MS.ID-IJPBS-7027
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2022) 12 (3): 38-47
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Development on Grafted Gellan Gum as Control Release Polymeric Carrier for Ocular Drug Delivery System

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Received: 14 Mar 2022 / Accepted: 2 Apr 2022 / Published online: 1 Jul 2022
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Abstract
Natural polymers are substances that arise naturally during the life cycles of bacteria, fungus, mammals, they have low costs, great biocompatibility, biodegradability, accessibility, stability, and lack of toxicity. The bacteria Sphingomonas elodea produces gellan gum, a linear, anionic exocellular polysaccharide that has been widely employed as a stabiliser, thickener, viscosifier or gelling agent due to its properties. When monovalent or/and divalent ions, which are present naturally in the eye, are present, polymers like gellan gum and alginate can change into a gel. Gellan gum (GG), a visually appealing substance, has already been used in the creation of dosage forms for the administration of drugs to the eyes because of its mucoadhesive qualities and capacity to create gels in situ. As a result, there are two phases to successful ophthalmic drug delivery: liquid formulation makes it easier to administer the drug to the eye surface, while following gelation aided by tear fluid delays ocular drainage and increase contact time. A promising candidate for creating sustained/controlled drug delivery systems is grafted Gellan Gum polysaccharide of natural origin. Gellan Gum's standout characteristics, such as its ability to gel, heat and ion sensitivity, mucoadhesion, and tunable physical and mechanical properties, encourage research interest in this biomaterial. It extends the therapeutic window of the medicine for a longer time, resulting in increased patient compliance and adherence and better therapeutic methods for the management of chronic ocular illness.

Keywords
Grafted gellan gum, ocular drug delivery system, eye, polymeric carrier, drug, control release drug delivery system.

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INTRODUCTION:
Natural polymers are substances that arise naturally during the life cycles of bacteria, fungus, mammals, and green plants. Polysaccharides, polypeptides, and polynucleotides make up the bulk of their classification [1-2]. Natural polymers, particularly those based on polysaccharides, have low costs, great biocompatibility, biodegradability, accessibility, stability, and lack of toxicity. The creation of nanocarriers uses a variety of polysaccharides, including starch, dextran, alginate, pectin, chitin, chitosan, gelatin, and guar gum [3-5]. The bacterium Sphingomonas elodea produces gellan gum (GG), a linear, anionic exocellular

polysaccharide made up of a tetrasaccharide repeating unit consisting of one -L-rhamnose, one -D-glucuronic acid, and two -D-glucose residues. It is a member of the sphingan family and has been widely used as a stabiliser [6] It also goes by the name S-60. The primary chain of Gellan Gum has four repeating carbohydrates, including two d-glucose, one L-rhamnose, and one d-glucuronic acid. At high temperatures, gellan molecules appear as random coils; at low temperatures, they appear as double helices. In its solid state, gellan gum appears like a triple coaxial double helix. Each repeat unit has a main chain that contains, on average, 1 glycerate and 0.5 acetate molecules in its original form. By using a hot alkaline treatment, it can be eliminated, producing the deacetylated version, also known as low-acyl gellan gum.

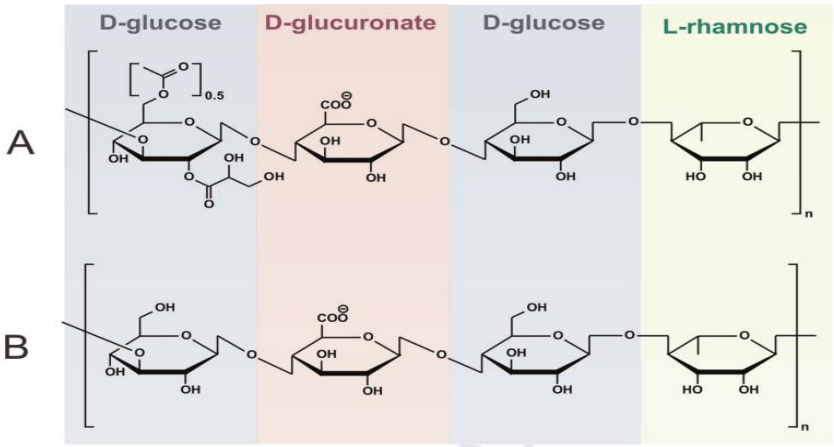

Figure 1 the structure of native (A) and low-acyl (B) form of gellan gum.

