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Polysaccharide-Based Graft Copolymers in Controlled Drug Delivery

Sabyasachi Maiti[1]*, Somdipta Ranjit[1], Biswanath Sa[2]

[1]Department of Pharmaceutics, Gupta College of Technological Sciences, Ashram More, G.T. Road, Asansol-713301, West Bengal, India.

[2]Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700032, India

*Corres.author: sabya245@rediffmail.com

Tel: +919474119931

ABSTRACT: Natural polysaccharides, due to their outstanding merits, have received more and more attention in the field of controlled drug delivery. Graft copolymerization improves the properties of natural polysaccharides to give them a new property. On grafting, the host biopolymer gains some of the desired properties of monomer used for grafting. Polysaccharide-based graft copolymers are of great importance to develop various stimuli-dependent controlled release systems. The present review deals with the techniques employed for the synthesis of grafted polysaccharides and the recent developments in designing novel drug delivery systems.
KEYWORDS: polysaccharides, graft copolymers, controlled drug delivery.

INTRODUCTION

Natural polysaccharides and their derivatives represent a group of polymers widely used in the pharmaceutical and biomedical fields for the controlled release of drugs. The advantages of controlled drug delivery systems are mainly the achievement of an optimum concentration, usually for prolonged times, the enhancement of the activity of labile drugs, due to their protection against hostile environments, and the diminishing of side effects due to the reduction of high initial blood concentrations.[1] The polysaccharides do hold advantages over the synthetic polymers, generally because they are nontoxic, less expensive, biodegradable, and freely available, compared to their synthetic counterparts. Natural gums can also be modified to have tailor-made materials for drug delivery systems.[2] Therefore, in the years to come, there is going to be continued interest in the natural gums and their modifications with the aim to have better materials for drug delivery systems.

In recent years, controlled drug delivery formulations and the polymers used in these systems have become much more sophisticated, with the ability to do more than simply extend the effective release period for a particular drug. For example, intelligent or smart polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released.[3] The stimuli that induce various responses of these polymeric systems include physical (temperature, electric fields, light, pressure, sound,magnetic fields), chemical (pH, ions) or biological/biochemical (biomolecules) ones.[4] In addition, materials have been developed that should lead to targeted delivery systems, in which a particular formulation can be directed to the specific cell, tissue, or site where the drug it contains is to be delivered.[5]

Several polysaccharides such as sodium alginate,[6-10]chitosan,[11-15] guar gum,[16-18] xanthan gum,[19-22]pectin,[23-24] gellan gum[25-26] have been employed either alone or in combination with their native or modified forms to control the drug release from different types of delivery system, but these just had a limited degree of success. In recent years, graft copolymers designed primarily for medical applications have entered the arena of controlled release.

A graft copolymer is a macromolecular chain with one or more species of block connected to the main chain as side chain(s).[27] Thus, it can be described as having the general structure, where the main polymer

backbone, commonly referred to as the trunk polymer, has branches of another polymeric chain emanating from different points along its length.[28] This fascinating technique may be considered as an approach to achieve novel polysaccharide-based materials with improved properties including all the expected usefulness of these biomaterials. This article gives a comprehensive review on the techniques employed for the graft copolymerization of polysaccharides and the application of polysaccharide-based graft copolymers for controlled dug delivery. The present article includes majority of the relevant research works published in this field.

GRAFT COPOLYMERIZATION OF POLYSACCHARIDES

Grafting of synthetic polymer is a convenient method to add new properties to a natural polymer with minimum loss of the initial properties of the substrate. Due to their structural diversity and water solubility, natural polysaccharides could be interesting starting materials for the synthesis of graft copolymers. Most of the copolymers are prepared through graft polymerization of vinyl or acryl monomers onto the biopolymer backbone.[29] The chemistry of grafting vinyl/acryl monomers is quite different from that of grafting non-vinyl/acryl monomers. Non-vinyl/acryl graft copolymerization is possible via polycondensation; however this has not been widely used for preparing graft copolymers of polysaccharides usually due to susceptibility of the polysaccharide backbone to high temperature and harsh conditions of the typical polycondensation reactions.[28]

Vinylic/acrylic graft copolymerization

Grafting of polyvinylic and polyacrylic synthetic materials onto the polysaccharides are mainly achieved by radical polymerization. Graft copolymers are prepared by first generating free radicals on the biopolymer backbone and then allowing these radicals to serve as macroinitiators for the vinyl or acrylic monomer. The chemical and radiation initiating systems are employed to graft copolymerize these monomers onto polysaccharides.

