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Research paper

Glucomannan, a promising polysaccharide for biopharmaceutical purposes

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ABSTRACT

Over the last few decades, polysaccharides have gained increasing attention in the biomedical and drug delivery fields. Among them, glucomannan (GM), has become a particularly attractive polymer. In this paper, we review the physicochemical and biological properties which are decisive for the exploitation of GM as a biomaterial. These properties include the structural organization, molecular weight, solubility, viscosity, gelling properties and degradation behavior. Moreover, herein we analyze the possibilities of combining GM with other hydrophilic polymers, as well as the preparation of semisynthetic derivatives of GM, which may be of interest in the pharmaceutical context. Finally, we discuss the specific applications of GM in the drug delivery field.

1. Introduction

Natural polysaccharides, as well as their derivatives, have been classically used in pharmaceutical formulations as solubilizers or adhesives. Over the last few years, the evolution of these polysaccharides from the concept of "pharmaceutical excipient" to "bioactive material" has raised their potential use in the design of drug-delivery carriers. This conceptual change has, partially, been motivated by the recent emphasis in the design of biomimetic and intelligent drug delivery nanostructures, which can be recognized and assimilated in the body [1–4]. In fact, polysaccharides can be used as ligands in order to facilitate the interaction of a nanostructure with a specific biological surface [5,6]. As a consequence of these new potential applications, the number of publications dealing with the use of polysaccharides for drug delivery has remarkably increased over the last 10 years (see Fig. 1).

A very promising polysaccharide, which has been lately incorporated into the drug delivery field is glucomannan (GM) [7–11]. GM is a hydrocolloidal polysaccharide consisting in β-1,4 linked mannose and glucose residues [12]. Despite its potential in drug delivery, most of the review articles about GM have been focused on its chemical and physicochemical properties, such as chemical structure, molecular weight, gelation behavior, and ability to interact with other polymers, such as carregeenan or xanthan [13,14]. Just a few recent reports have only considered the pharmaceutical and therapeutic applications of GM [15,16]. In this paper, we review the critical aspects about GM, closely related with its promising utility in the design and development of new drug delivery systems.

2. Glucomannan: origin and structure

Glucomannan (GM) is a polysaccharide of the mannan family, very abundant in nature, specifically in softwoods (hemicellulose), roots, tubers and many plant bulbs [17–23]. Despite the variety of sources, the most commonly used type of GM is named konjac GM, which is extracted from tubers of *Amorphophallus konjac* [24,25]. Irrespective of its origin, GM is composed of β-1,4 linked D-mannose and D-glucose monomers (Fig. 2) [12]. However, the mannose/glucose monomer ratio may vary depending on the original source of GM. For example, it has been reported that konjac GM has a molar ratio of around 1.6:1, whereas GMs extracted from Scotch pine and orchid tubers have ratios of 2.1:1 and 3.6:1, respectively [20,26]. These values should be regarded cautiously given the variability observed depending on the studies and, in particular, on the analytical procedures.

In addition regarding the variable glucose/mannose ratio, the diverse types of GM may differ in their acetylation degree. The typical acetylation degree values are 5–10%. On the other hand, it is known that native GM can be easily acetylated with acetic anhydride in the presence of a catalyst [27–29].

Despite the information on the GM chemical structure, additional work is needed in order to fully understand how its structure

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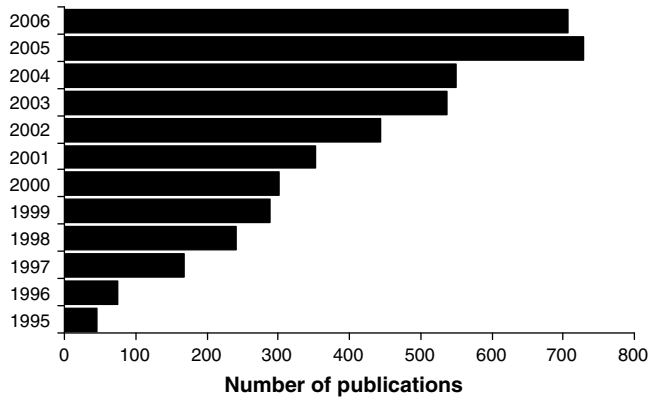

Fig. 1. Number of scientific publications published on the topic of hydrophilic polysaccharides in the drug delivery field as function of the publication year. Taken from CAPLUS and MEDLINE (*SCIFINDER SCHOLAR2006 Edition*). Keywords entered: Polysaccharides and Drug Delivery.

