



# Polymeric *In Situ* Gel for Ophthalmic Drug Delivery: An Insight

Mahua Bera\*<sup>1</sup>, Suman Pattanayak<sup>1</sup>, Lakshikanta Kanthal<sup>1</sup>, Pritish Kumar Panda<sup>1</sup>, Bipratip Santra<sup>1</sup>, Rohit Maity<sup>1</sup>, Sudip Bhowmik<sup>1</sup>, and Indrajit Maity<sup>1</sup>

<sup>1</sup>Department of Pharmaceutics, Haldia Institute of Pharmacy, (An Institute of ICARE), Hatiberia, Haldia, Purba Medinipur, West Bengal-721657, India

Received: 12 Oct 2024/Accepted: 8 Nov 2024/Published online: 01 Jan 2025

\*Corresponding Author Email: [mahua.bera25@gmail.com](mailto:mahua.bera25@gmail.com)

## Abstract

Ophthalmic drug delivery is recently an emerging approach as the eye is one of the utmost sensitive organs of the body. The prime challenges to the researcher to develop an effective ophthalmic drug delivery is not easy because of its administration route complexity such as impermeability of drugs to cornea, drainage, non-productive absorption, induced lacrimation and tear turnover, etc. There are various approaches for ophthalmic delivery but the 'in situ gel' system has appeared to be one of the best innovative drug delivery systems. The system is unique due to its inherent characteristics feature of sol-to-gel transition. Moreover, it is easy to prepare, easy to use, improves adherence, and also provides patient compliance by minimizing drug administration frequency. The in situ gels are one type of hydrogels that are the solution in form and undergo gelation in contact with body fluids or change in PH. Recently, it has been revealed that the in-situ gelling system are prepared by using various polymers such as PLGA, chitosan, guar gum, gellan gum, xanthan gum, carrageenan, xyloglucan, pectin etc. for ophthalmic delivery. This review mainly focused on the recent approaches of various polymeric in situ gel for ophthalmic drug delivery.

## Keywords

Ophthalmic drug delivery; in situ gel; polymers; PLGA; chitosan; pectin

\*\*\*\*\*

## 1. INTRODUCTION

The eye is one of our most important sensory organs. The eye is a complex organ with a unique anatomy and physiology. Many eye diseases can affect the body and loss of vision as well. A wide range of vision-threatening disorders impact the eye's anterior and posterior parts.

As a result, there are numerous eyeballs in medication delivery systems. Both innovative and classic drug development systems fall under this category. The most common and well-acknowledged method of administering medications for the treatment of different eye conditions is topical application to the eye. Ocular diseased conditions like glaucoma, conjunctivitis, uveitis, keratitis sicca,

etc, are treated by topical application of ophthalmological active drugs. The most common and preferred ocular dosage form is eye drops as they are easily available and offer ease in their formulation and administration. However, because of the eye's effective defence mechanisms, ophthalmic medicines have relatively low absorption. Drugs and other quickly foreign substances are removed from the surface of the eye through winkle, baseline and shedding tears, and drainage. There are numerous eye conditions that can harm the eye and cause blindness. As a result, there are numerous ocular medication delivery methods accessible. These fall into two categories: traditional and non-traditional (more recent)

medication delivery methods. Since eye drops and ointments are the most widely available ophthalmic medications, they make up around 70% of the eye dosage formulations available on the market. However, when similar preparations are placed in the cul-de-sac, the lachrymal nasal drainage and tear flow quickly drain them out of the ocular cavity.

Due to the limited amount accessible for its therapeutic impact, regular dosage is required. More contemporary pharmaceutical ophthalmic preparation like in-situ gel, nanoparticles, liposomes, nano suspensions, micro emulsions, iontophoresis, and ocular inserts, have been created over the past three decades to address these problems. These formulations increase the drug's bioavailability in a controlled and sustained manner [1,2]. However frequent ocular administration of drugs exposes the ocular tissues to very high drug doses and is even not clinically possible for disease which require multiple administration for prolonged time period. Frequent administration of the drug is required to achieve the desired therapeutic efficacy. The dose may instilled also pass through the lacrimal-nasal drainage system and if it is absorbed into the systemic circulation, then it may give rise to undesirable adverse effect [3]. To create a stable sol/suspension system, a gelling agent is used to hold the dispersed medication and additional excipients is used in the formulation of the in-situ gel system. Ionic complexation brought on by a pH shift is what causes this sol/suspension mixture to gel in a stomach environment. Sodium alginate solution or gellan gum that contains sodium citrate and calcium chloride are used to prepare this solution. This solution complexes the free calcium ions, which are only released in the stomach's acidic environment. Final texture was formed using gelling agent like sodium alginate or gellum gum and from fluid gels to stiff, brittle, non-elastic gels. When free calcium ions are bound by the polymeric chains of sodium alginate or gellan gum, the chains crosslink and acquire a matrix-like structure. After completion of gelation process, the double helical segments rearranged differently and form network like structure in junctional zone. Complexation was achieved using cations and hydrogen bonding with water [4].

Through the solution-gel transition, for example, the in situ gelling mechanism has some significance, in situ ocular gel regulates the prolonged release of medications in ophthalmic drug delivery systems, minimal dosages necessary, with no potential for drug build up or adverse effects, decreases the frequency with which medications are administered, improve bioavailability, increase residence time of application because of gel formation, reduce wastage of drug [5–7]. When a drug product that already exists as a liquid comes into touch with bodily

fluids and body temperature, it changes from a gel to an in situ gel [8].

One of the greatest innovative drug delivery methods is the "in situ gel" technology. In the early 1980s, the innovative idea of creating in situ gel was initially proposed. By using phase transition, viscoelastic gels are created in the conjunctival cul-de-sac due to structural alteration of polymer by physiological environment, known as "in situ gel-forming systems". The velocity of in situ gel development is crucial because the fluid mechanism of the eye produces a solution or weak gel between instillation and the formation of a strong gel. By switching from "Sol to Gel," the in-situ gel drug delivery system's unique feature helps to increase patient compliance, comfort, and the prolonged and regulated release of the medications. Gels comprise both liquid and solid ingredients. The component consists of a network in three dimensions [9].

