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# TRACING THE DEVELOPMENT OF IN-SITU GELS FOR OCULAR DRUG DELIVERY

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## ABSTRACT

In-situ gels have emerged as an innovative strategy in ocular drug delivery, offering a promising alternative to conventional eye drops and ointments. These systems are formulated as liquid solutions that undergo a sol-to-gel transition upon exposure to physiological stimuli, such as temperature, pH, or ionic concentration present in the ocular environment. This unique property enables prolonged retention of the drug on the ocular surface, enhancing bioavailability and therapeutic efficacy while reducing the frequency of administration. In-situ gels also minimize systemic absorption and associated side effects, improving patient compliance. Recent advancements have incorporated biodegradable polymers, stimuli-responsive materials, and nanotechnology-based carriers to further optimize drug release kinetics and targeting to specific ocular tissues. By combining ease of administration with controlled and sustained drug delivery, in-situ gel systems represent a significant advancement in the management of both anterior and posterior segment eye disorders. Their development not only addresses the limitations of traditional ophthalmic formulations but also opens new avenues for personalized and precision ocular therapy.

**Key words:** In situ-gels, Ocular delivery, Biodegradable polymers

## 1.Introduction:

Ocular drug delivery is widely recognized as one of the most challenging and scientifically demanding areas within pharmaceutical research. The eye is a highly specialized and relatively isolated organ, making it difficult to investigate drug transport and distribution using conventional experimental approaches. Direct access to human ocular tissues following drug administration is extremely limited due to ethical and practical constraints. As a result, preclinical animal models are frequently employed as substitutes to understand ocular pharmacokinetics and drug disposition. However, these models do not always accurately predict human ocular behavior, leading to incomplete or uncertain information regarding the intraocular distribution of many clinically important drugs (1).

Despite these constraints, notable advancements have been achieved in the field of ocular drug delivery. Most of these developments have focused on prolonging the residence time of drugs at the site of action to enhance therapeutic efficacy. The unique anatomical structure, physiological mechanisms, and biochemical composition of the eye serve as robust defense systems against the entry of foreign substances. These inherent protective barriers make it particularly challenging for formulators to design delivery systems capable of transporting drugs to the intended biophase or site of action in adequate concentrations while maintaining safety and effectiveness (2).

In situ gelling systems offer a painless and cost-effective strategy for ocular drug delivery while ensuring precise dosing and ease of manufacture. These systems help minimize drug loss to adjacent ocular tissues, leading to improved therapeutic outcomes, greater patient comfort, and better compliance with prescribed therapy. In situ gels are initially administered as low-viscosity liquids, making them convenient for ocular use, and subsequently undergo gelation under physiological conditions. The polymers employed in these formulations display pseudoplastic characteristics, allowing their viscosity to decrease during blinking, which facilitates uniform spreading of the drug across the ocular surface (3).

In situ gel formation in the eye is achieved by using polymers that respond to specific external stimuli and can be prepared using simple manufacturing methods. Gelation may occur due to changes in temperature, pH, or

ionic strength. Thermosensitive systems remain in liquid form below a defined lower critical solution temperature and convert into a gel when the temperature rises above this point, while reverting back to a solution at lower temperatures. pH-responsive systems utilize polymers containing acidic or basic groups that gel when exposed to physiological pH. In ion-activated systems, the presence of tear electrolytes such as sodium, calcium, and magnesium ions induces the sol-to-gel transition (4).

Ocular drug delivery is particularly challenging due to barriers such as poor corneal permeability, tear turnover, drug drainage, reflex tearing, and non-productive absorption. Topical administration remains the most common and accepted method for treating eye disorders including dry eye, conjunctivitis, and keratitis. To overcome the limitations of conventional formulations, polymer-based drug delivery systems have been widely explored for targeting both anterior and intraocular tissues. These smart polymeric systems undergo a sol-to-gel transition after administration, forming gels under physiological conditions. By increasing drug residence time in the cul-de-sac and enhancing corneal penetration, such systems significantly improve ocular bioavailability and extend therapeutic action (5).

Gel-based materials represent a versatile class of drug delivery systems with broad applications in ophthalmology. Their adaptability allows their use in various dosage forms, including gel-containing eye drops, in situ gelling formulations, therapeutic contact lenses, and intravitreal delivery systems (6).

In situ ocular gels offer several advantages in ophthalmic drug delivery, including improved local bioavailability, prolonged drug release, and increased precorneal residence time, which collectively reduce nasolacrimal drainage and dosing frequency while enhancing patient convenience and compliance. However, these systems also present certain limitations, such as their dependence on sufficient ocular fluid for effective gelation and the increased susceptibility of drugs in the sol state to chemical degradation, which may lead to stability concerns. Additionally, in situ gels are generally suitable only for low-dose drugs, as achieving uniform drug loading particularly for hydrophobic compounds can be challenging. Their relatively low mechanical strength may also result in premature dissolution or displacement from the application site, and temporary lifestyle restrictions may be required following administration (7).

## 2. Structure of the eye:

The eyes are among the most vital organs of the human body. Maintaining good eye health is essential for clear vision, which strongly influences daily activities and overall quality of life. Humans possess binocular vision, in which both eyes work together to form a single, unified visual image. Light entering the eye is focused by various optical structures to produce an image, which is then transmitted through neural pathways to the brain. The brain processes and interprets these signals, allowing us to perceive our surroundings. This entire visual process operates through a highly complex and well-coordinated system (8). The human eye is a highly complex and specialized sensory organ composed of multiple interconnected structures, as illustrated in Figure 1. It is divided into anterior and posterior segments. The front segment includes the tear film, cornea, pupil, lens, and ciliary body, while the posterior segment contains the conjunctiva, sclera, choroid, retina, vitreous body, and optic nerve. Tear production and maintenance are regulated by orbital glands and epithelial secretions. Light first enters the eye through the cornea, which plays a crucial role in vision. The cornea consists of three main layers: the epithelium, stroma, and endothelium. The epithelial layer is made up of tightly packed cells that act as a protective barrier, the stroma forms the thick, hydrated framework, and the endothelium maintains corneal clarity by regulating fluid balance (9).

The iris determines eye color and controls the amount of light reaching the retina. At its center lies the pupil, a dark circular opening whose size changes according to light intensity. The transparent lens further bends and focuses incoming light onto the retina. The ciliary body, which contains both pigmented and non-pigmented epithelial layers along with smooth muscle fibers, supports lens accommodation and fluid movement. Blood vessels within the ciliary body help link the anterior and posterior regions of the eye (10). Behind the lens lies the vitreous humor, a clear, non-vascular gel that fills the space between the lens and the retina. It is composed mainly of water, collagen fibers, hyaluronic acid, and electrolytes, providing structural support and shock absorption to the eye (11).

The conjunctiva is a thin mucous membrane that covers the sclera and lines the inner surface of the eyelids. It consists of an outer epithelial layer, a substantia propria rich in nerves and blood vessels, and a submucosal layer that anchors it to the sclera. The sclera itself is formed primarily from collagen and mucopolysaccharides, giving the eye strength and shape. Located between the sclera and retina, the choroid is a vascular layer that supplies nutrients to the outer retinal tissues. The retina is a delicate, light-sensitive layer made up of neurons and supporting glial cells. Visual signals generated in the retina are transmitted through the optic nerve to the brain, where they are interpreted as vision (12).

