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Modification Approaches of Xanthan Gum and their Applications: An Overview

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Abstract:

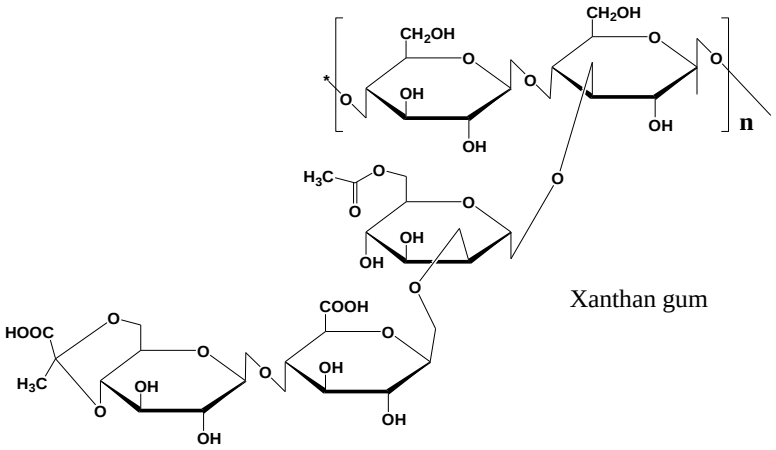
Natural polymers are non-toxic, biodegradable and biocompatible. Xanthan gum is one of such natural polymer displaying various applications in pharmaceutical field. This polysaccharide produced by fermentation using bacterium *xanthomonas campestris*. Xanthan gums have some limitations including microbial susceptibility, improper water solubility, low mechanical and thermal stability, unusable viscosity. Modified xanthan gum circumvents these limitations and fulfills desired needs of drug delivery system. In this review various methods of chemical modification of xanthan gum via acetalation, amidation, etherification, esterification and oxidation are discussed.This article discuss about various derivatives of xanthan gum. The physico-mechanical alterationas well as its effect on characteristics of xanthan gum isdiscussed. In all advancement,MXGare very promising for further research in polysaccharide.

Introduction:

Natural polysaccharides are nontoxic, biodegradable, biocompatible and bioadhesive. These properties are utilizedin food, pharmaceutical, biomedical and cosmetic

applications[1].Out of these natural polysaccharides, xanthan gum has acquired lot of interest. It is an extra-cellular polysaccharide produced by the bacteria *Xanthomonas campestris*. XG is derived bysubmerged aerobic fermentation method from a purebacterium culture on commercial basis.[2] The microorganism occur naturally on the Brasica leaves such as cabbage.

It is a linearβ-D-glucose backbone having (1- 4) linkage having glucose with a trisaccharide side at C- 3 and aresidue of glucuronic acid at (1- 4) tosecond mannoseat (1- 2) and terminal unit of mannose connects to backbone.[3]Side chainof glucuronic acid impartpolyanionic characters to XG .



Xanthan gum

Under reverse condition XG appear in single or double helix conformation .[4] XG has approximately 2 X 10^5 g\mole molecular weight but it may be as high as 13- 50 X 10^5 g\mole.[5,6]

To prevent lumps formation intensive agitation of XG solution is required even though it has solubility in cold and hot water . Solution of XG is show non-Newtanian and highly pseudo plastic behaviour. The carboxy and hydroxyl hydrophilic part of XG describe about intra and inter-molecular interactions of hydrogen bonding in aqueous solution[7.] A high peculiar viscosity exhibited by aqueous solution of XG at low concentrationbecause of huge interactions of hydrogen bonding and molecular weight [8] and behaves like a pseudo plastic flow.[9] XG is used as suspending agent and thickener[10 ,11] and stabilizer for, pharmaceutical, food, cosmetics[12 to 15] and drug reducer in oil drilling[16] due to its pH/salt resistant propertyand high viscous rheology . As a biomaterial XG has been utilized as wombfor micro-particles,hydrogels, nano-particles,transdermal /buccal patches, tablets and scaffolds tissue engineeringsuccessfully.[17]

Reason for modification of xanthan gum:

Chemical or physical modification of XG alone or together emphasize on their desired characteristics , drainunwanted properties or put on new characteristics. xanthan gum has some limitations such as susceptibility to microbial contamination, improper water solubility , low shear resistance, inadequate mechanical and thermal stability, unusable viscosity, poor adsorption performance, uncontrolled rate of hydration, insufficient gelling, slow dissolution rate, insufficient gelling and substantial swelling. Modifications overcome these limitations and alter the characteristics of native xanthan gum to fulfill the discontent need of cosmetic base drug delivery, oil drilling, tissue engineering and other applications.

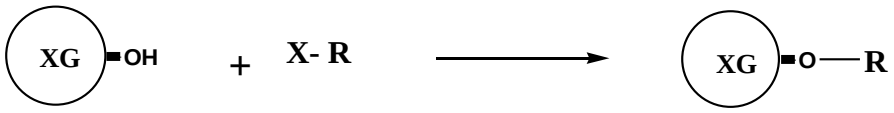
Modification of XG:

XG is modified by various techniques such as chemical, physical, mechanical, chemoenzymatic grafting and cross linking.

