

# Ocular In Situ Gel

Shinde Vishal Sanjay

## Abstract –

The eye is the body's most delicate organ. Because of the complicated anatomical structure of the eye, designing an ocular drug delivery system is the most difficult task for pharmaceutical scientists. Less than 5% of administered drugs enter the eye. poor corneal transparency, a tiny absorptive surface, and corneal lipophilicity drug's bonding with the epithelium, pre-corneal loss (due to nasolacrimal drainage), and proteins in tear fluid, blinking, and a small conjunctival sac, which limit the drug's molecule entering the place of action, which ultimately results in poor ocular health therapy. Numerous studies in this field support the idea that in situ gelling systems are advantageous for delivering drugs to the eyes. In situ gel forming systems are drug delivery systems that are in solution form before administration in the body but once administered, undergo in situ gelation, to a gel triggered by external stimulus such as temperature, pH etc. 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. In contrast to typical eye drops, post-transplanting gel chooses viscosity and bio-adhesive qualities that lengthen the gel's stay in the ocular area and also release the medicine in a long, continuous manner and lotions. In these articles, ophthalmic medication delivery systems are classified. Review of situ gel system, gel system mechanism, polymers employed, and evaluations.

**Keywords:** - Ocular, Gel, Anatomy , Barrier, Drug delivery.

## Introduction –

The eye has been referred to as the window to the human soul since it is a complex and distinctive component of the human body. The human eye can be roughly divided into the anterior and posterior portions<sup>[4]</sup>. The precise conditions that cause eye disease are corresponding to each of these main parts. For instance, glaucoma, conjunctivitis. Ones that affect the anterior portion of the eye include blepharitis and cataract. age-related macular degeneration and diabetic retinopathy are recognised to impact the back portion. The peculiar anatomy of the eye inhibits the drug molecules into the targeted region, the medicine's ophthalmic delivery has been one of a pharmaceutical scientist's difficult tasks<sup>[3]</sup>. Eye drops comprise more than 90% of ophthalmic preparations on the markets. The composition of conventional medicines, such as solutions, suspensions, and lubricants has many problems.

- Immediate termination of precorneal due to trauma benefit
- Regular installation
- Enzymatic metabolism
- Nasolacrimal drainage
- Conjunctival absorption
- Blurred vision
- Lack of controlled release<sup>[8]</sup>

Various drug delivery methods, including the use of chemical injectors, gel prodrugs, stimuli responsive in-situ, liposomes, nano- or microparticles, noisome, dendrimers, and microneedles, have been developed over the years. The size of the eye area all ocular barriers, passing time, drug penetration, and ophthalmic bioavailability<sup>[8]</sup>. One of the most promising methods is the in-situ gelling system. extend the time that drugs are retained in the ocular area. Gels at certain locations. Employ carbohydrates and alternative, extra acidic polymers if they are susceptible to a higher pH, and the low pH of these substances will irritate the attention's surface. The best ophthalmic drug delivery should be able to keep the medicine released and stay near the eyes for an extended period of time<sup>[9]</sup>. There will be completion-to-viewing gel activity because:

- Physical stimuli: they include variations in light, electrical fields, and temperature.
- Chemical stimulation: permits pH and created by biological fluids' activated ions.
- Organic chemistry stimuli, including variations in quantities of atomic number 20<sup>[5]</sup>.

The in-situ gel system is made as a liquid preparation for instillation into the eyes that, when exposed to the physiologic environment, transforms into gel, prolonging the precorneal residence time of the delivery system and boosting the drug's ocular absorption. Bioavailability 2. Factors like a shift in the temperature can have an impact on how gels are produced an element of physio-chemistry (such as pH, temperature, or ion sensitivity) that medication must be administered in a steady, controlled manner.

The following novel dosage forms are among them: in situ gel, nanosuspension, nanoparticulate system, liposomes, dendrimers, ocular iontophoresis, collagen shield, minidisc, ocular film, implants, and others 3. Due to the ocular route's drawbacks, such as non-productive absorption, medication discharge, induced lachrymation, tear turnover, and corneal impermeability Creating devices for ocular medication administration has never been simple. various kinds of polymers (including poloxamer, poly-N-isopropylacrylamide-hyaluronic acid copolymers, gellan gum, hydroxyethylcellulose, and polyacrylic acid) Several in situ gelling systems comprising (acid) have been developed. medicines that are not put into micelles, nanoparticles, or microemulsions on D-tocopheryl polyethylene glycol succinate, a non-ionic surfactant. Additionally, methoxy polyethylene glycol was combined with thermosensitive di-block polymers like PLGA or PCL, which were able to go through a sol-to-gel transition and create micelles for the transport of CyA to the eye<sup>[4]</sup>.

## Anatomy of Eye :-

- Iris -

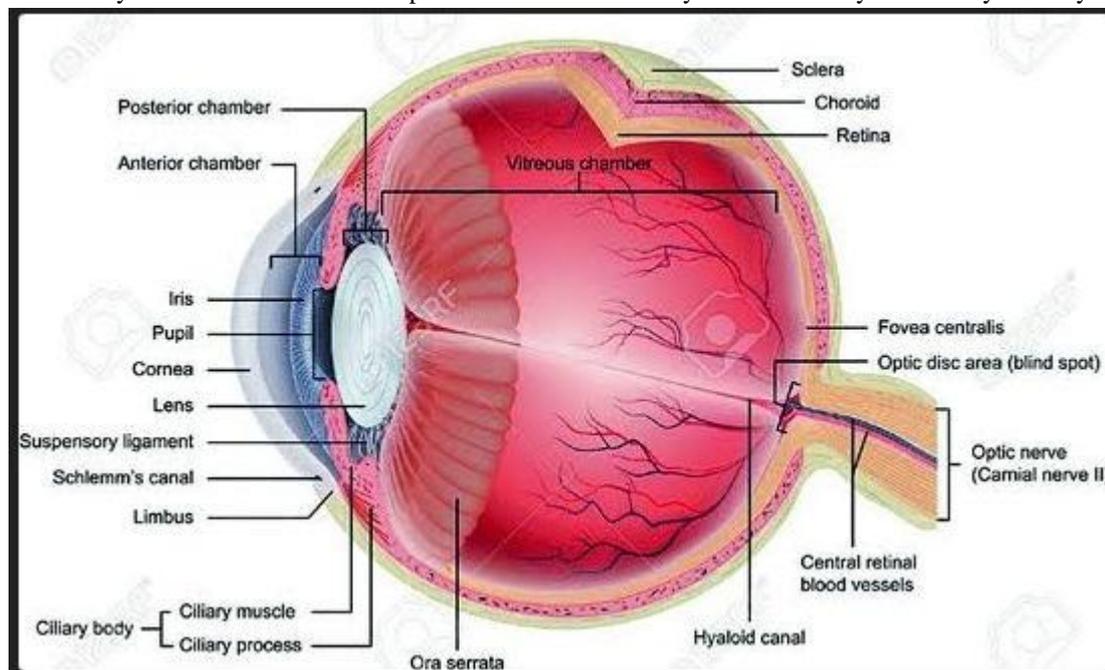
Iris However, below the cornea is a diaphragm of changeable size whose function is to control the amount of light let into the eye by regulating the size of the pupil with the help of the iris, a thin circular contractile curtain of the dilator muscle and iris sphincter<sup>[4]</sup>.

