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REVIEW

Xanthan gum: A versatile biopolymer for biomedical and technological applications

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ABSTRACT: Xanthan gum is an extracellular polymer produced mainly by the bacterium *Xanthomonas campestris*. Traditionally it plays an important role in industrial applications as thickener, emulsion stabilizer and it has been added to water-based drilling fluids due to its pseudoplastic behavior and thermal stability. The structural properties of xanthan in solution can be tuned by the temperature and ionic strength; under high ionic strength or low temperature, xanthan chains are arranged in helical conformation, whereas under low ionic strength or high temperature, xanthan chains are coiled. Xanthan high molecular weight favors the building up of physical and chemical networks, which have been used as carriers for drugs and proteins and as scaffolds for cells. In combination with other polymers xanthan has been applied as excipient in tablets or as supporting hydrogels for drug release applications, particularly due to its acid resistance. The large versatility of xanthan gum opens the possibility for the creation of new architectures and additional applications involving this fascinating polymer. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42035.

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AIMS

The purpose of this review is to report on the applications of xanthan gum in biomedical and technological products over the last ten years, but revisiting the background and the highlights of traditional applications as thickener. The *in vivo* biodegradability and biocompatibility of xanthan gum are fundamental characteristics that allow its use in biomedical applications. The ability to form networks and acid resistance make xanthan gum, as pure excipient or in combination with other polymers, very attractive as drug carriers. The recent combinations with inorganic particles open a range of new applications.

BACKGROUND

Polysaccharides with high affinity for water and able to increase the solution viscosity, even at small concentrations, are usually called gums. They can be found in many plants,[1] seaweeds or in bacterial fermentation. Xanthan gum is a branched polysaccharide produced by bacterial fermentation; the backbone has cellobiose as repeating unit and side-chains consisting of a trisaccharide composed of D-mannose (β-1,4), D-glucuronic acid (β-1,2) and D-mannose, which are attached to alternate glucose residues in the backbone by α-1,3 linkages,[2] as schematically represented in Figure 1. Approximately one-half of the terminal D-mannose contains a pyruvic acid residue linked via keto group to the 4 and 6 positions, with an unknown distribution. D-mannose unit linked to the main chain contains an acetyl group at position *O*-6. The average composition of xanthan chains depends on the *Xanthomonas* pathovar used and fermentation conditions.[3]

Xanthan gum is the most important microbial polysaccharide commercially. It was discovered in the 1950s by Allene Rosalind Jeanes at the United States Department of Agriculture, USA. The approval by the FDA (Fed. Reg. 345376) in 1969 as a nontoxic and safe polymer allowed the use of xanthan as thickener and stabilizer in many food products. In the USA the industrial production of xanthan started already in early 1960s by the Kelco Company, today CP Kelco. In Europe, Jungbunzlauer Austria AG and Solvay, under the trade name Rhodopol, produce xanthan gum at industrial scale. Since 2005 China has become one of the largest xanthan producer.[4]

Xanthan gum is produced by Gram negative bacteria of the genus *Xanthomonas*, which present many different strains, as for instance, *X. arboricola, X. axonopodis, X. campestris, X. citri, X. fragaria, X. gummisudans, X. juglandis, X. phaseoli, X. vasculorium.*[4,5] *X. campestris* is the most commonly pathovar employed for industrial production of xanthan gum.[6] The effect of production parameters, such as type of bioreactor, continuous or batch operation, type and concentration of nutrients in the growth medium, optimum pH and temperature of growth medium and oxygen transfer rate, on the fermentation yield

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and xanthan molecular characteristics are well reported in excellent reviews available in the literature.[6–8] The biosynthetic pathway[9] of xanthan is complex and will be described here in a simplified way. It starts with the transformation of glucose into pyruvate using the Entner-Doudoroff pathway. Pyruvate may enter both the tricarboxylic acid and glyoxylate cycles, producing ATP molecules.[7] Other metabolic pathways allow the sequential addition of monosaccharides from nucleotide phosphor-sugars (sugar donors), involving acetyl-CoA, phosphopyruvate and polyprenolphosphate (sugar acceptor); the latter is a lipid anchor located at the cytoplasmic membrane.[10] Specific glycosyltransferases are responsible for the transfer of sugar donors to the lipid anchor and, therefore, for the resulting sugar sequence.[11] Then acetyl and pyruvyl residues are added to the trisaccharide side chain. The gene clusters drive the oligosaccharide synthesis on the lipid anchor, translocation and polymerization. The pyruvyl content is an important parameter for applications, since it affects the viscosity of xanthan aqueous solution; low content yields low viscosity, whereas high content promotes gel behavior.

