

Hydrogels Made up of Natural Gums Based on Polysaccharides for Applications in Biomedicine: Brief Review

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ABSTRACT

Natural gums based on polysaccharides such as guar gum, gum arabic and xanthan gum possess structure and properties that have been used for various applications in pharmaceutical, food and biomedicine. Due to their high presence of hydroxyl and/or carboxylate groups in their glycosidic skeletons, they can retain water molecules, forming matrices in the hydrogel state. These hydrogels have high biocompatibility that has been exploited in the biomedical field in strategies as controlled release of therapeutic agents, regenerative medicine, tissue engineering and modulation of cell growth. The objective of this review is to detail the chemical characteristics of natural gums and their use for the design of different hydrogel systems for applications in biomedicine.

Keywords: Hydrogel, Guar gum, Gum Arabic, Xanthan gum, Biomedicine.

1. Introduction

Hydrogels for application in biomedicine are promising, mainly due to their degree of tolerance in the organism. The investigation of these biomaterials is not only responsible for the development of their structure, but also seeks to ensure that their mechanical properties are good, as well as to rigorously evaluate their interaction in the biological system [1]. In tissue engineering and regenerative medicine, hydrogels are designed to mimic and improve the biocompatibility with the human body. This type of biomaterial is optimal for applications in the biotechnological areas mentioned above, since due to their degree of crosslinking they form matrices with a high degree of hydration, which is like an extracellular matrix where cells are sustained [2].

Hydrogels are characterized by being biocompatible, biodegradable, and non-cytotoxic. These properties and their high-water content make hydrogels like soft tissues and can be applied in the diffusion and release of exogenous components inside and outside the matrix [3,2]. For the repair of soft tissue, the hydrogel must preserve moisture within the wound dressing, be immune to bacteria avoiding secondary infections, must be responsible for absorbing and diffusing exudates, as well as creating an ideal microclimate to promote healing [4].

Currently, various researchers are working on the development of biodegradable polymer-based hydrogels for wound treatment and tissue regeneration that meet the above properties and are affordable [5,6]. Natural gums based on heteropolysaccharide skeletons such as guar gum, gum arabic and xanthan gum meet these requirements to generate hydrogels for successful biomedical application.

These biopolymers can be degraded by enzymes such as amylases and glycosidases, which makes them useful for the release of drugs in the treatment of wounds, and they are not affected by pH or ionic strength, which makes them capable of protecting the drug. Natural gums manage to delay the degradation time of hydrogels for

biomedical applications, adapting their biocompatibility and their mechanical properties [7]. Accordingly, this review reveals the chemical and structural aspects of polysaccharide-based natural gums, and their application in the design of hydrogels for biomedical applications (Fig. 1).