• **Ciliary muscle :-**

The ciliary muscle is a ring of smooth muscles in the central layer of the eye that regulates space for objects at different distances<sup>[6]</sup>.

• **Lens:-**

A thin transparent coating surrounds a transparent biconvex structure that forms the lens. It is a malleable structure composed of tissue layers that is enclosed in a capsule. It is redirected away from the ciliary muscles by the very thin fibres called zonules<sup>[3]</sup>.



**Fig [1]: – Anatomy Of Eye**

• **Conjunctiva :-** The interior of the eyelids and sclera are lined by the conjunctiva, a mucous membrane that extends from the corneal edge to the limbus. It guards the eyes by secreting mucus that lubricates them and prevents pathogens from getting inside<sup>[8]</sup>.

• **Sclera:** - The outermost, protective coating of the eye, also referred to as the "white the eye," thus maintaining the shape of the eye. As the initial line of defence, it protects the bodily organs. Between the retina and the choroid, a highly vascularized tissue and the sclera, which is situated between the retina and sclera<sup>[5]</sup>.

• **Choroid :-** The choroid is a small, densely vascular membrane with a dark brown colour. It contains a pigment that absorbs extra light to prevent blurry vision. Between the sclera and the retina, it is the second layer of the eye. It contains the arteries that supply blood to the retina's outer layers<sup>[10]</sup>.

• **Retina:-** The retina is a complex and intricate structure made up of nerve fibres, vascular, glial, and neuronal cells. It is located in the back chamber of the human eye. A photosensitive structure, it takes in light rays and changes them into energy electrical impulses to them. These impulses are interpreted as they travel down the visual nerve in the brain into images<sup>[7]</sup>.

• **Vitreous Chamber:-** A little space in front of the eye is called the vitreous chamber. consisting of a watery, thin jelly-like fluid distributed between the retina and the lens<sup>[5]</sup>.

**Table (1): –Routes of Absorption of drug in eye<sup>[2]</sup>**

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 ( $\beta$ -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.

**CLASSIFICATION OF OCULAR DRUG DELIVERY SYSTEM**

**• Conventional Drug Delivery System**

- Gel,
- ointment
- moisterizers

**• Administering Drugs to Lateral Segments**

- Implant Intravitreal
- Particulate injector system

**• Delivery Of Drugs To The Anterior Segments**

- Cal-D-Sack inserts
- Subjunctive
- Episcleral implants <sup>[1]</sup>

**• Vesicular Devices.**

- Liposome
- Noisome
- Discome
- Lacrisert

**• Particulate**

- Nanoparticles
- Micro particles

**• Physical Devices**

- Iontophoresis <sup>[4]</sup>

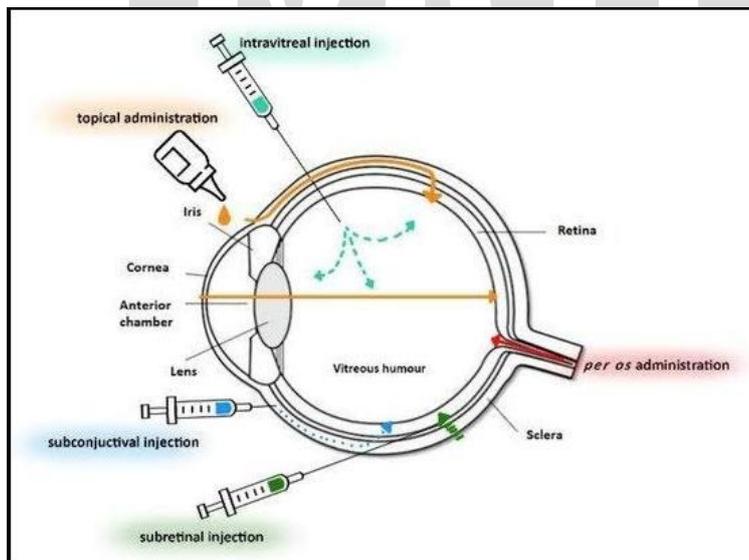
**• Controlled Delivery**

- In situ gel systems
- Micro emulsion
- Contact lens
- Collagen shield
- Nano suspensions
- Micro needle

**• Advanced Delivery System**

- Gene therapy
- Stem cell therapy
- Aptamer
- Therapy siRNA
- Protein and peptide therapy
- Stem cell therapy<sup>[5]</sup>

**Routes of administration of drug in eye :-**



**Fig [2]:- Routes of administration of drug in eye**

**• Topical Administration –**

Eye drops are used to deliver topical ocular medications, but their interaction with the eye's surface is brief<sup>[4]</sup>. The most popular approach is the topical line to administer eye medication, but these drops quickly evaporate owing to eye blinking, and the precorneal region resurfaces to preserve a 7-l seating capacity. gels and jellifies Inserts, ointments, and formulations can all be used to increase the contact time and hence pharmacological activity's duration<sup>[1]</sup>. Topical medications for high patient risk self-control and obedience led to more tears. It is utilised to identify diseases such as conjunctivitis, keratitis, and uveitis<sup>10</sup>. Model showing medication transport from a topical injection into the precornea and the eye. For the majority of drugs used topically, it is the drug delivery technique that is most frequently used<sup>[11]</sup>. several levels of the cornea, conjunctiva, sclera, and additional anterior segment tissues including the ciliary and iris. Usually, the body is the locus of action. structural obstacles and precorneal variables diminish after administration, topical formulations' bioavailability<sup>[1]</sup>.

#### • Oral Administration

Oral administration has been studied both separately and in combination with topical delivery for a number of reasons<sup>[5]</sup>. Topical application was unable to produce therapeutic concentrations in the posterior region. Oral administration was also contrasted with Parenteral administration is the method of choice for treating persistent retinal health issues<sup>[8]</sup>. However, the scarcity of many of the targeted ocular tissues places restrictions on the treatment. The effectiveness of oral delivery, which requires a high dose to have a treatment effectiveness. Systemic adverse effects may occur as a result of such dosages. As a result, while trying to achieve a therapeutic response in the eye after oral delivery, criteria including safety and toxicity must be assessed<sup>[7]</sup>.

