**IJPSR (2025), Volume 16, Issue 12** **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 22 May 2025; received in revised form, 23 June 2025; accepted, 27 June 2025; published 01 December 2025

# ADVANCEMENTS AND FUTURE PERSPECTIVES IN OPHTHALMIC *IN-SITU* GEL: SMART DRUG DELIVERY FOR ENCHANCED OCULAR THERAPY

Mohammed Lubna and Venu Madhav Katla *

Department of Pharmaceutics, St. Pauls College of Pharmacy, Turkayamjal, Hyderabad - 501510, Telangana, India.

**Keywords:**

Ophthalmic *in-situ* gel, Smart drug delivery, Sustained release, Enhanced bioavailability, Stimuli-responsive gel, Ocular therapy

**Correspondence to Author:**
**Prof. (Dr). K. Venu Madhav**

Professor,
Department of Pharmaceutics,
St. Pauls College of Pharmacy,
Turkayamjal, Hyderabad - 501510,
Telangana, India.

**E-mail:** drkatla@stpaulscollege.ac.in

**ABSTRACT:** Ocular *in-situ* gel systems are an improvised formulation in ocular drug administration, successfully addressing the limitations of standard eye drop formulations, such as low bioavailability and the necessity for frequent dosing. This review focuses on the formulation strategies, working mechanisms, and therapeutic applications of these gels in enhancing treatment outcomes. These systems rely on intelligent polymers that respond to physiological signals such as in temperature, pH, or ionic concentrations in the eye, convert from sol-to-gel, allowing for regulated release and prolonged drug residence time. The review delves into different polymer types, methods for drug incorporation, and factors that affect gelation behaviour. It also examines the latest developments limits that exist now and potential paths for the field. Special attention is given to preclinical and clinical evidence supporting the ability of *in-situ* gels to boost drug effectiveness, minimize adverse effects, and increase patient adherence. Overall, this detailed overview highlights the crucial role of ocular *in-situ* gels in the evolution of ophthalmic drug delivery systems.

## INTRODUCTION:

**Background:** The unique physiological and anatomical barriers of the eye, including nasolacrimal drainage, restricted corneal permeability, and fast tear turnover, make ocular drug delivery extremely difficult and frequently result in low bioavailability of drugs applied topically. Although eye drops and ointments are examples of conventional ophthalmic dosage forms that have been used extensively to treat ocular illnesses, they have limitations such as limited residence times, the need for frequent administration and low patient adherence. They have drawbacks, such as short residence durations, the need for frequent administration, and poor patient compliance. Medication loss due to blinking and tear dilution commonly lowers treatment effectiveness, emphasising the need for advanced drug delivery strategies [1]. In recent years, *in-situ* gel systems have received a lot of attention as a potential remedy to the shortcomings of standard ocular drug delivery techniques. When these formulations are subjected to particular physiological variables, such temperature, pH, or ionic strength in the eye, they change from their initial liquid state into gels.

By extending the drug's residence period, this change enhances bioavailability and lowers the need for frequent dosing. Additionally, by reducing nasolacrimal drainage, the gelation process maintains a larger concentration of drug in contact with the ocular surface, allowing for a prolonged therapeutic impact [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(12).3248-60

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(12).3248-60

The polymers employed determine how *in-situ* gels are formed. Polymers including chitosan, poloxamer, gellan gum, and Carbopol have been extensively researched for their superior mucoadhesive qualities and propensity to gel in response to physiological stimuli [3]. Because of its mucoadhesion, biocompatibility, and capacity to increase ocular permeability, chitosana naturally occurring biopolymerhas attracted special attention as a potential ingredient for ophthalmic *in-situ* gels. Additionally, adding thermos responsive and pH-sensitive polymers has demonstrated potential for prolonging medication release, reducing drug loss, and enhancing patient adherence [3].

To improve therapeutic effectiveness and optimize drug release kinetics, recent developments have investigated merging *in-situ* gels with nanoparticle drug delivery systems. A poloxamer-based *in-situ* gel with oxytetracycline-loaded gelatine-polyacrylic acid nanoparticles, for example, has been shown to have a longer ocular residence duration and considerable antibacterial efficacy against bacterial keratitis. These hybrid nanoparticle-*in-situ* gel systems have shown increased drug delivery to ocular tissues, controlled release, and greater penetration [3].

Looking ahead, the future of ocular *in-situ* gel formulations focuses on integrating nanotechnology, stimuli-responsive biomaterials, and personalized medicine to achieve site-specific and controlled drug delivery. Advanced formulations, including ion-sensitive, thermoresponsive, and bio adhesive *in-situ* gels loaded with nanoparticles, liposomes, and nano micelles, have shown promising results in enhancing ocular drug bioavailability [1]. Ongoing research in this area is critical to addressing current challenges and transitioning these innovative systems into clinical practice to improve the therapeutic outcomes of ocular diseases.

The eye has unique physiological and anatomical characteristics, making it a highly functional organ. **Fig. 1** shows that primarily separated into the anterior and posterior portions. The posterior section of the eye accounts for two-thirds of the total, with the anterior half accounting for around one-third. The cornea, conjunctiva, iris, ciliary body, lens, and aqueous fluid are all located in the anterior segment. The posterior segment consists of the retinal pigment epithelium, choroid, neural retina, optic nerve, sclera, and vitreous humour. Several conditions can affect both portions and cause visual impairment. Disorders affecting the anterior area include acute conjunctivitis, glaucoma, cataracts, and anterior uveitis. In contrast, diseases like diabetic retinopathy and age-related macular degeneration (AMD) frequently damage the rear of the eye.

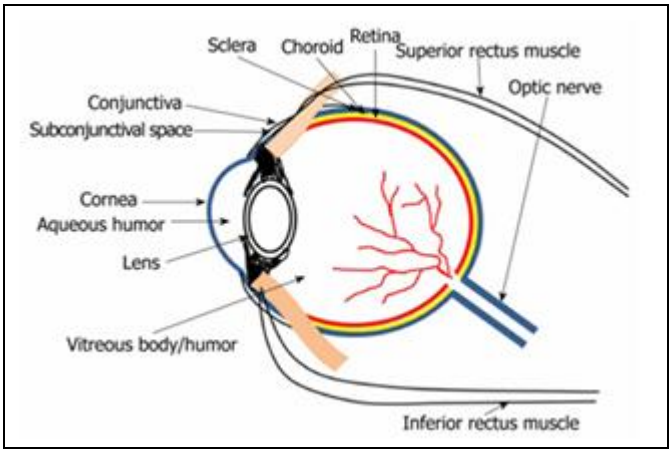


**FIG. 1: STRUCTURE OF EYE** [4]

The most popular non-invasive medication delivery technique for treating problems of the anterior segment is topical instillation. The majority of ophthalmic formulations on the market are available as eye drops or other conventional dosage forms. Both patient compliance and convenience of administration may be at fault [5, 6]. However, topical drops have very limited ocular absorption. Deeper ocular medicine penetration is hindered by physiological and anatomical limits such as reflex blinking, nasolacrimal drainage, tear turnover, and static and dynamic ocular barriers [7].

Consequently, below 5% of a topically applied medication dosage penetrates deeper ocular structures [8]. A variety of physiological restrictions make topical administration of therapeutic amounts of drugs to the posterior area of the eye exceedingly difficult. Systemic administration, intravitreal injections, and periocular injections are also other ways of delivery. However, due to the protective nature of the blood-retinal barriers and the eye's small size in comparison to the rest of the body, systemic distribution is frequently ineffective. Intravitreal injections are the most popular and well-known way to address posterior

segment issues. Frequent intravitreal injections may cause endophthalmitis, haemorrhage, retinal detachment, and low patient acceptability [9].

