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NATURAL POLYSACCHARIDE HYDROGELS AS NOVEL EXCIPIENTS FOR MODIFIED DRUG DELIVERY SYSTEMS : A REVIEW

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ABSTRACT: Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines. Drug dosage forms contain many components in addition to the active pharmaceutical ingredient(s) to assist in the manufacturing process as well as to optimize drug delivery. Due to advances in drug delivery technology, excipients are currently included in novel dosage forms to fulfill specific functions and in some cases they directly or indirectly influence the extent and/or rate of drug release. Developments of several drug delivery systems are based on natural polysaccharides act as excipients that do not change their chemical structure but these materials degrade within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Furthermore, polysaccharides are chemically well-defined and have attracted worldwide attention as excipients due to their novel and unique physico-chemical properties can be relatively low cost and can be chemically modified to suit specific needs. Some natural polysaccharides have even shown environmental-responsive gelation characteristics with the potential to control drug release according to specific therapeutic needs. This review discusses some of the most important natural polymeric compounds that are used or investigated as excipients in drug delivery systems.

Keywords: Natural polysaccharides; polymers; excipients; drug delivery; Modified release; Drug release modifiers.

INTRODUCTION

Pharmaceutical excipients are substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system. Traditionally, excipients were included in drug formulations as inert vehicles that provided the necessary weight, consistency and volume for the correct administration of the active ingredient, and performance of technological functions that ensure ease of manufacture. The specific application of natural polysacccharide polymers in pharmaceutical formulations include to aid in the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use.[1] The design of effective drug delivery systems has recently become an integral part of the development of new medicines. The goal is to provide a therapeutic quantity of medicine(s) to the proper site in the body in order to achieve the desired effect and maintain such effect for the entire

period of treatment. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile. Developments of several drug delivery systems are based on natural polymers that do not change their chemical structure but these materials degrade within the body as a result of natural biological processes, eliminating the need to remove a drug delivery system after release of the active agent has been completed. Moreover these modify, drug release to achieve the dosage forms to release the drug in a constant manner and maintain steady state plasma concentration for the entire period of treatment to reduce the dose related adverse effects. The recent rediscovery of polysaccharide based materials is also attributable to new synthetic routes for their chemical modification, with the aim of promoting new biological activities and/or to modify the final properties of the biomaterials for specific purposes. [2]

Polymers have been successfully employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of modified release drug delivery systems. Both synthetic and natural polymers have been investigated extensively for this purpose [3] but the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, and capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible. Because of their wide diversity in structure and physical properties natural polysaccharides have found a wide range of applications in the food, pharmaceutical and other industries.[4] Some of these applications include their use as emulsi-fiers, stabilizers, binders, gelling agents, coagulants, lubricants, film formers, thickening and suspending agents. These biopolymers are rapidly emerging as a new and industrially important source of polymeric materials which are gradually becoming economically competitive with natural gums produced from marine algae and other plants.

Drug delivery

The aim of our drug delivery research is to optimize the bioavailability of drug compounds by innovative formulation development. Our overall hypothesis is that intrinsic drug delivery of drug candidates may be manipulated by chemical and/or excipient formulation strategies aiming to:

- increase drug candidate solubility in biofluids such as intestinal fluid
- increase drug stability in the formulation and in biofluids
- increase drug candidate permeability across biomembranes, such as the small intestinal membrane
- increase drug candidate delivery to the pharmacological target
- Decrease drug candidate metabolism, and/or decrease its elimination.

Solubility in biofluids may be influenced by salt or prodrug formation, for example, or by the formation of excipient-drug-candidate complexes. Stability can be optimized by using excipients such as detergents, or by freeze-drying the formulation for long-term storage. It is possible to increase permeability across biomembranes by designing drug candidates as drugs or prodrugs that are substrates for absorptive membrane transporters, or by developing lipid or particulate drug-excipient systems such as emulsions, liposomes and nano particles that influence permeability. Increased delivery to pharmacological targets can also be influenced by pH or enzyme sensitive controlled release formulations based on either chemical or excipient formulation strategies. First pass metabolism in the liver and elimination of drug candidates can be influenced by designing them as non-substrates for metabolizing enzymes, or as substrates for reuptake transporters, or by applying excipients that are regulators for efflux transporters or metabolizing enzymes, or by using alternative administration routes [5]

Pharmaceutical technology

There is a complex interplay between the physical and chemical properties and related unit operations of the active pharmaceutical ingredients as well as the excipients. This research area addresses the issue and focuses on the molecular-based formulation of solid-state pharmaceutics. The main target is to widen and deepen our understanding of material properties during the manufacture of pharmaceutics, with special focus on the processability of solid-state forms in relation to the bioavailability of these forms. This research area will pay special attention to the identification of the mechanisms of solid-state transitions by real time analysis of the complex phenomena occurring in process environment. Understanding material properties in relation to the processability of pharmaceutics opens new perspectives for improved quality and more efficient production.[6]

Optimal drug therapy

Medicines are the dominating treatment technology in health care and in the population's self care, and consumption is still increasing. Besides the beneficial effects, the use of medicines is also related to a wide variety of problems, which include interactions, adverse effects, misuse and non-compliance. In addition, drug costs may be a burden to the individual and to society. The overall aim of this central research area is to

optimize the prescribing and use of medicines by minimizing drug-related problems and costs. The research area deals with analyses of: determinants of medicine use and associated health and economic outcomes; the behaviours and perceptions of medicines by professionals and consumers; the efficacy and safety of medicine use in the clinic and in the population; processes of knowledge creation in drug development and use; professional practice. Interventions aiming to optimise drug use and therapy are also conducted and evaluated. Research integrates scientific skills from a multiplicity of disciplines including epidemiology, health economy, clinical pharmacy and social pharmacy.[7]

Polymers in drug delivery

One of the most remarkable and useful features of a polymer's swelling ability manifests itself when that swelling can be triggered by a change in the environment surrounding the delivery system. Depending upon the polymer, the environmental change can involve pH, temperature or ionic strength and the system can either shrink or swell upon a change in any of these environmental factors of these sensitive systems. Drug release is accomplished only when the polymer swells and because many of the potentially most useful pH-sensitive polymers swell at high pH values and collapse at low pH values, triggered drug delivery occurs upon an increase in the pH of the environment. Such materials are ideal for systems such as oral delivery, in which the drug is not released at low pH values in the stomach, but rather at high pH values in the upper small intestine [8]

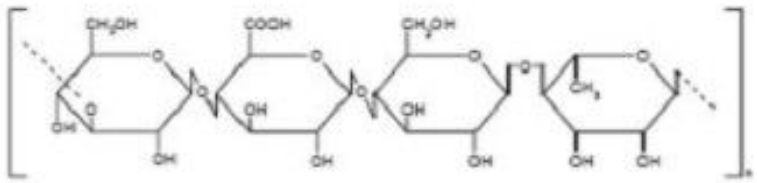
Need for excipients in drug delivery

Pharmaceutical excipients are substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system. For example, excipients can: aid in the processing of the drug delivery system during its manufacture, protect, support or enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use. To meet emerging challenges, the pharmaceutical industry is currently in the midst of reinventing itself. These challenges include continually increasing drug development costs, slowing new product approval, blockbuster drug patent expirations, price pressure and global competition. Concurrently, significant opportunities exist for the pharmaceutical industry, including an increasing patient population, numerous unmet medical needs, growing disease awareness, globalization of operations and markets, and advances in efficiency.