Chemical initiating system

Cerium in its tetravalent state is a versatile oxidizing agent used most frequently in the graft copolymerization of vinyl monomers onto cellulose and starch. It forms a redox pair with the anhydroglucose units of the polysaccharide to yield the macroradicals under slightly acidic conditions.[27,30]

Acrylic and methacrylic acids were graft polymerized onto chitosan by Shantha et al.[31] and the grafting was initiated by ceric ion. Kim and his coworkers[32] reported the ceric-induced graft copolymerization of N-isopropylacrylamide onto chitosan at 25°C to prevent a high level of homopolymer formation. A grafting yield of 48% was obtained at 0.5 M of monomer concentration, 0.002 M of ceric ammonium nitrate initiator and 2 h of the reaction time. They found a decreased percent of grafting when the initiator concentration was higher than 0.002 M. Vinyl acetate monomer was graft copolymerized onto chitosan using the same initiating system at 60°C. With an addition of 0.5-7.5g of chitosan based on 50g vinyl acetate, the monomer conversion was found to be 70-80% after 2 h of reaction.[33]

Castellano and his coworkers[34] performed graft copolymerization of methyl methacrylate on various natural substrates such as carboxymethyl cellulose, hydroxypropyl cellulose, carboxymethyl starch and hydroxypropyl starch in aqueous medium by the same radical system. The graft copolymerization of sodium alginate with polyacrylamide[35] and ethyl acrylate[36] using ceric ammonium nitrate as an initiator has also been reported. Moreover, ceric ion induced solution polymerization technique has been employed for the synthesis of carboxymethyl cellulose-g-polyacrylamide copolymer.[37]

In another study by Zohuriaan-Mehr and Pourjavadi,[38] various natural and modified polysaccharides (*i.e.* arabic gum, tragacanth gum, xanthan gum, sodium alginate, chitosan, sodium carboxymethyl cellulose, hydroxyethyl cellulose, methyl cellulose) were modified using ceric-initiated graft polymerization of acrylonitrile under inert atmosphere. They pointed out that polyacrylonitrile-grafted polysaccharides were thermally more stable than the corresponding non-grafted substrates. Potassium persulphate (KPS)-initiated graft copolymerization of acrylonitrile and methylmethacrylate onto chitosan has been reported.[39] A maximum graft yield of 249% was obtained with 0.12 M of acrylonitrile and 0.00074 M of KPS at 65°C for 2 h for 1% chitosan solution. For chitosan-*g*-polymethylmethacrylate, 0.14 M of methylmethacrylate at 65°C gave a maximum grafting of 276%. No residual monomers were found by HPLC in the graft copolymers. Later, grafting of fatty acid on the starch was done by Simi and Abraham[40] using potassium persulphate as catalyst. Same chemical system was used for the initiation of polyacrylamide grafting with cashew gum.[41] In a subsequent study by Kulkarni and Sa,[42] a pH-sensitive graft copolymer of polyacrylamide and sodium alginate was synthesized by free radical polymerization using ammonium persulphate (APS) under a nitrogen atmosphere. The synthetic pathway of pH-sensitive polyacrylamide-g-sodium alginate co-polymer has been represented in Fig. 1.

