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Review

Xanthan gum in drug release

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Abstract: Controlled release is of vital relevance for many drugs; thus, there is a keen interest in materials that can improve the release profiles of formulations administered via buccal, transdermal, ophthalmic, vaginal, and nasal. The desirable effects of those materials include the improvement of stability, adhesiveness, solubility, and retention time. Hence, different synthetic and natural polymers are utilized to achieve these objectives. In this respect, xanthan gum is an anionic polysaccharide that can be obtained from *Xanthomonas* bacteria. It is a natural polymer broadly employed in numerous food products, lotions, shampoos, and dermatological articles. Furthermore, due to its physicochemical features, xanthan gum is growingly utilized for the development and improvement of drug delivery systems. In this regard, encouraging findings have been revealed by recent formulations for pharmaceutical applications, including antiviral carriers, antibacterial transporters, transdermal patches, vaginal formulations, and anticancer medications. In this article, we perform a concise description of the chemical properties of xanthan gum and its role as a modifier of drug release. Furthermore, we present an outlook of the state of the art of research focused on the utilization of xanthan gum in varied pharmaceutical formulations, which include tablets, films, hydrogels, and nanoformulations. Finally, we discuss some perspectives about the use of xanthan gum in these formulations.

Key words: Xanthan gum; Drug release; Natural polymers; Controlled release; Drug delivery systems.

Introduction

Currently, the sustained release is a central concern for many drug delivery systems, including those for buccal, transdermal, ophthalmic, vaginal, and nasal administration (1). Many medications need to possess an extended-release profile to exert efficacious therapeutic effects (2–5). Thus, there is an increasing interest in compounds that can enhance these release profiles through the improvement of stability, adhesiveness, solubility, and retention time.

In order to accomplish this goal, different complexes have been investigated for the fabrication of controlled release formulations, including natural and synthetic polymers (6). However, those polymers must gather specific attributes, such as be biocompatible, biodegradable, non-immunogenic, with low toxicity, and inexpensive. Therefore, natural polymers are often chosen because they generally put together these properties; moreover, they are usually easy to obtain from plants, animals, and microorganisms, which are usually abundant in nature (7).

In this regard, xanthan gum is a polymer naturally produced by various types of *Xanthomonas* bacteria, including *X. campestris*, *X. phaseoli, X. arboricola*, *X.vasculorium, X. gummisudans, X. fragaria, X. citri,* and *X. axonopodis* (8). Although its industrial production is through of *X. campestris*, mainly (9).

Xanthan gum is an anionic polysaccharide approved by the FDA in 1969 as a safe polymer, and it is frequently employed for technological and industrial applications due to its properties (10). For example, it is

widely used as a stabilizer and thickener in a plethora of food products (11). Likewise, xanthan gum is utilized for the manufacturing of shampoos, lotions, and dermatological products (10), as well as in the petroleum industry (12,13), and tissue engineering (7).

Furthermore, xanthan gum can be used in controlled drug-release systems (6). Consequently, in recent years, this polymer has been extensively explored for a substantial number of biomedical and pharmaceutical purposes. In this respect, a variety of xanthan gum-based formulations demonstrated promising results for numerous applications, including periodontal diseases (14), antiviral carriers (15), antibacterial carriers (16), transdermal patches (17), vaginal delivery (18), anticancer drugs (19), controlled-release tablets (20), and hydrogels for the administration of various drugs (21–25).

Here, we present an overview of the chemical properties of xanthan gum and its role as a modifier of drug release. Moreover, we perform a concise description of current research focused on the utilization of xanthan gum in diverse pharmaceutical formulations, including tablets, films, hydrogels, and nanoformulations. Finally, we discuss some perspectives about the use of xanthan gum in future formulations.

Xanthan gum chemistry

The Xanthan gum has a primary structure constituted by a cellulose-like backbone (3 → 1) linked to a side chain of α-D-mannose-(2 → 1)-β-D-glucuronic acid-(4 → 1)-β-D-mannose (Figure 1). In this regard, the constituent elements generally exist in a molar ratio of 2.8:2.0:2.0 for D-glucose, D-mannose, and D-glucuronic acid, respectively (26,27). Moreover, the xanthan gum can exist as a single, double, or triple helix (26).