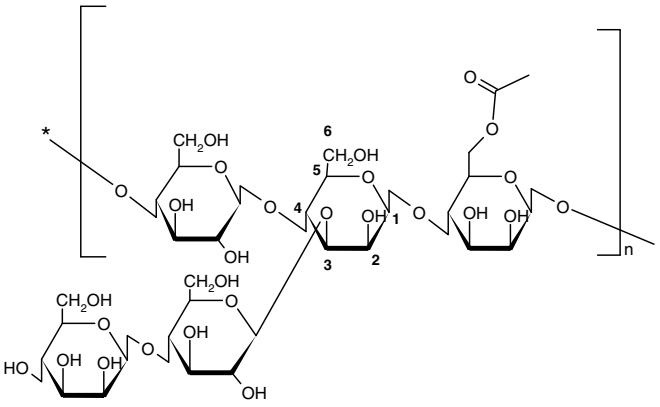

Fig. 2. Chemical structure of GM.

and composition affect its physicochemical and pharmaceutical behavior.

3. Physicochemical properties

3.1. Solubility

Although GM is a hydrophilic molecule, its solubility in water can be reduced due to the formation of strong hydrogen bonds after purification or drying processes [30,31]. Among the parameters that affect the aqueous solubility of GM, the acetylation degree appears to be particularly important. More specifically, the presence of acetyl groups in the GM has been described to inhibit the formation of intramolecular hydrogen bonds, thus improving the GM solubility [29]. Moreover, a number of GM derivatives (discussed in Section 5) have been synthesized in order to increase the GM aqueous solubility. This versatile solubility behavior could be of special interest for a variety of pharmaceutical applications that will be later described.

3.2. Molecular weight

The molecular weight (M_w) of GM has been determined by light scattering, viscosimetry and Gel Permeation Chromatography (GPC). One of the main problems in the determination of GM M_w relies on its limited water solubility. In fact, some of M_w studies have been performed with GM, which has been chemically modified in order to increase its solubility in water or other solvents [30]. Mark-Howinks parameters were fixed according to $\eta = 3.8 \times 10^{-2} \times M_w^{0.723}$ for a solution of konjac GM in water at 25 ± 0.5 °C [32].

The most frequently used and commercially available GM has a M_w in the range of 1.9×10^6–1×10^4 [30,33,13,14]. Nevertheless, there is also the feasibility to depolymerize GM in order to obtain low M_w GM. This strategy may offer interesting possibilities in the pharmaceutical field. In fact, it is known that the polymer M_w has an influence on the physicochemical characteristics of the drug delivery systems [34,10], as well as on their efficacy *in vitro* and *in vivo*. As an example, polymeric nanoparticles based on low M_w chitosan showed higher transfection efficiency *in vitro* and *in vivo*, than those prepared with high M_w chitosan [35,36].

Among the techniques described until now to decrease the GM M_w, acid, alkaline and enzyme hydrolyses are the most important [19,37,12,38,39].

It is well known that certain enzymes can convert polysaccharides into oligosaccharides. The complete degradation of the GM backbone requires the action of β-mannanase, β-mannosidase and β-glucosidase [40–42].

β-Mannanase is of special interest in polysaccharide degradation because it catalyzes the random cleavage of β-D-1,4-mannopyranosyl linkages. The breakdown of these linkages in GM leads to mannobiose and mannotriose [43–50]. The ability of β-mannanase to degrade the GM backbone depends on several factors, such as the number and distribution of the substituents on the backbone and the ratio of glucose to mannose [51]. This enzyme is in bacteria (*Bacillus* sp., *Aeromonas* sp., *Penicillium* sp., *Pseudomonas* sp. or *Vibrio* sp.) [52–57] fungi (*Streptomyces* sp., *Tyromices* sp., *Trichosporum* sp., *Sclerotium* sp. and *Aspergillus* sp.) [58–62,50], as well as in plants (*A. konjac*) [40], in animals [63,49] and in the colonic region of humans [64,65].

The enzyme β-mannosidase, which catalyzes the removal of D-mannose residues from β-1,4-linked manno-oligosaccharides, leads to the conversion of GM into D-mannose [43,66]. As in the case of mannanase, this enzyme is present in many microorganisms, plants and animal tissues [67].

Finally, the degradation by β-glucosidase occurs only at a terminal glucose unit and stops at terminal oxidized residues or mannose units [68] (Fig. 3).

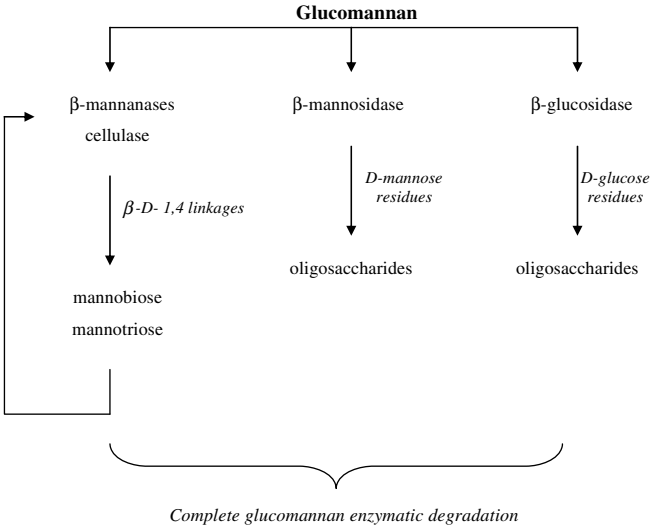

Fig. 3. Scheme of the enzymatic degradation of GM.

