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Recent Advancement of In-Situ Gel for the Treatment of Ocular Disorder

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ABSTRACT

The ocular drug delivery system is very crucial and difficult because the eye is the most sensitive part of the body. The *in-situ* drug delivery system is the smart way to deliver the drug in an ocular disorder with fewer risk factors. The in-situ drug delivery system promises to give fewer side effects and more effectiveeffects. In the in-situ drug delivery system most of the drugs are formed from natural polymers. The formation of in situ gel is done in a way that they are solid at room temp and gel after it is administered inthe eye. The in-situ drug delivery system is the safest system to deliver drugs for ocular disorders. There are many recent advancements in in situ drug delivery systems that are used to treat ocular disorders. innovative polymers and nanotechnologies offer tailored drug delivery effectively improving biocompatibility and biodegradation and reducing systemic side effects. By offering sustained drug release these devices solve problems with traditional drug delivery systems. The review highlights the in-situ gel drug delivery system for the treatment of the ocular disorder.

Keywords: Ocular Disorder, In-Situ Gel, In Situ Gel Drug Delivery System, Polymers.

Introduction

The ocular drug delivery system is considered crucial and challenging as the human eye is an isolated organ where the delivery of the drug is quite difficult because drugs introduced to the eye are rapidly washed away by the tear film resulting in very short precorneal residence time. Poor bioavailability that only a small percentage of the administered drugs reach the target within the eyes such as the retina and the aqueous humor rapid elimination by the tear film and other factors can significantly reduce the bioavailability of drugs in traditional ophthalmic formulation.[1] To address these issues the researcher and the pharmaceutical companies have developed various strategies such as –

1. Thickening agents can be added to ophthalmic formulations to increase their viscosity; it helps to prolong the contact time of the drug with the ocular surface, improving its residence time.
2. Drugs with nanoparticles and liposomes can enhance drug delivery to the eye; this delivery system can protect the drug from rapid elimination and allow for controlled release.
3. In-situ gel formulation is designed to transform into the gel upon contact with the ocular surface this will increase the contact time and controlled release.
4. Some drugs are modified into prodrugs that are more stable and improve penetration into the eyes once they get inside the eye they can convert back to their active form.
5. In some cases, implants can be used for sustained release within the eye providing a longer duration of action.[2, 3]

The formation of the gel depends upon factors such as physicochemical properties [pH, temperature, ion

sensitivity] by which the drug can be released in a controlled manner. Refers to the amount of API presentin the present formulation the clarity will show how clear the formulation is. Maintaining the pH is the most important for stability. Gelling capacity is relevant if the drug formulation is intended to be gel. Viscosity refers to the flow of the formulation. Texture analysis is to check the smoothness, stickiness, and hardness of the formulation. Sterility testing is to check that the formulation is free from the microorganism. Isotonicity evaluation ensures that the formulation is of similar osmotic pressure to the surrounding tissue to prevent damage or irritation. Accelerated studies will help to predict the shelf life and stability of the formulation. The irritancy test is to check whether the formulation will show any adverse effect on the skin.[4, 5]

Anatomy of eye

Three layers make up the wall of an eye which is spherical, in shape and composed of the sclera on the outside, the choroid layer in the middle, the ciliary body and the iris, and the retina on the inside, which is composed of nerve tissue. The sclera which covers the outer part of the eye, the choroid layer which contains the ciliary body and the iris, and the retina which is the inner layer of the nerve tissue make up the wall of this spherical structure. The choroid layer which is in the sclera is home to numerous blood vessels that have changed to become the pigmented iris or colored component of the eyes [blue, green, brown, hazel]. The cornea, which is a transparent protrusion at the front of the eyes, transmits images to the rear of the nervous system. Aqueous, humor, lachrymal fluid, and blood vessels at the interface of the cornea and sclera supply the nutrients and oxygen to the vascular tissue that makes up the adult cornea, which has a radius of about 7-8mm. The stroma, descents, bowman's layer endothelium, and the five-layer that make up the cornea are the primary routes via which drugs enter the eyes. Compared to many other epithelial tissues [intestinal, nasal, bronchial, and tracheal], which are respectively impermeable, the corneal epithelium serves as the primary barrier to drug absorption into the eyes. The satisfied squamous consists of five to six layers of cell and has a thickness ranging from 50 to 100 μm.