1. Chemical modification:

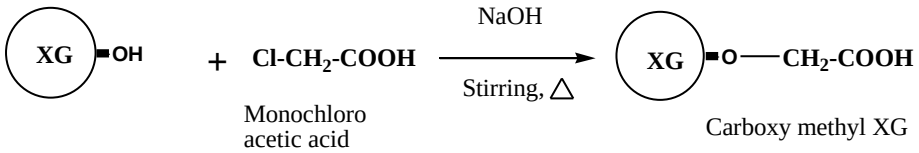
OH and COOH part of XG bring about chemical alteration causing enhancement in its physicochemical characteristics particularly enhancement in metal activated gelation, solubility, swelling and mechanical and thermal stability. This involves etherification, esterification, acetalation, ionic and covalent cross linking.

1.1 Etherification :



1.1.1 **Carboxy methyl xanthan gum** :[18]

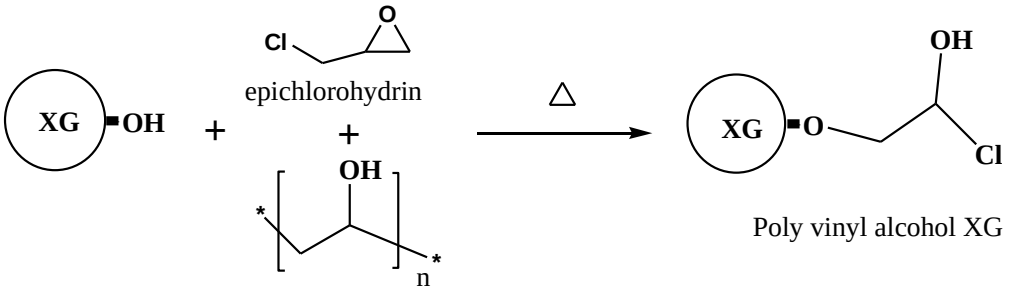
Xanthan gum undergo carboxymethylation in alkaline condition by reacting monochloroacetic acid with XG. Xanthan gum has moreviscositythanCMXG. Diclofenac sodiummatrix tablet using CMXG and xanthan gum were prepared showing faster drug release.



1.1.2 **Poly(vinyl alcohol) XG:** [19]

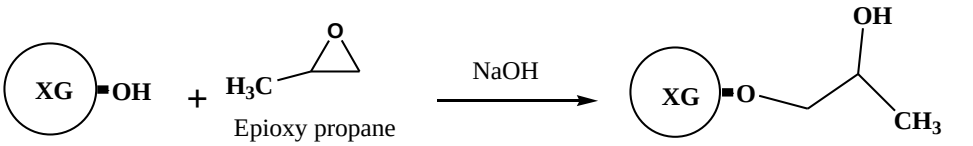
The hydrogel prepared from poly(vinyl alcohol) modified XG possesses good reusable absorption properties. PVAXM modification increase the swelling ratio

and decrease compression properties due to formation of hydrogen bond between PVAXG. This modification result in best adsorption performance which in turn form basis for water treatment application.



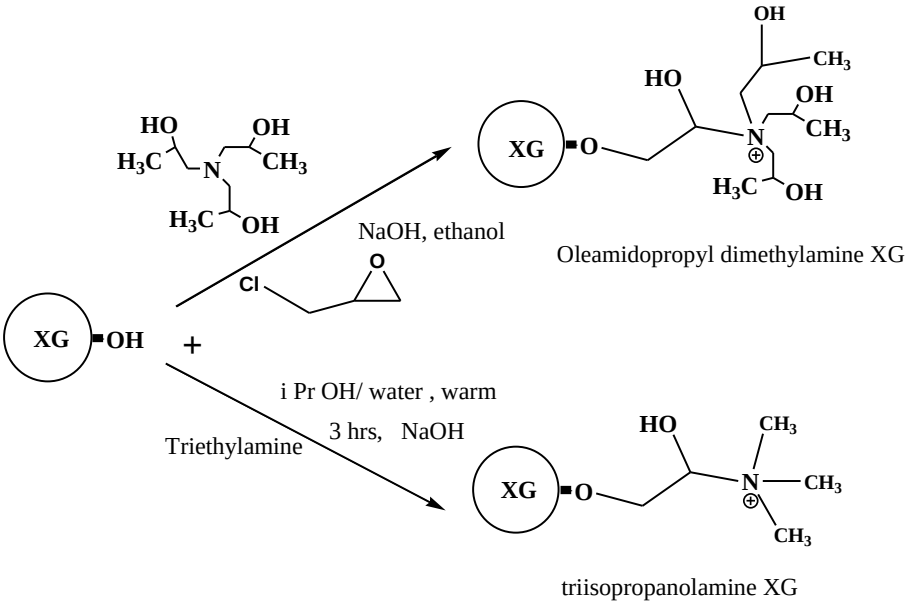
1.1.3 Carboxy methyl hydroxy propyl xanthan gum:[20]

Carboxymethyl hydrox propyl xanthan gum was synthesized by reacting epoxy propane in presence of sodium hydroxide. This modification explore greater temperature, viscosity, elastic modulus property, and poor shear resistance property as compared to native XG solution at same strength. These derivativesconvenient as an additive of fracturing fluid due to its better proppant carrying ability.