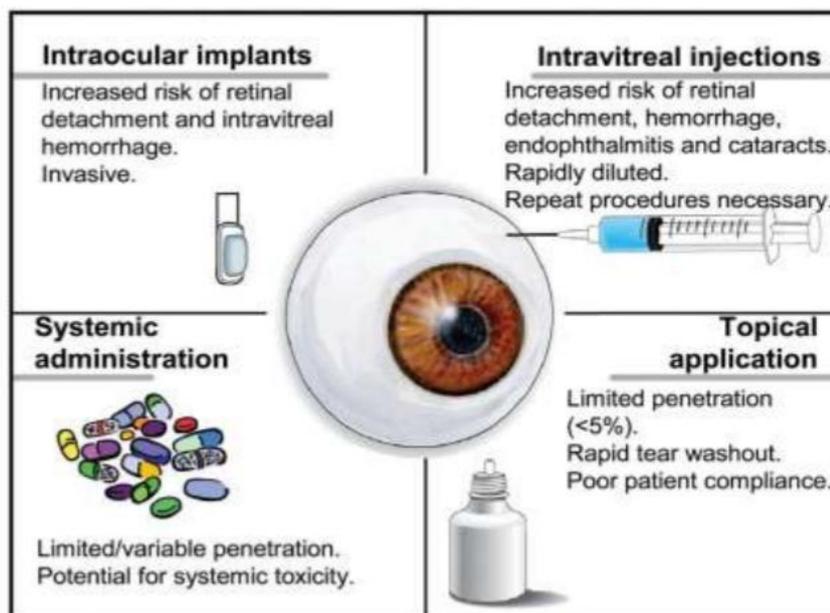
#### • Systematic Administration

The blood-aqueous and blood-retinal barriers are, in the anterior and posterior segments, respectively, the main obstacles to ocular medication delivery after systemic injection. The effectiveness of systemic administration in delivering has been limited. due to the presence of blood retinal vessels, drugs to the vitreo-retinal tissues barrier. Due to non-specific effects, this method of distribution could result in systemic cytotoxicity. drug adherence to nearby organs. The blood-retina barrier, which severely restricts drug permeability from blood to the retina, continues to be a barrier, even though it is ideal to deliver the medication to the retina by systemic administration. Therefore, special intravenous To get chemicals through the choroid and into the target tissue, targeting mechanisms are needed deeper layers of the retina<sup>[6]</sup>.

#### • Intravitreal Administration

Drugs can be injected directly into the vitreous, allowing them to reach both the retina and vitreous. Big molecules, especially those that are positively charged, have a restricted ability to move through the vitreous. Resulting from the RPE Transport from the vitreous to the choroid is more difficult because of the (Retinal Pigment Epithelium) barrier difficult. Inequitable medication distribution is present in the vitreous. Additionally, this depends on the pathophysiological state and the molecular weight of the medication. This method of management resulted in a larger vitreous concentration and a longer retention time for medicines<sup>[11]</sup>.

Fig [3]:- Complications associated with in situ gel system



#### Critical Barriers In Ocular Therapeutics<sup>[7]</sup>

##### • Drug loss from the ocular surface

After injection, the injected compounds are removed from the eye's surface by the lacrimal fluid flow. The excess volume of implanted fluid is promptly transferred to the nasolacrimal space despite the lacrimal turnover rate being only about 1 l/min duct<sup>[12]</sup>. Either quick or delayed systemic absorption from the conjunctival sac either after the fluid has flowed through the nasal cavity or through nearby blood vessels. However, the majority of the dosage that is delivered that has a low molecular weight is readily absorbed into the body's bloodstream. Less than ideal ocular absorption of contrasted sharply with less than 5%<sup>[4]</sup>.

##### • Lacrimal fluid-eye barriers

The corneal barrier is generated when the epithelial cells mature. They go from the limbal area to the cornea's center and then to the apical surface. Tight connections occur restricting the passage of paracellular drugs between the cornea's most apical epithelial cells<sup>[9]</sup>. Because of this, lipophilic drugs frequently have corneal permeability that is at least an order of magnitude higher than that of hydrophilic medications. Trans the primary way that drugs enter the aqueous humour from the lacrimal fluid is through the cornea, despite the corneal epithelial layer's tightness, humour<sup>[11]</sup>.

#### • Blood ocular barriers

Blood-ocular barriers guard against xenobiotics in the bloodstream entering the eye. The two types of barriers are the blood-aqueous barrier and the blood-retina barrier<sup>[3]</sup>. Blood-retinal and blood-aqueous barriers (BAB and BRB, respectively) control blood flow, the movement of molecules between the anterior and posterior ocular chambers and the systemic circulation tissue<sup>[4]</sup>. The intravitreal medication levels of poorly fat-soluble antibiotics were observed to be less than 10% of the amount in their blood<sup>[8]</sup>.

#### • Gel

Innovative materials that blend liquid and solid components are called gels. Three-dimensional solid networks are used in its construction<sup>[11]</sup>. Gels are split into two types based on the bond structure because they comprise a three-dimensional solid network. They have a number; Weak links, including electrostatic and hydrogen bonding, create the gel network. Van der Waal ties and interactions. Chemical gels arise when the gel network contains many covalent bonds. The Network evidence suggests that cross-links help avoid hydrophilic polymer aqueous medium breakdown<sup>[3]</sup>.

#### • In situ gel

The term "in situ" alludes to a Latin term that means "in location." Drug delivery systems called in situ gels are injected into the body before they are organised, but they undergo in situ gelation to form a gel until they are targeted. In situ gels genital, injectable, oral, visual, rectal, and genitalia are the five organisational categories. intraperitoneal<sup>[6]</sup>. One of many has been recognised as the "in situ gel" framework. innovative techniques for medication delivery. The assisted and facilitated in-situ gel structure results in Medication delivery is controlled, which enhances patient quality and comfort. Outstanding "Sol a Gel" trademark from development 22. An aircraft that is a part of a structure outstanding ring the body, however under certain conditions, that will change to a gel state.

Temperature, pH fluctuation, solubility trading, UV radiation, and the proximity of certain atoms or particles are a few factors that influence the transition from sol to gel<sup>[4]</sup>. For continued planning, drug transport facilities with the aforementioned "evolution from sol to gel" properties are frequently used. various vehicles for moving bioactive materials. Several benefits of the "in-place gelling system" include the ease of administering medications, the reduction in organisational Recurrences, as well as protecting medications against deteriorating environmental conditions. A variety of characteristics and manufactured polymers are tested using in situ gel frames, It can be used for parenteral, intraperitoneal, transdermal, visual Applications 23 include injection, rectal, and vaginal.

