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Review Article

A Recent Overview: In Situ Gel Smart Carriers for Ocular Drug Delivery

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Abstract

Delivery of the drug to the ocular area is blocked by the protective layers covering the eyes; it has always been a major problem to find effective bioavailability of the active drug in the ocular area due to the short duration of precorneal majority ocular stay. Direct delivery systems combine as well as oil, solution, and suspension, as a result, many delivery systems are not able to effectively treat eye diseases. Many works have been done and are being done to overcome this problem one of which is to use in-situ to build polymeric systems. Ocular In-situ gelling systems are a new class of eye drug delivery systems that are initially in solution but are quickly transformed into a viscous gel when introduced or inserted into an ocular cavity where active drugs are released continuously. This sol-to-gel phase conversion depends on a variety of factors such as changes in pH, ion presence, and temperature changes. Post-transplanting gel selects viscosity and bio-adhesive properties, which prolongs the gel's stay in the ocular area and also releases the drug in a long and continuous way unlike conventional eye drops and ointments. This review is a brief overview of situ gels, the various methods of in situ gelling systems, the different types of polymers used in situ gels, their gel-based methods, and the polymeric testing of situ gels.

Keywords: *In-situ* gel, Polymers, and ion triggered in-situ gel, Mechanism, Evaluation parameters

INTRODUCTION

The eye is a unique and vital organ. Many eyes diseases can affect the body and loss of vision. Therefore, more eyes on drug delivery systems are available. They are classified as traditional drug and (newer) development programs. Eye drug use is the most common a well-known and wellreceived management system for the treatment of various eye diseases. The bioavailability of ophthalmic drugs, however, is very poor due to effective preventive measures for an eye. Blinking, foundation and reflex lachrymation, and drainage remove foreign objects quickly, including drugs, on the surface. Many eye diseases affect the eyes, and one can lose sight again. So many ophthalmic drug delivery systems are available. These are classified as normal and uncommon new drug delivery systems1. Typical dosage forms such as eye drops make up 90% of the commercially available ophthalmic formulations. The reason may be due to the ease of management and patient compliance. However, ocular bioavailability is very low with topical descent treatment². The composition of conventional medicines, such as solutions, suspensions, and lubricants has many problems³.

- a. Immediate termination of precorneal due to trauma benefit
- b. Regular installation

- c. Enzymatic metabolism
- d. Nasolacrimal drainage
- e. Conjunctival absorption
- f. Blurred vision
- g. Lack of controlled release

Over the decades, various delivery systems such as the use of chemical injectors, gel prodrugs stimuli responsive in-situ, and drug delivery carriers such as liposomes and nano- or microparticles, noisome, dendrimers, and microneedles have been developed, to increase the eye area Time, drug penetration into all ocular barriers, and ophthalmic bioavailability. The in-situ gelling system is one of the most promising ways to improve the duration of drug retention in the eye area. After the application of an aqueous solution, consisting of reacting polymers such as pH-sensitive polymers, thermosensitive polymers, and ion-sensitive polymers, viscous and mucoadhesive gels formed on the surface, later, the ocular retention time and the ocular bioavailability of ophthalmic drugs is improved. Therefore, in this review, we summarize and discuss the latest research findings.4,5

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ANATOMY OF HUMAN EYE

The human eye is divided into two main parts namely the anterior segment which includes the cornea, conjunctiva, iris,

pupil, ciliary body, chamber anterior, aqueous humor, lens, and trabecular meshwork and the posterior segment includes vitreous humor, sclera, retina, choroid, macula, and optic nerve.

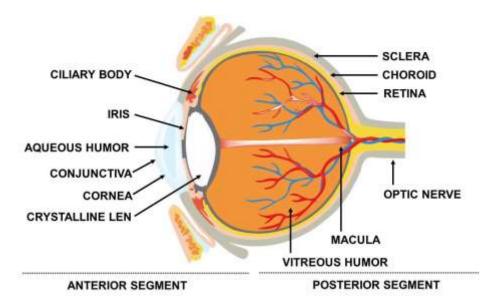


Figure 1: Structure of the human eye6.