1.1.4 Oleamidopropyl dimethylamine XG& Triisopropanolamine XG:[21]

Modification of XG into oleamidopropyl dimethylamine and triisopropanolamine XG lead to enhance viscosity property.

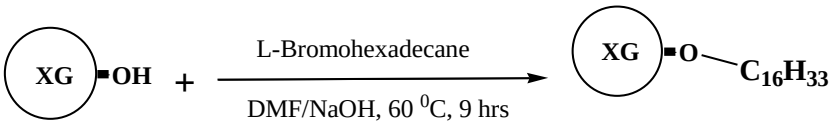


Oleamidopropyl dimethylamine XG

triisopropanolamine XG

1.1.5 Hexadecyl etherification of XG: [22,23]

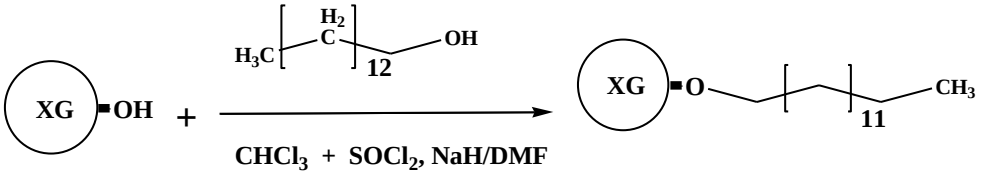
Conversion of XG into hexadecyl XG by esterification produces a polymer which will help to enhance solubility of glibenclamide through polymeric micellization process.Micellization process result in release of glibenclamide upto 8 hrs in simulated biological fluids. This modification showed 4 fold higher viscosities and better thermal resistance as compared to XG.



Hexadecyl XG

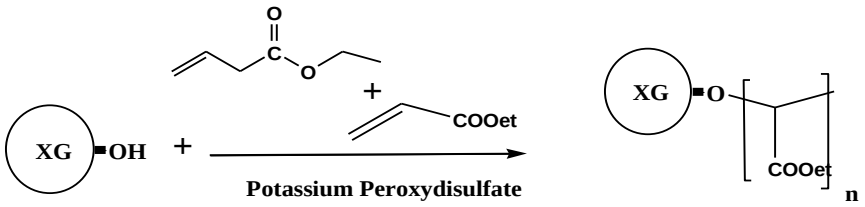
1.1.6 4 or 8 tetradecyl XG:[24]

It was observed that hydrophobical modification of XG did not change the structure of XG. But it showed improvement in thermal resistance and salt resistance property along with enhanced viscosity.



1.1.7 Ethyl acrylated XG:

Pandey *et al*was successfully synthesized ethylacrylate grafted copolymer of xanthan gum utilizingKPS in an air atmosphere as an initiator by free radical polymerization.

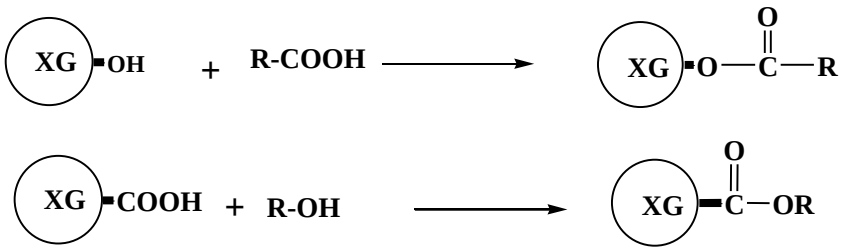


Ethyl acylated xanthan gum

Enhancement in their sorbing capacity, solubility as well as stability was observed by the grafted copolymer. Thus these graft copolymer may found applications in drug delivery and in metal ion removal .

1.2 Esterified XG:

Ester modification also reform XG which have enormous uses.