With respect to the influence of GM properties on its enzymatic degradation, some studies have shown that the acetyl groups inhibit β-mannanase and β-mannosidase activity [62,69].

3.3. Gelation properties

The knowledge of the GM gelation mechanism, as well as the variables that affect this process, is useful in the design and understanding of the mechanism of formation of GM-based delivery systems. GM gels can be prepared by heating a GM solution containing alkaline compounds or higher amounts of neutral salt [33,70]. The gelation process occurs due to the interaction of the GM acidic moieties with alkalis [71]. This interaction induces structural changes in the GM molecules, which facilitate the establishment of hydrogen bonds and hydrophobic interactions between the GM chains, consequently, leading to the formation a network gel structure (Fig. 4) [27,33,14,71,29].

There are a number of parameters which affect the GM gelation behavior and, thus, the properties of the final gel structure. These parameters are the GM acetylation degree, the GM M_w, the temperature and also the concentration of both GM and the alkali involved in the gelation process (see Table 1). The specific influence of each parameter is described as follows.

Since acetylation hinders the aggregation of GM, the increase in the GM acetylation degree leads to a delay in the gelation process [71,29]. On the contrary, gelation is favored when the M_w, alkali concentration or temperature increases. This is not only due to the enhancement of the interactions between GM chains [14], but also due to the formation of hydrogen bonds in the junction zones requiring energy [27,71,14,29].

At low GM concentrations, the formation of the GM gel is impaired by the distance between molecules. In this situation a previous deacetylation process is required in order to facilitate the approximation of the GM molecules. However, at high GM concentrations the proximity of GM molecules promotes the interaction between them, favoring the formation of the network [33,27,14,71,29].

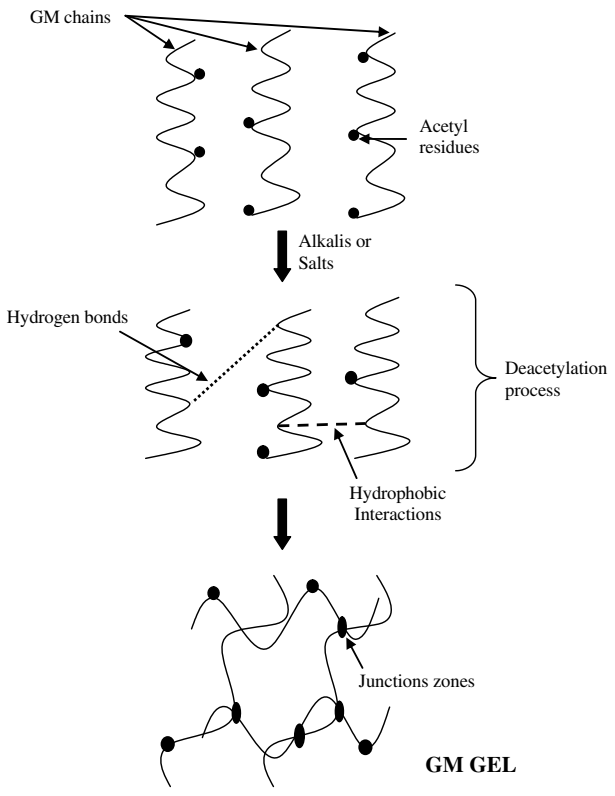

Fig. 4. Scheme of gelation mechanism of GM.

Table 1
Influence of different variables on the gelation mechanism of GM

Variable		Gelation mechanism
↓ Acetylation degree	↑ Formation of hydrogen bonds	Promote the formation of GM gel
↑ GM M_w	↑ Number of junction zones ↑ Length of connecting chains	
↑ GM concentration	↑ Number of molecules ↑ Proximity between molecules	
↑ Temperature	↑ Formation of hydrogen bonds	
↑ Alkali concentration	↑ Deacetylation process ↑ Formation of hydrogen bonds	

4. Interaction of glucomannan with other polymers

The possibility to combine GM with other polymers increases its versatility in the drug delivery field. In fact, the interaction of GM with other polysaccharides has been extensively investigated in order to produce new gels with improved gelling properties [72–74].

Carrageenan, xanthan, acetan, gellam gum, alginate and chitosan are some examples of polysaccharides which were combined with GM [75,31,76,14,24,25].

