DRUG DELIVERY SYSTEMS BASED ON GELLAN DERIVATIVES

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Abstract. *This paper proposes a review of the literature that reports valuable and interesting results regarding the biomedical applications of gellan and its derivatives. The different types of formulations for which this microbial exopolysaccharide is suitable are listed, which depend on the condition to be treated and their administration method: tablets, films, gels synthesized in situ, hydrogels, different types of particles, especially micro- and nanoparticles , mice etc. Research on the biomedical uses of gellan and its derivatives is far from being exhausted, newer directions regarding the creation of nanocomposites (with clays, for example), of mixtures or semi- and interpenetrated networks with other polymers revealing the obtaining of new extremely valuable biomaterials not only as supports for the encapsulation, transport and release of drugs, but also in the field of tissue engineering.*

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1. Introduction

Polymers constitute a category of absolutely indispensable materials in contemporary society. There is currently an extremely varied range of polymers made on an industrial scale - synthetic or artificial polymers -, which have applications in all fields of activity, medicine being no exception from this point of view. But their use in biomedical applications imposes a series of restrictions that many such synthetic compounds cannot fulfill: biocompatibility, lack of toxicity, biodegradability, etc. For this reason, the researchers' attention was directed towards the polymers that nature generously provides us with: proteins and especially polysaccharides.

Polysaccharides are mainly obtained from the vegetable kingdom, although some are also found in living organisms (chitin, hyaluronic acid). They are predominantly obtained from plant tissues (cellulose, acacia, hatti, tragacanth, etc.), but also from seaweeds (agar-agar, alginates, carrageenans, etc.) or seeds

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(guar gum, konjac gum, etc.). The last 4-5 decades have marked the industrial production of some polysaccharides produced by microorganisms – microbial exopolysaccharides -, which have found numerous applications in the biomedical, cosmetic and food fields as a result of their exceptional properties, such as: biocompatibility, low cytotoxicity, bioresorbable character, chemical stability, chemical reactivity imprinted by functional substituent groups basic chain, environmental-friendly character, ease of obtaining and processing, low production costs with high reproducible quality [1,2]. The best known among them are gellan, xanthan, rhamsan and welan.

Gellan Gum (GG), or simply gellan, was discovered in 1978 and is produced on an industrial scale by Sphingomonas elodea (Pseudomoas Elodea) [3]. It was used in biomedical applications initially as an adjuvant in various medicinal formulations (tablets) after the FDA approved it in 1992 for this purpose. From this moment, the research on the exploration and exploitation of its biological, chemical and physical properties in the field of tissue engineering, cosmetics and nanomedicine experienced an exponential development [4].

From a structural point of view, GG is a linear anionic polymer, made up of tetrameric units composed of two residues of D-glucose, one residue of D-glucuronic acid and another one of L-rhamnose. The –OH group from the anomeric carbon of the first D-glucose residue can be esterified (a glyceryl or sometimes acetyl radical), the degree of esterification being high (high acyl - haG) or low (low acyl - laG) [5] (Figure 1). Usually, the name "gellan" is attributed to the deacetylated or weakly acetylated form of the polysaccharide.

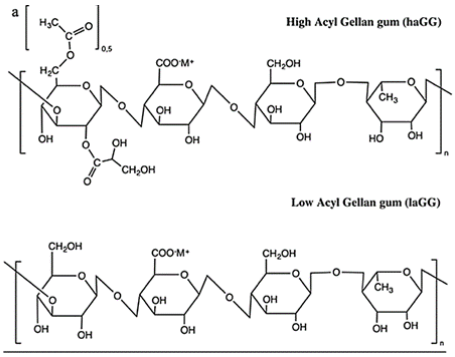


Fig. 1. Chemical structure of haGl and laGl [4].

The existence of functional groups of the type –COOH, respectively –OH facilitates the realization of numerous chemical reactions that lead to functional derivatives with new physical and chemical properties, which have found applications in various fields, especially the medical one. It is known that polymers, in general, can be formulated in different ways to create supports capable of encapsulating and releasing drugs - tablets, gels and hydrogels,

particles (micro- and nano-), capsules, micelles, etc. -, this paper aims to review the literature of recent years regarding the ways of formulating GG derivatives for biomedical applications.