The industrial production of xanthan is mainly based on the fermentation of glucose using *X. campestris*. After fermentation process the broth is pasteurized to eliminate microorganisms, xanthan is precipitated in alcohol, spray-dried, or re-suspended in water and precipitated.[7] However, for *in vivo* applications xanthan gum purification protocol includes several steps (adsorption, enzymolysis, filtration, and precipitation) in order to achieve high degree of purity.[12]

The average molecular weight of xanthan chains might range from 1×10^6 to 20×10^6 mol/g, depending on the biosynthesis conditions and interchain association.[6] Xanthan gum behaves as a polyanion at pH > 4.5 due to the deprotonation of *O*-acetyl and pyruvyl residues. The molecular conformation of xanthan chains in aqueous solution is well reported in the literature [Reference 13 and references therein]. Just after extracting from the broth and without any heating, xanthan chains are arranged as single helices stabilized by Ca^{2+} ions, which can be irreversibly denatured, changing to coils.[14–18] The coiled conformation can be reversibly renatured to double-helical structure. The ordered or disordered state of xanthan chains is controlled by temperature and ionic strength. The helix conformation is stabilized by H bonds and destabilized by electrostatic repulsion between carboxylate groups along the chains. Thus, at low ionic strength or high temperature (at the thermal transition temperature for a given ionic strength) chains assume coil conformation with persistence length of $\sim$ 50 Å.[16,19] On the other hand, under high ionic strength or low temperature, xanthan chains are arranged in helical conformation with persistent size $\sim$ 350 Å.[19] The enthalpy variation involved in the transition from helix to coil conformation was determined as 13.9 J/g.[20]

XANTHAN GUM AS AN IMPORTANT ADDITIVE FOR INDUSTRIAL AND TECHNOLOGICAL APPLICATIONS

Xanthan gum has been largely applied in the food industry because (i) it is an efficient thickener, the solution viscosity increases even at a very low concentration[21,22]; (ii) in aqueous solution it presents pseudoplastic behavior,[21,22] which helps mixing, pumping, filling and pouring; (iii) it has high stability in a wide range of pH, temperature and ionic strength; (iv) it is stable under shear during processing and packing.[23] Moreover, xanthan improves the colloidal stability of emulsions; the shelf life of edible emulsions of oil in water increases considerably in the presence of xanthan because the medium viscosity of continuous phase (water) increases, retarding the coalescence and/or Ostwald ripening process. Therefore, not only the emulsion stability is favored, but also the amount of primary emulsifier is reduced. Such positive effects make xanthan gum an excellent emulsion stabilizer in salad dressings and sauces. Xanthan gum is used in bakery fillings to prevent water migration from the filling to the pastry. More recently, xanthan has been added to gluten-free baked goods due to the elasticity it lends to dough. In the food formulations the content of xanthan gum ranges from 0.05 to 0.7 wt %.[24] The benefits of using xanthan gum as additive in food formulations are also found in cosmetic formulations, as for instance in tooth pastes, lotions and shampoos[25] and in dermatological products.[26,27] In the petroleum industry xanthan gum is an important component of water-based drill-in drilling fluid formulations. Because of its rheological properties and thermal stability, xanthan gum is used for drilling fluid rheology control,[28–31] together with modified starch, which controls the fluid loss of drilling fluids.[32] A typical water-based drilling fluid formulation contains 4.28 g/L xanthan, 22.28 g/L modified starch and 100 g/L $CaCO_3$, which has been used as weighting agent due to its high specific gravity.[29,32–34] Weighting agents are added to adjust the density of drillings fluids, ensuring that its hydrostatic pressure is equal or larger than that of the pore pressure of the drilled formation and avoid fluid loss.[32] The volume of drilling fluids consumed by the petroleum industry is large and the xanthan cost is high; both factors motivate the search for xanthan substitutes. However, it is not trivial to find an environmental friendly water soluble branched polymer with high molecular weight, which imparts the desired rheological behavior to the drilling fluid, as xanthan gum does. Drilling fluids were prepared replacing xanthan by

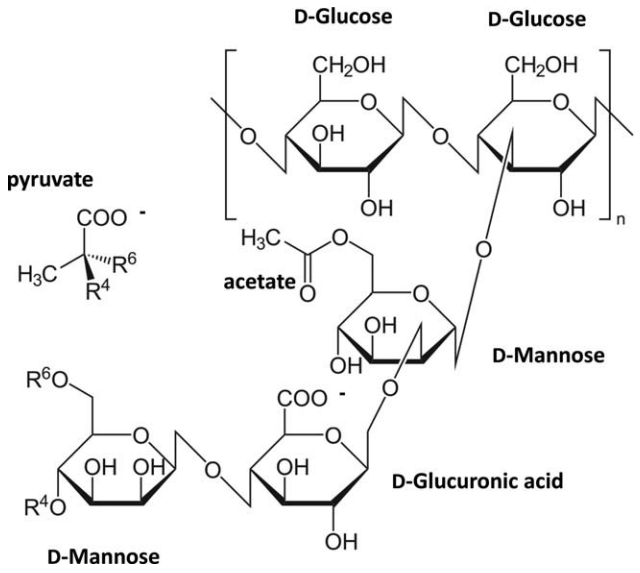


Figure 1. Representation of the chemical structure of xanthan repeating unit. Na^+, K^+, and Ca^{2+} are the most frequent counter-ions stemming from fermentation process.

xyloglucans.[34] Xyloglucan, a hemicellulose extracted from plants cell walls, has backbone of $\beta 1 \rightarrow 4$-linked glucose residues, most of them substituted with 1–6 linked xylose side chain (Supplementary Material SI1) and usually it has high molecular weight ($\sim$ 800,000 g/mol). The replacement of xanthan by xyloglucan extracted from tamarind seeds was not successful because the resulting drilling fluids presented inferior rheological performance, as shown in Figure 2(a) (details in the Supplementary Information SI2). However, formulations with mixtures of xanthan (75 wt %) and xyloglucans (25 wt %) containing $Ca_3(PO_4)_2$ as weighting agent instead of $CaCO_3$, presented increased pseudoplasticity and consistency in comparison to the conventional formulation.[34] The improvement was attributed mainly to the hydration of $Ca_3(PO_4)_2$ particles, which is more favored than that of $CaCO_3$ particles, as schematically represented in Figure 2(b). The commercial viability of these formulations is based on the Xyl price, which is approximately 1/10 of xanthan price, and the low environmental impact of $Ca_3(PO_4)_2$ particles.