The focus on drug development costs is driving the industry to consider outsourcing, relocating production and sourcing ingredients from lower-cost locations. These options are continually being explored to meet the challenge of utilizing a more robust, streamlined and efficient manufacturing process, and to secure a supply chain. To overcome the challenges of price pressure due to "generitization" of branded drugs, as well as severe global competition, even in the generic sector, many pharmaceutical companies are seeking new proprietary drug delivery formulations. Innovative, new excipients offered by various excipient suppliers enable the development of new dosage forms, improve efficiency and may reduce the cost of drugs. Excipients can add functionality to pharmaceutical products. They offer opportunities to introduce new dosage forms, and thus facilitate the extension of patent life.[9]

GELLAN GUM

Deacylated Gellan gum (Gellan) is an anionic microbial polysaccharide, secreted from *Sphingomonas elodea*, consisting of repeating tetrasaccharide units of glucose, glucuronic acid and rhamnose residues in a 2:1:1 ratio: [→3)—D–glucose–(1→4)—D–glucuronic acid–(1→4)––D– glucose–(1→4)–□–L–rhamnose–(1→]. In the native polymer two acyl substituents, L-glyceryl at O(2) and acetyl at O(6), are present on the 3-linked glucose. On average, there is one glyceryl per repeating unit and one acetyl for every two repeating units. Deacylated Gellan gum is obtained by alkali treatment of the native polysaccharide. Both native and deacylated Gellan gum are capable of physical gelation [10] To induce Gellan gelation it is necessary to warm up preliminarily a concentrated water solution of the polysaccharide: when the temperature is decreased, the chains undergo a conformational transition from random coils to double helices (Coil-Helix Transition). Then a rearrangement of the double helices occurs leading to the formation of ordered junction zones (Sol-Gel Transition) [11] thus giving a thermo-reversible hydrogel [12] Much stronger physical thermo-reversible hydrogels are also obtained by addition of mono and divalent ions to Gellan solutions or in acidic conditions.[13] The physical gelation properties make this polysaccharide suitable as a structuring and gelling agent



[→3)-β-D-Glcp-(1→4)- β- D -GlcpA-(1→4)- β- D - Glcp- (1→4)- α- L-Rhap-(1→]n

Figure;1 Chemical structure of Gellan gum

PHYSICOCHEMICAL PROPERTIES

Gelling Properties of Gellan Gum.

Gelation of gellan solutions occurs abruptly upon heating and cooling of gellan gum solutions in the presence of cations. Such sol-gel transitions are considered as phase transition. The gelation of gellan gum is a function of polymer concentration, temperature, and presence of monovalent and divalent cations in solution. At low temperature gellan forms an ordered helix of double strands, while at high temperature a single-stranded polysaccharide occurs, which significantly reduces the viscosity of the solution. The transition temperature is approximately 35^0C, but can range from 30-50^0C. Below transition temperature, a stiff structure is obtained (setting point), and results in gel formation. The mechanism of gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water.[14] Addition of monovalent or divalent cations during cooling markedly increases the number of slat bridges at junction zone, thereby improving the gelling potential of gellan gum. Various studies have been carried out to study the effect of different factors on the gel strength. Some of the important factors affecting gel strength are discussed bellow.

Acetyl content

Acetyl content is the most important factor affecting the gel strength. Gellan gum with different acetyl content gives gels with different properties. Native gellan gum provides soft, elastic, thermoreversible gels, and is very weak because of bulky acetyl and glyceryl groups that prevent close association between gellan polymer chains in bulk-helix formation, and hinder compact packing of the cross-linked double helix. Deacetylated gellan gum forms firm, brittle and thermoreversible gel because of the absence of acetyl and glyceryl groups.[15]

Type and concentration of ions

Ions have an impact on gel strength and brittleness. Gellan does not form gel in deionised water, but the addition of salts of calcium, potassium, sodium, and magnesium causes an increase in these two properties. Notably, divalent cations are more effective in achieving this; even in gellan gels of very low concentration (0.2%, by mass per volume), a high strength was achieved with a maximum at about 0.004% (by mass per volume) calcium and 0.005% (by mass per volume) magnesium. Similar gel strength can be achieved with 0.16% sodium or 0.12% potassium (by mass per volume). Gellan high salts concentration (1%, by mass per volume). A concentration of 0.1-0.2% gellan is suitable for many food systems. It is important economically that strong gels can be obtained at low concentration of gellan, with the incorporation of trace amount of salt [16]

Gel pH

Sanderson and Clark showed the gel strength to be enhanced within pH range of 3.5 to 8, which corresponds to the natural pH range of most foods. Change in pH does not alter the setting point of the gel, but affects melting temperature in some cases. For example, gels prepared with very low levels of monovalent ions melt at around 70^0C at neutral pH, but at pH=3.5 the melting temperature is slightly increased. This trend is not seen for divalent ions.[17]

Presence of hydrophilic ingredients

Addition of hydrophilic ingredients like sucrose (at about 10%, by mass per volume) tends to decrease the ion concentration required for optimal gellan gel strength. Kasapis et al used transmission electron microscopy to examine the changing nature of a polysaccharide network with increasing levels of sugar. Mixtures of deacylated gellan (<1%) with low (0-20%) and high (80-85%) levels of sugar were prepared and studied. Micrographs of the high sugar / gellan gels

produced clear evidence of reduced crosslinking in the polysaccharide network, which exhibits a transition from rubber to glass-like consistency upon cooling. [18]

Tang et al. studied the effects of fructose and sucrose on the gelling temperature, clarity, and texture properties of gellan gels cross-linked with calcium or sodium ions. They reported the gelling temperatures of gellan solutions to generally increase on the addition of sucrose, whereas addition of fructose up to 35% (by mass per volume) had no effect. Incorporation of fructose and sucrose markedly increased the gel clarity. Effect of sucrose on gel strength was found to be dependent on cation concentration. At low cation concentrations, sucrose strengthened the gels; but at high cation concentrations, sucrose weakened them. [19]

Temperature stability and flexibility of the melting point

Gellan gum is stable at higher temperatures and maintains its strength at 90^0C, whereas xanthan gum looses 74% of its original strength after heating up to 90^0C. According to Sanderson and Clark, the melting temperature can be below or above 100^0C, depending on the conditions of gel formation. The most important factor responsible for the flexibility of the melting point is concentration of cations in the gels because monovalent and divalent cations markedly increase the number of junction zones in gels and make them more resistant to temperature. Modification of the melting point can successfully replace other conventional thickeners / stabilizers, while used in much lower concentration. [20]