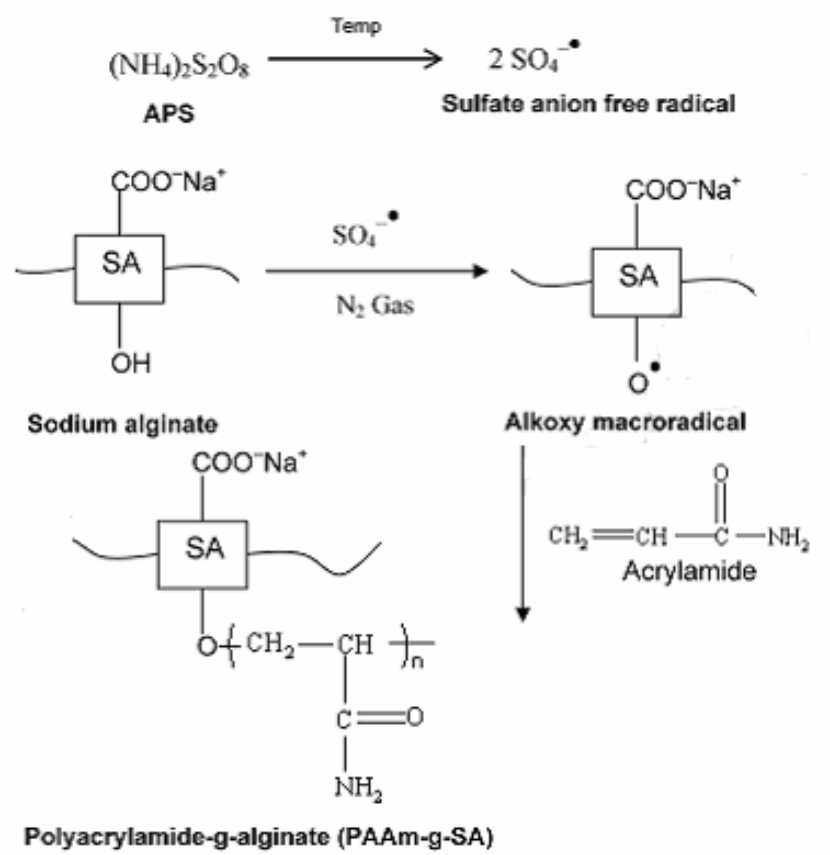

Fig. 1: Proposed mechanistic pathway for the synthesis of polyacrylamide-g-sodium alginate copolymer

In addition to the above chemical systems, various redox initiating systems have been tried for the synthesis of polysaccharide-based graft copolymers. A study by Behari et al.[43] revealed that the graft copolymerization of acrylamide onto xanthan gum could be initiated by the Fe^{2+}/BrO_3^- redox system in aqueous medium under a nitrogen atmosphere. They observed that grafting takes place efficiently when acrylamide concentration and temperature were 4.0×10^{-3} moldm^{-3} and 35°C, respectively.

Graft copolymerization of guar gum with N-vinyl formamide[44] and acrylic acid[45] has been established using potassium bromate/ascorbic acid and peroxydiphosphate (PDP)-silver(I) redox pairs, respectively. Mahmoud[46] utilized PDP/Fe^{2+} redox initiation system for the polymerization of acrylic acid with native locust bean gum. More recently, graft copolymers of sodium alginate with itaconic acid has been prepared in aqueous solution using benzoyl peroxide (BPO) as the initiator. They identified the optimum grafting conditions for maximum graft yield with a reaction time of 1 h, reaction temperature of 85 °C, itaconic acid concentration of 1.38 M, BPO concentration of 1.82×10^{-2} M and percentage of alginate 1.5 g/dl.[47]

Radiation initiating system

Employing high-energy γ-radiation is an efficient basic method for initiating radical graft polymerization onto polysaccharides. Although the radiation-based grafting is cleaner and more efficient in this regard than chemical initiation methods, they are harder to handle under technical conditions. Hence, few research reports are available for the synthesis of graft copolymers using radiation initiation system. Singh and Ray[48] graft copolymerized 2-hydroxyethylmethacrylate onto chitosan films using ^{60}Co γ-radiation to improve their blood compatibility. They found that the level of grafting could be controlled by the grafting conditions, namely solvent composition, monomer concentration, dose rate, and total dose. They achieved a maximum graft yield of 108% under the conditions of solvent water-methanol volume ratio 1:1, monomer concentration 20 vol%, dose rate 90 rad/s and total dose 0.216 Mrad.

