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Nanoparticles Based on Modified Polysaccharides

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1. Introduction

Nanoparticles may be comprised of several kind materials being classified as non-degradable and biodegradable. Biodegradable systems have an advantage over non-degradable systems in that they are non-toxic, biotolerable, biocompatible, biodegradable, and water-soluble. Among these systems, the role of natural polysaccharides in developing prepared nanoparticles has significantly increased (Zhang et al., 2011; Yang et al., 2008a; Leonard et al., 2003).

On the other hand, polysaccharides are the most abundant macromolecules in the biosphere. The complex carbohydrates constituted of monosaccharides joined together by glycosidic bonds are often one of the main structural elements of plants and animals exoskeleton (cellulose, carrageenan, chitosan, chitin, etc.) or have a key role in the plant energy storage (starch, paramylon, etc.) (Aminabhavi et al., 1990). Polysaccharides have a large number of reactive groups, a wide range of molecular weight, varying chemical composition, which contribute to their diversity in structure and in property. The amphiphilic nature imparted upon polysaccharides after modification gives them a wide and interesting application spectrum, for instance as rheology modifiers, emulsion stabilizers, surface modifiers for liposomes and nanoparticles and as drug delivery vehicles (Sinha and Kumria, 2001; Gurruchaga et al., 2009; Chen et al., 2003a; Durand et al., 2002; Gref et al., 2003). Recently, the hydrophobically modification of polysaccharides has been received increasing attention because they can form self-assembled nanoparticles for biomedical uses. In the aqueous phase, the hydrophobic cores of polymeric nanoparticles are surrounded by hydrophilic outer shells. Thus, the inner core can serve as a nano-container for hydrophobic drugs. Starch, chitosan, dextran, cyclodextrin, cellulose and pullulan are polysaccharides that have been modified with various reactants and after the modification step the nanoparticles based on modified polysaccharides were prepared with using various methods (Onyuksel et al., 2003; Aumelas et al., 2007; Ragauskas et al., 2007; Kwon, 2003; Namazi and Dadjkhah, 2010; Namazi and Mosadegh, 2011).

Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm (P., 1988; Hamidi et al., 2008). Depending upon the method of
preparation, nanoparticles, nanospheres or nanocapsules can be obtained. These nano-sized objects, e.g., “nanoparticles”, take on novel properties and functions such small size, modified surface, improved solubility and multi-functionality. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Nanoparticles based on modified polysaccharides have been prepared most frequency by these methods: solvent evaporation method, spontaneous emulsification or solvent diffusion method, self-assembly of hydrophobically modified and dialysis method (Kim et al., 2001; Aumelas et al., 2007; Sun et al., 2006; Couvreur, 1998). Modified polysaccharide could be used as stabilizers to produce stable hydrophilic nanoparticles by the o/w emulsion/evaporation technique. Modified polysaccharides were shown to exhibit surface active properties and to act as efficient emulsion stabilizers. Surface modified colloidal carriers such as nanoparticles are able to modulate the biodistribution of the loaded drug when given intravenously, but also to control the absorption of drugs administered by other routes (Durand et al., 2004).

This review presents the several mechanisms to prepare polysaccharides-based nanoparticles after discusses about modification of polysaccharides with various agents. Also characterization of nanoparticles such as size particles, surface coverage, colloidal stability and enzyme degradability have been described and also provided are examples of use of the polysaccharide nanoparticles and their derivatives as medical applications.

2. Polysaccharides

Polysaccharides with polymeric carbohydrate structures, formed from repeating units joined together with glycosidic bonds. Their structures are often linear, but may contain various degrees of branching. In nature, polysaccharides have various resources from algal origin, plant origin, microbial origin and animal origin. Polysaccharides have a general formula of C\(_x\)(H\(_2\)O\(_y\)) where x is usually a large number between 200 and 2500. Considering that the repeating units in the polymer backbone are often six-carbon monosaccharides, the general formula can also be represented as (C\(_6\)H\(_{10}\)O\(_5\))\(_n\) where 40 ≤ n ≤ 3000 .(Aminabhavi et al., 1990)

2.1 Starch

Starch is made up of two types of polymers: amylose and amylopectin. Amylose is a linear homopolymer of \(\alpha\)-1,4-linked glucose. Amylose may have a low level of branching with a \(\alpha\)-1,6-linkage (Fig 1). Amylose makes up ~35% of starch. In solution amylose forms hydrogen bond with other amylase molecules to yield rigid gels. Amylopectin is highly branched form of “amylose”. The linear \(\alpha\)-1,4-linked glucose backbone is branched at every ~20 residues by an \(\alpha\)-1,6-linkage which is extended by \(\alpha\)-1,4-linked linkages (Namazi and Dadkhah, 2008; Della Valle et al., 1998; Namazi et al., 2009; Namazi and Dadkhah, 2010)

![Chemical structure of the starch](https://www.intechopen.com)
2.2 Chitosan and chitin

Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit) (Fig 2). It has a number of commercial and possible biomedical uses. Chitosan is produced commercially by deacetylation of chitin, which is the structural element in the exoskeleton of crustaceans (such as crabs and shrimp) and cell walls of fungi (Thanou et al., 2005; Tharanathan and Ramesh, 2003; Yuan and Zhuangdong, 2007). Chitin (C\textsubscript{6}H\textsubscript{13}O\textsubscript{5}N\textsubscript{n}) is a long-chain polymer of a N-acetylglucosamine, a derivative of glucose (Fig 2), and is found in many places throughout the natural world. It is the main component of the cell walls of fungi, the exoskeletons of arthropods such as crustaceans (e.g., crabs, lobsters and shrimps) and insects, the radulas of mollusks, and the beaks of cephalopods, including squid and octopuses. In terms of structure, chitin may be compared to the polysaccharide cellulose and, in terms of function, to the protein keratin. Chitin has also proven useful for several medical and industrial purposes (Kumar, 2000; Kurita, 2001).

![Chemical structure of chitosan and chitin](image)

Fig. 2. Chemical structure of the chitosan and chitin

2.3 Dextran

Dextran is a polysaccharide consisting of glucose molecules coupled into long branched chains, mainly through a 1,6- and some through a 1,3-glucosidic linkages as shown in Fig 3. Dextrans are colloidal, hydrophilic and water-soluble substances, inert in biological systems. It is used medicinally as an antithrombotic (anti-platelet), to reduce blood viscosity, and as a volume expander in anemia (Bertholon et al., 2006; Durand et al., 2004).

![Chemical structure of dextran](image)

Fig. 3. Chemical structure of the dextran

2.4 Pullulan

Pullulan is a polysaccharide polymer consisting of maltotriose units, also known as α-1,4-; α-1,6-glucan (Fig 4). Three glucose units in maltotriose are connected through an α-1,4-glycosidic bond, whereas consecutive maltotriose units are connected to each other by an α-1,6 glycosidic bond. Pullulan is produced from starch by the fungus Aureobasidium pullulans (Bataille et al., 1997; Glinel et al., 1999).
2.5 Cyclodextrins

Cyclodextrins (CDs), also using the name cycloamyloses, cyclomaltoses, or Schardinger dextrins, are natural macrocycles connected through α-(1-4)-linked glucose units in a rigid 4C1 chair conformation. CDs can be produced through the enzymatic degradation of starch derived from potatoes, corn, rice or other sources. The number of glucose units per CD ring varies from 6-13, (Saenger et al., 1998; Larsen, 2002; Ueda, 2002; Hennink et al., 2009; Namazi and Kanani, 2009) as the enzyme produces a range of oligosaccharides. Because of steric factors, cyclodextrins constructed from less than six glucose units such as the five-membered cyclic oligomer, cyclomaltopentaose, has been obtained by chemical synthesis in small quantities. (T. Nakagawa et al., 1994) A chemical synthesis for other CDs has been reported, but it is too tedious for commercial production of cyclodextrins. (Ogata and Takahashi, 1995) The most common CDs contain 6, 7, and 8 D-glucose units and are known as αCD, βCD, and γCD, respectively, (Saenger, 1980) (Figure 5), while greater cyclodextrins have been reported as well. (Larsen et al., 1998; French et al., 1965; Fujiwara et al., 1990; Miyazawa et al., 1995)

