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REVIEW OF NOVEL IN SITU GEL FOR OCULAR DRUG DELIVERY

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Abstract:

The traditional dosage form has many limitations due to factors such as naso-lacrimal drainage & shorter contact time. Ophthalmic in-situ gelling system composed of environmentally sensitive polymers that will be structurally changed in response to small changes in specific condition. Environmental pH, temperature, & ionic strength, Response to environmental changes, the in- situ are liquids when installation into the eyes and then undergo rapidly gelation into the Cul- de-sac of the eye to form visco-elastic gel. This tends to increase ocular residence time and decreases Precorneal drug loss as a result. The goal of this study is to prepare and evaluate In- situ Gel for ocular drug delivery by using mucoadhesive polymers to increase ocular residence time and minimize Precorneal drugs loss of given formulation.

Keywords: *Ocular Drug Delivery, In-situ Gelling System, Conjunctivitis.*

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1. INTRODUCTION:

The eye is a one-of-a-kind and extremely valuable organ. In most cases, topical drug implementation is the preferred method of ocular chemotherapy due to the ease and safety. There are numerous eye diseases which can affect the body and cause loss of vision. As a result, there are many eyes in drug delivery systems. They are divided into two categories: conventional drug development systems and new drug development systems [1]. The most common and very well route of administration for the identification of different eye disorders is topical application of drugs to an eye. The anatomy, physiology, and biochemistry of the eye make it highly resistant to foreign substances. The physiological constraints imposed by the eye's protective mechanism result in low drug absorption and a short duration of therapeutic action in ophthalmic drug delivery systems. Noncompliance is associated with a high frequency of eye drop instillation [2]. Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages such as, high variability in efficiency, blurred vision and increased pre-corneal elimination results into poor bioavailability of drug in the ocular cavity [3]. The bioavailability of ophthalmic drugs is, however, very poor due to efficient protective mechanisms of the eye. The formulation scientist faces a significant challenge in circumventing (bypassing) the protective barriers of the eye without causing permanent tissue damage [4]. Blinking, baseline and reflex lachrymation, and drainage rapidly remove foreign substances, including drugs, from the eye's surface. Tears wash the surface of the eye permanently and have anti-infective properties due to the lysozyme and immunoglobulins [5]. Finally, the nasolacrimal pathways drain the lachrymal fluid. All of these protective mechanisms are to blame for the rapid and widespread Precorneal loss of topically applied drugs on the eye. The primary objective of diagnostic system strategy is to obtain the optimal concentration of a drug at the binding site for the appropriate duration

1.1 Anatomy & Physiology of Eye:

Eye is divided into several compartments, including the tear compartment, and back compartment. The cornea, iris, Ciliary body, and aqueous humor are all found in the anterior chambers. The retina, vitreous humor, choroid, and sclera are all found in the posterior chambers [7].