An emerging alternative is transscleral drug delivery via the periocular route, which offers a less invasive, simpler, and more patient-friendly option. However, drug penetration through this route remains suboptimal due to several ocularbarriers. There are two categories into which these barriers retinal pigment epithelium (RPE), choroid, and sclera are examples of static barriers; and dynamic barrierssuch as conjunctival and episcleral lymphatic drainage, and the blood circulation in the conjunctiva and choroid [10, 11].

Poor bioavailability of eye-instilled drugs arises from several physiological and anatomical barriers. Binding to lachrymal proteins reduces the availability of the active drug, while the natural drainage of instilled solutions leads to rapid elimination from the ocular surface. Additionally, continuous tear production and turnover further contribute to drug loss. The limited corneal surface area and low metabolic activity restrict drug absorption, making penetration into deeper ocular tissues more challenging. Non-productive absorption and adsorption also decrease the drug's effectiveness. Furthermore, tear evaporation and permeability variations impact drug retention, posing significant challenges to effective ocular drug delivery [12]. Numerous traditional and cutting-edge medication delivery methods have been developed to enhance the bioavailability of the eyes and get past obstacles to drug administration. Nano-micelles, liposomes, nanoparticles, dendrimers, contact lenses, implants, nanosuspensions, microneedles, emulsions, suspensions, ointments, aqueous gels, and *in-situ* thermosensitive gels are among the products used to treat the aforementioned eye disorders.

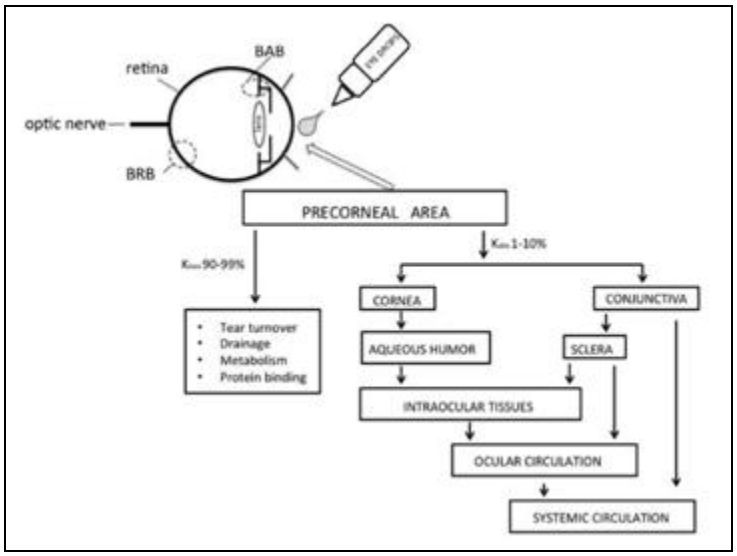


**FIG. 2: SHOWS FLOW OF DRUGS FROM TOPICAL INJECTIONS INTO THE PRECORNEAL AND OCULAR REGIONS**

Pharmaceutical specialization in ophthalmic medication administration is expanding. To treat glaucoma, dry eye disease, and macular degeneration, eyedrops are necessary. The delivery of medications to the eye poses special difficulties due to its limitations [14]. Eye obstacles must be overcome in order to administer medication. The cornea, tear film, and blood-retina barrier are among them. Because of the continuous eye movements, it might be challenging to keep medications in place long enough for them to be effective. Historically, ocular medications have been administered by injections, ointments, and eye drops [15]. These approaches have limited absorption, cause systemic side effects, and result in noncompliance from patients.

The delivery of eye medications might be completely transformed by new *in-situ* gel technology. Enhancement of patient comfort the *in-situ* gel formulation aims to provide better comfort compared to traditional eye drops, as the gel will remain in place longer, reducing irritation and the reduce frequent dosing.

***In-situ* Gels:** The idea of creating gel in place, like as in the eye's cul-de-sac, was initially proposed in the early 1980s. It is well accepted that a medicine formulation's increased viscosity in the precorneal region improves bioavailability because the cornea drains the drug more slowly. Several ideas for *in-situ* gelling systems have been investigated [16].

*In-situ gels* (solutions or suspensions) are liquid formulations that gel at the target location in response to physiological parameters such as pH, temperature, ionic strength, UV exposure, or the presence of particular ions or biomolecules[17]. In recent years, these gel-forming technologies have seen a considerable increase in research and patent activity for a number of therapeutic applications, most notably drug administration [18].

Polymer-based *in-situ* drug delivery devices have benefits such as easy to administration, lower dosage frequency, increase patient adherence, and improved treatment comfort[19]. In the early 1970s, researchers began looking into the use of natural and synthetic polymers for controlled medicine release. Biodegradable polymers are frequently employed in medical applications, including *in-situ* drug delivery systems, because of their multiple advantages [20].

**Advantages & Disadvantages:** *In-situ* gels Advantages of ophthalmic drug administration include increased bioavailability through extended contact with the eye surface, resulting in sustained drug release [21]. This approach enhances patient compliance by requiring less frequent administration than standard eye drop [22]. *In-situ* gels can gel in response to physiological cues like pH, temperature, or ionic concentration, enhancing ocular retention [23]. Using natural or synthetic polymers in these systems improves mucoadhesion, reducing medicine loss from tear turnover [24] and increasing drug duration at the application site. *In-situ* gels promote localised pharmaceutical action and reduce systemic unfavourable effects by limiting absorption through the nasolacrimal duct [25]. In order to improve patient comfort, the viscosity of *in-situ* gels can also be adjusted to lessen visual blurring [26].

Despite their benefits, *in-situ* gels can have certain limits. One restriction is the need for a large fluid volume to provide adequate drug loading, which might induce ocular irritation or discomfort [27]. Furthermore, the gelling process may result in unequal drug distribution, which causes changes in drug release patterns[28]. Another significant drawback is the increased possibility of premature gelation, especially with temperature-sensitive gels resulting in early drug loss before reaching the target site [29]. For hydrophobic drugs, the low drug loading capacity poses a major challenge, limiting the therapeutic efficacy [30]. Furthermore, polymer degradation in some *in-situ* gels may lead to drug instability, reducing the overall effectiveness of the delivery system [31].

**Mechanisms of *In-situ* Gel Formation:** *In-situ* gel formation is an ophthalmic drug delivery system and it is a unique approach where the formulation is administered as a liquid and undergoes gelation in response to physiological conditions, enhancing ocular retention time and bioavailability [32]. The mechanism of gel formation can occur through various stimuli, including

**Temperature-Triggered Gelation:** In this technique, the formulation remains in liquid state at ambient temperature (20-25°C), but undergoes a phase transition into a gel when it is contact to the eye's natural temperature range (35-37°C) [33]. Poloxamers, especially Poloxamer 407 (Pluronic F-127), are commonly used as temperature-sensitive polymers. Upon administration into the conjunctival sac, the increase in temperature induces micellization and gelation, leading to prolonged drug release [34].