To graft *N*-isopropylacrylamide onto alginate, varying dosages of ^{60}Co γ-radiation were irradiated onto alginate films in deionized water and methanol media. At 50 kGy of irradiation dose, *N*-isopropylacrylamide monomers were grafted on the alginate with graft ratio of 18.7%.[49] Using microwave irradiation grafting of polyacrylonitrile onto guar gum in water was done without using any radical initiator or catalyst within a very short reaction time. The extent of grafting was adjusted by controlling the reaction conditions and a

maximum percentage grafting of about 188% was obtained under optimum conditions in 1.66min.[50] Xyloglucan, a water soluble polysaccharide was graft copolymerized with acrylonitrile under the influence of ceric ion under nitrogen atmosphere and microwave irradiation.[51]

APPLICATIONS OF GRAFTED POLYSACCHARIDES IN DRUG DELIVERY

In recent years, a wide variety of grafted polysaccharides have been used to fabricate different types of drug delivery system. Among these, colon targeted drug delivery systems have attracted many researchers due to the distinct advantages they present such as near neutral pH, longer transit time and reduced enzymatic activity. Moreover, in recent studies, colon specific drug delivery systems are gaining importance for use in the treatment of local pathologies of the colon and also for the systemic delivery of protein and peptide drugs. A hydrogel system composed of konjac glucomannan, copolymerized with acrylic acid and cross-linked by *N*, *N*-methylene-bis-(acrylamide) was developed by Chen and his coworkers[52]. *In vitro* release of 5-aminosalicylic acid from the pH-sensitive hydrogel was studied in pH 7.4 phosphate buffer containing Cellulase E0240. The drug release reached 95.19% after 36h and the drug release has been said to be controlled by the swelling and degradation of the hydrogels.

Later, Mundargi et al.[53] prepared metronidazole tablets using various polysaccharides or indigenously developed graft copolymer of methacrylic acid with guar gum for colon targeted drug delivery. Drug release studies were performed in simulated gastric fluid for 2h followed by simulated intestinal fluid at pH 7.4. Uncoated tablets containing xanthan gum or mixture of xanthan gum with methacrylic acid-g-guar gum showed 30-40% drug release during the initial 4-5h, whereas for tablets containing guar gum with the graft copolymer, it was 70%. After enteric coating with Eudragit-L 100, the release of metronidazole was drastically reduced to 18-24%. Since the cost of synthesizing a new polymeric substance and testing for its safety is enormous, polymeric physical blends are frequently used as excipients in controlled drug delivery systems due to their versatility. It was observed that physical blends of starch graft copolymers offer good controlled release of drugs, as well as of proteins and present suitable properties for use as hydrophilic matrices for colon-specific drug delivery.[54]Polyacrylamide-*g*-guar gum (pAAm-g-GG) was prepared by taking three different ratios of guar gum to acrylamide (1:2, 1:3.5 and 1:5) and were hydrolyzed to induce carboxylic functional groups. Diltiazem tablets were prepared with these graft copolymers and hydrolyzed copolymers. *In vitro* drug release was carried out in simulated gastric and intestinal conditions. The drug release continued up to 8 and 12h, respectively, for graft copolymers and hydrolyzed graft copolymers. Drug release was found to be dissolution-controlled in case of unhydrolyzed copolymer. With hydrolyzed copolymers, drug release was swelling-controlled initially in 0.1 N HCl solution, but at later stage, it became dissolution-controlled in pH 7.4. Hydrolyzed graft copolymers were pH sensitive and can be used for intestinal drug delivery.[55]

In a study, polyacrylamide grafted pectin was cross-linked with varying amount of glutaraldehyde and it was noticed that the cross-linked product showed better film forming property and gelling property than pectin. The pH dependent release of salicylic acid was observed due to pH dependent swelling of the cross-linked hydrogel.[56] Atenolol-loaded polyacrylamide-g-xanthan gum films were fabricated by solution casting method for transdermal application. All the thin films were slightly opaque, smooth, flexible, and permeable to water vapor, indicating their permeability characteristics suitable for transdermal studies. The films were non-irritant to the mice skin and released the drug in phosphate buffer saline solution in a controlled manner.[57]An electroresponsive transdermal hydrogel films using polyacrylamide-g-xanthan gum and poly (vinyl alcohol) was developed for the on-demand release of ketoprofen.[58] A pulsated pattern of drug release was observed as the electric stimulus was switched on and off. The skin histopathology study demonstrated that, after the application of an electrical stimulus, there were changes in the structure of stratum corneum and cell structure. In another study, they developed an electrically responsive hydrolyzed polyacrylamide-*grafted*-sodium alginate-based membrane-controlled transdermal drug delivery system and observed the similar characteristics.[59]