In the presence of mono-, di-, and trivalent cations, hygrogels can be formed by both native and low-acyl Gellan Gum. Temperature affects the process. First, heat to at least 70°C in order to create a clear water solution. Following cooling, the polymer chains' conformation modifications bring about the shift from coil to helix. While the deacetylated gellan produces hard and brittle gels, the native gellan produces soft, easily malleable gels. The cations can quickly build bridges between polymer chains after deacetylation. The procedure produces a network with branches (Fig 2). [7]. Gellan Gum gels upon cooling, and if heated once more, the gel liquefies once again. Insignificant concentrations of mono- and divalent metal cations can also help to induce gelation, though this is not always the case with gelling polysaccharides. The strong strength and thermal and enzymatic stability of Gellan Gum make it superior to other polysaccharides that aid in gel formation [8]. Gellan Gum has a molecular weight of 500 kDa on average [9–13]. Gellan gum hydrogels are employed for cell encapsulation because they preserve cell functioning and exhibit non-cytotoxic effects when progressively implanted into mice. Their ability to encapsulate various cell types has been compared to gellan hydrogels utilising the lyophilization method in which they were created [14]. Gellan gum hydrogels demonstrated encouraging results when used to deliver therapeutic molecules via several routes, including transdermal, ocular, nasal, and oral. Gellan gum hydrogels deliver the cells for various tissue rejuvenation processes, including bone, cartilage, neuron, and skin [15].

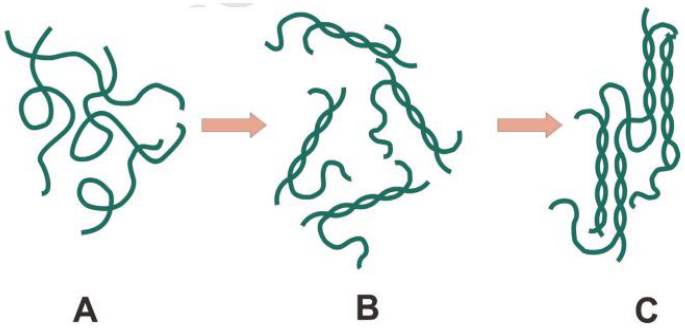

Figure 2. Gradual transformation of gellan gum from aqueous solution [7]

