Review Article

MODIFIED POLYSACCHARIDE AS DRUG DELIVERY: REVIEW

Nawaz Mahammed, Rohan D. Deshpande*, D. V. Gowda,
JSS College of pharmacy, SS Nagar, Mysore- 570015, India.
***Corresponding author's E-mail:** rohan11in@gmail.com

Accepted on: 21-07-2011; **Finalized on:** 20-10-2011.

ABSTRACT

Natural polysaccharides, due to their outstanding merits, have received more attention in the field of controlled drug delivery. Modification of natural polysaccharides gives them a new or improved property. Modified Polysaccharide is of great importance to develop various controlled release systems. The present review deals with the techniques employed for the modification of polysaccharides and the recent developments in designing novel drug delivery systems.

Keywords: Polysaccharide, Modification, Controlled Release.

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]. Several polysaccharides such as sodium alginate, chitosan, guar gum, xanthan gum, pectin, gellan gum 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. Modifications which are done to the polysaccharides are:

CHEMICAL MODIFICATION

The chemical modification of polysaccharides is the most important route to modify the properties of the naturally occurring biopolymers and to use this renewable resource in the context of sustainable development. In general, all chemical reactions known from low molecular organic chemistry may be carried out. However, up to now only a limited number of products is produced commercially. Recent research and development is focused on the improvement of the known products and synthesis paths as well as on new derivatives and alternative synthesis concepts[4]. The various chemical modifications useful in control drug delivery:

1) Carboxymethylation
2) Grafting

1. Carboxymethylation

Carboxymethylation of polysaccharides is a widely studied conversion since it is simple and leads to products with a variety of promising properties. In general, the polysaccharide is activated with aqueous alkali hydroxide mostly sodium hydroxide and converted with monochloroacetic acid or its sodium salt according to the Williamson ether synthesis yielding the carboxymethyl (CM) polysaccharide derivative. Not only cellulose and starch but also various polysaccharides form different sources are applied as starting materials.

Sung-Ching Chen *et al*[5] Developed pH-sensitive hydrogel system composed of a water-soluble chitosan derivative (*N*,*O*-carboxymethyl chitosan, NOCC) and alginate blended with genipin for controlling protein drug delivery. Swelling characteristics of these hydrogels as a function of pH values were investigated. Additionally, release profiles of a model protein drug (bovine serum albumin, BSA) from test hydrogels were studied in simulated gastric and intestinal media. Their results clearly suggested that the genipin-cross-linked NOCC/alginate hydrogel could be a suitable polymeric carrier for site-specific protein drug delivery in the intestine.

Jian Du *et al*[6] Prepared Nanoparticals by cross-linking Carboxymethyl Konjac Glucomannan and Chitosan (CKGM-CS). Their study showed that the nanoparticulate

system driven by complex formation has potential as an advanced drug-delivery system for water-soluble drugs.

Gurpreet Kaur *et al*[7] evaluated the possible use of inter polymer complexed (IPC) films of chitosan (CH) and carboxymethyl tamarind kernel powder (CMTKP) for colon release of budesonide. They found that the results strongly indicate versatility of CH-CMTKP IPC films to deliver budesonide in the colon.

Federica Corrente *et al*[8] synthesized carboxymethyl derivative of scleroglucan (Scl-CM) with a 65±5% carboxylic group degree of derivatization (DD). By an appropriate combination of the hydrogels prepared using different amounts of salt, it was possible to obtain a system able to release diclofenac with zero-order kinetics. Their results suggest a potential of the new hydrogels for the development of modified delivery systems in topical formulations.

2. 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[10]. 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.[9]

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 acroinitiators 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.[11]

Shantha *et al* graft polymerized Acrylic and methacrylic acids onto chitosan and the grafting was initiated by ceric ion. [12]

Kim *et al*[13] 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.

Castellano *et al*[14] 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[15] and ethyl acrylate[16] 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-gpolyacrylamide copolymer[17].

Zohuriaan-Mehr *et al*[18] modified various natural and modified polysaccharides (*i.e.* arabic gum, tragacanth gum, xanthan gum, sodium alginate, chitosan, sodium carboxymethyl cellulose, hydroxyethyl cellulose, methyl cellulose) using ceric-initiated graft polymerization of acrylonitrile under inert atmosphere. They pointed out that polyacrylonitrile-grafted polysaccharides were thermally more stable than the corresponding nongrafted substrates. Potassium persulphate (KPS)-initiated graft copolymerization of acrylonitrile and methylmethacrylate onto chitosan has been reported[19]. 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.