The FDA approved xanthan gum as a safe polymer in the food industry in 1969; thus, the xanthan products can be found in four grades: crude, industrial, food, and medical auxiliary (28). Despite its high molecular weight (regularly between 2 x 10^6 to 20 x 10^6 Da), the xanthan gum is soluble in cold and hot water, and ethanol, but in this case, intense stirring is needed for dismiss agglomeration. Xanthan gum is identified based on the formation of a firm rubbery gel when a hot aqueous solution of a mixture of xanthan gum and carob bean gum (0.5% w/v each) is cooled below 40°C. The molecular stiffness of xanthan gum induces an extended conformation of the molecules in solution, obtaining high viscosity solutions compared with other polysaccharide solutions (26,27,29–31).

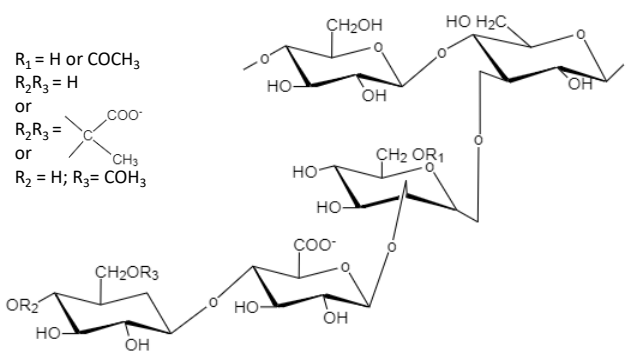

Figure 1. Chemical structure of xanthan gum.

Xanthan gum solutions have non-Newtonian fluid properties and high pseudoplastic behavior, decreasing its viscosity with the increase in shear rate from 0.01-100 Hz at 25 °C in a 0.6% solution. Nevertheless, the content and distribution of acyl groups in the molecular chain could affect the rheological behavior. In this regard, there are six units of the pyruvate and acetyl ones in natural xanthan. The pyruvate molecules could destabilize the helical conformation, whereas a high pyruvate presence increases the viscosity (27,29,32).

On the other hand, the conformational transition temperature (T_m) is one of the main evaluation indexes of xanthan products; this temperature describes the dramatic modulus changes in the polymer. The time/temperature superposition principle is applied over all the temperature range for shear and elongation measurements to compare the structural changes induced by the transition (33). The T_m can be determined through *in situ* heating (25–80 °C) and cooling (80–25 °C) at a rate of 3 °C/min, as previously reported by Wu Ma et al. The increase in temperature promotes a structural change in xanthan gum from a double helix to a single helix conformation, followed by a disordered coil structure (27,29). These conformational transitions depend on the ionic strength and pH, as well as the structural features, such as the pyruvic and acetic acid content. Likewise, other measurements as optical rotation, calorimetry, and circular dichroism support the coincidence between the viscosity and the conformational changes (34).

The molecular properties of the xanthan gum provide higher stability against degradation or hydrolysis than other polysaccharides, which allow the application of heating (in processes such as sterilization), as well as a wide range of pH values (30). These properties make xanthan gum suitable for the production of drug delivery systems. For example, Mikac et al. evaluated the release of pentoxifylline tablets or gel, by magnetic resonance imaging (MRI) assay. The authors found some changes in the xanthan gum molecular conformation at physiological conditions, reporting that the pH and the ionic strength quickly influenced the structure and the drug release kinetic (10,35).

Besides its desirable physicochemical properties, the xanthan gum possesses high biocompatibility, low toxicity, and immunological properties. Thus, it can be blended with other polysaccharides to take advantage of its attributes. For example, Da-Lozzo et al. mixed xanthan gum with galactomannan to form a hydrogel. This hydrogel exhibited excellent biocompatibility after the implantation in an angiogenic model (avian chorioallantoic membrane extra-embryonic), indicated for no neovascularization or fibrosis (36). Moreover, due to its low toxicity, xanthan gum is widely employed as a complement in several products, including infant formulas (31).