Gelatin is the root of the term "gel," and the Latin word gelu, which means "freeze" or "congeal," can be traced back to both "gel" and "jelly." With both liquid and dependable components (semi-liquids or semi-solids), gels are a transitory state of matter. According to the origin, a liquid solidifies into a substance that is elastic and retains some liquid properties but does not flow. Since gels have a larger density of physical bonds, more covalent crosslinks, or are just less liquid than jellies, they are typically thought to be stiffer than jellies. Gel-forming polymers result in a variety of rigidities, starting with a sol and progressing to mucilage, jelly, gel, and hydrogel. Some gel systems are as transparent as water, while others are murky due to the presence of aggregates that disperse light or partially dispersed (soluble or insoluble) components. With few exceptions, the gelling agents' concentration is typically in the range of 0.5% to 2.0%, which is less than 10%.

Sterile liquid, semisolid, or solid preparations that are administered to the eye and may contain one or more active pharmaceutical ingredients are known as ophthalmic drug delivery systems. It is implanted between the eyeballs and the eyelids.

Ocular medication delivery is currently one of the most challenging problems facing pharmaceutical scientists. The structure and function of the eye make it extremely resistant to external chemicals. Getting beyond the eye's protective layers without permanently damaging the tissue is a significant challenge for the formulator. The main issues with traditional liquid ophthalmic formulations include the drug's rapid removal from the pre-corneal region after instillation due to nasolacrimal drainage, persistent lachrymal secretion, and the solution's brief precorneal residence duration. Various ophthalmic administration systems, including

viscous solutions, ointments, gels, suspensions, or polymeric inserts, are utilized to extend precorneal residence duration and ocular bioavailability. By employing an in situ gel-forming ocular drug delivery system made of polymers that show a sol-to-gel phase transition as a result of a change in a particular physio-chemical parameter (pH, temperature, ion-sensitive), this issue can be resolved [10].

## 2.METHOD OF PREPARATION OF IN SITU GEL

First, weigh HPMC with 50 ml purified water, add HPMC K15M and Carbopol 934 solution hydrate at overnight. Then stirrer above solution and dissolve buffer salts (Disodium hydrogen Phosphate, citric acid). Next, the drug was dissolved in water and add benzalkonium chloride. Then make up volume upto 100ml and sterilized with autoclave for 20 minutes [11]. In another formulation different concentration of gellum gum was prepared with sodium citrate (0.17 %w/v) containing water and the mixture was warmed up at 90°C temperature. The resultant solution was then allowed to cool to below 40°C before the proper concentrations of ranitidine (1% w/v) and calcium carbonate (0.75% w/v) were dissolved [12]

Accurate weights were taken of the medication, gelling agent, and other excipients. Subsequently, distilled water with varying percentages of calcium chloride and sodium citrate was heated to 60°C while being constantly stirred. Another beaker, various concentration of sodium alginate solutions was prepared. The resultant solution was then mixed with the proper amount of ranitidine hydrochloride, and formulations were created [13]. In another formulation, deionized water was utilized as a gelling agent to manufacture this composition. The gel gets stiff when it comes into touch with the ions in the buffer system. Then, while stirring constantly, add 0.9%w/v sodium chloride and benzalkonium (a preservative). After adding the medicine to the polymer solution while stirring to create a homogenous solution, top up the volume to 100 milliliters. Next, formulation was tested for ocular irritation study[14]. It was first dissolved by calcium carbonate (CaCO<sub>3</sub>). Next, dissolve 0.2g of medication in 10ml of 0.1N HCL solution. Now, in another beaker, gradually swirl the water containing trisodium citrate while adding sodium alginate. Combine three solutions. Aspartame should now be added to a 9:1 solution of propylparaben and methylparaben in filtered water. Various HPMC concentrations have now been added to the appropriate batches[15]. Using a magnetic stirrer, the necessary amount of sodium alginate was added as the primary polymer, and HPMC-E 50LV and HPMC-K4M were added as co-polymers in water until the polymers were fully dissolved. The polymeric

solution was continuously stirred while an aqueous solution of moxifloxacin hydrochloride was added. Benzalkonium chloride was added to the resultant solution along with buffering and osmolality agents. The solution's pH was brought down to 6.5 using 0.1N N/0.1N Hcl[16]. Melt Drops technology use hot-melt extrusion (HME) to produce ISGS continuously. In order to control glaucoma, timolol maleate (TIM) and dorzolamide hydrochloride (DRZ) loaded Melt drops were successfully manufactured utilizing HME. This resolved concerns with the batch manufacturing of ISGS and improved bioavailability by extending the retention time. The Melt drops technology involves one-step, i.e., feeding all the ingredients through an extruder at a screw speed between 20 and 50 rpm and barrel temperature of 80 °C. In comparison to batch-processed ISGS, melt drops showed superior physical and chemical content consistency, according to the evaluation. Significant effects of screw speed and extrusion temperature were seen in the Melt Drops for consistency of the content [17].

## 3.POLYMERS USED IN IN SITU GELLING OPHTHALMIC PREPARATIONS

### 3.1 Natural Polymers

- 3.1.1 Alginic Acid
- 3.1.2 Carrageenan
- 3.1.3 Chitosan
- 3.1.4 Guar gum
- 3.1.5 Carbopol.
- 3.5.6 Gellan gum
- 3.5.7 Pectin
- 3.5.8 Sodium hyaluronate.
- 3.5.9 Xanthan Gum
- 3.5.10 Xyloglucan

### 3.2 Synthetic or Semi-Synthetic Polymers

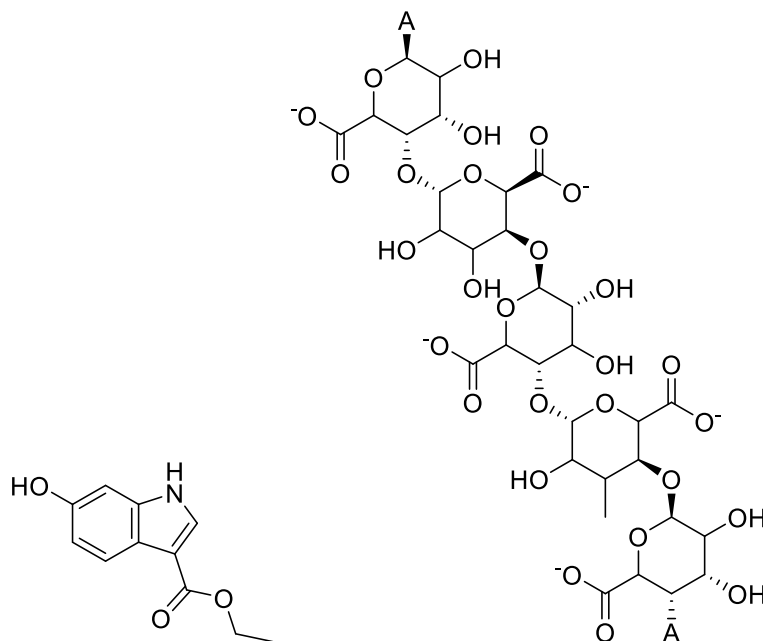
- 3.2.1 CAP
- 3.2.2 HPMC
- 3.2.3 MC
- 3.2.4 PAA
- 3.2.5 PLGA
- 3.2.6 Poloxamers