The outer membrane of the eye cornea is a clear, transparent, small vascular tissue composed of five layers: epithelium, bowman's layer, stroma, Descemet's membrane, and endothelium. Aqueous jokes contain clear liquids that fill the back and front of the eye chambers. It is a great source of nutrients for the cornea. The iris is a small circular curtain located in front of the lens but behind the cornea, it is a diaphragm of variable size whose function is to adjust the size of the pupil to control the amount of light entering the eye and adjust it with assistance. Iris sphincter and dilator muscle. The ciliary muscle is a smooth muscle ring in the middle part that controls the visual space. The lens is a transparent bi-convex structure covered with a small transparent lens cover. It is a flexible unit consisting of layers of tissue embedded in a capsule. It is secreted into the ciliary muscles by very small fibers called zonules. The conjunctiva is a mucous membrane that begins at the edge of the corner and extends to the inside of the eyelid and the sclera up to the limbus. It protects the eyes by removing mucous membranes and rubbing the eyes. The sclera is the outer

layer of the eye called the "white of the eye" and retains the shape of the eye. It acts as primary protection against internal organs. The sclera is composed of multicellular tissue known as choroid between the retina as well sclera. The choroid is a thin layer of veins with dark brown veins and contains a pigment that absorbs excess light and thus prevents blurred vision is the second layer of the eye and is located between the sclera and retina. It contains blood vessels that supply nutrients to the outer parts of the retina. The retina is a multi-layered and complex structure consisting of vascular glial and neural cells and nerve fibers. It is located behind the human eye. A light-sensitive structure consists of photosensitive cells that capture light rays and convert them into electrical impulses. These senses travel with the visual cortex to the brain, where they are converted into images. The vitreous humor is a small front that contains a fluid-like transparent thin-jelly-like substance that spreads between the retina and the lens^{6, 8}. Structure of human eye is shown in figure 1.

Table 1: Routes of absorption of drug in eye

Target Site	Salient Features
Cornea	Bowman's capsule is lipophilic, allows diffusion of small lipophilic molecules. Stroma is hydrophilic, allows diffusion of hydrophilic and larger molecules.
Conjunctiva	Main barrier for drug absorption, allows absorption of hydrophilic and large molecules. Absorption of peptides is less due to enzymatic degradation.
Sclera	Some drugs (β-blockers) diffuse readily. Tran's sclera Iontophoresis is used for intravitreal administration.
Aqueous Humor	Drugs absorbed through cornea discharge through aqueous humor into systemic routes.
Vitreous Humor	Drugs absorbed through sclera and conjunctiva discharge through vitreous humor into systemic routes.

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CLASSIFICATION OF OCULAR DRUG DELIVERY SYSTEM 7

- Conventional Drug Delivery System
- Gel
- Ointment
- ocuserts
- Drug Delivery To Posterior Segments
- Intravitreal implant
- Inject able particulate system
- Drug Delivery To Anterior Segment
- · cal du sac inserts
- Subconjectival
- · Episcleral implants
- ❖ Vesicular Devices
- Liposome
- Noisome
- Discomes
- Lacrisert
- Particulates

- Nanoparticles
- · Micro particles
- Physical Devices
- Iontophoresis
- Controlled Delivery
- In situ gel systems
- Micro emulsion
- Contact lens
- Collagen shield
- Nano suspensions
- · Micro needle
- * Advanced Delivery System
- Gene therapy
- · Stem cell therapy
- Aptamer
- Therapy siRNaA
- Protein and peptide therapy
- Stem cell therapy

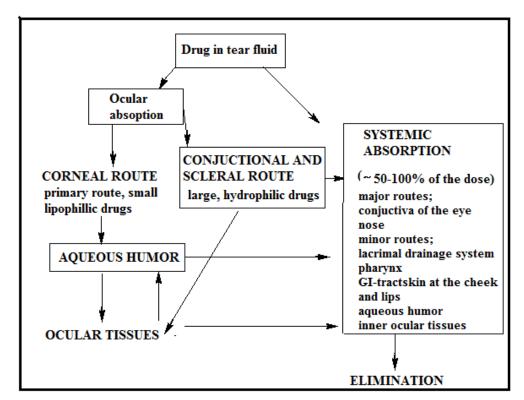


Figure 2: Diagram of ophthalmic drug delivery systems²⁵

ROUTES OF ADMINSTRATION OF DRUG INTO EYE

1. Topical Administration-

The topical line is the most common way to give eye medicine, but such drops come out quickly due to the blink of an eye, and the precorneal area returns to maintain a

sitting capacity of about 7μ l. The presence of drug overload in precorneal fluid enables the drug to be transported throughout the cornea⁹. The Topical medication used for high patient compliance, and self-regulation increased tears. It is used to diagnose a disease such as uveitis, keratitis Conjunctivitis¹⁰. Model depicting precorneal and ophthalmic drug movement from topical instilled dose is shown in figure 3.