XANTHAN GUM NETWORKS

Xanthan chains have the ability to build up physical networks with bivalent cations; the complex involves two disaccharide units of the main chain and *O*-acetyl and pyruvyl residues at side chains, leading to intramolecular cross-linking and chains contraction, as revealed by conductometric and viscometric titrations and nuclear magnetic resonance spectroscopy.[29,33–36] The binding of heavy metal ions, such as Cd^{2+} and Pb^{2+}, to xanthan chains seems to be stronger than to lighter cations, such as Ca^{2+} and Mg^{2+} (Ref. 35); this characteristic is particularly interesting for the separation of metal ions present in waste water. The gel-like behavior of xanthan complexes with soluble and insoluble calcium salts was systematically investigated. Xanthan chains naturally carry Ca^{2+} ions, which stabilize the native helices structures.[14] The addition of Ca^{2+} ions at 100% stoichiometric equivalence might lead xanthan solution to gel-like state.[37] However, at 200% stoichiometric equivalence the solutions might go to a minimum gel-like state, which might be assigned to the partial replacement of intermolecular site binding of Ca^{2+} ions by binding to individual carboxyl groups, decreasing the degree of complexation and network formation.[37] Electrostatic interactions drive not only network formation between xanthan carboxylate groups and divalent cations, but also between xanthan and protein positively charged patches.[38]

Investigations about the flow behavior of solutions prepared with xanthan and $CaCl_2$ or $Ca(NO_3)_2$ at 100% stoichiometric equivalence (1 : 1), and at Ca^{2+} excess (1 : 10 and 1 : 100) evidenced that (i) the monovalent counter-ion type (chloride or nitrate) has no influence on the flow consistency index or on the flow behavior index, (ii) the flow consistency index increased, as the ionic strength increased (1 : 100), mainly because the ordered state of xanthan chains was favored and (iii) the solutions became less pseudoplastic, as the ionic strength increased (1 : 100).[36,39,40] The flow behavior of xanthan solution in the presence of insoluble salts ($CaSO_4$, $CaCO_3$ and

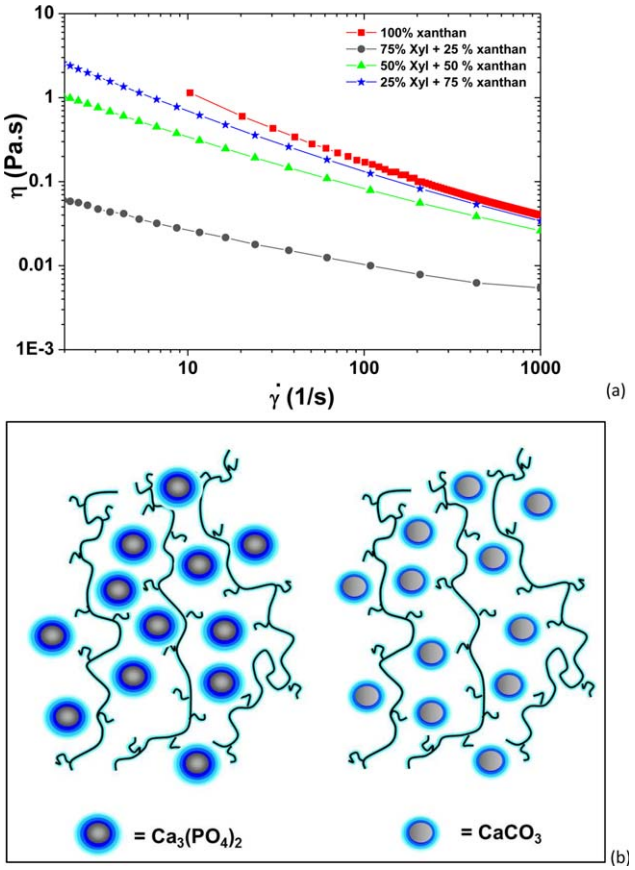
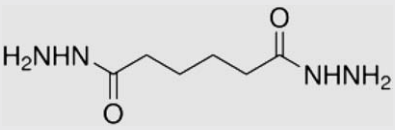
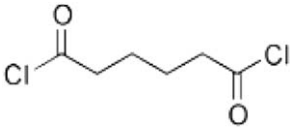
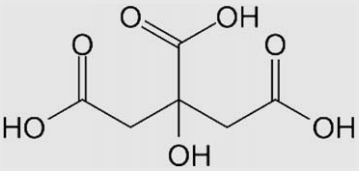
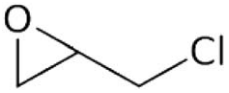
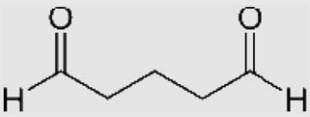
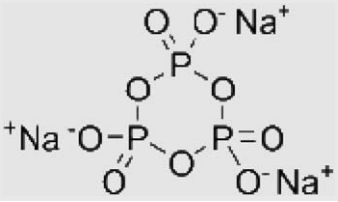
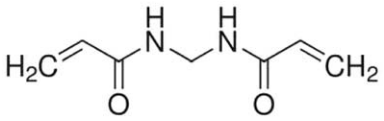
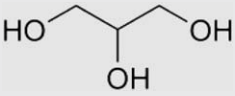
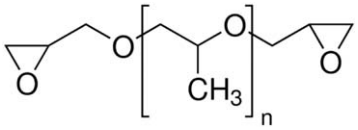