Kulkarni and Sa fabricated different pH-sensitive polysaccharide-based hydrogel bead systems for controlled drug delivery. They prepared ketoprofen-loaded polyacrylamide-*g*-alginate beads by ionotropic gelation/covalent cross-linking.[42] The copolymer exhibited considerable pH-sensitive behavior and the drug release in pH 1.2 solution was much slower as compared to that in pH 7.4 buffer solution. This was due to higher swelling of the beads in alkaline pH condition. The glutaraldehyde treated graft copolymer beads demonstrated satisfactory *in vitro* drug release of 12% and 74% after 2h and 8h of dissolution. Stomach histopathology of albino rats indicated that the beads were able to retard the release of the drug in the stomach, and gastric side-effects like ulceration, hemorrhage and erosion of gastric mucosa were diminished when the drug was entrapped into these hydrogel beads. Following the same procedure, they

developed carboxymethylcellulose-(polyacrylamide-*g*-sodium alginate) interpenetrating network hydrogel beads loaded with ketoprofen.[60] The erosion was observed with the beads containing only ionic crosslinks whereas it was negligible with the beads containing both ionic and covalent crosslinks. The swelling of the beads and drug release was significantly increased when pH of the medium was changed from acidic to alkaline. Drug release followed case II transport mechanism in acidic medium whereas anomalous/non-Fickian transport mechanism was observed in alkaline dissolution medium. Further, they developed ketoprofen-loaded pH-sensitive interpenetrating network hydrogel beads of polyacrylamide-*g*-xanthan and sodium carboxymethyl cellulose and evaluated the pH sensitivity and drug release characteristics.[61] Scanning electron microscopy revealed that the interpenetrating polymer network beads possess porous matrix structure in alkaline pH whereas nonporous matrix structure was observed in acidic pH. As pH of the medium was changed from 1.2 to 7.4, a considerable increase in swelling and drug release was observed for the beads. They postulated that at higher pH values, the carboxyl functional groups of hydrogels undergo ionization and the osmotic pressure inside the beads increases resulting in higher swelling. The drug release mechanisms were the same to that observed in polyacrylamide-*g*-alginate beads in the respective dissolution medium. In a subsequent study, they formulated pH-sensitive ketoprofen-loaded hydrolyzed polyacrylamide-*g*-xanthan beads by ionotropic gelation with trivalent aluminium ions.[62] Release of drug from the copolymeric beads was much lesser than that from pristine xanthan beads. While pristine xanthan gum beads discharged the drug completely in 5h, a maximum of 92.6% drug release was recorded from the copolymeric beads at the end of 8h. Pharmacodynamic activity and stomach histopathology of albino rats indicated that the beads were able to retard the drug release in stomach, and gastric side effects such as ulceration, hemorrhage and erosion of gastric mucosa were diminished when the drug was entrapped into polyacrylamide-*g*-xanthan gum beads. Several novel functionalized graft copolymer nanoparticles consisting of chitosan and the monomer methyl methacrylate, *N*-dimethylaminoethyl methacrylate hydrochloride, and *N*-trimethylaminoethyl methacrylate chloride, have been devised. The protein-loaded nanoparticles (150-280 nm) showed a maximal encapsulation efficiency of 100%. *In vitro* release study showed that these nanoparticles could provide sustained drug release for more than 24h.[63] Nonirritant bioadhesive drug release systems based on starch-acrylic acid graft copolymers were developed for buccal application. The release rate of theophylline depended on the ratio of starch to acrylic acid and on the presence of cations in the graft copolymers, but was practically not affected by the pH (between pH 3 and 7) of the dissolution medium nor by the type of starch used (corn, rice, or potato). In general, the release behavior of the graft copolymers was found to be non-Fickian suggesting that the release was controlled by a combination of tablet erosion and the diffusion of the drug from the swollen matrix. Incorporation of divalent cations into the graft copolymers led to a significant decrease in swelling erosion of the tablets as well as a substantial retardation of drug release. Highest work of adhesion was obtained with graft copolymers containing calcium ions as well as longer time of adhesion on dog's gingival.[64] Some researchers investigated the flocculation behaviors of graft copolymers. The flocculation characteristics of polyacrylamide-*g*-alginate copolymer were evaluated in 0.25 wt% kaolin and 10 wt% iron ore suspensions. The flocculation characteristics of these grafted polymers were also compared with various commercially available polymeric flocculants. Among the grafted alginates, it was observed that, the graft copolymers containing longer polyacrylamide chains were the most efficient flocculating agent and it was found that the graft copolymer showed better performance than the commercial flocculants.[65-66]Six graft copolymers of hydroxypropyl guar gum were synthesized with variation in the number and length of grafted polyacrylamide chains. Flocculation jar tests were carried out in 0.25 wt % kaolin, iron ore, and silica suspensions. Among the series of graft copolymers, the one with fewest but longest polyacrylamide chains showed the better performance.[67] It has been reported that a novel superabsorbent hydrogel of hydrolyzed alginate-*g*-polymethacrylamide could exhibit high swelling capacity at basic pH and reversible pH-responsiveness property, and therefore this hydrogel may be considered as an excellent candidate to design controlled drug delivery systems.[68] Research efforts have also been directed toward the development of semi-interpenetrating polymer network microspheres of grafted polysaccharides.