### Alginate Acid or Sodium Alginate

The linear block copolymer polysaccharide is composed of β-D-mannuronic acid and α-L-glucuronic acid residues connected by 1, 4-glycosidic bonds, and it is biodegradable, hydrophilic, and non-toxic. It is used as a method of administering ocular drugs. In reaction to divalent cations such as Ca<sup>2+</sup> and Mg<sup>2+</sup>, alginate cross-links the carboxylate groups, forming a persistent gel that is difficult for tear fluid to break down. The order of each block along the molecule varies according on the algal source. Subsequent glucuronic residues in the α-L-glucuronic acid blocks of the alginate chain combine to form solid gels when di and trivalent metal ions

are introduced to diluted aqueous solutions of alginates [18]. For sustained release ocular drug delivery of ciprofloxacin, sodium alginate was used as polymer [19]. For ocular therapeutic targeting,

sodium alginate offers several advantages, including mucoadhesive qualities, non-toxic and biodegradable behaviour, and ion-sensitive in situ gelation [20].



**Figure 1: Structure of Alginic Acid / Sodium Alginate**

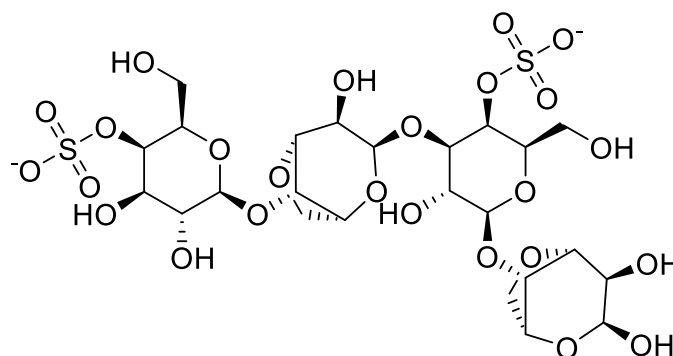
### Carrageenan

As gelatin, it is used as a home treatment for colds and coughs. There are three types of carrageenan-

A. Iota carrageenan: It is fully soluble in hot water and forms an elastic gel when calcium or potassium ions are present.

B. Kappa carrageenan: Like locust bean gum, it dissolves in warm water and solidifies into a "gel" in presence of potassium ions [21]

C. Lambda carrageenan: It produces less viscous solutions and is fully soluble in refrigerated water, despite the fact that it does not result in gel formation.



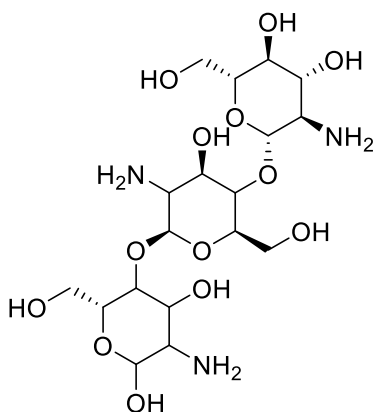
**Figure 2: Structure of Carrageenan**

### Chitosan

Biodegradable, thermosensitive, cationic, and biocompatible, it is a pH-dependent cationic polymer. Up to 6.2 pH, it can dissolve in aqueous solutions. Chitosan gels in response to temperature and pH changes. Chitosan's remarkable mucoadhesive properties are due to the extreme hydrophobic interactions led to the formation of gels with electrostatic forces at low critical solution

temperatures. Displaying polymers at the maximum critical solution temperature is used in the chitosan gelation process. This polysaccharide is the second most commonly used after cellulose since it is easily accessible, non-toxic, reasonably price. A hydrated gel is produced due to neutralisation of pH greater than 6.2 for aqueous chitosan solution. Further, the formation of gel by using chitosan happens by changing the critical solution temperature [22].

Chitosan is also used as bioadhesive timolol maleate liposome shows longer retained in corneal surface [23].



**Figure 3: Structure of Chitosan**

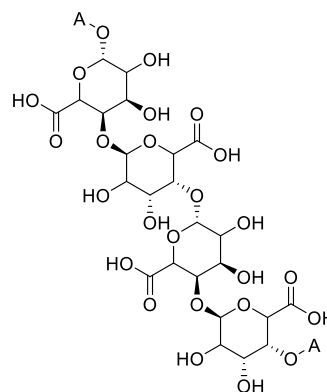
### Pectin

The residues of  $\alpha$ -(1, 4)-D galacturonic acid form a family of linear, cationic polysaccharides. When  $H^+$  ions are present, pectin gels to produce monovalent, divalent, and trivalent ions. It is suitable for only those formulations which dissolve in water and where organic solvents cannot be used. Pectin dissolves in water, as do pectic acid monovalent cations (alkali metal) salts. Di and trivalent cationic chemicals, on the other hand, are either insoluble or only faintly soluble in water. Because dry powdered pectin has a tendency to hydrate, clumps are formed when water was added. Water soluble carrier was used to solubilize the clusters. The fraction of carbonyl groups esterified with methanol is known as the degree of methylation (DM).