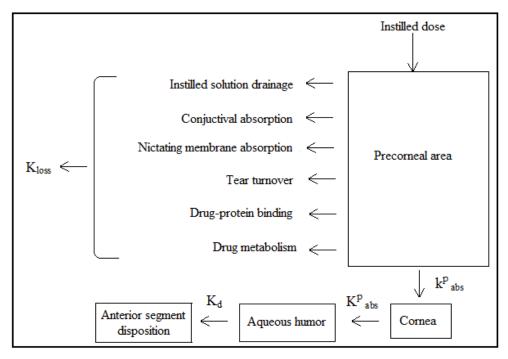


Figure 3: Model depicting precorneal and ophthalmic drug movement from topical instilled dose²¹

2. Oral Administration-

Oral submissions alone or combined with the presentation of topics have been researched for a variety of reasons. Submission of articles failed to generate therapeutic focus in the posterior stage. Oral delivery was also studied as a patient's preferred treatment for chronic retinal infections compared with the parenteral route. However limited availability of targeted ocular tissue binds oral use that requires high dosage to achieve effective therapeutic efficacy. Such doses can lead to adverse system effects. Barriers such as safety and toxicity, therefore, need to be measured when trying to obtain an eye treatment response to oral administration ⁸.

3. Systemic Administration-

Managing the system is also up to him failing to deliver the drug to the previously targeted ocular tissue and the back parts of the eye due to its presence of eye barriers. These barriers are known to contain water barrier and bloodretinal barrier, respectively. The water is bloody Inhibition is caused by the iris / ciliary endothelium blood vessels and

ciliary epithelium colour less, while the blood-retinal barrier is formed by the retinal capillary endothelial cells and retinal pigment epithelium cell (RPE). Because of the obstacles mentioned above; medical focus. The drug is not found in the required ocular muscles and beyond high volume management. Therefore, this route also did not gain momentum in the treatment of eye diseases. After orally, the drug must go through the initial metabolism before system exposure. Therefore, this route did not it is considered a potential alternative to various therapies, and posterior stage diseases ¹¹.

4. Intravitreal Administration-

Intravitreal and periocular routes of administration have gained momentum in the last decade to deliver drugs to the targeted ocular tissues especially to the retina. Intravitreal administration of drug leads to rapid achievement of higher concentration in retinal tissue to treat posterior segment diseases. However, the administration the process is very painful and hence this route suffers from poor patience compliance¹¹.

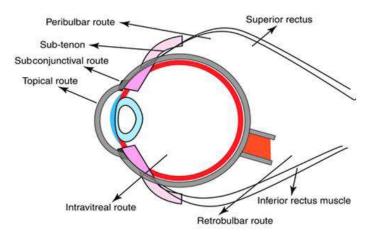


Figure 4: Various routes of administered for Ophthalamic drug delivery⁵¹

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IN SITU GELLING SYSTEM

In-gel gel formulation systems are drug delivery systems that are in solution before being administered to the body but once processed, they are injected with gelation in situ, forming a gel that is activated by an external storm such as temperature, pH, etc. and release the drug continuously or controlled. way. This novel concept of situ gel production was first introduced in the early 1980s. Gelation occurs by bonding polymer chains that can be achieved by bonding (chemical bonding) or bonding bond formation (physical bonding). In situ gel-forming systems can be described as low viscosity solutions that transcend phase transformation into a conjunctival cul-de-sac to form visco-elastic gels due to the alignment of the polymers in response to the living environment. The level of in situ gel formation is important because, between the eye and before the solid gel is formed; a solution or a weak gel is produced with an eye fluid. Both natural and synthetic polymers can be used to form situ gel⁷,

IMPORTANCE OF IN-SITU GELLING SYSTEM⁴⁰

- Assists in controlled and continuous release of medicine with its special 'Sol-Gel transition'
- It helps to reduce the frequency of medication drug administration in the body. A low dose of the drug is required and will be available with no drug overdose and no side effects.
- ➤ The bioavailability of the drug will be higher.
- Sitting time will be extended drug due to gel formation.
- > The in situ gel system reduces the loss of Drug
- A liquid dose form that can facilitate drug release & stay in touch with the cornea of the eye long term is appropriate.