2. Tablets

The residence time of the drugs at the site of action is an essential factor in peroral delivery. In the case of diseases of the digestive tract, prolongation of gastric residence can be achieved with sustained release devices - among which tablets occupy an important place -, which have a high mucoadhesivity, usually amplified by the presence of -COOH substituent groups in the polymer from which the system is made. If -COOH groups are not present, they can be introduced by different methods, including poly(acrylic acid) grafting. Sarkar et al. synthesize a graft copolymer of GG, used further as an adjuvant in obtaining mucoadhesive tablets carrying metformin hydrochloride [6]. Wet granulation method was employed to prepare matrix tablets of metformin with GG and poly(acrylic acid) grafted GG. *Ex-vivo* mucoadhesion testing was performed on goat stomach mucosa. It was found that while the tablet composed of native GG showed no such adhesion (muchoadhesion time of 0.07h and strength of 2.3±0.02 N), the tablets composed of grafted GG showed high mucoadhesion time (8.3±0.67h to more than 10 h) and strength of 51.09±0.8N to 75.14±1.9 N. The explanation could be attributed to the presence of a high number of -COOH groups in the grafted polysaccharide, which have the ability to form numerous hydrogen bonds with the mucin, improving the mucoadhesivity. Sustained release tables of sodium-diclofenac were also prepared with a poly(methacrylamide)-grafted GG. *In vitro* studies revealed the ability of these systems to release the drug for 8h [7]. Tablets were prepared by incorporating antidiabetic drug metformin hydrochloride (MTF) in acrylamide grafted GG along with excipients. *In vitro* studies were performed on prepared tablet formulations showing release up to 8 h [8].

3. Films

Depending on the conditions and method of preparation, GG samples can be in the form of a disc, film, membrane, framework, fiber, dispersed particles. GG and some of its derivatives are excellent materials for encapsulating drugs, cells, replacing cartilaginous tissue, etc., but in the literature there is little information regarding the use of GG derivatives in film form. A mucoadhesive vaginal film containing the antimicrobial agent metronidazole was obtained, too, by crosslinking gellan with 2-(2-aminoethyldisulfanyl) nicotinic acid with a thiolation rate of 81 and 174 mol/g [9]. These films, along with antibacterial properties, showed good biocompatibility, low cytotoxicity, high adhesion to the vaginal mucosa, and turned out to be therapeutically effective dosage forms.

A thiolate derivative of GG has been used to obtain mucoadhesive films for the treatment of vaginal infections. Compared to Gl films, thiol functionalized gellan gum films showed 3-fold improved adhesion on mucosal surface over a period of 3 h along with significant antimicrobial activity, so proved to be a promising novel excipient for casting vaginal films, exhibiting strongly improved mucoadhesive and antimicrobial properties [10].
Anti-adhesive films based on cinnamic ester of GG, obtained by photocrosslinking with an efficiency of 82% after 16 min exhibited high gel contents (88 ± 2%) and suitable mechanical properties [11]. These were tested in vivo on rats, without forming any tissue adhesion.
GG-ofloxacin films for ophthalmic applications were prepared by mixing a GG solution with ofloxacin (2:1 mol/mol) and adding $CaCl_2$ to achieve a uniform dispersion and gelation. Casting of the mixture for 24h at room temperature allowed the formation of an insoluble in water gellan-ofloxacin flexible film [12].