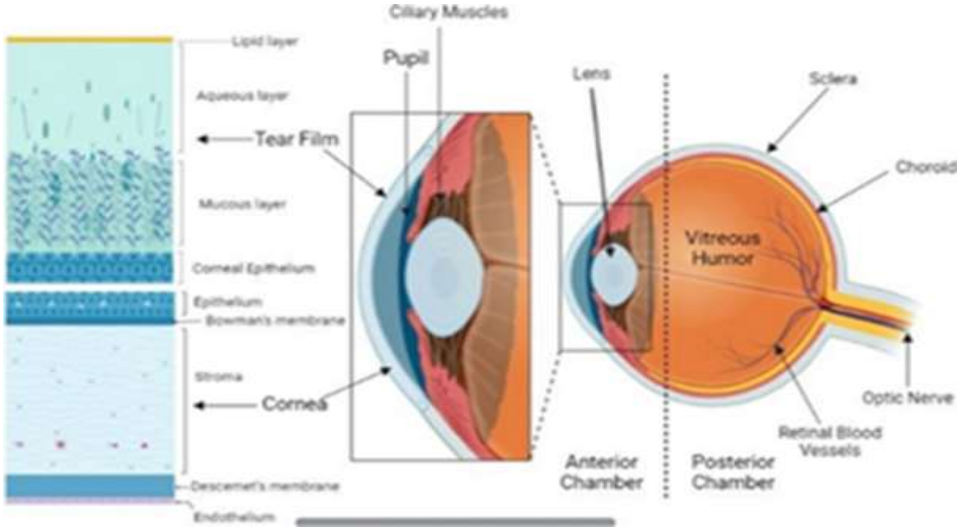



Fig.1 A schematic representation of the human eye illustrates its principal anatomical components, including the sclera, cornea, iris, ciliary body, choroid, retina, vitreous humour, and optic nerve, along with the internal and external segments of the eye. The vitreous humour is a transparent, gel-like medium that fills the posterior cavity and plays a crucial role in maintaining ocular structure and supporting retinal integrity (13).

## 3. Ocular Barriers:

### 3.1 Eyelids and Tear Film

The eyelids act as a physical shield that protects the eye from bacteria, dust, and other external agents. Blinking, which is triggered by corneal sensory nerves, helps remove foreign material but also washes away a significant portion of eye drops; around 10–20% of an instilled dose can be lost with each blink. This loss may increase when eye drops have irritating acidic or alkaline pH, as they stimulate rapid blinking (14). The tear film is another protective barrier and consists of three layers. The outer lipid layer reduces tear evaporation and maintains tear stability. The middle aqueous layer keeps the eye moist and contains protective proteins, enzymes, antibodies, and growth factors that support ocular health and prevent infection. The inner mucin layer forms a thin, viscous coating that prevents pathogens from sticking to the eye surface and helps in their removal. The normal tear volume of about 8–10 microlitres also contains enzymes that can break down or inactivate certain drugs, influencing ocular drug delivery (15).

### 3.2 The Conjunctiva

The conjunctiva acts as a barrier to drug and pathogen entry due to tight junctions between its epithelial cells. These junctions restrict the passage of large molecules, allowing mainly small to medium-sized compounds to pass. Overall, the conjunctival barrier is relatively weak, and molecules larger than about 20–40 kDa show limited penetration (16). Even when drugs cross the conjunctiva, their entry into the eye is reduced by enzymatic breakdown and rapid removal through blood and lymphatic vessels. A large portion of absorbed molecules is quickly drained into the systemic circulation rather than reaching deeper ocular tissues. Factors such as aging, high tear osmolarity, reduced mucus, and tear film instability can further affect drug penetration (17). Despite these limitations, some topically applied drugs, including atropine, latanoprost, carbonic anhydrase inhibitors, antihistamines, and insulin, can still be partially absorbed through the conjunctival route (18).

### 3.3 The Cornea

The cornea is the main barrier to drug entry into the eye, with the epithelial layer providing most of the resistance, especially for molecules larger than 500 Da. Tight junctions between epithelial cells greatly limit drug passage, making the cornea a highly resistant barrier. Drug penetration occurs mainly through transcellular, paracellular (for small hydrophilic molecules), or transporter-mediated pathways. Negatively charged molecules cross the cornea poorly due to the negative charge of epithelial cell membranes (19). Structurally, the cornea has a layered arrangement with a lipid epithelium, an aqueous stroma, and a lipid endothelium. This structure restricts both hydrophilic and lipophilic drugs, as each layer presents different permeability challenges. Bowman's and Descemet's membranes do not significantly limit drug transport. Only amphiphilic drugs or weak acids and bases at physiological pH can efficiently cross the cornea into the aqueous humor. For most drugs, enhanced corneal absorption requires special excipients or advanced formulations to overcome this barrier (20).

### 3.4 The Sclera

The sclera is a fibrous tissue made mainly of collagen and elastin, forming a porous structure that allows the slow movement of macromolecules. Its thickness varies across the eye, but its large surface area makes it an important route for ocular drug delivery. Scleral permeability decreases as molecular size increases; however, even large proteins such as antibodies can pass through the sclera at a slow rate, especially in the equatorial and posterior regions. Drug movement through the sclera is influenced not only by molecular weight but also by molecular size and shape, with compact proteins crossing more easily than linear molecules. With aging, scleral thickness remains mostly unchanged, but permeability decreases due to collagen crosslinking and reduced hydration, which limit the movement of large molecules (21).

Physical treatments can modify scleral permeability. Increased tissue hydration and surgical thinning enhance macromolecule transport, whereas crosslinking reduces permeability near the treated area. Cryotherapy and laser treatments show little effect. Physiologically, proteins that cross the sclera are rapidly cleared through blood vessels and lymphatic pathways, limiting their retention within the eye (22).

### 3.5 The Choroid

The choroid is a vascular layer of the eye made up of a dense network of blood vessels, including arteries, veins, and capillaries. It also contains various cell types such as melanocytes, fibroblasts, immune cells, and smooth muscle cells, along with rich nerve supply. The main function of the choroid is to supply oxygen and nutrients to the retina. It also forms part of the outer blood–retinal barrier, protecting the retina from harmful substances in the bloodstream. Blood flow in the choroid is very high compared to most other tissues. The capillaries of the choroid have specialized endothelial cells with tight junctions and small openings called fenestrations. These fenestrations allow controlled movement of substances while limiting the passage of large molecules. Although the openings appear large, diaphragm-like structures reduce their effective size and prevent unwanted proteins from passing through. The movement of substances is further regulated by surface charges on the endothelial cells (23).