Water uptake

The water uptake capability is an important parameter for materials to be used in biomedical applications. Water uptake was evaluated, in different media, for the Gellan physical and chemical hydrogels. The physical hydrogels show a similar behaviour in the different media, meaning that their different composition does not affect their water uptake: only the physical hydrogel [Gellan 2%] show slightly lower values of the parameters swelling [S] and water uptake ratio [wR], especially in SGF (Simulated Gastric Fluid, HCl 0.1 M, pH = 1) solution. This behaviour is probably due to the low pH environmental conditions, which induce the formation of more stable junction zones. In fact, at pH = 1, a suppression of the polyelectrolytic behaviour of Gellan chains occurs, because the carboxylate groups are in their acidic form. In these conditions the polymer chains can be closer one another leading to the macroscopic shrinking of the gel. For the chemical crosslinked samples the water uptake is strongly dependent both on hydrogel and solution compositions. As expected, water uptake is inversely proportional to the crosslinking degree of the sample. When the hydrogels are swollen in water, their behaviour is quite similar to that of the super-absorbent materials [16], showing very high values of the swelling parameter (e.g., S = 350 for the [Gellan 2% + Lys 0.3]Chem, and S = 1,070 for the [Gellan 2% + Lys 0.1]Chem). In physiological solution (NaCl 0.9% w/v) and in SIF (Simulated Intestinal Fluid, Phosphate Buffer, pH = 7.4) the crosslinked and physical hydrogels show low S values, similar to those of the Gellan gum hydrogels, due to the presence of a large amount of Na+ counterions that reduce the electrostatic repulsions among the carboxylic groups of the polymeric chains, leading to a more compact overall structure. The sample [Gellan 2% + Lys 0.1]Chem represents an exception to this general behaviour: in this case the water uptake is significantly higher, because the polymer chains are in a random coil conformation (as depicted in the model) and the network, with a quite low crosslinking degree, is able to absorb high amounts of water. Again, in SGF, a reduced water uptake is observed. Similar comments can be made about the wR parameter.[21]

Table 1. wR ratio (weq/w0) for the different hydrogels, swollen in different media at 37 °C.

	Water	Sodium Chloride [0.9%w/v}	SGF	SIF
[Gellan 2%]Phys	0.96 ± 0.03	0.99 ± 0.04	0.77 ± 0.02	0.97 ± 0.02
[Gellan 2% + Lys0.1]Phys	1.03 ± 0.04	1.04 ± 0.03	0.93 ± 0.02	1.02 ± 0.04
[Gellan 2% + Lys 0.2]Phys	1.02 ± 0.02	1.02 ± 0.04	1.00 ± 0.04	1.03 ± 0.03
[Gellan 2% + Lys 0.3]Phys	0.99 ± 0.02	1.02 ± 0.02	0.98 ± 0.02	1.02 ± 0.04
[Gellan 2% + Lys 0.1]Chem	21.95 ± 0.20	1.48 ± 0.03	1.34 ± 0.04	1.54 ± 0.03
[Gellan 2% + Lys 0.2]Chem	12.98 ± 0.15	1.04 ± 0.02	0.75 ± 0.03	1.02 ± 0.03
[Gellan 2% + Lys 0.3]Chem	7.06 ± 0.15	0.99 ± 0.04	0.70 ± 0.02	0.98 ± 0.02

The data are presented as arithmetic mean of three different measurements ± SD.

Effects of other natural hydrocolloids on the textural properties of gellan gum.

Various studies to find out the changes in the textural properties of gellan gum when mixed with other food hydrocolloids have been carried out.

Sodium alginate

Sodium alginate dissolved in calcium chloride solution at 90^0C shows weak gel properties similar to those of ordered xanthan. The solutions show a sharp increase in rigidity on cooling, and convert to permanent gels on storage at low temperature. The gelsattain maximum hardness at about 40% calcium conversion (for alginate with a polyguluronate content of 58%), and their elasticity can be readily controlled by adjustment of Ca^{2+} concentration around this optimum value. Papageorgiou et al. observed that incorporation of moderate concentrations of gellan (0.1-0.3%, by mass per volume, in combination with 2%, by mass per volume, alginate and 5 mM trisodium citrate, increased the strength of the gels, but did not significantly change their elasticity, indicating that the gellan acts as strong 'filler' in an alginate matrix.[22]

Gelatin

Lau et al. carried out texture profile analysis on mixed gellan-gelatin gels to assess the effect of the ratio of the two components and calcium ion concentration. Hardness, brittleness, cohesiveness and springiness were measured. The results suggested that there was a weak positive interaction between gellan and gelatin when no calcium was added; at higher concentrations, gellan formed a continuous network and gelatin the discontinuous phase. Hardness was dependent on the concentration of gellan gum in the mixture, whereas brittleness, springiness and cohesiveness were very sensitive to low levels of calcium (0-10 mM), but less sensitive to higher calcium concentrations and gellan/ gelatin ratio.[23]

Carrageenan and xanthan

Rodriguez-Hernandez and Tecante studied exture properties of gellan – carrageenan and gellan-xanthan mixtures in order to determine the contribution of both polysaccharides to the viscoelastic behaviour of the mixture. Admixtures having a constant total concentration of 0.5% (by mass) with different proportions was prepared in the presence of 0.01 mol/kg $CaCl_2$. It was observed that gel strength of 0.5% gellan alone was the highest, and gel strength of the two-component gels decreased as the proportion of gellan was reduced. Mixed gels having a gellan concentration equal to or lower than 50% mass of the total concentration were less stiff and brittle, hence were more elastic.[24]

Effect of chelatants on textural properties of gellan gum

Camelin et al. studied the effect of various concentrations of sequestrants (sodium citrate, sodium metaphosphate, and EDTA) on gellan gel setting temperature and rheological properties. Addition of EDTA between 0 and 0.8% (by mass per volume) progressively decreased the setting temperature. Citrate and metaphosphate decreased this parameter when added up to 0.4 or 0.6%, depending on gellan gum concentration, eventually resulting in the absence of gel formation at room remperature for the 1.5% gellan solution containing 0.4% citrate. This effect was accompanied by a significant decrease of gel strength, and might be attributed to the binding of divalent cations required for chain association during gelatinization by chelatants.[25]

PHARMACEUTICAL APPLICATIONS:

In the presence of counterions, this polymer is capable of forming gels that are particularly strong when formed with divalent ions. The degree of acylation also influences the strength of the resulting network. Indeed, when gellan is acylated it forms soft, elastic, transparent and flexible gels while de-acylation leads to hard, non-elastic and brittle gels.The gels are thermoreversible, with a melting temperature, T_m, at about 50 ^{0}C, depending on the concentration and presence of cations that, stabilizing the gel, increase the T_m value. The polymer, initially used mainly as a food ingredient, has been widely investigated to devise novel ophthalmic formulations due to its ability to gelify in the presence of tear fluid cations thus providing drug ocular bioavailability. Hydrogels, in fact, show high patient compliance and *in situ* forming gels are even preferred since they are dropped as a solution in the eye where the transition into a gel actually takes place. Important parameters, like the gel strength, were studied to find a reliable indicator of the gel ocular bioavailability. *In vivo* experiments showed that only when the gel strength was within set limits, an appreciable increase in ocular bioavailability was obtained. The ocular contact time increased with increasing gellan concentration; on the other side, the autoclaving process, carried out to sterilize the gellan solutions, led to a significant reduction in the finished product of the gel strength due to a breakdown of the polymeric chains that was proportional to the autoclaving time.[26] Due to the decisive role of rapid gel formation in the use of *in situ*-gelling systems, contact times with different osmolalities were measured. As expected, gels formed with hypotonic solutions maintained their integrity for several hours.