The microspheres of acrylamide grafted on dextran (AAm-*g*-Dex) and chitosan were prepared by emulsion-crosslinking method using glutaraldehyde as a crosslinker. Acyclovir, an antiviral drug with limited water solubility, was successfully encapsulated into the microspheres by varying the ratio of AAm-*g*-Dex and chitosan, percentage drug loading and amount of glutaraldehyde. Encapsulation of acyclovir in the microspheres (265-388 μm) was up to 79.6%. *In vitro* release studies indicated the dependence of drug release rates on both the extent of crosslinking and amount of AAm-*g*-Dex used in preparing

microspheres; the slow release was extended up to 12h.[69] The synthesis of capecitabine-loaded semi-interpenetrating network hydrogel microspheres of chitosan-poly(ethylene oxide-g-acrylamide) by emulsion crosslinking using glutaraldehyde has also been described.[70] Scanning electron microscopy confirmed spherical shapes and smooth surface morphology of the microspheres. Capecitabine, an anticancer drug, was successfully encapsulated into the microspheres (82-168µm) and the encapsulation efficiency varied from 79 to 87%. *In vitro* release studies were performed in simulated gastric fluid (pH 1.2) for the initial 2h, followed by simulated intestinal fluid (pH 7.4) until complete dissolution. The release of capecitabine was continued up to 10h. Poly(vinyl alcohol)-gellan gum interpenetrating network microspheres were prepared by the emulsion cross-linking method.[71] Carvedilol, an antihypertensive drug, was successfully loaded into these microspheres. Formation of interpenetrating network and the chemical stability of carvedilol after preparing the microspheres was confirmed by Fourier transform infrared spectroscopy. Scanning electron microscopy confirmed the spherical nature and smooth surface morphology of the microspheres produced. Carvedilol was successfully encapsulated up to 87% in the microspheres (230-346µm). The drug release of carvedilol was continued up to 12h. Soppimath et al[72] also reported the preparation of nifedipine-loaded spherical, poly(vinyl alcohol)-guar gum interpenetrating network microspheres (300µm) by cross-linking with glutaraldehyde.

CONCLUSION

Recently, much attention has been paid to the graft copolymerization of natural polysaccharides in order to obtain novel tailored hybrid materials. After a thorough literature survey, it was concluded that polysaccharide-based graft copolymers are mainly synthesized by free radical polymerization under the influence of different chemical initiating systems. These graft copolymers could be applied in the design of various stimuli-responsive controlled release systems such as transdermal films, buccal tablets, matrix tablets, microsphers/hydrogel bead system and nanoparticulate system. This contribution is intended to stimulate further research on polysaccharide-based graft copolymers in order to use these precious renewable biomaterials instead of the fossil-based materials used in bioscience and technology.

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