ADVANTAGE OF IN SITU GEL 12, 13

- In situ gel improves bioavailability and prolongs the retention time
- > Immediate drug administration by reducing the frequency of medication.
- Provides ongoing control and delivery of drugs.
- In-situ gel is made of natural polymers and this polymer is biocompatible and biodegradable.
- Providing important in vivo function due to hydrophilicity increases the duration of the in-vivo release cycle.
- To avoid a protective barrier such as the absorption of a water connection
- Provide better patient interaction and enhance the therapeutic response of the drug.
- Provide only eye tissue to avoid loss of other ocular tissue.

DISADVANTAGE OF IN SITU GEL 14

- Only a small dose of the drug can be given and requires a high level of fluid.
- Problems with gel stability due to high chemical degradation and require high levels of fluid.
- Food and drink can be avoided a few hours after taking the medicine.

The sun's shape is severely deteriorating

MECHANISM OF IN SITU GEL

Physical Mechanism

- a) Diffusion- In the distribution process, the tree is released continuously at a controlled rate, the membrane enters the tearing fluid if the implant is made up of a solid, non-abrasive body with holes and dissolved wood. Drug disposal is possible by spreading through the pores. Controlled output can also be directed by the gradual dispersion of solid dispersed solids within this matrix due to the internal dispersion of aqueous solutions. In melting material, true dissolving occurs mainly by polymer swelling. In controlled inflammatory devices, the active agent is evenly dispersed in the glass polymer. Since glass polymers are not drug-resistant, no diffusion by dry matrix occurs. When the implant is inserted into the eye, water from the stagnant fluid begins to enter the matrix, then inflammation and as a result, loosening the polymer chain and drug distribution occurs. Completion of the matrix, which follows the inflammatory process, depending on the structure of the polymer; amorphous polymers dissolve much faster than glued polymers or part of a crystal. Removal from these devices usually follows the fiction 'square root of time' kinetics; in some cases, however, known as case II transport, zero-order kinetics has been considered16.
- b) **Swelling-** The in-situ formation also occurs when the equipment it absorbs water from nature to expand to make the place you want happen. One such substance is myverol 18-99 (glycerol mono-oleate), a polar lipid that dissolves in water to form lyotropic fluid. Crystalline phase frames. Contains certain Bioadhesive properties and can be reduced by invoice by enzymatic action¹⁷.

Chemical Mechanism

- 1. Enzymatic cross-linking- In-situ production Causes of natural enzymes have not occurred, and have been thoroughly investigated but appear to have benefits in addition to chemical and chemical methods. For example, the enzymatic process works well under physiologic conditions without the need for potentially harmful chemicals such as monomers and start-ups. Intelligent motives that respond to delivery systems using insulated hydrogels were investigated. Cationic pH-sensitive Polymers contain stable insulin and glucose oxidize, which can be caused by inflammation. Because of the high blood sugar levels, it releases insulin that binds to the heart. Adjusting the enzyme level also provides an easy way to control the formation of the gel level, which allows the compounds to be 'injected before the gel is formed18.
- 2. Ionic cross-linking In- ionic cross-linking the polymer bonding passes the phase transition to different ions due to the formation of gels. In certain polysaccharides from ion-sensitive ones, carrageen and form expandable gels especially in the presence of (Ca2 +) and K-carrageen forms cracked and solid gels in front of a small amount of (K +). The Glean gum was a polymer expressed in the name of Gel rite is a widely used anionic polysaccharide. Which passes in-situ gelling in the presence of monoand divalent cations, including (K +, Ca2 +, Na +, and Mg2 +), Gelation of the low-methoxy pectin can be caused by divalent cations, especially (Ca2 +). Similarly, alginic acid is digested in the presence of divalent/polyvalent cations in (+ -g). Ca2 + due to interaction with a glucuronic acid block in alginate chains 19,20.

