that the hydrogels had haemocompatibility indicating that these hydrogels can have possible applications in drug delivery system in case of bleeding ulceration (Thakur and Thakur, 2014).

**Polysaccharide Drug Loaded Nanoparticles by Self-assembly**

Hydrophilic polysaccharides backbones when introduced with hydrophobic segments form self-assembly structures like nanoparticles (Nitta and Numata, 2013), micelles (Lale et al., 2015), liposomes, and mesosomes (Fattoruso et al., 2014). Hydrophobic segments like cholesterol, carboxyl group, deacetylic acid and other hydrophobic polymers are used to form nanoparticles by minimizing the interfacial free energy by optimizing molar ratio of the polymers employed (Arzrabi and Peer, 2012). The formation of hydrophilic polysaccharides backbones and hydrophobic polymers forming the self-assembled structure is shown in Figure 5. Hydroxyl, amino or carboxyl groups of the hydrophilic polysaccharides backbones can be used to graft with the hydrophobic segments creating amphiphilic macromolecules by intra- and/or inter-molecular interaction forming nanoparticles (Tran et al., 2014). This helps the water insoluble drugs to be encapsulating in the hydrophobic region and hydrophilic shell helps to solubilize the drug (Lu and Park, 2013), which is released with outer layer stimuli like pH, temperature and ionic strength.

Recently, interest in forming self-aggregated nanoparticles for drug delivery systems using hydrophilic polysaccharides such as amylose, guar gum, pectin, chitosan, dextran, locust bean gum (Zhou et al., 2013; Plouzeau et al., 2015) are concentrated by the researchers. These polysaccharides are very suitable for colon targeted drug delivery because polysaccharides are stable within the physiological environment of stomach and intestine and the colonic bacteria in the colon cause the degradation of the polysaccharides and release the drug at colon (Leutenenschläger et al., 2014). Polysaccharides based nanoparticles are synthesized such as chitosan nanoparticles loaded with drugs such as doxorubicin, paclitaxel, ibuprofen, and the amphotericin dextran (Nitta and Numata, 2015). The amino groups on chitosan are chemically modified by grafting hydrophobic groups via acylation by acyl chloride or acylhydride coupling and further crosslinked with deacetylic acid. Deacetylic acid-grafted chitosan nanoparticles (160 nm) loaded with Plasmid DNA transferred in COS-1 cells was detected (Sahulakalin et al., 2012).

Another novel polymer, dextran is also been equipped as a candidate for self-assembly nanocarriers. Various biological fluids like bile acids, natural amphipilic steroidal hydrophobic β-side and a hydrophobic α-side, or lauryl chains have been grafted onto...
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Polymer A + Polymer B conjugated with drug 1

Drug 2

Nanoparticles

Figure 5 Polysaccharide drug loaded nanoparticles by self-assembly.

dextran (Stojanović et al., 2013). Chemically modified, azido-bearing dextran nanoparticles are conjugate with mannose groups exhibits enhanced antigen response due to internalization and activation of antigen presenting cells (Denis et al., 2014). Acrylic acid is grafted onto dextran to produce pH sensitive nanoparticles ranging from 40 to 140 nm. Inter polymer nanocomplexes are prepared using poly(acrylic acid) PAA by forming hydrogen bonds between carbohydrate groups and glucose units (Yakov et al., 2012). Modified dextran has shown that it has successfully increased the uptake of doxorubicin and this nano-carrier was easily uptaken by the N9-SYSV cells and this could become a promising carrier for doxorubicin (Li et al., 2013a). Another study on crosslinked microphases of dextran and chitosan showed the microphases were capable to control release of a hydrophobic drug such as ibuprofen that withstand the stomach pH. Modified cellulose, the hydroxypropyl and hydroxyethyl celluloses are also employed to create similar kind of nanoparticles (Abdel-Halim et al., 2015). Non-viral gene delivery was performed using comb shaped poly ((2-dimethyl amino)ethyl methacrylate) which is cationic and dextran backbone via atom transfer radical polymerisation (Li et al., 2013b).

Dextran nanogel loaded with doxorubicin (DOX) was formed via chemical crosslinking using glyoxal and ulronification. The doxorubicin loaded dextrin nanogel could significantly reduce DOX toxicity towards normal cells that reduces the side effects (Machin et al., 2014).

Similar to dextran and chitosan, chemically modified hyaluronic acid (HA) with 5-β-cholanic acid to form nanoparticles ranging from 200 to 400 nm that has shown more specific targeting in exploitation of passive tumors in CD44 (Lee et al., 2015). HA when conjugated with poly(β-benzyl-L-glutamate)-block forming amphiphilic block copolymers (Gulisie et al., 2014). These particles loaded with doxorubicin that forms a self-targeting drug carrier to CD44 over-exposes glycoprotein cells in the cancer tumors (Li et al., 2014).

Some negatively charge polysaccharide like heparin, which is also a very good anticoagulant, is exploited to form nanoparticles (Mead et al., 2014). Poly-β conjugated with chemically modified poly(β-benzyl-L-aspartate) heparin is loaded with paclitaxel and proposed for targeted site specific drug delivery (Li et al., 2012). These nanoparticles not only exhibits high cell uptake through endocytosis but also enhanced drug toxicity in KB cells (Li et al., 2011). Heparin is also modified with deoxysphingoid acid to produce nanoparticles for drug delivery (Park et al., 2015).