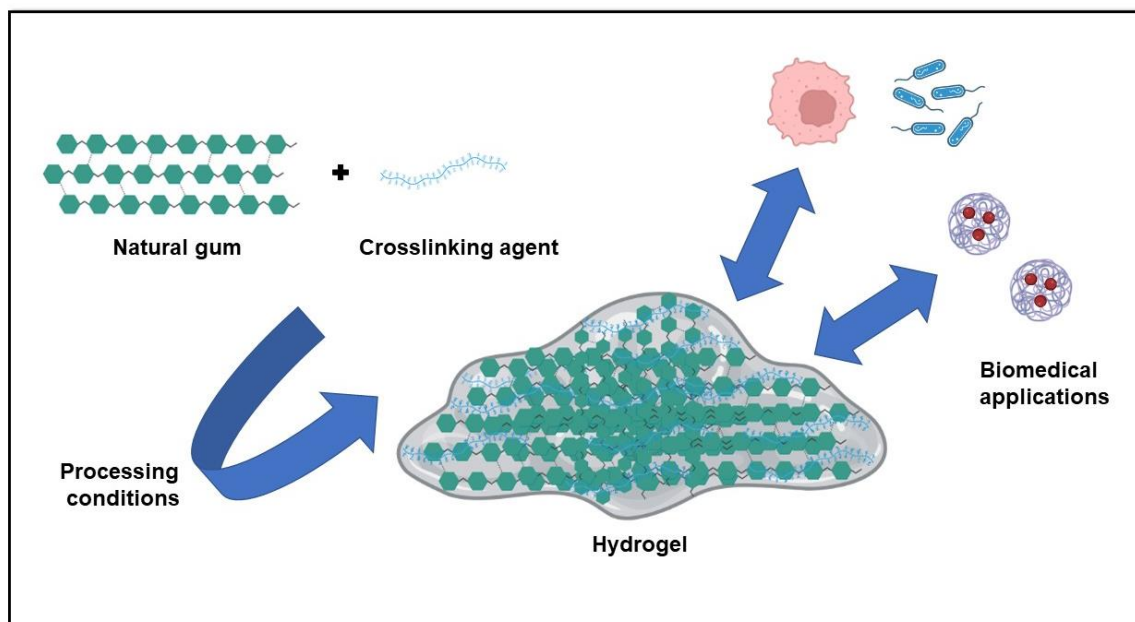


Fig.1. Production of hydrogels based on natural gums for applications in biomedicine

2. Chemical and Structural Aspects of Natural Gums

2.1. Guar Gum

Guar gum (GG) is a heteropolysaccharide, which is composed of the D-mannopyranose monosaccharides linked together by β -(1, 4) glycosidic bonds, and a branched part of D-galactopyranose molecules linked by a β -(1, 6) bond to the lineal chain as shown in Figure 2. For every two mannose molecules, one galactose molecule is found forming very short side branches. It is extracted from an extract of the seeds of *Cyamopsis tetragonolobus*, a legume plant, where it is stored as an energy reserve. This extract contains about 80 % GG, 12 % water, 5.0 % protein, 2.0 % acid insoluble ash, 0.7% inorganic ash, 0.7% fat [8]. GG hydrates easily in aqueous media, forming a viscous solution due to the formation of hydrocolloids. Due to its gelling property and enzymatic degradation, guar gum is used in oral drugs such as those directed to the colon, antihypertensives and transdermal [9].

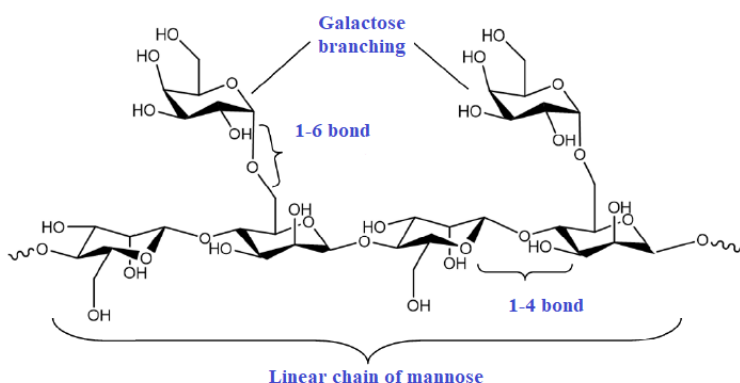


Fig.2. Chemical structure of guar gum

It has one of the highest molecular weights (approximately 220 kDa) among naturally occurring water-soluble polysaccharides [8, 9]. Galactomannans, being in an aqueous medium even in low concentration, not only hydrate, but also form colloidal solutions with high viscosity characteristics. The entanglement of the polymeric chains of the guar gum added to the anchorage with the pendant groups cause the increase in viscosity. From this, the gelation of the polysaccharide can be induced [9]. In addition, its ability to form hydrogen bonds with water makes the formation of hydrogels possible, which makes it worthy of wide biomedical applications [10]. The recommended use of guar gum is below 1 wt.%, generally up to 0.5 wt.%, since if it is exceeded, the solutions take time to reach an equilibrium viscosity, behaving as non-Newtonian systems [9, 10].

2.2. Gum Arabic

Gum Arabic (GA) is extracted from the resin of *the Acacia senegal* and *Acacia seyal* sub-Saharan varieties. It has a wide variety of uses as a stabilizer, in the pharmaceutical area, and in the food industry it is used as a thickener and emulsifier [11]. This heteropolysaccharide has a branched chain and is neutral or slightly acidic, as shown in Figure 3, it is found as a mixed salt of calcium, magnesium, and potassium of polysaccharide (arabic acid), its main chain is composed of units of D-galactopyranose linked with β -(1, 3) glycosidic bonds.