4.1. Interaction with kappa carrageenan

Kappa carrageenan forms thermoreversible gels and its gelation depends on the temperature, concentration of counterions or other polysaccharides. More specifically, its interaction with GM gives thermoreversible gels [75], in which the structure is affected by the GM M_w [31] and also by the addition of a small amount of sugars [13].

The potential of these hydrogels for drug delivery applications has been suggested [77]. However, so far we have not found any evidence of this in the literature.

4.2. Interaction with xanthan

Xanthan gum does not naturally gel at any concentration, however gelification can be induced by temperature, ionic strength of the solution, the pH and the type of electrolyte (K^+, Cs^+, Na^+, NH_4^+, Ba^{2+}, Mg^{2+}, Ca^{2+}). The interaction with GM is ruled by a preferred stoichiometry, where the ratio xanthan:GM is 1:2 [78–80].

It has been recently reported the application of xanthan–GM gels and solutions as drug delivery systems of macromolecules and low M_w drugs has been recently reported [80–82].

4.3. Interaction with acetan (xylinan)

The polysaccharide acetan, secreted by the bacterium *Acetobacter xylinum*, has a similar chemical structure to xanthan [83,84]. It has been reported that deacetylation of acetan provides stability to the molecule and improves the establishment of intermolecular binding with GM [85,86,76], obtaining transparent thermoreversible gels at sufficiently high polymer concentrations and theoretical deacetylated acetan/GM ratios above 6/4 [76].

To our knowledge, there are no references on the use of acetan–GM complexes for drug delivery. However, taking into account the similar chemical structure reported for xanthan and acetan, com-

parable applications could be allocated to both these polymers and to their combination with GM.

4.4. Interaction with gellan gum

The interaction of gellan gum with GM molecules is promoted with increasing concentration of cations, such as sodium or calcium. However, an excessive salt content leads to a separation phase, caused by the formation of aggregates of gellam gum helices with different thermal stabilities [87,14].

With regard to the drug delivery applications of gellam gum–GM mixtures, the only report found in the literature refers to blended films as releasing active agent systems for food packaging purposes [88].

4.5. Interaction with alginate

Previous studies have shown that the interaction between GM and alginate is mediated by hydrogen-binding and electrostatic interactions [24,8]. This interaction has been the basis for the formation of GM–alginate beads intended for the controlled delivery of proteins [8]. In this work it was shown that the introduction of GM led to the formation of stronger and more stable gels than those composed only of alginate.

4.6. Interaction with chitosan

Using IR and X-ray spectroscopy it was found that the interaction between chitosan and GM is due to the formation of intermolecular hydrogen bonds between the amine groups of chitosan and the hydroxyl and carboxymethyl groups of GM [25,8].

The combination of GM with chitosan has been reported to offer an interesting potential in the drug delivery field. In fact, films, beads, micro and nanoparticles have been prepared, based on the combination of these polymers, and presented as new drug and protein carriers [25,8,11,10,9,89–91]. These specific applications will be described in detail at the end of this review article.

5. Glucomannan derivatives

The poor water solubility of GM [30,31,68] together with its specific advantages [14,13,65] has motivated active research towards the formation of GM derivatives of different solubility. Indeed, the most frequent chemical modification of GM has been intended to obtain derivatives with improved solubility properties and/or enhanced capacity to interact with other polymers (Table 2).

Table 2
Characteristics of semisynthetic GM derivatives

Derivative	Main characteristics
Dicarboxy-GM	Negative charge Higher water solubility
Carboxymethylated-GM	Negative charge Higher water solubility
Methylated-GM	Non charge Higher water solubility
Tosylated-GM	Non charge Higher solubility in organic solvents
Palmitoyl-GM	Non charge Water in oil emulsifier
Benzoyl-GM	Non charge Higher solubility in polar solvents

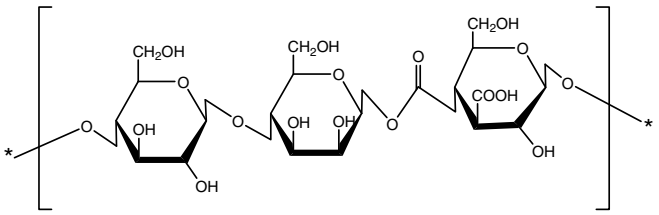

Fig. 5. Chemical structure of dicarboxy-GM.

5.1. Dicarboxy-GM

Matsumura et al. [92] proposed the preparation of dicarboxy-GM, a negatively charged derivative, which presents carboxylic groups between the sugar residues and at C-3 position (Fig. 5). This chemical modification has resulted in an important increase in GM water solubility, and also in its ability to interact with positively charged polymers. These new features are very attractive for the design of new drug carriers. On the other hand, this chemical modification may also affect its biological activity.

For example, Ohya and co-workers found that the inherent ability of GM to stimulate macrophages could be modulated by varying the dicarboxy substitution degree [5,68].