Starch and cellulose based nanoparticles are been widely studied. These are also the most abundant available natural polysaccharides found in all natural biomasses. Starch mainly consists of amylose and amylopectin (Dufresne, 2014), whereas cellulose consists of β-glucose units (Reese, 2013). Chemical modifications like addition of hydroxyl and carboxyl groups to these polymers have increased their solubility in organic solvents, which helps in increasing drug loading efficiency. Diethylstarch nanoparticles conjugated with doxorubicin (Li et al., 2015). Hydrophobic propyl starch was loaded with doxorubicin via solvent emulsification/dispersion/evaporation technique (Dandeker et al., 2012).

In another attempt to delivery poor water soluble, hydrocortisone (HC), a carrier for HC was designed. The HC nano-carrier was made from chitosan and modified β-cycloexetrin by ionotropic gelation. The β-cycloexetrin was used due to its lipophilic nature of the cavity that a lipophilic drug such as HC could be loaded and this formulation allows for pH controlled drug released (Füller et al., 2014). Another similar hydrogel formed from chitosan and modified β-cycloexetrin using EDC crosslinker. It showed promising capability to deliver anticancer drugs such as 5-Fluouracil, doxorubicin and vincristine in controlled manner (Tan et al., 2013). Alginate and chitosan were crosslinked by coevaporation to provide controlled β-lapachone delivery system.
The beads were resistant to the acid medium and may be an alternative for β-lapachone therapy of colorectal cancer (Torelli-Sousa et al., 2012).

Polysaccharide-Supported Drug Loaded Nanoparticles

A new class of materials called polymer-supported nanoparticles with two distinctly different phases, namely, a functionalized polymeric phase and a metal oxide phase (Sarkar et al., 2011).

The nature of functional groups on the polymeric phase will change the properties of the hybrid material along with the size and nature of the nanoparticles dispersed (Sinha and Suparak, 2012). The diversity in the functional groups will often control the size and nature of the dispersion of the nanoparticles in the hybrid matrix (Nicole et al., 2014). These often retain the nature of the individual materials, yet seen to offer a synergy with which would not be possible individually. Several methods are equipped to synthesize these hybrid materials, but in situ method (Paole et al., 2012) have exhibited more promising and can produce a wide variety of formulations. It is very simple and flexible which made it attractive. Biopolymers such as alginate and chitosan nanocomposites have various formulations with simple variations were synthesized. The possibility is huge where different metal can be loaded (Puglisi et al., 2013). It is also possible to load two or more different nanoparticles to enhance the material. These combinations of diverse functional groups, physical and morphological properties have paved a way to synthesis these hybrids materials with various properties and applications.

Laser-induced therapy using biopolymer-gold nanoparticles are recent advances where optical amplification is induced to produce therapeutic effects (Viswanath et al., 2013), although size of the nanoparticles play a vital role in this. Alginate matrix enhanced with ferrous nanoparticles is used for drug delivery (Mahmoudi et al., 2011), contrasting material for MRI imaging and also for hyperthermia treatment of malignant tumors. Super paramagnetic ferrous oxide nanoparticles immobilized in polysaccharides like alginate, cellulose, and chitosan (Ivanova et al., 2011) have been synthesized for various applications like drug delivery, magnetic resonance imaging contrast agent and site targeting drug release. Chitosan conjugated with gold nanoparticles have been used to deliver plasmid DNA (Pissuwan et al., 2011). This will help in making conventional free DNA vaccine to increase the therapeutic efficiency by 10 folds. Bactericidal polymer conjugates with metal nanoparticles have been used for disinfectant treatments: silver nanoparticles have antimicrobial activity have gained particular interest. Silver alginate and silver carbonyl cellulose have used for wound dressing that enhanced the wound healing due to the antibacterial activity of the silver nanoparticles. It is found that silver nanoparticles embedded in these polysaccharides are pH sensitive and the results indicating poorer wound healing at alkaline pH. The carbonyl cellulose has a better wound healing could be caused by the ionization of the carbonyl side chain at higher pH that leads to swelling and liberate the silver nanoparticles (Percival et al., 2012).

Conclusion

A significant limitation in the administration of conventional drugs is related to their probable toxicity to the body. Toxicity may also depend on the presence, in the pharmaceutical preparations, of molecules necessary to improve the poor solubility in water of many small molecule organic drugs. It is important to develop optimal delivery materials to greatly improve their therapeutic effectiveness. Additionally, appropriate delivery materials may allow the combined administration of conventional drugs, possibly potentiating their therapeutic effects.

Among the different delivery materials studied so far, polysaccharides represent ideal candidates for drug delivery and biomedical applications as they are easily obtained from natural sources. Furthermore, they can be subjected to a wide range of chemical and enzymatic reactions, have biocompatible and biodegradable properties and are inherently low in immunogenicity. Polysaccharides could be the materials of choice for the development of "smart" delivery systems capable to release, at the right time and in the right place, the encapsulated drugs. However, the development of such delivery systems needs to take into account several aspects. First, the polysaccharide-drug interaction must be optimized, this is a variable that is heavily dependent on the physical-chemical properties of the polysaccharide and of the drug. Second, the optimization of the pharmacokinetics and pharmacodynamics has to be carried out through the careful consideration of the ADME phenomena. Third, the conjugation of a targeting moiety to the polysaccharide will be useful to limit the off targeting to healthy tissue. Lastly, applications requiring drug delivery from a gel must be carefully studied for release mechanisms of the drug from the gels. When taken together, these considerations and challenges show explicitly that only a multidisciplinary approach can successfully tackle the task of the selection of optimal delivery materials for the drug and application of interest. In cases where an ideal delivery system is not yet available, the examples reported in the present review indicate that many interesting options, based on the use of polysaccharides, are emerging. Thus, whereas additional research is required, the promising results obtained thus far fully justify further efforts in terms of both economic support and investigations in the field.
References


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Further Reading