Figure 2. (a) Flow curves obtained for drilling fluids prepared with polymer concentration at 4 g/L: 100% xanthan (red symbols) and mixtures of xanthan and xyloglucan (Xyl) extracted from tamarind seeds at xanthan : Xyl contents 75% : 25% (blue symbols), 50% : 50% (green symbols), 25% : 75% (grey symbols). (b) Schematic representation of hydrated $Ca_3(PO_4)_2$ and $CaCO_3$ particles in xanthan solution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table I. Crosslinkers, with the Corresponding Chemical Structures, Frequently Used for Network Buildup Involving Xanthan

Crosslinker	Chemical structure	Crosslinked polymers	Reference
Adipic acidic dihydrazide		Xanthan + xanthan	42
Adipoyl chloride		Xanthan gum + Starch + poly(vinyl alcohol)	43
Citric acid		Xanthan + xanthan	41,44–47
Epichlorohydrin		Xanthan gum + Starch + poly(vinyl alcohol)	43
		Xanthan + hydroxypropyl starch	48
		Xanthan + konjac glucomannan	49
		Xanthan + cellulose	50
		Xanthan + chitosan	51
		Xanthan + chondroitin sulfate	52
		Xanthan + poly(vinyl alcohol)	53
		Xanthan + xanthan	54
Glutaraldehyde		Xanthan + alginate	55,56
Sodium trimetaphosphate		Xanthan + xanthan	42
		Xanthan + starch	57
N,N-methylenebisacrylamide		Xanthan + poly(acrylic acid)	58,59
Glicerol		Xanthan + pectin Xanthan + starch	60
Polypropylene diglycidyl ether		Xanthan + lignin	61