A variety of characteristics and manufactured polymers are tested using in-situ gel frames, which can be used for rectal, vaginal, oral, transdermal, intraperitoneal, parenteral, injectable, and oral applications. 23. Constant improvements to in-situ gels have made it possible to use physiological uniqueness to advance medicine. consumption, space requirements, and patient satisfaction in distinct digestive tract regions 24, 25, For the in situ gelation structure, common polymers include Alginate acid, guar gum, galvamic acid, chitosan, xyloglucan, guar gum, Carbopol, and xanthan Poloxamer, gum, HPMC, and other substances 26<sup>[12]</sup>.

#### • In situ gel 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 is accomplished by joining polymer chains, which can be done chemically or via bonding bond creation (physical bonding). Low viscosity systems can be used to explain in situ gel-forming systems. Solutions that form a conjunctival cul-de-sac after transcending phase change. Because the polymers are aligned in reaction to the live organism, viscoelastic gels are formed environment. Because in situ gel production between the eye and skin is critical, Additionally, a solution or weak gel is created with the use of an eye before the solid gel forms fluid. Situ gel can be created using both organic and synthetic polymers. n-situ gelling devices have also shown a number of additional potential advantages, including a straightforward production method, ease of administration, and precise dosage delivery dose types in liquids. As eye drops, liquid dosage forms are well-liked by the patient population. Drug release can be sustained using a delivery system made of phase transition polymers, which are injected in liquid form and switch to a gel phase once they reach the eye. It is optimal for these materials to stay in contact with the cornea of the eye for lengthy periods of time. If a drug's precorneal residence duration could be lengthened from a few minutes to a few hours later, local bioavailability improved, dosage concentrations were lowered, and dosing frequency and higher level of patient acceptance<sup>[9]</sup>.

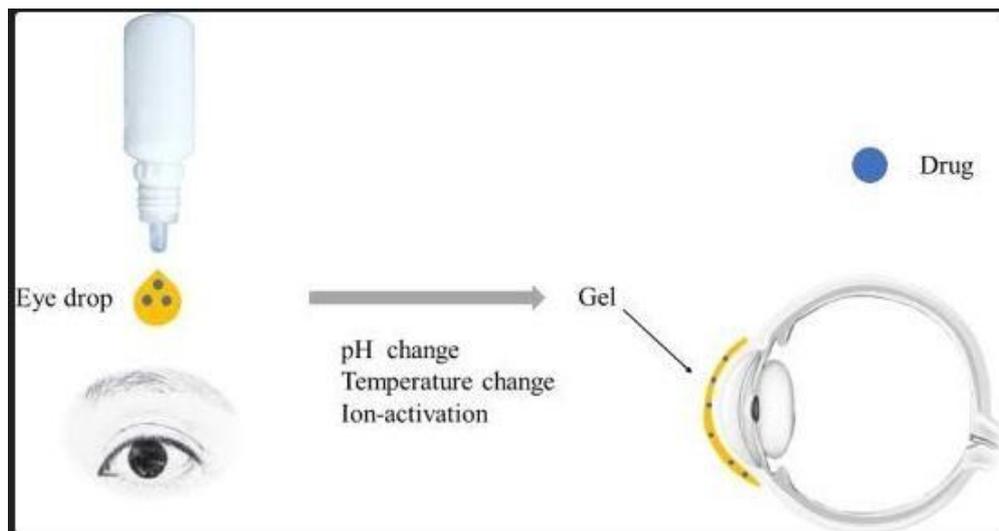


Fig [4]:– Ocular In Situ Gel System

### Mechanism in situ Gel system

#### • Diffusion-

If the implant is made comprised of a solid, non-abrasive body with holes and dissolved wood, the tree is released continually at a controlled pace throughout the distribution process, and membrane penetrates the tearing fluid otherwise. Drug removal is achievable by infiltrating the pores<sup>[3]</sup>. The progressive increase in output can likewise be used to control attributable to the internal dispersion of solids, dispersion of solids within this matrix water-based solutions. True dissolving in melting material is primarily caused by polymers swelling<sup>[9]</sup>. The active ingredient is equally distributed in controlled inflammatory devices the polymer of glass. Glass polymers lack drug resistance, hence there is no dry diffusion matrix happens. When the implant is placed inside the eye, water from the stagnant fluid starts to enter the matrix. This causes inflammation, which causes the polymer chain to loosen and causes drug distribution<sup>[9]</sup>. fulfilment of the matrix, which comes after Depending on the polymer's structure, an inflammatory reaction may occur; amorphous polymers Unlike bonded polymers or a portion of a crystal, disintegrate significantly more quickly<sup>[7]</sup>. Getting rid of these Instruments typically follow the kinetics of the "square root of time" in literature; nonetheless, However, zero-order kinetics has been taken into account for case II transport<sup>[6]</sup>.

#### • 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 action<sup>17, [5]</sup>.

### Chemical Mechanism

#### • Enzymatic cross-linking

In-situ manufacturing Natural enzymes do not have known causes and have been thoroughly studied, but they do seem to have advantages over chemical and chemical treatment approaches. For instance, the enzymatic method functions effectively. under physiological circumstances, without the use of potentially dangerous substances such as start-ups and monomers. Motives with intelligence that react to delivery methods employing Hydrogels with insulation were studied. Stable Cationic pH-sensitive Polymers Inflammation may be the cause of insulin and glucose oxidation. Considering the high It produces insulin, which binds to the heart and lowers blood sugar levels. modifying the enzyme's activity gives a simple method for controlling the gel level's formation as well, allowing the substances to be "injected" prior to the gel's formation<sup>[3]</sup>.

#### • Ionic cross- linking

Due to the development of gels, in ionic cross-linking, the polymer bonding undergoes a phase transition to various ions. Carrageen and other ion-sensitive polysaccharides can create expanding gels, especially in the presence of When (Ca<sup>2+</sup>) and K-carrageen are exposed to a little amount of (K), they create fractured and solid gels.+). A commonly used polymer by the name of Gel rite was the Glean gum. polysaccharidepolysaccharide with anion. This, in the presence of mono- and, passes in-situ gelling divalent cations, such as K<sup>+</sup>, Ca<sup>2+</sup>, Na<sup>+</sup>, and Mg<sup>2+</sup>. Gelation of the low-methoxy Divalent cations, notably (Ca<sup>2+</sup>), can lead to pectin. Likewise, alginic acid is ingested with divalent/polyvalent cations present in (+ -g). due to contact, Ca<sup>2+</sup> with blocks of aglucuronic acid in the chains of alginate<sup>[6]</sup>.