Gels of gellan can be formed in the tear fluid even when the polymer concentration is very low and sodium proved to be the best gel-promoting ion *in vivo* though in physiological conditions the instilled drops are diluted, gels with a high elastic modulus can be formed. In fact, dilution of the tear fluid takes place upon instillation of a solution of salt free gellan, but an elastic "skin" is immediately formed keeping the drops somehow compacted.[27]

Gellan has also been tested *in vivo* for the nasal uptake of fluorescein dextran used as a model molecule.[28] The starting solution of gellan behaves like a fluid but it forms a rigid gel when exposed to cations. Hence, it is suitable for nasal spray pumps with its initial low viscosity and the subsequent gelling upon contact with animal mucosa. A rapid gelation an also be expected in humans, the surface area of their nasal cavity being much larger than that of a rat. Furthermore, in comparison to plain solutions, lower doses can be administered because of the rapid gelation. Although with divalent cations (Ca^{2+}) the gels are much stronger, *in vitro* experiments demonstrated that a strong gel is formed in physiological conditions of 0.9% NaCl and the gel obtained *in vivo* is strong enough to remain in the nasal cavity for the required time interval, showing a slow clearance due to a higher local concentration. Gellan has also been tested for the encapsulation of biological components inside a polyion complex formed between gellan and chitosan.[29] Apart from the sustained release, the use of capsules and microspheres offers several benefits. In particular, encapsulated substances can be protected, the small particle size enabling repetitive administration either orally or by injection as therapeutic bolus.

Selection of encapsulation method is crucial in achieving an encapsulation that allows enzymes and/or peptides to retain their catalytic activity or biological function. The method by complex coacervation is based on polyionic complexation through electrostatic interactions between cationic and anionic polymers resulting in the formulation of insoluble spherical capsules. It has been ascertained that gellan-chitosan capsules retain proteins but release low-molecular weight substances across the capsule membrane. Upon loading into the capsules, an enzyme behaves like a free enzyme. The permeation of the inner materials is obviously dependent on their molecular masses, molecular structures and electrical charges. Indeed, an exclusion limit for the diffusion out of the membrane has been experimentally found. Furthermore, it was evidenced that the loaded enzyme recovered its catalytic activity after the drying and selling steps, indicating that this formulation can be repeatedly used. Hence, it is a potentially powerful tool for applications in the field of biotechnology. It should be pointed out that both polymers are biodegradable and biocompatible, thus, the enzyme-encapsulating gellan-chitosan capsules can be implanted directly, eliminating the need for surgical removal because of their bio-resorbability. Finally it is important to underline that the enzyme encapsulating procedure does not need any chemical modification and can be conveniently performed in aqueous solution.

Formation of gellan beads has also recently experimented to evaluate the effect of various divalent cations on the encapsulation efficiency using a constant concentration of polymer and ionotropic medium. [30] It is well known that the gelling mechanism of gellan can be induced by cations and is temperature-dependent. In aqueous solution the gelation of gellan is accompanied by a two-step process which involves formation of double helices from random coil chains (coil-to-helix transition) and an aggregation of pairs of double helices. The coil-helix transition is greatly affected by the electrostatic interaction with the cations present in the solution. Gellan forms gels in the presence of mono (Na^+ and K^+) and divalent (Ca^{2+} and Mg^{2+}) cations but its affinity for the latter is much stronger than for the former. Preparing hard gelled beads with different cations has a significant effect on the aqueous solubility of the drug. Furthermore, drug loading increases as the atomic number of the divalent ion increases, thus suggesting that the electro-positivity of cations plays an important role in the ionotropic gelation of gellan. Although the drug loading efficiency was much higher in the presence of transition elements compared to alkaline earth metal ions, the beads prepared with Ca^{2+} were the best in terms of quality and mechanical strength.

Gellan has also been tested for oral drug delivery.[31] The formulation adopted was a gellan solution containing calcium chloride (as the source of calcium ions) and sodium citrate, which complexes the free calcium ions and only releases them in the highly acidic environment of the stomach. The formulation remained in its liquid form until it reached the stomach where the gelation occurred after a few minutes and lasted for several hours. Plasma drug levels, tested after oral administration of gellan solutions, showed that a sustained release was achieved, along with a higher bioavailability compared to that of a sustained release commercial solution product.

In terms of oral sustained delivery, gellan has been compared to sodium alginate which, as previously reported, is also capable of giving *in situ* gelation in the acidic environment of the stomach. The *in vivo* release curves from the gels had a profile similar to that of a commercial suspension. The sustained release effect of the gel formulation was a consequence of the resistance

of the gel structure to the diffusion of the drug whereas that of the suspension arose from the reservoir effect of the suspension particles as they slowly dissolved in the intestine. The gellan gels were detected *in vivo* for a longer period of time if compared to those formed with alginate, indicating the formation of a mechanically stronger gel. There is an obvious advantage of using polymer solutions because such formulations are homogeneous liquids and do not have the problems that may be associated with the formulation and oral administration of suspensions.

Beads prepared with gellan have also been studied in order to delay the delivery of loaded substances employed for weed control in agriculture (e.g. metribuzin) as well as model molecules for drug delivery (theophylline and benzamide)[32] Several formulations, containing different amounts of surfactants and/or oil, were tested. The beads were prepared by adding calcium ions to homogeneous slurries of the various components. The presence of the oil in the formulations reduced the penetration rate of water into the beads leading to a decreased delivery rate. Similar beads, prepared with alginate, showed a slightly faster release than those obtained with gellan. Hence, confirming previous researches, the strength of the gellan gels was higher than that of alginate, though a quantitative estimation was not given. It was also pointed out that, when the hydrophilicity of the model molecule was changed using a molecule more water soluble, a remarkable increase of the delivery rate was obtained. These results clearly indicate that, the swelling of the matrix together with the composition of the beads played a key role in the delivery process.