2.6 Cellulose

Cellulose is an organic compound with the formula (C₆H₁₀O₅)n, a polysaccharide consisting of a linear chain of several hundred to over ten thousand β(1→4) linked D-glucose units (fig. 6). Cellulose is the structural component of the primary cell wall of green plants, many forms of algae and the oomycetes. Some species of bacteria secrete it to form biofilms. Cellulose is the most common organic compound on Earth (Hinrichsen et al., 2000; Riedel and Nickel, 1999; Gassan and Bledzki, 1999).
Amphiphillic polysaccharides consisting of hydrophilic and hydrophobic fragments have been modified because they can form self-assembled nanoparticles and they show unique physicochemical characteristics such as a nanoparticle structure and thermodynamic stability. Natural biopolymers have various advantages, such as availability from replenishable agricultural or marine food resources, biocompatibility, and biodegradability, therefore leading to ecological safety and the possibility of preparing a variety of chemically or enzymatically modified derivatives for specific end uses. Recently, there has been considerable interest in developing modified derivatives of polysaccharides for biodegradable nanoparticles. These nanoparticles have shown the following advantages for biomedical applications such as drug protection and ability to control the drug release. Polysaccharides have a number of positive characteristics such biocompatibility, biodegradability, protein rejecting ability, receptor interaction through specific sugar moieties, and abundance of functional groups for modification or functionalization (Couvreur et al., 2004). The amphiphilic character imparted upon polysaccharides after hydrophobic modification gives them a wide and interesting use spectrum, for instance as rheology modifiers, emulsion stabilizers (Chen et al., 2003a; Durand et al., 2002), surface modifiers for liposomes and nanoparticles (Vyas and Sihorkar, 2001) and as drug delivery vehicles (Rodrigues et al., 2003; Leonard et al., 2003).

### 3.1 Modified starch

Starch is one of the polysaccharide that it has been modified with various reactants for preparation of nanoparticles. The use of starch nanoparticles is receiving a significant amount of notice because of the plentiful availability of natural polymer, inexpensive, renewability, biocompatibility, biodegradability and nontoxicity. Chemical modification of starch has been widely studied for producing modified starch by way of chemical reaction with hydroxyl groups in the starch molecule. Starch esters are a kind of modified starches which are synthesized with various reactants such as acid anhydrides octenyl succinic anhydride (OSA), dodecenyl succinic anhydride (DDSA) fatty acids and fatty acid chlorides (Tukomane and Varavinit, 2008; Wang et al., 2007a; Borredon et al., 1999; Fowler et al., 2002). Hydroxyethyl starch was esterified with the long chain fatty acids under mild reaction conditions using DCC and DMAP (Mader et al., 2007). The synthesis of modified hydrophobic starch using fatty acids was done by means of potassium persullphate as catalyst in DMSO (Abraham and Simi, 2007). Several substituted starches were prepared by acylation of starch with fatty acid chlorides in organic solvents, such as pyridine or dimethylacetamide (Kapusniak and Siemion, 2007; Wang et al., 2008). Hydrophilic
**Starch** | **Grafting agent** | **References**
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Amylopectin (from waxy corn) | Lactic acid | (Hong-Wei Lua and Li-Ming Zanga, 2011)

**Modification:** Amylopectin and aqueous lactic acid (LA) were added to a three-necked flask equipped. After the stirring at 75 °C for 30 min, the temperature of the reaction system was thermostated to be 100 °C. Then a required amount of Sn(Oct)$_2$ was added to the flask. Then the product was further purified by Soxhlet extraction to remove completely the unreacted LA monomer as well as PLA homopolymer that may be formed during the reaction.

Amylopectin-rich waxy maize starch | Stearic acid | (Dufresne et al., 2004; Dufresne et al., 2006)

**Modification:** Chemical modification of the nanoparticles was performed in a round-bottomed reaction flask under a nitrogen atmosphere while constantly stirring with amagnetic stir bar. The stearate modification was performed by the reaction of dry starch nanocrystals with stearic acid chloride in methyl ethyl ketone.

Amylomaize starch | n-Butanol | (Lim and Kim, 2009)

**Modification:** The amylomaize starch (0.5%, w/v) was dispersed DMSO solution with heating and stirring in a boiling water bath, and then magnetic-stirred at room temperature for 24 h. An aliquot of the starch solution was allowed to gravimetrically pass through a membrane filter into the bottom compartment filled with n-butanol. The precipitate in the butanol layer was collected by centrifugation, and then washed three times in the n-butanol.

Cassava starch | Monochloroacetic acid (MAC) ClCH$_2$COONa | (Wu et al., 2011)

**Modification:** Cassava starch in anhydrous ethanol was placed in a glass reactor. An aqueous solution of sodium hydroxide was added drop wise to the starch–solvent mixture under stirring until the whole amount of sodium hydroxide were added. Then, the solution of MAC was added drop wise to the starch–solvent–sodium hydroxide mixture under ultrasonic irradiation.

Waxy corn starch | | (Fowler et al., 2004; Namazi and Dadkhah, 2010)

**Modification:** Starch esterification was carried out in two steps. In the first step, starch nanocrystals dispersed in the reaction medium were alkali treated at room temperature with mechanical stirring under an atmosphere of N$_2$ for 10 min and in the second step, 0.5 mol equivalents of the required acid chloride was added drop wise and the reaction mixture was stirred for 20 min.

Cassava starch | CH$_3$(CH$_2$)$_7$CH=CH(CH$_2$)$_7$COOH | (Abraham and Simi, 2007)

**Modification:** For the graft copolymerization, about 1g starch was dissolved in 10 ml DMSO and was taken in a round bottom flask. Oleic acid, weighing was added and potassium per sulphate was the catalyst.
Hydroxyethyl starch (HES) | Fatty acid | (Mader et al., 2007)
---|---|---
**Modification:** HES was dried for 2 h before dissolving in 20 mL of dry DMSO. To the solution were added the fatty acid, DCC, and DMAP, and they dissolved for 24 h. The formed precipitate (dicyclohexyl urea, DCU) was removed by filtration, and the filtrate was added to 200 mL of precipitating solvent mixture.

Potato starch | (Namazi and Dadkhah, 2008; Dufresne et al., 1996)
---|---|---
**Modification:** A mixture of starch nanoparticle (1 g) and CL (2 mL) was first added to flask. A determined amount of Sn(Oct)$_2$ of total amount of reagents was then introduced via a conditioned syringe. Polymerization was stopped by fast cooling to room temperature.

Table 1. Functional molecules for modification of starch

Amylopectin was modified by grafting hydrophobic poly (lactic acid) chains (Hong-Wei Lua and Li-Ming Zhang, 2011). Since 1950, considerable effort has gone into hydrophobically modified derivatives of hydrophilic polysaccharides (Namazi et al., 2011).

Recent studies have been carried out to investigate the synthesis and the application of polysaccharide-based nanoparticles. In Table 1 functional molecule that used for modification of starch are listed which have been used for preparation of their nanoparticles.

### 3.2 Modified chitosan and chitin

Biopolymer chitosan with a lot of primary amino groups is a polysaccharide derived from deacetylation of chitin. Due to the excellent film-forming ability, biocompatibility, nontoxicity, high mechanical strength, cheapness of chitosan, it is used for synthesis and the application of polysaccharide-based nanoparticles (Payne et al., 2005; Kwon et al., 2003). Chitosan is one of the polysaccharides that modified with various groups such as 5β-cholanic acid, linoleic acid, Monomethoxy poly (ethyleneglycol) and etc. After modification process, modified chitosan are used for preparation of their nanoparticles. These groups are listed in Table 2.