### IDEAL CHARACTERISTICS OF POLYMERS FOR PREPARATION OF IN SITU GEL

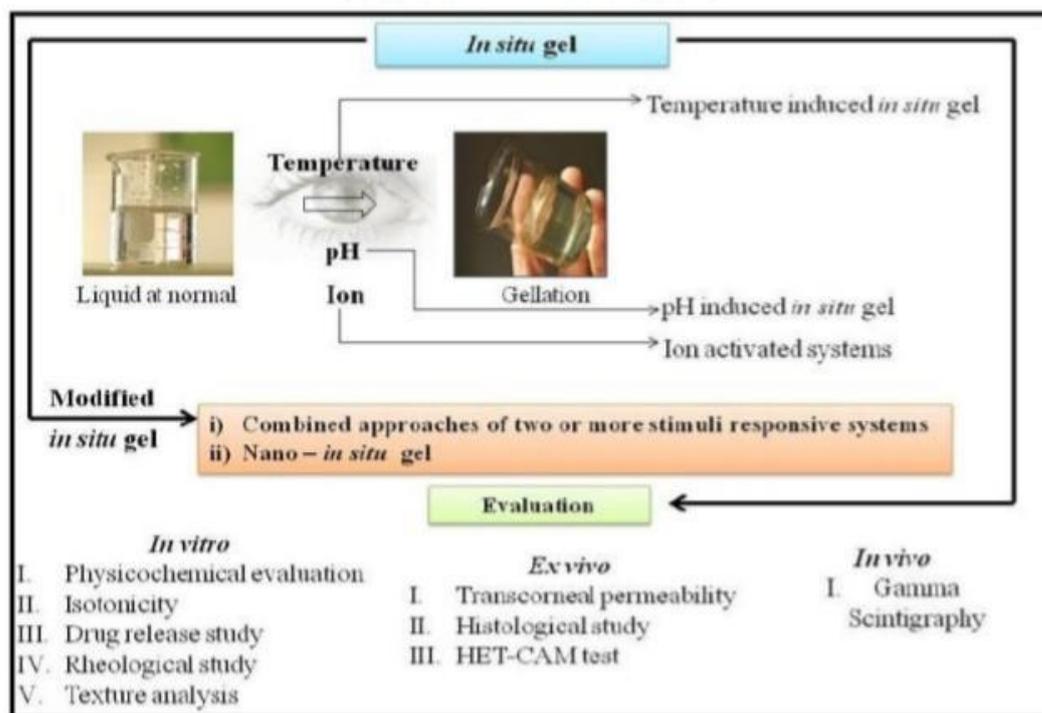
- The polymer must be compatible without becoming hazardous in order for the mucous membrane to adhere to it. Pseudoplasticity is also necessary.
- The polymer's cutting speed can be raised to lower viscosity.
- A high degree of tolerance and optical clarity are necessary for in situ gel production.
- It's important to affect tear behavior<sup>[2]</sup>.

### ADVANTAGES OF IN SITU GELS

- Less nasolacrimal drainage of the medication, which may result in unfavourable side effects because of systemic absorption, as compared to ointment (i.e. reduced systemic side effects).
- The ability to provide precise and repeatable doses, as opposed to Additionally encouraging precorneal retention and previously gelled formulations<sup>[2]</sup>.
- Continuous plasma profile maintenance and sustained release.
- Fewer applications, which leads to better patient compliance;comfort<sup>[9]</sup>.
- More pleasant than soluble or insoluble insertion, on the whole.

### DISADVANTAGES OF IN SITU GEL SYSTEM

- The drug's solar form is more biodegradable.
- Needs a lot of fluid.
- Limit your eating and drinking for a few hours after taking the medication.
- The medication load's volume and homogeneity in hydro gels can be Significantly decreased, particularly for drugs that are hydrophobic<sup>[5]</sup>.
- Only drugs in low doses are allowed.



Fig[5]:- Overview on In situ gel system

### Polymers used in ocular in situ gel system

In order to regenerate and repair tissue, polymers should be used safely as polymer therapies. The polymer functions as a drug carrier while not being employed as a medication, lowering immunogenicity, toxicity, or degradation while simultaneously improving circulatory period. Polymer in this situation need to be water soluble, non-harmful, non-It should be secure at all phases of drug delivery and immunogenic (from administration through eviction). Ideally, the size of the polymer should be lower below the renal threshold for simple removal, preventing the build-up of polymer the body. For instance, poly (meth) acrylates<sup>[3]</sup>.

If the polymer is biodegradable, the immunological response to the degradation product's toxicity should be taken into account. Stimulus-responsive polymers mimic biological systems, but changes in characteristics are caused by external stimuli like temperature or pH. Its solubility, conformation, or hydrophilic/lipophilic balance could all alter release of the active part<sup>[6]</sup>.

#### 1)Chitosan :-

The active component is continuously released by chitosan-based systems, albeit to a lesser level than tamarind gum. Chitosan and negative mucin mix because of the amino and hydroxyl groups, which increases the functional ocular bioavailability. By joining chitosan to hydrogels, hybrid hydrogels can be created performance polymers that are biocompatible<sup>[2]</sup>. A combination of an injectable gel-based on glycol chitosan was used to create Avastin for ocular administration after alginate had been oxidised<sup>[17]</sup>. The interaction between the amino group and chitosan produced the hydrogel structure and the alginate aldehyde group by constructing the Schiff foundation<sup>[5]</sup>. Chitosan Because glycol is more soluble than chitosan, it was chosen as the replacement.