On the other hand, in recent years, the attention in xanthan gum increased because some research groups reported an antioxidant activity against the effect of hydroxyl radical (·OH) on tissues (27). Similarly, Kang et al. investigated the ·OH scavenging effects of xanthan gum products obtained from *Xanthomonas campestris* supplemented with furfural, the systems with the lowest level of furfural (1 g/L) exposed the maximum scavenging activity. Nevertheless, reducing potential has no

difference (37). In this regard, although the presence of glucose and mannose in the xanthan gum suggests this antioxidant feature (38), Kang et al. indicated that the amounts of pyruvate, acetyl, and glucuronic acid are responsible for modifying the scavenging ability of ·OH in the xanthan gum (37).

Therefore, xanthan gum has suitable characteristics to be applied as a drug delivery system in a wide variety of presentations such as tables, films, hydrogels, or nanoformulations.

Matrix tablets

The use of xanthan gum as a matrix-forming polymer in sustained-release tablets started in the early 90s of the last century, prompted by the incorporation of natural/food grade alternatives of polymers in drug delivery (39–41). Aqueous dispersions of xanthan gum have shown tolerance to high concentrations of electrolytes, being the viscosity virtually independent of pH and temperature (39,42). Thus, these characteristics render xanthan gum an ideal and competitive excipient (frequently compared with hydroxypropyl methylcellulose) for the formulation of hydrophilic matrix drug delivery systems.

Due to the hydrophilic nature of xanthan gum, most of the model drugs incorporated in the matrix are highly soluble, limiting the incorporation of hydrophobic drugs at high concentrations (43). The drug release mechanism from the xanthan gum-based matrix depends on the drug solubility. In this regard, for insoluble drugs, the release mechanism is typically associated with swelling and matrix erosion, while the soluble drugs are released via a diffusion mechanism (40,44). However, Mikac et al. performed a complete study to evaluate the influence of high drug loading (high solubility), pH, and ionic strength on swelling and release in xanthan matrix tablets. The authors found that those factors did not modify the swelling behavior. In water and diluted acid medium with low ionic strength, the main release mechanism was by erosion. In contrast, in acidic media (pH 1.2, $\mu \geq 0.20$ M), anomalous transport dominates owing to changes in the polymer structure (45).

The slow-release presented in highly soluble drugs is mediated by the formation of a thick gel structure (swell state) that delays drug release from the matrix tablet, where hydration of individual xanthan gum particles results in extensive swelling that decelerates the rate of release (40,46). Also, it is crucial to know the mass transfer mechanism of the drug from the matrix, mediated by the nature of the polymer. For the xanthan gum matrix, the majority of drugs are transported by Case II diffusion, which is characterized by linear kinetics (zero-order) and a sharp diffusion front; it occurs in polymer penetrant systems in which the penetrant substantially swells the polymer. In zero-order release, the drug is released at a constant rate, which is the goal of all controlled-release drug delivery.

Xanthan gum matrix can be easily manufactured by conventional processes, such as direct compression or wet granulation; the method does not influence the release rate profile of the drug. On the other hand, the addition of water-soluble (e.g. Lactose) or water-insoluble excipients (e.g. dicalcium phosphate, magnesium stearate) could modify the porosity, swelling capacity, and release behavior of the xanthan gum hydrogels.

Recently, one study analyzed the blend of xanthan gum with other natural polymers to produce a matrix with better mechanical properties without detriments in drug release attributes. Xanthan gum in concentrations about 30-40 % tends to produce hard tablets and extends the time of release, while at low concentrations (10-20%), the mechanical strength lacks, and the matrix erosion is fast at the surface (burst effect) (20). Xanthan gum blended with other polymers seems to resolve part of the problems. Table 1 summarizes some characteristics of matrix based on xanthan gum and combinations.

Films

Besides the tablets, films based on xanthan gum have been extensively studied and applied. The use of films as a dosage form has a variety of possibilities of applications (buccal, oral, sublingual, ocular, transdermal, etc.) due to their versatility. Usually, a drug delivery film is a thin and flexible polymeric layer that could or not include a plasticizer. These characteristics make them less obstructive for the patient, resulting in a more acceptable form of administration (56,57).