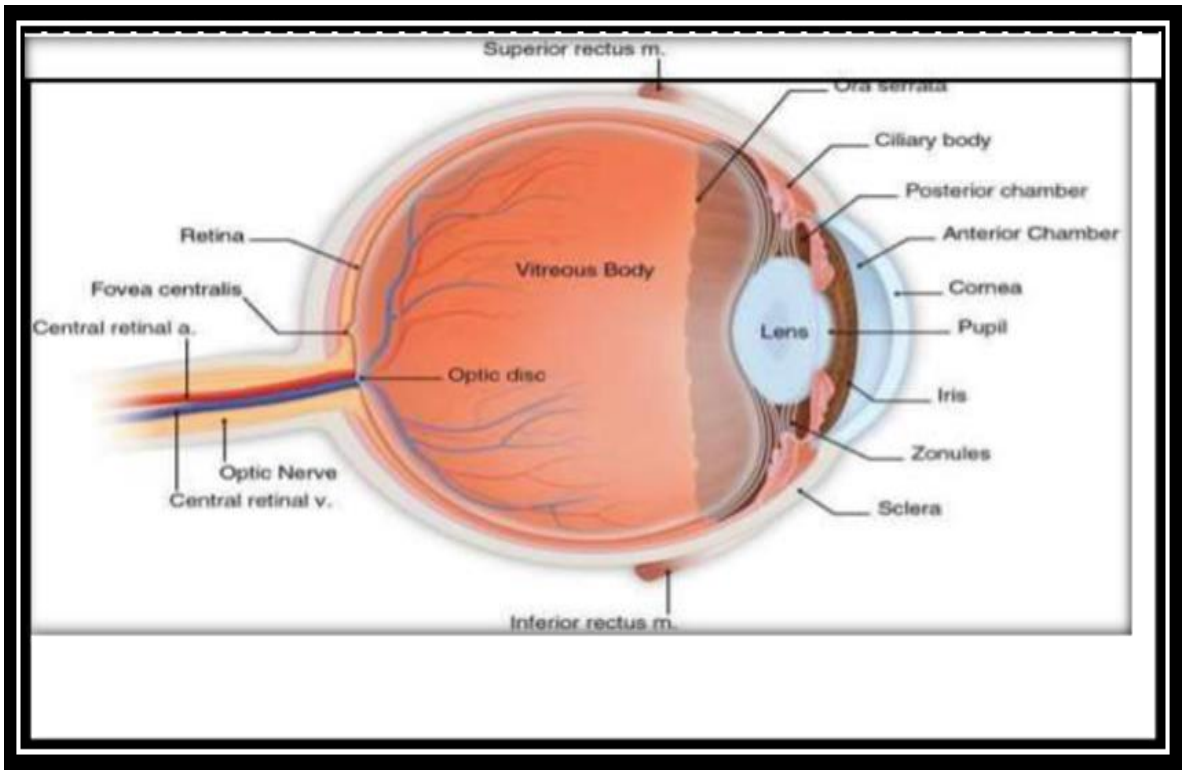


Fig.No-1 Anatomy & Physiology of Eye

1.1.1 Tear Chamber:

The tear chamber of the eye is the portion of the eye that is in contact with the outside world. Tears are produced by various parts of the eye, with the lacrimal gland producing the most. A portion of the accessory gland also contributes to tear production, such as lipid, mucous, and some substrate. The primary function of the eye is to remove foreign particles from the eye [8].

1.1.2 Anterior Chamber:

- **Cornea:** Cornea was its eye's outer layer. The human cornea has a width of 0.5mm. Bowman's membrane, Descemet's membrane, corneal epithelium, stroma, & endothelium are the 5 layers that make up the cornea. The outer edge layer is composed of non-squamous cells linked together by tight junctions. The inner layer has a columnar shape and is commonly referred to as the germinal layer. Bowman's membrane, like the stroma, is primarily made up of collagen fibrils. Descemet's membrane is the dense basal lamina here between stroma and the endothelium. Endothelium is made up of single-cell squamous cells [9].

- **Iris:** The pigmented epithelial cells that make up the iris. When the iris sphincter muscles contract, cholinergic nerves innervate them, causing miosis. The contraction of the pupil is known as miosis. Conciliate mydriasis is caused by the iris dilator muscle becoming radially oriented in response to sympathetic stimulation. Mydriasis is a condition in which the pupil dilates [10].

- **Ciliary Body:** The Ciliary muscles and processes are in charge of the ciliary body's formation. The smooth muscle of the ciliary muscle is made up of fibrous bundles. The fibrous bundles have been vascularized and extend into the posterior chamber [10].

- **Aqueous Humor:** Aqueous humor is the protective and nutritive fluid that exists between cornea and the lens. Aqueous humor is made up of 99 percent water. The Ciliary body secretes aqueous humor (2-3l/min), which circulates to the anterior chamber from the posterior chamber. If the outer flow of aqueous humor is obstructed, the optic nerve suffers permanent damage as a result of elevated intraocular pressure [10].

1.1.3 Posterior Chamber:

- **Retina:** Retina is the eye's most sensitive tissue. The retina is divided into two layers: the retinal pigmented epithelial layer as well as the cognitive retina. The outer part in contact with the rod and cone is the retinal pigmented epithelium (neural cells). The main purpose of retinal pigmented epithelial cells is to transport nutrients from the choroid to the retina, [10].

- **Vitreous Humor:** Vitreous humor is made up of a gel solution matrix that is sandwiched between the retina and the lens. Vitreous layer is mostly made up of collagen fibrils Vitreous layer is mostly made up of collagen fibrils the water content in 4ml of vitreous humor is 98 to 99.7%, and the pH is 7.5 throughout.

- **Choroid:** Choroid is located within the sclera and the & retina. The choroid is a blood vessel-rich tissue. Bruch's membrane, choriocapillaris, and vessel layers are among thelayers of the choroid [10].

- **Sclera:** The choroid is protected by the scleral layer. Sclera's main duty is to maintain the inner organ of the eye. Sclera has a width ranging from 0.5 to 1 mm. The sclera is composed of collagen bundles, disbanded melanocytes, elastic tissue [10].

1.2 Composition and Formation of Tear:

Tears are produced by a variety of glands, which gives tear films their properties. Tear coatingis a thin fluid coating that covers the eye. Key function of tears is to protect the cornea and conjunctiva. Precorneal film refers to the tear coating that coats the eye's surface. Precorneal film has three distinct layers, which are as follows:

- **Lipid Layer:**

The lipid layer contains oil secreted by meibomian or tarsal glands. The lipid layer's primary function is to coat the aqueous layer, which acts as a hydrophobic barrier to tear [11]

- **Aqueous Layer:**

Water, electrolytes, and other substances such as antibodies, lysozyme, and so on are found in the aqueous layer. It produces tears by secreting lacrimal glands. The aqueous layer's function is to control infectious agents and osmotic regulation by spreading the tear film [13].