4. In situ synthesized gels

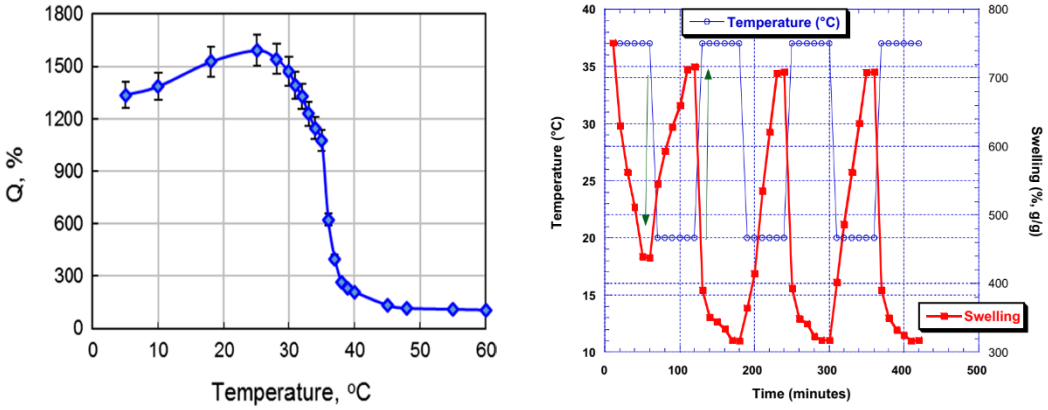
It is well known that water-soluble polymers exhibit mucoadhesive properties, more pronounced in the case of polyelectrolytes [13]. Some of them can be used to obtain in situ gelling systems; under normal storage conditions, their aqueous solutions are liquid, but form viscous gels upon administration on the eye or in the nose. Gel-forming properties of GG, as well as its biocompatibility, allow using this polysaccharide for biomedical purposes, including drug delivery. The sol-gel transition of GG in response to mono- (Na^+, K^+) and bivalent (Ca^{2+}, Mg^{2+}) makes it a suitable thickening or gelling component. Upon exposure to physiological concentrations of cations, as being present in body fluids like nasal fluid or in the tear fluid, gelling of the polymer is initiated [14]. Some attempts were also reported on chemical modification of GG aiming to enhance its mucoadhesive properties in the conditions of preserving or even amplifying the ability to form gels [1]. For example, the GG-thioglycolic acid conjugate was synthesized, but it was established that thiolation slightly decreased the sensitivity to Ca^{2+}-induced gelation [15]. However, formulations based on this derivative containing metronidazole showed 1.82-fold greater mucoadhesive strength compared to parent polymer, so the GG–thioglycolic acid conjugate is a promising bioadhesive excipient for application in ocular drug delivery.
In order to demonstrate the applicability of modified and unmodified *in situ* gelling GG formulations for ocular drug delivery, eye drop solutions were prepared. GG and methacrylated-Gl solutions in simulated tear fluid composed of NaCl, $NaHCO_3$ and $CaCl_2$ were prepared. Fluorescein sodium salt (NaFl) was employed as a model compound to load into these solutions. The *in vitro*

experiments demonstrated the gelling capacity of the polymer mixture and the significant increase in the retention of the formulations on the ocular mucosa [16].
An amine derivative of GG was obtained and studied from the point of view of its gelling capacity and mucoadhesive properties, in order to use it as an excipient for nasal dosage forms improving drug bioavailability. Comparing aminated with unmodified GG enhanced mucoadhesion was verified by a 32-fold increase in viscosity of polymer/mucus mixtures and by a 14-fold extended mucosal adhesion time. The addition of $CaCl_2$ improved the performance of formulations by forming a soft gel with good spreadability and sprayability [17].

5. Hydrogels

Hydrogels represent a three-dimensional network resulting from the hydrophilic polymer chains being held together by cross-linking. The crosslinks between the chains of the linear polymer can be physical or chemical. Because the bonds of a physical nature (hydrogen bonds, ionic bonds, van der Waals bonds) are weak, the hydrogels obtained in this way do not have high stability, chemical hydrogels being preferred in many applications. Being able to include high amounts of water as well as substances dissolved in it, hydrogels often possess physicochemical properties close to those of the native extracellular matrix.
A possibility of chemical crosslinking is the creation of disulfide bridges between the chains of a GG functionalized with cysteine [18]. The thiolate derivative is able to form inter- or intramolecular disulfide bonds in aqueous solution. The rheological tests performed reveal the fact that after 6 h of incubation at room temperature, storage modulus, loss modulus, and complex viscosity increased 300-, 6.4-, and 26.6-fold, respectively, relative to the non-thiolated polymer. Frequency sweep measurements demonstrated an increase in crosslinking of the thiolated polymer as a function of time. The obtained hydrogel represents a promising novel excipient for various drug delivery systems in which in situ gelling properties are favourable. The same type of hydrogel is obtained by Yu et al. who found that thiolated GG maintains the temperature-sensitive gelation properties of the original polysaccharide, and provides binding sites to laminin subsequently ensuring a controlled release [19].
Chemical cross-linking can also be achieved by polymerizing unsaturated derivatives of GG. To obtain thermosensitive hydrogels with potential applications in the treatment of ophthalmic diseases, Hamcerencu et al. used GG-maleate (with a degree of substitution of 15.4%) and N-isopropylacrylamide, the crosslinking being ensured by the presence of N,N′-methylene bisacrylamide. Hydrogels were synthesized by a free radical grafting–cross-linking using ammonium persulphate as initiator activated by N,N,N′,N′-tetramethylene diamine, at room temperature (20°C), for 24 h. The use of N-isopropylacrylamide