Therefore, xanthan gum films have been applied as a platform for different drugs and nanoformulations. In this regard, Huang et al. developed a xanthan-based film enriched with citric acid and silver nanoparticles (AgNPs) to evaluate its effectivity in infection prevention during the wound healing process. The microstructure of the films and the identification of AgNPs were analyzed by microscopy. The films displayed a porous structure (pore size ~100 μm), finding the nanoparticles well-dispersed all over the film, without agglomerations. The authors reported that the film's biocompatibility depended on the AgNPs concentration, being 10 μl the maximum content of nanoparticles to result nontoxic. However, the AgNPs were released from the xanthan film in a gradual way, increasing the action time, and preventing the cytotoxic effects of silver in dermal cells. Besides, the efficacy of the film was evaluated in an infected wound model, exhibiting a higher healing rate compared with gauze or film AgNPs-free conditions (58).

In the same way, the release of nicotine from xanthan gum films was studied (59). The drug delivery profile showed that, after 10 hours, 98% of nicotine was released from the xanthan gum film; in contrast, the control film (Carbopol) allowed the release of only 39% of the drug. This behavior is related to the high interaction between Carbopol and nicotine, restricting the drug release, and even the swelling capacity. Furthermore, the adhesive properties of the xanthan gum film (0.10 ± 0.08 mm of thickness) were evaluated and compared with the Carbopol film (0.14 ± 0.08 mm of thickness), revealing that the Carbopol film presented a higher adhesion. Similarly, films of xanthan gum have been employed in the zolmitriptan delivery as a buccal mucoadhesive patch (60). These patches were elaborated with the gum and polyvinyl alcohol (PVA), variating the concentrations of both to obtain different properties. The characterization of the films was carried out through several techniques such as swelling index, drug release,

Table 1. Matrix-based on xanthan gum and combinations.

Drug (s)	% of Xanthan gum	Matrix preparation method	Other excipients	Release mechanism	Ref
Acetaminophen, Chlorpheniramine maleate, Theophylline	5 – 19	Direct compression	Lactose, magnesium stearate	Soluble drugs: diffusion; insoluble drugs: erosion	(40)
Caffeine	4 – 33	Wet granulation and direct compression	Lactose, PVP, microcrystalline cellulose	n.d.	(39)
Caffeine and indomethacin (base and salt)	n.d.	Direct compression	None	Diffusion (Case II)	(41)
Pentoxifylline	3 – 30	Direct compression	Lactose, magnesium stearate	n.d.	(47)
Lamivudine	30 – 50	Direct compression	Magnesium stearate, talc, microcrystalline cellulose	Anomalous diffusion mechanism or diffusion coupled with erosion	(48)
Isosorbide-5 mononitrate	14 – 38	Direct compression	Cellulose microcrystalline	n.d.	(49)
Propranolol hydrochloride	27 – 82	Wet granulation	Lactose	Fickian diffusion	(50)
Propranolol hydrochloride	26 –78	Direct compression	Lactose, magnesium stearate	Diffusion	(46)
Cefixime trihydrate	8 – 20	Direct compression	Magnesium stearate, talc, microcrystalline cellulose	Diffusion	(51)
Propranolol hydrochloride, sodium diclofenac	24	Direct compression	Magnesium stearate, microcrystalline cellulose	Diffusion with erosion	(52)
Pentoxifylline	50 – 75	Direct compression	n.d.	Diffusion	(45)
Sodium diclofenac, metformin hydrochloride	12.5 – 50	Direct compression	Cashew gum, magnesium stearate, microcrystalline cellulose	Fickian diffusion	(53)
Theophylline	30 – 60	Direct compression	Magnesium stearate and hydrophilic fumed silica	n.d.	(54)
Metoprolol Succinate and Dyphylline	n.d.	Direct compression	Chitosan, Lactose	n.d.	(20)
Metoprolol succinate	8 – 30	Wet granulation	Carbomer, lactose, microcrystalline cellulose, talc, magnesium stearate	Diffusion	(55)

in vitro mucoadhesive strength, *ex vivo* mucoadhesion time, weight, and thickness. Based on the optimum results, the authors selected the formulation with 0.3% of gum (w/w) and 1% of PVA (w/w). Then, the evaluation of *ex vivo* drug permeation was performed, finding that the addition of DMSO as a penetration enhancer could be useful. The evaluation of the final formulation showed no cell damage in the buccal mucosa.