- **Mucus Layer:**

Mucins are found in mucus layers and are responsible for the secretion of conjunctival goblet cells. The mucus layer coats the cornea, creating a hydrophilic layer that allows the tear film to be distributed evenly [13]

1.3 Barriers in Ocular Drug Delivery

- **Precorneal Barrier:**

The tear film started to appear on the corneal surface as a layer with a relatively homogenous, good network-like structure and a width of 2 to 6 m. The Precorneal tear film is composed of 3 layers: an outer edge lipid layer containing lipids such as triglyceride levels, phospholipids, sterols, and fatty acids, a middle aqueous layer containing inorganic salts, retinol, ascorbic acid, glucose, lysozyme, urea, glycoprotein, and finally a mucin layer that coats the corneal layer and improves the stability and spread

- **Blood- ocular Barrier:**

The BOB shields the eye from potentially harmful substances while also preserving homeostasis. The blood-ocular system is divided into two major barriers: the blood-aqueous barrier (BAB) and the blood-retinal barrier (BRB) [13].

- **Blood -aqueous barrier (BAB**):

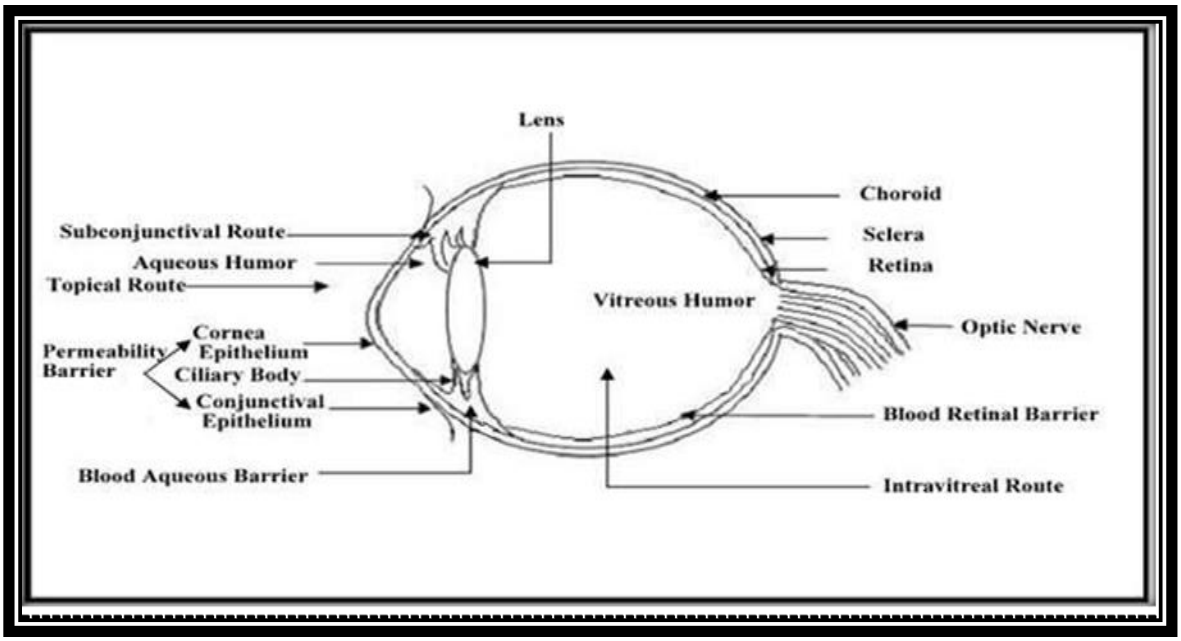
It is situated in front of the eye. Epithelial cells from blood vessels in iris and non-pigmented cells from the ciliary epithelium form this barrier, which has leaky tight junctions. Ocular inflammation, intra - ocular surgery, trauma, or vascular diseases can all cause variations in BAB. Inflammatory cells may also jeopardize the integrity of the barrier. BAB has an active transport mechanism, and ionic concentration gradients affect its passive permeability [13].

- **Blood-retinal barrier (BRB**):

The retinal epithelial layer (outer barrier) as well as endothelial cell of retinal blood vessels (inner barrier) form the posterior barrier, which has non-leaky tight junctions. Following systemic and peri-ocular administration, BRB prevents the movement of substances in the retina. Changes in the BRB may contribute to the progression of retinal diseases such as diabetic retinopathy and age-related macular degeneration.