### 3.6 Retinal Pigment Epithelium (RPE)

The retinal pigment epithelium (RPE) is an important part of the outer blood–retinal barrier because its cells are connected by tight junctions. Along with nearby structures, it helps control the movement of ions, nutrients, and fluids between the retina and the blood supply.The RPE maintains ionic balance during vision and actively removes excess fluid from the subretinal space through ion transporters and water channels. This function is essential for keeping the retina healthy and properly attached. The RPE also controls fluid levels by actively moving water out of the subretinal space toward the choroid. This process is supported by water channels and ion gradients, particularly chloride and bicarbonate transport, which together help maintain retinal attachment and normal visual function (24).

### 3.7 The Vitreous

The vitreous humor is a gel-like substance that is made up mostly of water, with small amounts of proteins, salts, and other small molecules. Its main structural components are collagen and hyaluronic acid, along with other minor polysaccharides. Together, these components form a three-dimensional network that can slow down the movement of large molecules (25). Large and positively charged substances tend to move more slowly through the vitreous. While diffusion is limited, eye movements create fluid flow that helps transport drugs within the vitreous and contributes significantly to their movement. Drug elimination occurs mainly through the front of the eye, and larger molecules are more likely to be cleared by this anterior route rather than reaching the retina (26).

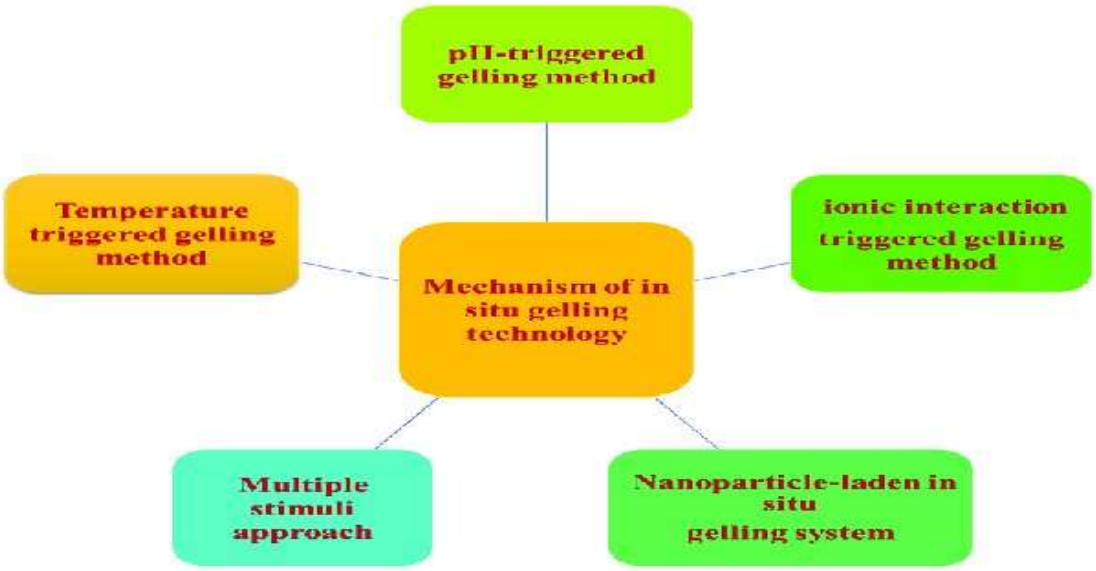
### 3.8 Inner Blood–Retinal Barrier

The inner blood–retinal barrier is formed by tight junctions between retinal capillary endothelial cells, along with supporting cells such as pericytes, astrocytes, and Müller glial cell end-feet. These components work together to protect the retina and regulate the movement of substances from the blood. The tight junctions in retinal vessels are very strong and create high resistance, similar to the blood–brain barrier. They contain specific junctional proteins that prevent free passage of proteins under normal conditions. Retinal capillaries do not have openings, so large molecules cannot easily pass through. Endothelial permeability can increase under certain conditions, especially in the presence of vascular endothelial growth factor (VEGF). VEGF mainly enhances transport across cells and can also disturb tight junction structure by affecting the cell cytoskeleton, leading to increased leakage (27).

## 4. Mechanism of in situ gelling technology:

In situ gel technology is a modern drug delivery method where a liquid formulation turns into a gel after coming into contact with the body. In eye treatments, it is applied as drops that gel inside the eye, allowing the medication to be released slowly and steadily. This increases the time the drug stays on the eye surface and helps improve its effectiveness. These gels are made from biocompatible ingredients that can safely form a gel inside the body. Compared to regular eye drops, this approach can reduce side effects, lower dosing frequency, and make treatment more convenient for patients. It is considered a promising option for improving the management of various eye diseases (28) In situ gel systems tend to cause fewer adverse effects, require smaller amounts of medication, and are generally easier for patients to use compared to traditional delivery methods. Because of these advantages, ongoing research in ophthalmic applications suggests that this approach could significantly improve the way eye diseases are treated (29).

In situ gel systems undergo a sol-to-gel transition, where a liquid “sol” made from organic or inorganic precursors gradually forms a gel through reactions such as hydrolysis, condensation, or polymerization. This change can be triggered by different physiological conditions (30). Some systems respond to temperature remaining liquid at room temperature and forming a gel once they reach the eye’s lower critical solution temperature. Others rely on pH shifts, using polymers that contain acidic or basic groups which rearrange when the environmental pH changes. There are also ion-activated gels that transform when ions in tear fluid interact with the polymer network. In addition to these, light-triggered reactions and enzymatic crosslinking can also initiate gel formation. With multiple activation mechanisms available, in situ gels provide a flexible and efficient platform for controlled drug delivery inside the body (31).




Different mechanism of in situ gel (29).

### 4.1 pH-triggered in situ gelling systems

pH-responsive in situ gels form an important class of sol–gel drug delivery platforms, especially for use in the eye. In these systems, the surrounding pH acts as the key trigger. They typically employ polyelectrolytes, polymers made up of repeating acidic or basic groups that change their structure depending on environmental pH. Formulations may remain fluid in acidic conditions but begin to swell or solidify as the pH increases. For example, at a lower pH (around 4.4) the material behaves like a normal liquid, while at physiological tear pH (about 7.4) it converts into a gel. Commonly used materials for this purpose include anionic polymers such as carbopol, carbomer, and related derivatives (31).

### 4.2 Temperature-triggered in situ gelling systems

In temperature-responsive systems, certain polymers remain liquid at lower temperatures but turn into a gel once they exceed a specific threshold known as the LCST (lower critical solution temperature). For ocular use, this temperature is close to body temperature, so the formulation can be applied as drops and will gel on the eye without external heating. Poloxamers are commonly used for this purpose because they form stable gels that hold drugs in place. Below the LCST the solution stays clear and fluid, but once the temperature rises above it, the polymer chains contract and begin to aggregate, making the solution cloudy and eventually separating into gel and liquid phases. This behavior makes such systems useful for prolonged drug delivery and better retention in the eye (32).

### 4.3 Ionic-interaction triggered systems

In this type of system, certain anionic polymers turn from liquid to gel when they come into contact with ions present in tear fluid. Divalent and monovalent cations (such as calcium, magnesium, and sodium) promote crosslinking between polymer chains, which increases viscosity and causes gel formation. As tear fluid mixes with the formulation, the ion concentration rises, strengthening the gel network. This slows down drainage from the eye, improves drug residence time, and enhances overall drug absorption (29).