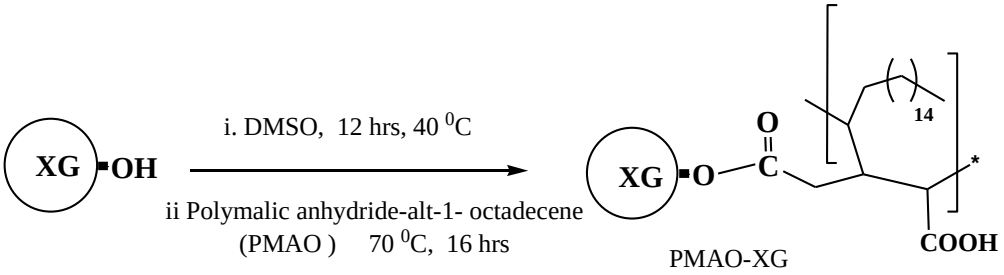


1.2.1 1- Bromooctane XG:[25]

Qian *et al brought* esterification ofCOOH groups of XG by using 1-Bromo-octane. This esterification assists lipophillic association and futher increased the viscosity of XG.Enhance water solubility.

1.2.2 Poly(maleic anhydride) 1-octadecene XG:[26]

This modification provides magnificent hindrance to shear forceexhibiting viscoelastic behavior resulting from the hydrophobic association of C_{16} non polar side chain with polyanhydride. This modification could be beneficial in food industry and in oil recovery pharmaceutical as a result of temperature resistance and excellent salt tolerance properties.

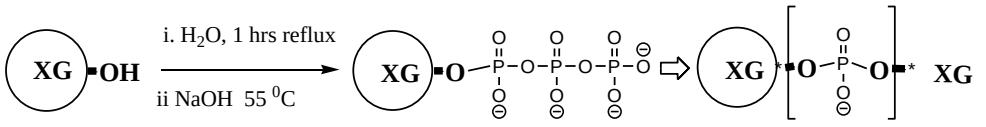


PMAO-XG

Showed outstanding hindrance to shear force exibiting viscoelastic behaviors. Mgnificienttemperature resistanceas well as salt tolerance would be beneficial in field ofpharmaceutical , oil recoveryand food.

1.2.3 **Sodium trimetaphosphate XG [STMP-XG]:** [27]

For designing hydrogel disks, Tao et al endorsed STMP to hydroxyl group of XG under alkaline condition. This modification produces mechanically stable and more elastic hydrogel disk than physical hydrogels. Above reaction generate porosity in the hydrogel, which brings aboutswelling in the first hour and accomplished equanimityin 28 hrs in phosphate buffer solution (ph-7.4).This derivative promote more water uptake due to more anionic charges into XG.



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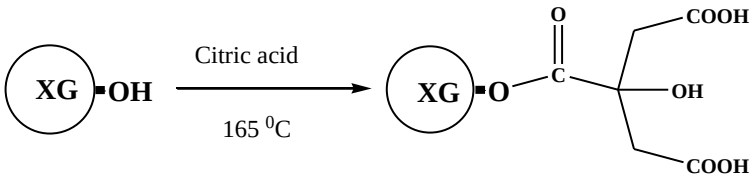
Endorsed STMP water soluble and a non toxiccyclic triphosphate which crosslink with hydroxyl groups of XG chain

1.2.4 **Citric acid crosslinked XG:** [28,29]

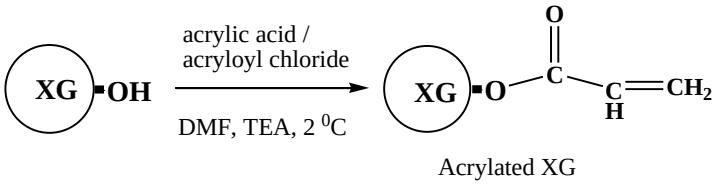


Citric acid produced porous homogenous film without nanofibrils. It decreased the mechanical strength of film. Huang et al constructed newdressing material for wound using citric acid crosslinking with xanthan gum. This nanocomposite film loadedusing nanoparticle of silver which was non cytostatic to fibroblasts at 10µ/ml. This banned the production of biofilm, reduces the inflammation and generate neovascularization of the tissue in unhealed area defiled with *S.aureus*.It provides bactericidal activity in wound dressing.

1.2.5 **Poly acrylic acid XG:**[30]

XG undergoesterification with an acid reactive derivatives like maleic anhydride,acryloyl chlorideoracrylic acid followed by grafting with N-

isopropylacrylamidegives modified XG which having thermo and pH sensitive hydrogel.

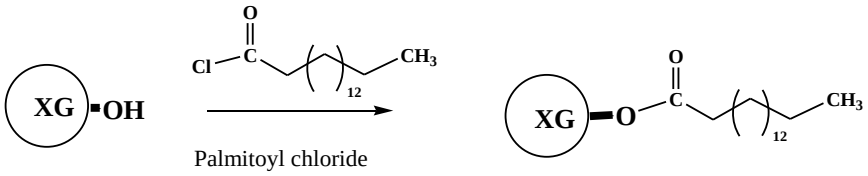


Acrylated XG

This resulted in thermal & pH sensitive hydrogel.