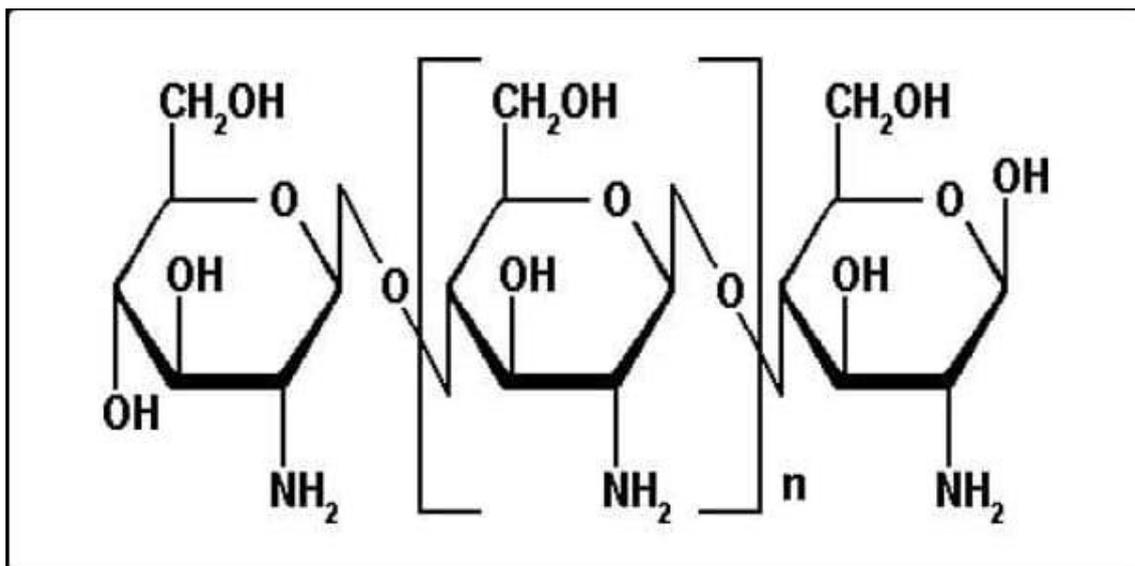


Fig [6]:- Structure Of Chitosan

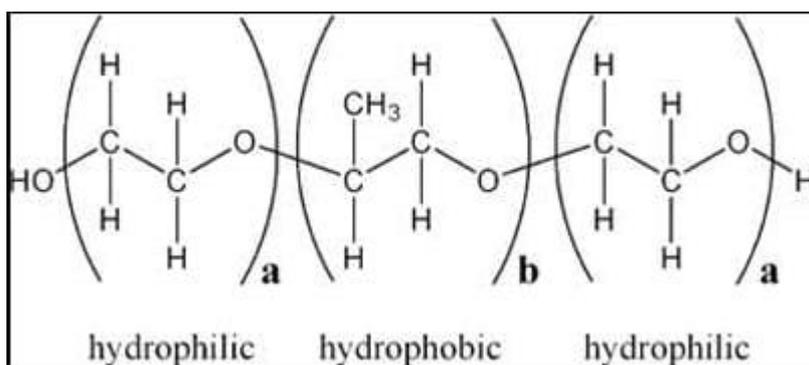
The deacetylation levels and molecular weights of the resulting chitosan, which define the quality and characteristics of the polymer, vary widely. These chitosan properties have a significant impact on solubility. Specifically Chitosan compounds that average more than 50% deacetylation are soluble exclusively in acidic solutions; they demonstrate no solubility in alkaline or pH-neutral solutions. Additionally, the chitosan structure includes amino and hydroxyl groups. In a corrosive media the molecule becomes polycationic and can therefore interact with different macromolecules and negatively charged compounds. Researchers have also created glucocorticoid-based remedies; particularly, they were successful in developing a system of methyl-cyclodextrin and ammonium chitosan that is insoluble in water and shown cytocompatibility and mucoadhesiveness<sup>[16]</sup>. Nanoscale formulations also included the use of chitosan. Researchers created nanoparticles made of polycaprolactone, polyvinyl alcohol, and chitosan in an effort to increase the ocular delivery of dorzolamide hydrochloride. The particles produced as a result showed delayed release, biphasic behaviour, and the capacity to enter the cornea without irritating the eye. A different team of researchers created chitosan and Glycol and dexamethasone, which is its active component<sup>[3]</sup>. These conjugates exhibited self-replication in aquatic conditions, assemble and create nanoparticles. As opposed to the watery media these nanoparticles demonstrated enhanced precorneal retention and mucoadhesion in the solution. The use of chitosan as an excipient in hydrogels also has a lot of promise. A hydrogel is crosslinked polymer networks with potentially useful physicochemical characteristics them ideal for delivering ocular medications<sup>[11]</sup>.

#### Properties of Chitosan

- Chitosan is a naturally occurring cationic polysaccharide made of copolymers of glucosamine and N-acetylglucosamine, which are made by deacetylating chitin.
- Due to electrostatic interactions between molecules, chitosan possesses a mucoadhesive characteristic negatively charged mucin and positively charged amino group.
- It is also known as an ophthalmic carrier and is a polycationic polymer.
- It is a non-toxic, biocompatible, and biodegradable polymer.

#### 2) Poloxamer

Poloxamers are nonionic copolymers of the ABA type made of polyoxyethylene and polyoxypropylene, which are two separate units. Poloxamers are known as amphiphilic because of the characteristics of these two units, which are hydrophilic and hydrophobic, respectively. In-situ gels are frequently created using poloxamers as surfactants<sup>[4]</sup>. They come in liquid, paste, or flakes form and are offered for sale under the following such as Pluronic, Synperonic, and Tetronic, among other brand names. The combination of these copolymers are constructed by adding the two distinct block types (methyl and Propylene glycol is an organic substance having a low molecular weight and solubility in water. This synthesis is performed with a catalyst present, like potassium or sodium hydroxide. The length of the lipophilic and hydrophilic units, which govern the copolymer's characteristics, is what distinguishes the various poloxamers. The two most popular varieties are poloxamers 407 and 188 whose names correspond to the methoxide and epoxide groups' molecular weights, in that order<sup>[10]</sup>. Because both hydrophilic and hydrophobic groups are present. The characteristics of poloxamers include. They are thermoreactive and respond to temperature by changing their physical characteristics. The change of the poloxamer is referred to as the reversible phenomena known as gelation.



Fig[7]- Poloxamer

### 3)Hyaluronic Acid :-

A naturally occurring linear polymer, hyaluronan (hyaluronic acid, HA) is made up of two different sugars: the amino sugar N-acetyl-D-glucosamine and the uronic sugar D-glucuronic acid, which are connected by -1,4-glycosidic bonds<sup>[19]</sup>. This biopolymer is one of many biopolymers that Glycosaminoglycans are polysaccharides (GAGs). The various compounds Members to the GAG family share a similar molecular weight and structure and are produced in the endoplasmic reticulum and Golgi bodies<sup>[18]</sup>. But with regard to most Among the aforementioned, HA is unique from other GAGs. Specifically,hyaluronan is not synthesized in the Golgi but in the plasma membrane by synthases, while it has a higher molecular weight compared with other members of the group. The difference in molecular weight seems to play a crucial role in the properties of hyaluronan, such as viscosity, which progressively increases with molecular weight<sup>[5]</sup>.