The tight junction that packs the basal cells serves as both a barrier against dust particles and most bacteria and facilitates the absorption of the drug. The transcellular or Para cellular pathway is the principal mechanism of drug penetration through the corneal epithelium.[4, 6]

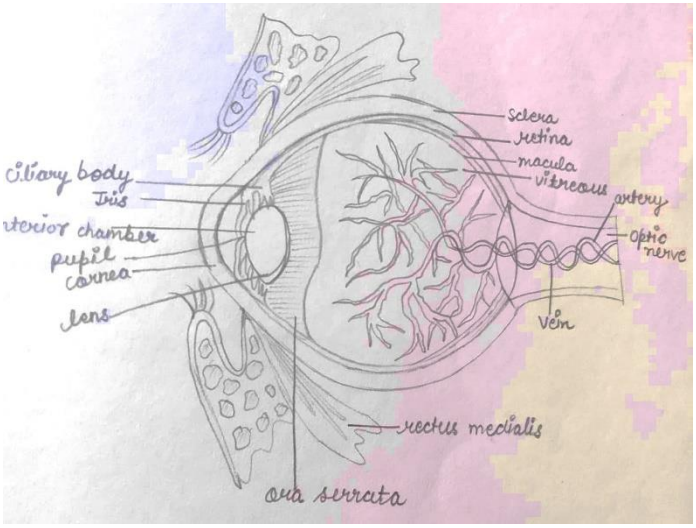

Figure 1: Anatomy of Eyes.[4]

Types of ocular disorder

1. Amblyopia [lazy eye]
2. Cataracts
3. Diabetic retinopathy
4. Farsightedness [hyperopia]
5. Ocular histoplasmosis syndrome OHS.

i. **Amblyopia:** Amblyopia also known as lazy eye is a type of poor vision that usually happens in just 1 eye but less commonly in both eyes. It develops when there's a breakdown in how the brain and the eye work together, and the brain can't recognize the site from one eye over time, the brain relies more and more on the other, stronger eye- while vision in the weaker eye gets worse. It's called lazy eye because the stronger eye works better. However, people with amblyopia are not lazy, and they can't control the way their eyes work. Amblyopia starts in childhood, and it's the most common cause of vision loss in kids. Up to 3 out of 100 children have it. The good news is that early Symptoms of amblyopia can be hard to notice. Kids with amblyopia may have poor depth perception, they have trouble telling how near or far something is. Parents may also notice signs that their child is struggling to see, in many cases, parents don't know their child has amblyopia until a doctor diagnosis it during an eye exam. That's why all kids need to get a vision screening at least once between the ages of 3 to 5. [7]

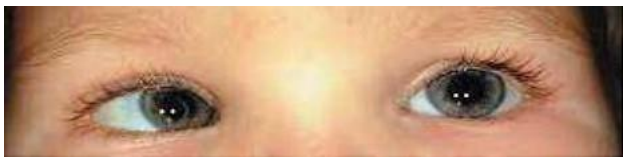

Figure 2: Amblyopia. [8]

ii. **Cataract:** A cataract is a clouding of the lens of the eye, which is typically clear. For people who have cataracts, seeing through clouded lenses is like looking through a frosty window. Most cataracts develop slowly and don't disturb eyesight early on. But with time cataracts will eventually affect vision. [9, 10]

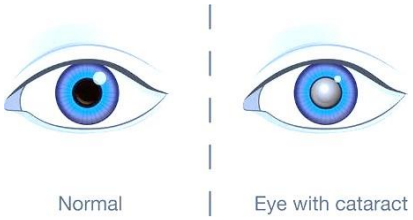

Figure 3: Cataract

Symptoms:

- Clouded, blurred, and dim vision.
- Trouble seeing at night.
- Sensitivity to light.

Types of cataracts

A. cataracts affecting the center of the lens, called nuclear cataracts.
B. cataracts that affect the edge of the lens, called cortical cataracts.
C. cataracts that affect the back of the lens, called posterior subcapsular cataracts.