### 4.4 Multiple responsive-based systems

Using combinations of polymers that respond to more than one trigger has led to better drug performance and improved patient comfort. Modern ocular in situ gels often rely on multiple stimuli, meaning they can solidify in response to changes in pH, temperature, ion levels, or even enzymes. This allows tighter control over how and when the drug is released.

Different dual and multi-responsive designs exist, such as:

- Temperature + pH gels, which transition at body temperature and tear pH, improving gel formation and drug retention.
- pH + enzyme gels, which react both to pH shifts and enzymes in tear fluid, allowing more biologically adaptive gelation.
- Ion + temperature gels, which solidify in response to ion concentration and heat from the eye.
- Triple-responsive gels, combining pH, temperature, and ion triggers for highly customizable release profiles.
- Sequential gels, which partially gel with pH changes and fully gel at higher temperatures, offering controlled, stepwise drug release.

These multi-trigger systems can enhance bioavailability, prolong drug residence time, and improve patient adherence. However, designing them requires careful coordination of stimuli and precise control over gelation and release behavior, which remains a challenge for developers (30).

### 4.5 Nanoparticle-laden systems

Nanoparticles have gained significant attention as drug carriers because they can transport therapeutic agents directly to specific tissues, improving treatment performance and minimizing unwanted effects. These particles are extremely small, typically just a few to a few hundred nanometers and can either dissolve the drug within their structure or encapsulate it inside a polymer matrix. This makes them particularly useful in ophthalmic delivery, where maintaining drug stability and penetration is challenging. Nanoparticles can be produced using several methods. A common approach involves dissolving a polymer in an organic solvent and then dispersing the drug into this solution to form a water-in-oil emulsion, which is later emulsified into an aqueous phase. Although effective, the use of organic solvents requires caution because residual solvent may be harmful if not properly removed, and regulatory limits exist for their use. Other solvent-reduced techniques, such as salting-out or supercritical fluid processing, are also used to prepare polymeric nanoparticles (29).

Drugs may be loaded into nanoparticles through two main strategies: during particle formation (which typically yields higher loading efficiency) or by mixing pre-formed nanoparticles with a drug solution. Once formulated, the drug-loaded nanoparticles are incorporated into an in situ gel matrix. This combination allows the gel to provide prolonged residence time on the eye surface while nanoparticles help improve drug absorption and penetration into ocular tissues. Overall, pairing nanoparticles with in situ gelling systems creates an advanced platform for sustained and targeted ocular therapy, often utilizing lipid-based carriers, nano-suspensions, and other nanoscale delivery tools to boost bioavailability and therapeutic outcomes (33).

## 5. Polymers used in in-situ gelling technology:

Ocular in situ gels represent a major advancement in eye drug delivery by combining the ease of traditional liquid drops with prolonged precorneal residence and sustained drug release. These systems are initially instilled as low-viscosity solutions and undergo a stimuli-triggered sol-to-gel transition when exposed to physiological conditions such as pH, temperature, or ions present in tear fluid. This phase conversion enhances contact time on the ocular surface, reduces nasolacrimal drainage, and can improve therapeutic bioavailability compared to conventional eye drops, which often suffer from poor retention and rapid elimination. The mechanisms behind this transition are based on structural changes in the polymer network triggered by environmental cues. The design of these polymers must balance biocompatibility, gelation responsiveness, mechanical stability, and patient comfort to be effective for clinical use (34).

### 5.1 Polymers in pH-Triggered Systems

a) Carbopol

Carbopol is a polyacrylic acid–based polymer that turns from a liquid dispersion into a gel once the environmental pH rises above its pKa, which is close to 5.5. At acidic pH values, the carboxyl groups on the polymer chain remain protonated, causing the structure to stay in a compact form. When the pH increases,

these groups ionize and repel one another, leading to expansion of the polymer network and gradual drug diffusion. In ophthalmic formulations, Carbopol is mainly used to prolong precorneal drug residence. Although it exhibits mucoadhesion through interactions such as hydrogen bonding, hydrophobic interactions, interpenetration, and charge effects with mucin, its adhesive ability is considered weaker compared to certain other bioadhesive polymers (35). One drawback of Carbopol is its acidic character, which can irritate ocular tissues when used at higher concentrations. To overcome this limitation, researchers have designed blends combining Carbopol with more neutral polymers like HPMC or chitosan, which improves comfort while retaining gelation behavior (36).

### 5.2 Polymers in Temperature-Triggered Systems

a) Poloxamers

Poloxamers (also known as Pluronics) are triblock copolymers composed of a hydrophobic polypropylene oxide core and two hydrophilic polyethylene oxide segments. These polymers are liquid at lower temperatures, but when their concentration reaches around 15% (w/w) and the temperature increases to physiological levels, they undergo gel formation due to micellar aggregation and changes in polymer packing. Several grades exist as L, P, and F representing liquids, pastes, and flakes respectively. Commonly used pharmaceutical grades include Poloxamer 188, 237, 338, and especially 407. Poloxamer 407 (F-127) contains roughly 70% ethylene oxide, making it highly water-soluble, non-toxic, and fluid at cold temperatures. As the temperature approaches body levels, hydrogen bonding patterns change and the polymer forms a semi-solid gel. This thermoreversible feature makes F-127 valuable for ocular drug delivery (37).

b) Xyloglucan

Xyloglucan, often obtained from tamarind seed polysaccharide, becomes thermoresponsive after partial enzymatic removal of its galactose side chains using β-galactosidase. The temperature at which it converts from sol to gel depends largely on how much galactose has been cleaved. When more than one-third of the galactose units are removed, the polymer forms a gel in dilute aqueous systems. Due to its water solubility and reversible gelation behavior, xyloglucan has been considered suitable for delivering medications through oral, ocular, rectal, and intraperitoneal routes (38).

c) Cellulose Derivatives

Cellulose-based polymers such as methylcellulose and hydroxypropyl methylcellulose (HPMC) have been widely incorporated into ophthalmic preparations. These derivatives remain liquid until heated to a critical gelation temperature, which varies between types (39). For instance, methylcellulose typically gels around 45–50 °C, whereas HPMC gels at significantly higher temperatures, approximately 70–90 °C. Formulation tweaks, including the addition of salts like sodium chloride, can lower the gelation temperature, making these systems more practical for biomedical use (40).

d) Chitosan

Chitosan is a naturally occurring polysaccharide produced by deacetylating chitin from shellfish sources. It is valued for being biocompatible, biodegradable, and minimally immunogenic. Current research has explored chitosan combined with polyols such as glycerol, sorbitol, and ethylene glycol to develop thermosensitive gels. A modified form, known as thiolated chitosan (TCS), is synthesized by attaching thiol groups to amino sites on the polymer backbone. Thiolated chitosan demonstrates strong mucoadhesive capabilities due to its ability to form disulfide bonds with mucosal glycoproteins, enabling prolonged drug retention. Gelation occurs through oxidation-induced disulfide linkages within or between chains at physiological pH (41).