for this type of applications have aimed to modify or to shift the value of LCST in order to meet the physiological temperature (that of the human body), the effect having previously been proven in the case of hydrogels based on macromers (acrylates, maleates) of xanthan [20, 21]. Hydrogels synthesized in this way can be classified as smart materials, given their ability to respond to various stimuli, in this case pH and temperature [22, 23]. In order to evaluate the GG-maleate based hydrogel as "intelligent", the swelling degree at different temperatures was determined, as well as the response to temperature changes, by swelling–contraction (below and above LCST) study, and the obtained results are presented in Figure 2 [24].



a b

Fig. 2. GG-maleate based hydrogel maximum swelling degree variation with temperature in physiological saline solution (a) and swelling–contraction kinetics in physiological serum at temperatures between 20 and 37 °C (b) [24].

It was found that the presence of GG-maleate in the structure of the hydrogel has the effect of a slight increase in the LCST, which approaches the physiological temperature, reaching 36°C, (Fig. 2a.), as well as the fact that the hydrogel presents a good and reproducible response to the alternation between the specific temperature of the human body and the ambient temperature at a sufficiently high rate (Fig. 2b). These results have demonstrated and confirmed the fact that the new hydrogel is an "intelligent" material [25].

A hydrogel based on graft copolymer of GG with acrylamide and acrylic acid, crosslinked with trimethylolpropane triglycidyl ether as a cross-linking agent was reported by Zheng et al. [26]. The initiation of the grafting reaction was carried out with $K_2S_2O_8$, in different concentrations. The main intended application was the use for the retention of dyes from waste water, but the interesting properties of the hydrogel also recommend it for the creation of drug release systems.

The methacrylic ester of GG was used by Chen et al. to create a hydrogel in combination with collagen. First of all, the collagen was modified with vinyl

groups, and the gelation point of GG-methacrylate was optimized through changing the grafting ratio of methacrylic anhydride. The mixture of the two polymers was ionically pre-crosslinked by treatment with low concentrations of Ca^{2+} ions (1 min), the crosslinking being then completed by the photochemical co-polymerization of the two component polymers (365 nm, 3 min) [27].

Starting from a derivative of GG obtained by introducing ethylene diamine as a substitute for the H atom from the primary –OH group, Calogero et al. synthesized a hydrogel by creating crosslinks between the –COOH groups of native GG and the newly introduced $–NH_2$ ones [28]. Rheological analysis has shown that the establishment of intra- and interchemical bonds allows the formation of a hydrogel with further mechanical stability over time in physiological conditions.

For the treatment of some skin conditions, Pacelli et al. synthesize nanocomposite hydrogels (NC) by using GG-methacrylate as a matrix in which laponite was dispersed in different concentrations. By photocrosslinking, depending on the laponite content, hydrogels with superior mechanical properties were obtained. The highest mechanical property was found for the NC hydrogel containing 1% w/v of laponite. These new nanocomposite systems were used as a carrier of the model drug ofloxacin. [29].