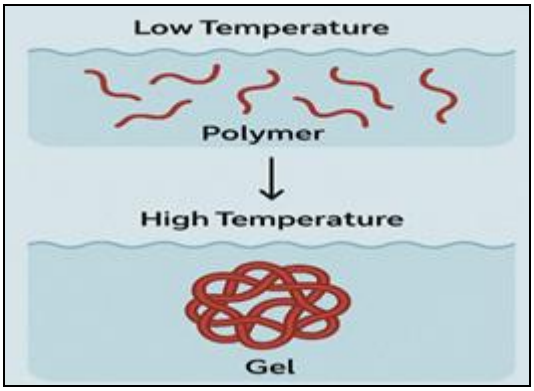


**FIG. 3: SHOWS MECHANISM INVOLVED IN TEMPERATURE TIGGERED GELATION**

**pH-Triggered Gelation:** pH-sensitive *in-situ* gels are formulated using pH-sensitive polymers, such

as Carbopol 934, Polyacrylic acid, and Chitosan. These polymers remain as liquid at acidic pH (4.0-4.5) but form gel at the physiological pH (7.4) of the tear fluid [35]. When the formulation exposed to the alkaline tear fluid, the ionization of acidic functional groups in the polymer leads to increased viscosity and gelation, enhancing ocular drug retention [36].

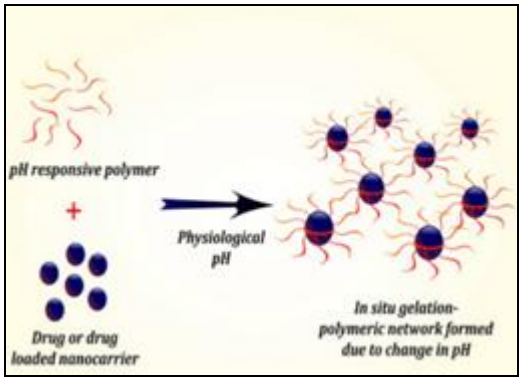


**FIG. 4: SHOWS MECHANISM INVOLVED IN PH TRIGGERED GELATION**

**Ion-Activated Gelation:** The formulation is based on ion-activated *in-situ* gels that react with tear fluid. This approach typically uses polymers like xyloglucan, sodium alginate, and gellan gum. Ionic crosslinking between polymer chains in the eye occurs when divalent cations ($Ca^{2+}$, $Mg^{2+}$) are present in the tear film [37].

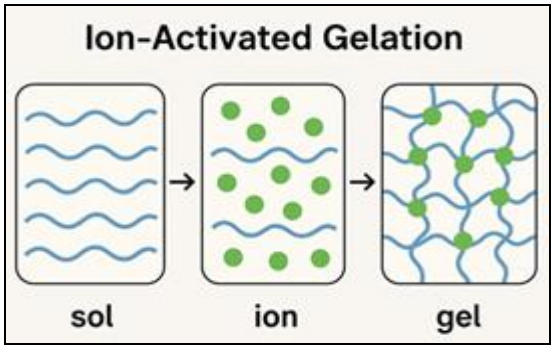


**FIG. 4: SHOWS MECHANISM INVOLVED IN ION-ACTIVATED GELATION**

**Enzymatically-Triggered Gelation:** Enzyme-triggered *in-situ* gels involve the use of enzymes naturally present in tear fluid, such as lysozymes, lipases, or esterase, which activate prodrug to active drug conversion and lead to *in-situ* gelation[38]. This approach has been explored for prodrugs like Timolol and Dorzolamide, where enzymatic activity in tear fluid promotes gelation and prolonged drug release. However, this method is still under clinical investigation.

**UV Light-Triggered *In-situ* Gel Formation:** UV light-triggered *in-situ* gels utilize photo-polymerizable polymers that undergo gelation upon exposure to ultraviolet (UV) light (365 nm or 254 nm). This mechanism relies on photo initiators such as Irgacure 2959, which generate free radicals upon UV exposure, leading to rapid crosslinking of polymer chains and gel formation [39]. Commonly used photo-polymerizable polymers include polyethylene glycol diacrylate (PEG-DA), methacrylate derivatives, and polyvinyl alcohol (PVA). This approach enables controlled drug release, improved ocular retention, and enhanced bioavailability. However, potential phototoxicity to ocular tissues and limited light penetration remain challenges [40]. Recent research focuses on low-intensity UV light exposure and biocompatible photo initiators to overcome these limitations [41].

**Polymers and Other Additives:**

**Polymers:** In order to improve therapeutic efficacy, polymers are essential to the formulation of *in-situ* gels because they regulate drug release, retain drug, and facilitate the gelation process. Depending on where they come from, polymers are divided into:

**Natural Polymer:** The Natural Polymers because they are biocompatible, biodegradable, and low in toxicity, natural polymers which can come from plant, animal, or microbiological sources are frequently utilized in *in-situ* gels. Improved therapeutic results are guaranteed by these polymers' increased mucoadhesion, bioavailability, and extended drug release [42,43].

**Gellan Gum:** It is an ion-activated polymer obtained from *Sphingomonas elodea*. Upon interaction with tear fluid containing divalent cations ($Ca^{2+}$, $Mg^{2+}$), it undergoes gelation, providing prolonged ocular retention time.

**Chitosan:** This pH-sensitive polymer is derived from chitin (shells of crustaceans) and forms a gel at physiological pH (7.4). It also exhibits bio adhesive, antimicrobial, and penetration-enhancing properties, making it highly suitable for ocular *in-situ* gels.

**Sodium Alginate:** A polymer derived from brown algae that exhibits ion-sensitive gelation in the

presence of divalent cations. This enhances ocular bioavailability and prolongs drug retention time.

**Xanthan Gum:** A microbial polysaccharide produced by *Xanthomonas campestris*, it improves viscosity, mucoadhesion, and gel strength, ensuring sustained drug release.

**Pectin:** Derived from citrus fruits, pectin forms pH-sensitive gels in alkaline conditions (pH 7.4), allowing for controlled and prolonged drug release.

**Synthetic Polymers** Synthetic polymers are chemically synthesized macromolecules that provide enhanced mechanical strength, controlled drug release, and prolonged ocular retention. These polymers' capacity to gel in response to physiological stimuli makes them popular for use in *in-situ* gel compositions [44,45].

**Polymer 407 (Pluronic F-127):** This temperature-sensitive polymer gels at body temperature (35–37°C) but stays liquid at normal temperature (25°C). Long-term drug retention and sustained drug release are made possible by this characteristic.

**Carbopol 934:** A pH-sensitive polymer that turns into a gel at ocular pH (7.4) but stays liquid at acidic pH (4.5). This reduces precorneal outflow and increases medication absorption.

**Hydroxypropyl Methylcellulose (HPMC):** It increases mucoadhesion and works as a viscosity enhancer, which prolongs drug release and increases drug retention duration.

**Polyvinyl Alcohol (PVA):** A water-soluble polymer that ensures extended ocular medication retention by improving gel strength and viscoelasticity.

**Gelling agent:** These are the polymers that cause gelation in reaction to physiological stimuli such as ionic strength, pH, or temperature. They improve the duration of drug retention and regulate the drug release profile.

**pH-Sensitive Agents:** Undergo sol-to-gel transition at physiological pH (~7.4) , Maintain drug stability and release kinetics [46].

Examples: Carbopol, Polyacrylic Acid.

**Temperature-Sensitive Agents:** Gelation occurs at physiological temperatures (~35-37°C), enhances patient compliance by allowing easy administration as a liquid, which later forms a gel [47].

Examples: Poloxamer 407, Pluronic F-127.

**Ion-Activated Agents:** Undergo gelation upon contact with tear fluid ions (e.g., $Ca^{2+}$, $Na^{+}$), improve mucoadhesion and prolong drug contact time [48].