D. Cataracts you're born with are called congenital cataracts.

Prevention

- Regular eye exam
- Wear sunglass
- Reduce the use of alcohol.[11]

iii. Diabetic retinopathy: Diabetic retinopathy is a diabetes complication that affects the eyes. It's caused by damage to the blood vessels of the light-sensitive tissue at the back of the eyes [retina]. At first, diabetic retinopathy might cause no symptoms or only mild vision problems. But it can lead to blindness.[12]

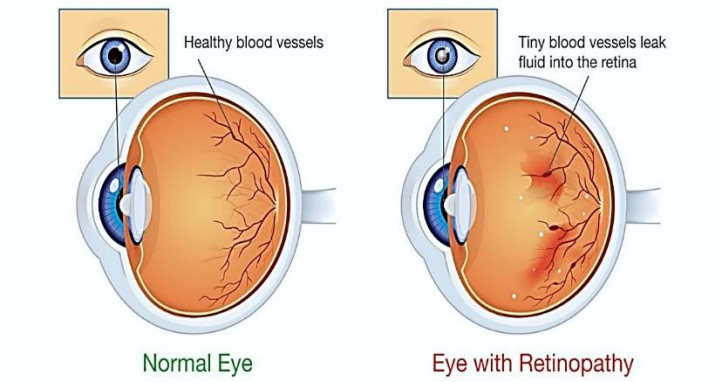

Figure 4: Diabetic retinopathy.[13]

Symptoms

- Spots of dark strings floating in your vision.
- blurred vision

Causes

- Early diabetic retinopathy: in this more common form called no proliferative diabetic retinopathy [NPDR]. New blood vessels aren't growing When you have NPDR the wall of blood vessels in your retina weakens.
- Advanced diabetic retinopathy: Diabetic retinopathy can progress to this more severe type, known as proliferative diabetic retinopathy. In this type, damaged blood vessels close off, causing the growth of new, abnormal blood vessels in the retina.[14]

Prevention

- manage your diabetes.
- monitor your blood sugar level.
- keep blood pressure in control.
- pay attention to vision changes.[14]

iv. Farsightedness: Farsightedness (hyperopia) is a common vision condition in which you can see distant objects clearly, but objects nearby may be blurry.[15]

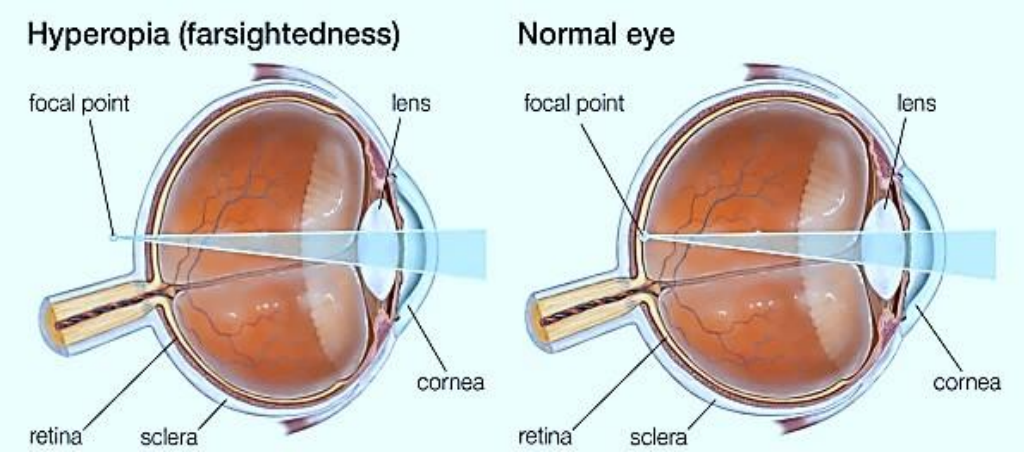

Figure 5: Farsightedness.