Simi *et al*[20] grafted fatty acid on the starch using potassium persulphate as catalyst. Same chemical system was used for the initiation of polyacrylamide grafting with cashew gum[21].

Kulkarni *et al*[22] developed 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-gsodium alginate co-polymer has been represented in Fig. 1.

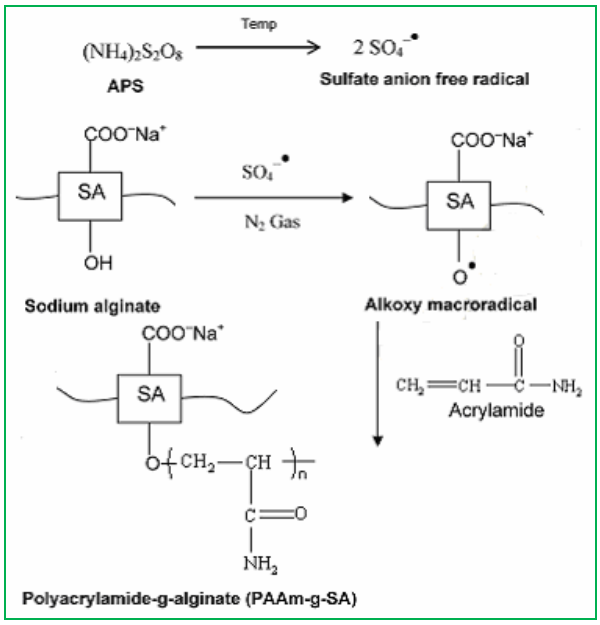

Figure 1: Proposed mechanistic pathway for the synthesis of polyacrylamide-g-sodium alginate Copolymer.

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*[23] revealed that the graft copolymerization of acrylamide onto xanthan gum could be initiated by the Fe2+/BrO3− 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[24] and acrylic acid[25] has been established using potassium bromate/ascorbic acid and peroxydiphosphate (PDP)-silver(I) redox pairs, respectively.

Mahmoud *et al*[26] utilized PDP/Fe2+ 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[27].

Chen L-G *et al*[28] prepared hydrogel system composed of konjac glucomannan, copolymerized with acrylic acid and cross-linked by *N*, *N*-methylene-bis-(acrylamide) . *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.

Mundargi *et al*[29] 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.

Silva I *et al*[30] 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.

Toti U.S. *et al*[31] prepared Diltiazem tablets with Polyacrylamide-*g*-guar gum (pAAm-g-GG) and hydrolyzed 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.

Sutar P.B *et al*[32] crosslinked polyacrylamide grafted pectin 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 crosslinked hydrogel.

Mundargi R.C *et al*[33] fabricated Atenolol-loaded polyacrylamide-g-xanthan gum films 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.

Kulkarni R.V and Sa B[34] developed electroresponsive transdermal hydrogel films using polyacrylamide-g-xanthan gum and poly (vinyl alcohol) for the ondemand release of ketoprofen.

Setty C.M *et al*[35] developed an electrically responsive hydrolyzed polyacrylamide-*grafted*-sodium alginate-based membrane-controlled transdermal drug delivery system and observed the similar characteristics.

Kulkarni R.V. and Sa B[36] developed carboxy methylcellulose -(polyacrylamide-*g*sodium alginate) interpenetrating network hydrogel beads loaded with ketoprofen. The erosion was observed with the beads containing only ionic crosslinks whereas it was negligible with the beads containing both ionic and covalent crosslinks.

Kulkarni R.V. and Sa B[37] 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. 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.

Kulkarni R.V. and Sa B[38] they formulated pH-sensitive ketoprofen-loaded hydrolyzed polyacrylamide-*g*xanthan beads by ionotropic gelation with trivalent aluminium ions. Release of drug from the copolymeric beads was much lesser than that from pristine xanthan beads.

Qian F *et al*[39] prepared 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.

Geresh S *et al*[40] investigated that highest work of adhesion was obtained with graft copolymers containing calcium ions as well as longer time of adhesion on dog's gingival.

Tripathy T *et al*[41-42] investigated 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.

Nayak B.R *et al*[43] synthesizedsSix graft copolymers of hydroxypropyl guar gum 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.

Pourjavadi A *et al*[44] reported that a novel superabsorbent hydrogel of hydrolyzed alginate-*g*-polymethacrylamide could exhibit high swelling capacity at basic pH and reversible pHresponsiveness property, and therefore this hydrogel may be considered as an excellent candidate to design controlled drug delivery systems.