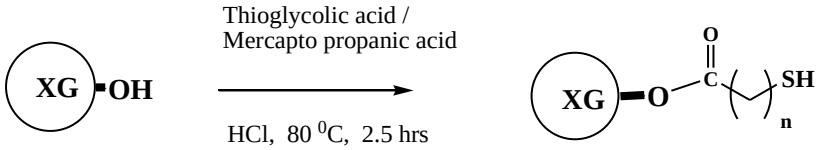
1.2.6 **Palmitoylation of XG:**[31]

Palmitoylated XG furnished a compatible environment for cell microencapsulation.



1.2.7 **Thiol & mercaptothiol of XG:**[32]

Thiol derivatization of XG with thioglycolic acid and mercaptopropionic acid. Comparative Mucoadhesion property of XG and thiolated XG showed higher ex. Vivo bioadhesion time of thiolated XG. Disulfide bondformation between thiolated XGand mucus result into improved bioadhesion property of thiolated XG. The metronidazole loaded buccal pallets prepared using thiolated XGshowed sustained release over a prolonged period.



1.2.8 **Ester of diphenyl maleic anhydride & phthalic anhydride & epichlorohydrin phenol of XG:**[33]

XG esterified with help of diphenylmaleic anhydride or phthalic anhydride gaves modified XG which stabilize suspension effectively. For carbon nanotubes XG is a poor distributing agent. But can stabilize the suspension of carbon nanotubes at 0.5% w/w concentration in acidic media.Waterdispersion of carbon nanotubes viv interaction of p-p stacking occur due to existence of scented

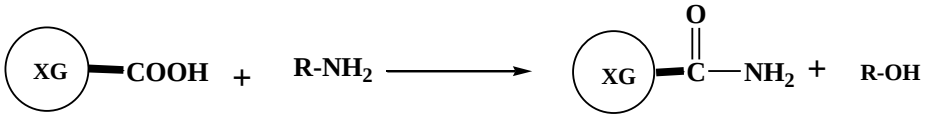
moiety in XG backbone. Suspensionof carbon nanotubes are stabilized by these modifications.

1.2.9 **Succinoyl XG:**[34]

Synthesis ofsuccinoyl XG was done by reacting succinic anhydride reactedwith XG to give succinoyl XG using activator 4-dimethyl-aminopyridine at normal temperature. Succinoylation bring about generation of secondary bonds, providing great elasticity to the hydrogel.Gentamicin hydrogel reacted to ionic strength and prolong the release at PBS Ph 7.4 for 9 days. The hydrogel prepared using succinoyl XG discreted the development of biofilm and exhibited exceptional bacterial function in S. aureus infected mode of rabbit subcutaneously. Hence these modifications were used as suitable material for drug delivery having antibacterial applications.

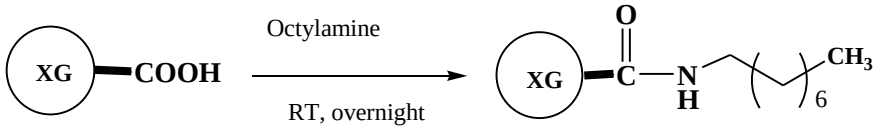
1.3Amide functionalized XG:

COOH functional group of xanthan gum might be the centerpiece for developed amide bond. Substitution on XG backbone occur by long chain hydrophobic alkylvia carbodimiide chemistry. Various amide modifications has been reported such as



1.3.1 Octylamine XG:[35]

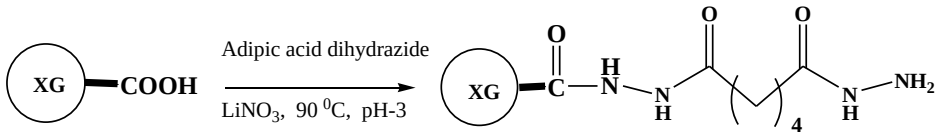
Octylamide XG was prepared by reacting octylamine into the carboxy moieties under order conformation in water at room temperature. It was observed that grafting of long hydrophobic alkyl chain did not changechain conformation and viscoelasticity of XG. The hydrophobic interactions strengthened the suspending ability. Therefore this modified XG can be used as stabilizer and thickener in pharmaceutical formulations. It was further observed that octylamide XGat 0.2% w/w concentration stabilize oil in water emulsion , without the use of additional surfactant.



Octylamide XG

1.3.2 Xanthan ADH grafting[36]

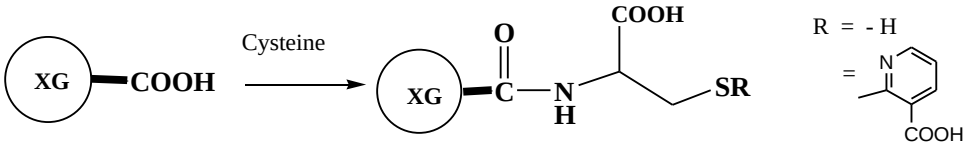
The hydrogel prepared using ADH-XG exhibited pH dependent swelling behavior.pH 3 showedminimalswelling, whereas neutral pH shoewedmaximum swelling. The hydrogel release the dye at faster rate in saltsolution than in acidic solution after absorbing nearly 98% methylene blue in 24hrs.