- **Permeability Barrier:**

The permeability barrier serves as an eye protective measure by limiting drug absorption from lachrymal fluid into the eye. Tran's corneal drug permeation is limited by the cornea's strict epithelium. Lipophilic drugs have greater corneal absorption. The corneal epithelium behaves also as a rate limiting barrier for hydrophilic drug permeation due to these tight junctions. The anterior corneal epithelium tight junctions include a diffusion barrier for drug absorption from tear fluid to the anterior chamber of the eye. Drug absorption in the cornea is affected by viscosity and tonicity modifiers, buffers, as well as pH [13]. The conjunctiva is another barrier that restricts drug permeation due to its multicellular structure and tight junctions. The conjunctival epithelium has 2 times higher pores and 16 times higher pore density than the corneal epithelium, resulting in 15 to 20 times greater permeability [13]. Passive transport, active diffusion, and facillate diffusion can all occur in the cornea and conjunctiva.



1.4 Mechanism Involves in Ophthalmic Drug Delivery:

Drugs should enter the eye via the cornea as well as the non-corneal route if it is administered by instillation [14].

- **Corneal route:**

The drug enters the corneal membrane via the Precorneal space. The rate and extent of the transport process determine the absorption process. Drug transcorneal permeation occurs through three layers: epithelium, stroma, and endothelium. Endothelium and epithelium contain 100 times more lipid than the stroma. Low polarity compounds have higher diffusionalresistance in the hydrophilic stroma layer. Endothelium is a diffusion barrier for ionic or polar species due to its highly lipoidal structure [15].

- **Non-corneal route:**

Diffusion across intracellular aqueous media is the primary mechanism of drug permeation through sclera. The possibility of a partitioning mechanism cannot be ruled out.

1.5 Pharmacokinetic Considerations:

Lacrimal fluids are mixed with the drug for the period of eye drop administration. As a result, the drug's contact time with ocular tissue is extremely short. Half of the drugs are then drained through the upper canaliculus and the other half via the lower canaliculus. The drug penetrates the corneal epithelium via the Transcellular or paracellular pathway. Transcellular routes are appropriate for lipophilic drugs, while paracellular routes are appropriate for hydrophilic drugs. Transcorneal penetration is hampered due to drug binding to corneal tissues. So because corneabehaves as a drug reservoir, the drug is slowly released into the aqueous humor, accompaniedby distribution to intra - ocular tissues as well as eventually elimination via the aqueous humor[16].

1.6 Initial Efforts to Enhance the Ocular Bioavailability:

To overcome the ocular bioavailability of topical application medications, eye drops, ointments, as well as suspensions have been used. Despite the fact that eye drops are advantageous and reliable, drug loss occurs as a result of faster drainage or a short contact timebetween both the drug and the absorbed surface. Furthermore, suspensions and ointments were regarded to address the issues that caused rapid drainage of instilled dose from the application site. Suspensions exhibited increased drug retention [17].

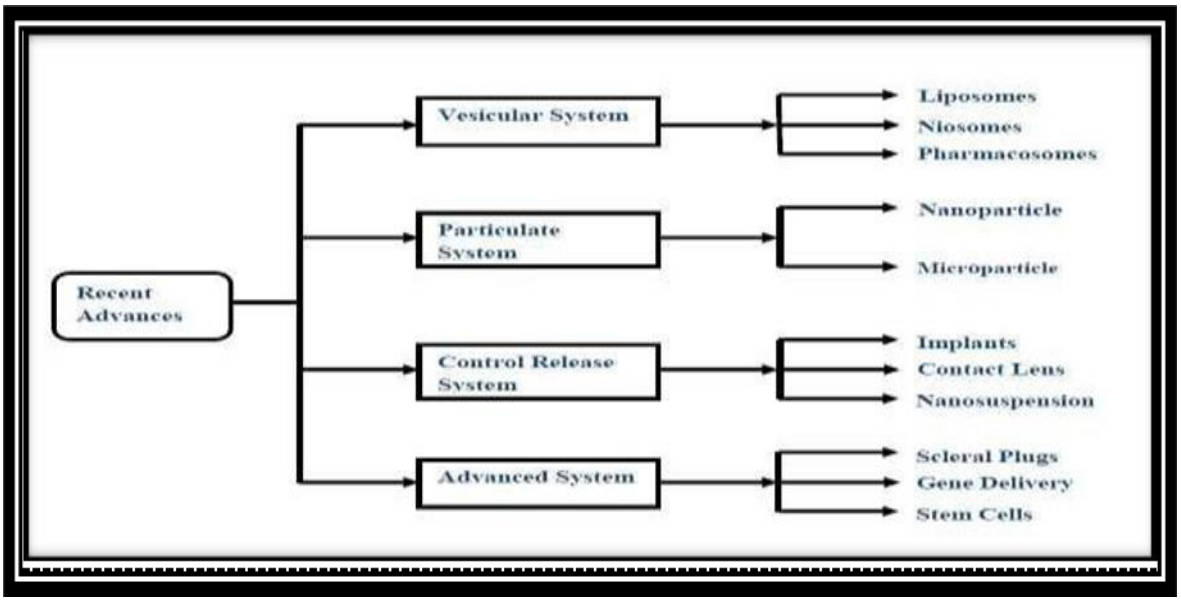
1.7 Recent Approaches to Improve The Ocular Bioavailability:

Use of dispersions has some drawbacks, such as suspended solids sediment deposition during storage. Besides that, ointments were designed with viscosity in mind that also aids in trying to extend residence time and restricting rapid drainage. However, it causes blurred vision, which decreases patient compliance. Region of the eye, particularly in children and the elderly, placement complexity, particle contamination, surgical problems [18].