Examples: Gellan Gum, Sodium Alginate.

**Penetration Enhancers:** These substances increase corneal permeability, allowing for better drug absorption. Common penetration enhancers include EDTA (Ethylenediaminetetraacetic acid) and Sodium Lauryl Sulphate (SLS) [48].

**Buffering Agents:** These agents maintain the pH of the formulation (7.4) to match the tear fluid pH, minimizing ocular irritation. Common buffering agents include sodium phosphate, boric acid, and citrate buffer [49].

**Preservatives:** Preservatives help to avoid microbial contamination during storage and usage. Preservatives used often include Benzalkonium Chloride (BAK), Chlorobutanol, and Thiomersal [49].

**Osmotic Agents:** Osmotic agents maintain isotonicity of the formulation with tear fluid to prevent ocular irritation. Common osmotic agents are sodium chloride, mannitol, and dextrose[50].

**Mucoadhesive Agents:** Increase adhesion to the corneal surface, improve drug absorption and bioavailability. Examples: Chitosan, Carbopol, Sodium Alginate[51].

**Surfactants:** Improve drug solubility and dispersion. Reduce surface tension for better spreading on the ocular surface. Examples**:** Polysorbates (Tween 80), Cremophor EL[52].

**Drug Loading & Release Mechanism:** In *in-situ* gel systems, drug loading is the process of adding a drug in a liquid form to the polymer matrix, which subsequently gels at the administration site. The drug release profile, bioavailability, and therapeutic effectiveness are all significantly influenced by the

drug's loading capacity in the gel formulation [53]. Drug retention duration in the ocular cavity is influenced by loading efficiency and gel strength, which are strongly influenced by the polymer type, drug solubility, and concentration.

In temperature-sensitive gels, drugs are loaded in a liquid polymeric solution which, upon instillation into the eye, transforms into a viscous gel, allowing sustained release. In pH-sensitive gels, the drug is loaded in an acidic environment and gelation occurs when the pH increases to physiological pH, thereby prolonging drug retention time [54]. The process by which pharmaceuticals are released from *in-situ* gels differs depending on the polymer type, gel structure, and external stimuli. The primary methods for drug release are:

**Diffusion-Controlled Release:** In this method, the medication diffuses via a concentration gradient out of the gel matrix. The drug solubility, mesh size, and gel viscosity all affect how quickly the drug diffuses across the barrier. [55]. This release mechanism promotes sustained drug delivery, thereby reducing frequent administration.

**Swelling Controlled Release:** In swelling-controlled release, the polymer matrix absorbs tear fluid, causing it to swell. Because of the expansion of the polymer network, this swelling allows the medication to diffuse gradually, facilitating controlled drug release [56]. Polymers that are often employed in swelling-controlled release mechanisms include sodium alginate, Carbopol, and HPMC.

**Erosion-Controlled Release:** This happens when the polymer matrix gradually erodes on the outside after being exposed to tear fluid. This method is commonly observed in biodegradable and bio erodible polymers, such as poloxamers, chitosan, and xanthan gum [57]. As the gel gradually erodes, the drug is released over a sustained period, ensuring long-lasting therapeutic effects.

**Ion-Activated Release Mechanism:** In ion-activated *in-situ* gels, gelation occurs due to the interaction between divalent cations ($Ca^{2+}$, $Mg^{2+}$) in tear fluid and the polymer (e.g., Gellan gum, Sodium Alginate). Upon contact with tear fluid, the polymer network cross-links, entrapping the drug and allowing for sustained release over time [58].

**Controlled and Sustained Drug Release:** The idea of *in-situ* gels regulated and prolonged drug release has greatly improved ocular bioavailability and therapeutic results. Controlled release refers to the release of a drug at a predetermined rate, minimizing systemic side effects and fluctuations in drug concentration[59]. On the other side, sustained release maintains constant therapeutic drug levels over a period of period, eliminating the need for frequent dosing.

**Sustained Drug Release:** *In-situ* gels significantly reduce drug clearance rates and prolong ocular contact time, ensuring consistent drug release for 6-12 hours.

**Controlled Drug Release:** The polymer composition, cross-linking, and gel network control the release rate of the drug, ensuring predictable pharmacokinetics.

**Effect of In-*situ* gels on Bioavailability and Therapeutic Efficacy:** *In-situ* gelling methods have been developed to overcome the physiological barriers of the eye, hence improving the bioavailability and therapeutic effectiveness of ophthalmic medicines. Tear turnover, blinking, and nasolacrimal drainage all contribute to the quick precorneal removal of the administered medication, which is the primary factor influencing ocular bioavailability. Only 1–5% bioavailability is usually offered by conventional eye drops, which leads to subtherapeutic medication concentrations at the target location. On the other hand, *in-situ* gels offer a longer retention duration on the ocular surface by employing gelation mechanisms (such as pH, temperature, or ion activation), which reduces drug clearance and improves bioavailability [60]. The necessity for frequent dosage is lessened by this extended contact time, which ultimately enhances treatment outcomes and patient compliance [61].

The sustained and regulated release capability of *in-situ* gels leads to optimised drug release kinetics, resulting in longer drug exposure at the ocular location. Drug release from *in-situ* gels is typically regulated by diffusion, swelling, and erosion, resulting in a stable therapeutic concentration throughout time [62]. This delayed drug release lessens the likelihood of drug fluctuation, prevents

rapid peaks in drug concentration, and minimises the possibility of systemic adverse effects. *In-situ* gels reduce nasolacrimal drainage, allowing drugs to stay in touch with the ocular surface for extended periods of time. This improves corneal drug penetration and bioavailability [63]. Long-term medication availability is essential for the treatment of chronic ocular conditions like glaucoma, bacterial conjunctivitis, and keratitis, which is eventually aided by this controlled release mechanism. Moreover, the enhanced therapeutic efficacy of *in-situ* gels is attributed to reduce systemic absorption and target the ocular tissues directly. Conventional eye drops often face challenges in delivering drugs to posterior ocular tissues due to limited corneal permeability. *In-situ* gels, especially those formulated with mucoadhesive polymers like chitosan, Carbopol, and sodium alginate, facilitate better adhesion to the corneal and conjunctival surface, allowing higher drug penetration [64]. This enhances drug retention, absorption, and therapeutic action while minimizing dose frequency and systemic side effects. Additionally, the incorporation of biocompatible and biodegradable polymers further improves patient safety and comfort, ensuring sustained therapeutic effects with a single dose. Therefore, *in-situ* gels are revolutionizing ocular drug delivery by maximizing bioavailability and optimizing therapeutic efficacy [65].

**Evaluation of *In-situ* Gels:**

**Visual Inspection, Drug Content, pH, and Clarity:** The purity of the final formulations was visually assessed against a white background. The pH of the formulations was evaluated using a pH meter. After dilution with a suitable buffer, the drug content was examined using a UV spectrophotometer [66].

**Rheological Evaluation:** The spindle S31(small sample adapter) and Brookfield viscometer (RV model) were used to characterize the rheological of the *in-situ* gel at different temperature (25°C and 37°C) and angular speeds (30,50,75and 100 rpm) [67].

**Differential Scanning Calorimetry:** It is used to examine the thermal behaviour of the drug, the physical combination of the drug and polymer, and the lyophilized product. The 5 mg dry powder sample was placed in the holder after being crimped onto an aluminium pan in a nitrogen gas (20 ml/min) atmosphere, the samples were scanned at 40–400 C at a rate of 5 ºC/min.