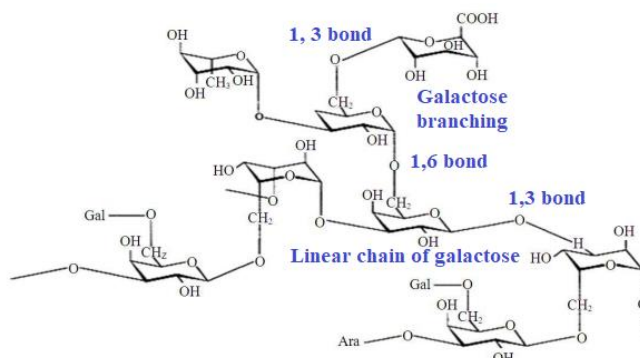


Fig.3. Chemical structure of gum arabic

The side chains are composed of two to five D-galactopyranose units linked with β -(1, 3) bonds, these chains are bonded to the main chain by β -(1, 6) glycosidic bonds. Both chains contain L-arabinofuranose, L-rhamnopyranose, D-glucuronyranose, and 4-O-methyl-D-glucuronyranose units [12]. Its chemical composition depends on the origin, climatic conditions, and soil environment; it has been reported that GA is composed of 39-42 wt.% galactose, 24-27 wt.% arabinose, 12-16 wt.% rhamnose, 15-16 wt.% glucuronic acid, 1.5-2.6 wt.% protein, 0.22-0.39 wt.% nitrogen, and 12.5-16.0 wt.% moisture [13]. Gum arabic is widely used as an excipient for the formulation of various syrups for therapeutic uses. Its adsorptive capacity has been used to combat kidney diseases. Due to its branched structure, gum arabic exhibits antibacterial properties [14, 15].

2.3. Xanthan Gum

Xanthan gum (GX) is a heteropolysaccharide secreted by *Xanthomonas spp.* It is a high molecular weight heteropolysaccharide that is found naturally in the extracellular matrix of these microorganisms, mainly formed by various fermentation processes. It is formed by a main chain of D-glucopyranoses linked by β -(1, 4) glycosidic bonds, this chain is branched by D-manopyranose and D-glucopyranosyluronic acid residue by β -(1, 3) bonds. The

α -(1, 2) bonded mannopyranose residues have 6-O-acetyl substituents. An average of about half of the α -D-mannosyl end groups have 4,6-O-(1-carboxyethylidene) substituents (Fig. 4). It can be isolated in the form of calcium, magnesium, and sodium salts. Xanthan gum has enormous applications ranging from the food and pharmaceutical industries to oil extraction, due to its properties as a thickener, emulsion stabilization, water retention and oil recovery. It is typically used in the food industry in salad toppings, sauces, dairy products, sauces, candies, and low-calorie foods, in general. Xanthan gum is also used in the manufacture of cleaners, varnishes, polishes, and agricultural fluids [16].

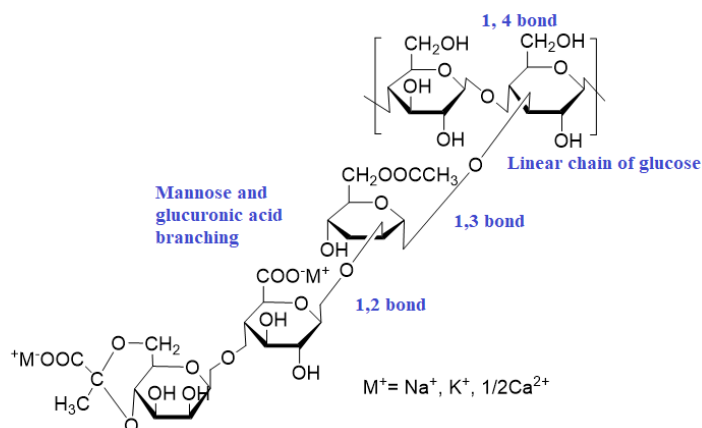


Fig.4. Chemical structure of xanthan gum

GX hydrates easily in aqueous media, forming a viscous solution. For applications in encapsulation and drug release with therapeutic interest, it is usually used in the presence of other polymers to modulate their properties. Among these polymers, galactomannan stands out for having a controlled release mechanism of theophylline by diffusion of the hybrid matrix and glucomannan for rapid release of drugs such as diltiazem in times of less than 24 h [17].