Various approaches have been taken to improve bioavailability. And therapeutic action. Thereare two types of substances that aid in increasing bioavailability. The first is based on the application of drug delivery systems. The second purpose is to increase corneal drug penetration while minimizing precorneal drug loss. Continuous, controlled, and sustained drug delivery systems accomplish therapeutic effects to lower concentrations and fewer side effects. Particulate, vesicular, advanced, and control release systems are examples of such systems [19].

These delivery systems also had drawbacks, including such blurred vision and discomfort caused by movement.

There are several important factors to consider when designing an ocular delivery system for rapid onset of action with minimal dose and side effects, and also increased bioavailability. Properties like solubility, stability, and permeability must be considered for dissolution and diffusion. One of the general formulation parameters for developing an ocular drug delivery system is the drug molecule, which can be lipophilic or hydrophilic. To cross the corneal epithelium, unionized compounds must be less than 10A0 in size. The pH of the formulation should be between 5.6 and 8 to avoid ocular irritation and lacrimation. Ophthalmic formulations should have a viscosity of 15cps-50cps to increase contact time. The lowest buffer concentration (0.1M) should be used to achieve the best ocular bioavailability and efficacy [20]. A better dosage form would be one that delivers the drug as a solution, tends to cause no vision problems, has no side effects, and limits dosing to once or twice a day.



1.8 In-Situ Gelling System:

Over the last two decades, the researchers have worked to develop a novel approach that can avoid the obstacles subsidized by conventional ocular formulations. Formation of in-situ gel is unquestionably the most important benefit of this exercise. Primary in 1980, the concept of in situ gel was introduced. Because of the viscous gels, it reduces drainage and increases contact time [21]. Cross linking occurs during gelation and can be accomplished through covalent and non- covalent bonding. In-situ gels are introduced into the conjunctival sac as a solution. That undergoes stage transition due to changes in temperature, ion concentration, or ph. In response to environmental changes, in-situ hydrogel formation after instillation into a cul-de- sac produces viscoelastic gels [22]. This gelling system delivers accurate drug doses while also extending residence time at delivery sites, thereby overcoming the issues associated with semi- solid dosage forms. The bioavailability of a drug in ocular delivery is increased by using an in- situ gelling system, which prolongs drug retention at the delivery site. Effective adherence to the corneal surface is achieved by using a suitable polymer. The following are the various approaches for preparing an in situ gelling system [23].

1.8.1 Temperature Sensitive in -Situ Gelling System:

Temperature-sensitive in-situ gel is almost certainly a subset of environmentally sensitive in- situ gel used for drug delivery. Some sol-gel polymer transitions react to changes in temperature. It has a fluid behavior at low R.T. (20-250 C) and a gel behavior at high or physiological conditions (35-370C). Once temperature sensitive in situ gels are used, their temperature before even being dropped into the eyes is lower than the body temperature, and they have a high flow ability and low viscosity, making administration simpler. Temperature sensitive in situ gel is almost certainly a subset of ecologically sensitive in situ gel used in drug delivery. Some sol-gel polymer transitions respond to temperature changes. It has a fluid property at low or room temperature (20-250C) and a gel property at elevated or physiological conditions (35-370C). When temperature sensitive in situ gels are used, the temperature of the gels before it is dropped into the eyes is lower than the body temperature

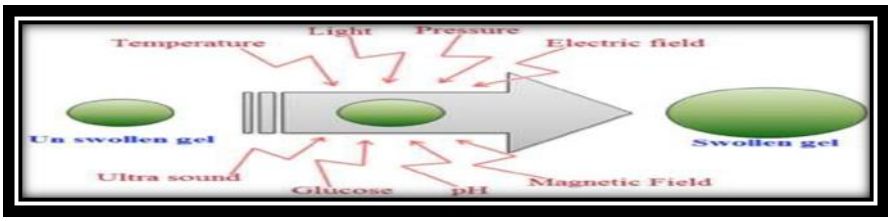
1.8.2 PH Gelling System with pH Sensitivity:

pH is another important environmental factor for drug delivery. A change in pH causes the transformation in such gelling systems. The composition is a free running solution at pH 4.5, but it coagulates when the pH is raised to pH7.4 by tear fluid. The highly fluid latex quickly transforms into the viscous gel after installation of the formulation into the tear film [25]. All pH sensitive polymers have acidic (carboxylic or sulfonic) or basic (ammonium salts) groups which accept or contribute protons in response to pH changes. At different pH levels, the ionizable groups in pH sensitive polymers alter the degree of ionization as well as solubility in water. Electrostatic repulsive forces as well as osmotic forces caused by the help with ions cause PH-dependent swelling or deswelling of in situ gel.