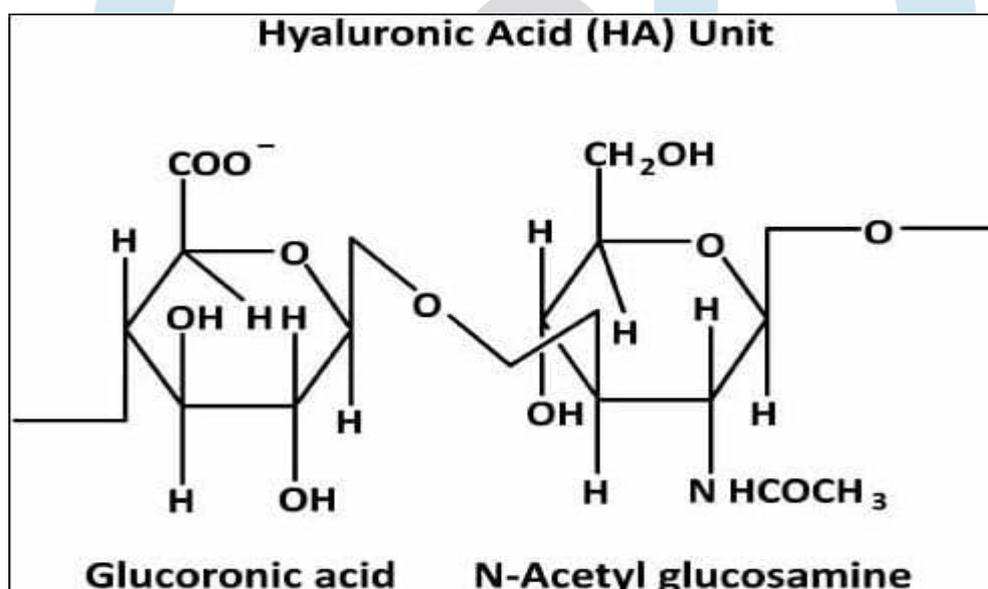


Fig [8]:- Structure of Hyaluronic Acid

Due to the carboxylate groups in the molecule, HA is anionic at physiological pH and, when balanced with cations, creates salts known as hyaluronans. The chain's structure and interactions are determined by its charge changing the water solubility and rheological characteristics of nearby tissues the plastic<sup>[2]</sup>.

#### Evaluation of Ocular in situ gel

Ocular in situ gel can be tested for various parameters in order to ensure that prepared formulation safety guidelines for ocular drug delivery system (ODDS)<sup>[18]</sup>.

##### • Physical Parameter :-

Clarity, pH, gelling capacity, and drug content estimation are the physical characteristics that need to be assessed for in-situ gel solutions<sup>[12]</sup>.

##### • Clarity and presentation

The created in situ formulation's clarity and visual appeal are examined for presence under fluorescent lighting with a white and black background of any particulate debris.

##### • pH

Drug solubility and stability in ocular formulations are both impacted by pH. It should be such that the formulation is capable of maintaining stability at that pH at the same .After administration, the patient wouldn't feel uncomfortable. Digital pH metres are used to measure it.

##### • Gallon capacity

A drop of the formulation is placed in a vial containing 2.0 ml of freshly made simulated tear fluid to measure its gelling capacity, and the amount of time it takes to gel is recorded. It is measurable. Inserting can be used to evaluate it. A specific amount of simulated lacrimal fluid, the created formulation, and measuring the length of time needed for the gel that produces the dosage form to form capability for gelling<sup>[15]</sup>.

- **Isotonicity**

Isomerization Important ophthalmic formulation features include isotonicity. must be kept in good condition to avoid any tissue damage or eye irritation. It alludes to the pressure that salts in aqueous solution exert through osmosis. Ocular formulation is necessary exhibit an osmotic pressure of between 290 and 310 mOsmol/kg. Tonality is quantified by using osmometer<sup>[4]</sup>.

- **In vitro drug release study :-**

The Franz diffusion cell is used for in vitro drug release studies. Freshly made artificial tear fluid (ATF) is put in the receptor compartment. A membrane for dialysis is positioned between the donor and receptor compartments. The entire assembly is maintained on magnetic stirrer with thermostatic control to replicate in vivo conditions and The medium's temperature is held constant at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ . Continuous medium stirring occurs at 20 rpm. The donor compartment is filled with 1ml of the formulation. At predefined intervals, the sample (0.5ml) is removed and replaced with ATF. Samples are examined using an HPLC or UV spectrophotometer<sup>[14]</sup>.

- **Rheological research**

The Brookfield viscometer is primarily used to measure the viscosity of in situ eye gels. When measuring viscosity before and after gelation, angular velocity is gradually increased from 0.5 to 100 rpm<sup>[12]</sup>.

- **Texture examination**

In situ gel's consistency, stiffness, and cohesiveness are Utilizing a texture profile analyzer, evaluate This primarily denotes the gel's strength and simplicity in execution. Information about hardness is provided by texture analysis. The factors like compressibility and adhesiveness, which can be associated with good spreadability on the corneal surface, ease of removal from the container, and adhesion to the mucous layer in order to extend the time spent there<sup>[15]</sup>.

- **Study of transcorneal permeability**

Use of goat eye cornea allows for the evaluation of drug transcorneal permeability. Fresh goat eyeballs are brought in a regular solution to the lab from a nearby butcher shop ( $4^{\circ}\text{C}$ ). Then the cornea is carefully examined 2-4 mm of the surrounding sclera tissue must also be removed before washing with saline solution. Between the donor and receptor compartments of the Franz diffusion, excised cornea is placed.the donor compartment with the epithelial surface facing it. Receptor fresh artificial tear fluid has been made and placed in the compartment (ATF). complete assembly is set on a magnetic stirrer with a thermostat that controls the temperature at ( $37.5 \pm 0.5^{\circ}\text{C}$ ) moreover, a constant stirring speed of 20 rpm is used. Place 1ml of the prepared formulation in recipient compartment. 0.5 ml samples are taken at specified intervals of 1hr to 5hr and same volume is replaced by ATF. Samples are then diluted up to 10ml and analysed on either UV spectrophotometer or HPLC<sup>[20]</sup>.

- **Research on ocular irritation**

Since the Draize research is prohibited in many nations, one of the following methods<sup>[8]</sup> can be used to conduct an in situ formulation ocular irritation study.

- **Histological research**

To assess how an in situ formulation affects corneal shape and The corneas of recently slaughtered animals are removed in order to assess the risk for discomfort. goat and 5 hours of incubation in the formulation at  $37^{\circ}\text{C}$ . Dodecylsulfate of sodium (SDS) The positive control is a solution in phosphate buffer saline (PBS) 0.1% (w/w). The corneas are immediately fixed in formalin (8%, PBS) upon incubation (w/w). Tissues are deposited in melted paraffin, dehydrated in an alcohol gradient, and block-like in solidification. When cutting cross sections, use haematoxylin and eosin stains (H&E). Microscopically, cross sections are seen for any modification<sup>[12]</sup>.

- **Hen's Egg Test-Chorioallantoic Membrane (HET-CAM)**

Incubating the eggs for 10 days at  $37^{\circ}\text{C}$  and a relative humidity of roughly 70% while automatically flipping them once per hour is how the HET-CAM test is carried out. Each egg shell retains a fraction after the incubation phase is taken off, and a drop of water is applied to the membrane of the air bag to prevent capillary harm suffered during removal. Following that, the CAM is cautiously exposed to 0.1 ml or 0.1 gramme of After 30 seconds of exposure, test materials are removed using a normal saline solution. CAM is exposed to 1% and saline solution (negative controls) simultaneously. SDS remedy (positive control). Each CAM is examined under a microscope after five minutes. For lysis, coagulation, and haemorrhage. For each, an annoyance score (IS) is calculated. By applying the formula:  $=301 \text{ h } 3005+(301)3007+301 \text{ } 3009$  Score for irritation is given according to following scheme; 0=no<sup>[12]</sup>.