DIFFERENT WAYS OF IN-SITU GELATION

Ideally, in situ, the gelling system should be low viscous, free-flowing fluid to allow for repeated administration of the eye as drops, and the gel forms the next phase of change should be strong enough to stand the shear strength in the cul-de-sac and show long periods sitting in the eyes. Increasing the effectiveness of the drug should be chosen in terms of dosage increases the contact time of the drug in the eye. This may be the lifespan of a locally made gel and its ability to continuously release the drug will help to improve its bioavailability reduce systemic absorption and reduce the need for routine management leading to improved patient compliance^{21,22}.

- 1. pH-Triggered System In situ gels can be formed due to changes in pH. At a rate of 4.4, they occur in the form of cohesive solutions when the pH rises. After contact with the weeping liquid, a viscous gel was formed. These polymers contain acidic or basic groups that receive or release proteins in response to changes in the natural pH, which then degrade, thereby releasing the drug. Hydrogel inflammation increases with age external pH in the case of groups with weak (anionic) acids. Many pHsensitive polymer polymers are based on carbopol, carbomer, or derivatives, but those based on polyacrylic acid (PAA) are also effective. PAA solution gel at pH 7.4 with high concentration and this, given the low pH of the PAA solution, may cause damage to the ocular area before reducing the irritating fluid. This limit was handled by consolidating the PAA by HPMC, a viscosity polymer, which leads to the formation of pH-sensitive polymer mixtures at pH 4 and a gel at pH 7.4. Blends of poly-methacrylic acid (PMA) and polyethylene glycol (PEG) have also been used as pH-sensitive systems. To achieve gelation in this regard, Dawood and Kassab have developed, and tested the behavior of sensitive 'ocular naproxen gel, in situ to increase eye duration. These The structure was adjusted using different carbomer concentrations (0.5%, 0.6%, 0.7%) combined with(HPMC K40) (0.75%, 1%, 1.5%) or HPMC K100 (0.75%, 1%, 1.5%), 5%). The gels found tested for appearance, pH, gelling volume, tonicity, viscosity, in vitro release, and drug content, and subject to the release of kinetic analysis, FTIR studies, ocular studies, and irritation tests. showed an increase results Carbomer concentrations have improved both gelling volume and digestion time. In addition, the higher the hydro-philic HPMC polymer, the higher viscosity of formation, there by affecting release, gelling ability, and time. Therefore, make-up F10, made of CB 0.7% and HPMC K100 0.75%, showed the excellent duration of in situ gel activated by pH, as well as the continuous release of naproxen for 3 hours with a release rate of more than 90% 23,24,
- 2. Temperature Dependent System -In thermo systems, the flow of solution is due to temperature changes. Continuous drug delivery may be provided by the use of heat-sensitive polymers that change from solvent to gel at eye temperature (37°C). These preparations are not liquid at room temperature (20°C-25°C) and can be a gel at body temperature (35°C-37°C) due to temperature changes. These temperature sensors are divided into three types namely, sensitive temperature, positively thermosensitive, and thermal reversible. Hydrogels that are resistant to extreme temperatures with lowtemperature sensitivity (LCST) and lower temperature than LCST i.e. Copolymers of (N-isopropyl acrylamide) (NIAam) show the release of closed drugs at low temperatures and extinguish at high temperatures. . To allow pulsatile drug release. LCST systems are essential

- for the controlled release of drugs, as well as proteins in particular. Hot polymers may be deposited in the liposome membrane; in that case, liposomes show control of their content release. Heat-resistant hydrogel has a high-temperature sensitivity solution (UCST), such a hydrogel holds the contract when cooling below (UCST). Poly (acrylic acid) (PAA) and polyacrylamide (PAAm) or multiple networks (acryl amide-co-butyl methacrylate) has a positive effect on the optimal temperature of inflammation^{26,27}.
- 3. Ion Activated System The pH-initiated systems can be described as those systems of oculars in situ gel-forming systems which when applied normally as a decrease in the short term are converted to a gel due to exposure to a different pH level (here pH of the anterior corneal area). Occurs due to the presence of pH-sensitive substances or polymers in the structure. At low pH (pH 4- 4.4) the corrected composition remains a free-flowing solution but when applied, it is converted to a viscous gel due to the high pH of the lachrymal fluid pH 7.4²⁸.