Polymers that are pH sensitive Include cellulose acetate phthalate, carbopol46, polycarbophil, Polyacrylic acid, as well as chitosan. [26].

1.8.3 Ion Activated In Situ Gelling System:

This type of gelling system undergoes phase transition in the presence of various ions, primarily Na, Ca and various cations found in tear fluid. The sol-gel process takes place when anionic polymers react with cation. Gelation occurred as a result of the ionic interaction of polymer and tear fluid ions. The rate of gelation is determined by the osmotic gradient and canbe accelerated by a change in ionic strength. Alginates and gellan gum, polymers used in in- situ gelation [27].



1.9 Common Eye Infections:

➢ **Conjunctival infection:**
Conjunctival infection (also known as pinkeye) is an inflammation of the conjunctiva' causedby one of three different causes: bacterial, viral, or allergic [27].

- **Symptoms:**
  Bacterial conjunctivitis is characterized by a creamy discharge that is unilateral Watering and swollen eyes are symptoms of viral conjunctivitis.

❖ **Bacterial conjunctivitis:** antibiotics including such ciprofloxacin, norfloxacin, pefloxacin, and ofloxacin eye drops or ointment can be used to treat it. Antibiotics hasten recovery and have had no negative consequences [27].

❖ **Viral Conjunctivitis:** There is no treatment or cure for viral conjunctivitis, but artificial tears and cold compresses can provide relief. People are also advised to maintain good hygiene and refrain from touching their eyes [27].

❖ **Allergic conjunctivitis:** This type of conjunctivitis can be treated with antihistamines, mast cell stabilizers, as well as steroid These are the bacterial infections that cause the oil-producing gland in the eyelids to become clogged. It manifests as a small bump on either the upper or lower eyelids.

- **Symptoms:** Include redness with minor pain, uneasiness, and a gritty sensation when blinking, as well as sensitivity to light.
- **Management:**
  Style will heal on its own within a couple of days. Warm compresses can be used on the eyelids to relieve pain and inflammation. It is never a good idea to squeeze a sty
  Will eventually open and drain the pus Style can also be treated with antibiotic creamsand ointments. Most importantly, to avoid a style, keep your eyelids and lashes clean [29].

➢ **Keratitis:**
Keratitis is a corneal infection. It is caused by an infection from a contact lens or an eye injury. Keratitis progresses rapidly and can result in vision loss if left untreated. Staphylococcus aureus and Pseudomonas aeruginosa are the bacteria that cause this type of infection.

- **Symptoms:**
  Include redness, blurred vision, sensitivity to light, and discharge from the eye.
  Keratitis progresses quickly and necessitates immediate antibacterial therapy to eliminate the pathogen. Antibacterial solutions such as levofloxacin, moxifloxacin, andgatifloxacin can be used. It is also advised to stop wearing contact lenses [30].

➢ **Blepharitis:**
➢ It is an inflammatory condition of the eye's margins.

- **Symptoms:**
  Include insistent redness and crusting on the eyelids, as well as a burning sensation and itchiness.
- **Management:**

Cortisone-containing antibiotic drops or ointments should be used, but not for an extended period of time [32]

- **Corneal ulcers:**
  Corneal lesions are an inflammatory condition of the cornea which involves the interruption of the epithelium layer's uppermost layer.
- **Symptoms:**
  Blurred vision, photophobia, pain, redness and watering of the eyes, and dischargefrom the eyes all are symptoms.
- **Management:**
  Antibiotic, antifungal, and antiviral eye solution are the most commonly used treatments. Various eye drops usually containing fluoroquinolones are commonly usedto treat the aforementioned bacterial eye infections. The traditional ocular drug delivery system utilizes frequent dosing to achieve optimal concentration at the target site in theeye. An ocular drug delivery is a fascinating and challenging field that has captivated the interest of pharmaceutical researchers. The structure of the eye is critical for understanding the design of ocular formulations.
  Because of its distinctive structure, the eye is the most delicate organ in the body. Eye the soul of the window in our body. Eye also has a variety of pharmacokinetic and pharmacodynamics properties. Nature's beauty cannot be appreciated without the use of one's eyes. The unique characteristics of the eye are not only used to assess local delivery but also to recognize disease pathogenesis and challenges. Topical drug delivery is generally preferred because many parts of the eye are not even accessible for systemic delivery. Topical delivery is distorted due to Precorneal barriers such as the blinking reflex, low corneal permeability, and effective removal mechanisms. Oraltherapy necessitates a high dose of therapeutic agent to achieve maximum concentrations at the desired place, which causes severe adverse effects. Permeation of hydrophilic & hydrophobic compounds through the cornea is poor, resulting in less than 10% absorption into the anterior segments [32].

