Available online on www.ijcpr.com
International Journal of Current Pharmaceutical Review and Research 2014-15, 5(4), 138-155

ISSN: 0976-822X

Review Article

Review on Natural Polysaccharide Based Particulate Drug Delivery Systems: An Inimitable Tactic in Novel Drug Delivery Systems

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Available Online: 1st November, 14

ABSTRACT

Polysaccharides seem to be the most promising materials in the preparation of micro and nanometeric carriers. Micro and nanoparticles may be comprised of several kind materials being classified as nondegradable and biodegradable. Biodegradable systems have an advantage over nondegradable systems in that they are non-toxic, biocompatible, biodegradable, and water soluble. The application of natural polysaccharides in novel drug delivery systems to deliver the bioactive agents has been hampered by the synthetic polymers. The main benefits of the natural polysaccharides are their being biodegradable, biocompatible, non-toxic, richly available and less expensive. Because of the advances in drug delivery technology, natural polysaccharides are included in novel drug delivery to fulfill multitask functions. Substantial research efforts have been directed towards developing safe and efficient natural based polysaccharide particulate drug delivery systems. In this review, brief information on natural polysaccharides is covered. This review also covers modification techniques for natural polysaccharides and the newest developments in the preparation of polysaccharide based micro and nanoparticles with their characterization techniques and their applications are covered.

Keywords: Natural Polysaccharides; Modification; Particulate drug delivery systems; Fabrication and characterization; Applications.

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INTRODUCTION

In this developing world, there is an immense demand for novel drug delivery systems, and there is a noteworthy increase in the approvals of similar systems. Natural excipients and their application in the pharmaceutical industry are super imposed by the presence of synthetic excipients. Natural excipients are preferred over the synthetic as they are inert, safe, non-toxic, biocompatible, biodegradable, low cost, eco-friendly and abundantly available in nature.[1-3] Conventionally, excipients were incorporated in dosage forms as inert vehicles but in modern pharmaceutical dosage forms they often accomplish multitask roles such as improvement of solubility of poorly soluble drugs enhance bioavailability, desired drug release, target specific in the form of microparticles, and nanoparticles.[4] Most of natural polysaccharides used in the food industry are regarded as safe for human consumption.

Natural polysaccharides are often included in the design of controlled drug delivery such as those target delivery of the drug to a specific site in the gastro intestinal tract (GIT), this can be achieved by various mechanisms including coating granules, pellets, tablets with polysaccharides having pH dependent solubility, or incorporating non-digestible polysaccharides that are degraded by bacterial enzymes present in the colon, this property makes these polysaccharides potentially useful in the formulation of colon-targeted drug delivery systems. The polysaccharides can also be modified in different ways to obtain tailor-made materials for drug delivery systems and thus can compete with the available synthetic excipients.[5,6]

Natural Polysaccharides: Polysaccharides are composed of many monosaccharide residues that are joined one to the other by *O*-glycosidic linkages. Polysaccharides are commonly known as Cinderella of biopolymers, with wide range of applications.[7]

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 $Cx(H_2O)y$ 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 $(C_6H_{10}O_5)n$ where $40 \leq n \leq 3000$.[8-10]

Classification of Natural Polysaccharides: Polysaccharides are extracted and isolated from plant seeds. (locust bean gum, guar gum, tara gum, and tamarind gum). They also play a major role in the structural integrity and mechanical strength of plant tissues by forming a hydrated cross-linked three dimensional network (pectin). On the other hand, cellulose an essential

ingredient of the cell wall in higher plants is most abundantly available biopolymer present in the nature.

Another most important classification of polysaccharide are tree exudates with an history of 5,000 years which are known for their properties like thickening, emulsifying, stabilizing, binding agents and matrix formers in both food and pharmaceutical industry (gum acacia, gum tragacanth and gum karaya). Gums are present in huge quantities in varieties of plants, animals, marine and microbial sources. Plant gums are very common with different structural and metabolic functions commonly found in family Leguminosae, Sterculiaceae, Bixaceae, Compositae, Combretaceae, Gigarginaceae.

The different available polysaccharides can be classified as follows:[8-11]

Based on the ionic charge: Gums have been classified into anionic, cationic and non-ionic. (a) Anionic charged gums: tragacanth, arabic, karaya, gellan, agar, pectin, algin, carrgeenans. (b) Cationic charged gums: chitosan. (c) Non-ionic charged gums: guar gum, locust bean gum, tamarind gum, arabinans, xanthan gum, amylase, cellulose.

Based on the origin:

(a) Marine (sea weeds gum): alginates, agar, Carrageenans. (b) Animal origin: chitin and chitosan, Chondroitin sulfate, hyaluronic acid. (c) Plant origin: i) Seed gums–locust bean, guar, starch, cellulose, amylase. ii) Tree exudates-gum arabia, tragacanth, ghatti, karaya. iii) Tubers-Potato starch. iv) Extracts-pectin. (d) Microbial origin (fungi and bacteria): glycan, pullulan, dextran, xanthan, gellan.