Rokhade A.P *et al*[45] prepared microspheres of acrylamide grafted on dextran (AAm-*g*-Dex) and chitosan 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.

Agnihotri S.A[46-47] synthesized of capecitabine-loaded semiinterpenetrating network hydrogel microspheres of chitosan-poly(ethylene oxide-g-acrylamide) by emulsion crosslinking using glutaraldehyde. 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 crosslinking method.

Soppimath *et al*[48] also reported the preparation of nifedipine-loaded spherical, poly(vinyl alcohol)-guar gum interpenetrating network microspheres (300µm) by cross-linking with glutaraldehyde.

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 *et al*[49] graft copolymerized 2- hydroxyl ethylmethacrylate onto chitosan films using 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 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%.[50] 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[51]. Xyloglucan, a water soluble polysaccharide was graft copolymerized with acrylonitrile under the influence of ceric ion under nitrogen atmosphere and microwave irradiation[52].

CONCLUSION

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 such as transdermal films, buccal tablets, matrix tablets, microsphers/hydrogel bead system and nanoparticulate system. This contribution is intended to stimulate further research on modified polysaccharide in order to use these precious renewable biomaterials instead of the fossil-based materials used in bioscience and technology.

REFERENCES

1. Parmar N.S. and Shivprakash., Biopharmaceutical and pharmacokinetic considerations. In: Controlled and novel drug delivery, Jain N.K (Ed)., 1st ed. CBS publishers and Distributors, New Delhi, 1997, pp. 1-2.
2. Bhardwaj T.R., Kanwar M., Lal R., Gupta A., Natural gums and modified natural gums as sustained-release carriers. Drug Dev. Ind. Pharm., 26, 2000, 1025-1038.
3. Soppimath K.S., Aminabhavi T.M., Dave A.M., Kumbar S.G., Rudzinski W.E.,Timulusresponsive "smart" hydrogels as novel drug delivery systems. Drug Dev. Ind. Pharm., 28, 2002, 957-974.
4. Heinze, T. and T. Liebert, Progr. Polym. Sci. 26: 2001, 1689.
5. Sung-Ching Chen , Yung-Chih Wu , Fwu-Long Mi , Yu-Hsin Lin , Lin-Chien Yu and Hsing-Wen A novel pH-sensitive hydrogel composed of *N*,*O*-carboxymethyl chitosan and alginate cross-linked by genipin for protein drug delivery. J Cont. Rel, 96, 2004, 285-300.
6. Jian Du, Rui Sun, Sheng Zhang, Thirumala Govender, Li-Fang Zhang, Cheng-Dong Xiong, Yu-Xing Peng Novel Polyelectrolyte Carboxymethyl Konjac Glucomannan–Chitosan Nanoparticles for Drug Delivery Macromolecular Rapid Communications, 25, 2004, 954-958.
7. Gurpreet Kaur, Subheet Jain, Ashok K. Tiwari, Chitosan-Carboxymethyl Tamarind Kernel Powder Interpolymer Complexation: Investigations for Colon Drug Delivery, Sci Pharm. 78: 2010; 57–78.
8. Federica Corrente , Pietro Matricardi , Patrizia Paolicelli , Beatrice Tita , Federica Vitali and Maria Antonietta Casadei, Physical Carboxy methylscleroglucan/Calcium Ion Hydrogels as Modified Drug Delivery Systems in Topical Formulations, Molecules 14, 2009, 2684-2698.
9. Mahdavinia G.R., Zohuriaan-Mehr M.J.,Pourjavadi A., Modified chitosan. III.Superabsorbency, salt- and pH-sensitivity of smartampholytic hydrogels from chitosangpolyacrylonitrile.Polym. Adv. Technol., 15, 2004, 173-180.
10. Fernandez M.J., Casinos I., Guzman G.M., On thegraft copolymerization: Effect of the way of addition of reactants in the graft copolymerization of a vinyl acetate methyl acrylate mixture onto cellulose. J. Polym. Sci. Part A: Polym. Chem., 28, 1990, 2275-2292.
11. Shantha K.L., Bala U., Rao K.P., Tailor-made chitosans for drug delivery. Euro. Polym. J**.,** 31, 1995, 377-382.
12. Kim S.Y., Cho S.M., Lee Y.M., Kim S.J., Thermoand pH-responsive behaviors of graft copolymer and blend based on chitosan and Nisopropyl acrylamide. J. Appl. Polym. Sci., 78, 2000, 1381-1391.