5.2. Methylated-GM

The methylation of GM (Fig. 6) has also been aimed at increasing the water solubility of this polysaccharide. This modification was first proposed by Kishida et al., in 1979, in order to improve the rheological properties of GM [93,94].

Up to now, no pharmaceutical or medical application has been specifically reported for this derivative; however, it can be deduced that the increase of GM water solubility could promote its use as a pharmaceutical excipient.

5.3. Carboxymethylated-GM

A high degree of substitution (DS) (DS > 0.1), in carboxymethylated-GM (Fig. 7), leads to a soluble product in water. This deriva-

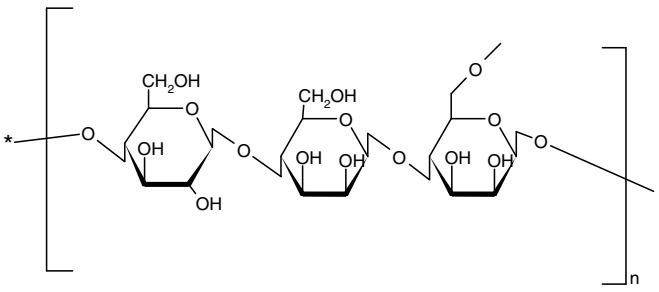

Fig. 6. Chemical structure of methylated-GM.

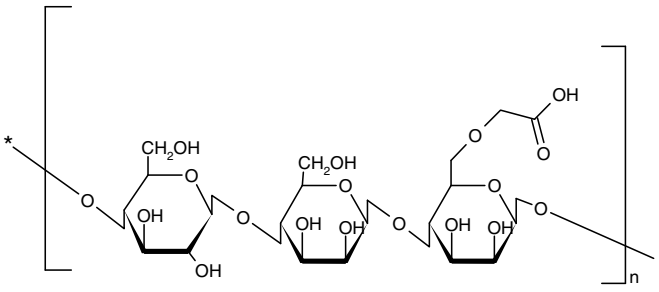

Fig. 7. Chemical structure of carboxymethylated-GM.

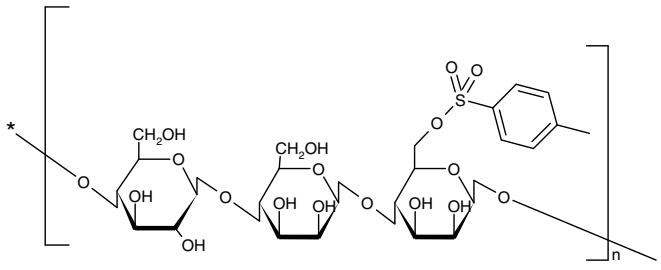

Fig. 8. Chemical structure of tosylated-GM.

tive is a negatively charged polyelectrolyte, which is susceptible to interacting with positively charged polymers by electrostatic attraction [95,96,68].

A biomedical application of this derivative has been reported by Du et al. [9,89,90], who prepared polyelectrolyte chitosan–carboxymethylated-GM nanoparticles by simple mixing of both polymers using sonication.

5.4. Tosylated-GM

A few years ago, Takechi et al. synthesized tosylated-GM (Fig. 8), with the idea of improving the solubility of GM in a variety of organic solvents [97]. Although this derivative offered certain advantages in pharmaceutical technology, the most attractive use of this derivative is as a precursor in polysaccharide chemistry. Indeed, the tosyl group is a good leaving group, allowing the easy modification on this position [97].

5.5. Palmitoyl-GM

Various degrees of palmitoylated GM were prepared by Tian and colleagues following a heterogeneous method previously reported by Fujii [98]. This synthesis was based on similar work on chitosan [99] and cellulose [100]. It was found that palmitoylated-GM may work as a water in oil (w/o) and oil in water (o/w) emulsifier, being active at very low concentrations (0.1–0.01%) [101]. Despite this specific application, no references were found reporting the use of palmitoylated-GM in the drug delivery field.

5.6. Benzoyl-GM

Benzoyl-GM (Fig. 9) with a degree of substitution of 1.6 is highly soluble in polar solvents. This derivative plays an important role in coating films, enhancing the mechanical properties and water resistively of the coated films [102]. The use of benzoyl-GM has been reported for the preparation of coating films [103,104]; however, no reference has been published on its use in the drug delivery field.

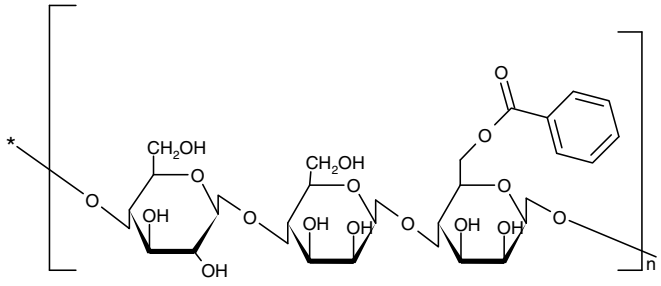

Fig. 9. Chemical structure of benzoyl-GM.