Depending on esterification pectin is distinguished into two groups-

- Less than half of the pectin is low methoxy pectin which is methylated by the carboxyl groups.
- High methoxy pectin which is the pectin is methylated by over 50% of the carboxyl groups.
- Free calcium ions and low methoxy pectin levels cause them to gel in an aqueous media. Moreover, the aforementioned solution can be mixed with sodium citrate to create a compound with the calcium ions, which causes gelation. The formulation will stay in solution form until the breakdown of complex

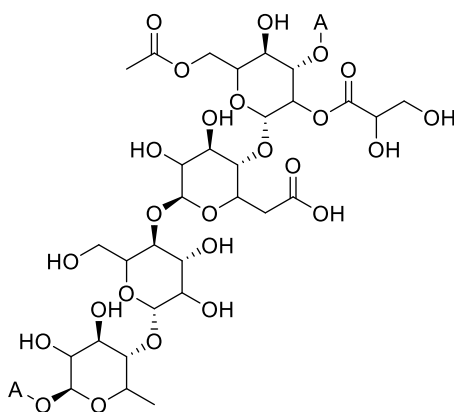
in the stomach, where gelation occurs by the release of calcium ions from the complex [24]



**Figure 4: Structure of Pectin**

### Gellan Gum

Gellan gum produces gels which are temperature dependent, or cation induced. *Pseudomonas elodea* secretes this anionic deacetylated exocellular polymer. In presence of divalent cation in polymer like calcium or magnesium ions which is responsible for gel formation. Formation of gel from gellan gum happens when solution comes into contact with mucosal layer of stomach. Compared to traditional eye drops, the viscous gels' longer pre-corneal contact durations resulted in a longer duration of drug release from these in situ gels. This gellan gum is an extracellular, hetero, anionic, linear, water-soluble, temperature-dependent polymer that gels in the presence of mono- or divalent metal cations. It is sold under the names Gelrite or Kelcogel. Cross-linking gelation is brought on by monovalent cations ( $Na^+$  or  $K^+$ ) and divalent cations ( $Ca^{2+}$  or  $Mg^{2+}$ ). During the gelation process, double-helical junction zones are formed, next the double helical segment agglomerates and form three dimensional network through complexation was achieved using cations and hydrogen bonding with water. One of the important polymers for preparation of in situ gel is gellan gum. Gellan gum and hydroxyethylcellulose were used to create in situ ophthalmic medication administration for a prolonged precorneal retention period [25]. For preparation of ion triggered liposome used for intraocular pressure for rapid reduction and effective time will be longer [26].

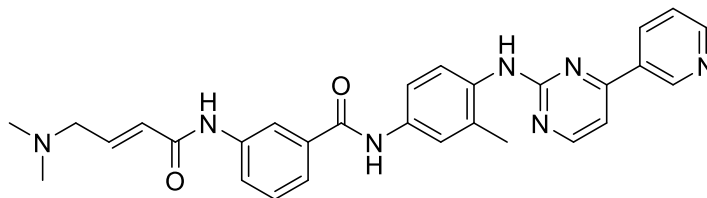


**Figure 5: Structure of Gellan Gum**

### Carbopol

At alkaline pH, this well-known pH-dependent material gels with low viscosity, but at acidic pH, it stays in solution form. When mixed with HPMC, it makes the carbopol solution less acidic and more

viscous. One major drawback of carbopol is that, despite its good mucoadhesive properties, the acidity of the gel irritates and damages ocular tissue. To get around this problem, carbopol mixes with other polymers, like chitosan and HPMC [27].

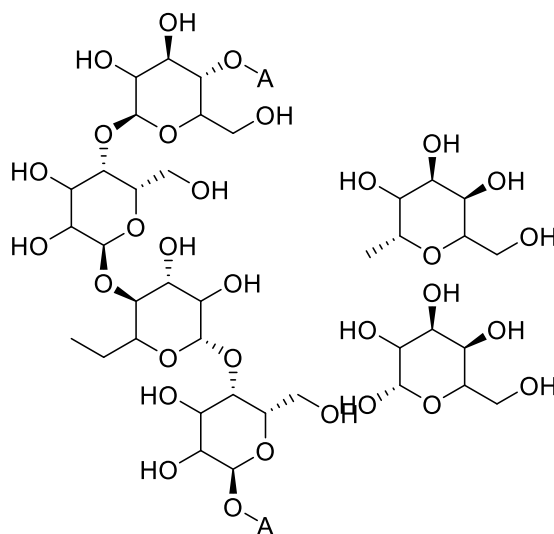


**Figure 6: Structure of Carbopol**

### Guar Gum (Guran)

While it dissolves in water, it does not dissolve in lipids, alcohols, ketones, hydrocarbons, or ester. It exhibits superior dispersibility and, when combined with modest volumes of hot and cold water, generates highly viscous colloidal solutions. A reversible shift in gel formation is brought about by

temperature fluctuations [26]. Furthermore, by lengthening the corneal contact period, guar gum overcomes the quick removal from the ocular region and possesses a significant bio adhesive potential. Because of the extended corneal surface retention, it has demonstrated encouraging outcomes in ocular administration [28].



**Figure 7: Structure of Guar Gum**

### Xanthan Gum

Xanthan gum dissolves in both warm and refrigerated water and exhibits better stability in both alkaline and acidic environment. Because it contains both pyruvic and glucuronic acid groups, it has an anionic character. Compared to commercial eye drops and oral tablets, the ion-triggered acetazolamide nanoemulsion, which was made using gellan gum, xanthan gum, and HPMC/carbopol, showed higher therapeutic efficacy and a long-lasting intraocular pressure-lowering effect [29].

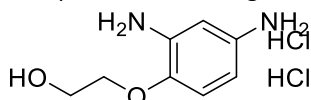


Figure 7: Structure of Xanthan Gum

### Xyloglucan (Tarmind Gum)

A common hemicellulose polysaccharide, xyloglucan is non-toxic, biocompatible, and biodegradable, polymer is used in various drug delivery system. The irresponsive reaction gels it after  $\beta$ galactosidase partially breaks it down. When taken orally, the gelation time might reach minutes, and the stomach can gel when it is cooled. Similar to poloxamer, it gels at higher temperatures, such as when heated or refrigerated. Xyloglucan can get over a broad pH range when combined with alcohols or sugars (40–65%). Nevertheless, a gel is formed by significantly reducing the sugars in the mixture (20 % alcohol). This polymer exhibits thermally reversible gelation when  $\beta$ -galactosidase partially breaks it down by causing rod-like polymer chains to stack laterally when the body temperature changes. The polysaccharide xyloglucan, sometimes referred to as tamarind gum, is taken out of the endosperm of seeds. The number of galactose side chains varies across the three different oligomers that comprise xyloglucan: octasaccharide, non-saccharide, and heptasaccharide. Typically, it is employed in ocular, rectal and oral medication administration. For preparation of gel it shows good characteristic like non-toxic, biodegradable, and biocompatible, just as poloxamer. To create an in-situ gel filled with triamcinolone acetonide for ocular administration, tamarind seed xyloglucan and kappa-carrageenan were utilized [30].