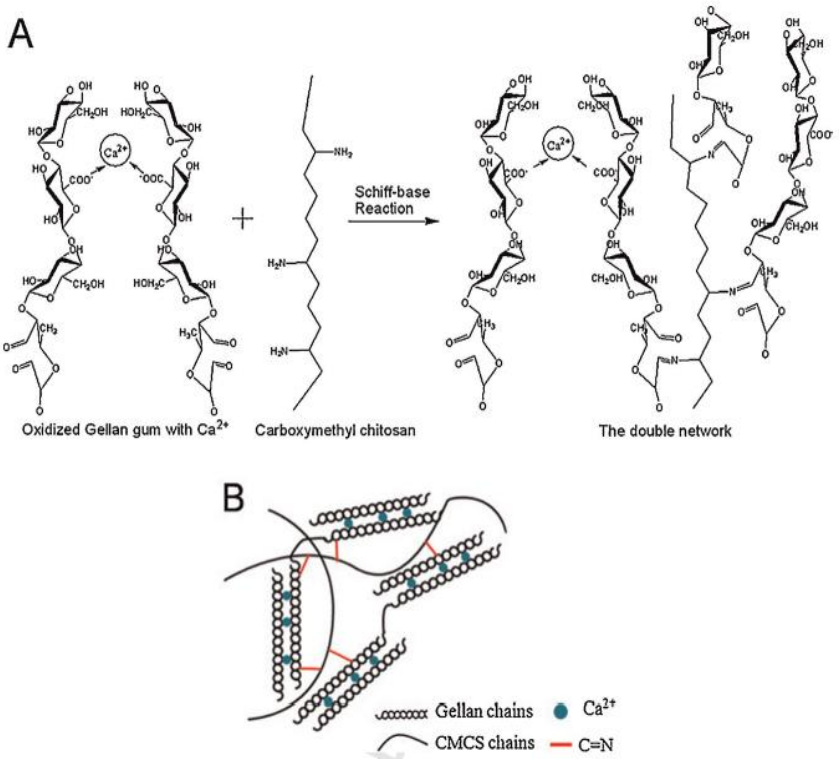

Figure 3 Schiff-base formation between amino groups of CM-chitosan and aldehyde groups of oxidized gellan gum (A). In gellan chains, cis-dihydroxyl of rhamnose was oxidized to dialdehyde, the addition of Ca2+ introduced ionic bonds between the carboxyl groups of gellan via electrostatic interaction, subsequently aldehyde groups and amino groups of CM-chitosan formed the second network via the Schiff-base reaction. The crosslinking mechanism of complex hydrogel(B). Gellan gum chains formed double helix conformations with Ca2+, and then CM-chitosan chains link the aldehyde zones to the formation of a three-dimensional network, that created the gel.

Tissues may be injected with gellan gum. It has been applied to humans in vivo as an ocular medication delivery system. It is now known that any artificial material inserted into a patient's body will cause a cellular reaction, which makes the traditional selection criterion of biomaterials important in the development of medical implants and dictates the choice of a passive, "inert" material for a safe, stable implant [16].

Rheologically speaking, gellan gum gels are a little soft, which makes extrusion challenging; however, this can be modified by combining gellan gum gels with alginate or other polymers [17].

No manmade substance is completely "inert"; even some of the least reactive ones, such polysiloxane and polyethylene, can trigger strong inflammatory reactions. The science of biomaterials is focused on leveraging control over cellular interactions with biomaterials in order to ensure that a biomaterial interacts with tissue in a physiologically relevant manner [18].

Due to their resemblance to the extracellular matrix, polymers made from natural resources have been employed most frequently to create the next generation of skin substitutes. Natural hydrogels are less cytotoxic, biocompatible, and biodegradable than some of their manufactured counterparts [19,20]. The diffusion of the drug from the micellar core and the partition coefficient of the drug over the micellar core and aqueous phase can be used to control the release of drug molecules depending on the characteristics of the therapeutic agent and the kind of nanocarrier [21].

By enhancing the pharmacological efficacy and dosage of numerous already approved medications, polymer-drug conjugates have had a significant clinical impact.

OPTIMIZED DRUG CARRIERS WITH POLYMER:

Hydrogels- 3D crosslinked networks of water-soluble polymers make up hydrogels (figure 4). When used as drug carriers, hydrogels can offer spatiotemporal control over the release of therapeutics, leverage therapeutically beneficial drug delivery outcomes, and act as a platform for a variety of physiochemical interactions with the biomolecules that regulate drug release and improve therapeutic efficacy [22].

Microneedles- Microneedles have been used in the clinic as a drug delivery device because they offer an

alternative mode of administration through surface skins [23]. A microneedle patch typically consists of clusters of microscopic needles with a height of 500–800 mm that can pass the epidermis' transport barrier and minimally invasively locate therapeutic substances (Figure 4). These needles may be composed of biodegradable or water-soluble polymers that contain drugs that dissolve or degrade inside the needle, releasing the medication at the site of entry [24].

Microparticles- The drawback of microneedles, which are frequently employed for local medication delivery, is overcome by particle drug delivery. When it comes to the direct deposition at the therapeutic site with a high local drug concentration and minimal systemic toxicity, particles have similar advantages to hydrogel implants and microneedles. They can also be utilised as reservoirs, allowing the medicine to be slowly delivered for a more methodical impact while being supplied through a handy way [25].

Nanoparticles- Some of the constraints that microparticles experience are overcome by nanoparticles. They also have a large surface-to-volume ratio, intracellular drug release, and variable surface chemistry, which makes them potential delivery platforms for treating diseases including obesity[26]. Effective medication distribution to particular therapeutic targets is never easy. For effective navigation to the therapeutic areas, nanoparticles can be modified with surface ligands, targeting compounds, or peptides [27].

Liposomes- Another vehicle for drug delivery is the liposome, a sphere-shaped vesicle made up of one or more concentric lipid bilayers [28]. These carriers can be exploited for contact-facilitated administration thanks to lipid-lipid exchange between cell membrane and the lipid layer of liposomes, which tends to interface or fuse with cells randomly throughout systemic circulation [29].