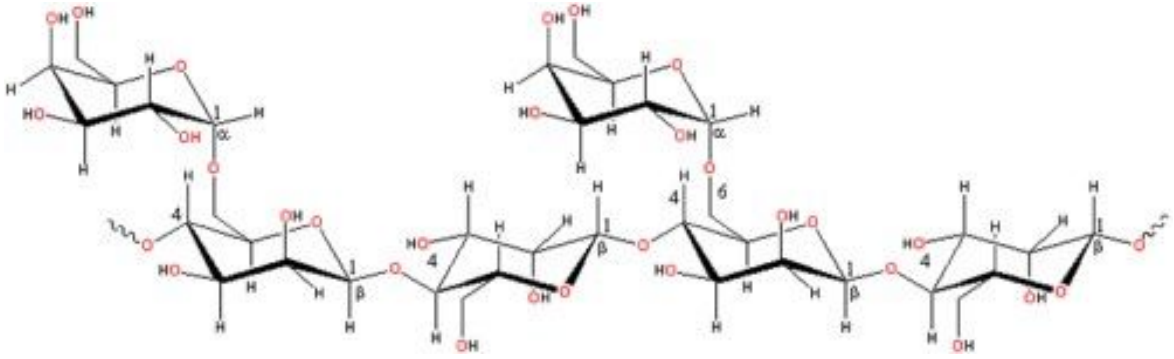
A recent study reports the preparation of microspheres obtained by the emulsion cross-linking method of gellan and poly (vinyl alcohol) in the presence of different amonts of glutaraldehyde as a cross-linking agent and of an antihypertensive drug.[33] The use of such IPN improved the mechanical strength obtained when only gellan was used. The new microspheres were spherical, with smooth surfaces and with a narrow unimodal size distribution. By increasing the cross-link density, microspheres with smaller size were obtained due to the formation of a more rigid network. An increase in the amount of gellan in turn increased the size of microspheres with the formation of a more crystalline matrix. Similarly the drug-loaded microspheres also showed a crystalline dispersion of the drug into the polymer matrix. In comparison to microspheres prepared with only gellan, the new IPN microspheres showed a higher tensile strength. The *in vitro* studies evidenced that the drug release rates were higher for microspheres with a lower amount of gellan, while the different diffusion media produced differences related to the solubility of the drug in the two environments [34]

GUAR GUM

Guar gum is a naturally occurring galactomannan polysaccharide; consists of chiefly high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages and shows degradation in the large intestine due the presence of microbial enzymes. It contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat. Guar gum has a molecular weight of approximately 1 million, giving it a high viscosity in solution. The high viscosity of guar gum results from its high molecular weight and long chain structure.[35, 36, 37]

Chemistry of Guar Gum

A guar gum molecule is made up of about 10,000 residues, which are non-ionic polydisperse rod-shaped polymers (longer than found in locust bean gum).



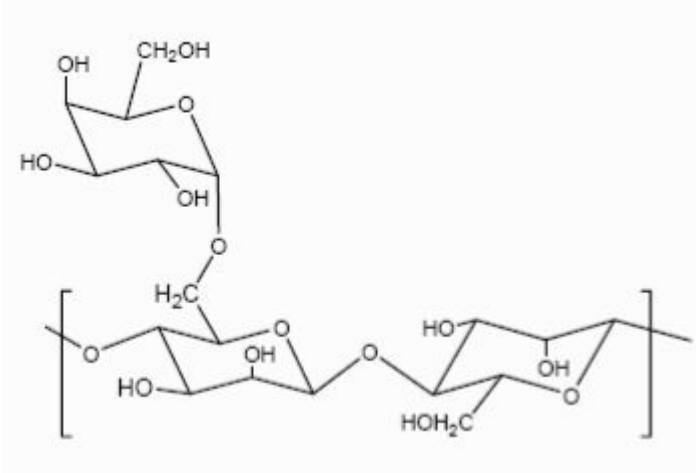


Figure 2: Chemical structure of guar gum.

The structure of guar gum is a linear chain of β-D-mannopyranosyl units linked (1→4) with single member α-D-galactopyranosyl units occurring as side branches.[38] Galactomannan residues which cannot be digested by human and animals itself are well fermented by the microbes in the GI tract, which produce high amounts of short chain fatty acids.

Guar gum hydrates well in aqueous solutions, but concerns about solution clarity, alcohol solubility and improved thermal stability led to the development of a number of chemically modified guar gums. On average three hydroxyl groups are available for derivatization on D-mannose or D-galactose sugar units in guar gum. The maximum theoretical degree of substitution (DS) in such molecule is three. The substitution of hydroxyl groups with ethers such as hydroxylpropyl will allow side groups extension which may change the solubility and other characteristics of the guar gum. The molar substitutions (MS) is defined as the average number of hydroxyl bearing substituents per sugar unit and can exceed three due to the additional availability of hydroxyl groups.[39]

Properties of Guar Gum

The most important property of guar gum is its ability to hydrate rapidly in cold water to attain uniform and very high viscosity at relatively low concentrations. Apart from being the most cost-effective stabilizer and emulsifier it provides texture improvement and water binding, enhances mouth feel and controls crystal formation. The main properties of guar gum are: It is soluble in hot & cold water but insoluble in most organic solvents and has strong hydrogen bonding properties. It has excellent thickening, emulsion, stabilizing and film forming properties, excellent ability to control rheology by water phase management. The viscosity of guar gum is influenced by temperature, pH, presence of salts and other solids.[40]

Table 2. Guar Gum Substitution Patterns[39]

Type of Derivative	Structure of Substituent	Ionic Charge
Hydroxypropylguar (HPG)	$-CH_2-CH(OH)CH_3$	Nonionic
Carboxymethylguar (CMG),	$-CH_2-COO^- Na^+$	Anionic
Carboxymethylhydroxypropylguar (CMHPG)	$-CH_2-COO^- Na^+$ $-CH_2-CH(OH)CH_3$	Anionic

Colonic Properties of Guar Gum

Guar gum is being used to deliver drug to colon due to its drug release retarding property and susceptibility to microbial degradation in the large intestine[41, 42]. The anaerobic bacteria that are responsible for the degradation of guar gum in the colon are *Bacteroides species (B. fragilis, B. ovatus, B. Variabilis, B. uniformis, B. distasonis and B. thetaiotaomicron*). The gelling property retards release of the drug from the dosage form as well as it is susceptible to degradation in the colonic environment. Homogenized and diluted feces from human source were incubated with the guar gum to investigate the degradation of polysaccharide by intestinal microflora. It produced a rapid decrease in viscosity and fall in pH while no such results were observed when it was incubated with autoclaved fecal homogenates[43]

It is to be noted that the utility of guar gum as a colon-specific drug delivery carrier is based on its degradation by colonic bacteria. The colon is rich in anaerobic bacteria. It implies that guar gum in the form of either a matrix tablet or as a compression coat over the drug core might have been degraded to a larger extent by the action of anaerobic microbial population of large intestine[44, 45].