Based on the shape:

(a) Linear: amylase, pectin, cellulose. (b) Branched: i) Short branched-guar gum, locust bean gum; ii) Long branched-amylopectin, karaya gum, gum tragacanth, gum arabic.

Modification of Natural Polysaccharides for Designing Novel Drug Delivery: There are various methods for modifying the structures of polysaccharides. The introduction of hydrophobic, acidic, basic, or other functionality into polysaccharide structures can alter the properties of materials based on these substances.

There are two methods for modification or grafting of natural polysaccharides: Physical methods and chemical methods.[12,13]

Physical Modification of Polysaccharides

Physical Cross linking: In physical crosslinking, polysaccharides forms crosslinked network with counterion at the surface. High counterion concentration would require longer exposure times to achieve complete crosslinking of the polysaccharides. For physical crosslinking different methods have been investigated such as:

i) Cross linking by ionic interaction

ii) Cross linking by Crystallization

iii) Hydrophobised polysaccharides

Microwave modification: Microwaves generate electromagnetic radiation in the frequency range of 300 MHz to 300 GHz. On exposure to microwaves, the polar or charge particles tend to align themselves with electric field component of the microwaves which reverses its direction e.g. at the rate of 2.4 × 109/s at 2.45 GHz microwave frequency. As the charged or polar particles in a reaction medium fail to align themselves as fast as the direction of the electric field of microwaves changes, friction is created, which heated the medium.

Chemical Modification of Polysaccharides

Chemical crosslinking: Chemical crosslinking of polysaccharide is a versatile method with good mechanical stability.

During crosslinking counterions diffused into the polymeric and crosslinking agent reacts with polysaccharides forming either intermolecular or intramolecular linkages.[12]

i) Crosslinking by radical polymerization

ii) Crosslinking by addition reaction

iii) Crosslinking by condensation reaction

Graft copolymerization of polysaccharides: Graft copolymers by definition, consists of a long sequence of one polymer with one or more branches of another polymer. With the help of preformed polymer (polysaccharide in case of grafted polysaccharides) the synthesis of graft copolymer process will start. The free radical sites will create on this preformed polymer with the help of external agent. The agent should be effective enough to create the required free radical sites, at the same time should not be too drastic to rupture the structural integrity of the preformed polymer chain. Once the free radical sites are formed on the polymer backbone, the monomer can get added up through the chain propagation step, leading to the formation of grafted chains.[13]

i) Vinyl/acryl graft copolymerization

ii) Chemical initiating system

iii) Radically initiating system

Other methods

i) Ester and ether formation using saccharide oxygen nucleophiles, including enzymatic reactions and aspects of regioselectivity

ii) The introduction of heteroatomic nucleophiles into polysaccharide chains

iii) The oxidation of polysaccharides, including oxidative glycol cleavage, chemical oxidation of primary alcohols to carboxylic acids, and enzymatic oxidation of primary alcohols to aldehydes

iv) Reactions of uronic-acid-based polysaccharides, nucleophilic reactions of the amines of chitosan and the formation of unsaturated polysaccharide derivatives.[14]

Table 1: Examples of Modified Polysaccharides and Applications

Gums and Mucilage	Modification Technique	Application	Reference
Karaya gum	Heat Treatment at various temperatures in a hot air oven	Disintegrating agent	15
Agar and Guar gum	Heat Treatment at various temperatures in a hot air oven along with co-grinding of both materials	Disintegrating agent	16
Acacia gum	Chemical modification of acacia gum using epichlorhydrine	Disintegrating agent	17-19
Starch	Physico-chemical treatment of to starch for modification	Disintegrating and binding agent	20-25
Sesbania gum	Chemical modification of *Sesbania*gum with tartaric acid for a sustained release formulation and chemical modification of gum with acetone: chloroform mixture for gelling agent	Sustained release formulation, gelling agent	26
Guar gum	Chemical modification of guar gum with glutaraldehyde for colonic delivery, chemical modification using isopropanol as a filmcoating material	Colonic delivery, film coating, disintegrating agent, hydrogel	27,28
Tamarind Powder	Chemical modification of tamarind powder using epichlorohydrin and partial degradation of β-galactosidase	Sustained release formulation, rectal drug delivery	29
Okra gum	Chemical modification with acrylamide synthesis	Controlled drug delivery	30-32

Polysaccharide Based Particulate (Micro and Nano Particulate) Drug Delivery Systems: One of the most important goals of drug delivery research is the design of micro and nano systems able to deliver drugs at the right place in the body sites at the rate required for a specific treatment and at the right dosage forms. The application of polymeric materials for medical purposes is growing very fast. Polymers have found applications in various biomedical fields such as: implantation of medical devices and artificial organs, tissue engineering, prostheses, ophthalmology, dentistry, bone repair, drug delivery systems. Among them, the use of the natural polymers for diversified applications in life science has advantages as biocompatibility and biodegradability, leading therefore to ecological safety and possibility of preparing a variety of chemically and enzymatically modified derivatives for specific uses. Polysaccharides as a class of natural polymers are extremely bioactive, biocompatible and are generally derived from agricultural feedstock or crustacean shell wastes. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as: microparticles, nanoparticles, microspheres, nanospheres, liposomes, niosomes etc., which modulates the release and absorption characteristics of the drug. Micro and nanoparticles constitute an important part of particulate drug delivery systems by virtue of their small size and efficient carrier characteristics.[33-36]