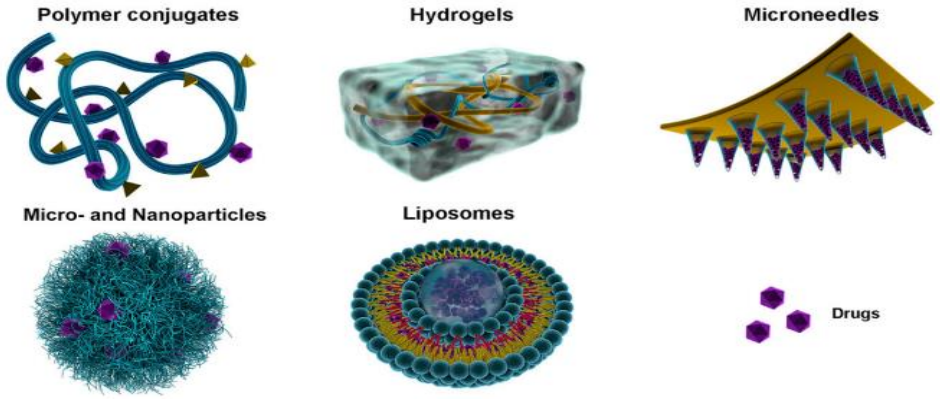

Figure 4 Advanced Drug Delivery Carriers Drugs can be conjugated to the polymer chain (e.g., polymer conjugates), encapsulated into polymers (e.g., microand nanoparticles) or lipids (e.g., liposomes), or embedded within the carrier matrix (e.g., hydrogels and microneedles) to form the drug delivery system.

Drug Encapsulation and Release

The development of medication delivery through the conjugation of pharmaceuticals and small molecules in nanocarriers is a strategy that shows incredible promise. By effectively packing drug molecules inside nanocarriers, modern drug conjugation lowers the systemic toxicity of pharmaceuticals [30]. It can be created using one of the following methods: integration, absorption/adsorption, trapping, encapsulation, dissolution, or dispersion. These nanocarriers can be loaded with a wide variety of hydrophobic and hydrophilic medicines for medication delivery. The solid-state solubility of the drug in the matrix material, polymer composition, molecular weight, and the drug-polymer interaction all affect how effectively a drug is loaded. By encapsulating pharmaceuticals in polymeric carriers, the solubility of the medications is also improved. Drug release from polymeric nanocarriers is crucial for drug production and incorporation and is influenced by a number of variables, including the length of the polymer segment that forms the core, the drug's affinity for the core, and the quantity of loaded drug [31]. The diffusion of the drug from the micellar core and the partition coefficient of the drug over the micellar core and aqueous phase can be used to control the release of drug molecules depending on the characteristics of the therapeutic agent and the kind of nanocarrier [32].

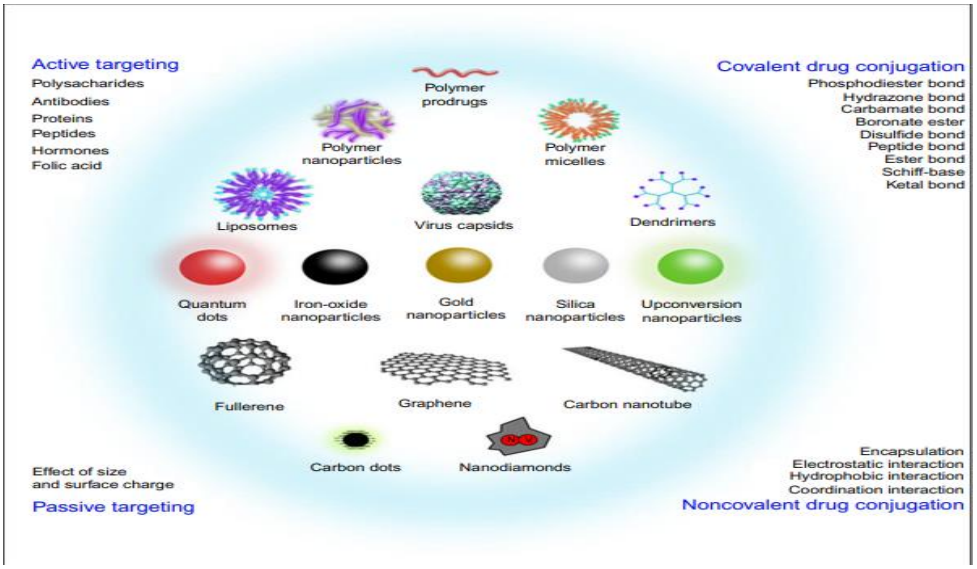

Figure 4 Schematic representation of polymers, nanoparticles, and other drug-delivery systems with possible drug targeting and their conjugation