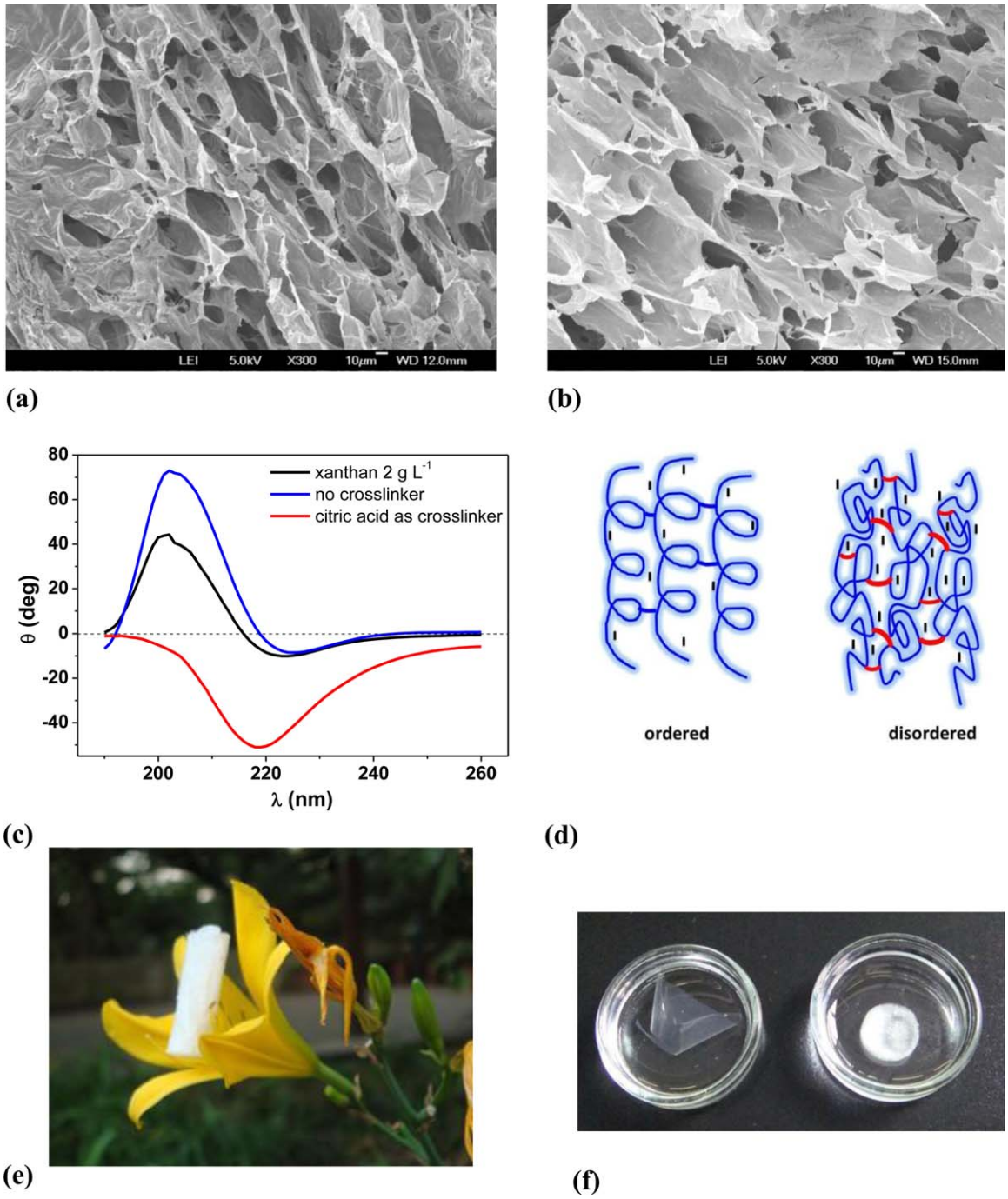


Figure 3. Scanning electron microscope images of cryofractured xanthan networks prepared in the (a) absence and (b) presence of citric acid (adapted from Ref. 37, with permission from Elsevier). (c) Circular dichroism Spectra of xanthan chains in solution (2 g/L, black line), xanthan networks prepared in the absence (blue line) and (b) presence of citric acid (red line), both swollen in water (adapted from Ref. 45, with permission from Elsevier). (d) Schematic representation of ordered and disordered states of xanthan chains in the networks prepared in the absence and presence of citric acid, respectively. (e) Xanthan aerogel on a flower; it was produced by freeze-drying xanthan networks crosslinked with citric acid (density = 5 ± 1 mg/cm^3). (f) Xanthan networks crosslinked with citric acid produced as films (left) and aerogels (right) after six months immersed in HCl 0.1 mol/L (pH 1) at 24 ± 1°C. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$Ca_3(PO_4)_2$) is particularly important for the development of drilling fluids because they act as weighting agent.[29,32–34] Fluids containing particles with large density values and strong hydration, such as $CaCO_3$ and $Ca_3(PO_4)_2$, present high flow consistency indices, as discussed above.

The branched structure of xanthan chains favors not only the buildup of physical networks, but also of chemical networks. For instance, just by simply heating (in the absence of any crosslinker) xanthan films (80 μm thick) at 165°C for seven minutes the esterification reaction among hydroxyl and *O*-acety

Table II. Xanthan in the Absence or in the Presence of Other Polymer Prepared Under Different Physical Forms for the Delivery of Actives (Drug, Protein, or Inorganic Salt)

Polymers	Form	Active	Remark	Reference
Xanthan + galactomannan	Tablets	Theophylline	Release rate (about 90% at the end of 8 h), with zero-order release kinetics. The release mechanism was a combination of diffusion and polymer chain relaxation.	94
Xanthan + konjac glucomannan	Tablets	Diltiazem hydrochloride	Zero order release, entire drug load within 24 h in the presence of beta-mannanase	95
Xanthan + konjac glucomannan	Tablets or gel	Cimetidine	Synergistic interaction between konjac glucomannan and xanthan gum retarded the drug release from the matrix tablets or gels.	96
Xanthan + chitosan	Tablets	Metronidazole	Strong bioadhesivitiy on duodenum, and high *in vivo* bioavailability	97
Xanthan	Tablets or gels	Pentoxifylline	Low pH and increased ionic strength influenced xanthan molecular conformation, driving the xanthan bio-responsiveness under different microenvironmental conditions.	98
Xanthan gum+ guar gum+ +hydroxypropylmethylcellulose (HPMC)	Tablets	Propranolol hydrochloride	Drug release from tablets containing 30% guar gum and 30% xanthan gum followed Fickian diffusion	99
Xanthan + microscrystalline celulose + starch	Tablets	Aceclofenac	Protection from premature drug release in the upper gastrointestinal (GIT) tract	100
Xanthan + galactomannan	Tablets	Theophylline	Drug release mechanism was complex and composition dependent	101
Xanthan + CaSO4	Tablets	Buspirone hydrochloride	Increase in calcium sulfate concentration resulted in faster drug release and decreased the bioadhesive strength of the tablets	102
Xanthan + HPMC	Tablets	KNO_3 (model fertilizer)	Non-Fickian diffusion, with release exponents ranging from 0.85 to 1.01, suggesting polymer relaxation as the major process controlling fertilizer release.	103
Xanthan + lignin	Hydrogel	Vanillin	The release of vanillin was slower from gel xanthan/lignin 70/30 than 90/10 due to interactions between matrix and vanillin	104
Xanthan + starch	Hydrogel	Pyrogallol red, methylene blue, ibuprofen (sodium salt), caffeine, sodium salicylate, vitamin B12, Fluorescein isothiocyanate-inulin, and Fluorescein isothiocyanate-dextrans	Permeability of anionic drugs across the polymeric films was lower than their neutral form due mainly to the electrostatic repulsion between the negatively charged drugs and the polymer.	105