Symptoms

- Nearby objects may appear blurred.
- Eyestrain, including burning eyes, and aching in or around the eyes.[15]

v. **Ocular histoplasmosis syndrome:** Ocular histoplasmosis syndrome (OHS) is an eye condition that can develop in people who have a lung infection called histoplasmosis. If you have histoplasmosis, the infection can move from the lungs into the eyes, leading to vision loss.[16]

Symptoms

- Straight lines looking crooked or wavy.
- Blind spots in vision.[16]

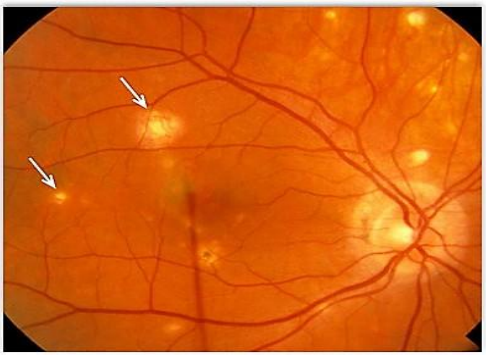

Figure 6: Ocular Histoplasmosis Syndrome.[17]Drugs Used for the Treatment of Ocular Disorders:

Table 1: List of drugs used in the treatment of various ocular disorders.

Ocular Drug	Classification	Mode of Action	Ref. No.
Acetazolamide	Anti-Glaucoma	Lowering aqueous humor production	[18, 19]
Ciprofloxacin	Antibiotic	Inhibition of bacterial DNA gyrase and topoisomerase IV	[18, 19]
Dexamethasone	Steroid	They work to reduce inflammation by blocking phospholipase A2, which in turn blocks the pathways of both cyclooxygenase and lipoxygenase.	[18, 19]

Dorzolamide	Anti-Glaucoma	Reduce IOP by decreasing the production of aqueous humor by the ciliary body	[18, 19]
Ethoxzolamide	Anti-Glaucoma	It will bind and inhibit carbonic anhydrase	[18, 19]
Timolol	Anti-Glaucoma	It will decrease the secretion of aqueous humor in the eye	[18, 19]
Ketotifen Fumarate	Antihistamine	In vitro, ketotifen can suppress the production of inflammatory and allergic mediators, including histamine, leukotrienes C4 and D4, and platelet-activating factors. It also stabilizes mast cells.	[18, 19]
Gentamicin	Antibiotic	Inhibition of bacterial protein binding	[18, 19]
Hyaluronic Acid	Corneal Healing Acid	It can attract water to swell create volume and provide structural support	[18, 19]
Levofloxacin	Antimicrobial	Levofloxacin is bacterial and exerts via inhibition of bacterial DNA replication	[18, 19]
Nanosilver	Antimicrobial	The mode of action of silver nanoparticles is cell membrane dissolution	[18, 19]
Puerarin	Antioxidant	Puerarin decreased ROS (reactive oxygen species) generation.	[18, 19]

There are various novel approaches used for the treatment of ocular disorders, such as in-situ gel. This innovative method involves gels that undergo a phase transition in the eye, ensuring sustained drug release for prolonged therapeutic effects. By optimizing drug delivery and minimizing side effects, in-situ gel approaches enhance drug bioavailability, contributing to improved outcomes for a range of ocular conditions.

***In-situ* gel system:**

It is very difficult to take gel through the oral- route so we need such a system in which after reaching the formulation inside the body it is converted into gel form. *In-situ* gels are the solutions or suspensions that undergo gelation after reaching the site due to contact with body fluids or physicochemical changes (i.e., pH, temperature, ionic concentration, UV radiation, presence of specific molecules or ions, external triggers, etc.). In situ, gels have been potentially used for buccal, intraperitoneal, nasal, ocular, oral, parenteral, rectal, subcutaneous, transdermal, and vaginal routes. The gel formulations enhance potential lead compounds' local and systemic exposure in the discovery phase, ideal for establishing animal modelsfor various conditions quickly and cost-effectively.[20, 21]