## 6. Role of in situ gelling approach to deliver the drug to inner compartments of the eye:

Efficient delivery of pharmacological agents to the posterior and inner ocular compartments remains a persistent challenge due to the highly restrictive anatomical and physiological barriers of the eye. Among these barriers, tight junction complexes within the corneal and conjunctival epithelia significantly limit paracellular drug transport, thereby preventing adequate therapeutic concentrations from reaching intraocular targets such as the aqueous humour, vitreous cavity, or retina. Consequently, conventional topical formulations often

exhibit poor bioavailability and require frequent administration, increasing patient burden and diminishing therapeutic efficacy (42).

In situ gelling systems have emerged as a promising platform to mitigate these limitations. These systems are administered as low-viscosity liquids and undergo rapid gelation upon exposure to ocular stimuli (e.g., temperature, ionic strength, or pH), thereby enabling the formation of a viscoelastic gel matrix on the ocular surface. The resulting depot prolongs precorneal residence time by resisting natural clearance mechanisms such as blinking and tear turnover, thus sustaining drug exposure at the barrier interface. The mucoadhesive behaviour associated with many in situ gelling polymers enhances intimate contact with the corneal and conjunctival epithelia, which is critical for improving transcorneal and transconjunctival permeation. Additionally, the three-dimensional gel network enables controlled and diffusion-modulated drug release, reducing burst clearance and supporting a more consistent therapeutic profile over extended durations. These characteristics collectively facilitate improved drug flux across tight junctions through prolonged concentration gradients and extended interaction with epithelial membranes (43).

From a formulation engineering perspective, in situ gels can be further optimized by incorporating penetration enhancers, membrane-modifying agents, or bioresponsive polymers. Such components can transiently alter tight junction integrity or enhance lipid bilayer fluidity, thereby augmenting paracellular or transcellular transport without inducing irreversible tissue damage. Tailoring polymer composition, viscosity profiles, and gelation kinetics is also essential for achieving desirable rheological properties, ocular tolerability, and patient compliance (44).

Topical administration of in situ gelling systems confers an additional clinical advantage by minimizing systemic absorption via the nasolacrimal pathway, thereby reducing the incidence of off-target systemic effects. This localized delivery approach is particularly valuable for posterior segment disorders, where systemic or intravitreal routes often pose greater risks or procedural complexity (45).

Collectively, the sustained residence time, controlled drug release, mucoadhesive interactions, and tunable permeability characteristics of in situ gelling platforms highlight their relevance as an emerging strategy for overcoming ocular epithelial barriers. These systems demonstrate substantial potential to enhance bioavailability and therapeutic outcomes in diseases involving deeper ocular tissues, positioning them as a notable advancement within the broader field of ophthalmic drug delivery research (46).

## 7. Evaluation of Ocular In-Situ Gel:

Ocular in situ gels are evaluated using several parameters to confirm that the developed formulation complies with safety and quality requirements for ocular drug delivery systems.

### 7.1 Visual appearance and clarity

The prepared in situ gel formulation is visually inspected under fluorescent light against both white and black backgrounds. This examination helps to identify any visible particulate matter, turbidity, or lack of clarity in the formulation (47).

### 7.2 pH measurement

The pH of ocular formulations plays a critical role in maintaining drug stability, solubility, and patient comfort. The formulation pH should be compatible with ocular tissues to prevent irritation while ensuring chemical stability. A calibrated digital pH meter is used to measure the pH of the formulation (48).

### 7.3 Gelling capacity

The gelling ability of the formulation is assessed by adding a single drop of the formulation into a vial containing 2.0 mL of freshly prepared simulated tear fluid. The time required for sol-to-gel transition is recorded to evaluate the formulation's gelling performance (49).

### 7.4 Isotonicity

Isotonicity is an essential requirement for ophthalmic preparations, as deviations can lead to ocular discomfort or tissue damage. It refers to the osmotic pressure exerted by dissolved salts in the formulation. The osmotic pressure of ophthalmic products should typically fall within the range of 290–310 mOsmol/kg. This parameter is measured using a tonicity osmometer (50).

### 7.5 In vitro drug release study

In vitro drug release studies are carried out using Franz diffusion cells. Freshly prepared artificial tear fluid (ATF) is placed in the receptor compartment, while a dialysis membrane separates the donor and receptor chambers. To simulate physiological conditions, the system is maintained at 37 ± 0.5 °C using a thermostatically controlled magnetic stirrer operating at 20 rpm. One milliliter of the formulation is introduced into the donor compartment. At predetermined time intervals, 0.5 mL samples are withdrawn and replaced with an equal volume of fresh ATF. The collected samples are analyzed using either UV spectrophotometry or high-performance liquid chromatography (HPLC) (51).

### 7.6 Rheological studies

The viscosity of the in-situ gel formulation is measured using a Brookfield viscometer. Viscosity measurements are taken both before and after gel formation by gradually increasing the rotational speed from 0.5 to 100 rpm. These studies help in understanding the flow behavior of the formulation under different shear conditions (52).

### 7.7 Texture analysis

Texture profile analysis is performed to evaluate mechanical properties such as cohesiveness, firmness, and consistency of the in-situ gel. Parameters including hardness, compressibility, and adhesiveness are measured using a texture analyzer. These properties are associated with practical performance attributes such as ease of administration, spreadability over the corneal surface, retention on the ocular mucosa, and ease of removal from the container (53).

### 7.8 Transcorneal permeability study

Transcorneal drug permeation is evaluated using excised goat corneas. Fresh goat eyes are obtained from a local slaughterhouse and transported to the laboratory in normal saline maintained at 4 °C. The cornea, along with 2–4 mm of surrounding scleral tissue, is carefully excised and washed with saline. The isolated cornea is mounted between the donor and receptor compartments of a Franz diffusion cell, with the epithelial surface facing the donor side. Fresh artificial tear fluid is added to the receptor compartment, and the system is maintained at 37 ± 0.5 °C with constant stirring at 20 rpm. One milliliter of the formulation is placed in the donor compartment. Samples of 0.5 mL are withdrawn at regular intervals over a period of one to five hours and replaced with fresh ATF. The samples are suitably diluted and analyzed using UV spectrophotometry or HPLC (54).

### 7.9 Ocular irritation study

The Draize test is used to evaluate the ocular irritation potential of ophthalmic formulations before clinical use. In this method, 100 µL of the test formulation is instilled into the lower conjunctival sac of the eye. Ocular reactions are observed at fixed time intervals of 1, 24, 48, and 72 hours, as well as after one week, to assess any signs of irritation. Male albino rabbits weighing between 1.5 and 2.0 kg are used for the study. The sterile formulation is administered twice daily for seven days. A cross-over design is followed with a three-day washout period using normal saline to reduce variability between treatments (55).