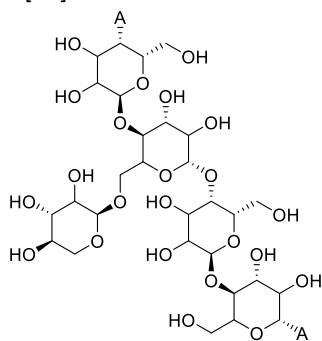


Figure 8: Structure of Xyloglucan

### Sodium Hyaluronates

It is a type of water loving formation of sodium salt of hyaluronic acid. It is an endogenous, natural polysaccharide that assist formation of collagen which helps body elasticity. Also, it decreases the oxygen probably and improves formulation stability. Because it is hydrophilic, sodium hyaluronate readily blends with water. It draws moisture to the cells of the skin when applied topically. This improves skin moisture and decreases dryness and flaking. Sodium hyaluronate loaded timolol maleate was used as extended release ophthalmic formulation [31]. Sodium hyaluronate was used to treat dry eye condition [32]. Additionally, hyaluronic acid was discovered in the vitreous humor, outer cornea, and tear film [33].

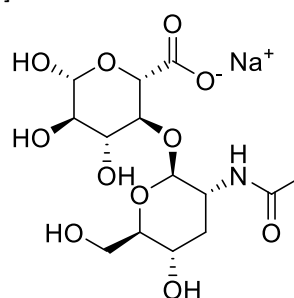


Figure 9: Structure of Sodium Hyaluronate

### Synthetic Polymers

#### Cellulose Acetate Phthalate (CAP)

CAP is often referred to as pseudo latex. A pre-existing polymer is dispersed to create artificial latex in an aqueous media. Cross-linked polyacrylic polymers that are sensitive to pH have beneficial for long-term drug delivery to the eye because latex, which is a free-running solution at 4.4 pH, tear fluid coagulates at pH 7.4. In  $\gamma$ -scintigraphy, CAP is used to calculate the ocular residence time of an ophthalmic solution. The enteric coating polymer cellulose acetate phthalate (CAP) is frequently utilized. Numerous techniques have been used to investigate CAP powder in order to identify features that affect its functionality. Cellulose Acetate Phthalate was also employed as a polymer to treat dry eye [34].

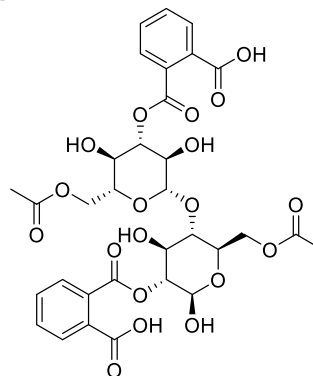
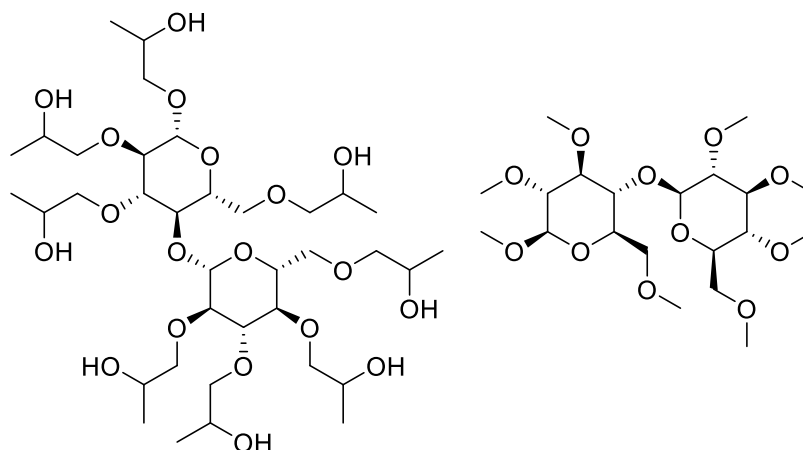


Figure 10: Structure of Cellulose Acetate Phthalate

### Hydroxypropyl Methylcellulose (HPMC)

This polymer has mucoadhesive, thermoreversible, and biocompatible properties. It is a kind of cellulose ether and have thermal gelation properties due to high swellability. The solution becomes less acidic and more viscous when HPMC and carbopol are combined. Due to the interaction of the hydrophobic

polymer at higher temperatures, HPMC converts as gels. It was actively involved in the development of topical eye treatment aqueous solutions. When temperature decreases viscosity of cellulose derivative like MC, HPMC increases. With addition of HPMC in eye drops to improve the formulation's viscosity, stability, and mucoadhesion [35–39].

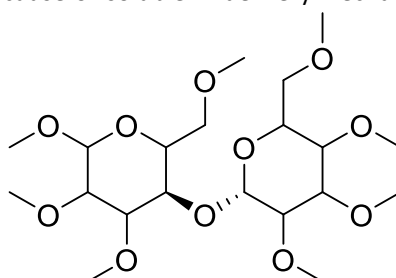


**Figure 11: Structure of Hydroxypropyl Methylcellulose**

### Methylcellulose (MC):-

It is another cellulose derivative used in preparation of in situ gel. At 40-50 °C and 75–90°C the aqueous solution of MC and HPMC undergoes phase transition into gel. The phase transition temperature of MC and HPMC is lowered by physically and chemically altering the polymers, even if it is higher than the physiological temperature. Hydrophobic interactions between methoxy group-bearing molecules lead HPMC and MC solutions to gel. At low temperatures (30 °C), the solution is liquid but at higher temperatures (40–50 °C), gelation takes place. In ophthalmic preparation methyl cellulose is used for viscous, white transparent and refractive index comparable to cornea. It is used because of soluble

water, and nonirritating, chemically inert characteristics. In addition to being an emollient and cohesive solution that may be used with contact lenses and gonioscopic prisms, this solution would be helpful as a bland vehicle for ocular medications and as a natural secretion substitute in cases of keratoconjunctivitis sicca. In this preparation another polymer like gelatin, tragacanth also used as preservative, but disadvantage is that chemically unstable. Methylcellulose is used to relieve dryness and discomfort caused by a reduction in tear production. It helps avoid eye damage in some eye disorders. Methyl cellulose functions as an anionic polymer in this in situ gelling ocular medication delivery mechanism [40].