The creation of aldehyde-type oxidized groups through the oxidation of GG allows the realization of chemical co-crosslinking reactions with polymers containing amine groups, such as chitosan. The existence of the –COOH groups in GG actually allows a double reticulae, in the chemical one associating gelation with Ca^{2+} ions [30]. In this strategy, complex, double-crosslinked hydrogels can be obtained by ionotropic gelation with Ca^{2+}, respectively by condensation with the formation of Shiff base bonds with carboxymethyl chitosan, which constitute a suitable matrix for the encapsulation of chondrocytes (Figure 3).

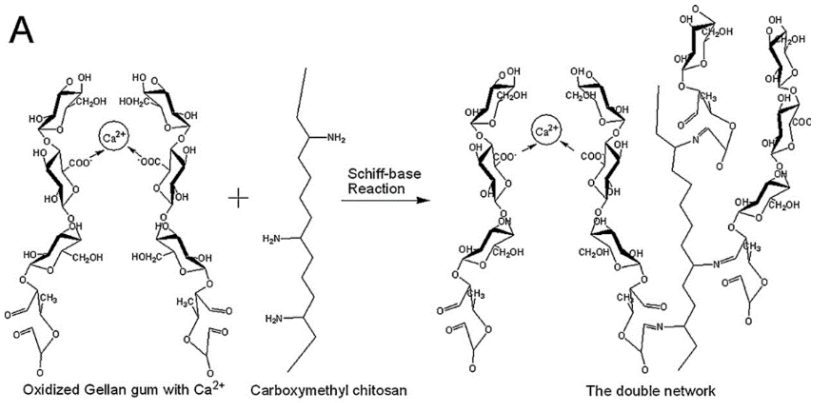


Fig. 3. Double cross-linked structure (ionic and covalent) of a hydrogel based on oxidized GG and carboxymethyl chitosan chitosan [63].

A combination of oxidized GG and carboxymethyl chitosan was used by Zhang et al. to obtain a double cross-linked hydrogel, built by a double cross-linking involving oxidized Gl pre-cross-linked with Ca^{2+} ions and making Schiff base bonds between the two polysaccharides. The hydrogel served as a matrix in which GG microspheres loaded with tetracycline hydrochloride and silver sulfadiazine were dispersed [31]. The best performance was obtained for a gravimetric ratio of 16/7 in favor of carboxymethyl chitosan, when the duration of gelation was only 139 min and the degradation of the hydrogel was practically total after 7 days.

6. Particles

The ability of GG to be easily cross-linked by ionotropic gelation with Ca2+ is exploited in order to obtain particles that have found their use as encapsulation systems for some drugs, especially for the treatment of some diseases of the digestive system. The resistance of GG to the stomach passage, where the pH is strongly acidic, allows the drug-laden particles to pass without important losses of biologically active compound in the intestine, where the pH is weakly alkaline. Diseases of the intestine or colon, including cancer, can thus be targeted by oral administration of such a particulate system. GG derivatives can also be used to obtain water-based particles for the encapsulation of various drugs.

6.1. Microparticles

Nayak et al. obtain particles based on grafted copolymer of GG with poly(methacrylamide) partially hydrolyzed in a basic medium, when part of the amide groups transforms into carboxylic groups, resulting in fact the -COONa group. By preparing a common solution of the copolymer with tamarind seed gum in which sodium diclofenac is dissolved, followed by extruding the obtained solution through a syringe needle in an ionotropic gelation bath (CaCl2 solution), spherical particles are obtained, according to the method shown schematically in Figure 4 [32, 33]. The use of a 32 full factorial design allowed the evaluation of several influencing factors on the diameter of the particles and their ability to encapsulate the drug.