1.10 Importance of In- Situ Gelling System:

- It is unique 'Sol-Gel transition,' in situ gels promote controlled and sustained release profile after administration.
- Because of the drug's sustained release, the frequency of drug administration can be decreased.
- Because of the accuracy of dosing and the controlled release of drugs from in situ gels, there is no drug accumulation and no side effects.
- Significant increases in a drug's bioavailability and dose reduction
- Increased drug residence time and drug-tissue contact as a result of gel formation.
- When compared to already formed gels, in-situ gelling systems can deliver correct and frequent doses.
- Because of their physical form, in-situ gel systems are easier to administer, which improves patient compliance and comfort [33].

1.10.1 Advantages of In-Situ Gel:

1. Inadequate bioavailability its problem of conventional ophthalmic solutions can be accomplished by using gel instilled as drops into the eyes.
2. It lengthens the drug's contact time at the site of maximum absorption.
3. Less frequent administration.
4. Drug systemic absorption of drugs drained through the nasolacrimal duct may be lowered, resulting in some undesirable side effects.
5. It has benefits such as delivering drugs with narrow absorption windows in the small intestinal region.
6. The GRDDS are useful for drugs that are absorbed through the stomach, such as ferrous salts, as well as drugs that have target specificity in the stomach and are used to treat peptic ulcer disease, such as antacids [33].

1.11 Problems In Develops an Ophthalmic Drug Delivery System:

- **Anatomical and physiological features of the eye:** There are many excellent reviews in the publications that describe the anatomical and physiological features of the eye from the standpoint of drug delivery. Many of these anatomical and physiological features interfere with the drug's fate. Blinking, tear secretion, and nasolacrimal drainage are the most important. The closure of the lid during reflex blinking protects the eye from external aggression; there are numerous excellent reviews in the literature

that describe the anatomical and physiological features of the eye from the perspective of drug delivery. Many of these anatomical and physiological characteristics impede the drug's fate. The most important are blinking, tear secretion, and nasolacrimal drainage. The lid closing during reflex blinking provides protection to the eye from external threats [34].

- **Drug delivery to the internal regions of the eye:** Drugs Prescribed locally to the Eye Penetration: If the drug is not designed to act on the outer surface of the eye, the main ingredient must enter the eye. The most important route, according to consensus, is transcorneal; however, a non-corneal route has been proposed and may contribute significantly to ocular bioavailability of some ingredients, such as timolol and insulin. Furthermore, the sclera has been shown to be highly permeable to a variety of obstructing drugs. Tear secretion produces a Precorneal tear film, which is spread by the motion of the eyelids during blinking, to maintain the cornea moist, clear, and healthy. Drugs that affect tear secretion, as well as physicochemical agents. Eye penetration of systemically administered drugs: There are blood-eye barriers. Aqueous humor is produced by the ciliary epithelium in the ciliary processes. It is often so-called an ultra-filtrate, since the ciliary epithelium prevents the passage of large molecules, plasma proteins, and many antibiotics. Some molecules can be secreted in aqueous humor during its formation. Inflammation associated with injury, infection, or an ocular disease, e.g., uveitis, disrupts the blood–aqueous humor barrier and drugs enter the aqueous humor and reach the tissues of the anterior segment.There is a blood retina barrier and there is one between blood and vitreous humor complicatedby the high viscosity of the latter, which prevents diffusion of the drugsin the posterior part of the eye [34].

1.12 Ion Activated In Situ Gelation:

The gelation of the instilled solution is triggered due to change in concentration of this method.It is predicted that the rate of gelation is affected by the osmotic gradient across the gel's surface. Gellan gum, Hyaluronic acid, or Alginates are examples of polymers that show osmosis induced gelation [34].

1.13 Ionic Cross Linking:

The ion sensitive polymer is used in this method. In the presence of ions such as Na++, K+, Ca++, and Mg, ion sensitive polymers may undergo phase change. Ion-sensitive polysaccharides include some polysaccharides. While k-carrageenan forms rigid gels with a low amount of K, e gels form in carrageenan primarily in the presence of Ca++. Gelrite is another name for gellan gum. It is an anionic natural polysaccharide that gels in situ when monovalent and divalent cations are present. Alginic acid reduces reflux due to its floating, foaming, and viscous features. When Alginic acid reacts with gastric acid, it forms a physical barrier, or "raft," that displaces the postprandial acid pocket. The polymer that undergoes immediate gel formation due to calcium alginate formation via interacting with the divalent cation (Ca++) present in ocular fluid was chosen as Na- alginate, an ophthalmic gel forming mucoadhesive polymer[24].