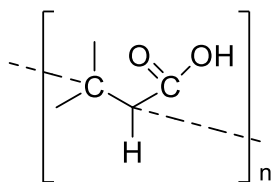


**Figure 12: Structure of Methylcellulose (MC)**

### Polyacrylic Acid (PAA)-

PAA is marketed under the name carbopol. It is commonly used to enhance pre-corneal retention in ophthalmology. It might have exceptional mucoadhesive qualities in contrast to other cellulose derivatives. When compared to various grades, such carbopol 910, 934, 940, 941, etc., 940 was

determined to perform the best. Mucoadhesion is believed to be caused by the protonated form of polyacrylic acid at an acidic pH, which is the original mucoadhesive polymer. To treat dry eye condition, it is used as an artificial tear substitute. The polyacrylic acid's -COOH groups and the mucin glycoprotein's sialic -COOH groups create a hydrogen bond [41].

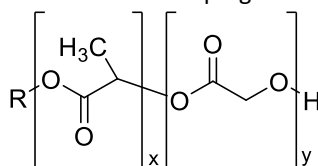


**Figure 13: Structure of Polyacrylic Acid (PAA)**

**Poly (lactic-co-glycolic acid) or PLGA-**

This polymer degrades and is biocompatible. Some synthetic co polymer like polylactic acid, polyglycolic acid, which is used for in situ implants, macroparticles for controlled drug delivery system. One of the best polymers is PLGA for developing

tissue engineering and drug delivery applications due to its vast clinical experience. Sparfloxacin is delivered to the eyes via a chitosan in situ gel that contains a polylactic glycolic acid nanoparticle [42].

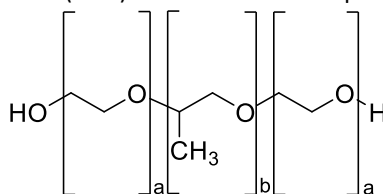


**Structure 1: of Poly – (lactic-co-glycolic acid)**

**Poloxamers: -**

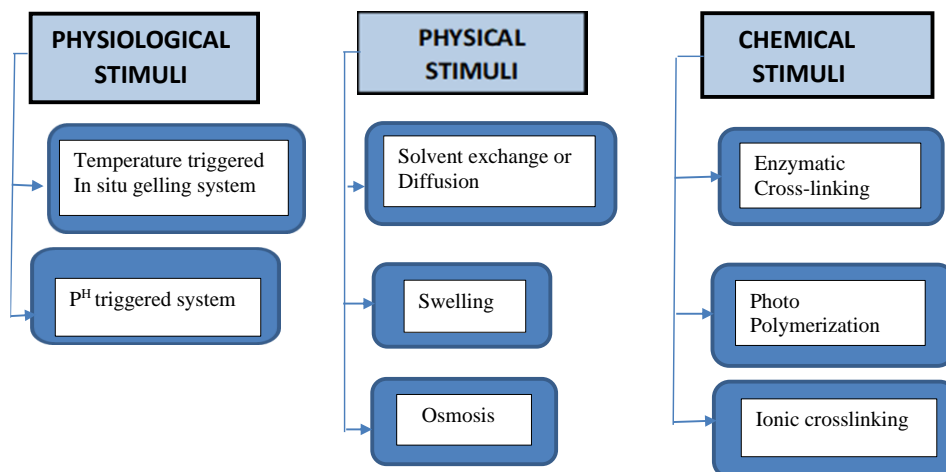
Poloxamers are utilized in thermosensitive in situ gels and are marketed as pluronic. It increases the duration of the drug's residence period and has remarkable thermal setting qualities. For preparation of colorless, translucent gels, Polyethylene oxide (PEO) and polypropylene oxide (PPO) water soluble copolymer were used. Among them pluronic F127 poloxamer polymer is an important polymer for formulation. PEO (70%) and

PPO (30%) make up its composition. To increase the absorption of the eye medications and prolong their residence time, in situ gelling vehicles were made using the copolymer pluronic F127-g-poly (acrylic acid) [43]. Curcumin (Cmn) delivered locally in the form of periodontal formulations tailored to a given site may provide new options for the treatment of periodontal illnesses by using poloxamer [44]. Poloxamer 407 is also used for Brinzolamide, sustained ophthalmic drug delivery system [45].



**Figure 14: Structure of Poloxamers**

**Approaches of in situ Gel: -**



In general, the body forms in-situ gel after delivery due to three distinct mechanisms [46–49].

## CONCLUSION:

The present review concludes that in situ gel system has emerged as one of the best novel drug delivery systems for ophthalmic preparation. In situ gelling systems have wider applications as it overcome the drawbacks associated with conventional ocular dosage forms as well as enhances the patient compliance. Besides, it shows the ease of administration as it can take the solution form, while it shows controlled release after administration because of its gel formation behavior. Furthermore, it has also observed that it administered in accurate and reproducible quantities of drugs. It reduced frequency of administration, increased pro corneal contact time, and prolonged drug release and drug delivery to deeper tissues.