***In-vitro* Drug Release Studies:** A semi-permeable dialysis membrane method is employed to test drug release from both commercially available ophthalmic solutions and developed *in-situ* gel. A pre-conditioned dialysis bag containing a precise amount of each formulation is submerged in 100 millilitres of simulated tear fluid (STF) at pH 7.4. The system is rotated at 50 rpm and kept at 37±2°C. To maintain consistent sink conditions, samples are taken at predefined intervals throughout the day and promptly replaced with an equivalent amount of fresh STF to compute the standard deviation, each sample is examined three times. To further understand the drug release process, the collected data is applied to a variety of kinetic models, including Higuchi, Korsmeyer-Peppas, and Hixson-Crowell. There are two orders: zero and first [66].

**Ocular Irritation Studies:** To evaluate this research, (HET-CAM) Hen's Egg Test on the Chorioallantois Membrane technique is used. Fertilised eggs measuring 45-65 g with no apparent flaws are picked and incubated for 10 days under regulated circumstances (37±2°C temperature and 55±7% relative humidity). On day ten, the eggshell is gently removed and the inner membrane pulled aside to reveal the chorioallantois membrane. A 0.5 mL of the test formulation is then applied directly to the membrane and allowed to interact for 5 minutes. The membrane is inspected for vascular abnormalities such as haemorrhage, hyperaemia, and coagulation, and the time of onset for each is noted. 0.1 M sodium hydroxide and normal saline serve as positive and negative controls, respectively[68].

**Antimicrobial Efficacy Studies:** Agar well diffusion is used to assess the antibacterial activity of the *in-situ* gel against *E. coli* and *Staphylococcus aureus*. Samples from *in-vitro* drug release study and commercial eye drops are placed in separate agar plate wells and allowed to diffuse for two hours. The plates are then incubated for 24 hours at 37 degrees Celsius. A zone measurement tool [68] is used to measure the breadth of the zones of

inhibition in order to assess the antibacterial activity.

**Sterility Evaluation:** The optimised *in-situ* gel's sterility is assessed using the membrane filtering method (0.22 µm pore size) in accordance with Indian Pharmacopoeia criteria. The formulation was incubated for 14 days in fluid thioglycolate medium and in soybean casein digest medium at 35°C and 25°C respectively if any microbial growth is present documented to determine sterility [69].

**Stability Studies:** It is carried out in accordance with the International Council for Harmonization's (ICH) requirements. The *in-situ* gel formulation is kept at three temperatures (25±0.5°C, 30±0.5°C, and 40±0.5°C) with 75% RH. It is tested for stability throughout time at intervals of 0, 30, 60, 90, and 180 days for pH, clarity, viscosity, and medicinal content [70].

**Applications of *In-situ Gel* in Ocular Diseases [71–74]:**

**Conjunctivitis:** *In-situ* gels loaded with antibiotics like moxifloxacin provide sustained drug release, enhancing therapeutic efficacy in bacterial conjunctivitis.

**Glaucoma:** Formulations containing timolol maleate have been developed to successfully lower intraocular pressure, with improved patient adherence due to less frequent dosage.

**Dry Eye Syndrome:** Chitosan-based *in-situ* gels offer prolonged ocular surface retention, providing sustained lubrication and relief for dry eye patients.

**Uveitis:** *In-situ* gels containing corticosteroids like loteprednol etabonate have been formulated to manage intraocular inflammation, offering improved therapeutic & sustained drug release outcomes**.**

**Fungal Keratitis:** *In-situ* gels including antifungal drugs such as voriconazole have been created to treat fungal infections of the cornea, enabling longer drug contact time and increased antifungal activity. The functional of *in-situ* gels in responding to ocular physiological conditions makes them a valuable tool in treating various ocular diseases, enhancing drug efficacy, and patient adherence.

**Natural *In-situ* Gels for Ophthalmic Drug Delivery:** Natural polymers mucoadhesive, biodegradable, and biocompatible qualities have drawn a lot of interest in ophthalmic *in-situ* gel compositions. When these natural polymers are exposed to physiological stimuli, they change from a sol-to-gel state enhancing drug retention and improving therapeutic outcomes [75].

**Examples of Natural Polymers:** sodium hyaluronate, xanthan gum, xyloglucan, guar gum, gellan gum, pectin, alginic acid, carrageenan, and chitosan.

**Advantages & Disadvantages [48,75–78]:** Advantages of natural based *in-situ* gels are Biocompatibility & safety, mucoadhesive properties for better absorption, sustained drug release & enhanced retention, responsive to physiological stimuli (pH, ion, or enzyme activation) natural antimicrobial properties (e.g., chitosan). Natural-based *in-situ* gels provide sustained drug release, increased bioavailability, and enhanced ocular retention, making them excellent alternatives to conventional eye drops., alginate, gellan gum, chitosan, xyloglucan, and pectin are widely researched due to their biocompatibility & effective gelation properties. The disadvantages of natural based *in-situ* gels are poor stability & short shelf life, low mechanical strength & rapid degradation, sensitivity to physiological variations, potential allergic reactions & irritation.

**TABLE 1: MARKETED OPHTHALMIC GEL PRODUCTS [79]**

| Polymeric Base | Brand(s) | Manufacturer | Therapeutic Agent (s) |
|---|---|---|---|
| Gellan gum | Timoptic® XE | Merck | Timolol maleate |
| Carbomer with polyvinyl alcohol | Nyogel® | Novartis | Timolol |
| Polyethylene glycol | ReSure® Sealant | Ocular Therapeutix, Inc. | Trilysine acetate |
| Crosslinked polycarbophil (divinyl glycol) | Azasite®, DuraSite®, Azasite Plus® | Inspire Pharmaceuticals | Azithromycin, Azithromycin + Dexamethasone |
| Carbomer 980 | Viscotears®, Lumecare® Gel, Xailin® Gel, Clinitas® Gel, | Alcon, Medicom, Nicox, Altacor, Bausch & Lomb | Carbomer 980 |

| | | | |
|---|---|---|---|
| | GelTears® | | |
| Xanthan gum | Timoptic® GFS | Alcon | Timolol maleate |
| Hypromellose | Akten™ | Akten | Lidocaine hydrochloride |
| Carbomer-based gels | Zirgan®, Fucithalmic®, Pilopine HS® | Sirion, Concordia Int., Alcon | Ganciclovir, Fusidic acid, Pilocarpine |
| Carbomer 940 | Pilogel® | Alcon | Pilocarpine |
| Carbomer 974P | Liquivisc® | Spectrum Thea | Carbomer 974P |
| Carbomer-based formulation | Virgan® | Thea Pharmaceuticals | Ganciclovir |

**Recent Advances & Novel Formulation:** The creation of smart stimuli-responsive hydrogels and in situ gels based on nanoparticles has resulted from recent developments in drug delivery systems, providing notable enhancements in targeted treatment. Nanoparticle-based in situ gels are liquid formulations that transform into gels upon administration, facilitating localized and sustained drug release. These systems enhance bioavailability and therapeutic efficacy by sustaining long-term therapeutic concentrations at the intended location [80].

Smart stimulus-responsive hydrogels respond to certain physiological environment condition such as light, pH, or temperature, allowing for controlled medicine delivery. For example, at body temperature, thermoresponsive nanogels composed of polymers undergo a sol-gel transition, allowing for precise drug administration. Similarly, pH-responsive hydrogels can release their payload in response to the acidic environment of tumor cells, enhancing the selectivity and effectiveness of anticancer therapies [81]. These novel materials represent a huge step forward in the construction of intelligent drug delivery systems, allowing for more effective and personalized therapeutics [82].