### 7.10 Histological study

Histological evaluation is performed to study the effect of the in-situ gel on corneal tissue and to assess its irritation potential. Corneas obtained from freshly slaughtered goats are incubated with the formulation for five hours at 37 °C. A 0.1% (w/w) sodium dodecyl sulfate (SDS) solution prepared in phosphate buffer saline (PBS) is used as a positive control. After incubation, the corneas are rinsed with PBS and immediately fixed in 8% formalin. The tissues are then dehydrated using graded alcohol concentrations, embedded in molten paraffin, and allowed to solidify. Thin cross-sections are cut, stained with hematoxylin and eosin, and examined under a microscope to detect any structural alterations in the corneal tissue (55).

### 7.11 Hen's Egg Test–Chorioallantoic Membrane (HET-CAM)

The Hen's Egg Test–Chorioallantoic Membrane (HET-CAM) assay is performed to evaluate the irritation potential of ophthalmic formulations. Fertilized hen eggs are incubated for ten days at a temperature of 37 °C with approximately 70% relative humidity, while being automatically rotated once every hour. After the incubation period, a small section of the eggshell is carefully removed. A drop of water is added to the air sac membrane to prevent damage to the underlying capillaries during membrane removal. The chorioallantoic membrane (CAM) is then gently exposed.

A volume of 0.1 mL or 0.1 g of the test formulation is applied directly onto the CAM and allowed to remain in contact for 30 seconds, after which it is rinsed with normal saline. At the same time, normal saline is applied as a negative control and a 1% sodium dodecyl sulfate (SDS) solution is used as a positive control. Each CAM is examined under a microscope after five minutes to observe signs of haemorrhage, vascular lysis, or coagulation. An irritation score (IS) is calculated based on the time of appearance of these reactions using a standard formula. Based on the obtained score, irritation is classified as no reaction (0), slight reaction (1), moderate reaction (2), or severe reaction (3) (56).

### 7.12 In Vivo Scintigraphy Studies

Gamma scintigraphy is a well-recognized in vivo technique used to assess the ocular residence time of ophthalmic formulations. Although rabbits are commonly employed as experimental models for ocular studies, human volunteers are preferred for scintigraphic evaluation due to notable physiological differences between rabbits and humans, particularly in blinking frequency. This technique provides reliable information regarding formulation retention and distribution in the ocular region (57).

### 7.13 Accelerated Stability Study

Accelerated stability studies are conducted in accordance with International Council for Harmonisation (ICH) guidelines to evaluate the physical stability of in situ gel formulations under stressed storage conditions. The formulation is stored at different temperature and humidity settings, namely 25 ± 1 °C with 60% relative humidity, 30 ± 1 °C with 65% relative humidity, and 40 ± 2 °C with 75 ± 5% relative humidity. Samples are withdrawn at predetermined intervals of 0, 30, 60, and 90 days and analyzed for changes in active drug content and overall formulation stability (58).

### 7.14 Sterility Testing

Sterility testing is a critical quality control parameter for ophthalmic preparations to ensure patient safety. The test is carried out in accordance with the procedures described in the Indian Pharmacopoeia. The direct inoculation method is employed, wherein 2 mL of the test sample is aseptically withdrawn from the container using a sterile syringe or pipette. The sample is then separately transferred into fluid thioglycolate medium (20 mL) and soyabean–casein digest medium (20 mL). The inoculated media are gently mixed and incubated for a minimum period of 14 days. Fluid thioglycolate medium is incubated at 30–35 °C, while soyabean–casein digest medium is maintained at 20–25 °C. The media are regularly observed for any signs of microbial growth, indicating contamination (59).

## 8. Recent progress in the field of ocular in-situ gels:

### 8.1 pH-Triggered In-Situ Gelling Systems

pH-responsive in situ gels have been widely investigated for ocular drug delivery due to their ability to undergo sol–gel transition upon exposure to tear fluid pH. Wu et al., developed a pH-responsive in situ ocular gel for baicalin using Carbopol 974P in combination with HPMC E4M as a viscosity modifier. The formulation was characterized through rheological studies and advanced in vitro and in vivo techniques, including confocal microscopy, gamma scintigraphy, and microdialysis. Under physiological conditions, the gel exhibited a marked increase in gel strength and sustained baicalin release for up to eight hours. Pharmacokinetic evaluation showed significantly improved ocular exposure, with AUC and Cmax values approximately 6.1-fold and 3.6-fold higher than those of the reference solution (60).

In a more recent study, Alsaidan et al., designed ciprofloxacin-loaded bilosome-based in situ gels to minimize precorneal drug loss caused by blinking and nasolacrimal drainage. Bilosomes composed of cholesterol, Span 60, and sodium deoxycholate were incorporated into a gel matrix containing Carbopol 934P and HPMC K100M. The optimized formulation exhibited efficient gel formation, appropriate viscosity, prolonged drug release, enhanced corneal permeability, and superior antimicrobial performance when compared with standard ciprofloxacin gels (61).

Pang et al., reported that ocular in situ gels can significantly limit systemic drug exposure, thereby lowering the risk of systemic side effects. In their study, a brimonidine tartrate in situ gel formulated with Carbopol 974P and HPMC E4M was compared with a conventional eye drop. The gel showed superior intraocular pressure–lowering efficacy in rabbit eyes. Importantly, pharmacokinetic analysis revealed a lower plasma AUC for the in-situ gel, indicating reduced systemic absorption and improved ocular targeting (62).

### 8.2 Temperature-Triggered In-Situ Gelling Systems

Thermosensitive in situ gels undergo gelation in response to ocular surface temperature and have gained attention for prolonged drug delivery. Li et al., developed a thermosensitive in situ gelling system for brinzolamide based on a drug–resin complex, employing Poloxamer F127 in combination with Carbopol 934P. The optimized formulation underwent sol–gel transition close to ocular surface temperature and provided diffusion-controlled drug release for up to eight hours. In vivo findings indicated improved ocular retention of brinzolamide compared with marketed formulations (63).

Targeting posterior segment disorders, Oswald et al., developed an injectable drug delivery system by encapsulating anti-VEGF agents (ranibizumab or aflibercept) within poly (lactic-co-glycolic acid) microspheres, which were subsequently dispersed in a thermo-responsive poly(N-isopropylacrylamide) hydrogel. The therapeutic performance was assessed in a laser-induced choroidal neovascularization rat model using fluorescein angiography, along with monitoring of intraocular pressure and electroretinographic responses over a 12-week period. Animals treated with the anti-VEGF-loaded system consistently showed significantly reduced CNV lesion areas compared with untreated controls, highlighting the potential of this delivery platform for sustained treatment of posterior segment ocular disorders (64).

Iohara et al., recently reported a thermoresponsive ocular gel based on hydrophobically modified hydroxypropyl methylcellulose (HM-HPMC), in which a small quantity of α-cyclodextrin was incorporated to alter its gelation behavior. The modified HM-HPMC/α-cyclodextrin system showed a reversible sol–gel transition within the physiological temperature range, in contrast to the original HM-HPMC formulation. Upon ocular administration, the gel formed rapidly on the eye surface and significantly enhanced the ocular absorption of diclofenac sodium (65).