CONTROLLED RELEASE POLYMERIC CARRIER FOR DRUG DELIVERY:

The objectives of controlled drug delivery are to regulate the time and volume of drug release, deliver the medicine to a particular area of the body, cross tissue barriers, and cross cellular barriers. Drugs can be administered intravenously, orally, through the skin or muscles, the digestive system, or the respiratory system. Drug delivery techniques are designed to regulate the quantity of the drug in the body, the area to which it is delivered, and even to get past cellular barriers. In contrast to having the drug administered into the system all at one time, controlled release refers to the rate at which a drug is released into the body. Diffusion, chemical reaction, solvent activation, and solvent transport are the primary methods for controlled release. A polymeric substance is used in the diffusion mechanism to provide a reservoir for the drug or a substance in which the drug can be evenly disseminated. The biomaterial used to create the delivery vehicle in chemical delivery degrades when exposed to water or another agent. To release the medicine that has been locked inside the capsule or by the osmotic action, solvent delivery uses a substance that can swell in the presence of water. The majority of biomaterials used for medication delivery and controlled release are made of polymers [34].

DEVELOPMENT OF CONTROLLED RELEASE POLYMERIC CARRIER FOR DRUG DELIVERY:

Based on their size, different polymeric systems have been created to deliver medications to different tissues in a controlled manner. These systems range from macroscopic (1-10 mm, for example, polymeric implants and contact lenses) to microscopic (1-100 m, for example, hydrogels) to nanoscopic (1-100 nm, for example, polymer nanoparticles, capsules, and micelles). The type of the tissue and the ease and technique by which it can be reached determine the design of a polymeric carrier to deliver a specific treatment to a target tissue. For instance, polymeric implants are favoured for therapeutic drug delivery to the skin and eyes, two external organs of the body. More advanced polymeric carriers are currently being developed, which can either autonomously react to queues (such as changes in physiological temperature or pH or the presence of particular biomolecules) presented in vivo or react to external stimuli (such as magnetic fields or near-infrared (IR) irradiation) to trigger on-demand release of the therapeutic at the desired location [34].

OCULAR DRUG DELIVERY SYSTEM:

The structure and physiology of the eye are distinct, making it a complex organ. The anterior segment and posterior segment are the two primary sections that make up the eye's structure. The anterior section is made up of tissues such the cornea, conjunctiva, aqueous fluid, iris, ciliary body, and lens. Sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitreous humour make up the posterior portion of the eye. Various vision-threatening conditions include glaucoma, allergic conjunctivitis, anterior uveitis, and cataract affect the anterior portion of the eye. While the two conditions that most frequently affect the posterior portion of the eye are age-related macular degeneration (AMD) and diabetic retinopathy.

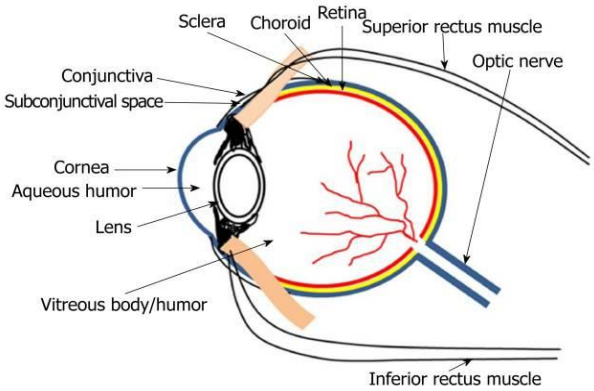

Figure 5 Structure of the eye.

The most popular non-invasive drug delivery method for treating illnesses of the anterior segment is topical instillation. 90% of the commercially available ophthalmic formulations are in conventional dose forms like eye drops. [35,36].

With topical drop delivery, the bioavailability for the eyes is quite low. Deeper ocular medication absorption is hampered by a variety of anatomical and physiological restrictions, including tear turnover, nasolachrymal drainage, reflex blinking, and ocular static and dynamic barriers [37]. Different traditional and novel drug delivery systems, including emulsions, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermosensitive gels, have been developed to overcome the barriers to ocular drug delivery and improve ocular bioavailability.