## REFERENCES

- [1] Li S, Chen L, Fu Y. Nanotechnology-based ocular drug delivery systems: recent advances and future prospects. *J Nanobiotechnology* 2023; 21:232. <https://doi.org/10.1186/s12951-023-01992-2>.
- [2] Gorantla S, Rapalli VK, Waghule T, Singh PP, Dubey SK, Saha RN, et al. Nanocarriers for ocular drug delivery: status and translational opportunity. *RSC Adv* 2020; 10:27835–55. <https://doi.org/10.1039/D0RA04971A>.
- [3] Tangri P& KS. Basics of ocular drug delivery systems. *International Journal of Research in Pharmaceutical and Biomedical Sciences* 2011; 2:1541–52.
- [4] Kalia Neha NHS. IN SITU GELLING SYSTEM: A REVIEW. *Journal of Drug Delivery and Therapeutics* 2014; 4:93-103.
- [5] Ahmed B, Jaiswal S, Naryal S, Shah RM, Alany RG, Kaur IP. In situ gelling systems for ocular drug delivery. *Journal of Controlled Release* 2024; 371:67–84. <https://doi.org/10.1016/j.jconrel.2024.05.031>.
- [6] Pradip Ganesh Landge DrSSARSPDDVD. SMART POLYMERS FOR STIMULI RESPONSIVE DRUGS. *INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES* 2022; 9:374–81.
- [7] Dhage AN, Mulla ZI, Kulkarni AS, Borge AR, Ghosalkar MK. In-Situ Gel-New Formulation Trend. *Int J Sci Res Sci Technol* 2022; 9:665–75. <https://doi.org/10.32628/IJSRST229697>.
- [8] Kaur H, loyee S loyee, Garg R. Formulation and Evaluation of In-Situ Ocular Gel of Gatifloxacin. *International Journal of Pharma Research and Health Sciences* 2016; 4:1365–70. <https://doi.org/10.21276/ijprhs.2016.05.05>.
- [9] Sarada K FSPK. In-Situ Gelling System: A Review. *International Journal of Current Pharmaceutical Review and Research* 2014; 5:76–90.
- [10] Dibyalochan Mohanty1 DrVB 2, NSMAHCKS. A Review on in situ Gel: A Novel Drug Delivery System. *Int J Pharm Sci Rev Res* 2018; 50:175–81.
- [11] Harpreet Kaur SLRGarg. FORMULATION AND EVALUATION OF IN – SITU GEL OF GATIFLOXACIN (2016);4(5):1365-1370. . *International Journal of Pharma Research and Health Sciences* 2016; 4:1365–70.
- [12] Xu H, Shi M, liu Y, Jiang J, Ma T. A Novel In Situ Gel Formulation of Ranitidine for Oral Sustained Delivery. *Biomol Ther (Seoul)* 2014; 22:161–5. <https://doi.org/10.4062/biomolther.2013.109>.
- [13] Neha Jameel CVSRK and VK. FORMULATION AND EVALUATION OF FLOATING ORAL IN-SITU GEL OF RANITIDINE HYDROCHLORIDE. *INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY* 2016; 6:75–81.
- [14] Swapnil D SLS. Design and evaluation of ion-induced in situ gel formulation for levofloxacin hemihydrateocular delivery. *Int J Pharm Sci Invention* 2014; 3:38–43.
- [15] Ramesh Pareek, Pawan Kumar Sharma, Vandana Sharma. Development of Sustained Release of Gatifloxacin by Using Floating Oral in Situ Gelling System. *Pharmaceutical and Biosciences Journal* 2019:11–6. <https://doi.org/10.20510/ukjpb/7/i6/1581325597>.
- [16] Mandal S, Prabhushankar G, Thimmasetty M, Geetha M. Formulation and evaluation of an in-situ gel-forming ophthalmic formulation of moxifloxacin hydrochloride. *Int J Pharm Investig* 2012; 2:78. <https://doi.org/10.4103/2230-973X.100042>.
- [17] Tambe SM, Jain DD, Hasmukh Mehta C, T. A, Yogendra Nayak U, Amin PD. Hot-melt extruded in situ gelling systems (MeltDrops Technology): Formulation development, in silico modelling and in vivo studies. *European Journal of Pharmaceutics and Biopharmaceutics* 2023; 188:108–24. <https://doi.org/10.1016/j.ejpb.2023.05.008>.
- [18] G. S. Deokar SSR and SJK. AN ATTEMPT TO UNDERSTAND AND VALIDATE THE FACTORS CONTROLLING IN-SITU RAFT FORMATION PROCESS. *Int J Pharm Sci Res* 2019; 10:4657–67.
- [19] Ashish Singh\* SK and SA. FORMULATION AND EVALUATION OF IN-SITU GELLING SYSTEM FOR SUSTAINED RELEASE OPHTHALMIC DRUG DELIVERY OF CIPROFLOXACIN. *World J Pharm Res* 2020,9.
- [20] Karmakar S, Manna S, Kabiraj S, Jana S. Recent progress in alginate-based carriers for ocular targeting of therapeutics. *Food Hydrocolloids for Health* 2022; 2:100071. <https://doi.org/10.1016/j.fhfh.2022.100071>.
- [21] Russo Spena S, Pasquino R, Sarrica A, Delmonte M, Yang C, Grizzuti N. Kinetics of acid hydrolysis of k-Carrageenan by in situ rheological follow-up. *Food Hydrocoll* 2023; 144:108953. <https://doi.org/10.1016/j.foodhyd.2023.108953>.
- [22] Bhattacharjee T, Islam M, Chowdhury D, Majumdar G. In-situ generated carbon dot modified filter paper for heavy metals removal in water. *Environ Nanotechnol Monit Manag* 2021; 16:100582. <https://doi.org/10.1016/j.enmm.2021.100582>.
- [23] Preeti Upadhyay MK and KP. Norfloxacin Loaded pH Triggered Nanoparticulate in-situ Gel for Extraocular Bacterial Infections: Optimization, Ocular Irritancy and Corneal Toxicity. *Iranian Journal of Pharmaceutical Research* 2016;15.