Research Work Conducted on Guar Gum

Guar gum is always a favorite agro-based commodity, attracting wide interest of researchers all over the world. Following is the research work conducted during the last 10 years on guar gum in many national and international laboratories to prepare value added products from this renewable source of hydrocolloid. Grafting of poly (*N*-isopropylacrylamide) (PNIPAAm) was carried out onto *O*carboxymethyl- *O*-hydroxypropyl guar gum (CMHPG) in aqueous solutions by using potassium persulfate (KPS) and *N*,*N*,*N*′-tetramethylethylene diamine (TMEDA) as the initiation system, resulting in new stimuli-responsive grafted polysaccharides. The resulting grafted polysaccharides showed lower critical solution temperatures in aqueous media.[46]

The rheology of binary mixtures of two alginates and one carboxymethyl guar (CMG) was determined. Two reactive dyes were printed from pastes based on these 6 mixtures. The printing and the final print (color yield, levelness and fabric stiffness) were assessed. From the results, it can be concluded that mixture of CMG with alginates can be used in reactive printing. With a view that hydroxypropyl guar (HPG) may replace hydroxyethyl cellulose (HEC) from water based paints, chemical modification of guar gum via hydroxypropylation was carried out at lab/commercial level. The comparative study reveals that HPG is a perfect choice of rheological agent, which governs excellent properties for aqueous paints. This product has similar/ better properties of HEC. Graft copolymerization of methacrylic acid (MAA) onto guar gum was carried using potassium persulfate (PPS) as free radical initiator. Using PPS, the maximum percent grafting was ascertained to be 241 at the optimum conditions of 60°C reaction temperature, 3 h of reaction time, 1.1 mmol of PPS and 0.058 mol of MAA. The prepared graft copolymer could find applications in drug delivery systems. Chemical modification of guar gum was carried out through substitution and grafting reactions and products so obtained were tested against kaolin suspension to check their efficacy as flocculants. It was found that flocculation efficiency of the chemically modified products is better than Deftech and has potential to replace synthetic flocculants. Flocculants were also synthesized by grafting of polyacrylamide (PAM) onto hydroxypropyl guar gum (HPG) using a ceric ion-induced solution polymerization technique. Flocculation efficiency of grafted products was determined against kaolin, iron ore and silica suspensions. Among the series of graft copolymers, the one with fewest but longest PAM chains shows the better performance. Graft copolymerization of various monomers like *N*-vinyl-2-pyrrolidone, 4- vinylpyridine, acrylamide and acrylic acid onto guar gum was carried out by using initiator systems viz. potassium peroxymonosulfate / glycolic acid, potassium 7monopersulfate / thioacetamide, Cu+2-mandelic acid redox couple and peroxydiphosphate-silver (I) respectively. The effect of different reactants along with reaction time and temperature were studied by determining the grafting parameters: grafting ratio, efficiency, conversion, add-on, homopolymer, and rate of grafting. It was observed that the graft copolymers were thermally more stable than the pure gum. Guar gum / poly (acrylic acid) semi-interpenetrating polymer network (IPN) Hydrogels have been prepared via free radical polymerization in the presence of a crosslinker of *N*,*N*′-methylene bisacrylamide (MBA). Hydrogels showed enormous swelling in

aqueous medium and displayed swelling characteristics, which were highly dependent on the chemical composition of the hydrogels and pH of the medium (ionic strength I = 0.15 mol/L) in which hydrogels were immersed.[47]

The water uptake behavior of barium ions crosslinked sodium alginate/carboxymethyl guar gum bipolymeric beads in the media of varying pH was also studied. The beads swelled to nearly 15±4% in simulating gastric fluid (SGF) of pH 1.2 in 3 h. On transferring the hydrogel into simulated intestinal fluid (SIF) of pH 7.4, the swelling was enhanced to nearly 310±12%. When

loaded with the model drug vitamin B12, the 8 total release in SGF in 3 h was nearly 20%, while nearly 70% was released in SIF in the next 7 h. The percent entrapment was nearly 50% when the beads were crosslinked with a 5-6% (w/v) BaCl2 solution.[48]

Guar gum was chemically modified by sulphonation using chlorosulphonic acid (ClSO3H) as a reagent. Activated partial thromboplastin time (APTT) assay showed that the guar gum sulphate could inhibit the intrinsic coagulant pathway. The anticoagulant activity strongly depended on the degree of substitution (DS) and molecular weight (Mw) of polysaccharides. DS>0.56 was essential for anticoagulant activity. The guar gum sulphate with the DS of 0.85 and the Mw of 3.40×104 had the best blood anticoagulant activity. The optimum reaction conditions for affording maximum percentage of grafting for grafting of acrylonitrile (AN) onto sodium salt of partially carboxymethylated guar gum (DS 0.497) using ceric ammonium nitrate (CAN) as a redox initiator, in an aqueous medium, by successively varying reaction conditions such as concentrations of nitric acid, ceric ammonium nitrate, monomer (AN) as well as reaction time, temperature and amount of substrate was also established by an expert. The IR-spectroscopic, thermal (TGA/DSC) and scanning electron microscopic (SEM) techniques were used for the characterization of the graft copolymer. Using microwave (MW) irradiation grafting of polyacrylonitrile (PAN) onto guar gum in water was done without using any radical initiator or catalyst within a very short reaction time. The extent of grafting could be adjusted by controlling the reaction conditions and maximum percentage grafting (%*G*) of about 188% was obtained under optimum conditions in 1.66 minutes.[49]

Grafting of acrylamide onto guar gum is achieved by Ce(IV) induced free-radical polymerization to prepare interpenetrating polymer network (IPN) beads of polyacrylamide-*g*-guar gum with sodium alginate by crosslinking with glutaraldehyde. Two widely used pesticides, solid chlorpyrifos and liquid fenvelarate, were loaded up 9 to 60-70% efficiency in the IPN beads. Equilibrium swelling experiments indicate that the swelling of the beads decreases with an increase in crosslinking, as well as an increase in pesticide loading. The action of a cationic polyelectrolyte (ammonium hydroxy-propyl-trimethyl chloride of the polysaccharide guar gum, commercially know as cosmedia guar, CG) in aqueous alumina suspension was investigated. This polymer was used aiming to find alternatives for synthetic polymers, as for instance, sodium polyacrylate-PANa, normally used as a deflocculating agent of alumina suspension. The measurements of particle size, as a function of time, showed that the addition of this polyelectrolytic macromolecule (CG) keeps the particles dispersed for a longer time, in comparison with the suspension containing only alumina. The ceric-ammonium-nitrate-initiated graft copolymerization of polyacrylamide onto hydroxypropyl guar gum by solution polymerization technique was studied. The synthesized products were then characterized by various instrumental techniques like viscometry, elemental analysis, IR, thermal, XRD and SEM studies. The percentage of grafting increases with increasing catalyst concentration and decreases with monomer concentration taking other parameters constant.[50]