***In-Situ* Drug Delivery System-**

In recent times, controlled and sustained drug administration has emerged as the norm in contemporary pharmaceutical design, with extensive research efforts aimed at improving medicinal product efficacy, dependability, and safety. The advantages of the in-situ forming polymeric delivery system, such as its ease of use and lower administration frequency, which improved patient compliance and comfort, have spurred interest in this research. The medicine is released in a regulated and sustained manner from the gel based on factors such as pH change, ultraviolet light, the presence of ions, and temperature modulation. The formulation of in situ gel uses a variety of biodegradable polymers, such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL-lactic acid), and polycaprolactone. In situ gels are

mostly supplied intraperitoneally, orally, ocularly, rectally, vaginally, and via injection. When compared to traditional drug delivery methods, the in-situ gel-forming polymeric formulation has many benefits, including sustained and prolonged action.[22]

Mechanism of *In-Situ* Gelling

Polymeric formulations known as in situ gelling systems are those that are solutions before they reach the body and turn into gels when exposed to physiological circumstances. A single stimulus or a combination of them, such as a pH shift, temperature changes, solvent exchange, UV light, and the presence of ions or molecules, can cause the sol-gel transition. Such features make drug delivery systems particularly useful for preparing bioactive compounds for sustained distribution. Easy application, lower administration frequency, and protection of the medication from changes in the environment are some of these smart systems' key benefits. Many natural and synthetic polymers go through the process of in situ gel formation, which may have applications in the oral, buccal, rectal, vaginal, ophthalmic, intraperitoneal, and parenteral domains.[23, 24]

Key Features of *In-Situ* Gel Drug Delivery System

- **Smart ocular delivery:** Because these systems have stimuli-responsive phase transition features, they can be simply delivered into the eye, much like typical eye drops.
- **Unique gelling properties:** A system that is liquid at room temperature but gels when it encounters the body or experiences a pH shift.
- **Long-acting:** Polymeric in situ forming depots have emerged as extremely promising drug delivery methods for long-acting applications.
- **Essential characteristics:** Their efficacy is related to key properties such as biocompatibility, biodegradability, and the ability to form a stable gel or solid upon injection.
- **Regulated and sustained medication release:** It facilitates controlled and prolonged medication release through its unique 'Sol-Gel transition.'
- **The medicine is administered less often in the body:** It contributes to a decrease in the frequency of drug administration in the body.
- **No side effects:** A low amount of the drug is required, and there will be no drug accumulation or side effects.
- **Residence time:** Because of the gel formation, the drug's residence period will be prolonged.
- **Reduce systemic absorption:** Reduced systemic absorption of drugs drained through the nasolacrimal duct may result in several unwanted side effects.
- **Improved patient comfort:** Comfortable for patients because it has less risk assessment and is easy touse.[20, 21]

Advantages of *In-Situ* Drug Delivery System:

- **It can be administered to unconscious patients:** Because of good permeability, and low molecular weight.
- **Minimum drug frequency:** Have minimum drug frequency and the drug is less toxic.
- **Use of natural polymers:** provide biocompatibility and biodegradation.
- **Use of synthetic polymer:** Have well-defined structures that can be altered to produce acceptable

degradability and functionality.

- **Exhibit bioadhesive:** *In-situ* gels can also be developed to be bioadhesive to facilitate drug targeting, particularly across mucus membranes, for noninvasive drug administration.[20, 21]

Disadvantages of *In-Situ* Drug Delivery System

- **It necessitates a high degree of fluid:** A high degree of fluid is necessary in in situ gel.
- **Stability problem:** Stability issues may arise because of chemical degradation.
- **Medicines with low dose requirements can be administered:** Drugs with low dose requirements can beonly administered.
- **Restriction for a few hours:** After taking the dose there should be a break of 1-2 hours can't eat or drink after the dose.
- **Lower mechanical strength:** Lower mechanical strength may result in the hydrogel prematurely dissolving or flowing away from a specified local spot.[20, 21]

Polymers Used in *In-Situ* System

Table 2: List of polymers used in in-situ gel preparation:

Polymers	Properties	Mechanism of the formation of gel	Ref. No.
Pluronic F 127	Due to the amphiphilic nature of its block units, PLF-127 behaves likea nonionic surfactant.	Temperature Change	[25, 26]
Carbomer 974 P	Increasing the concentration of carbomer increased gelling capacity as well as gelling time	pH Change	[25, 26]
Carbopol 934	extended the drug retention time, prevented drug drainage, and hence released the drug for lengthiertimes.	pH Change	[25, 26]
Gellan gum	Posaconazole transmucosal ocular administration system was developed by creating a gellan gum-based in situ gelling nanosuspension.	The process of gelation entails the creation of zones where double-helical segments converge, subsequently forming a three-dimensional network by complexation with cations and hydrogen bonding with water.	[25, 26]
Tragacanth gum	Tragacanth adds thixotropy to a solution (makes pseudoplastic solutions).	Provide thixotropy to a solution	[25, 26]
Chitosan	Chitosan improves the permeability of hydrophilic medicines, nucleic acids,	Chitosan binds to the negatively charged bacterial walldisrupting the cell	[25, 26]

	proteins, and peptides over the nasal epithelium, which is problematic due to their limited permeability.		
Xyloglucan	It act as a thickener and a stabilizing agent	Act as tether between adjacentcellulose microfibrils	[25, 26]
Poloxamer 407	The ability to generate translucent gels and thermoreversible gelation	Solidifies as a gel at ambient temperature but liquefies at 4 °C (39 °F).	[25, 26]
HPMC	Eye drop viscosity enhancer, injectable gelling agent, and polymeric matrix in films, filaments, and inserts.	minimally viscous acidic liquids that gel when the pH rises	[25, 26]
Gelrite	Its ability to hold matrine, the gelrite/alginate aqueous system can be employed as an in situ gelling vehicle for ocular drug administration.	Formation of double-helical junction zones, followed by aggregation of double-helical segments to create a three-dimensional network.	[25, 26]

Recent Advancement of *In-Situ* Gel in the Treatment of Ocular Disorder

In situ gel drug delivery technologies have been increasingly popular in recent years, and they are currently widely used in ophthalmic formulations. When subjected to environmental conditions such as pH, specific ions, and temperature, *in situ* gels undergo a sol-gel phase shift. To improve patient compliance, *in-situ*, gel formulations are created as solutions or suspensions before being turned into a gelwhen administered. Various polymers or polymeric combinations can be employed to extend/modify the release profile of *in situ* gel compositions intended for eye application. *In-situ* gel is a simple transparent polymer solution that is liquid when stored but converts into a viscoelastic gel when placed in the eyes due to the polymer's phase shift capabilities. Poloxamers are triblock copolymers made up of two copolymers, polyoxyethylene (PEO), which is normally hydrophilic, and polyoxy propylene (PPO), which is hydrophobic. The temperature-dependent feature of these compounds allows the system to transition from sol to gel at key temperatures, which is widely recognized as a promising ocular drug delivery vector since it can prolong drug release from eye tissues. Nonetheless, one downside of poloxamer 407 is its limited adhesion activity. As a result, several ophthalmic preparations have previously been enhanced by the addition of adhesion-based polymers such as hydroxypropyl methylcellulose (HPMC) and sodium hyaluronate.[27]

In situ technologies have indeed made significant advancements in recent years. leading to improved drugeffectiveness and reduced side effects. refers to the ability of the substance for the ocular surface.

1. **Prolonged drug release:** *In-situ* drug delivery system prolonged the time of the drug so that the drug sustained its therapeutic effect and reduced the dosing frequency.
2. **In situ gelling system used as vehicle:** *In-situ* gelling systems can also be utilized as vehicles for drug-loaded NSs, which improves the solubility and corneal permeability of medicines with poor ocular bioavailability.