- [24] Itoh K, Hatakeyama T, Shimoyama T, Miyazaki S, D'Emanuele A, Attwood D. *In situ* gelling formulation based on methylcellulose/pectin system for oral-sustained drug delivery to dysphagic patients. *Drug Dev Ind Pharm* 2011; 37:790–7. <https://doi.org/10.3109/03639045.2010.541465>.
- [25] Destruel P-L, Zeng N, Seguin J, Douat S, Rosa F, Brignole-Baudouin F, et al. Novel *in situ* gelling ophthalmic drug delivery system based on gellan gum and hydroxyethylcellulose: Innovative rheological characterization, *in vitro* and *in vivo* evidence of a sustained precorneal retention time. *Int J Pharm* 2020; 574:118734. <https://doi.org/10.1016/j.ijpharm.2019.118734>.
- [26] Mondal A, Barai S, Bera H, Patel T, Sahoo NG, Begum D, et al. Ferulic acid-g-tamarind gum/guar gum based *in situ* gel-forming powders as wound dressings. *Int J Biol Macromol* 2024; 277:134382. <https://doi.org/10.1016/j.ijbiomac.2024.134382>.
- [27] Sheshala R KYNJTRDK. *In Situ Gelling Ophthalmic Drug Delivery System: An Overview and Its Applications*. *Recent Patents on Drug Delivery & Formulation*. 2015 Jan 1;9(3):237-48. 2015; 9:237–48.
- [28] Shi Q, Anishiya Chella Daisy ER, GeqiangYang, Zhang J, Mickymaray S, Alfaiz F, et al. Multifunctional guar gum based drug delivery system for the delivery of ofloxacin drug to treat ophthalmic diseases. *Arabian Journal of Chemistry* 2021; 14:103118. <https://doi.org/10.1016/j.arabj.2021.103118>.
- [29] Morsi N, Ibrahim M, Refai H, El Sorogy H. Nanoemulsion-based electrolyte triggered *in situ* gel for ocular delivery of acetazolamide. *European Journal of Pharmaceutical Sciences* 2017; 104:302–14. <https://doi.org/10.1016/j.ejps.2017.04.013>.
- [30] Khan MS, Ravi PR, Mir SI, Rawat PS. Optimization and *in vivo* evaluation of triamcinolone acetonide loaded *in situ* gel prepared using reacted tamarind seed xyloglucan and kappa-carrageenan for ocular delivery. *Int J Biol Macromol* 2023; 233:123533. <https://doi.org/10.1016/j.ijbiomac.2023.123533>.
- [31] Battistini FD, Tártara LI, Boiero C, Guzmán ML, Luciani-Giacobbe LC, Palma SD, et al. The role of hyaluronan as a drug carrier enhances the bioavailability of extended-release ophthalmic formulations. Hyaluronan-timolol ionic complexes as a model case. *European Journal of Pharmaceutical Sciences* 2017; 105:188–94. <https://doi.org/10.1016/j.ejps.2017.05.020>.
- [32] Hynneklev L, Magno M, Vernhardsdottir RR, Moschowits E, Tønseth KA, Dartt DA, et al. Hyaluronic acid in the treatment of dry eye disease. *Acta Ophthalmol* 2022; 100:844–60. <https://doi.org/10.1111/aos.15159>.
- [33] Posarelli C, Passani A, Del Re M, Fogli S, Toro MD, Ferreras A, et al. Cross-Linked Hyaluronic Acid as Tear Film Substitute. *Journal of Ocular Pharmacology and Therapeutics* 2019; 35:381–7. <https://doi.org/10.1089/jop.2018.0151>.
- [34] Kim J, Mondal H, Jin R, Yoon HJ, Kim H-J, Jee J-P, et al. Cellulose Acetate Phthalate-Based pH-Responsive Cyclosporine A-Loaded Contact Lens for the Treatment of Dry Eye. *Int J Mol Sci* 2023; 24:2361. <https://doi.org/10.3390/ijms24032361>.
- [35] Liu D, Wu Q, Chen W, Lin H, Zhu Y, Liu Y, et al. A novel FK506 loaded nanomicelles consisting of amino-terminated poly (ethylene glycol)-block-poly(D,L)-lactic acid and hydroxypropyl methylcellulose for ocular drug delivery. *Int J Pharm* 2019; 562:1–10. <https://doi.org/10.1016/j.ijpharm.2019.03.022>.
- [36] Yusufu M, Liu X, Zheng T, Fan F, Xu J, Luo Y. Hydroxypropyl methylcellulose 2% for dry eye prevention during phacoemulsification in senile and diabetic patients. *Int Ophthalmol* 2018; 38:1261–73. <https://doi.org/10.1007/s10792-017-0590-7>.
- [37] Dubashynskaya N, Poshina D, Raik S, Urtti A, Skorik YA. Polysaccharides in Ocular Drug Delivery. *Pharmaceutics* 2019; 12:22. <https://doi.org/10.3390/pharmaceutics12010022>.
- [38] He Y, Li J, Zhu J, Jie Y, Wang N, Wang J. The improvement of dry eye after cataract surgery by intraoperative using ophthalmic viscosurgical devices on the surface of cornea. *Medicine* 2017;96: e8940. <https://doi.org/10.1097/MD.0000000000008940>.
- [39] Tundisi LL, Mostaçõ GB, Carricondo PC, Petri DFS. Hydroxypropyl methylcellulose: Physicochemical properties and ocular drug delivery formulations. *European Journal of Pharmaceutical Sciences* 2021; 159:105736. <https://doi.org/10.1016/j.ejps.2021.105736>.
- [40] Dasankoppa F, Solankiy P, Sholapur H, Jamakandi V, Sajjanar V, Walveka P. Design, formulation, and evaluation of *in situ* gelling ophthalmic drug delivery system comprising anionic and nonionic polymers. *Indian Journal of Health Sciences and Biomedical Research (KLEU)* 2017; 10:323. [https://doi.org/10.4103/kleuhsj.kleuhsj\\_131\\_17](https://doi.org/10.4103/kleuhsj.kleuhsj_131_17).
- [41] Eslami H, Ansari M, Darvishi A, Pisheh HR, Shami M, Kazemi F. Polyacrylic Acid: A Biocompatible and Biodegradable Polymer for Controlled Drug Delivery. *Polymer Science, Series A* 2023;65:702–13. <https://doi.org/10.1134/S0965545X2460011X>.
- [42] Dipiksha Sawant PMDAPG. Formulation and evaluation of sparfloxacin emulsomes-loaded thermosensitive *in situ* gel for ophthalmic delivery. *J Solgel Sci Technol* 2016; 77:654–65.
- [43] Gu D, O'Connor AJ, G.H. Qiao G, Ladewig K. Hydrogels with smart systems for delivery of hydrophobic drugs. *Expert Opin Drug Deliv* 2017; 14:879–95. <https://doi.org/10.1080/17425247.2017.1245290>.
- [44] B. Samal H, Boyeena L, Ch. Patra N, Sriram S, J. Das I. Curcumin *In Situ* Gel for Local Treatment Of Periodontitis: Preparation, *In Vitro* Evaluation And Clinical Assessment. *Indian Drugs* 2022; 59:21–36. <https://doi.org/10.53879/id.59.11.13253>.
- [45] Li J, Liu H, Liu L, Cai C, Xin H, Liu W. Design and Evaluation of a Brinzolamide Drug-Resin;

- Thermosensitive Gelling System for Sustained Ophthalmic Drug Delivery. *Chem Pharm Bull (Tokyo)* 2014; 62:1000–8.  
<https://doi.org/10.1248/cpb.c14-00451>.
- [46] Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, et al. Research progress of in-situ gelling ophthalmic drug delivery system. *Asian J Pharm Sci* 2019; 14:1–15. <https://doi.org/10.1016/j.ajps.2018.04.008>.
- [47] Almeida H, Amaral MH, Lobão P, Lobo JMS. In situ gelling systems: a strategy to improve the bioavailability of ophthalmic pharmaceutical formulations. *Drug Discov Today* 2014; 19:400–12. <https://doi.org/10.1016/j.drudis.2013.10.001>.
- [48] Rupenthal ID, Green CR, Alany RG. Comparison of ion-activated in situ gelling systems for ocular drug delivery. Part 2: Precorneal retention and in vivo pharmacodynamic study. *Int J Pharm* 2011; 411:78–85. <https://doi.org/10.1016/j.ijpharm.2011.03.043>.
- [49] Majeed A, Khan NA. Ocular in situ gel: An overview. *Journal of Drug Delivery and Therapeutics* 2019; 9:337–47. <https://doi.org/10.22270/jddt.v9i1.2231>.