Grafted chitosan has been studied by many researchers. These studies have been intensified since 1992 because chitin and chitosan show excellent biological properties such as biodegradation in the human body. Modification can marginally improve the solubility of chitosan. As a polymeric amphiphile, grafted-chitosan with monomethoxy poly (ethyleneglycol) can aggregate into core–shell nanoparticles in aqueous media because in the aqueous phase, the hydrophobic cores of chitosan nanoparticles are encircled by hydrophilic outer shells. Thus, the internal core can serve as a nano-container for hydrophobic drugs. Modified chitosan is appropriate for decreasing severe side effects such as cytotoxicity in usual tissue (Fang et al., 2006; Gorochovceva et al., 2005; Opanasopit et al., 2006).
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3.3 Modified dextran

The development of existing materials to prepare modified dextran is the subject of numerous researches due to their surface-active properties and potential pharmaceutical, biochemical and medical applications. Modified dextran gives a large range of properties, allowing the selection of the carrier which proves the most useful for a particular drug encapsulation and release. Dextran is one of the water-soluble polysaccharides that have been modified to obtain amphiphilic polymers capable of forming micellar structures and binding organics solutes in the hydrophobic domain. Also, it is amphiphilic block copolymers that can self-assemble in selective solvents to form micelles with a core and a shell containing insoluble and soluble blocks (Lu et al., 1994; Ichinose et al., 2000; Lu and Tjerneld, 1997). Core-shell type nanoparticles of a poly (DL-lactide-co-glycolide) (PLGA) grafted-dextran copolymer are prepared with varying graft ratio of PLGA. The DexLG copolymer was able to form nanoparticles in water by self-aggregating process (Song et al., 2008).
Dextran was chemically modified by the covalent attachment of hydrocarbon groups (aliphatic or aromatic) via the formation of ether links. According to the extent of modification, either water-soluble or water-insoluble dextran derivatives were obtained. The latter exhibited solubility in organic solvents like tetrahydrofuran or dichloromethane saturated with water (Bertholon et al., 2006; Durand et al., 2004; Leonard et al., 2003; Aumelas et al., 2007; Leonard et al., 2000; Osterberg et al., 1995). Biodegradable hydrogel nanoparticles were prepared from glycidyl methacrylate dextran (GMD) and dimethacrylate poly(ethylene glycol) (DMP). GMD was synthesized by coupling of glycidyl methacrylate to dextran in the presence of 4-(N,N-dimethylamino)pyridine (DMAP) using dimethylsulfoxide (DMSO) as an aprotic solvent (Kim et al., 2000; Vandijkwolthus, 1995). Dextran also was modified using click-chemistry. Each reaction step was done under aqueous conditions, including the introduction of azide functionalities to the backbone of the polysaccharide. The reaction consisted of the synthesis of 1-azido-2,3-epoxypropane, which was etherified onto the backbone of the polysaccharide using base-catalysis in water/isopropanol mixture at ambient temperature (Fringuelli et al., 1999; Seppala et al., 2010). Modified dextran was synthesized by conjugating the various groups to dextran such as poly(lactic-co-glycolic acid, p-hexylbenzoyl chloride. These groups are listed in Table 3.

| Dextran | Grafting agent | References |
|---------|----------------|------------|
| Dextran (average molecular weights: 77,000) | Poly(lactic-co-glycolic acid) | (Tiera et al., 2003) |
| **Modification:** The DexLG graft copolymer was synthesized by conjugating the carboxylic acid end of PLGA and the hydroxyl group of dextran using DCC as a coupling agent. | | |
| Dextran T40 δMw < 40; 000 | P-Hexylbenzoyl chloride | (Tiera et al., 2003; Bertholon et al., 2006) |
| **Modification:** Dextran was dissolved under stirring in 5 ml of water containing 1.8 g of triethylamine. The resulting solution was heated at 20°C and 1.4 g of p-hexylbenzoyl chloride was added under vigorous stirring for 1h. | | |
| Dextran | 1,2- Epoxy-3- phenoxypropan | (Durand et al., 2002; Sun et al., 2006; Song et al., 2006) |
| **Modification:** Water-soluble amphiphilic dextran, i.e. dextran with lowsubstitution ratio – here DexP15 – was obtained after reaction with 1,2- epoxy -3-phenoxypropane in 1M NaOH as previously described. | | |
| Dextran (Mw ) 30 200 | Bile acid | (Melo et al., 1999; Akiyoshi et al., 1993) |
| **Modification:** modified dextran were obtained by reacting dextran (Mw) 30 200, (Mw/Mn) 1.112) with a bile acid in the presence of N,N-dicyclohexylcarbodiimide as a coupling agent and 4-(N,N-dimethylamino)pyridine as a catalyst. | | |
| Dextran methoxypolyethylene | Glycol/poly (e-caprolactone) | (Zhang et al., 2008; Cao et al., 2005) |
| **Modification:** A series of amphiphilic copolymers, dextran-graft-methoxypolyethylene glycol/poly (e-caprolactone) (Dex-g-mPEG/PCL) were synthesized by grafting both PCL and mPEG chains to dextran, and subsequently the micellar self-assembly behavior of resultant copolymers was investigated. | | |

Table 3. Functional molecules for modification of dextran.
3.4 Modified pullulan

Due to their amphiphilic structure, modified pullulan has potential high surface and interfacial properties. They diffuse through the bulk phase and adsorb at the interface, inducing a sharp reduction in the surface or interfacial tension of a polymer solution (Muller et al., 2003). Like other polysaccharides pullulan have been used to modify with various groups for preparation of their nanoparticles (table 4). Pullulan which is partly modified by relatively higher hydrophobic groups such as cholesteryl groups, it shows unique association behavior. Cholesterol-bearing pullulans have been studied in detail by Akiyoshi and Sunamoto. It was designed as a self-aggregate to form monodisperse and stable nanogels due to the hydrophobic moieties in an aqueous solution. The nanogels formed complexes with various drugs and proteins by hydrophobic interaction and released them upon exposure to specific proteins (Akiyoshi et al., 1997; Akiyoshi et al., 1993; Cheng et al., 2008). Hydrophobically-modified pullulans of moderate molar mass and differing in hydrophobic modification ratio, charge ratio and the nature of the hydrophobic chains were prepared (Bataille et al., 1997; Glinel et al., 1999; Fischer et al., 1998). Poly (DL-lactide-co-glycolide)-grafted pullulan can form self-assembling nanospheres and control adriamycin release. Pullulan acetate (PA) is the other important hydrophobized pullulan, which can form self-aggregation nanoparticles as well as its modified materials (Zhang et al., 2009; Na et al., 2007).

| Pullulan Grafting agent | References |
|-------------------------|------------|
| Pullulan carboxymethylpullulan | (Akiyoshi et al., 1998) |
| Modification: Cholesterol-bearing pullulan forms a spherical and monodisperse nanoparticle which is a self-aggregate of 10–12 CHP molecules. This nanoparticle has several hydrophobic domains of four to five associated cholesteryl moieties. |
| Algyl bromide (octyl, decyl or dodecyl) | (Bataille et al., 1997; Glinel et al., 1999) |
| Modification: Hydrophobically-modified carboxymethylpullulans (HMCMPs) were obtained by a synthetic pathway adapted from that used by Della Valle for gellan and Fischer et al. for pectin. |
| Pullulan with molecular weight of 50,000–100,000 (g/mol) | Poly(DL-lactide-co-glycolide) | (Jeong et al., 2006) |
| Modification: Pullulan (1 g) was dissolved in DMSO (15 ml) for 3 h. Various amounts of PLGA were dissolved in DMSO (5 ml) with a 1.3 equiv. amount of DCC and DMAP. |
| Pullulan (Mw = 200,000) | Acetic anhydride | (Na et al., 2007; Zhang et al., 2009) |
| Modification: 2 g of pullulan, suspended in 20 ml of formamide, was dissolved by vigorous stirring at 54 °C. To this solution, 6 ml pyridine and 15 ml, 10 ml or 7.5 ml of acetic anhydride were added to change the acetylation degree. |

Table 4. Functional molecules for modification of pullulan
3.5 Modified cyclodextrins