Table II. *Continued*

Polymers	Form	Active	Remark	Reference
Xanthan–galactomannan	Hydrogel	Curcumin	Microemulsion or ethanol was used for drug dispersion. *In vitro* permeation test indicated adequate drug release rate	106
Xanthan gum + guar gum + poloxamer	Hydrogel	Atropine sulphate	*In situ* gel-forming eye drops containing poloxamer-407, XG–GG (3 : 7), decreased the drug release rate and increased biocompatibility	107
Xanthan	Hydrogel	Lysozyme or BSA	pH controlled released	45
Xanthan + cationic lipid adjuvant	Nasal insert gels	Hemagglutinin	Formulation for influenza vaccine enhanced the serum IgG as well as the nasal IgA response *in vivo*	108
Xanthan	Mucoadhesive patches	Nicotine	Fast initial *in vitro* release profile followed by controlled drug release over a 10-h period.	109
Xanthan gum and guar gum	Mucoadhesive nasal gels	Metoclopramide hydrochloride	The best nasal inserts formulation containing xanthan gum and guar gum ratio 1 : 5, showed good release (91.83%) and bioadhesion	110
Xanthan + sodium carboxymethyl cellulose	Interpenetrating network beads	Diclofenac sodium	Enhanced intestinal drug release	111
Xanthan + poly(vinyl alcohol)	pH sensitive interpenetrating network	Dichlofenac sodium	*In vivo* slow and prolonged drug release in the intestine	56
Xanthan + low molecular weight poly(vinyl alcohol)	Membranes produced by electron beam irradiation	Diltiazem hydrochloride	Slow and sustained diltiazem release	112
Xanthan + poly(vinyl alcohol) + hyaluronic acid sodium salt + carrageenan + hydroxypropylmethyl cellulose	Extruded paste	Tetracycline HCL	Zero-order release kinetics of tetracycline	113
Xanthan + poly(vinyl alcohol)	Microspheres	Ciprofloxacin hydrochloride	Non-Fickian release behavior	114
Xanthan gum- + ethyl cellulose + carbopol	Microsponges	Diclofenac sodium	Drug entrapment efficiency as high as 64.1%, Drug diffusion from the microsponge-loaded gel formulation was slower at the drug/polymer ratio of 0.4 : 1 (*m*/*m*)	115
Xanthan + low molecular weight chitosan	Physical blends in capsules	Ciprofloxacin hydrochloride	Zero-order drug release	116
Xanthan+chitosan on liposomes	Coating for liposomes	Protein C-phycocyanin	Xanthan/chitosan in a 8.0/0.5 (w/w) ratio provided Fickian drug release and excellent mucoadhesive properties	117
Xanthan + gellan	Coating for ion exchange resin particles	Cefotaxime sodium salt	The adsorption process of drug on the particles was endothermic and spontaneous. Polysaccharides coating increased adsorption ability	118

Table II. *Continued*

Polymers	Form	Active	Remark	Reference
Xanthan+chitosan on liposomes	Coating for liposomes	Rifampicin	Coating with xanthan/chitosan in a 0.5/1 (w/w) ratio was able to improve drug delivery at a higher dose to the lower stage of the impinge in comparison with corresponding uncoated liposomes	119
Xanthan + HPMC + PVA	Film	Zolmitriptan	*In vitro* drug release studies of optimized formulation showed initially rapid drug release; 43.15% within 15 min, followed by sustained release profile over 5 h. Incorporation of 4% dimethyl sulfoxide enhanced drug permeability by 3.29 folds, transported 29.10% of drug after 5 h and showed no buccal mucosal damage	120

and pyruvyl groups is promoted, yielding ester bonds among the chains and releasing water molecules.[41] Nevertheless, the number of network connections can be increased by the addition of a crosslinker, which is a small molecule carrying functional reactive end groups. Table I comprises different crosslinkers[42–61] used to obtain xanthan networks either in the absence or in the presence of a second polymer. One should note that if the final application is related to biomedical purposes, one must be very careful with unreacted residual crosslinkers. For instance, unreacted epichlorohydrin[62] or *N,N*-methylenebisacrylamide[63] must be removed, because they might present carcinogenic effects. On the other hand, citric acid is a very interesting crosslinker because it is cheap and non-toxic.[44] Xanthan hydrogels produced by heating at 165°C in the presence of citric acid have higher crosslinking, higher gel content, homogeneous porous structure [Figure 3(a)] and higher charge densities, while those produced at 165°C in the absence of citric acid presented lower gel content, heterogeneous porous structure and nanofibrils [Figure 3(b)].[41] The diffusion mechanism of water into xanthan networks was investigated by tensiometry at 25°C.[41] It can be divided into two steps: an initial one controlled by wicking properties and a second one, which follows either Fickian (water diffusion does not depend on chains relaxation), in the case of low charge density hydrogels, or anomalous (there is interaction between diffusive water and polymeric matrix), in the high charge density hydrogels, behavior. Xanthan hydrogels are stable under acidic or neutral conditions, but under alkaline conditions ester bonds are hydrolyzed[41]; such behavior enables their use as drug enteric vehicles. The conformation of crosslinked xanthan chains in the swollen state was investigated by means of circular dichroism (CD) spectroscopy [Figure 3(c)]. The helix conformation was observed for the xanthan chains in the swollen networks prepared without citric acid and for xanthan free in solution (2.0 g/L)[45] [Figure 3(c and d)]. Xanthan chains in networks produced with citric acid are coiled when swollen in water [Figure 3(c and d)], but upon increasing the ionic strength they undergo a conformational transition to ordered state (not shown).[45] The ordered conformation of xanthan in solution or gel phase favors the interaction between side xanthan chains with a second polysaccharide,[64] as galactomannan[65,66] or glucomannan.[67] The thermodynamic stability of such gelation processes depends on cooperative interactions over long ranges or small dynamic segments. For instance, the intermolecular associations between xanthan disordered segments and locust bean gum, a galactomannan, are responsible for the outstanding gel properties of their mixtures.[68–70]

Another interesting possibility refers to freeze-drying swollen xanthan hydrogels crosslinked with citric acid, generating aerogels with very low density (5 ± 1 mg/cm^3) [Figure 3(e)]. The combination of aerogels with reinforcements opens the possibility to create materials with new properties; for instance, xanthan, clay and agar together yield aerogels with compressive modulus of 4.8 MPa and improved flame retardancy.[71] However, xanthan based aerogels are still seldom explored. Xanthan networks crosslinked with citric acid were produced as films [Figure 3(f) left] and aerogels [Figure 3(f) right] and were

immersed in HCl 0.1 mol/L (pH 1) at 24 ± 1°C; the original swollen form was retained after six months, indicating the high stability.