ADH-XG

1.3.3 L-cystein conjugated XG:[37,38]

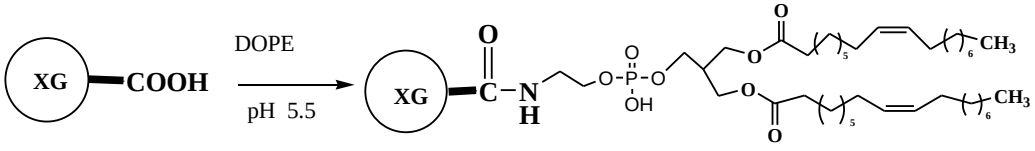
Laffleur *et al* showed that buccal patch prepared using cysteine conjugation worked better in term of stability, buccal Mucoadhesion and tensile strength compared to unmodified XG. It was observed that tannic acid buccal patch showed non cytotoxicity against carey 24 cell lines and persistent swelling in simulated saliva solution (pH6.75). Thiolation of XG result into more distinct water vapor uptake and mucoadhesion property.



Menzel et al prepared XG-cysteine-MNA conjugate by treating with L-cysteine 2-mercapto-nicotinic acid by exchanging disulfied and treated with xanthan gum by forming amide bond via carbodi-imide . This conjugation showed about 1.7 and 2.5 time more mucoadhesion than XG-cysteine and xanthan gum respectively.

1.3.4 XG -DOPE conjugation:[39]

Mendes et al prepared phospholipid conjugated XG by reacting phospholipids(1,2 dioleoyl—glycero phosphoetilamine DOPE) to the XG. Degree of substitution was about 1.16 indicate two units were substituted on XG. Formation of droplets by microfluidic approach and microcapsules produced byDOPE-XG conjugation in an environment suitable for proliferation and survival of cell.



DOPE-XG

1.3.5 Lysozyme XG conjugation: [40]

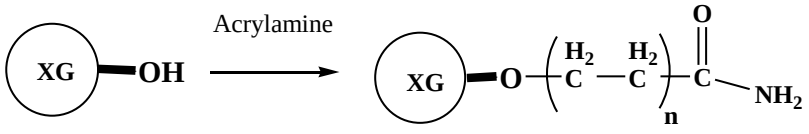
Under mild maillard reaction condition, XG lysozyme conjugate were synthesized. These conjugate showed temperature and pH dependent solubility, emulsion foaming property along with heat stability. In a dose dependent manner, this conjugates inhibit the growth ofE. coli andS. aureus bacteria hence these finding might could be used in food and pharmaceuticals.

1.3.6 Poly (acrylamide) grafted XG:[41,42]

It was producedemployinggraft copolymerization induced by ceric andmicrowaveassisted. With the help of that grafting, diclofenac sodium matrix tabletwasprepared. Matrix obtained fromgraft copolymer showedfasterdrug release as compared to the XG matrix. Grafting also enhance erosion and decreased the swelling behavior of XG.

Badwaik *et al* prepared poly(acrylamide) grafted carboxymethyl XG copolymer by polymerization free radical reaction using ammonium per-sulphate as an indicator. This grafting onto carboxymethyl XG backbonemay be utilised as a carrier for drug delivery systemand increased its thermal stability.

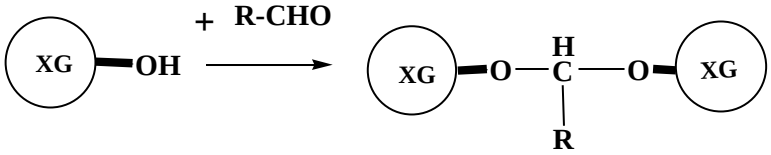
Behari *et al* studied the effect ofH^+, Bro_3, Fe^{2+}on polyacrylamide copolymerization. An increased parameters of grafting causesenhancement in, concentration of bromated ion, grafting ratio, conversion and efficiencywere found to be reduced.



XG-poly(acrylamide)

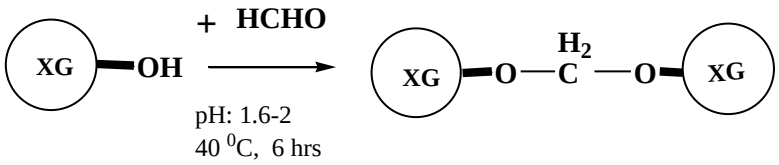
1.4 Acetalated XG:

The hydroxy group of XG could react to aldehyde under acidic condition to form acetal linkage.