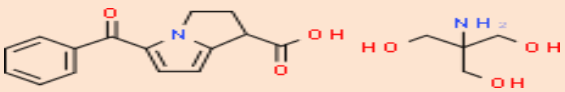
NSAIDs are one of the most prescribed classes of pain and inflammation medications. They are responsible for about 5-10% of all medications taken each year. In the practice setting, the prevalence of N.S.A.I.D. use in patients over the age of 65 is as high as 96 %. In one year, approx. 7.3 % of elderly patients over the age of 60s filled at least one N.S.A.I.D. prescription.NSAIDs have antipyretic and analgesic properties in addition to anti-inflammatory properties.These drugs block COXs 1 and 2, which are rate-determining enzymes in the synthesis of prostaglandins, and other prostanoids, like thromboxane [35].

COX-2 inhibitors (also known as coxibs) inhibit only COX-2 enzymes, as opposed to non- selective N.S.A.I.D.Ds, which inhibit both COX-1 and COX-2 enzymes. COX-2 is more involved in prostaglandin-mediated pain and inflammation, whereas COX-1 is involved in platelet hemostasis and gastric mucosa protective measures. While COX-2 inhibitors' gastrointestinal safety profiles have enhanced, the cardio-nephrotoxic side effect remainsignified [35]

Adverse effects of NSAID in the have been studied; though, recent publications, suggests that the anti-inflammatory action of N.S.A.I.Ds important roles in target such a cognitive function enhancer. Ketorolac Tromethamine is a medication used to prevent and treat eye swelling caused by a specific type of eye surgery (cataract removal).

2. DRUG PROFILES:

2.1 Ketorolac Tromethamine:

Parameter	Description
Drug name	Ketorolac Tromethamine
Synonyms	Ketorolac (+/-)-form Tromethamine salt / Ketorolac trometamol[1]
Appearance	Crystalline ,odourless,white
Molecular weight	376.409
Melting point	164-1670c
Molecular formula	C19H24N2O6
Chemical name	1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylate[2]
Chemical structure	
BCS class	I
Half life	5-6 hours
Bioavailability	The ocular bioavailability of 0.5% [14C] nonsteroidal anti-inflammatory administered topically (50 µL) to the attention determined. The ocular bioavailability of Ketorolac was 4% in anesthetized rabbits and was firm by comparing drug concentrations within the aqueous humour after topical application with those obtained after intracameral injection of a similar dose of 0.25 mg of Toradol per eye. Although Ketorolac administered to the attention was completely absorbed systemically, concentrations of Ketorolac (AUC) were, on the typical, 13 times higher within the liquid body substance than in plasma after topical administration[3]
Protein binding	Its oral bioavailability is estimated to range from 80 to 100%. The drug is extensively bound (>99%) to plasma proteins and encompasses a volume of distribution (0.1 to 0.3 L/kg) comparable those of other NSAIDs[4]
Drug category	Nonselective COX inhibitor
Solubility	Practically soluble in water, Soluble in DMSO, soluble in ethanol
Dose	Depends upon weight and age. Topical -5%
Absorption	Ketorolac Tromethamine was absorbed rapidly (T max but 1.0 hr) and efficiently (greater than 87%) following po and im doses altogether species. The plasma half-life of Ketorolac (K) ranged from 1.1 hr. (rabbits) to six.0 hr. (humans).
Mechanism Of Action	Ketorolac inhibits key pathways in prostaglandin synthesis which is crucial to its mechanism of action. Although Ketorolac is nonselective and inhibits both COX-1 and COX-2 enzymes, it's clinical efficacy springs from its COX-2 inhibition. The COX-2 enzyme is inducible and is liable for converting arachidonic acid to prostaglandins that mediate inflammation and pain. By blocking this pathway, Ketorolac achieves analgesia and reduces inflammation. Ketorolac is run as a racemic mixture; however, the "S" enantiomer is basically to blame for its pharmacological activity[4]
Use	Ophthalmic solution is also administered in conjunction with other topical ophthalmic medications like alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered a minimum of 5 minutes apart.[4]

3. CONCLUSION:

In-situ Gel for ocular drug delivery is prepares by using mucoadhesive polymers to extend ocular duration and minimize precorneal drugs loss of given formulation. Ophthalmic in-situ gelling system composed of environmentally sensitive polymers which will be structurally changed in response to small changes in specific condition like Environmental PH, temperature, & ionic strength. In response to environmental changes, installed liquid in-situ rapidly undergoes gelation into the Cul- de-sac of the attention to create visco-elastic gel. This tends to extend ocular continuance and reduces Precorneal drug loss as a result.

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