Particulate drug delivery systems (Micro and Nanoparticles) have following advantages:[37]

a) They can pass through the smallest capillary vessels because of their ultra-tiny volume and avoid rapid clearance by phagocytes so that their duration in blood stream is greatly prolonged.
b) They can penetrate cells and tissue gap to arrive at target organs such as liver, spleen, lung, spinal cord and lymph.
c) They could show controlled-release properties due to the biodegradability, pH, ion and/or temperature sensibility of materials.
d) They can improve the utility of drugs and reduce toxic side effects; etc.

Fabrication Techniques for Polysaccharide Based Particulate Drug Delivery Systems (Micro and Nanoparticles)

Ionic Gelation Method: In this method, polysaccharides (alginate, gellan and pectin) are dissolved in water or in weak acidic medium (chitosan). These solutions are then added dropwise under constant stirring to the solutions containing other counterions. Due to the complexation between oppositely charged species, polysaccharides undergo ionic gelation and precipitate to form spherical particles. The beads are removed by filtration, washed with distilled water and dried. The counterions used for ionotropic gelation can be divided into two

major categories: Low molecular weight counterions (e.g. $CaCl_2$, $BaCl_2$, $MgCl_2$, $CuCl_2$, $ZnCl_2$, $CoCl_2$, pyrophosphate, tripolyphosphate, tetrapolyphosphate, octapolyphosphate, hexametaphosphate and High molecular weight ions (*e.g.* octyl sulphate, lauryl sulphate, hexadecyl sulphate, cetylstearyl sulphate). The ionotropic gelation method is very simple and mild. In addition, reversible physical crosslinking by electrostatic interaction instead of chemical crosslinking avoids the possible toxicity of reagents and other undesirable effects.[38]

Covalent Crosslinking: Covalent crosslinking is the early method of preparation for polysaccharide nanoparticles. Chitosan is the early one to be used to prepare nanoparticles among various polysaccharides. Glutaraldehyde has been usually used as a cross-linker to obtain nanoparticles by cross-linking method. Due to the toxicity of glutaraldehyde on cell, viability limits its utility in the field of drug Delivery, but still some chitosan nanoparticles were still crosslinked by glutaradehyde. Some biocompatible cross-linkers, such as natural di- and tri-carboxylic acids, including succinic acid, malic acid, tartaric acid and citric acid, are used for intermolecular cross-linking of chitosan nanoparticles**.** The condensation reaction was performed between the carboxylic groups of natural acids and the pendant amino groups of chitosan, through which biodegradable chitosan nanoparticles were obtained. This method allows the formation of polycations, polyanions, and polyampholyte nanoparticles with an average size in the range of 270–370 nm depending on the pH. The prepared nanoparticles were stable in aqueous media at low pH.[39-41]

Ionic Crosslinking: In this technique, synthesis of nanoparticles is absolutely done in aqueous media. When compared with covalent cross-linking this method shows more advantages like simple procedures and mild preparation. For charged polysaccharides, low MW of polyanions and polycations could act as ionic crosslinkers for polycationic and polyanionic polysaccharides, respectively. Very dilute solutions of the polysaccharide are used to perform the gelation process, in which the chains of the polymer reacting with the gelling agent are forming small clusters. These clusters are stabilized by forming complex with opposite charged electrolytes. The most widely used polyanion crosslinker is tripolyphosphate. The cationic nature of chitosan when it is dissolved in an acidic aqueous solution (pH 4-6) can be exploited to form nanoparticles by adding small amounts of tri-polyphosphate (TPP) included in an alkaline phase (pH 7-9), upon mixing of the two phases through inter and intra molecular linkages are created between TPP phosphates and chitosan amino groups. TPP is non-toxic and has multivalent anions. It can form a gel by ionic interaction between positively charged amino groups of chitosan and negatively charged counter ions of TPP. Recently, water-soluble chitosan derivatives were also be ionically crosslinked to prepare nanoparticles. Compared

with chitosan itself, its derivatives can easily dissolve in neutral aqueous media, avoiding the potential toxicity of acids and hence protecting the bioactivity of loaded biomacromolecules. Some water-soluble chitosan derivatives, like N-(2-hydroxyl) propyl-3-trimethyl ammonium chitosan chloride or N-trimethyl chitosan, have been also ionically crosslinked to prepare nanoparticles. The average size of the obtained systems is between 110 and 350 nm. Not only TPP is used as a cross-linker to obtain chitosan nanoparticles by ionic gelation method.[42-45]