Modification with formaldehyde[43]

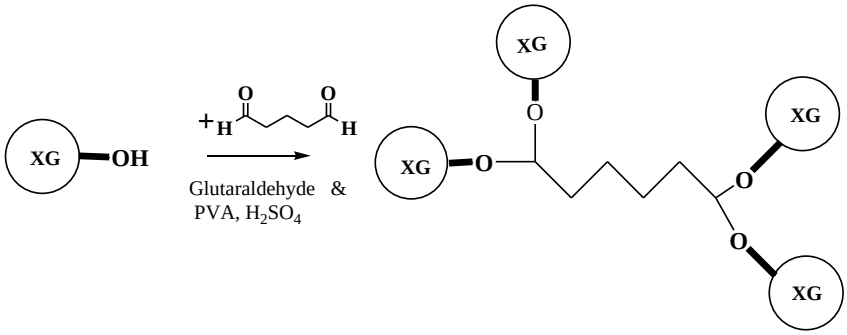
Su*et al* prepared acetalated XG by treating XG with formaldehyde at pH 1.6-2.



Acetal linkage loss the crystallinity but this reaction caused enhancement of solubility and viscosity of XG.

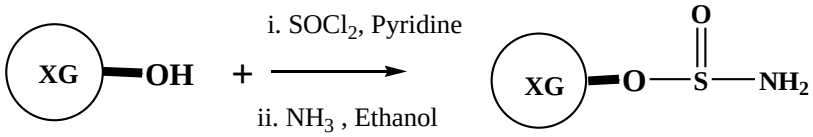
Modification with glutaraldehyde[44]

Ray *et al* brought about acetalation of XG usingglutaraldehyde. He prepared microparticles system which showed 84% drug entrapment efficiency and controlled drug delivery of diclofenac. However, for its utility in drug delivery matrices the toxicity profile poses a major concern.



1.5 **Sulfoxyamine XG:**[45,46]

Sulfoxyamine modification can be prepared by treating XG with thionyl chloride in presence of pyridine to form chlorosulfoxy XG. Further amination was prepared by treating with ammonia to give Sulfoxyamine XG. Mucoadhesion strength, gelling property, viscosity and swelling property were enhanced as compared to XG.



Sulfoxy amine XG

Developed *insitu* gel of ciprofloxacin hydrochloride for ophthalmic drug delivery.

1.6 Oxidized Xanthan gum:[47,48,49,50,51]

Creation of additional functional site for covalent crosslinkage by oxidation of XG.

Guo and coworker oxidized XG with different content prepared by periodate oxidation and used as crosslinking agent for palatable film of gelatin.Raised group ofC=N by Schiff 's

base formation largely enhanced the mechanical and thermal stability and hydrophobicity of film of gelatin.

Paiva *et al* prepared oxidation of XG using sodium metaperiodate which act as adhesive for naturally prepared cork stopper. During drying at high temperature reaction of hydroxyl group with aldehyde group on the cork surface in turns gives good performance.

Ma *et al* prepared hydrogel using XG aldehyde which was sensile to stimuli likeheat,pH, papainandhistidine enzyme. It providesmarvelous atmosphere for encapsulation ofcell useful in tissue engineering andshowed curative ability.

Hydrogel prepared from oxidized XG & chitosan hadgood mechanical strength along with self curing property at normal temperature & pressure.

Xiong *et al* showed that oxidized XG exhibited better antioxidant activity when oxidized under alkaline media as compared to the native XG. During synthesis of silver nanoparticlesdialdehyde XG was served as reducing agent along with biocompatible composite dressing for burn healing.

2. Physical modified XG:

Physical modificationschanges physicochemical properties of XGwith the help ofdry heating,annealing,moistureandheat.

2.1 **Extrusion method:**[52,53]

XG is extrudedwith co rotating screws under flow in a twin screw extruder and dried undervaccum over 65^0 C for 72 hrs under a pressure. Sereno et al observed the improvement in the viscosity and dispersibility in water after extrusion process.

polyelectrolyte particle behavior ofextruded XG, demonstrating fabulous dispersibilty &firm salt dependence on the degree of swelling.

2.2 **Freezing & thawing method**:[54]

Zhang *et al* determined mechanical, rheological and adsorption properties along with swelling behavior ofhydrogel of PVAXG overthawing and freezing cycles. Thefunctionalcarboxy&hydroxy group of the polymer acquired a 3D network through interaction of hydrogen bonding & produced a hydrogelphysicallyhaving more elasticity in term of release of water,cations oranions or absorption.

2.3 **Heating method:** [55]

Disha *et al*formed hydrogel by heating of glycerine,potassium sorbate , sodium benzoate&XGat 85^0c.This hydrogel showed biodegradable character along with antimicrobial activity against Klebsiella spp &E coli.

3. Mechanical Modification[54]

High pressure homogenization:[56]

Eren *et al* showed that viscosity of XG solution getprecipitated at 6Mpa due to breakdown of structural network byhigh pressure homogenization. It reduces the molrcular weight and enhancepolydispersibility andhydrodynamic volume.