POLYMERS USED IN THE INSTRUCTION OF INSITU GEL

- 1. Poloxamer
- 2. Chitosan
- 3. Gellan Gum
- 4. Xanthan Gum
- 5. Carbopol
- 6. Alginate
- 7. Hydroxypropyle Methyl Cellulose
- 1. Poloxamer Poloxamer is a water-soluble tri-block copolymer that combines dual polyethylene oxide and polypropylene oxide core in ABA activation. Poloxamer commercially also known as pluronic and has a good place to keep the temperature and duration of the drug growing. It is 'used as a gelling agent and solubilising agent. Poloxamer offers a clear, transparent gel. The poloxamer method is as follows: At room temperature (25 ° C), it acts as a transparent liquid and is 'converted into a transparent gel as the temperature rises (37 ° C). At low temperatures, it forms a small micellar subunit in solution and 'increases the effects of rising temperatures in viscosity, leading to inflammation to form a large micellar cross-linked network.29, 30. Pluronic (F-127) is an 'important polymer used to produce an In-Situ gelling system and demonstrates its action by changing temperature. Pro Latin, a polymer protein after 'investigation and research, has been found to undergo a stable sol in the transformation of the gel when injected as a solution in the body, and the substances form a powerful solid gel within minutes. It stays in place for an extended period to help the drug hold up longer from weeks to $months^{31}$. Pluronic (F-127) used as an in situ gel forms a polymer as well mucoadhesive polymers Carbopol 934 and hydroxypropylas methylcellulose (HPMC) to ensure longevity time in the application area. Poloxamer 407, and(poloxamer 188) are among the most widely used 'ocular poloxamers, delivery of drugs due to their good solubility in water, clarity of their aqueous solutions, concentrated viscosity, the shear-thinning behavior of their solutions, and their Ocular tissue safety . The poloxamer 407 was used for its excellent solvent, low toxicity, Good properties for drug release, and its compatibility with many

biomolecules and chemical assistants^{32, 33, 34}. Structure of poloxamers 'shown in figure no 5.

Table 2: Different grades of poloxamers 35

Poloxamer	Pluronic	Molecular weight
124	L44NF	2200
188	F68NF	8400
237	F87NF	7959
338	F108NF	14600
407	F127NF	12600

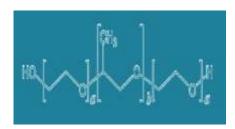


Figure 5: Structure of poloxamer 14

2. Chitosan- Chitosan-based systems have a continuous release of the active ingredient, although to a lesser extent than tamarind gum. Due to the amino and hydroxyl groups, chitosan combined with mucin containing negative mucin, which enhances the functional ocular bioavailability thing. Chitosan may form hybrid hydrogels by linking them to biocompatible performance polymers. Xu et al. try to combine an injectable gel based on glycol chitosan once oxidized alginate to synthesize Avastin for ocular delivery. The hydrogel structure was the effect of interaction between the amino group chitosan and the alginate aldehyde group by building the foundation of Schiff. Chitosan glycol instead of chitosan was used because of its better solubility. By adjusting the concentration of glycol

chitosan and oxidized alginate, the flow rate of the system varies between 10 seconds and 5 minutes. The accumulation of oxidized alginate has contributed to the rate of Avastin release. According to research, the injectable gel is a flexible system for Avastin delivery. Chitosan use in excipient in oral preparation and other pharmaceutical formulate Use in non-toxic and non-irritant material^{36, 37}. Structure of chitosan in figure 6.