Polyelectrolyte Complexation: Polyelectrolyte complexes (PECs) are formed by the interaction between oppositelycharged polymers by intramolecular electrostatic interactions. Polysaccharide based PEC nanoparticles can be obtained by means of adjusting the MW of component polymers in a certain range. In theory, any polyelectrolyte could interact with polysaccharides to fabricate PEC nanoparticles. However, in practice, these polyelectrolytes are restricted to those water soluble and biocompatible polymers in view of safety purpose. PECs are very interesting materials for different applications. Some of their properties, like swelling or permeability, can be easily modified by external stimuli, such as the pH of the medium. Among the existing polyanionic and polycationic polysaccharides to form PEC nanoparticles, chitosan is widely used because it satisfies the needs of safety and solubility. It can be seen in the literature that much research has been carried out on PECs with chitosan as polycation and different negative polymers, such as negative polysaccharides, poly (acrylic acid) (PAA) or nucleic acids. Positively or negatively charged nanoparticles with a core/shell structure can be obtained according to the nature of the polyelectrolyte used in excess. The hydrophobic core is composed by the complexed segments whereas the excess of component not incorporated in the polyelectrolyte complex is segregated in the outer shell ensuring the colloidal stabilization of the nanoparticles against coagulation and conferring the charge of the nanoparticle surface. This charge could affect to the interaction between cells and nanoparticles. Moreover, molecular weight of the two polyelectrolytes influences the size of the nanoparticle. Apart from chitosan, polyelectrolyte complexes with nanometric size can be formed using alginate, a negatively charged polysaccharide, combined with polylysine, a positively charged peptide.[46,47]

Self-assembly of Hydrophobically Modified Polysaccharides: When hydrophilic polymeric chains are embedded with hydrophobic segments, amphiphilic copolymers are synthesized. Amphiphilic molecules in aqueous solutions orientate themselves to attain a state of minimum free energy and the hydrophobic blocks are detached from the aqueous environment. Consequently, polymeric micelles with core/shell structure are formed. Thanks to their hydrophobic domain, surrounded by a hydrophilic outer shell, they can serve as reservoir for

various hydrophobic drugs. The synthesis and application of polysaccharide based self-aggregate nanoparticles as drug delivery systems have been recently investigated. There are various hydrophobic molecules that can be attached to polysaccharides in order to obtain these kinds of systems, such as poly (ethylene glycol) derivatives, long chain fatty acids, poly (ε-caprolactone), pluronic copolymers, cholesterol and poly (isobutyl cyanoacrylate) (PIBCA). Some long-chain fatty acids like hexanoic acid, linoleic acid, linolenic acid, palmitic acid or stearic acid have been used for modifying polysaccharides and obtaining polymeric micelles. Nanoparticles based on linoleic acid chitosan have been obtained through a Carbodiimide-mediated reaction and their size ranged between 200-600 nm. Dextran has been also employed to obtain nanoparticles by coupling lipoic acid to the structure of dextran and forming nanoparticles in water, whose size varied from 145 to 221 nm. The combination of the hydroxyl groups of dextran with the carboxylic function present on preformed PCL monocarboxylic acid results in the formation of nanoparticles of less than 200 nm.[48-51]

Emulsion- Solvent Evaporation Method

Single emulsion method: This method involves oil-in-water (o/w) emulsification. The o/w emulsion system consists of an organic phase of a volatile solvent with dissolved polymer in an aqueous phase containing a dissolved surfactant. A surfactant is included in the aqueous phase to prevent the organic droplets from coalescing once they are formed. The polymer – drug solution is emulsified (with appropriate stirring and temperature conditions) to yield an o/w emulsion. The emulsion created by using a propeller or magnetic stirrer for mixing the organic and aqueous phases. Once the emulsion is formed, the solvent removed by either evaporation or extraction process to solidify the polymer droplets. One of the disadvantages of the o/w emulsification method is the poor encapsulation efficiency with water soluble drugs.[52]

Double emulsion method: It has been usually applied for drugs not soluble in organic solvents. A solid-in -oil-in-water emulsion (s/o/w) method could be used to encapsulate a drug, provided it's in the form of small size. Smaller crystals will be homogeneously distributed throughout the organic droplets created in emulsion, so hydrophilic drug has been used in this method for encapsulation. The problem with encapsulating hydrophilic drug is loss of drug to the external aqueous phase during the formation of the micro particle. To minimize these problems, the organic droplets should be solidified in to micro particles as quickly as possible following their formation.

Another alternative to encapsulate hydrophilic drugs is to employ the water-in-oil-in-water (w/o/w) emulsion method. An aqueous solution of the drug is added to an organic phase consisting of the polymer and organic solvent with vigorous stirring to form the first w/o

emulsion. The emulsion is then dispersed in another aqueous phase containing more surfactant to form the w/o/w emulsion. A number of hydrophilic drugs like the peptide leuprolide acetate, luteinizing hormone, vaccines, protein/ peptides have been successfully encapsulated by this method.[52]