- **Antimicrobial study :-**

This antimicrobial efficacy tests can be done by using simple procedure called cup and plate technique. In this test agar is used as nutrient medium in which the test organisms are inoculated and incubated for their growth later two solutions namely test and standard are prepared and the standard solution is the sterile solution of the drug whereas the test is the diluted solution to different concentrations from the test formulation. Later wait for around two hours which leads to the proper diffusion of the applied formulation later these plates are incubated for one day at  $37^{\circ}\text{C}$ . Then the zone of inhibition of the organisms in the plate is tested and can be compared with the control. The process should be done in the sterile area such as laminar air flow cabin. For obtaining proper results positive and negative controls should be maintained<sup>[13]</sup>.

### • In vivo Scintigraphy Studies Gamma

Scintigraphy is a well-established technique for in vivo evaluation of ophthalmic retention time. Although the rabbit is the commonly recommended animal model for evaluation of ophthalmic formulations, but human volunteers are preferred for this study due to physiological differences between rabbits and humans, especially the blinking rate 45<sup>[4]</sup>.

### • Accelerated stability study

To ascertain the physical stability of the formulation under accelerated storage circumstances, a stability study for in situ formulation is conducted in accordance with ICH principles. Temperatures above normal are applied to formulation, and three different humidity levels: 25°C/60%RH, 30°C/65%RH, and 40°C/75%RH. At 0, 30, 60, and 90 days, samples are taken out, and the presence of active 46 drug content .

### Conclusion

The eye is the body's most delicate organ. Because of the complicated anatomical structure of the eye, designing an ocular drug delivery system is the most difficult task for pharmaceutical scientists. There are various types of formulations are available for eye .But due to complicated structure of eye in situ gel formation is made for reduce this complication.To reduce various eye disease like glaucoma ,conjutivitis ,and other symptoms gel is most suitable form .For checking the stability ,side effects, pH ,Clarity ,Isotonicity of gel with eye fluid various evaluations parameters also studied .In this review classification of ophthalmic drug delivery system ,in situ gel system ,mechanism of gel system ,polymers used and evaluations are studied .

### Reference

- Majeed, A. and Khan, N.A., 2019. Ocular in situ gel: An overview. *Journal of Drug Delivery and Therapeutics*, 9(1), pp.337-347.
- Singh, M., Dev, D. and Prasad, D.N., 2021. A Recent Overview: In Situ Gel Smart Carriers for Ocular Drug Delivery. *Journal of Drug Delivery and Therapeutics*, 11(6-S), pp.195-205.
- Koutsoviti, M., Siamidi, A., Pavlou, P. and Vlachou, M., 2021. Recent Advances in the Excipients Used for Modified Ocular Drug Delivery. *Materials*, 14(15), p.4290.
- Kapila, S., Dev, D. and Prasad, D.N., 2021. In-Situ Ocular Gel Pharmaceutical Delivery System: A Recent Review. *Journal of Drug Delivery and Therapeutics*, 11(6-S), pp.173-180.
- KURNIAWANSYAH, I.S., SOPYAN, I., RUSDIANA, T., PRAMASHELA, F.S. and SUBARNAS, A., 2021. A COMPREHENSIVE CHEMICAL CHARACTERIZATION OF IN SITU OPHTHALMIC GEL. *International Journal of Applied Pharmaceutics*, pp.47-53.
- Terreni, E., Zucchetti, E., Tampucci, S., Burgalassi, S., Monti, D. and Chetoni, P., 2021.
- Combination of nanomicellar technology and in situ gelling polymer as ocular drug delivery system (ODDS) for cyclosporine-A. *Pharmaceutics*, 13(2), p.192.
- Wu, Y., Liu, Y., Li, X., Kebebe, D., Zhang, B., Ren, J., Lu, J., Li, J., Du, S. and Liu, Z., 2019.
- Research progress of in-situ gelling ophthalmic drug delivery system. *Asian journal of pharmaceutical sciences*, 14(1), pp.1-15.
- DEKA, M., AHMED, A.B. and CHAKRABORTY, J., 2019. Development, evaluation and characteristics of ophthalmic in situ gel system: A Review. *International Journal of Current Pharmaceutical Research*, pp.47-53.
- Jothi, M., Harikumar, S.L. and Aggarwal, G., 2012. In-situ ophthalmic gels for the treatment of eye diseases. *International Journal of Pharmaceutical Sciences and Research*, 3(7), p.1891.
- Rukari, T.G., Jadhav, A.S., Londhe, R. and Phalke, P.L., 2019. A review on ophthalmic in situ gels. *Am. J. Pharm. Tech. Res.*, 9, pp.159-170.
- Meshram, S. and Thorat, S., 2015. Ocular in Situ gels: Development, evaluation and advancements. *Sch. Acad. J. Pharm.*, 4, pp.340-346.
- Kondepati, H.V., Kulyadi, G.P. and Tippavajhala, V.K., 2018. A Review on In Situ gel pp.380-386.
- Jain GK, Pathan SA, Akhter S. Microscopic and spectroscopic evaluation of novel PLGA-chitosan nanoplexes as an ocular delivery systems. *Colloids and Surface B* 2011; 82: 397-403.
- Aishwarya JJ, Sheetal BG, Ravindra BS. A review on nasal drug delivery system. *World J Pharmacy and Pharm. Sci* 2014; 3:231-54.
- Laddha UD, Mahajan HS, Patel RC. An insight to ocular in situ gelling systems. *Int J Adv Pharm.* 2017; 06(02):31-40.
- Mali MN, Hajare AA. In-situ gel forming systems for sustained ocular drug delivery system. *European Industrial Pharmacy.* 2010; 5:17-20.
- Nerkar, T., Gujarathi, N. In situ gel: novel approach in sustained and controlled drug delivery system. *Pharma science monitor*, 2013; 4(4):1-18.
- Gaudana R, Ananthula HK, Parenky, K.Mitra A. Ocular drug delivery. *American Association of Pharmaceutical Scientists.* 2010; 12(3):348-360. <https://doi.org/10.1208/s12248-010-9183-3>
- Sandeep DS, Narayana CR, Anoop NV, Smart in situ gels for glaucoma- An overview. *Int. J. Pharm. Sci. Rev. Res.* 2018; 50(1):94-100.
- Ramachandra LU, Vikas DG, Gadhave MV, Jadhav SL, Gaikwad DD. Design and development of pH-triggered in situ gelling system of Ciprofloxacin. *Int. Res. J Pharmacy.* 2012; 3(5):418-22.