**Challenges & Future Perspectives:** The development of in situ gels for medication delivery into the eyes raises concerns about stability, scalability, regulatory compliance, and safety. Ensuring the long-term stability of these formulations is crucial, as physicochemical changes can affect therapeutic efficacy. Scaling up production while maintaining consistency poses significant hurdles, requiring advanced manufacturing techniques to ensure uniformity and quality. Regulatory agencies necessitate comprehensive evaluations of these novel systems to address potential safety concerns, including immunogenicity and biocompatibility. Future trends in ocular drug delivery systems (ODDS) focus on enhancing patient compliance and therapeutic outcomes through minimally invasive methods. Advancements in in situ gel technology exemplify this shift, offering sustained treatment effects with reduced intervention frequency. Ongoing research aims to optimize these delivery platforms, addressing existing challenges to fully realize their potential in clinical applications.

The future of ophthalmic *in-situ* gels lies in the development of advanced natural polymer blends that overcome current limitations, such as faster and more consistent gelation, and improved mechanical properties. There is also the possibility of developing personalised medication delivery systems that respond to individual tear fluid composition and enzyme levels. Nanotechnology and biomaterials are likely to play important roles in improving medication penetration and sustained release. Because of their eco-friendliness, natural-based *in-situ* gels will continue to gain popularity, and creative ways will enhance patient outcomes in ophthalmic treatment. Future directions in this subject include the use of stimuli-responsive polymers that react to environmental changes, allowing for regulated medication delivery. Additionally, combining in situ gels with other delivery platforms, such as contact lenses, offers potential for synergistic effects in ocular therapy. Addressing challenges related to formulation stability, scalability, regulatory compliance, and patient acceptance will be crucial for the successful translation of these advanced systems into clinical practice.

**CONCLUSION:** Ophthalmic drug administration, particularly using *in-situ* gel systems, is an effective technique for increasing medication bioavailability, extending ocular residence duration, and improving patient adherence. When exposed to physiological circumstances, these formulations change from sol to gel, allowing for long-term drug release and reducing the need for

regular dosage. Biopolymers such as chitosan, sodium alginate, and pectin are widely used because to their safety, biodegradability, and high mucoadhesive properties, making them ideal for ocular application. Developing and obtaining these gels necessitates several factors, including pH sensitivity, gelation behaviour, and viscosity modulation, all of which contribute to effective drug delivery. Nonetheless, issues such as gelation unpredictability, limited mechanical strength, and worries about long-term stability must be addressed in order to develop these systems.

**ACKNOWLEDGEMENTS:** One of the authors, Mohammad Lubna wants to thank the supervisor Dr. Venu Madhav Katla providing necessary guidance in completing the review.

**CONFLICTS OF INTEREST:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

## REFERENCES:

1. Sheshala R, Kok YY, Ng JM, Thakur RR and Dua K: *In-situ* gelling ophthalmic drug delivery system: An overview and its applications. Recent Patents Drug Delivery Formulations 2015; 9(3): 237-248.
2. Varela-Garcia A, Concheiro A and Alvarez-Lorenzo C: Chitosan-based *in-situ* gels loaded with drugs: Design, characterization, and ocular applications. Marine Drugs 2018; 16(10): 373.
3. Khan S, Baboota S, Ali J and Narang RS: Nanoparticles loaded thermoresponsive *in-situ* gel for ocular antibiotic delivery against bacterial keratitis. Polymers (Basel) 2022; 14(6): 1135.
4. Patel A, Cholkar K, Agrahari V and Mitra AK: Ocular drug delivery systems: An overview. World Journal of Pharmacology 2013; 2(2): 47-64.
5. Bourlais CL, Acar L, Zia H, Sado PA, Needham T and Leverge R: Ophthalmic drug delivery systems- recent advances. Program Retinal Eye Research 1998; 17: 33-58. doi:10.1016/S1350-9462(97)00002-5. [PubMed: 9537794]
6. Gulsen D and Chauhan A: Ophthalmic drug delivery through contact lenses. Investigative Ophthalmology & Visual Science 2004; 45: 2342-2347. doi:10.1167/iovs.03-0959. [PubMed: 15223815]
7. Dey S, Sinha N, Basu B and Dey A: Overview of recent advances in nano based ocular drug delivery. Int J Mol Sci 2023; 24(20): 15352.
8. Ahmed S, Amin MM, El Korany SM and Sayed S: Nanocarriers for ocular drug delivery: recent advances and translational opportunity. Biomater Sci 2023; 11: xxx–xxx. doi:10.1039/D3BM00505D.
9. Bochot A and Fattal E: Liposomes for intravitreal drug delivery: a state of the art. Journal of Controlled Release 2012; 161: 628-634. doi: 10.1016/j.jconrel.2012.01.019. [PubMed: 22289436]
10. Khan NZ, Patel RV and Gupta R: Polymer- and lipid-based nanocarriers for transscleral ocular drug delivery: overcoming static and dynamic barriers. Int J Pharm 2023; 615: 122496.
11. Lee DH, Choi JH and Park YH: Microneedle-assisted periocular drug delivery: limitations imposed by ocular barriers and possible enhancements. Eur J Pharm Biopharm 2024; 190: 121–130.
12. Patel A, Cholkar K, Agrahari V and Mitra AK: Ocular drug delivery systems: An overview. World Journal of Pharmacology 2013; 2(2): 47-64.
13. Rathore KS: *In-situ* gelling ophthalmic drug delivery system: An overview. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2(4): 30-34. ISSN: 0975-1491.
14. Conrady CD and Yeh S: A review of ocular drug delivery platforms and drugs for infectious and non-infectious uveitis: the past, present, and future. Pharmaceutics 2021; 13(8): 1224. doi:10.3390/pharmaceutics13081224.
15. Shastri DH, Silva AC and Almeida H: Ocular delivery of therapeutic proteins: a review. Pharmaceutics 2023; 15(1): 205. doi:10.3390/pharmaceutics15010205.
16. Smith A, Patel D and Kumar R: *In-situ* gelling systems for ocular drug delivery: a comprehensive systematic review. J Control Release 2024; 380: 45–60.
17. Whitlock DR, Weiss L and Ambrogio LN: Inventors; AOBIOME LLC, assignee. Ammonia oxidizing microorganisms for use and delivery to the gastrointestinal system. United States patent application US 16/318,583. 2019.
18. Patel N, Dhuliya R, Padiyar N, Singh A, Khaudiyal S, Jakhmola V and Nainwal N: Innovative niosomal *in-situ* gel: elevating ocular drug delivery synergies. J Appl Pharm Sci 2024; 14(9): 1–17.
19. Peppas N and Langer R: New challenges in biomaterials. Science 1994; 263(5154): 1715-1720. doi:10.1126/science.8134835.
20. Tsung TH, Tsai YC, Lee HP, Chen YH and Lu DW: Biodegradable polymer-based drug-delivery systems for ocular diseases. Int J Mol Sci 2023; 24(16): 12976. doi:10.3390/ijms241612976.
21. `Khan S, Baboota S, Ali J and Narang RS: Nanoparticles loaded thermos responsive in situ gel for ocular antibiotic delivery against bacterial keratitis. Polymers (Basel) 2022; 14(6): 1135. doi:10.3390/polym14061135.
22. George J, Kumar P and Sharma A: *In-situ* gelling systems for ocular drug delivery: enhancing patient compliance through sustained release. J Control Release 2023; 385: 85–98. doi:10.1016/j.jconrel.2023.05.012.
23. Basant A and Abdelwahab I: Comparative evaluation of nano-ocular delivery systems loaded pH- and thermosensitive in situ gels for *Acanthamoeba keratitis* treatment. Sci Rep 2025; 15: 19430.
24. Alsaidan M, Alanazi FK and Shakeel F: Development of ion-activated and mucoadhesive *in-situ* gel for ocular delivery of ketorolac tromethamine. Pharmaceutics 2023; 15(6): 1623. doi:10.3390/pharmaceutics15061623.
25. Rathapon T, Apirak C, Chutima B and Pattaraporn A: Development of an ophthalmic *in-situ* gel system for controlled delivery of levofloxacin. Asian Journal of Pharmaceutical Sciences 2017; 12(5): 433-440. doi:10.1016/j.ajps.2017.04.002.
26. Abbas MN, Khan SA, Sadozai SK, Khalil IA, Anter A and El Fouly M: Nanoparticles loaded thermoresponsive *in-situ* gel for ocular antibiotic delivery against bacterial keratitis. Polymers 2022; 14(6): 1135. doi:10.3390/polym14061135.
27. Szalai B, Jójárt-Laczkovich O, Kovács A, Berkó S, Balogh GT, Katona G and Budai-Szűcs M: Design and