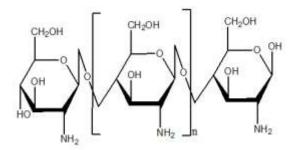


Figure 6: structure of chitosan 27

3. Gellan gum- GelriteR is a low-density acetyl gellan, which forms a clear gel in the presence of mono- or divalent cations. Liquid electrolytes and especially Na +, Ca2 +, and Mg2 + cations are particularly suitable for initiating polymer flow when applied as a liquid solution in the cul-de-sac. Once the gel has been applied, the mold resists the natural drainage process in the preprecorneal area. The concentration of the drug is increased and, later, the bioavailability of the drug increases. Compared to xanthan gum, gellan gum is a suitable vehicle due to its gelation properties. However, in a recent publication, Schenker et al. compare commercial product Timoptic XE 0.5% R with timolol maleate forming gel using xanthan gum as a gelling polymer (Timolol GFSR 0.5% Alcon Research). The preparation of xanthan gum is designed to be taken once a day³⁸. Structure of gellan gum in figure 7.

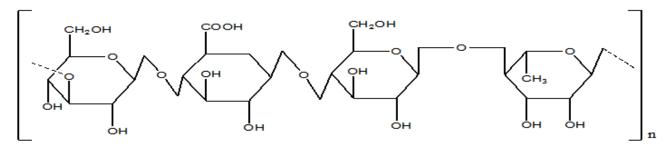


Figure 7: Structure of Gellan gum 39

4. Carbopol - Carbopol is a polyacrylic acid (PAA) polymer that is turned into a gel as the pH rises from (4.0 to 7.4). Carbopol remains in a state of solution at acidic pH however converts into low viscosity gel to alkaline pH. HPMC is used in combination with carbopol which enhances the viscosity of the carbopol solution while reducing the acidity of the solution. Comparing different types of poly (acrylic acid) (Carbopol 940-934-941 and 910) 47 concluded that Carbopol 940 showed a higher and clearer appearance⁴⁰. Structure of carbopol 'shown in figure no 8.

Table 3: Different grade of carbopol 7

Grade	Cross linking density
Carbopol-934	Lowest
Carbopol-940	highest
Carbopol-981	intermediate

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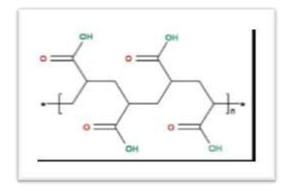


Figure 8: Structure of carbopol 14

5. Xanthan gum- Xanthan gum is a high molecular weight polysaccharide produced Gram-negative by fermentation. Xanthomonas-bacterium The main structure of these natural cellulose extracts contains the cellulosic core β -D-glucose residues and the adverse effects of trisaccharide B-D-mannose-β-D-glucuronic acid-α-D-mannose linked to others main glucose traces like tango. The anionic character of this polymer is due to the presence of both groups of glucuronic acid pyruvic acid in a different series 17 . Structure of xanthan gum in figure 9.

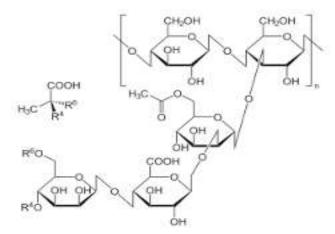


Figure 9: Structure of xanthan gum 41

6. Alginate - Alginate is a water-soluble polysaccharide extracted from the brown sea. It is composed of 1-4 glued -L-glucuronic and -D - mannuronic acid residues. Alginate mesalazine tablets are used in the intestinal drug delivery system. Alginate also acts as a composite for the delivery of controlled drugs to mucosal tissues. It is also used to repair adhesive drug delivery systems⁴². Structure of alginate in figure 10.

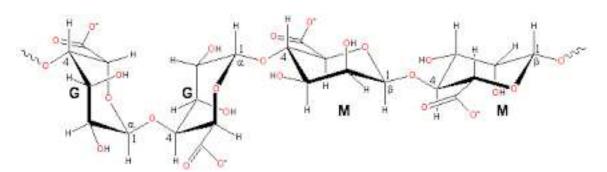


Figure 10: Structure of Alginate 36

7. Hydroxy propyl methyl cellulose (HPMC) - HPMC is derived from a non-ionic component of cellulose ether, stable over a pH range of 3.0-11. Hydroxy propyl methyl cellulose [HPMC] is a semi-synthetic polymer. It is used

as a first choice in the construction of hydrophilic matrix systems as it provides a robust control of the drug release and the choice of viscosity ranges.