Phase Separation: The method yields two liquid phases such as polymer containing coacervative phase and polymer containing supernatant phase. The drug which is dispersed/dissolved in the polymer solution is coated by the coacervation. This method includes the following 3 steps: The 1st step consists of formulation of three immiscible chemical phase. The core material is dispersed in polymer solution. The second steps consist of deposition of coating polymer absorbed on the liquid vehicle phase. The final step comprising the rigidity of coating material by thermal cross-linking or desolvation techniques to form microparticles. This method is suitable to encapsulate both water-soluble drugs as well as water-insoluble drugs. However, the coacervation method is mainly used to encapsulate water- soluble drugs like peptides, proteins and vaccines. First non-solvent is added such that the polymer solvent is extracted slowly, allowing sufficient time for the polymer to deposit and coat evenly on the drug particle surface during the coacervation method. The concentration of the polymer used is important, because high concentration would result in rapid phase separation and non uniform coating of the drug particles. To rectify this problem the stirring rate and temperature can be adjusted. Dichloromethane, acetonitrile, ethyl cellulose and toluene have been used as non-solvents in this method. The non-solvents should not dissolve the polymer or the drug, and should be miscible with the polymer solvent, So that the non-solvent affects both aqueous separarion and coacervation process.[52]

Spray Drying: Spray drying is a widely used method in the pharmaceutical industry. The method typically use the drug being dissolved or suspended in a polymer solution (depending upon the polymer used either organic or aqueous solvent). The solution/suspension is then fed in to the spray drying apparatus through the nozzle and polymer/drug solution is mixed with in the air and forced through the small diameter orifice and resultant droplets are very quickly dried by the evaporation of the micro particles.[52]

Interfacial Polymerization Method: Interfacial polymerization is the one in which oil soluble and another one is water soluble drug, are employed and the polymer is formed on the droplet surface to formed micro particles.[52]

Emulsion Extraction Method: The drug and polymer used in forming the micro particles are mixed with a suspension of proteins like agar, gelatin or albumin. One method is alginate plus ca^{+2} to produce the micro particles. Then the mixture is dispersed to produce desired sized

particles. If the drug is insoluble in gas and gas is soluble in liquid. The drug is dissolved in suitable solvents for polymeric solvents to form the micro particles.[52]

Formulation Considerations

Stabilizer: Stabilizer plays an important role in the formulation of microparticles. In the absence of an appropriate stabilizer, the high surface energy of micro-sized particles can induce agglomeration or aggregation of the drug crystals. The type and amount of stabilizer has a pronounced effect on the physical stability and in-vivo behavior of microparticles. In some cases, a mixture of stabilizers is required to make stable microparticles. The drug-to stabilizer ratio in the formulation may vary from 1:20 to 20:1. Stabilizers that have been explored include cellulosics, poloxamers, polysorbates, lecithins. Lecithin is the stabilizer of choice if one intends to develop a parenterally acceptable and autoclavable microparticles.[52]

Organic solvents: Organic solvents may be required in the formulation of microparticles. As these techniques are still in their infancy, elaborate information on formulation considerations is not available. The acceptability of the organic solvents in the pharmaceutical area, their toxicity potential and the ease of their removal from the formulation need to be considered when formulating microparticles using emulsions or microemulsion as templates. The pharmaceutically acceptable and less hazardous water-miscible solvents, such as ethanol and isopropanol, and partially water miscible solvents, such as ethyl acetate, ethyl formate, butyl lactate, triacetin, propylene carbonate and benzyl alcohol, are preferred in the formulation over the conventional hazardous solvents, such as dichloromethane. Additionally, partially water miscible organic solvents can be used for the microemulsion when the microparticles are to be produced using a microemulsion as a template.[52]

Co-surfactants: The choice of co-surfactant is critical when using micro emulsion to formulate micro particles. Since co-surfactants can greatly influence phase behavior, the effect of co-surfactant on uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated.The literature describes the use of bile salts and dipotassium glycerrhizinate as effective surfactants, and various solubilizers such as transcutol, glycofurol, ethanol and isopropanol can be safely used as co-surfactants in the formulation of microemulsions.[52]

Other additives: Microparticles may contain additives such as buffers, salts, polyols, osmogent and cryoprotectant depending on either the route of administration or the properties of the drug moiety.[52]

Characterization of Particulate Drug Delivery Systems

Morphological characterization: Morphology of micro/nanoparticles can be investigated by Transmission Electron Microscope (TEM), Scanning Electron Microscope (SEM), Atomic Force Microscope (AFM) and X-Ray Diffraction (XRD).

Structural characterization: Structural features of nanoparticles are estimated by Fourier transform infrared (FTIR) and Nuclear magnetic resonance (NMR).

Particle characterization: Particle size, size distribution, polydispersity index (PDI) and zeta potential of particles can be measured by Zetasizer, based on the Dynamic Light Scattering (DLS) technique.[51-53]

Applications of Micro and Nanoparticles Based on Natural Polysaccharides: Drug loading in microparticle/nanoparticle system can be done by two methods, i.e. during the preparation of particles (incorporation) and after their formation (incubation). In these systems drug is physically embedded into the matrix or adsorbed through the surface. Various methods of loading have been developed to improve the efficiency of loading, which largely depends upon the method of preparation as well as on the physicochemical properties of the drug. Maximum drug loading can be achieved by incorporating the drug during the formation of particles, but it may get affected by the process parameters such as the preparation method, presence of additives, etc.[51,52]

Various therapeutic agents such as antidiabetic, anti-inflammatory, antibiotics, proteins and enzymes have been incorporated in polysaccharides (chitosan, alginate, gellan, pectin) beads to achieve a controlled release system.