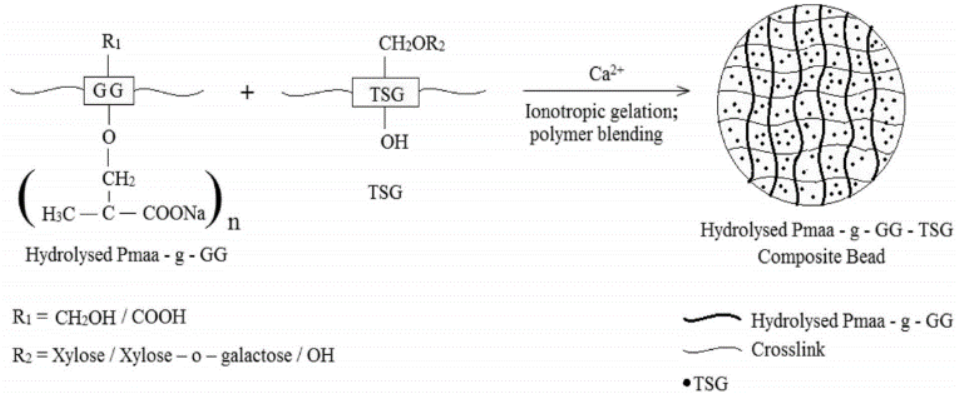


Fig. 4. Schematic presentation of the method of obtaining particles based on Gl (GG) grafted with partially hydrolyzed poly(acrylamide) (Pmaa) and tamarind seed gum (TSG), through ionotropic gelation with Ca^{2+} ions [32, 33].

Vieira et al. obtained calcium-enriched beads by crosslinking GG-methacrylate derivative with Ca^{2+} cations [34]. To prepare the hydrogel beads, GG-methacrylate solutions were added dropwise into a $CaCl_2$ stirred crosslinking bath, using a syringe coupled with a 30G needle. The obtained bead hydrogel is compatible with efficient drug delivery applications, in a wide range of molecular weights.

Complex hydrogel beads were fabricated by an ionic crosslinking method in the presence of $CaCl_2$ as cross-linking agent. A derivative of oxidized GG controlled at the primary –OH group in the structural unit was used for this purpose due to the greater contents of carboxyl groups that can strongly cross-link with Ca^{2+} and because it presents pH-sensitivity in media with varying pH values. Resveratrol-β-cyclodextrine complexes (obtained at a molar ratio of 1:1) were included in the GG derivative solution, and different concentrations of type III resistant starch were added during the fabrication process to improve the stability of hydrogel beads under gastrointestinal tract. After that, mixtures were further injected drop-wise using a syringe into the cross-linking solution (2 M $CaCl_2$) and the particles were formed instantly. It was proven that the fabricated hydrogel beads exhibited a pH-sensitivity, and the morphology and swelling capacity were significantly influenced by the added RS [35]. The concentration of Ca^{2+} ions and the degree of oxidation (DO) of GG influence the physicochemical and morphological properties, as well as those of resveratrol release [36].

As shown in Figure 5, all the hydrogel beads are uniformly spherical. As the concentration of Ca^{2+} ions increases, the particles become increasingly opaque, due to the formation of more compact structures. For a certain concentration of Ca cations, smaller and more rigid hydrogel beads are obtained by increasing oxidation degree (DO). Of course, the effect is due to the participation of an

increasing number of -COOH groups in the ionic gelation, with the formation of a tighter gel network.

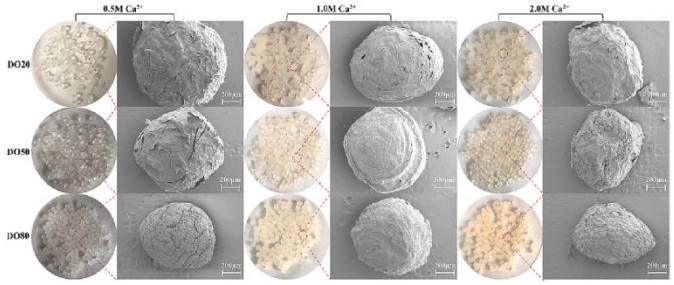


Fig. 5. Macroscopic (photographs) and microscopic (SEM images) morphologies of resveratrol loaded hydrogel beads that differ as a function of the degree of oxidation of the GG derivative and the concentration of Ca^{2+} ions used for crosslinking [36].

Another possibility for the preparation of particles is the condensation reaction of the complementary groups of two polymers. Novac et al. prepared microparticles based on quaternized GG and chitosan, activating the condensation reaction of the –COOH group from gelan with the $–NH_2$ group from chitosan by using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide and NHS. The authors work with quaternized GG with the highest degree of substitution, at three molar ratios compared to chitosan. When the chitosan solution is introduced into the quaternized GG solution containing the activators, the opalescence appears instantly, and after vigorous stirring overnight, the particles are obtained. Later they were used as a support for the inclusion of ciprofloxacin [37]. The particles have an irregular shape, an average equivalent diameter of 5 μm and a wide polydispersity.