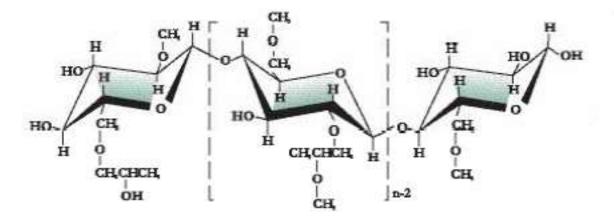


Figure 11: structure of HPMC

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Its non-ionic nature reduces coagulation problems when used in acidic, basic, or electrolytic systems and provides productive release profiles. It's expensive too. Metrics containing [HPMC] do not affect the pH of the liquid. It found that the best marks could be used for the formation of continuous release by K4M and K100M due to their gravitational strength. When water is immersed in water the polymer chains reverse in the matrix. HPMC matrix systems are classified as systems controlled by inflammation and controlled by the level of media infiltration and matrix

erosion. In hydrophilic polymers, the degree of inflammation determines the presence of different components within the matrix, and where the movement of these precursors aligns then the rate of drug release remains constant (Colombo 1993). HPMC is a compound of alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. The hydration level of HPMC depends on the substitute's environment which forms the polymer e.g. cellular structure, transformation rate (Alderman 1984) 43,44,45.

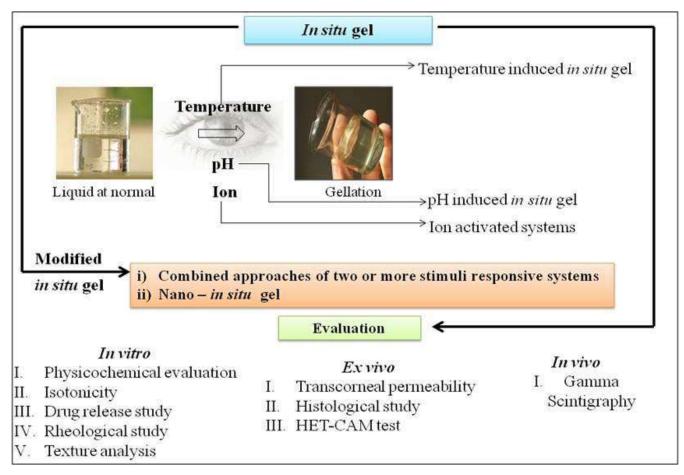


Figure 12:- Overview on in-situ gel 46

EVALUATION OF OCULAR IN SITU GEL^{46, 47, 48,}

- > Drug polymer interaction study and thermal analysis
- > PH of gel
- General appearance and clarity
- Sol to gel transition temperature and gelling-time
- ➤ Gel-strength
- > PH of gel
- > Isotonicity evaluation
- ➤ Draize irritancy test- Designed for the ocular irritation power of the eye product before marketing. According to the Draize test, the value is The object used for the eyes is usually (25µl)placed in the lower de-sac position by observation of the various designs made in the design the required time interval is [1 hour, 24 hours, 45 hours,

72 hours, and 1 week after administration]. Three rabbits male weighing [1.5 to 2 kg] are used lesson. Sterile construction is installed twice a day for [7 days], and crossover Research is done (washing time 3 days with saline is made before crossing reading). Rabbits are looked after from time to time redness, swelling, eye irritation 50,51 .

Table 4: Some examples of Marketed Products of ocular in- situ gels⁵²

Product Name	Drug used	Mfg. Company
Timoptic-XE	Timolol maleate	Merck and Co.Inc
Cytorym	Interleukin-2(IL-2)	Macromed
Azasite	Azithromycin	Insite vision
Aktentm	Lidocaine Hydrochloride	Akten

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Virgan	Ganciclovir	Spectrum thea Pharmaceuticals
pilocarpine	Pilocarpine Hydrochloride	Alcon laboratories Inc

CONCLUSION

In-situ gel used as a solution reduces the problem of blurred vision, precision volume, and repetitive volume and due to the phase change system, increased premature ejaculation, and decreased nasolacrimal fluid flow of the drug. Therefore improve bioavailability and reducing dose frequency and improving patient compliance is key requirement for a successful delivery system. The use of natural, biodegradable, and water-soluble polymers in their formulation makes them more acceptable and the excellent drug delivery systems have better stability and biological compatibility. Profit from an industrial point of view is easy to produce and thus a very small process and reduces the production costs and the commercial construction available.

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