Some important applications are discussed below:

Antidiabetic agents: Mucosal delivery of insulin is one of the most intensively studied subjects, among which achieving oral delivery has been an elusive goal for many investigators. Pan et al. prepared the insulin-loaded chitosan nanoparticles by ionotropic gelation of chitosan with TPP anions. Insulin loaded chitosan nanoparticles have been prepared by mixing insulin with TPP solution and then adding this to chitosan-solution under constant stirring. The ability of chitosan nanoparticles to enhance the intestinal absorption of insulin and the relative pharmacological bioavailability of insulin was investigated by monitoring the plasma glucose level of alloxan-induced diabetic rats after the oral administration of various doses of insulin-loaded chitosan nanoparticles.[53]

Anti-inflammatory drugs: Spherical pellets of poorly soluble drugs (ibuprofen, indometacin, ketoprofen, piroxicam, sodium diclofenac) can be prepared by dispersing the drug in solution of ionic polysaccharides: chitosan, sodium alginate or pectin, and then dropping these

dispersions into solutions containing the respective counterions TPP or $CaCl_2$. The droplets instantaneously forms gelled spheres by ionotropic gelation.[53]

Ocular delivery: Chitosan nanoparticles of dorzolamide hydrochloride (Dorzo) were prepared by the Ionotropic gelation method and their in vitro properties were studied by Papadimitriou et al. Based on wide angle X-Ray diffractometry (WAXD) data, Dorzo was dispersed in the nanoparticles in crystalline form, probably due to the weak interaction developed between Dorzo and chitosan/TPP matrix as FT-IR data indicated. The nanoparticles exhibited mucoadhesive properties which diminished with increasing drug content. In vitro drug release was observed with the Dorzo-loaded chitosan nanoparticles in PBS (pH 7.4) in simulated intestinal fluid. The results suggest that the Dorzo-loaded chitosan nanoparticles could be further evaluated for the controlled ocular delivery of Dorzo.[53]

Antibiotics: Spherical beads containing azathioprine were prepared from deacetylated gellan gum by ionotropic gelation method by Singh and Kim. Divalent cations affect both the aqueous solubility of azathioprine as well as encapsulation efficiency of deacetylated gellan gum. The pH of the ionotropic medium does not seem to affect the solubility of azathioprine, whereas it affects the encapsulation efficiency of gellan gum in a negative and significant manner. The encapsulation efficiency of gellan is much higher in the presence of transition elements (Cu^{2+} and Zn^{2+}) comparatively to alkaline earth metal ions (Ca^{2+}, Mg^{2+} and Ba^{2+}) when used at the same concentration level. Higher concentrations of Ca^{2+} tend to decrease the percentage encapsulation efficiency, which may be related to a decrease in gel strength.[53]

Proteins and enzymes: The bioactivity of β-lactamases upon entrapment in calcium-pectinate beads was evaluated by Bourgeois et al. Nonamidated (NAP) and amidated pectin (AP) beads were prepared according to the ionotropic gelation method using $CaCl_2$ as gelling agent, washed and dried at 37^0C in an oven for 2 h. The encapsulation of the protein is function of the type of pectin used (NAP or AP) but mostly the presence of a large amount of free calcium in beads considerably influences the activity of encapsulated β-lactamases. A drastic elimination of free $CaCl_2$ from Ca-pectinate network reduces moisture content in beads and avoids the risk of protein hydrolysis. Finally, the drying process of beads also modified the activity of encapsulated protein. However, such process and formulation parameters can be easily controlled in order to preserve the activity of encapsulated β-lactamases.[53]

CONCLUSION

Natural materials have advantages over synthetic ones since they are chemically inert, non-toxic, less expensive, biodegradable and widely available. Polysaccharides show variability

and versatility, due to their complex structure. Thus polysaccharides and their derivatives are emerging in the last years as one of the most used biomaterials in the field of novel drug delivery system, especially being chosen by a lot of researchers as carriers to be used in the preparation of particulate drug delivery systems. Recently, much attention has been paid to the modification of natural polysaccharides in order to obtain novel hybrid materials. These modified polysaccharides could be applied in the design of various stimuli-responsive controlled release systems. This contribution is intended to develop other natural sources as well as with modifying existing natural materials for the formulation of novel drug delivery systems, biotechnological applications and other delivery systems. Majority of investigations on natural polymers in novel drug delivery systems plays around polysaccharides. Natural gums can also be modified to have tailor-made products for drug delivery systems and thus can compete with the synthetic excipients available in the market. Though the use of traditional gums has continued, newer gums have been used and some of them with exceptional qualities. There is huge scope for research on newer natural gums and mucilages obtained from plants and could be further exploited in future as a novel natural polymer for development of different drug delivery systems in pharma industry.