Modifications to the cyclodextrins (Namazi et al., 2005; Namazi and Kanani, 2009) lead to a wide range of photochemistry of cyclodextrin complexes, through which the improvement of guest reactivity occurs; in addition, light harvesting molecular devices and photochemical frequency switches may be constructed. A few amphiphilic β-CD derivatives such as β-CDC₆ modified on the secondary face with 6C aliphatic esters and 6-N-CAPRO-β-CD modified on the primary face with a 6C aliphatic amide were demonstrated to give stable nanoparticles of high drug loading capacity and reduction of burst effect during the drug release process when nanoparticles are prepared directly from preformed drug/amphiphilic CD inclusion complex (Lemos-Senna et al., 1998). A new nanoparticle carrier system was obtained from amphiphilic cyclodextrin bearing fatty acids (with a chain length of either 6 or 12 carbon atoms) grafted O₂ and O₃ position of the cyclodextrin. Nanoparticles with a mean diameter of several hundred nm were prepared by dispersion. Amphiphilic cyclodextrins (CDs) are obtained by the chemical per-modification of natural CDs (β-CD or γ-CD) by the selective substitution of aliphatic chains of varying length (2C to 18C), structure (linear or branched) linked with varying bonds (ester, ether, amide, thio, fluoro) of high purity. These CD derivatives were demonstrated to yield nanospheres or nanocapsules spontaneously using the nanoprecipitation technique with or without the presence of surfactants. Carboxymethyl-β-cyclodextrin modified nanoparticles were fabricated for removal of copper ions from aqueous solution by grafting CM-β-CD onto the magnetite surface via carbodiimide method. The grafted Carboxymethyl-β-cyclodextrin on the Fe₃O₄ nanoparticles contributes to an enhancement of the adsorption capacity because of the strong abilities of the multiple hydroxyl and carboxyl groups in CM-β-CD to adsorb metal ions. Double hydrophilic copolymers with one polyethylene glycol (PEG) block and one β-cyclodextrin (β-CD) flanking block (PEG-β-PCDs) were synthesized through the post-modification of macromolecules. The self-assembly of PEG-β-PCDs in aqueous solutions was studied by a fluorescence technique (Choisnard et al., 2006).

3.6 Modified cellulose

Modified cellulose have received wide applications for the stabilization of disperse systems, in particular suspensions and emulsions (Namazi and Rad, 2004). The most important types of associating polymers are water-soluble amphiphilic polymers, notably block or graft copolymers, with hydrophobic blocks or grafts. Cellulose is the most abundant polysaccharide available worldwide and exhibits attractive structure and single properties, which are quite attractive for both academic and industrial researchers. Recently, cellulose based polymers have been widely investigated for its positive characteristics such as safety, biodegradability, biocompatibility, and protein rejecting ability, and so on (Namazi and Jafarirad, 2008). However, there have been few reports on the utilization of self-assembled micelles based on amphiphilic cellulose derivatives as delivery carriers for poorly water-soluble pharmaceutical active ingredients (Klemm et al., 2005; Cheng et al., 2008; Dong et al., 2008). Poly (ε-caprolactone) (PCL) and poly (L-lactic acid) (PLLA) are biodegradable polymers that are potential candidates as matrixes in biocomposites. Several studies have been conducted on the PCL and PLLA modification of soluble cellulose and its derivate (Nishio and Teramoto, 2003; Nishio et al., 2002; Burt and Shi, 2003). Modified cellulose was prepared with hydrophilic groups that it can be self-assemble into polymeric vesicle or as
nontoxic surfactants. Sulfate was firstly introduced as hydrophilic groups, then the hydrophobic groups for cellulose derivatives. The aqueous self-assembly of the modified cellulose was investigated using transmission electron microscopy (TEM) and dynamic laser scattering (DLS). Results showed that modified cellulose were capable of forming polymeric micelles in water with an average particle diameter ranging from 20 to 67 nm (Cheng et al., 2008). Novel modified cellulose derivatives were synthesized long chain alkyl groups as hydrophobic moieties and quaternary ammonium groups as hydrophilic moieties. The results of measurements (DLS, TEM) revealed that modified cellulose can be self-assembled into cationic micelles in distilled water with the average hydrodynamic radius of 320–430 nm (Zhou et al., 2011).

4. Preparation methods and characterization of polysaccharide-based nanoparticle

As for polysaccharide-based nanoparticles, Alonso et al. (Alonso et al., 2001) and Prabaharan et al. (Prabaharan and Mano, 2005) have made excellent reviews in 2001 and 2005, respectively, focusing on the preparation and application of chitosan nanoparticle carriers. Many studies have demonstrated that nanoparticles have a number of advantages over microparticles (Panyam and Labhasetwar, 2003). It has been reported that micro particles are less effective drug delivers than particle having size ranging in between nanometers for e.g. Nanoparticles having size range greater than 230 nm acquire in the spleen shown by body distribution studies (Kreuter, 1991). As time goes on, more polysaccharide-based nanoparticles emerge, which greatly enriches the versatility of nanoparticle carriers in terms of category and function. In this section, several mechanisms are introduced to prepare these nanoparticles, that is, emulsification solvent evaporation method, solvent diffusion method, self-assembly of hydrophobically modified, dialysis method and other methods. The select of method depends on a number of factors, such as, particle size, particle size distribution, area of application and etc. Particle size is the greatest important characteristics of nanoparticles. Some methods for the determining particle size are (Labhasetwar et al., 2003)

a. Photon-correlation spectroscopy.
b. Dynamic light scattering.
c. Brownian motion and light scattering properties.
d. Scanning or transmission electron microscopy (SEM or TEM).

They determine the in vivo distribution, biological fate, toxicity and targeting ability of these delivery systems. In addition, they can influence drug loading, drug release and stability of the nanoparticles.

4.1 Polysaccharides-based nanoparticles through emulsification solvent evaporation method

Emulsification solvent evaporation is the most widely employed technique to prepare nanoparticles of polymers in the current literature on techniques using a dispersion of preformed polymers (Vanderhoff et al., 1979). In the conventional methods, two main strategies are being used for the formation of emulsions: the preparation of single-emulsions, e.g., oil-in-water (o/w) or double-emulsions, e.g., (water-in-oil)-in-water, (w/o/w).
In a single emulsification solvent evaporation process, polymer dissolved in a volatile water-immiscible organic solvent such as dichloromethane, chloroform, ethyl acetate, which is also used as the solvent for dissolving the hydrophobic surfactant. This solution is emulsified in an aqueous phase containing a surfactant or stabilizer (emulsifying agent) resulting in oil-in-water (o/w) emulsion. (ODonnell and McGinity, 1997; I. et al., 2004; Lee, 2001) The coalescence of the organic droplets can be avoided by continuous stirring. Emulsification can also be enhanced by using sonication or microfluidization with a homogenizer, which reduces the droplet size of the organic dispersed phase. After the formation of stable emulsion, the organic solvent is evaporated either under stirring at room temperature or by rotary evaporation under reduced pressure to transform the nano-emulsion into a nanoparticle suspension. Formed nanoparticles are harvested from the aqueous slurry by lyophilization.

For the water-soluble surfactants, a double-emulsion (water-oil-water) variation of the process is utilized. An aqueous solution of the active agent (internal water phase, w1) is emulsified into an organic solution containing the biodegradable polymer and lipophilic surfactant (oil phase, o) for resulting primary emulsification. Then, this emulsion (w1/o) is added to the large aqueous phase with emulsifier (external water phase, w2) to create w1/o/w2 double emulsion. The emulsifier amount is much higher in the first emulsion than in the second emulsion, because the droplet size of the first emulsion needs to be much smaller than in the second outer emulsion. The organic solvent is removed by evaporation or extraction and solid nanoparticles are formed. The nanoparticles are collected by centrifugation or filtration and are subsequently lyophilized.

Wouessidjewe and coworkers (Lemos-Senna et al., 1998) using this method for preparing nanospheres from an amphiphilic 2,3-di-O-hexanoyl-γ-cyclodextrin (γCDC6). This preparation method involves in emulsifying an organic phase having the cyclodextrin in an aqueous phase containing Pluronic F68 as surfactant. This solution was dispersed in aqueous phase by using a high speed homogenizer. Afterward, the organic solvent was evaporated by mechanical stirring at room temperature. The influence of the process parameters, i.e. surfactant concentration and initial γCDC6 content, on the characteristics of nanosphere preparation, as well as on the nanosphere loading of a hydrophobic drug, progesterone, was calculated. Cyclodextrin nanospheres presenting a mean diameter varying from 50 to 200 nm were obtained, even in the presence of low surfactant concentration.