13. Don T-M., King C-F., Chiu W-Y., Synthesis and properties of chitosan-modified poly (vinylacetate). J. Appl. Polym. Sci., 86, 2002, 3075-3063.
14. Castellano I., Gurruchaga M., Goñi I., The influence of drying method on the physical properties of some graft copolymers for drug delivery systems. Carbohydr. Polym., 34, 1997, 83-89.
15. Tripathy T., Pandey S.R., Karmakar N.C., Bhagat R.P., Singh R.P., Novel flocculating agent based on sodium alginate and acrylamide. Euro. Polym.J., 35, 1999, 2057-2072.
16. Shah S.B., Patel C.P., Trivedi H.C., Ceric-induced grafting of ethyl-acrylate onto sodium alginate. Die. Angewandte. Makromolekulare. Chemie., 214, 2003, 75-89.
17. Biswal D.R. and Singh R.P., Characterisation of carboxymethyl cellulose and polyacrylamide graft copolymer. Carbohydr. Polym., 57, 2004, 379-387.
18. Zohuriaan-Mehr M.J. and Pourjavadi A., New polysaccharide-g-polyacrylonitrile copolymers: synthesis and thermal characterization. Polym. Adv. Technol., 14, 2003, 508-516.
19. Prashanth K.V.H., Tharanathan R.N., Studies on graft copolymerization of chitosan with synthetic monomers. Carbohydr. Polym., 54, 2003, 343-353.
20. Simi C.K. and Abraham T.E., Hydrophobic grafted and cross-linked starch nanoparticles for drug delivery. Bioprocess Biosys. Engg., 30, 2007, 173-180.
21. Silva D.A., de Paula R.C.M., Feitosa J.P.A.,Graft copolymerization of acrylamide onto cashew gum. Euro. Polym. J., 43, 2007, 2620-2629.
22. Kulkarni R.V. and Sa B., Polyacrylamide-graftedalginate-based pH-sensitive hydrogel beads for delivery of ketoprofen to the intestine: in vitro and in vivo evaluation. J. Biomater. Sci., Polymer Edn., 20, 2009, 235-251.
23. Behari K., Pandey P.K., Kumar R.,Taunk K., Graft copolymerization of acrylamide onto xanthan gum.Carbohydr. Polym., 46, 2001, 185-189.
24. Kunj B., Java B., Arti S., Mishra D.K., Studies on graft copolymerization of N-vinyl formamide onto Guar gum initiated by bromate/ascorbic acid redox pair. Indian J. Chem. Tech., 12, 2005, 664-670.
25. Taunk K. and BehariK., Graft copolymerization of acrylic acid onto guar gum. J. Appl. Polym. Sci., 77, 2000, 39-44.
26. Mahmoud R.I., Preparation and characterization of poly acrylic acid-locust bean gum. J. Reinforced Plastics and Composites., 28, 2009, 2413-2427.
27. Işıklan N., Kurşun F., İnal M., Graft copolymerization of itaconic acid onto sodium alginate using benzoyl peroxide Carbohydr. Polym., 79, 2010, 665-672.
28. Chen L-G., Liu Z-L., Zhuo R-X., Synthesis and properties of degradable hydrogels of konjac glucomannan grafted acrylic acid for colonspecific drug delivery. Polymer., 46, 2005, 6274-6281.
29. Mundargi R.C., Patil S.A., Agnihotri S.A., Aminabhavi T.M., Development of polysaccharide-based colon targeted drug delivery systems for the treatment of amoebiasis. Drug Dev. Ind. Pharm., 33, 2007, 255-264.
30. Silva I., Gurruchaga M., Goñi I., Physical blends of starch graft copolymers as matrices for colon targeting drug delivery systems. Carbohydr. Polym., 76, 2009, 593-601.
31. Toti U.S. and Aminabhavi T.M., Modified guar gum matrix tablet for controlled release of diltiazem hydrochloride. J. Control. Rel., 95, 2004, 567-577.

32. Sutar P.B., Mishra R.K., Pal K., Banthia A.K., Development of pH sensitive polyacrylamide grafted pectin hydrogel for controlled drug delivery system J. Mater. Sci: Materials in Med., 19, 2008, 2247-2253.

33. Mundargi R.C., Patil S.A., Agnihotri S.A., Aminabhavi T.M., Evaluation and controlle release characteristics of modified xanthan films for transdermal delivery of atenolol. Drug Dev.Ind. Pharm., 33, 2007, 79-90.

34. Kulkarni R.V and Sa B., Electroresponsive polyacrylamide-grafted-xanthan hydrogels for drug delivery. J. Bioactive Compatible Polym., 24, 2009, 368-384.