The interactions between polysaccharides and proteins or polypeptides are dominated by pH and ionic strength of medium, temperature, shearing conditions, xanthan concentration and the molar ration between biopolymers.[72] In general, the hydrophilicity of polysaccharides provides a suitable environment for the immobilization of enzymes with preserved conformation. For instance, complexes of chitosan and xanthan served well for the immobilization of proteases, xylanases and lipase.[72–74] The preparation of such complexes was based on the mixture of a 0.65 wt % xanthan solution and the desired enzyme, which was added dropwise in a 0.65 wt % chitosan solution.[73] The enzymatic activity of immobilized enzymes increased with the increase of enzyme concentration in the xanthan solution and the immobilized enzymes presented higher thermal stability.[73] Xanthan hydrogels proved to be efficient carriers for lysozyme (LYZ),[45] an enzyme with isoelectric point (pI) at 10.7[75] and biocidal properties.[45,76–79] At pH 7 the release of LYZ tends to be very low due to attraction between positively charged residues of LYZ and negatively charged xanthan.[45] The LYZ loaded xanthan hydrogels films presented substantial bactericidal activity because they preserved the native structure, as indicated by CD spectra, making them useful as bactericidal coatings or wound dressings. The topic application of xanthan hydrogels is favored by the high adherence onto skin. For proteins with low pI values, such as bovine serum albumin (BSA) which has pI at 4.8,[80] hydrogels with low charge density seem to be more adequate to be used under neutral conditions because the electrostatic repulsion is reduced.[81] The delivery of BSA from xanthan hydrogels, which have large density of negative charge, was complete after 1 h, in the pH range from 2 to 10, except for pH 4.8, which is very close to its pI. At pH 4.8, the release is hindered because BSA solubility is reduced and BSA positively charged patches can bind to xanthan carboxylate groups. Similar behavior was observed for oxidized galactomannans,[82] carboxymethylcellulose,[83,84] oxidized xyloglucans.[85] The complex between xanthan and casein, a protein with pI at 4.6,[86] acts as emulsifier for oil in water emulsions.[87]

XANTHAN APPLICATION FOR THE DELIVERY OF DRUGS, PROTEINS OR BIOSOLUTES

For drug release applications xanthan has been used as excipient in tablets or as supporting hydrogels. In most cases xanthan gum is used in combination with other polymers, which help tuning the desired properties.[88,89] For instance, long term stability of β-carotene-loaded liposomes was achieved when the mixture of xanthan and guar gums was used as a protective network,[90] curcumin-loaded hydrogels made of xanthan and galactomannan from *Schizolobium parahybae* were successfully applied as anti-inflammatory dermatological gel.[91] Superabsorbent hydrogels for medical or food applications were prepared by crosslinking xanthan and lignin with polypropylene diglycidyl ether.[61] Aloe loaded hydrogels of chitosan and xanthan can be used for skin repairing or skin diseases.[92]

Alternatively xanthan gum can be modified by conventional chemical methods like carboxymethylation, and grafting such as free radical, microwave-assisted, chemoenzymatic and plasma assisted chemical grafting.[93] Table II comprises examples[93–120] of xanthan based systems used for the release of drugs, proteins or biosolutes. Each system has its intrinsic remarks because the interactions between polymeric matrix and released substance are controlled by medium ionic strength and pH, particularly in the case of xanthan, because changes in xanthan molecular conformation are also medium dependent. For instance, Mikac and co-workers investigated the swelling behavior of xanthan tablets by means of magnetic resonance imaging under different pH and ionic strength.[98] Initially xanthan chains are dried, then in contact with water they assume a hydrated glassy state, changing to a rubbery state at high swelling degree. Moreover, they observed that drug release was faster when the gel layer thickness was smaller. More recently xanthan was used not only as coating, but also as reducing agent for gold nanoparticles, which were loaded with doxorubicin hydrochloride, a drug used for the treatment of various cancers, hematological malignancies, soft tissue sarcomas and solid tumours.[121] All these examples show that xanthan gum can be successfully used as carriers for drug or biomolecules, particularly because (i) it presents high stability at low pH, protecting the drug in the stomach and (ii) the drug release might be easily controlled by the medium pH (high release under alkaline conditions) and ionic strength.