optimization of *in-situ* gelling mucoadhesive eye drops containing dexamethasone. Gels 2022; 8(9): 561. doi:10.3390/gels8090561.

28. Bhujbal SV, Mitra AK and Agrahari V: Challenges and advancements in ocular drug delivery systems. Expert Opinion on Drug Delivery 2020; 17(9): 1239-1259. doi:10.1080/17425247.2020.1795244.
29. Shastri DH, Silva AC and Almeida H: Ocular delivery of therapeutic proteins: A review. Pharmaceutics 2023; 15(1): 205. doi:10.3390/pharmaceutics15010205.
30. Zhao X, Liu Z and Li Q: Development of a poloxamer-based thermosensitive *in-situ* gel for ocular delivery of hydrophobic drug curcumin: formulation and evaluation. Pharm Dev Technol 2022; 27(5): 547–556.
31. Li W, Zhang X and Hong S: Impact of sterilization-induced polymer degradation on drug stability in ophthalmic *in-situ* gels. AAPS Pharm Sci Tech 2023; 24(4): 110. doi:10.1208/s12249-023-02567-9.
32. Baboota S, Ali J and Narang RS: Nanoparticles loaded thermos responsive *in-situ* gel for ocular antibiotic delivery against bacterial keratitis. Polymers (Basel) 2022; 14(6): 1135. doi:10.3390/polym14061135.
33. González M, Santos H and Villegas R: Thermoreversible hydrogel systems for ocular delivery: sol-to-gel transition at ocular temperature and drug release kinetics. Pharmaceutics 2022; 14(2): 238. doi:10.3390/pharmaceutics14020238.
34. Balaji A, Kumar SA and Raghavendra P: Temperature-sensitive *in-situ* gels for ophthalmic drug delivery: A review. Advanced Pharmaceutical Bulletin 2021; 11(2): 240-250. doi:10.34172/apb.2021.024.
35. Springer PC, Alsaidan M, Alanazi FK and Shakeel F: Development of a thermosensitive and pH-responsive *in-situ* ocular gel using carbopol–HPMC combination: formulation optimization and evaluation. Bull Natl Res Cent 2023; 47: 39.
36. Iqbal J, Shahnaz G, Pervez S and Sultana M: pH-triggered in situ gel for ocular delivery of ketorolac tromethamine: Formulation and in vivo evaluation. Int J Pharm Investig 2022; 12(4): 513–520. doi:10.4103/jphi.jphi_50_22.
37. Rathapon T, Apirak C and Chutima B: Development of an ophthalmic *in-situ* gel system for controlled delivery of levofloxacin. Asian Journal of Pharmaceutical Sciences 2017; 12(5): 433-440. doi:10.1016/j.ajps.2017.04.002.
38. Alkilani AZ, Alqudah DA and Kanan T: Enzyme-responsive *in-situ* gelling systems for ocular delivery of timolol prodrug: design, synthesis, and evaluation. Int J Pharm 2022; 620: 21757. doi:10.1016/j.ijpharm.2022.121757.
39. Zhao M, Guo C and Zhang H: UV light–induced photo-crosslinked hydrogel for controlled ocular drug delivery. Acta Biomater 2023; 161: 225–238. doi:10.1016/j.actbio.2023.02.019.
40. Ma Y, Ji Y, Huang G, Ling K and Zhang X: Photopolymerizable hydrogels for ocular drug delivery: Opportunities and challenges. Advanced Drug Delivery Reviews 2021; 174: 86-117. doi:10.1016/j.addr.2021.04.003.
41. Li X, Wang X, Liu L, Shen Y, Li Y and Hu Y: Photopolymerizable polyethylene glycol diacrylate (PEG-DA) hydrogels for ophthalmic drug delivery. Journal of Materials Chemistry B 2022; 10(15): 2829-2842. doi:10.1039/d2tb00237a.
42. Patel A, Gaba B and Kumar P: Chitosan- and alginate-based *in-situ* ocular gels: natural polymers enhancing mucoadhesion and sustained drug release. Pharmaceutics 2020; 12(8): 712. doi:10.3390/pharmaceutics12080712.
43. Patel KD, Bajpai J and Bajpai AK: Xanthan gum-based hydrogels for biomedical applications. Materials Science and Engineering C 2017; 77: 813-824.
44. Wang C, Lin X, Huang Y and Liu G: Poloxamer 407-based thermos responsive gels for ocular delivery. Acta Pharmaceutica Sinica B 2019; 9(6): 1213-1220.
45. Almeida H, Amaral MH, Lobão P and Lobo JMS: Design of controlled-release *in-situ* gels. Drug Delivery and Translational Research 2021; 11(4): 1702-1717.
46. Li J, Chen M and Liu C: Thermosensitive in situ gel incorporating poloxamer 407 for ocular delivery of brimonidine tartrate: formulation optimization and *in-vivo* evaluation. Int J Pharm 2021; 599: 120443. doi:10.1016/j.ijpharm.2021.120443.
47. Iqbal Z, Ahmad R and Ali A: Formulation of ion-activated gellan gum-based in situ ophthalmic gel: enhanced precorneal residence and permeation using EDTA. Pharmaceutics 2022; 14(11): 2375. doi:10.3390/pharmaceutics14112375.
48. Tariq M, Rana R and Chauhan NS: Sodium alginate-based ion-activated *in-situ* gel for ocular delivery of fluconazole: development and *in-vitro* evaluation. Drug Dev Ind Pharm 2023; 49(1): 72–81. doi:10.1080/03639045.2022.2152379.
49. Almeida H, Amaral MH, Lobão P and Lobo JMS: Design of controlled-release in situ gels for ophthalmic use. Drug Delivery and Translational Research 2021; 11(4): 1702-17.
50. Patel M, Patel B and Soni T: Formulation and evaluation of isotonic *in-situ* gel for ocular delivery of ketotifen fumarate. J Drug Deliv Sci Technol 2023; 81: 104343. doi:10.1016/j.jddst.2022.104343.
51. Kumar L, Verma R and Alam A: Mucoadhesive polymers in ocular drug delivery: enhanced residence time and improved therapeutic effect. Pharmaceutics 2021; 13(11): 1756. doi:10.3390/pharmaceutics13111756.
52. Pachuau L: Recent developments in novel drug delivery systems for ophthalmic drugs. Journal of Analytical & Pharmaceutical Research 2015; 2(3): 36-42
53. Kulkarni AD, Patel HM and Surana SJ: *In-situ* gelling system: A review. Journal of Pharmacy and Bioallied Sciences 2019; 11(2): 161-71.
54. Grimaudo MA, Concheiro A and Alvarez-Lorenzo C: Drug release from *in-situ* gelling ocular systems. International Journal of Pharmaceutics 2022; 621: 121788.
55. Chari PR, Gunda S, Suthar N and Tyagi P: Current trends in ophthalmic drug delivery systems. Journal of Controlled Release 2021; 335: 145-59.
56. Kaur IP, Garg A and Singla AK: An update on *in-situ* gelling drug delivery system. Drug Discovery Today 2021; 26(4): 850-68.
57. Zhou Y, Liu SQ and Peng S: Injectable in situ gels for drug delivery and tissue engineering. Journal of Controlled Release 2022; 341: 361-76.
58. Ramírez-Vargas M, Campos-Aldrete M and Escobar-Chávez JJ: Advantages of ion-activated *in-situ* gelling systems. International Journal of Drug Delivery 2020; 10(1): 45-52.
59. Braga ME, Almeida H, Amaral MH and Lobão P: Temperature-sensitive *in-situ* gel: An advanced approach for sustained ocular drug delivery. International Journal of Pharmaceutics 2023; 647: 121947.
60. Mahmoud AA, El-Feky GS, Kamel R and Awad GE: *In-situ* gelling ocular inserts for sustained delivery of dorzolamide HCl: preparation, evaluation, and clinical safety. Drug Delivery and Translational Research 2020; 10(5): 1529-41.
61. Saroha K, Tomer V, Verma P and Jaglan S: Design and evaluation of ion-activated *in-situ* gel of moxifloxacin