### 8.3 Ion-Activated In-Situ Gelling Systems

Several ion-activated ocular in situ gelling systems have been described in the literature. Rupenthal et al., developed ion-responsive formulations using gellan gum, xanthan gum, and carrageenan, and evaluated their in vivo drug release, precorneal residence, and ocular tolerance. The formulations were found to be non-

irritating and produced a marked increase in drug exposure, with the miotic response and AUC of pilocarpine enhanced by approximately 2.5-fold compared with an aqueous solution (66).

Similarly, Zhu et al., prepared ion-activated ketotifen eye gels employing deacetylated gellan gum as a natural polymer. Their findings showed that this polymer effectively prolonged ocular residence time, resulting in sustained and prolonged pharmacological activity when compared with conventional eye drops administered at the same dose (67).

In another study, Kesarla et al., designed a nanoparticle-loaded ocular in situ gel using gellan gum as an ion-sensitive gelling agent. The formulation underwent immediate gelation upon contact with tear fluid and remained at the ocular surface for an extended duration. Stability studies confirmed formulation robustness, while confocal microscopy demonstrated efficient corneal penetration of the drug-loaded nanoparticles, supporting reduced dosing frequency and improved therapeutic performance (68).

### 8.4 Multiple-Stimuli Responsive In-Situ Gels

To further optimize performance, multi-stimuli responsive systems have been developed. Khan et al., formulated a sparfloxacin-loaded ocular in situ gel using methylcellulose and sodium alginate that responded to both pH and ionic triggers. The formulation remained liquid under acidic conditions but rapidly gelled at physiological pH, sustaining drug release for up to 24 hours. Ex vivo studies using goat cornea confirmed significantly enhanced drug permeation compared with standard eye drops (69).

Similarly, Yu et al., developed a dual-responsive nepafenac in situ gel using poloxamer and carboxymethyl chitosan. The formulation demonstrated pH- and temperature-dependent gelation, sustained drug release, and negligible cytotoxicity to corneal epithelial cells. Comparable dual-triggered systems using sodium alginate and methylcellulose also showed rapid gelation and extended sparfloxacin release over 24 hours (70).

### 8.5 Nanoparticle Laden In-Situ Gelling Systems

Nanotechnology-integrated in situ gels represent a major advancement in ocular drug delivery. Liu et al., formulated a curcumin-loaded ocular nanogel by combining cationic nanostructured lipid carriers with a thermosensitive gelling polymer. The system was evaluated for drug release, corneal permeation, ocular tolerance, and precorneal retention, along with aqueous humor pharmacokinetics using a microdialysis approach. The nanogel exhibited markedly enhanced ocular bioavailability, with the AUC in the aqueous humor being approximately 9.2-fold higher than that of a curcumin solution (71).

Further supporting this approach, Ahmed et al., recently developed ketoconazole-loaded poly(lactide-co-glycolide) nanoparticles and incorporated them into an in situ forming ocular gel. The nanoparticle-based gel showed prolonged and enhanced drug release compared with formulations containing the free drug. Moreover, the in-situ gel system exhibited superior antifungal efficacy, while the optimized alginate–chitosan gel demonstrated increased ketoconazole permeation across epithelial cell models (72).

## 9. Clinical Applications and Representative Case Studies of Ocular In-Situ Gel Systems:

Over the past decade, ophthalmic in-situ gel systems have progressed well beyond experimental formulations and are now represented by marketed products as well as advanced clinical investigations. Their unique ability to transform from a low-viscosity solution into a gel after ocular administration allows prolonged residence time on the eye surface, sustained drug release, and improved ocular bioavailability. These characteristics make in-situ gels particularly valuable for the management of both anterior and posterior segment ocular disorders (73).

### 9.1 Application in Glaucoma Therapy

Glaucoma remains one of the most widely explored therapeutic areas for ophthalmic in-situ gel formulations due to the chronic nature of the disease and the need for long-term patient adherence. One of the earliest and most successful commercial examples is timolol maleate in-situ gel (Timoptic-XE®), which demonstrated extended intraocular pressure (IOP) control with once-daily administration compared to conventional eye drops. Clinical investigations have also shown that brimonidine-loaded gels formulated using poloxamer and

carbopol combinations produce a sustained reduction in IOP while minimizing systemic absorption and local adverse effects. Additionally, nanoparticle-incorporated in-situ gels containing dorzolamide have been reported to enhance patient compliance by reducing dosing frequency and maintaining therapeutic drug levels for extended periods (74).

### 9.2 Post-Operative Care and Ocular Infection Management

Sustained drug delivery is particularly important in post-surgical care and ocular infections, where frequent dosing of eye drops often compromises patient compliance. Clinical evaluations of ciprofloxacin-loaded gellan gum in-situ gels have demonstrated effective antimicrobial activity along with improved ocular comfort. Furthermore, dual-drug in-situ gel systems containing ofloxacin and dexamethasone have been studied for use following cataract surgery. These formulations were associated with faster resolution of inflammation and a reduced risk of infection recurrence. The use of combination in-situ gels also helps minimize the burden of multiple eye drop administrations, a major challenge in post-operative ophthalmic therapy (75).

### 9.3 Management of Dry Eye Syndrome

Dry eye syndrome (DES), a multifactorial and highly prevalent ocular disorder, has emerged as another promising indication for in-situ gel-based drug delivery systems. Small-scale clinical studies have reported that cyclosporine A-loaded in-situ gels improve tear film stability and enhance patient comfort compared to conventional formulations (76). Similarly, thermo-responsive gels based on carboxymethylcellulose have been shown to provide prolonged ocular surface hydration, reducing the need for frequent instillation associated with artificial tears. These systems serve a dual function by acting as lubricating agents while simultaneously enabling controlled drug release, thereby addressing both the symptoms and underlying inflammatory components of DES (77).

### 9.4 Emerging Use in Posterior Segment Disorders

Although most clinically available in-situ gel products are intended for anterior segment diseases, ongoing research is increasingly focused on their potential application in posterior segment disorders such as retinitis and age-related macular degeneration. Triamcinolone acetonide-loaded nano-enabled in-situ gels have shown encouraging results in preclinical models by providing sustained drug delivery to posterior ocular tissues (78). Despite these advances, clinical translation remains challenging due to physiological barriers that limit drug penetration. To overcome these limitations, hybrid systems combining nanocarriers with in-situ gel matrices are under development, particularly for intravitreal administration (79).

### Commercially Available and Investigational Products:

Several ophthalmic in-situ gel formulations have successfully reached the market or advanced stages of clinical evaluation:

**Timoptic-XE (Merck):** A gellan gum-based, ion-activated timolol maleate gel approved by the FDA and widely prescribed for glaucoma management.

**Nyxol (Ocubrex gel):** A pilocarpine hydrochloride in-situ gel evaluated in Phase III clinical trials for presbyopia, demonstrating effective pupil modulation with minimal adverse effects.

**Cyclosporine in-situ gels:** Currently under clinical investigation for keratoconjunctivitis sicca, with evidence of improved ocular surface integrity and tear film stability.

**Fluoroquinolone-based gels (levofloxacin and moxifloxacin):** Experimental studies have shown enhanced antimicrobial retention and prolonged therapeutic action compared to standard eye drops (80,81).