XANTHAN AS SCAFFOLDS FOR CELL ADHESION, PROLIFERATION AND DIFFERENTIATION

Materials for biomedical application should present physical and chemical properties, which enable cell adhesion, proliferation and differentiation. The interfacial phenomena between cell and scaffold depend on material stiffness, nanotopology and surface chemistry.[122] Scaffolds should mimic from soft neural[123] to hard non-mineralized bone[124] tissues, which have elastic moduli 0.1 kPa and 40 kPa, respectively. Xanthan based hydrogels are interesting materials to be explored as scaffolds because they are biocompatible and biodegradable.[125] Depending on the softness required, hydrogels can be prepared with different elasticity degrees, as for instance, by mixing xanthan with konjac gum, iota-carrageenan and kappa-carrageenan with precise compositions.[126] Xanthan based hydrogels have been used for skin regeneration,[127–129] as indicated in Table III. Fibroblasts proliferation onto hybrid nanocomposites of xanthan and magnetite nanoparticles was more pronounced than onto neat xanthan hydrogels, particularly under a magnetic field of 0.4 T.[47] The hybrid scaffolds of xanthan and nanomagnetites were also used successfully for *in vitro* neuronal differentiation of embryonic stem cell; the differentiated cells showed increased membrane potential amplitudes upon depolarization with KCl, indicating successful synapse formation.[130]

It has been suggested that the presence of magnetic nanoparticles in the scaffold surface and the magnetic field stimulates Ca^{2+} influx into fibroblasts. In agreement with the uptake of ions, polycaprolactone scaffolds containing magnetic nanoparticles induced more active osteogenic differentiation and improved

Table III. Xanthan-Based Hydrogels Used for *In Vitro* Cell Applications

Scaffold	Remarks	Reference
Xanthan	Human fibroblasts viability. No skin irritation.	127
Xanthan + chitosan (1 : 1)	Fibroblasts viability. Dermal dressing for skin treatment	128
Xanthan + chitosan-g-glycidyl methacrylate	Amorphous physical hydrogels suitable for fibroblasts proliferation	129
Xanthan + magnetic nanoparticles	Enhanced fibroblasts proliferation in comparison to neat xanthan hydrogels. Positive effect of external magnetic field on cell proliferation and Ca^{2+} ions influx	47
Xanthan + magnetic nanoparticles	neuronal differentiation of embryonic stell cell; the differentiated cells showed increased membrane potential amplitudes upon depolarization with KCl, indicating successful synapse formation	130
Xanthan + polypyrrole	Enhanced fibroblasts proliferation in comparison to neat xanthan hydrogels. Positive effect of external magnetic field on cell proliferation	133
Xanthan + hydroxyapatite	Enhanced activity of alkaline phosphatase and osteoblast viability	46

cellular mineralization in comparison to pure caprolactone.[131] Blends of xanthan and polypyrrole combined xanthan biocompatibility, high charge density and ability to form mechanically stable films with the PPy electronic properties.[132,133] Such combination of characteristics favored fibroblasts proliferation, particularly under external magnetic field.[133] Composites of xanthan and xanthan-nanohydroxyapatite or its equivalent strontium substituted were suitable for osteoblasts growth and induced high alkaline phosphatase activity.[46]

PERSPECTIVES FOR XANTHAN APPLICATIONS

Typical industrial applications of xanthan gum converge to food, cosmetics, cleaners, paints, ceramic glazes, inks and water-based drilling fluids formulations. The recent publications indicate the combination of xanthan gum with glycerides to improve the performance of drilling fluids[134] or with magnetic nanoparticles to enhance the adsorption capacity for pollutant dyes dissolved in water.[135] In the biomedical/biotechnological field novel applications of xanthan appear continuously. For instance, the intra-articular injection of xanthan (0.5–2.0 wt %) seems to be an alternative treatment method for osteoarthritis because it acts as an elastic shock absorber during low impact movements of the joint and as a viscous lubricant during high impact movement.[136] For this application xanthan seems to work better than sodium hyaluronate because it is more stable against hydrolytic and enzymatic reactions *in vivo*.

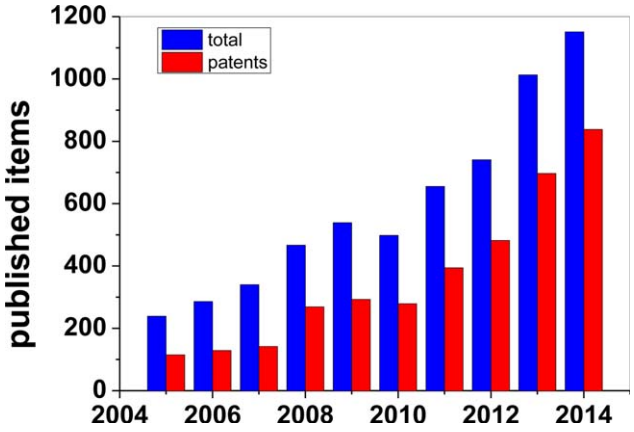


Figure 4. Number of published items from 2005 to date[137]. Blue and red columns correspond to total number and patents, respectively. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In the last ten years (from 2005 to 2014) the number of published items involving "xanthan" tends to increase continuously[137] according to the "web of science" records, presented in Figure 4. From the total of 5,929 publications, 3,638 items (or 61%) correspond to patents. Although these figures reveal the relevance of xanthan gum for new technologies/product formulations. Nevertheless, some fields of applications remains still poorly explored; one of them is the production of xanthan based aerogels, the other is the production of xanthan nanocrystals. Although the crystallinity of xanthan depends on the moisture content,[138] it is surprising that the literature reports about nanocrystals produced from the hydrolysis of many different natural polymers, but the production of xanthan nanocrystals by acid hydrolysis is scarcely explored.[139] Recently the production and luminescent properties of composites obtained by combining polysaccharides, such as cellulose, chitosan, alginate, starch, and luminescent fillers have been reviewed.[140] The potential of xanthan for biomedical applications in the form of

such luminescent composites is enormous. Xanthan gum is a fascinating biopolymer with many interesting properties, which can challenge and encourage researchers to create new architectures and functional systems based on it.

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