35. Kulkarni R.V., Setty C.M., Sa B., Polyacrylamide*g*- alginate-based electrically responsive hydrogel for drug delivery application: Synthesis, characterization, and formulation evelopment. J. Appl. Polym. Sci., 115, 2009, 1180-1188.

36. Kulkarni R.V. and Sa B., Novel pH-sensitive interpenetrating network hydrogel beads of carboxymethylcellulose-(polyacrylamide-graftedalginate) for controlled release of ketoprofen: preparation and characterization. Curr. Drug Del., 5, 2008, 256-264.

37. Kulkarni R.V. and Sa B., Evaluation of pHSensitivity and drug release characteristics of (polyacrylamide-grafted-xanthan)-carboxymethyl cellulose-based pH-sensitive interpenetrating network hydrogel beads. Drug Dev. Ind. Pharm., 34, 2008, 1406-1414.

38. Kulkarni R.V. and Sa B., Enteric delivery of ketoprofen through functionally modified poly(acrylamide-grafted-xanthan)-based pH sensitive hydrogel beads: preparation, in vitro and in vivo evaluation. J. Drug Target., 16, 2008, 167-77.

39. Qian F., Cui F., Ding J., Tang C., Yin C., Chitosan graft copolymer nanoparticles for oral protein drug delivery: Preparation and characterization. Biomacromol., 7, 2006, 2722-2727.

40. Geresh S., Gdalevsky G.Y., Gilboa I., Voorspoels J., Remon J.P., Kost J., Bioadhesive grafted starch copolymers as platforms for peroral drug delivery: a study of theophylline release. J. Control. Rel., 94, 2004, 391-399.

41. Tripathy T., Pandey S.R., Karmakar N.C., Bhagat R.P., Singh R.P., Novel flocculating agent based on sodium alginate and acrylamide. Euro. Polym. J., 35, 1999, 2057-2072.

42. Tripathy T., Karmakar N.C., Singh R.P., Development of novel polymeric flocculant based on grafted sodium alginate for the treatment of coal mine wastewater. J. Appl. Polym. Sci., 82, 2001, 375-382.

43. Nayak B.R. and Singh R.P., Development of graft copolymer flocculating agents based on hydroxypropyl guar gum and acrylamide. J. Appl. Polym. Sci., 81, 2001, 1776-1785.

44. Pourjavadi A., Amini-Fazl M.S., Hosseinzadeh H., Partially hydrolyzed crosslinked alginate *graft*polymethacrylamide as a novel biopolymer-based superabsorbent hydrogel having pH responsive properties. Macromol. Res., 13, 2005, 45-53.

45. Rokhade A.P., Patil S.A., Aminabhavi T.M., Synthesis and characterization of semiinterpenetrating polymer network microspheres of acrylamide grafted dextran and chitosan for controlled release of acyclovir. Carbohydr. Polym., 67, 2007, 605-613.

46. Agnihotri S.A. and Aminabhavi T.M., Novel interpenetrating network chitosan-poly(ethylene oxide-g-acrylamide) hydrogel microspheres for the controlled release of capecitabine. Int. J. Pharm., 324,2006, 103-115.

47. Agnihotri S.A., Aminabhavi T.M., Development of novel interpenetrating network gellan gumpoly(vinyl alcohol) hydrogel microspheres for the controlled release of carvedilol. Drug Dev. Ind. Pharm., 31, 2005, 491-503.

48. Soppimath K.S., Kulkarni A.R., Aminabhavi T.M., Controlled release of antihypertensive drug from the interpenetrating network poly(vinyl alcohol)- guar gum hydrogel microspheres. J. Biomater. Sci. Polym. Edn., 11, 2000, 27-43.

49. Singh D.K. and Ray A.R., Graft copolymerization of 2-hydroxyethylmethacrylate onto chitosan films and their blood compatibility. J. Appl. Polym. Sci., 53, 1994, 1115-1121.

50. Lee S.B., Seo S.M., Lim Y.M., Cho S.K., Lee Y.M., Nho Y.C., Preparation of alginate/ poly(*N*isopropylacrylamide) hydrogels using gamma-ray irradiation grafting. Macromol. Res., 12, 2004, 269-275.

51. Singh V., Tiwari A., Tripathi D.N., Sanghi R.,Grafting of polyacrylonitrile onto guar gum under microwave irradiation. J. Appl. Polym. Sci., 92, 2004, 1569-1575.

52. Mishra A., Clark J.H., Vij A., Daswal S., Synthesis of graft copolymers of xyloglucan andacrylonitrile. Polym. Adv. Technol., 19, 2007, 99-104.

****