Besides PVA, it has been reported the blend of xanthan gum with other polymeric materials such as guar gum, pullulan, or gelatin to enhance the film properties (61–63). For instance, Hazirah et al. evaluated the variation of the features of Gelatin-carboxymethyl cellulose (CMC)-xanthan gum films depending on the xanthan gum concentration. They found that the gum addition increased characteristics such as the moisture content and the water vapor permeability, besides the thickness of the films. However, new functional groups were not formed (64). Likewise, the effect of xanthan gum with different aldehyde content (by periodate oxidation) was analyzed in gelatin-xanthan gum films (65). The results suggested that the presence of the gum in the films re-

duced the moisture content and the water vapor permeability, improving mechanical and thermal properties. Therefore, in some instances, the films are not the best dosage form because a platform with a considerable thickness is needed. In this regard, the application of hydrogels could be an alternative.

Hydrogels

Hydrogels are materials formed through the cross-linking of hydrophilic polymer chains within an aqueous microenvironment. Gelation is achieved through several types of mechanisms that include physical cross-linking, electrostatic interactions, and covalent chemical cross-linking (66). The method used and the cross-linking grade are determining factors of the physicochemical properties and mechanical stiffness of these polymeric networks (67). The high hydrophilicity of hydrogels (capability of water retention from 70 to 99%) makes them suitable for encapsulating drugs, maintaining their structural integrity, and reducing the risk of enzymatic denaturation once inside the body (68). There are several reports of the use of hydrogels based on xanthan gum alone and crosslinked with other polymers such as karaya gum, guar gum, hydroxypropyl methylcellulose, and polyvinylpyrrolidone (50,69–71). Xanthan gum hydrogels have been applied as drug carriers and controlled drug release systems, allowing the controlled delivery of different drugs, including caffeine, azithromycin, ibuprofen, and propranolol HCl (39,72–75).

Recently, the conjugation of xanthan gum with chitosan was studied using 2-acrylamido-2-methylpropane sulfonic acid (AMPS) as a monomer, N′N-methylenebisacrylamide as a crosslinker, and potassium persulfate as free radical initiator. The resulting hydrogel was tested for the controlled release of acyclovir (15), showing that this pH-sensitive hydrogel presented potential as an antiviral drug carrier using pure polymers (chitosan, xanthan gum, and AMPS). Likewise, other researchers successfully grafted acrylic acid onto a xanthan gum/starch hydrogel assisted by microwave radiation. The hydrogel was polymerized using N′N-methylenebisacrylamide as a crosslinker agent and ammonium persulfate as a free radical initiator. This method allowed successful drug release of molecules such as aspirin and paracetamol (76). Interestingly, in the two previous works, the drug release was observed to be dependent on pH.

Similarly, the use of xanthan gum/chitosan-based hydrogels has also been explored in water-soluble drugs, such as tinidazole, theophylline, and tramadol (77–79). Experimental results showed a release of up to 99% of the drugs after 24 h. Comparable results have been obtained when xanthan gum is crosslinked with starch because this combination increases the thermal and mechanical stability of the hydrogels (69,76).

On the other hand, in another recent study, Rajput et al. designed an *in situ* formed gel based on xanthan gum and gellan gum, for the incorporation of a nanostructured lipid carrier of resveratrol to deliver it into the brain by nasal route. Resveratrol possesses some physicochemical properties that represent a challenge to transport this molecule to the target tissue successfully. Thus, the aim of the *in situ* formed gel was to preserve the resveratrol, improving its concentration in the nasal cavity and, in consequence, its absorption. *In vivo* experiments exhibited that amnesia induced rats presented a faster recovery when they were treated with the *in situ* gel formulation by nasal administration, rather than those rats treated with a resveratrol suspension by oral administration (80).

Controlled drug release

Drug encapsulation is a strategy that allows protecting molecules from degradation, controlling the release, or even promoting the targeting of pharmaceutical forms. The decrease in the rate of degradation allows reducing the dose of the drugs, and therefore the possible adverse effects. Whereas controlling the release of drugs is an appropriate strategy for chronic treatments because it decreases the number of administrations and maintains a stable plasma concentration profile. Furthermore, the targeting of encapsulation systems towards the site of action is revolutionizing the medical possibility by proposing efficient disposal of drugs, even well-known molecules.