A mild method for microencapsulation of sensitive drugs, such as proteins, employing a suitably derivatized carboxymethyl guar gum (CMGG) and multivalent metal ions like Ca2+ and Ba2+ was reported. The swelling data of Ca2+ and Ba2+ crosslinked beads suggest that Ba2+ crosslinks CMGG much more efficiently than Ca2+. The drug loading efficiency of these Ba2+/CMGG beads, as a function of concentration of both metal ion as well as drug, was then determined using Bovine Serum Albumin as a model drug. Results indicated that Ba2+ crosslinked carboxymethyl guar gum beads could be used for gastrointestinal drug delivery.[51]

The utility of guar gum in the preparation of chemical gels to be degraded in the large intestine has also been investigated. A problem arises in its excellent swelling properties and hydrophilicity, which requires its protection in the upper part of the GI tract. Cross-linking with glutaraldehyde has been proven to decrease its swelling properties.[52] Cross-linking density increases proportionally to increases in the amount of cross-linker, resulting in a corresponding reduction in solvent uptake. Guar gum as a hydrogel was not proven suitable with highly water-soluble drugs due to the resulting very fast delivery. On the other hand, it is potentially useful with poorly water-soluble drugs (even with no further coatings), to act as a specific carrier for colon delivery, with or without specific enzymes.

A further very recent study has also investigated the preparation of disc-shaped matrices of guar for colon specific delivery.[53]Specifically; the guar gum was again cross-linked with glutaraldehyde, the chosen model drug being ibuprofen. The drug loading was accomplished by immersion of the dried discs of the sample into a methanol ibuprofen solution. This kind of loading is not usually advisable since only very seldom it is efficient and the amount of drug present in the matrices is usually very small. Here the release was essentially governed by the presence of enzymes. Indeed, without an enzymatic source only a minimal diffusion of the drug was detected in simulated gastric and intestinal environments. Given the promising *in vivo* applications, this kind of network appears to be potentially quite useful. Nevertheless, a

clear picture of the cross-linking reaction is still lacking since it is well known that glutaraldehyde is capable of polymerizing, making it difficult to know the real length of the cross-linking between the macromolecular chains. Hence, further research is required since this problem can considerably limit the reproducibility of the samples that can be obtained. Furthermore, *in vivo* experiments have identified the specific group of enzymes capable of degrading the matrices of guar cross-linked with sodium trimetaphosphate.[54] By introducing modifications on the polymeric chain of guar, the dosage forms were prepared capable of carrying their hydrophobic drug load through the proximal portions of the GI tract, while maintaining their susceptibility to degradation by the colonic enzymes.

Another useful application of guar has been evidenced in the treatment of open-angle glaucoma, where guar was blended with carbopol 940 and sodium alginate.[55] The system was a free flowing liquid with low viscosity before use, turning into a hydrogel upon contact with artificial tears fluid. Here, the guar specifically increased the viscosity of the blend, a crucial parameter in obtaining the minimum rate of delivery.

SCLEROGLUCAN;

Scleroglucan is a natural exopolysaccharide produced by fungi of the genus sclerotium (Sclerotium Rolfsii) that has been extensively studied for various commercial applications and also shows several interesting pharmacological properties. The commercial product is termed scleroglucan; but it is also known with other names according to the company that produces the polysaccharide (eg: Actigum, clearogel, polytran FS Sclerogum)[22].Because of its peculiar rheological properties and its resistance to hydrolysis, temperature, and electrolytes, Scleroglucan has various industrial applications especially in the oil industry for thickening; drilling mud's and enhanced oil recovery. Other industrial use include the preparation of adhesives, water colors, printing inks, and liquid animal feed composition.[56]

In the cosmetic industry, Scleroglucan may be used in hair control compositions and in various skin care preparations, creams and protective lotions.[57] In pharmaceutical products Scleroglucan may be used as a Laxative in tablet coatings and in general to stabilize suspensions[25].In the food industry numerous Japanese patents describe quality improvements of frozen foods, Japanese cakes, steamed foods, rice crackers and bakery products.[58] The use of Scleroglucan as an antitumor, antiviral and antimicrobial compound has also been investigated. Sclg has shown immune stimulatory effects compared with other biopolymers and its potential contribution to the treatment of many diseases should be taken into account in therapeutic regimens. Recently it has attractive properties of the polysaccharide in controlled drug release and especially in immunopharmaceutical applications.[59, 60]

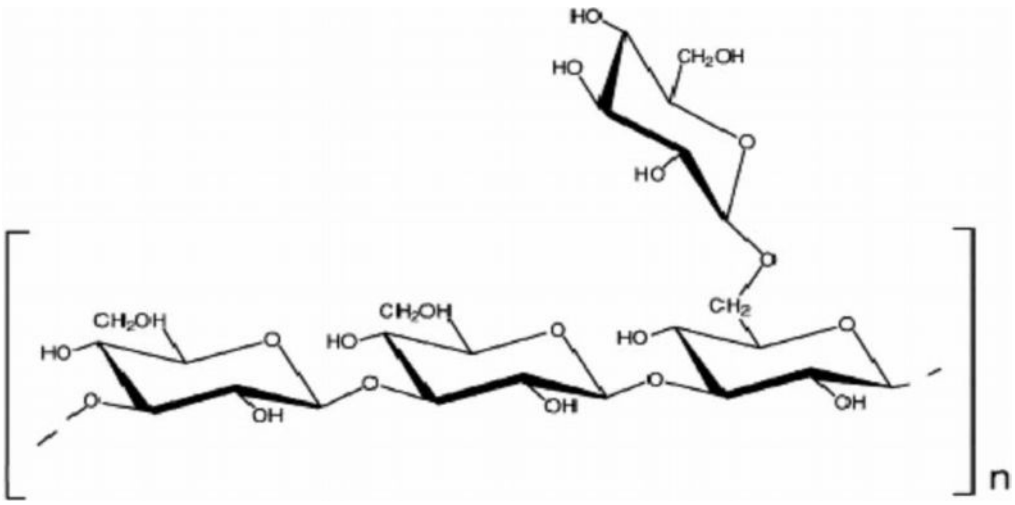


Figure: 3.Chemical structure of scleroglucan

Scleroglucan is a branched natural homopolysaccharide that gives only D-glucose after the complete hydrolysis. The polymer consists of a main linear chain of β-D- (1-3) - glucopyranosyl units; there is a β-D- glucopyranosyl unit (1-6) linked to every third unit.[61] The structure was first elucidated by periodic oxidation analysis and later verified by methylated sugar analysis and 13C nuclear magnetic resonance (NMR) the chemical structure of the tetrasaccharide repeating unit of sclg as established by NMR analysis. Sclg chains in aqueous media feature a triple helical conformation of remarkable stability. The side chain units can be derivatized by means of selective, controlled periodate oxidation; the ensuring aldehyde groups oxidized to carboxylate groups thus yielding polyeclectrolytes of variable, controlled charge density that exhibit interesting conformation-dependent solution properties.