CONTROL RELEASE POLYMERIC CARRIER FOR OCULAR DRUG DELIVERY SYSTEM:

The vehicle in which polymer-based carriers are delivered is crucial for achieving the optimum results in ocular delivery. Their exceptional adaptability enables administration in a variety of dose forms, including hydrogels, in situ-forming gels, eye drop solutions, and more. For instance, Zimmer et al. dispersed pilocarpine-loaded albumin nanoparticles in liquid formulations comprising viscous or bioadhesive polymers, such as methylcellulose, poly (vinyl alcohol), and hydroxypropyl methylcellulose, to prolong their residence time on the precorneal surface (hyaluronic acid, mucin, sodium carboxymethylcellulose and polyacrylic acid). Bioadhesive polymers provide the finest performances. When monovalent or/and divalent ions, which are present naturally in the eye, are present, polymers like gellan gum and alginate can change into a gel. For instance, dorzolamide-loaded chitosan nanoparticles prepared with sodium alginate in situ gelled more effectively than their straightforward counterparts and the free drug dispersed in the in-situ gel; gamma scintigraphy demonstrated that the formulation was well retained in the pre-corneal surface [38].

ROLE OF GRAFTED GELLAN GUM WITH POLYMERIC CARRIER FOR OCULAR DRUG DELIVERY SYSTEM:

- Because of its mucoadhesive properties and ability to produce gels in situ, gellan gum (GG), a cosmetically appealing material, has been exploited in the development of dosage forms for the administration of ocular medicines [39]. Due to the fact that tear fluid contains more than four times the cations required to promote the gelling of a Gellan Gum solution at a concentration of 1% [40]. Therefore, there are two stages to effective ophthalmic drug delivery: liquid formulation facilitates drug administration to the eye surface, while subsequent gelation assisted by tear fluid delays ocular drainage and lengthens drug retention duration. Fast ion-activated in situ gelling causes a significant increase in contact time [41]. These features have raised interest in PEtOx for biomedical applications [50-52]. In vitro testing was performed in order to assess the potential of the synthesized GG-g-PEtOx copolymers for ocular drug delivery. The validation of the biocompatibility of Gellan Gum and the GG-g-PEtOx copolymers at concentrations of 1, 0.1, and 0.01 mg/mL was performed by the investigation of the cell morphology, viability, and proliferation using L929 murine fibroblasts [41]. The results indicate that cells adhere strongly from the first day in culture under the induction of all polymers and concentrations, depicting their characteristic elongated fibroblast morphology [42-44]. Although minor vision blurring was noticed after solutions were administered to human and rabbit eyes, discomfort was modest [42]. Applications of GG's mucoadhesive characteristics are discussed above. Recent studies have shown that silica

nanoparticles with their surfaces modified with poly(2-methyl-2-oxazoline) and poly(2-ethyl-2-oxazoline) (PEtOx) have lower mucoadhesion and are more easily diffused into gastric mucus [43, 44]. Due to the amide group in its repeating units, PEtOx is chemically stable, non-toxic, and shares structural similarities with polypeptides. It has demonstrated stealth characteristics akin to poly(ethylene glycol), i.e., poor immune system recognition [45–49]. The application of the copolymers can take advantage of Gellan Gum's capacity to create transparent gels in situ when triggered by metal ions that are naturally present in tear fluid in order to extend the medication retention duration on the surface of the eye. These in vitro studies confirm the good cytocompatibility of the examined GG-g-PEtOx copolymers by showing a normal cell morphology and an increase in the vitality and proliferation of cells cultivated under their induction. These findings support the possibility of further developing the suggested materials for ocular medication delivery [50–53].