5.7. Glucomannan grafted acrylic acid

The preparation of the GM-grafted acrylic acid co-polymer was performed by free radical polymerization, leading to the introduction of the acrylic acid at the C1 position. The application of this derivative was aimed at the preparation of hydrogels for colonic drug delivery. The combination of both ingredients was chosen in order to obtain a more selected release at the colonic level. This hypothesis was supported by the biodegradation behavior of GM and pH dependence of acrylic acid [105].

5.8. Natural derivatives of glucomannan

Finally, besides the chemically synthesized derivatives of GM, there is a class of natural derivatives of GM, such as those obtained from the bacteria *Candida utilis*. This variety of GM is characterized by the presence of phosphate groups, a high content in mannose (mannose:glucose ratio 11.4:1) and α-1,6 linkages in the main backbone. Moreover, in contrast to the ordinary GM, the phosphorylated derivative presents low molecular weight (around 150 kDa) and high solubility in water and polar solvents, such as acetone and ethanol.

The negative charge of this derivative is a very attractive characteristic for its application in the pharmaceutical field. For example, our group has extensively investigated the formation and drug delivery applications of nanoparticles, made of chitosan and phosphorylated GM [10,11].

6. Biopharmaceutical applications

Traditionally, the use of konjac flour has been related with food applications. Indeed, konjac GM is a health product widely used in Asian countries and the United States for its unique properties. This thickening agent presents an extraordinary water absorption capacity, a unique viscosifying action and a synergistic behavior with other gums. In fact, konjac GM has been used to improve the bread texture, as a dietary fiber, etc. However, recently this polymer has gained increasing importance in the biomedical and pharmaceutical fields. More specifically, these applications include (see Table 3):

6.1. Glucomannan as a bioactive polymer

Although GM is not currently considered a drug, some biological effects described in the literature suggest its potential as a bioactive polymer. For example, GM has been found to decrease the serum glucose levels following oral administration to diabetes type 2 rats. This hypoglycemic effect was attributed to the inhibition of carbohydrate absorption [106–108] and also to the decrease of the postprandial insulin flow [109]. On the other hand, some studies

Table 3
GM biomedical and pharmaceutical applications

Applications		Advantages
Biomedical	Obesity	Weight loss
	Cholesterol	Decrease LDL cholesterol levels
	Diabetes type 2	Decrease the carbohydrate absorption
	Cancer	Antitumor activity against sarcoma-180 solid tumor
Pharmaceutical	Pharmaceutical forms	Sustained release profiles
		Increase of stability
		Improve the interaction between polymers
		Enhance protein association
	Coating	Antiseptic coating
	Targeting	Recognize mannose receptors

performed in rodents have suggested the activity of GM as a growth inhibitor of solid tumors, such as sarcoma [110–112]. Unfortunately, this effect and the corresponding mechanism of action have not been evaluated in further detail.

6.2. Pharmaceutical applications of glucomannan

GM has been investigated as a pharmaceutical excipient in tablets, films, beads and hydrogels, due to its gelling, solubility and biodegradable properties [7,8,25]. Interestingly, recent work in this field has highlighted the potential of GM for the targeting of nanocarriers to specific receptors, i.e., the mannose receptors on the cell surface [113]. This mannose receptor is a 180-kDa transmembrane protein with five domains, able to recognize several sugars, such as mannose [114]. This hypothesis is supported by previous reports which have shown that the presence of mannose residues on the particle surface increases their uptake by the M cells [115,5] and macrophages [6], where the mannose receptors are overexpressed.

6.2.1. Glucomannan-based films

A number of recent articles have described the preparation of films made of GM or its derivatives in combination with other polymers [116,88,117–119,95,120,25,24,121]. Among them, GM-methylcellulose and GM-poly(acrylic)acid films have been found particularly promising for drug delivery [116,88]. The role of GM in these films is the modulation of their swelling properties and, hence, their ability to control drug release.

6.2.2. Glucomannan-based beads

Beads made of GM in combination with other polymers have been prepared in order to be used for protein delivery [8]. The results have shown that the incorporation of GM into the alginate beads causes, not only the modification of the particle surface, but also the different disposition of the components inside the network. The resulting beads exhibited an improved protein-loading capacity and also a pH-dependent swelling behavior.

6.2.3. Glucomannan-based hydrogels

Due to the fact that GM is degraded by the enzymes secreted by the colonic bacteria, some authors have underlined the potential of GM-based hydrogels for colonic drug delivery [118,119,105]. These hydrogels were prepared using combinations of GM with acrylic acid or sodium tripolyphosphate. In addition, in order to achieve a selective colonic drug delivery, GM hydrogels were also formed using azo polymers as cross-linkers. It was concluded that GM is responsible for the enzymatic degradation of hydrogels, and thus, for the resulting drug release from the systems.