4. Chemoenzymetic amylase grafting:[57]

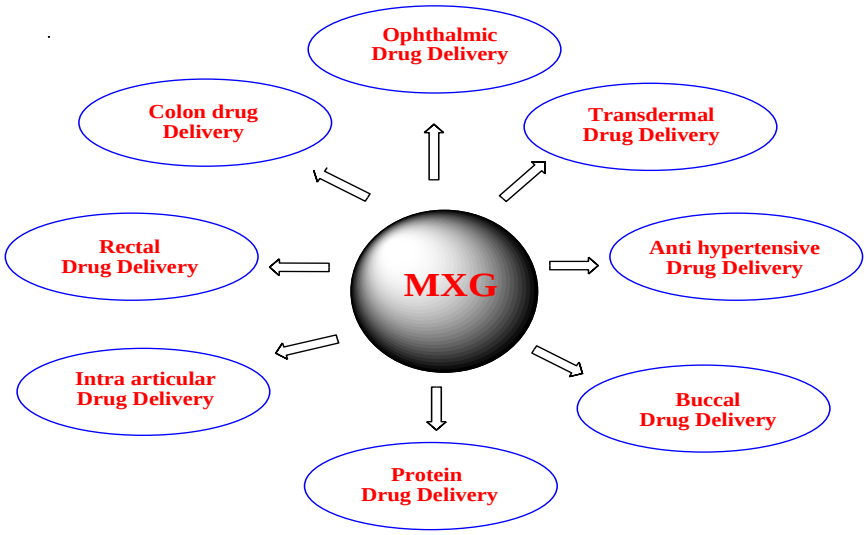
Chemoenzymetic amylase graftingxanthan gum leads toproduction of double helix conformation forminghydrogel with more elastic nature.

5. Crosslinking with other polymers[57]

Xanthan gum with other polymer	Dosage form	Research Outcome
Xanthan gum and Hydroxypropylmethyl cellulose	Matrix tablets	• Analyse comparatively to evaluate efficiency of hydroxypropylmethyl cellulose (HPMC) and Xanthan gum (XG) in respect of drug release behavior and compression. • Behavior of compaction was quite similar. • XG flowability is more than HPMC. • Hydrophilicity varies due to differences in drug release profile
Xanthan gum and Hydroxypropylmethyl cellulose	Matrix tablets	• Diffusion is notimportant factor for insoluble drug release like indomethacine through the hydrated mass from XG matrix tablet
XG:GG	Matrix tablets	*In-vitro* release of drug increased upto67.2% from 42.6% with 2% and with 4% rat caecal medium upto80.34% was observed.
XG and Galactomannan	Compressed	• Tablets having low concentrationof G (VO) showed complete erosion.

	tablets	• The higher polymer relaxation was observed with XG (SD) 8% matrix
XG and Ethyl cellulose	Mini-matrices	Drug release faster as a result of high uptake of liquid, swelling and rate of erosion which observed at higher xanthan gum concentrations .
Xanthan gum and Chitosan	Tablets	• Hydrogel prepared from HME tablets in 0.1N HCl inhibit release ofdrug in pH7.4 and 6.8 phosphate buffers. • In absence of chitosan a hydrogel formed from tablet in 0.1N HCl did not retard drug release
XG and sodium alginate	Beads	Reaction ofSA and XG generate high tortuosity in 0.3% DCA-XG bead matrixcauses inhibition of release of drug in distilled water • Drug release and physic-chemical characteristics of the DCA beads could be altered by XG.
Xanthan gum- sodium alginate	Transdermal Films	• By taking varying blend combinations viz0: 0 , 2:8, 4:6, 5:5, 6:4, 8:2and 10: 0 (XG/SA, wt /wt, %). of sodium alginate and xanthan gum films were prepared. • Enhanced bioavailability and controlled drug release can be achieved by transdermal films

Applications of Modified XG: [58]



Conclusion:

Above review conclude thatmechanical andphysicochemical properties of parent xanthan gum would be putative altered through oxidation, etherification, acetalation, esterification and amidation for desired final use. Covalent and/ ionic cross linking of XG permit production of beads of hydrogel, matrix-tablets, hydrogen films for transdermal and oral drug delivery applications. Incorporation of long chain ofalkyl in XG structure provokedxanthan gum assembly and aidincorporation of required quantity of molecules ofdrug in the hydrophobic atmosphere ofnano-micelles.XG octyl used as emulsifier where as thiolated XG distinctly enhance Mucoadhesion. Entrapped drug markedly improved pharmacokinetics of acetalated XG hydrogel. Aldehyde XG combined with carboxymethyl chitosan was showing promising self-healing property. Physical modification by high shear homogenization, extrusion and freezing-thawing remarkably improved mechanical properties of XG. Finally, the outcome insist that modified XG had significant prospective forpharmaceutical and biomedicalapplications. On account to discloseefficacy andsafety regarding drug delivery and biomedical application, in vivo assessment of modified XG had yet to be done.This review definitely motivate investigator to search other such polysaccharides for formulating new material for industrial usage.

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