Nanoparticles of dextran (Aumelas et al., 2007) could be simply prepared by the o/w emulsion solvent evaporation method, with using a low modified dextran (DexP15) as polymeric surfactant in the water phase and a highly modified dextran in the CH2Cl2 phase. After emulsification and solvent evaporation, core-shell particles with a dense dextran core and a dextran surface coverage are expected. Dextran segments originating from DexP15 chains which are not embedded in the dextran core are assumed to extend freely toward the aqueous solution and to form a hydrophilic shell. The size of DexP130 nanoparticles prepared by o/w emulsion process decreases as the amount of DexP15 in the water phase increases. Unpredictably, dextran nanoparticles were also obtained without any polymeric surfactant in the aqueous phase. For comparison, when poly (lactic acid) was used instead of hydrophobically modified dextran, it was not possible to obtain nanoparticles without the
presence of surfactant in the aqueous phase. This specific result can be explained assuming a limited solubility of highly hydrophobized dextrans in water. This solubility can be due to the presence of a fraction of low substituted dextran molecules in the final product or to partitioning of the highly substituted sample. This water-soluble fraction could act as a stabilizer for the transient oil droplets. Generally speaking, the size of bare dextran nanoparticles, i.e. prepared in the absence of DexP_{15}, increases with the substitution ratio of dextran, for example from 370 nm for DexP_{65} nanoparticles to 850 nm for DexP_{210} nanoparticles. Other dextran particles, in the size range 150–250 nm, were obtained in the presence of DexP_{15}. The colloidal stability of suspensions was also examined at various NaCl concentrations. For the targeted nanoparticles, surface coverage by hydrophilic loops is essential to provide a convenient colloidal stability in physiological conditions (especially with regard to the ionic strength).

In the o/w emulsion process, we showed that the size of particles is strongly related to the concentration of surfactive polymer in the aqueous phase. In generally, parameters in the emulsification solvent evaporation process that affect particle size, zeta potential, hydrophilicity, and drug loading include:

1. Homogenization intensity and duration.
2. Type and amounts of emulsifier, polymer and drug.
3. Particle hardening (solvent removal) profile (Zambaux et al., 1998).

4.2 Polysaccharides-based nanoparticles through solvent diffusion method

Spontaneous emulsification or solvent diffusion method is a modified version of solvent evaporation method. The different process variants are all based upon the use of solvents which are of limited water miscibility and capable of spontaneous emulsion formation. This method thus offers the advantage of the use of pharmaceutically acceptable solvents and does not require the use of high-pressure homogenizers for the formation of the o/w emulsion as the preliminary stage of nanoparticle formation (Allemann et al., 1998; Leroux et al., 1995). In this method, the water-miscible solvent along with a small amount of the water-immiscible organic solvent is used as an oil phase. Due to the spontaneous diffusion of solvents an interfacial turbulence is created between the two phases leading to the formation of small particles. In this technique, the phase separation is accompanied by vigorous stirring. On the opposite with o/w, the size of nanoparticles obtained using the solvent-diffusion method is poorly affected by the concentration of polymeric surfactant added to the aqueous phase. A reduction in particle size can be gained by increasing the concentration of water miscible solvent.

Nanoparticles of dextran (Aumelas et al., 2007) could be prepared by solvent-diffusion method. Dextran nanoparticles of similar size were obtained with or without using stabilizer such as DexP_{15}. This process avoids the use of any high energy input step. The colloidal stability of suspensions was also examined at various NaCl concentrations. The particular colloidal stability of DexC_{1052} nanoparticles up to high ionic strengths without DexP_{15} can be justified by assuming that the water-soluble fraction contained in that polymer is higher than in the others. Also this method was employed to prepare pullulan acetate (PA) nanoparticles. (Zhang et al., 2009) This technique had some advantages compared with other methods. It is a straightforward technique and the particle size increased from 185.7 nm to
423.0 nm with the degree of acetylation increasing from 2.71 to 3.0. Briefly, PA is readily soluble in dimethyl sulfoxide (DMSO), DMF, tetrahydrofuran (THF), dichloromethane, chloroform, acetone, and pyridine. To make nanoparticles by solvent diffusion method, only water-miscible solvents were considered because the solvents could diffuse into aqueous phase. The solvent selected to dissolve the polymer, as well as the type of polymer can influence the formation of nanoparticles, due to differences in the polymer-solvent and water-solvent interactions. It was supposed that the diffusion-stranding process might be altered, thus inducing changes in the mean size. Therefore, solvents are of primary importance in the formation of nanoparticles by the solvent diffusion method. In other study, five water-miscible solvents, i.e., DMSO, DMF, acetone, THF and pyridine were used. 0.5% poly (vinyl alcohol) [PVA] or distilled water served as aqueous phase. PA2 could form nanoparticles in anyone of the five organic solvents added to water or 0.5% PVA. However, PA1 could do only in DMSO and DMF added to 0.5% PVA. Really, PA2 led to the smallest nanoparticles (185.7 nm), and the largest was PA1 nanoparticles (423.0 nm).

4.3 Polysaccharides-based nanoparticles through self-assembly method

The literature survey showed that several studies have been carried out to investigate the synthesis and the application of polysaccharide based self-aggregate nanoparticles as drug delivery systems. When hydrophilic polymeric chains are grafted with hydrophobic segments, amphiphilic copolymers are formed. Upon contact with an aqueous environment, polymeric amphiphiles spontaneously form micelles or micelle-like aggregates via undergoing intra- or intermolecular associations between hydrophobic moieties, primarily to minimize interfacial free energy. These polymeric micelles display unique characteristics, such as small hydrodynamic radius (less than microsize) with core-shell structure, unusual rheology feature, thermodynamic stability, depending on the hydrophilic/hydrophobic constituents. In specific, polymeric micelles have been recognized as a promising drug carrier, since their hydrophobic domain, surrounded by a hydrophilic outer shell, can serve as a preservatory for various hydrophobic drugs (Letchford and Burt, 2007). Usually, these hydrophobic molecules can be divided into linear, cyclic hydrophobic molecules, hydrophobic drug, polyacrylate family, etc.