The formation of hydrogels from oxidized konjac GM and chitosan has been reported very recently [116]. In this gel GM works as a crosslinker agent for chitosan, thus improving the controlled release properties of the resulting hydrogels.

6.2.4. Glucomannan-based microparticles

We have recently developed GM and chitosan–GM microparticles intended for pulmonary drug delivery using a spray-drying technique. The results showed that the morphology and surface appearance of the microspheres, as well as their densities and aerodynamic diameters, are closely dependent on their composition (presence and amount of GM) (Fig. 10). Furthermore, studies performed on well-differentiated Calu-3 cells showed the ability of these chitosan–GM microspheres to closely interact with the mucus layer, remaining adhered to the epithelium [122].

6.2.5. Glucomannan-based nanoparticles

Nanoparticles made of carboxymethylated-GM and chitosan have been prepared by electrostatic interaction between the negative carboxylic groups of carboxymethylated-GM and the positive amino groups of chitosan, followed by a sonication step [89]. These nanoparticles exhibit a positive charge, and a size that can be modulated within the range of 50–1200 nm, depending on the polymer concentration. Additionally, these nanoparticles elicited an ability to entrap and release bovine serum albumin (BSA) [9,89,90]. The introduction of GM in these formulations was intended to increase their stability and their controlled release properties.

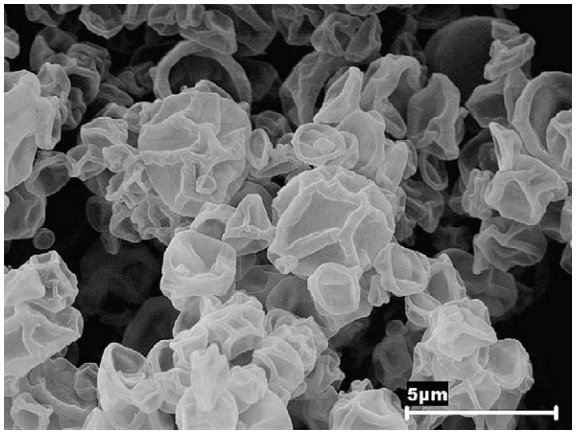

Fig. 10. SEM photograph of GM microspheres.

Similarly, in our lab, we have developed a new protein particulate carrier made of GM and chitosan. The difference with the above-mentioned nanoparticles relies on the preparation technique, which, in our case, was based on an ionotropic gelation process [10]. These nanoparticles are obtained spontaneously by the simple mixing of the components. These very mild conditions make this approach very attractive for the association of delicate macromolecules to the nanoparticles. The interaction between both polymers, GM and chitosan, is expected to be driven by hydrophobic interactions and hydrogen bonds. Moreover, the presence of TPP (sodium tripolyphosphate) helps to build up the nanostructure, resulting in round and homogeneous nanoparticles.

As expected, these nanoparticles exhibited an improved stability in ionic media and a delayed protein release [10,11]. This delay could be explained by the higher crosslinking degree of chitosan nanogels impaired by the presence of GM [8,10,7]. Furthermore, the results from our group have shown that the introduction of GM into the nanoparticles leads to a facilitated interaction with the intestinal epithelium both *in vitro* and *in vivo* [123,124]. In summary, GM–chitosan nanoparticles offer attractive features as carriers for transmucosal drug delivery applications (Fig. 11).

7. *In vivo* degradation of glucomannan

Traditionally, konjac GM has been considered a polymer non-susceptible to biodegradation in the human body. However, recently a number of GM-degrading enzymes have been identified in some microorganisms which are present in the human gut flora such as *Aerobacter mannanolyticus*, *Clostridium butyricum* and *Clostridium beijerinckii*. These bacteria produce endo-β-mannanase, an enzyme that catalyzes the cleavage of the β-1,4 linkages of GM to produce mainly the disaccharides β-1,4-D-mannobiose, cellobiose and 4-*O*-β-D-glucopyranosyl-D-glucopyranosyl-D-mannopyranose. These intermediate products are finally degraded to glucose and/or mannose by intestinal bacteria. Additionally, the monosaccharides serve as a carbon source for the proliferation of intestinal bacteria, which ferment them into short-chain fatty acids (mainly acetic, propionic and butyric acid) (Fig. 12). These fermentative products can be absorbed across the intestinal wall and metabo-