The carboxylated polymer (Sclerox) has been found to assume a single helical conformation in aqueous solution, the breakage of the triple helix occurs during the reaction leading to the aldehyde derivative until a degree of substitution equal or less than 40%, the stable conformation of the triple helix is retained, while introducing a percentage of aldehyde groups of the order of 50% or more the triple helix disentangles into single chains. Both Sclg and its oxidized derivatives have been proposed for the formulation of sustained drug release dosage forms.[62, 63]

Solubility:

Scleroglucan disperses rather easily in water at room temperature due to the presence of β-D-(1-6)-glucopyranosyl groups that increase the solubility of the polysaccharide and decrease the ability to form the gels. Refined grades of Sclg dissolve readily in hot and cold water to form pseudoplastic solutions with shear thinning characteristics that tolerate high temperature, broad range of pH and a variety of electrolytes. [64] The viscosity of scleroglucan solutions is affected only slightly by temperature variations. At 0.5 and 2%, it remains practically constant between 10 and 90^0C. At low temperatures, close to 7^0C, solutions of Sclg form thermoreversible gels that may be caused by weakly interacting triple helix cross-linking mechanism. The viscosity of Sclg is unaffected over a pH range of 1 to 11 in addition of dimethyl sulphoxide in aqueous solutions of pH = 12.5 or higher or at temperatures above 90^0, the reduced viscosity, specific rotation and sedimentation co-efficient indicates disruption of the triple helical structure to a single random coil.[65] Sclg forms stable gels in the presence of chromium salts and borax at pH 10-11, and can be precipitated by the addition of quaternary ammonium salts under alkaline conditions.

Compatibility:

Rehydrated Sclg is compatible with electrolytes such as 5% Sodium chloride, 5% Sodium sulphate, 20% Calcium chloride and 10%disodium hydrogen phosphate. However, when the electrolyte concentrations are very high, solutions may gel and flocculate. Sclg is compatible, without synergism with most other thickeners such as locust bean gum, alginates, Xanthan and Carrageenan and cellulose derivatives and produces most favorable properties to modify the drug release in various pharmaceutical products.[66]

Rheology:

Pseudoplasticity or shear thinning is the salient characteristic of Scleroglucan solutions. This is evident in the gum solutions of 0.2% or lower but the flow becomes progressively more Newtonian as the Concentration decreases below 0.2%. Solutions containing less than 0.8% of scleroglucan are not significantly thixotropic except at temperatures dropping to 10^0 and below. Due to high degree of Pseudoplasticity, gel states are not always clearly defined. Thus 1.2 – 1.5% solutions of purified gum form self-supporting sliceable gel at approximately 25^0 but at temperatures below 10^0, even much diluted solutions, from diffusely structured gels that tend to shrink and undergo synergism when left undisturbed for long periods of time. Such diffused gels disperse quickly with mild agitation. [67]

Suspending Properties:

A pseudoplastic flow system enherently combines a capacity for suspending fine particles with good pourability of suspension. Purified Scleroglucan at 0.1 – 0.2% effectively stabilizes 5-10% aqueous suspensions of fine powders such as Zinc-oxide, reprecipitated calcium carbonate and sulphamerazine. The viscosity of combinations of scleroglucan with bentonite suspensions is markedly synergistic. Thus, while the apparent viscosities of 0.15% of purified gum and 5% bentonite are around 200 and 300 cps respectively, a combination of the two yields the viscosity of > 4000 cps. Although not a primary emulsifier in the sense of a surfactant Sclg enables very low energy dispersion during the formation of stable oil-in-water emulsions. In addition to the suspending action of the pseudoplastic system, prevention of coalescence seems to underlie this kind of stabilization [68]

PHARMACEUTICAL APPLICATIONS OF SCLEROGLUCAN:

Pharmaceutical applications include the use in tablet coatings, ophthalmic solutions, injectable antibiotic suspensions and calamine lotion. Another important use

of scleroglucan is in the form of carboxylated derivative for use as a matrix for drug delivery in the form of tablets or films. For this purpose, hydrogels obtained by the crosslinking reaction between the polycarboxylated derivative of scleroglucan and alkane dihalides were evaluated for the diffusion experiments and water up-take[69] Here scleroglucan offers advantages of controlled release as well as compatibility, biodegradability, and bioadhesiveness and thermal and chemical stability. The peculiar physicochemical properties of scleroglucan suggested its suitability as a slow a remarkable swelling process that can slow down the diffusion of molecules previously loaded in the system. Furthermore, during the hydration process, the formation of a swelled layer slows down the penetration of the dissolution medium. This layer therefore represents the rate-limiting step of water penetration, which is very important for the release of model drugs. Coviello *et al* [70] reviewed the use of scleroglucan and some derivatives in the field of pharmaceutics and in particular for the formulation of modified release dosage forms. The native scleroglucan can be used for the preparation of sustained release tablets and ocular formulations; oxidized and cross linked scleroglucan can be used as a matrix for dosage forms sensitive to environmental conditions. Another interesting approach is the preparation of a co-cross linked network using aqueous medium instead of the usual organic solvents and gellan as cross-linker. At the beginning only physical entanglements between the different chains are effective; the network is subsequently "frozen" via chemical bonds, leading to a real physical-chemical gel with an improved stability. This new polymeric network showed a sustained release behavior that was better modulated than that obtained with the single polysaccharide [71]

Scleroglucan is one very clear example of a polymer whose microscopic structure corresponds to specific and peculiar properties of the macroscopic swelling behavior of the matrix. The exopolysaccharide can form gels in the presence of borate ions, showing a mixed network with both chemical and physical linkages between the cross-linker and the chains. According to the molecular dynamics approach, the rigid rods are almost forced to align and to form bundles in which the borate acts almost as a "Zipper". Cavities along the chains are thus formed that can allocate host molecules in function of their steric hindrance. This microstructure is obviously at the origin of the release profiles observed in vitro of different model drugs. It is also behind the unusual and anisotropic swelling found in the case of scleroglucan/borax tablets.[72]

CONCLUSION

Although excipients have traditionally been included in formulations as inert substances to mainly make up volume and assist in the manufacturing process, they are increasingly included in dosage forms to fulfil specialised functions for improved drug delivery because many new drugs have unfavourable physicochemical and pharmacokinetic properties. Several polymers from plant origin have been successfully used and others are being investigated as excipients in the design of dosage forms for effective drug delivery. Some natural polysaccharides as well as exopolysaccharide hydrogels like scleroglucan, Gellan, and Guar gum as promising well accepted excipients in various modified drug delivery systems. These hydrogels that have been obtained by means of different cross linking agents are suitable for release modulation from various dosage forms and their characterization, in terms of water uptake, diffusion studies rheological behaviours could evidence to use in sustained release and environmental-controlled delivery. Therefore Gellan gum, Guar gum and Scleroglucan are exopolysaccharide hydrogels as an interesting challenge for future researches to be further investigated since these already showed interesting and in some cases very peculiar properties indicating the wide potentiality in several pharmaceutical technologies.

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