Xanthan gum has also been used to generate scaffolds for application in tissue engineering, standing out for modulating the growth of human fibroblasts, without producing irritation reactions. Interestingly, intra-articular injection xanthan gum device (0.5-2.0 wt.%) appears 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 movements. For this application, GX seems to work better than sodium hyaluronate because it is more stable against hydrolytic and enzymatic reactions *in vivo* [18].

3. Hydrogels for Biomedical Applications

Hydrogels are polymeric matrices swollen in water with a specific three-dimensional structure. They were the first designs of biomaterials for use in the human body as controlled drug releases [19]. These polymers have some well-known characteristics, such as being hydrophilic, soft, elastic, and insoluble in water, in addition to the fact that they swell in the presence of it, appreciably increasing their volume while maintaining their shape until reaching physicochemical equilibrium. Additionally, they can have great mechanical resistance depending on the method with which they are obtained. The hydrophilic character is due to the presence of polar functional groups such as: -OH, -COOH, -CONH, among others [20].

Hydrogels are very suitable materials for biomedical applications given their good interaction with living tissues, since on the one hand they show good biocompatibility properties, mainly due to their soft, elastic consistency and water content. In addition, their swelling characteristic in a liquid medium gives them the property of absorbing, retaining, and releasing quantities of water under controlled conditions that regulate their structural conformation, desirable properties in wound dressings [21]. Because of their tailored mechanical and swelling properties, hydrogels have been used in a variety of biomedical applications such as contact lenses in ophthalmology, absorbable sealants in general surgery, fillers for esthetic scar correction and other cosmetic applications, as well as coatings anti-adhesives on meshes for abdominal wall and hernia repair [22]. In recent years, due to their ability to immobilize and release cells, genes, proteins, and drugs, hydrogels have become important materials in biomedicine in fields as tissue engineering, and regenerative medicine. The following sections focus on various approaches that use guar gum, gum arabic, and xanthan gum polysaccharides to obtain hydrogels with potential biomedical application.

3.1. Biomedical Hydrogels with Guar Gum

Guar gum has been used in combination with other natural and synthetic polymers to generate novel hydrogels with tailored properties for biomedicine. The capacity of guar gum to favor the hydrophilicity of low-polar polymers has been used to develop devices that show the ability to controlled release drugs, self-healing capacity, physiological gelation, biodegradation and tailoring of cell metabolism; these properties can be used to develop hydrogel formulations that could have potential application in tissue engineering and/or regenerative medicine; Table 1 presents hydrogel systems based on guar gum, indicating the production process and improved properties.

Table 1. Hydrogels formed by GG for application in biomedicine

Chemical Composition	Preparation method	Improved properties	Potential biomedical use	Reference
Polyurethane	Solution-casting method and crosslinking by light	Self-healing capacity, improved mechanical, improved thermal degradation and improved swelling.	Wound dressing Controlled release of drugs	[23]
Polyurethane Polyacrylonitrile	Formation of semi-interpenetrating polymeric networks (semi-IPN)	Biodegradation and improved mechanical behavior.	Wound dressing	[24]
Collagen Poly(N-isopropylacrylamide)	Generation of interpenetrating	Self-healing ability, high ductility,	Wound dressing	[25]

	polymeric networks (IPN)	physiological gelation.		
Collagen Metal-organic frameworks (MOFs)	Formation of semi-interpenetrating polymeric networks (semi-IPN)	Improved mechanical, high swelling, biodegradation, physiological gelation, modulation of the metabolism of fibroblasts and monocytes, enhances cell proliferation and promotes the secretion of important cytokines in the healing process.	Wound dressing Controlled release of drugs	[26]

3.2. Biomedical Hydrogels with Gum Arabic

GA has great potential in the design and preparation of biomaterials in form of hydrogel. The applications of the reported hydrogels are as diverse as the controlled release of drugs, cell scaffolds and self-healing hydrogels. Table 2 shows some examples of hydrogels based on gum arabic, highlighting their chemical compositions, preparation methodologies, advantages, and potential applications in biomedical areas.