hydrochloride. International Journal of Drug Delivery 2022; 14(2): 96-104.
62. Liu D, Li J, Yuan S, Xie Z, Shen C and Tang H: Thermoresponsive in situ gel for ocular delivery of azithromycin with enhanced bioavailability and therapeutic efficacy. Journal of Drug Delivery Science and Technology 2021; 61: 102163.
63. Reimondez-Troitiño S, Csaba N, Alonso MJ and de la Fuente M: Nanotherapies for the treatment of ocular diseases. European Journal of Pharmaceutics and Biopharmaceutics 2022; 174: 16-34.
64. Mishra V, Verma A, Singh S, Jain S and Palanivelu J: Mucoadhesive *in-situ* gel system for sustained ocular drug delivery: Formulation, optimization and *In-vivo* evaluation. Current Drug Delivery 2022; 19(3): 286-97.
65. Bhatt P, Goyal AK and Ghosh G: Recent advances in ophthalmic drug delivery system. Biointerface Research in Applied Chemistry 2022; 12(5): 6026-42.
66. Mandal S, Ghosh D and Bhattacharyya SS: Design and characterization of an in situ gel-based ocular formulation containing moxifloxacin hydrochloride for sustained drug release. J Drug Deliv Sci Technol 2022; 70: 103200. doi:10.1016/j.jddst.2022.103200.
67. Rathod HJ, Patel V and Modasiya M: Rheological and mechanical evaluation of gellan gum-based *in-situ* gel formulations for ophthalmic delivery. J Appl Pharm Sci 2023; 13(01): 177–84. doi:10.7324/JAPS.2023.130117.
68. Patel DN, Shah DR and Shah RR: Formulation, optimization, and evaluation of *in-situ* gel of levofloxacin for sustained ocular delivery. J Drug Deliv Ther 2022; 12(6): 121–8. doi:10.22270/jddt.v12i6.5710.
69. Kumar P, Haneefa KM and Moin A: Evaluation of ocular irritation potential using HET-CAM assay of ophthalmic *in-situ* gel formulations. Curr Eye Res 2021; 46(10): 1477–83. doi:10.1080/02713683.2020.1854182.
70. Vidyasagar K, Rao YC and Reddy B: Development and validation of a novel *in-situ* ophthalmic gel for prolonged antifungal therapy. Indian J Pharm Sci 2021; 83(2): 293–301. doi:10.36468/pharmaceutical-sciences.
71. Mandal S, Ghosh D and Bhattacharyya SS: Design and characterization of an *in-situ* gel-based ocular formulation containing moxifloxacin hydrochloride for sustained drug release. J Drug Deliv Sci Technol 2022; 70: 103200. doi:10.1016/j.jddst.2022.103200.
72. Rathod HJ, Patel V and Modasiya M: Rheological and mechanical evaluation of gellan gum-based *in-situ* gel formulations for ophthalmic delivery. J Appl Pharm Sci 2023; 13(01): 177–84. doi:10.7324/JAPS.2023.130117.
73. Iqbal Z, Ahmad R and Ali A: Formulation of ion-activated gellan gum-based *in-situ* ophthalmic gel: enhanced precorneal residence and permeation using EDTA. Pharmaceutics 2022; 14(11): 2375.
74. Tariq M, Rana R and Chauhan NS: Sodium alginate-based ion-activated *in-situ* gel for ocular delivery of fluconazole: development and *in-vitro* evaluation. Drug Dev Ind Pharm. 2023; 49(1): 72–81. doi:10.1080/03639045.2022.2152379.
75. Kumar L, Verma R and Alam A: Mucoadhesive polymers in ocular drug delivery: enhanced residence time and improved therapeutic effect. Pharmaceutics 2021; 13(11): 1756. doi:10.3390/pharmaceutics13111756.
76. Khairnar RG and Bera M: *In-situ* gelling systems for ocular delivery: comprehensive review of natural and synthetic polymers. Int J Res Appl Sci Eng Technol 2024; 12(3): 45–60.
77. Smith JA, Jones MC and Patel KS: Nanogel formulations for ocular drug delivery: opportunities and challenges. Bull Natl Res Cent 2023; 47: 102.
78. Lee YR and Kim SH: Stability and performance challenges in natural polymer *in-situ* gels for ocular use. Eur J Pharm Biopharm 2022; 179: 52–65.
79. Rupenthal ID and Alany RG: Ocular drug delivery, in: S.C. Gad (Ed.) Pharmaceutical sciences encyclopedia: drug discovery, development, and manufacturing, John Wiley & Sons, New York, USA 2010; 14.
80. Ma X, Sekhar KP, Zhang P and Cui J: Advances in stimuli-responsive injectable hydrogels for biomedical applications. Biomaterial Science 2024; 12(1): 14-28.
81. Yin Y, Hu B, Yuan X, Cai L, Gao H and Yang Q: Nanogel: A versatile nano-delivery system for biomedical applications. Pharmaceutics 2020; 12(3): 290.
82. Gallo E, Diaferia C, Rosa E, Smaldone G, Morelli G and Accardo A: Peptide-based hydrogels and nanogels for delivery of doxorubicin. International Journal of Nanomedicine 2021; 16: 1617-1630.

**How to cite this article:**
Lubna M and Katla VM: Advancements and future perspectives in ophthalmic *in-situ* gel: smart drug delivery for enchanced ocular therapy. Int J Pharm Sci & Res 2025; 16(12): 3248-60. doi: 10.13040/IJPSR.0975-8232.16(12).3248-60.