6.2. Nanoparticles

The need for administration by injection (parenteral, intravenous) of drug-carrying systems requires their preparation at submicron sizes. The literature mentions obtaining nanoparticles/nanogels using for this purpose derivatives of GG.
Manconi et al. report the preparation of nanohydrogels based on GG derivatives with cholesterol, using two techniques: sonication and autoclaving [38]. The autoclaved nanohydrogel seems to be the most promising carrier in terms of size, homogeneity, and rheological properties. The nanoparticles obtained by this process were small and more homogeneously dispersed (~350 nm, PI ≤ 0.30). The zeta potential value ensures the stability of the nanosuspensions upon storage, thanks to the superficial electrostatic repulsion of the nanoparticles. The drug loading efficiency was around 37%.

A system consisting of GG functionalized with sericin, in combination with rice bran albumin and loaded with doxorubicin was obtained in the form of composite nanoparticles. The average diameter of nanoparticles (with core protein-polysaccharide structures) was 218 nm and the polydispersity index was 0.23. After loading doxorubicin the average size of the SC-GG-RBA nanocomposites increased to 225 nm. Zeta potential of unloaded and drug loaded nanocomposites were −5.39 and −7.43 mV, proving a satisfactory stability of nanosuspensions. Drug loaded and plain nanocomposites show similar zeta value denotes that drug was not adsorbed on the surface of the nanocomposites [39]. The same group of authors obtained nanocomposite nanoparticles based on GG-maleate grafted with sericin, in combination with chitosan, in which they load rifampicin and pyrazinamide, the system being designed to overcome the problems associated with tuberculosis therapy. To prepare the nanocomposite, the GG-sericin maleate conjugate was dissolved in acetone and kept under stirring for 12 h and after was added drop wise to a chitosan solution under stirring. The average size and polydispersity index of the nanocomposites was 160 nm and 0.26, respectively. Zeta potential values of nanocomposites drug-loaded nanocomposites were −6.48 and −5.34 mV, respectively [40].

7. Micelles

Micelles are nanoentities formed by the self-assembly of amphiphilic copolymers, spherical in shape with a submicron diameter, capable of encapsulating especially hydrophobic drugs in their core, thus increasing their bioavailability and facilitating their administration in the body by injecting the nanosuspension into a biological fluid [41, 42].

An amphiphilic hexadecyl GG copolymer obtained by Kundu et al. has the capacity to self-assemble in water forming spherical nanostructures (the critical association concentration is 0.63 mg/ml). Simvastatin was loaded into micelles by solvent evaporation method. The nanosuspension showed negative zeta potentials (-27.4 to -28.2 mV), which indicates a high stability over time. The system increased the bioavailability of the encapsulated drug, increasing its water solubility up to 355 times [43]. The same group of authors obtained a micellar system based on cetyl-GG, with particle sizes around 832 nm, which caused a considerable rise in solubility of simvastatin in water. The drug entrapment efficiency of drug in micelles was found to be 90–94% [44].

A novel amphiphilic derivative of GG for the development of micellar solution of hydrophobic drugs was obtained by Maiti et al. [45]. A long alkyl chain (C18) was successfully grafted onto GG by etherification reaction. The solution of the derivative in water led to formation of spherical, nanomicellar structures, capable of encapsulating budesonide in a proportion of over 95%. The diameter of nanomicelles were in the range of 371–750 nm and the nanosuspension showed

negative zeta potential (−48.3 to −67.2 mV) values indicating their stability in aqueous medium. The micellar system was designed for the administration and control of the intranasal release of the medicine for the symptomatic relief of anti-rhinitis.

Shirani et al. obtain redox responsive micelles based on a derivative of GG synthesized in several steps [46]. The micellization is determined by the amphiphilic character of the derivative (introduced by abietic acid as a hydrophobic sequence), and the redox responsive character is imposed by cysteine. Figure 6 schematically illustrates the formation of micelles in an aqueous environment.