REFERENCES

1. Guo J, Skinner GW, Harcum WW. Pharmaceutical application of naturally occurring water soluble polymers. Pharmaceutical Science and Technology Today 1998; 1: 254-261.

2. The joint IPEC-PQG good manufacturing practice guide for pharmaceutical excipients, Europe, 2006.
3. Tommasina C, Matricardi P. Polysaccharide hydrogels for modified release formulations. Journal of Controlled Release 2007; 119: 5-24.
4. Hamman JH, Tarirai C. Functional excipients. Chem Today 2006; 24: 57-62.
5. Shirwaikar A, Prabhu SL. Herbal excipients in novel drug delivery systems. Indian Journal of Pharmaceutical Science 2008; 70: 415-422.
6. Beneke CE, Viljoen AM, Hamman JH. Polymeric plant derived excipients in drug delivery. Molecules 2009; 14: 2602-2620.
7. Stephen AM, Churms SC. Food polysaccharides and their applications. Taylor and Francies, CRC Press, New York, Edited by Stephen AM, Phillips GO and Williams PA, 2006: 1-24.

8. Koleng JJ, McGinity JW, Wiber WR. Handbook of pharmaceutical excipients. Pharmaceutical Press, Edition 6, Edited by Raymond C Rowe, Paul J Sheskey and Marian E Quinn, 2009: 1-3.
9. Kokate CK, Purohit AP, Gokhale SB. A Textbook of Pharmacognosy. Nirali Prakashan, Pune, Edition 22, 2003: 136-139.
10. Kottke KM. Modern Pharmaceutics. Marcel Dekker, New York, 2002: 287-333.
11. Richardson PH, Willmer J, Foster TJ. Dilute solution properties of guar and locust bean gum in sucrose solutions. Food Hydrocolloid 1998; 12: 339-348.
12. Patil S. Crosslinking of Polysaccharides: Methods and Applications. Latest Reviews 2008; 6: 1-18.
13. Ravi K, Anupama S, Mahadevan N. Grafting Modification of The Polysaccharide By The Use Of Microwave Irradiation- A Review, International Journal of Recent Advances in Pharmaceutical Research 2012; 2: 45-53.
14. Chand DK, Lee-Ruff E. Organic Chemistry, Private Practice, UK, 2013, 27.
15. Murali Mohan Babu GV, Himasankar K, Janaki Ram B. Studies on preparation and evaluation of modified form of gum karaya. Indian Journal of Pharmaceutical Science 2002; 64: 244-249.
16. Jani GK, Goswami JM, Prajapati VD. Studies on formulation and evaluation of new superdisintegrants for dispersible tablets. International Journal of Pharmaceutical Excipients 2005; 2: 37-43.
17. Rama Rao N, Rao UM. Hypochlorate modified potato starch: A new potato starch derivative as potential tablet disintegrant. International Journal of Pharmaceutical Excipients 2000; 3: 216-219.
18. Gohel MC, Patel SD, Shah NK. Evaluation of synthesized cross-linked tragacanth as a potential disintegrant. Indian Journal of Pharmaceutical Science 1997; 59: 113-118.
19. Trivedi BM, Patel PM, Patel LD. Crosslinked gum acacia as a disintegrant. Indian Journal of Pharmaceutical Science 1986; 48: 188-190.
20. Baveja JM, Misra AN. Modified guar gum as a tablet disintegrant. Pharmazie 1997; 52: 856-859.
21. Cartilier L, Mateescu MA, Dumoulin Y. Crosslinked amylose as a binder/disintegrant in tablets. U.S. Patent No. 5616343.
22. Cartilier L, Chebli C. Cross-linked cellulose as a tablet excipient. U.S. Patent No. 5989589.