Microparticles

Some studies have described the use of xanthan gum in the manufacture of microparticles for drug release. For example, Ray et al. developed xanthan gum carriers with PVA for gut release of diclofenac sodium, via emulsion cross-linking method with glutaraldehyde (81). The average diameter of the particles was from 310-477 μm, with an encapsulation efficiency of 82%. The release mechanism was of Fickian type following diffusion processes with a prolonged release. Furthermore, the microparticles exhibited a decrease in C_{max}, a prolonged t_{max}, and a reduction in the k_{el} elimination rate (81).

On the other hand, with the orifice-ionic gelation method was possible to obtain xanthan gum microparticles in combination with sodium alginate via cross-linking with $CaCl_2$ for encapsulation of Glipizide (82). That drug is a second-generation sulfonylurea that stimulates the release of insulin. Glipizide has a short $t_{1/2}$, low gastric residence time, and is considerably affected by gastric content; thus, the microparticle formulation would offer drug protection and prolonged release, whereas the combination of the gums could offer a self-adhesive system. The authors obtained microparticles with a diameter of 828 μm, and they observed an increase in the size of the particles according to a higher addition of xanthan gum (82). Another example involved the production of xanthan gum microparticles in combination with Arabic gum for the encapsulation of the *Eschweilera nana* Miers (an extract with high antioxidant activity) through the spray-drying method (83). The microparticles obtained were characterized as spherical particles with a mean particle size of 3.5 μm, smooth surface, and a hollow core. The release profile was of the prolonged type and provided thermal protection to the extract, while the encapsulation efficiency was 98.5%. Moreover, the presence of flavonoids and polyphenols of the extract in the new formulation decreased the reactive oxygen species (ROS) in human neutrophils. Although the authors

described the system as prolonged-release formulation, the effect on ROS depended on the exposure time of the microparticles (83). In another type of combination of dosage forms, one study reported the synthesis of xanthan gum microparticles in combination with chitosan for encapsulation of quercetin, a flavonoid with antioxidant/anti-inflammatory properties, but low absorption in the gastrointestinal tract (84). Subsequently, the microparticles constituted an excipient to formulate tablets coated with Eudragit to increase gastric resistance for oral administration. The particles exhibited a size of 5 µm with an encapsulation efficiency of 63%. On the other hand, the tablets displayed adequate mechanical properties, resistance to acid pH degradation, high swelling capacity, and prolonged-release (84).

Nanoparticles

The use of xanthan gum in the manufacture of nanoparticles for controlled release has been, to our best understanding, uniquely as a surface stabilizing agent.

One of the examples of such an application corresponded to the manufacture of PEGylated gold nanoparticles and stabilized with xanthan gum for improving the delivery of curcumin in cancer treatment (85). In this work, the authors utilized an oxide-reduction reaction to obtain the nanoparticles, and they employed xanthan gum immediately as a stabilizer. Later, the authors worked on the pegylation of the nanoparticle and, finally, the linkage of curcumin. The nanoparticles presented an average size of 80 nm. The research demonstrated that cellular-uptake and the cytotoxicity degree in a melanoma cell model (B16F10) depended on the concentration and the time (85).

Interestingly, in another similar research, the authors employed xanthan gum as a reducing and stabilizing agent for gold nanoparticles synthesis for the controlled release of doxorubicin hydrochloride (86). The nanoparticles exhibited a size of 15 nm and stable zeta potential of -29 mV; moreover, the formulation was stable in serum for up to 24 hours. The nanoparticles had a 3-fold superior cytotoxicity effect on A549 human lung cancer cells compared to the drug in solution. In another study similar to cancer, the authors synthesized gold nanoparticles utilizing xanthan gum as a reducing and stabilizing agent and green excipient. However, the difference in the methodological strategy was the use of the carboxymethyl xanthan gum derivative (87). Via microwave irradiation method, the nanoparticles exhibited a mean particle size less than 20 nm and a zeta potential higher than -20 mV. The drug doxorubicin hydrochloride was adsorbed on the surface by electrostatic charges through incubation. The authors described a 4.6-fold increase in anticancer efficacy in the LN-229 human glioma cell line, in addition to a rise in cellular-uptake, unlike the drug in solution. The idea of using xanthan gum as an environmentally friendly excipient has also been exploited by another group of authors who synthesized xanthan gum-stabilized Cerium oxide nanoparticles by a co-precipitation method (88). Cerium oxide nanoparticles have antibacterial and antioxidant activity. However, since it is a metallic oxide, it is necessary to demonstrate its biosecurity. In this respect, the authors evaluated the biocompatibility of the nanoformulation by continuous administration in Wistar rats for three weeks. Later, they carried out biochemical and histological tests to reveal possible alterations. The authors documented an increase in antioxidant activity with adequate internalization in hepatocytes applying low nanoparticle concentrations (30 mg/kg).