4.3.1 Linear hydrophobic molecules

Poly (ε-caprolactone) (PCL) is biodegradable industrial polyester with excellent mechanical strength, non-toxicity, and biocompatibility. It has been frequently used as implantable carriers for drug delivery systems or as surgical repair materials. It is hopeful to combine chitosan with the biodegradable polyester to create amphiphilic copolymer applicable to drug delivery systems. In 2002 and 2003, (Gref et al., 2002; Lemarchand et al., 2003) synthesized amphiphilic dextran by coupling between carboxylic function present on preformed PCL monocarboxylic acid and the hydroxyl groups on dextran. The comb-like copolymers (dextran-PCLn) consisted of a dextran back bone on to which preformed PCL blocks were grafted. Nanoparticles of less than 200 nm were successfully prepared by using the new materials (Rodrigues et al., 2003). Further, bovine serum albumin and lectin were incorporated in the nanoparticles. Lectins could also be adsorbed onto the surface of the nanoparticles. Surface-bound lectin conserved its hemagglutinating activity, suggesting the possible application of this type of surface-modified nanoparticles for targeted oral.
administration. Caco-2 cellular viability was higher than 70% when put in contact with the nanoparticles, even at concentrations as high as 660 mg/ml (Rodrigues et al., 2003). In addition, it was found that the modification of the surface with dextran significantly reduced the cytotoxicity towards J774 macrophages. Biodegradable amphiphilic PCL-graft-chitosan copolymer was synthesized (Jing et al., 2006). The copolymers could form spherical or elliptic nanoparticles in water. Poly (ethylene glycol) has been employed extensively in pharmaceutical and biomedical fields because of its outstanding physicochemical and biological properties including hydrophilic property, solubility, non-toxicity, ease of chemical modification and absence of antigenicity and immunogenicity. Therefore, poly (ethylene glycol) is widely used as a pharmacological polymer with high hydrophilicity, biocompatibility and biodegradability. In recent years, derivative poly (ethylene glycol)-g-derivative chitosan to obtain nanoparticles has been studied by many researchers (Ouchi et al., 1998; Jung et al., 2006) (Park et al., 2008) (Yang et al., 2008b) (Opanasopit et al., 2007). The grafted poly (ethylene glycol) methyl ether onto N-Phthaloyl chitosan chains, aggregated to obtain sphere-like nanoparticles (an et al., 2004). When the chain length of poly (ethylene glycol) methyl ether was as high as 5×10^3 Da, the sphere size became as small as 80-100 nm. By simply adjusting the hydrophobicity/hydrophilicity of the chitosan chain, stable nanospheres could be obtained directly. Also methoxy poly (ethylene glycol)-grafted chitosan to develop polymeric micelles for the drug delivery to brain tumor was synthesized (Jung et al., 2006) Methoxy poly (ethylene glycol)-grafted-chitosan conjugates by formaldehyde linking method was synthesized(Yang et al., 2008b). The conjugates formed monodisperse self-aggregated nanoparticles with a roughly spherical shape and a mean diameter of 261.9 nm. A poorly water-soluble anticancer drug, methotrexate was physically entrapped inside the nanoparticles. Other group synthesized amphiphilic grafted copolymers, N-phthaloyl chitosan-grafted poly (ethylene glycol) methyl ether (Opanasopit et al., 2007). These copolymers could form micelle-like nanoparticles. The CMC of these nanoparticles in water was similar (28 μg/ml). The nanoparticles exhibited a regular spherical shape with core-shell structure with sizes in the range of 100-250 nm. Camptothecin as a model drug was loaded into the inner core of the micelles. For modifying polysaccharides have been used some long-chain fatty acids such as hexanoic acid, decanoic acid, linoleic acid, linolenic acid, palmitic acid, stearic acid, and oleic acid. Choisnard et al. (Choisnard et al., 2006) prepared decanoate β-cyclodextrin esters (DS, 2-7) and hexanoate β-cyclodextrin esters (DS, 4-8) biocatalyzed by thermolysin from native β-cyclodextrin and vinyl hexanoate or vinyl decanoate used as acyl donors. Both esters self-organized into nanoparticles by a nanoprecipitation method. Chen et al. (Chen et al., 2003a) modified chitosan by coupling with linoleic acid through the 1-ethyl-3-(3-dimethylamino-propyl)-carbodiimide-mediated reaction to increase its amphipathicity for enhanced emulsification. The micelle formation of linoleic acid-modified chitosan in the 0.1 M acetic acid solution was improved by o/w emulsification with methylene chloride, an oil phase, the self-aggregation concentration from 1.0 g/L to 2.0 g/L. The addition of 1 M sodium chloride promoted the self-aggregation of linoleic acid-chitosan molecules both with and without emulsification. The micelles formed nanosize particles ranging from 200 to 600 nm. The nanoparticles encapsulated a lipid soluble model compound, retinal acetate, with 50% efficiency. The similar group modified chitosan with linolenic acid (the DS 1.8%) using the
same reaction. The self-aggregated nanoparticles of linolenic acid-chitosan were also used to immobilize trypsin using glutaraldehyde as crosslinker. Results indicated that the activity of trypsin immobilized onto the nanoparticles increased with increasing concentration of glutaraldehyde up to 0.07% (v/v) and then decreased with increasing amount of glutaraldehyde. On the other side, particle size increased (from 523 to 1372 nm) with the increasing concentration of glutaraldehyde (from 0.03 to 0.1% v/v) (Liu et al., 2005).

Water-soluble N-palmitoyl chitosan was prepared by swollen chitosan coupling with palmitic anhydride in dimethyl sulfoxide, which could procedure micelles in water (Jiang et al., 2006). The DS of N-palmitoyl chitosan was in the range of 1.2-14.2% and the CMC of N-palmitoyl chitosan micelles was in the range of 2.0×10⁻³ to 37.2×10⁻³ mg/ml. The loading capacity of hydrophobic model drug ibuprofen in the micelles was about 10%. Also stearic acid grafted chitosan oligosaccharide by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-mediated coupling reaction was synthesized (Hu et al., 2006). The CMC of the copolymer was approximately 0.06, 0.04, 0.01 mg/ml respectively. To increase the stability of the micelle in vivo and controlled drug release, the shells of micelles were cross-linked by glutaraldehyde. Paclitaxel was used as a model drug to incorporate into the micelles, and the surfaces of the micelles were further cross-linked by glutaraldehyde to form drug loaded and shell cross-linked nanoparticles. The higher drug entrapment efficiencies (above 94%) were observed in all cases. Zhang et al. (Zhang et al., 2007) developed self-assembled nanoparticles based on oleoyl-chitosan with a mean diameter of 255.3 nm. Doxorubicin was efficiently loaded into the nanoparticles with an encapsulation efficiency of 52.6%. The drug was rapidly and completely released from the nanoparticles at pH 3.8, whereas at pH 7.4 there was a sustained release after a burst release. Amylose-conjugated linoleic acid complexes were synthesized to serve as molecular nanocapsules for the protection and the delivery of linoleic acid (Shimoni et al., 2005).

Pluronic tri-block copolymers collected of poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) show lesser critical solution temperature behaviors over a broad temperature range depending on the composition and MW. They self-assemble to procedure a spherical micellar structure above the lower critical solution temperature by hydrophobic interaction of the poly (propylene oxide) middle block in the structure. Pluronic/heparin composite nanocapsules, which displayed a 1000-fold volume transition (ca. 336 nm at 25 °C; ca. 32 nm at 37 °C), and a reversible swelling and de-swelling behavior when the temperature was cycled between 20 and 37 °C is prepared (Choi et al., 2006). Core/shell nanoparticles with the poly (lactide-co-glycolide) core and the polymeric shell made-up of pluronics and hyaluronic acid was synthesized (Yuk et al., 2005).

### 4.3.2 Cyclic hydrophobic molecules

Cholesterol is an essential lipid in animals, which not only participates the formation of cell membranes but also works as a raw material for the synthesis of bile acids, vitamin D and steroid hormones. Conjugating hydrophobic cholesterol to hydrophilic polysaccharides may form amphiphilic copolymer which may further form self-assembly nanoparticles in aqueous solution. cholesterol-modified chitosan conjugate with succinyl linkages was synthesized (Wang et al., 2007c). The conjugates formed monodisperse self-aggregated nanoparticles.
nanoparticles with a roughly spherical shape and a mean diameter of 417.2 nm by probe sonication in aqueous media. Epirubicin, as a model anticancer drug, was physically entrapped inside the nanoparticles by the remote loading technique. Epirubicin-loaded nanoparticles were almost spherical in shape and their size increased from 338.2 to 472.9 nm with the epirubicin-loading content increasing from 7.97% to 14.0%. Also was prepared self-aggregated nanoparticles of cholesterol-modified O-carboxymethyl chitosan (Wang et al., 2007b).

Various cholesterol-bearing pullulans with different MWs of the parent pullulan and DS of the cholesteryl moiety was synthesized (Nishikawa et al., 1996; Akiyoshi et al., 1997). Irrespective of the MW of the parent pullulan and the DS, all of cholesterol-pullulans provided unimodal and mono-disperse self-aggregates in water. The size of the self-aggregate reduced with an increase in the DS of the cholesteryl moiety (hydrodynamic radius, 8.4-13.7 nm). However, the aggregation number of cholesterol-pullulans in one nanoparticle was almost independent of the DS. The polysaccharide density within the self-aggregate (0.13-0.50 g/ml) was affected by both the MW and the DS of cholesterol-pullulans. The characteristic temperature to cause a structural change of the nanoparticles decreased with an increase in the DS and the ionic strength of the medium. Moreover, they also prepared thermo-responsive nanoparticles by self-assembly of two different hydrophobically modified polymers, namely, cholesterol-pullulan and a copolymer of N-isopropylacrylamide and N-[4-(1-pyrenyl)butyl]-N-n-octadecylacrylamide via their hydrophobic moieties (Akiyoshi et al., 2000), as well as hexadecyl group-bearing pullulan self-assembly nanoparticles (Kuroda et al., 2002).