**Table.1** Commercial and Investigational Ocular In-Situ Gel Formulations

| **Product Name** | **Active Drug** | **Polymer / Gelation Mechanism** | **Therapeutic Indication** | **Development Status** |
|---|---|---|---|---|
| Timoptic-XE | Timolol maleate | Gellan gum (ion-activated) | Glaucoma | Marketed |
| Azopt Gel | Brinzolamide | pH-responsive gel | Ocular hypertension | Marketed |
| Pilopine HS Gel | Pilocarpine | Carbopol-based gel | Glaucoma | Marketed |
| Travoprost ISG | Travoprost | Thermo-responsive gel | Glaucoma | Clinical trials |
| Dexamethasone ISG | Dexamethasone | Nano-enabled in-situ gel | Post-operative inflammation | Experimental |

Some of the current marketed formulation of ocular in-situ gels (82)

## 10. Conclusion and Summary:

Delivering drugs to the eye has always been challenging due to natural protective mechanisms such as blinking, tear production, and rapid drainage through the nasolacrimal duct. Conventional eye drops often fail to maintain sufficient drug concentration at the site of action, leading to frequent dosing and reduced therapeutic effectiveness (83). To overcome these limitations, in situ gel systems have emerged as an innovative and efficient approach in ocular drug delivery.

An in-situ gel is a liquid formulation that undergoes a phase transition into a gel after administration into the eye. This transformation occurs in response to specific physiological triggers such as changes in temperature, pH, or ionic concentration in the tear fluid. Because the formulation is instilled as a liquid, it is easy to apply like traditional eye drops (84). Once it comes into contact with the ocular environment, it forms a semi-solid gel that remains in the eye for a longer duration. The key advantage of this system lies in its ability to enhance drug residence time on the corneal surface. By forming a gel matrix, the drug is released gradually and in a controlled manner, reducing the need for repeated administration. This sustained release improves bioavailability and minimizes drug wastage caused by tear turnover. As a result, patients experience better therapeutic outcomes and improved compliance (85).

Different mechanisms are used to trigger gel formation. Thermosensitive systems rely on temperature differences between room temperature and ocular surface temperature. pH sensitive systems respond to the slight increase in pH when the formulation mixes with tear fluid. Ion-activated systems gel in the presence of cations such as sodium and calcium found in tears. Polymers like chitosan, poloxamers, carbopol, and gellan gum are commonly employed due to their biocompatibility and gel-forming capabilities (86). In situ gels offer several benefits over conventional dosage forms. They reduce systemic absorption and associated side effects, maintain stable drug concentration, and provide prolonged therapeutic action. Moreover, since the formulation begins as a liquid, it avoids the discomfort sometimes associated with preformed gels or ointments that may blur vision (87). Despite these advantages, certain limitations exist. Factors such as polymer concentration, clarity of the gel, irritation potential, and stability must be carefully optimized during formulation. Regulatory approval and large-scale manufacturing can also pose challenges. Overall, in situ gel systems represent a promising advancement in ophthalmic drug delivery. By combining ease of administration with sustained drug release, they address many shortcomings of traditional eye drops and hold significant potential for improving the treatment of various ocular disorders.

In conclusion, in situ gel systems have emerged as a promising alternative to conventional ocular drug delivery approaches such as eye drops and ointments. Conventional formulations often suffer from rapid elimination from the ocular surface, resulting in limited drug absorption and the need for frequent administration.

In contrast, in situ gels undergo a phase transition after instillation into the eye, forming a gel matrix that enhances precorneal residence time. This characteristic improves drug bioavailability, supports sustained and controlled release, and decreases dosing frequency, thereby enhancing patient compliance and overall therapeutic effectiveness. Although substantial progress has been made in the development of these systems, several challenges still need to be addressed. One of the primary difficulties lies in maintaining consistent

therapeutic drug concentrations in ocular tissues over extended periods. Additionally, optimizing formulation variables such as polymer type and concentration, gelation mechanism, viscosity, sterility, and ocular tolerability is crucial to ensure long-term stability, safety, and patient comfort. Poorly optimized systems may lead to irritation, blurred vision, or inadequate drug release. With continued research and technological refinement, in situ gel formulations hold strong potential to revolutionize ocular drug delivery and significantly improve the quality of life for individuals affected by ocular disorders.

## 11. Future Perspectives:

### 11.1 Smart and Multi-Stimuli Responsive Platforms

Upcoming in-situ gel systems are expected to incorporate responsiveness to multiple physiological triggers such as changes in pH, temperature, ionic concentration, and specific ocular enzymes. Such multi-responsive behavior can enable precise control over sol–gel transition and drug release kinetics after administration. Advanced polymer engineering is focusing on biodegradable and biocompatible materials that gradually degrade without causing ocular irritation or toxicity. These materials reduce the need for removal and enhance safety in long-term therapy. Hybrid hydrogel networks combining natural and synthetic polymers are being designed to provide improved mechanical integrity while maintaining softness and comfort on the ocular surface. This balance between strength and flexibility is essential for prolonged residence without compromising patient tolerance (88).

### 11.2 Integration of Nanotechnology

The combination of nanocarriers with in-situ gelling systems has opened new possibilities for sustained and targeted ocular delivery. Nanoparticles such as liposomes, niosomes, polymeric nanoparticles, and dendritic systems can be dispersed within gels to enhance drug solubility and protect labile molecules from degradation. Nano-in-situ gels offer controlled and extended drug release by reducing rapid precorneal elimination and improving corneal permeation. These systems are particularly promising for posterior segment disorders, as nanoscale carriers may facilitate deeper tissue penetration and improved bioavailability compared to conventional topical formulations (89).

### 11.3 Delivery of Genes and Biologics

In-situ gels are being explored as supportive matrices for advanced therapeutics including nucleic acid–based treatments (such as siRNA and gene-editing platforms) and biologically derived agents like monoclonal antibodies, peptides, and growth factors. The protective gel environment can stabilize sensitive biomolecules and allow localized, sustained exposure at the target site. Such developments may significantly expand therapeutic strategies for chronic and degenerative retinal conditions by enabling minimally invasive and prolonged delivery approaches (90).

### 11.4 Patient-Centric Formulation Design

Future formulations are focusing on optical clarity and minimal visual disturbance to enhance patient acceptance and daily usability. Transparent gels that do not cause blurring are critical for routine administration. Extended-release systems capable of once-weekly or even once-monthly dosing are under development to improve adherence in chronic ocular diseases requiring long-term treatment. Improved ease of instillation, reduced irritation, and enhanced comfort are central considerations in next-generation product design (91).

### 11.5 Regulatory and Translational Advancements

The establishment of standardized evaluation parameters including viscosity profiling, gelation time assessment, residence time measurement, sterility assurance, and patient comfort evaluation will streamline product development and comparison across studies. Clear regulatory guidance specific to in-situ gelling ophthalmic systems is necessary to ensure consistent quality, safety, and efficacy standards. Strong collaboration among academic researchers, pharmaceutical industries, and regulatory agencies will be essential to accelerate clinical translation and commercialization of innovative in-situ gel technologies (92).

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