Table 2. Hydrogels based on GA for biomedical applications

Chemical Composition	Preparation method	Improved properties	Potential biomedical use	Reference
Polyacrylamide polyacrylate magnetite	Crosslinking/co-polymerization reaction in presence of magnetite	Magnetic particles allow release mechanisms to be activated and deactivated remotely.	Smart controlled release systems.	[27]
Gelatin	Chemical crosslinking by shift base formation	The scaffolds are non-cytotoxic and non-adherent and are suitable for culturing L-929 and Hep-G2 cell spheroids.	Cellular scaffolding	[28]

Gelatin polyacrylamide	Generation of interpenetrating polymeric networks (IPN)	The hydrogels have excellent mechanical properties, great adhesiveness on different surfaces. Materials self-heal up to 90% after 24 hours.	Self-healing hydrogels for tissular engineering	[29]
Hydroxyapatite	Freeze-drying process	The macroporous structure with a high mineral content promotes cell adhesion and proliferation of C2C12 cells. Materials with a high hydroxyapatite content increase calcium deposition in bone tissue.	Scaffolds for bone reconstruction	[30]
Chitosan gelatin	Electrospinning process	The addition of gum arabic in the formulation increases the viscosity of the solution significantly and allows the nanofibers to be obtained under milder processing conditions.	Tissue reconstruction	[31]
κ-carrageenan hydroxyapatite	Solution-casting method	The ternary mixture of biopolymers and hydroxyapatite accelerates the mineralization of an apatite layer.	Bone reconstruction	[32]
Poly(caprolactone) <i>Calendula officinalis</i> extract.	Electrospinning process	The controlled release of <i>Calendula officinalis</i> extract promotes the adhesion, proliferation and growth of fibroblasts.	Wound dressings	[33]

3.3 Biomedical Hydrogels with Xanthan Gum

Xanthan gum has been used to formulate novel hydrogels in the presence of other chemical components, highlighting its better physicochemical crosslinking, regulation of its mechanics, controlled release of components with therapeutic interest and capacity to modulate cellular metabolism. Table 3 shows various chemical compositions of hydrogels formed with GX, evidencing the synthesis methodologies, improved properties, and possible biomedical application.

Table 3. Hydrogels comprised from GX in their applications in biomedical fields

Chemical Composition	Preparation method	Improved properties	Potential biomedical use	Reference
Methacrylic derivative of chitosan	Physic crosslinking	Amorphous surfaces supporting proliferation of mouse dermal fibroblasts.	Soft tissue engineering	[34]
Polypyrrole	Generation of semi-interpenetrating polymeric networks (semi-IPN)	Higher hydrophobicity and much more elastic, allowing the proliferation of fibroblasts in the presence of a magnetic field.	Soft tissue engineering	[35]
Hydroxyapatite	Chemical precipitation	These hydrogels show improved mechanics and excellent performance in achieving bone mineralization.	Bone tissue engineering	[36]
Resorcinol bis(diphenyl phosphate) starch	Generation of semi-interpenetrating polymeric networks (semi-IPN)	Flame resistant hydrogel, without cytotoxic effects.	Wound dressings for burns	[37]

4. Perspectives and Conclusion

Natural gums based on polysaccharides such as GG, GA and GX allow modulating the structure, physicochemical and biological properties of various hydrogels that have been developed with other chemical components for biomedical applications.

The inclusion of natural gums in these hydrated matrices allows the generation of amorphous surfaces, where the physicochemical crosslinking is mediated by short-range interactions among the hydroxyl and/or carboxylate groups present in their glycosidic skeletons, mainly intermolecular hydrogen bonds, allowing the mechanics,

degradation, water absorption capacity to be tailored, besides allowing the encapsulation of molecules with therapeutic interest and their release in a controlled manner. The structures of these matrices have requirements for the diffusion of metabolites and nutrients in cell culture media, benefiting cell metabolism and the proliferation of various types of cells with biomedical interest, demonstrating its potential application in areas such as tissue engineering and regenerative medicine.

Due to this, the development of innovative formulations of hydrogels that contemplate these natural gums should continue to be explored, involving other chemical components and designing new routes for the generation of these biomaterials in order to offer novel hydrogels with both tailored structure and properties for a successful biomedical application.

Declarations

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Competing Interests Statement

The authors declare no competing financial, professional and personal interests.

Consent for publication

Authors declare that they consented for the publication of this research work.

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