3. **Reduce systemic side effects:** The *in-situ* drug delivery system is a smart system with good effects and fewer side effects in ocular disorders.
4. **Enhanced drug absorption:** It will enhance the absorption of the drug with low bioavailability and bad solubility in the eye.
5. **Improve patient compliance:** *In-situ* formulation may reduce the dose frequency leading to improved patient compliance. [22, 27]

***In-Situ* Gel Formation Technologies**

1. **Temperature and pH Triggered Novel *In-Situ* Gel System:** According to the pH and the temperature the *in situ* will convert from solid to gel form. A pH-triggered ophthalmic latex is a low-viscosity polymeric dispersion in water that undergoes spontaneous coagulation and gelation after installation in the conjunctival cul-de-sac. The alkali-induced thickening phenomenon of anionic latices was considered most interesting for the concept of an ophthalmic drug delivery system, because of the presence of a carbonic buffer system regulating the pH of tears [28]
2. **Ocular delivery using *in-situ* gel nanoemulsion:** There are several *in-situ* forming gels were prepared to prolong the time of the drug but poloxamer 407 with its thermoreversible gelation and surface-active characteristics was used to develop a novel dorzolamide hydrochloride in situ gel nanoemulsion (NE) delivery device for ocular usage.[29]
3. **Chitosan-Based *In-Situ* Gels for Ocular Delivery:** Chitosan is an appropriate option in ophthalmic formulations due to its biocompatibility, biodegradability, mucoadhesive nature, permeation enhancement Add Headings (Format > Paragraph styles) and they will appear in your table of contents. and corneal wound healing benefits, and antibacterial and antifungal capabilities. It has pseudoplastic and viscoelastic properties that do not disrupt the tear film.[30]
4. ***In-situ* hydrogels:** *In-situ* hydrogels are used for the *in-situ* drug delivery system and can control the rate of the drug.[31]

Recent advancement in *In-Situ* Gel for The Treatment of Ocular Disorder

Table 3: List of recent research work done in the *in-situ* gel for the treatment of ocular disorder

S.No.	Drug	Polymer Used	Uses	Ref. No.
1.	Acetazolamide	gellan gum	Diabetic retinopathy,to reduce intraocular pressure (IOP) in glaucoma patients	[32]
2.	Azithromycin	eudragit RLPO	HPMC demonstrated prolonged drug release as well as acceptable ocular tolerability.	[33]
3.	Betaxolol	Glaucoma	Glaucoma hypertension, used as a treatment paradigm for glaucoma and hypertension	[34]
4.	Ciprofloxacin	poly(dl-lactide-co-glycoside) PLGA	Ocularly used to treat conjunctivitisand corneal ulcers.	[35]
5.	Besifloxacin	Xanthan gum, Ethylcellulose, and Sodium alginate	It is used to treat infected conjunctivitis.	[36]

6.	Levofloxacin	Hydroxypropyl methylcellulose (HPMC) and sodium alginate	Bacterial conjunctivitis, to treat thebacterial infection of the eyes	[37]
7.	Moxifloxacin	HPMC	Conjunctivitis,conjunctivitis, keratitis, keratoconjunctivitis, and asa preventative measure in refractiveand cataract surgery	[38]
8.	Atropine	Sodium alginate, Carbopol, HPMC, and Polyacrylic acid	Myopia, Cycloplegia, mydriasis.	[39]
9.	Dexamethasone	Poloxamer	Cataracts, Keratitis, blepharitis, iritis,conjunctivitis, uveitis, macular edema, and post-operative eye surgery	[40]
10.	Brinzolamide	Poloxamer F 127	High IOP glaucoma, ocular hypertension	[41]

Future Prospective

The *in-situ* drug delivery system has promising prospects in the treatment of ocular disorders. targeted therapy is made possible by novel polymers with improved characteristics such as chitosan. The *in-situ* drug delivery system is the smart way to deliver the drug to the eye or to treat the ocular disorder. *In-situ* drug delivery systems provide biodegradation and biocompatibility.

Conclusion

The *in-situ* drug delivery system stands as a promising and innovative approach for addressing the challenges in treating ocular disorders. This system offers prolonged drug release, improved absorption, and reduced systemic side effects, enhancing patient compliance and comfort. Targeted ocular therapy has progressed a long way attributable to the latest developments in *in-situ* gel technologies, which use polymers like chitosan and innovative designs. The adaptability of *in-situ* gels for ocular drug administration has been proven by their incorporation of temperature and pH-triggered systems, hydrogels, and nanoemulsions. With continuous research and development, the future holds immense potential for refining and expanding the applications of *in-situ* gel formulations in ocular disorder treatments, providing more effective and patient-friendly solutions.

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