23. Rong-Kun C, Mirwais S, Michael L. Evaluation of the disintegrant properties for an experimental, cross-linked polyalkylammonium polymer. International Journal of Pharmaceutics 1998; 173: 87-92.
24. Fenyvest E, Antal B, Zsadon B, Szejtli J. Cyclodextrin polymer, a new tablet disintegrating agent. Pharmazie 1984; 39: 473-475.
25. Okafor IS, Ofoefule SI, Udeala OK. A comparative study of modified starches in direct compression of a poorly water soluble drug (hydrochlorothiazide). Boll Chim Farm 2001; 140: 36-39.
26. Patel GC, Patel MM. Preliminary evaluation of sesbania seed gum mucilage as gelling agent. International Journal of Pharmaceutical Technology and Research 2009; 1: 840-843.
27. Chaurasia M, Jain NK. Crosslinked guar gum microspheres: A viable approach for improved delivery of anticancer drugs for the treatment of colorectal cancer. AAPS PharmSciTech 2006; 7: E143-E151.
28. Gliko-KabirI, Yagen B, Penhasi A, Rubinstein A. Phosphated crosslinked guar for colon specific drug delivery: Preparation and physicochemical characterization. Journal of Controlled Release 2000; 63: 121-127.
29. Sandolo C, Coviello T, Matricardi P. Characterization of polysaccharide hydrogels for modified drug delivery. European Biophysics Journal 2007; 36: 693-700.
30. Miyazaki S, Suisha F, Kawasaki N. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. Journal of Controlled Release 1998; 56: 75-83.
31. Singh B, Chauhan GS, Kumar S. Synthesis characterization and swelling responses of pH sensitive psyllium and polyacrylamide based hydrogels. Carbohydrate Polymers 2006; 67: 190-200.
32. Gohel MC, Patel MM, Amin AF. Development of modified release Diltiazem HCl tablets using composite index to identify optimal formulation. Drug Development and Industrial Pharmacy 2003; 29: 565-574.
33. Mishra A, Clark JH, Pal S. Modification of Okra mucilage with acrylamide: synthesis, characterization and swelling behavior. Carbohydrate Polymers 2008; 72: 608-615.
34. Singh V, Tiwari A, Tripathi DN. Poly (acrylonitrile) grafted Ipomoea seed-gums: A renewable reservoir to industrial gums. Biomacromolecules 2005; 6: 453-456.
35. Mishra RK, Datt M, Pal K. Preparation and characterization of amidated pectin based hydrogels for drug delivery system. Journal of Material Science: Materials in Medicine 2008; 19: 2275-2280.

36. Domb AJ, Benitolila A, Teomin D. Biopolymers as drug carriers and bioactive macromolecules. Acta Polymerica 1998; 49: 526-533.
37. Hayashi T. Degradable polymers: principles and applications. Progress in Polymer Science 1994; 19: 663-702.
38. Jung T, Kamm W, Breitenbach A, Kaiserling E, Kissel T. Biodegradable nanoparticles for oral delivery of peptides: is there a role for polymers to affect mucosal uptake? European Journal of Pharmaceutics and Biopharmaceutics 2000; 50: 147-160.
39. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. Recent advances on chitosan-based micro and nanoparticles in drug delivery. Journal of Controlled Release 2004; 100:5-28.
40. Zhi J, Wang YJ, Luo GS. Adsorption of diuretic furosemide onto chitosan nanoparticles prepared with water in oil nanoemulsion system. Functional Polymers 2005; 65: 249-257.
41. Liu H, Chen B, Mao ZW, Gao CY. Chitosan nanoparticles for loading of toothpaste actives and adhesion on tooth analogs, Journal of Applied Polymer Science 2007; 106: 4248-4256.
42. Bodnar M, Hartmann JF, Borbely J. Preparation and characterization of chitosan-based nanoparticles. Biomacromolecules 2005; 6: 2521-2527.
43. Vauthier C, Bouchemal K. Methods for the preparation and manufacture of polymeric nanoparticles. Pharmaceutical Research 2009; 26: 1025-1058.
44. Janes KA, Calvo P, Alonso MJ. Polysaccharide colloidal particles as delivery systems for macromolecules. Advaned Drug Delivery Reviews 2001; 47: 83-97.
45. Jain D, Banerjee R. Comparison of ciprofloxacin hydrochloride-loaded protein, lipid, and chitosan nanoparticles for drug delivery, Journal of Biomedical Materials and Research 2008; 86: 105-112.
46. Xu YM, Du YM, Huang RH, Gao LP. Preparation and modification of N-(2-hydroxyl) propyl-3-trimethyl ammonium chitosan chloride nanoparticle as a protein carrier. Biomaterials 2003; 24: 5015-5022.
47. George M, Abraham TE. Polyionic hydrocolloids for the intestinal delivery of protein drugs: alginate and chitosan-a review. Journal of Controlled Release 2006; 114: 1-14.
48. Letchford K, Burt H. A review of the formation and classification of amphiphilic block copolymer nanoparticulate structures: micelles, nanospheres, nanocapsules and polymersomes. European Journal of Pharmaceutics and Biopharmaceutics 2007; 65: 259-269.
49. Chen XG, Lee CM, Park HJ. O/W emulsification for the self aggregation and nanoparticle formation of linoleic acid-modified chitosan in the aqueous system. Journal of Agricultural Food Chemistry 2003; 51: 3135-3139.

50. Li YL, Zhu L, Liu Z, Cheng R, Meng F. Reversibly stabilized multifunctional dextran nanoparticles efficiently deliver doxorubicin into the nuclei of cancer cells. Angew Chem Int Ed Engl 2009; 48: 9914-9918.
51. Lemarchand C, Couvreur P, Besnard M, Costantini D, Gref R. Novel polyester-polysaccharide nanoparticles. Pharmaceutical Research 2003; 20: 1284-1292.
52. Fathima A, Vedha Hari BN, Ramya Devi D. Micro Particulate Drug Delivery System for Anti- Retroviral Drugs: A Review. International Journal of Pharmaceutical and Clinical Research 2011; 4: 11-16.
53. Parepalli Y, Chellappa M, Chavali M. Polysaccharide Nanoparticles Based Drug Delivery-An Overview. International Journal of Nanoscience and Technology 2013; 2: 1-17.