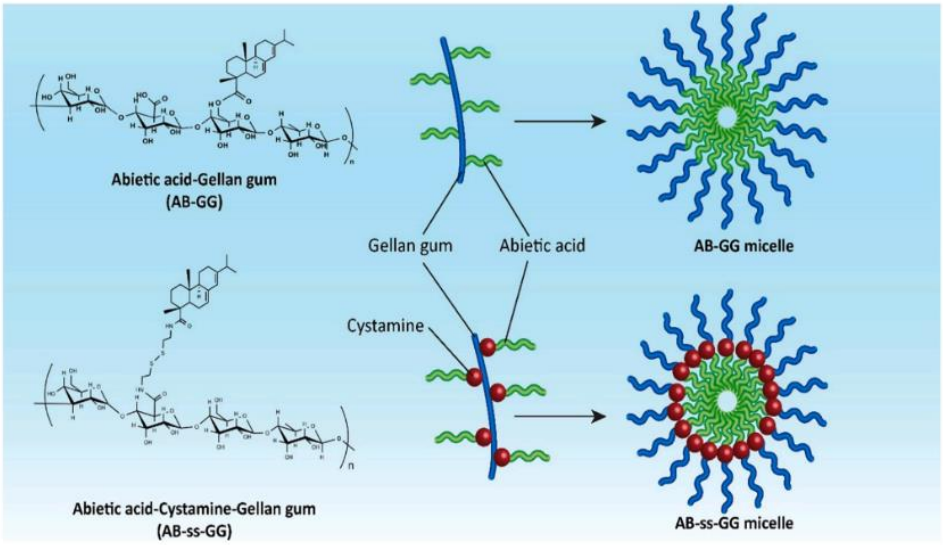


Fig. 6. Schematic illustration of the formation of redox-sensitive micelles based on the derivative of GG with abietic acid [46].

Micelles were obtained by sonicating the derivative solution for 20 min, followed by keeping it under stirring for 24 h at 25°C. The mean diameter ranged between 114.26 and 181.13 nm with polydispersity index values between 0.26 and 0.52.

8. Miscellaneous

Hybrid gels based on water-insoluble cholesterol derivative of GG and phospholipid P90G based liposomes were obtained by Zoratto et al. [47]. The obtained system can be depicted as a dispersion of liposomes networked by the polymer chains. By dispersing the liposomes in the derivative GG matrix, interactions occur between the lipid membrane of the liposomes and the cholesterol grafted to the polysaccharide chain, resulting in "not flowing" systems. Diclofenac sodium salt (anti-inflammatory drug) was encapsulated into liposomes

to obtain drug delivery systems in an aqueous environment.Very important is the fact that the two components can be combined locally, immediately stemming the gel. The study highlighted the fact that liposomes' dimensions increased as the concentration of GG derivative was increased, but their diameter remained in the submicron range (141-1732 nm). Part of the drug remains embedded in the gels, within the liposomes, acting as a reservoir system that can be exploited in in vivo conditions for long-lasting delivery applications.

Conclusions

More than four decades ago, it seemed that in the field of polysaccharides there were not many things left to research and discover. However, the possibility of obtaining drug release systems, which imposes a series of restrictions on the characteristics of the polymers that can be used as a support, as well as the discovery and production on an industrial scale of some polysaccharides of microbial synthesis - exopolysaccharides -, among which gellan, has brought attention back researchers this class of natural polymers. The obvious characteristics of GG derivatives, such as the gelling capacity, the sensitivity to the presence of some metal ions and to pH, the mucoadhesive character, the high reactivity of the functional groups (-OH and –COOH), the ability to be formulated in different ways (hydrogels, micro/nanoparticles, micelles, etc.), the possibility to model their physical-mechanical properties, etc. justifies the special interest enjoyed by these compounds from researchers. Derivatives of this polysaccharide were obtained, their combinations were made with other polymers or composites with filler material such as clays, which added value to the polymer through the new printed properties and opened new possibilities for application in the biomedical field.

Without any doubt, GG and its derivatives constitute a vein that must be further explored and exploited, leading to new valuable results with potential biomedical applications.

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