Bile acids such as deoxycholic acid and 5β-cholanic acid are known to form micelles in water as a result of their amphiphilicity, which plays an important role in the emulsification, solubilization, and absorption of cholesterol, fats, and lipophilic vitamins in human body. Therefore, it is expected that the introduction of deoxycholic acid or 5β-cholanic acid into chitosan would induce self-association to form self-aggregates. Covalently conjugated deoxycholic acid to chitosan via carbodiimide-mediated reaction to generate self-aggregated nanoparticles was prepared (Lee et al., 1998; Jeong et al., 1998). Adriamycin was physically entrapped inside the self-aggregates. The size of adriamycin-loaded self-aggregates increased with increasing the loading content of adriamycin (Lee et al., 2000).

Chemically modified chitosan oligosaccharides with deoxycholic acid was reported (Chae et al., 2005). Owing to the amphiphilic characters, the deoxycholic acid-chitosan formed self-aggregated nanoparticles in aqueous milieu. The particle size of the nanoparticles was in the range of 200-240 nm. Furthermore, deoxycholic acid-chitosan showed great potential for gene carrier with the high level of gene transfection efficiencies, even in the presence of serum. Deoxycholic acid-heparin amphiphilic conjugates with different degree of substitution of deoxycholic acid was synthesized (Park et al., 2004), which provided monodispersed self-aggregates in water, with mean diameters (120-200 nm) decreasing with increasing DS. Increasing DS enhanced the hydrophobicity of the self-aggregate inner core.

However, chitosan-based self-aggregates were difficult to be widely applied for drug delivery systems because chitosan aggregates are insoluble in biological solution (pH7.4) and they are readily precipitated within a few days. Recently, water-soluble chitosan
derivatives have been used to increase their stability in biological solution and decrease the cytotoxicity induced by acidic solution, where chitosan is soluble. Covalently modified glycol chitosan with deoxycholic acid self-aggregates as a new drug delivery system was prepared (Kim et al., 2005) and investigated in detail the effect of deoxycholic acid attached to glycol chitosan on the formation, physicochemical characteristics, and stability of self-aggregates in aqueous media. The same group (Kwon et al., 2003; Park et al., 2007) covalently attached the 5β-cholanic acid to glycol chitosan through amide formation using carbodiimide as catalyst. The 5β-cholanic acid-glycol chitosan formed self-aggregates (210-859 nm in diameter) in an aqueous phase by intra- or intermolecular association between hydrophobic 5β-cholanic acids attached to glycol chitosan.

FITC is a widely used hydrophobic fluorescein, the isothiocyanato of which can readily react with free amine to incorporate fluorescence labeling. Doxorubicin is an anti-tumor antibiotic, which can inhibit the synthesis of RNA and DNA and has a therapeutic effect on many tumors. FITC and doxorubicin themselves are hydrophobic cyclic molecules, which can be conjugated onto hydrophilic polysaccharides form amphiphilic copolymers. Hydrophobically modified glycol chitosans by chemical conjugation of FITC or doxorubicin to the backbone of glycol chitosan was prepared (Lee et al., 2006; Son et al., 2003). Biodistribution of self-aggregates (300 nm in diameter) was evaluated using tissues obtained from tumor-bearing mice, to which self-aggregates were systemically administered via the tail vein. Na et al. (Na et al., 2003) introduced vitamin H to pullulan acetate and prepared corresponding self-assembled nanoparticles (~100 nm) in order to improve their cancer-targeting activity and internalization. Three samples of biotinylated pullulan acetate, comprising 7, 20 and 39 vitamin H groups per 100 anhydroglucose units, were synthesized. In addition, synthesized successfully N-succinyl-chitosan, which could be self-assembly of well-dispersed and stable nanospheres in distilled water with 50-100 nm in diameter (Zhu et al., 2006). Experimental results indicated that a hydrophobic domain formed within these nanospheres. The assembly mechanisms were believed to be the intermolecular H-bonding of N-succinyll-chitosan and hydrophobic interaction among the hydrophobic moieties in N-succinyl-chitosan macromolecules. Park et al. (Park et al., 2006) described N-acetyl histidine-conjugated glycol chitosan self-assembled nanoparticles as a promising system for intracytoplasmic delivery of drugs.

4.3.3 Polyacrylate-based nanoparticles applicable as biomaterials

Poly (methyl methacrylate) and poly (isobutyl cyanoacrylate) (PIBCA) all belong to polyacrylate family and they were widely used for biomaterials. Containing carboxylic ester groups in their structures, they are hydrophobic. The efficient uptake of injected nanoparticles by cells of the mononuclear phagocyte system limits the development of long-circulating colloidal drug carriers. The complement system plays a major role in the opsonization and recognition processes of foreign materials. Since heparin is an inhibitor of complement activation, nanoparticles bearing heparin covalently bound to poly (methyl methacrylate) and evaluated their interactions with complement was prepared (Passirani et al., 1998a). Nanoparticles bearing covalently bound dextran instead of heparin were weak activators of complement as compared with cross-linked dextran or bare poly (methyl methacrylate) nanoparticles. In addition to the specific activity of bound heparin, the protective effect of both polysaccharides is hypothesized to be due to the presence of a
dense brush-like layer on the surface of the particles. Dextran nanoparticles were also eliminated very slowly over 48 h. bare poly (methyl methacrylate) nanoparticles were found to have a half-life of only 3 min. Both types of nanoparticles proved to be long-circulating. The potent capacity for opsonization of the poly (methyl methacrylate) core was hidden by the protective effect of either polysaccharide, probably due to a dense brush-like structure. In the case of heparin nanoparticles, the “stealth” effect was probably increased by its inhibiting properties against complement activation (Passirani et al., 1998b).

PIBCA-chitosan nanoparticles by emulsion polymerization of IBCA in the presence of chitosan as a polymeric stabilizer at low pH were prepared (Yang et al., 2000). Nimodipine as a model drug was successfully incorporated into the nanoparticles with mean particle diameter of 31.6 nm and a positive charge. Also PIBCA-chitosan, PIBCA-dextran and PIBCA-dextran sulfate core-shell nanoparticles by redox radical or anionic polymerization of IBCA in the presence of chitosan, dextran or dextran sulfate was prepared (Bertholon et al., 2006). Bravo-Osuna et al. (Bravo-Osuna et al., 2006; Bravo-Osuna et al., 2007a; Bravo-Osuna et al., 2007c; Bravo-Osuna et al., 2007b) developed PIBCA-thiolated chitosan nanoparticles by radical emulsion polymerization. The nanoparticles had mean hydrodynamic diameter around 200 nm and positive zeta potential values, indicating the presence of the cationic thiolated chitosan at the nanoparticle surface. Polysaccharide-coated nanoparticles by radical emulsion polymerization of IBCA in the presence of various polysaccharides (dextran, dextran sulfate, heparin, chitosan, hyaluronic acid, pectin) was synthesized (Chauvierre et al., 2003). They also measured the complement activation induced by different polysaccharide-coated nanoparticles and of the antithrombic activity of heparin. These nanoparticles maintained the heparin antithrombic properties and inhibited complement activation. This work demonstrated the hemoglobin loading on nanoparticle surface, rather than being encapsulated. With a size of 100 nm, these drug delivery systems made suitable tools in the treatment of thrombosis oxygen deprived pathologies (Chauvierre et al., 2004). In addition, they investigated for the first time the mobility of dextran chains on the PIBCA nanoparticles with electronic paramagnetic resonance. This technique opens an interesting prospect of investigating surface properties of polysaccharide-coated nanoparticles by a new physicochemical approach to further correlate the mobility of the polysaccharide chains with the fate of the nanoparticles in biological systems (Vauthier et al., 2004).

4.4 Polysaccharides-based nanoparticle through dialysis method

The preparation of nanoparticles was performed by a dialysis method without the use of any surfactant or emulsifiers. Dialysis offers a simple and effective method for the preparation of small, narrow-distributed polymer nanoparticle (Fessi et al., 1989; Jeong et al., 2001; Kostog. M et al., 2010; Jeon et al., 2000). Polymer is dissolved in an organic solvent and placed inside a dialysis tube with proper molecular weight cut-off. Dialysis is performed against a non-solvent miscible with the former miscible. The displacement of the solvent inside the membrane is followed by the progressive aggregation of polymer due to a loss of solubility and the formation of homogeneous suspensions of nanoparticles.