- Polymers carrying betaine units (PB), also known as polyzwitterions, are defined as polymers with both positive (onium group without hydrogen atoms) and negative (carboxylate group, sulfonate group, or phosphonate/phosphate/ phosphinate group) charges positioned within the same repeat unit and separated by an alkylene group [54–57]. Both one-step and multistep procedures can be used to produce the grafted polymer containing betaine units (PGB) [58, 59]. Grafting monomers with a betaine structure onto the polymer backbone allow for a one-step process, while a multistep process involves grafting monomers with both nitrogen and vinyl groups, followed by polymer-analogous reactions onto the grafted polymers in the presence of betainization agents [60]. According to numerous research, polymer coatings based on poly(phosphobetaine) can enhance the biocompatibility of some ophthalmic devices by reducing microbial and eukaryotic cell adherence [61, 62]. Staphylococcus aureus and Pseudomonas aeruginosa were exposed to poly (methyl methacrylate) discs coated with a layer of sulfobetainic copolymer, and it was discovered that the number of bacteria adhering to the surface of the discs coated with a layer of polybetaine decreased in comparison to discs that were left uncovered [63].
- Low absorption of ocular medicines is attributed to the cornea's restricted permeability [64]. The medication is removed from the nasal cavity and lachrymal duct by blinking. Due to these restrictions, larger API concentrations are needed to achieve the desired efficiency. Designing new in situ gelling technologies with delayed drug release would seem desirable given the ocular region's unique sensitivity to high drug concentrations. Gellan can be used as a thickening and gelling ingredient in these compositions with effectiveness. It can be administered without fear of any hazardous side effects because it is well tolerated. Timoptic XE1 is the most well-known gellan-based product that is now on the market and highly known. Timoptic XE1 applied to the rabbit's cornea increases the drug's bioavailability by three to four times when compared to the regular timolol solution. With Timoptic XE1, the undesirable systemic effects are less common. Similar results were seen when indomethacin was used with gellan in situ gelling systems. Additionally, gellan gum has been researched as a component of sophisticated ocular formulations. evaluated the characteristics of mucoadhesive systems containing either gellan alone or in combination with carboxymethylcellulose and sodium alginate. The model medication was gatifloxacin, which was utilised at a concentration of 0.3%. The prepared systems offered in vitro sustained drug release for more than 12 hours. investigated several Gelrite/alginate mixes with matrine combinations. Studies on in vivo precorneal retention showed that the used polymers are suitable for extending the retention of the active ingredient. All of the formulations showed shear-thinning behaviour during rheological experiments when an artificial tear fluid was included. In terms of application and distribution of the formulation on the surface of the eye, this property is advantageous for ophthalmic formulations. The results of the viscosity tests for gels alone and in combination with mucine suggested that the chains of gellan and mucine may interact. This suggests that there are adhesive forces holding gellan to biosurfaces.
- Electrospinning is another technique for turning polymers into fibres. In a recent study, different conjunctival fornix insert designs were tested for the sustained delivery of the antibiotic besifloxacin to the cornea in the treatment of bacterial keratitis [65]. The inserts were created by electrospinning and started out as PCL and PEG fibres. To add mucoadhesion, they were subsequently coated with biopolymers, either sodium alginate or thiolated sodium alginate.

Another ocular insert made of electrospun PCL was created to distribute fluocinolone acetonide to the retina and was tested in pre-clinical research [66]. It was designed to be inserted into the conjunctival fornix. Additionally, PCL and chitosan capsules were electrospun to create a hollow, bilayered form for intravitreal injection. Two distinct benefits of electrospun nanofiber-based delivery systems are their adjustable device porosity for regulated drug diffusion and their high surface area to volume ratio for improved chemoadsorption [67]. It was also studied whether triamcinolone acetonide could be delivered to the anterior and superficial portions of the eye using electrospun conjunctival fornix inserts [68]. The best formulation had only PVP and chitosan, according to researchers who examined the characteristics and release patterns of nanofiber formulations with different amounts of PVA, poly(vinylpyrrolidone), zein/eudragit, and chitosan [69]. The fibre lens hydrates when it is applied to the ocular surface, forming a film or hydrogel. In a different study, hydrogels for drug administration were made using electrospun PVP and HA nanofibers [70]. In order to treat diseases of the ocular surface, this study concentrated on creating an ocular insert that would administer ferulic acid and Epsiliseen®-H. PVP was used to make it possible for HA to be electrospun, even though HA was the polymer in charge of the drug delivery system. Recently, the use of a porous resorbable film as a bandage contact lens after corneal injury was examined. The films were made of antioxidant kaempferol and structural nanofibrils of bovine serum albumin (BSA) [71].

CONCLUSION:

The analysis demonstrates that naturally occurring grafted Gellan Gum polysaccharide is a possible candidate for creating sustained/controlled medication delivery systems. The distinctive qualities of GG, including as its capacity for gelling, heat and ion sensitivity, mucoadhesion, and tunable physical and mechanical properties, encourage research interest in this biomaterial. It extends the therapeutic window of the medicine for a longer time, resulting in increased patient compliance and adherence and better therapeutic methods for the management of chronic ocular illness.

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