On the other hand, drug release has been investigated in xanthan gum-functionalized span nanoparticles for gene targeting. In this research, the incorporation of xanthan gum improved the targeting of nanoparticles toward the mannose receptor and facilitated the uptake of diverse glycoconjugate ligands (89). In particular, these formulations can target the cellular endothelium, the place of residence of some diseases such as diabetes, chronic kidney failure, venous thrombosis, heart disease, and viral infections. To corroborate the effectiveness of the formulation, the authors incorporated the Enhanced Green Fluorescent Protein plasmid (pEGFP) to track the degree of transfection in Human Umbilical Vein Endothelial Cells (HUVECs), accompanied with biodistribution studies after systemic administration in mice. The authors mentioned adequate protection of the plasmid by the nanoparticles and an efficient transfection capacity in HUVECs.

Interestingly, *in vivo* biodistribution studies revealed the expression of green fluorescent protein in the vascular endothelium of the lung, liver, and kidney. The gene targeting to mannose receptors by the presence of xanthan gum in the nanoparticles confirmed the central hypothesis. Finally, in addition to providing a negative charge coating on the nanoparticles and a high degree of hydrophilicity, xanthan gum has also been used to manufacture wheat gluten nanoparticle complexes to stabilize Pickering emulsions containing oil droplets coated by protein particles (90). These applications prove the extensive versatility of xanthan gum in the manufacture of nanoparticles (Figure 2).

Conclusion and Perspectives

Xanthan gum is an attractive natural polysaccharide in terms of its high potential for biomedical applications. It offers numerous possibilities for researchers to develop new sustained-release formulations. In this regard, despite the high potential of xanthan gum for the fabrication of controlled-release systems, its extensive utilization in those formulations is relatively recent;

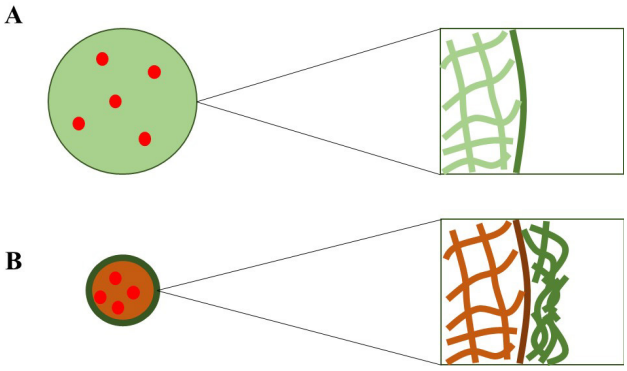

Figure 2. Xanthan gum is used as a matrix material for the manufacture of microparticles in the release of drugs (A). In contrast, in the preparation of nanoparticles, its use predominates only as a surface stabilizing agent (B). Xanthan gum is represented in green fibers, and drug molecules are symbolized in red dots.

thus, some possible drawbacks still should be considered. For example, as a result of the extended-release, preparations such as tablets could reach the colon before its total dissolution, which would lead to a decrease in the adsorption process and deficient bioavailability of drugs. In this regard, the evidence mentioned above suggests that the mixture of xanthan with other biopolymers could improve their properties. Therefore, further investigation will be needed to establish the proportions of xanthan gum and other excipients accurately to overcome this potential disadvantage

On the other hand, the utilization of xanthan gum in different formulations, including films, hydrogels, microparticles, and nanoparticles, offers fascinating prospects. Microparticles and nanoparticles result of particular interest since these systems may serve as carriers and avoiding degradation of drugs. Concerning this, xanthan gum can modify and optimize these preparations, improving the release control, and decreasing the degradation rate, which would be very useful for chronic pharmacological treatments. However, the addition of xanthan gum to these types of preparations has been scarcely investigated, which represents an opportunity area.

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Interest conflict
The authors declare no conflict of interest.

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