Paclitaxel-loaded HGC (PTX-HGC) nanoparticles were simply prepared by this method (Kwon et al., 2006). The incorporation of PTX into the HGC nanoparticles occurred
simultaneously during dialysis. The loading efficiency of PTX into HGC nanoparticles was determined by varying the feed weight ratio of PTX to HGC nanoparticles. When the feed ratio was less than 0.1, the loading efficiency was above 90%. Importantly, the PTX-HGC nanoparticles were well dispersed in an aqueous medium. However, if the feed ratio was above 0.1, the loading efficiency significantly decreased to about 42% and the excess of PTX molecules precipitated during dialysis. Thus, the maximum loading content of PTX into HGC nanoparticles was determined to 10 wt%.

To make core-shell type nanoparticles, poly (DL-lactide-co-glycolide) (PLGA) grafted-dextran (DexLG) graft copolymer was dissolved in DMSO and the core-shell type nanoparticles were prepared by dialysis method against water. The morphology of core-shell type nanoparticles of DexLG copolymer was observed by SEM and the particle size was evaluated by DLS. Core-shell type nanoparticles of DexLG copolymer has spherical shapes in their morphology and particle size was around 50-200 nm.

Starch ester nanoparticles were prepared by the dialysis method. Appropriate amount of graft polymer was dissolved in DMSO, the sample was dialysed against water using a dialysis membrane of MW 12,000 g mol–1 cut off. Starch nanoparticle formed was studied by atomic force microscopy. Nanoparticles in DMSO water solution were transferred to freshly cleaved mica sheet by drop and analyzed by tapping mode. Size of the particles was found to be in the range of 65–75 nm (diameter), and 17–19 nm (height).

5. Medical applications of polysaccharide-based nanoparticles

Polysaccharide-based nanoparticles have received considerable attention in recent years as one of the most promising nanoparticulate drug delivery systems owing to their unique potentials. Nanoparticle drug delivery systems are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm and with various morphologies, including nanospheres, nanocapsules, nanomicelles, nanoliposomes, and nanodrugs, etc. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix (Kommareddy et al., 2005; Lee and Kim, 2005). Drug delivery systems of nanoparticles have several advantages, such as high drug encapsulation efficiency, efficient drug protection against chemical or enzymatic degradation, unique ability to create a controlled release, cell internalization as well as ability to reverse the multidrug resistance of tumor cells (Soma et al., 1999). The use of starch nanoparticles is receiving a significant amount of attention due to their good hydrophilicity, biocompatibility and biodegradability. Starch nanocrystals have also been found to be excellent reinforcements (Elvira et al., 2002). Hydrophobic grafted and cross-linked starch nanoparticles were used for drug delivery and Indomethacin was taken as the model drug (Abraham and Simi, 2007). Hydrophilic amylopectin was modified by grafting hydrophobic poly (lactic acid) chains (PLA) for the fabrication of polymeric micelles for drug delivery. When these spherical nano-aggregates were used as the drug carrier, it was found that they had a good loading capacity and in vitro release properties for hydrophobic indomethacin drug (Brecher et al., 1997; Dufresne et al., 2006).

A novel amphiphilic copolymer (dextran-g-polyethylene glycol alkyl ether) was synthesized which resulted in polymeric micelle formation, encapsulating cyclosporine in the hydrophobic core and providing a hydrophilic corona (Na et al., 2003; Francis et al., 2003).
Nanoparticles of poly (DL-lactide-co-glycolide)-grafted dextran were synthesized for use as a nanoparticulate oral drug carrier. These nanoparticles were able to form nanoparticles in water by self-aggregating process, and their particle size was around 50 nm~300 nm. Core-shell type nanoparticles of DexLG copolymer can be used as a colonic drug carrier (Tiera et al., 2003). Superparamagnetic chitosan–dextran sulfate hydrogels as drug carriers was synthesized. The 5-aminosalicylic acid was chosen as model drug molecule (Saboktakin et al., 2010). Dextran sulfate–chitosan nanoparticles were prepared to overcome the pharmacokinetic problems and to obtain the full benefits of the drug (Anitha et al., 2011). Self-assembled hydrogel nanoparticles composed of dextran and poly (ethylene glycol) was synthesized and prepared nanoparticles used for drug carrier with hydrophobic model drug in vitro (Kim et al., 2000).

Hydrophobized pullulan has been used as drug delivery carrier, Specifically, cholesterol-pullulan and a copolymer of N-isopropylacrylamide and N-[4-(1-pyrenyl)butyl]-N-n-octadecylacrylamide via their hydrophobic moieties, as well as hexadecyl group-bearing pullulan self-assembly nanoparticles (Akiyoshi et al., 1998; Akiyoshi et al., 1993; Jung et al., 2004). These hydrophobized pullulan self-associate to form colloidally stable nanoparticles with inner hydrophobic core. This hydrophobic core can only encapsulate hydrophobic substances like insoluble drugs and proteins (Gupta and Gupta, 2004). Amphiphilic polysaccharides composed of pullulan and poly (DL-lactide-coglycolide) (PLGA) were synthesized to give amphiphilicity and biodegradability as novel drug carriers. Due to its biodegradability, PLGA is commonly used for the controlled release of drugs (Jeong et al., 2006). Hydrophobically modified glycol chitosan (HGC) nanoparticles showed potential as carriers for anticancer peptides and anticancer drugs because of their biocompatible in vivo (Kwon et al., 2003; Yoo et al., 2005). Modified chitosan derivatives, are emerging as novel carriers of drugs because of their solubility and biocompatibility in vivo (Sinha et al., 2004; Jiang et al., 2006; Chen et al., 2003b). Nanoparticles of carboxymethyl chitosan (CM-chitosan) as carriers for the anticancer drug, were prepared by gelification with calcium ions and Doxorubicin (DOX) was chosen as a model drug.

6. Conclusions and future trends

The literature survey showed that in the last decades a lot of attention has been focused to the combination of polysaccharides based polymers with inorganic nanoparticles, to benefit from the advantages of both organic and inorganic composite components. As this chapter showed the use of polysaccharides-based nanoparticles is receiving a significant amount of interests because of the plentiful availability of natural polymer, inexpensive, renewability, biocompatibility, biodegradability and nontoxicity. Therefore, a number of formulations of such bionanocomposites exhibits some excellent characteristics such as magnetic, optical, antimicrobial functionalities, size particles, surface coverage, colloidal stability, enzyme degradability and interesting applications of the polysaccharide based nanoparticles and their derivatives for biotechnological and biomedical applications was explained. The preparation of this kind of materials strongly relies on earlier steps of their production and modification steps which emphasises the relevance of preparative strategies that take in consideration their final applications. With this respect, we introduced various methods for the preparation of polysaccharides-based nanoparticles such as: solvent evaporation
method, spontaneous emulsification or solvent diffusion method, self-assembly of hydrophobically modified and dialysis method. On the other hand, the modified polysaccharides exhibit considerable potentials to utilize as stabilizers to produce stable hydrophilic nanoparticles through the o/w emulsion/evaporation technique. Modified polysaccharides were shown to exhibit surface active properties and to act as efficient emulsion stabilizers. Surface modified colloidal carriers such as nanoparticles are able to modulate the biodistribution of the loaded drug when given intravenously, but also to control the absorption of drugs administered by other routes. The amphiphilic character imparted upon polysaccharides after hydrophobic modification gives them a wide and interesting use spectrum, for instance as rheology modifiers, emulsion stabilizers, surface modifiers for liposomes and nanoparticles and as drug delivery vehicles. The recent attempts toward finding new methods for the earlier diagnosis of diseases and more effective therapies to synthesize the new generation of multifunctional nanostructured materials based on polysaccharides, modified polysaccharides and polysaccharide-based dendrimers is very fast emerging. As time goes on, more polysaccharide-based nanoparticles emerge, which greatly enriches the versatility of nanoparticle carriers agents in terms of category and function.

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8. References

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