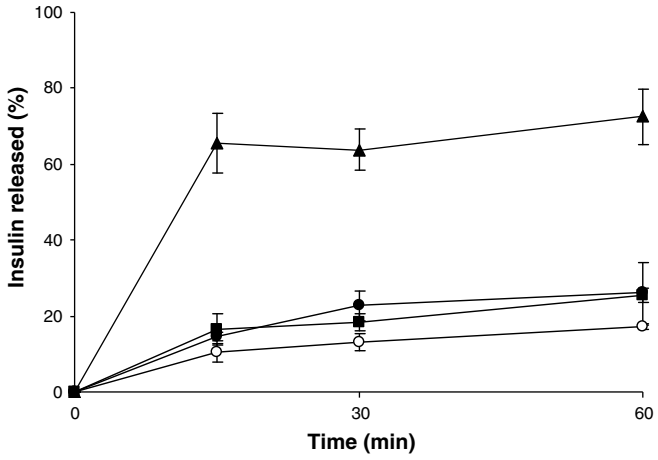

Fig. 11. Release profiles from insulin-loaded chitosan–GM nanoparticles. Insulin release profiles of CS/TPP (CS/TPP ratio: 6/1) (▲); CS/TPP/GM (CS/TPP/GM ratio: 6/1/1.8) (loading 29%) (■); CS/TPP/GM (CS/TPP/GM ratio: 6/1/1.8) (loading 15%) (●) and CSreac/TPP/GM (CSreac/TPP/GM ratio: 6/1/1.8) (loading 15%) (○) nanoparticles in artificial gastric juice (pH 1.2) for 1 h at 37 °C (mean ± SD, $n = 4$).

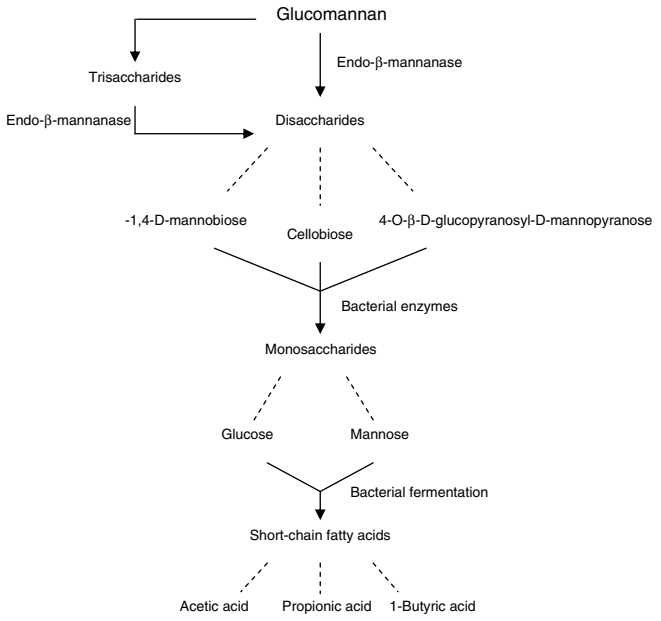

Fig. 12. Scheme of the *in vivo* degradation of GM.

lized efficiently [64,65]. In fact, it is known that short-chain fatty acids are rapidly absorbed from the colon of humans [125,126]. Consequently, these results indicate that GM is a biodegradable polymer, of which the degradation products are natural compounds present in the human body.

8. Toxicity of glucomannan

It is well known that GM has been traditionally used as a food additive in China and Japan, most specifically as a dietary fiber and, hence, considered good for health [14]. Despite this long-lasting tradition, the results of the toxicity studies are very promising but still limited. For example, several authors have found no evidence of toxicity in rats after the long-term feeding of rats with a GM dose equivalent to an intake of 500 mg/kg body weight per day [127,128]. Other authors have performed more detailed toxicity studies aimed at identifying signs of toxicity such as oral toxicity, sensitization studies in the skin, sub-acute and sub-chronic intestinal toxicity studies, cell-aging, embryocitoxicity and genotoxicity studies [129,130]. Interestingly, none of these studies has revealed significant signs of toxicity and only minor side-effects, such as diarrhea, abdominal pain and flatulence, were reported at doses higher than 5 g/day [131–133].

Finally, concerning the regulatory aspects, in 1996 the European Commission in its "Report of the scientific committee for food" (41st series) considered that even when the GM toxicity studies were not enough to establish an Acceptable Daily Intake (ADI) "the use of konjac gum as an additive at intended levels up to 1% in food is acceptable provided that the total intake from all sources did not exceed 3 g/day".

9. Conclusion

The polysaccharide GM and the family of related polymers present very attractive characteristics from the biopharmaceutical point of view. Over the last few years a number of GM-based drug delivery systems, intended for their administration by different routes, have been designed. More specifically, hydrogels, beads, micro and nanoparticles made of GM or its derivatives have been obtained and evaluated for their ability to associate and deliver drugs. Even if the interest of the pharmaceutical field for GM is still recent, a general conclusion is that GM is a promising and versatile polysaccharide for the preparation of new drug delivery systems.

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