REVIEW ARTICLE

A Bird Eye View on *In-situ* Ophthalmic Gel: Challenges and Opportunities

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ABSTRACT

Ophthalmic *in-situ* gel is an advanced formulation that converts from liquid to gel upon contact with the eye, providing SR of a drug. Precise examination is crucial because of the delicate nature of ocular drug administration. Traditional methods are inefficient, leading to the rapid elimination of drugs. This article explores polymers utilized in ophthalmic delivery of drugs, detailing their applications in addition to limitations. *In-situ* gelling mechanisms convert liquid preparations toward gels beneath specific conditions, enhancing the delivery of the drug upon contact with the eye. Various mechanisms like temperature, pH, and ion-induced gelation are employed based on drug characteristics and desired properties. Understanding these mechanisms allows for the design of ophthalmic gels that progress drug bioavailability and patient compliance. These polymers also aid in prodrug investigation as well as enhancing ophthalmic penetration. Overall, *in-situ* ocular gels offer a hopeful approach to incapacitating challenges in the ophthalmic delivery of drugs, providing efficient and versatile drug administration with prolonged retention and enhanced bioavailability.

Keywords: *In-situ* gel, Ophthalmic, Ophthalmic delivery of drug system, Bioavailability, Polymers, Application.

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INTRODUCTION

A gel, known for its soft and stable properties, combines liquid and solid components and significantly represents an intermediate state between solids and fluids.[1] Its fundamental structure forms a stable three-dimensional network of components, with the polymer network established through either chemical or physical crosslinking of polymer chains.[2] Gels are classified into physical and chemical types, with physical gels characterized by weaker bonds similar to hydrogen and electrostatic interactions.[3] There's enhancing attention in physically crosslinked gels because of concerns over the toxicity of chemically crosslinked gels, which form strong covalent bonds.[4,5]

Hydrogels, characterized by their 3-D polymeric chain structures, can be easily shaped into various sizes and forms.[6] They possess remarkable absorption properties and smoothly conversion between liquid and gel states, making them a type of water-loving formulation.[7] Crosslinks within hydrogels allow them to hold significant quantities of H_2O as well as biological fluids, resulting in swelling. Hydrogels are divided into preformed and *in-situ* types.[8]

Preformed gels, also referred to as preformed particle gels (PPG), are simple viscous solutions that remain unchanged after application. PPG, containing highly absorbent crosslinking polymers capable of swelling significantly, acts as an agent to redirect fluids for conformance control.[9] This approach addresses specific limitations of *in-situ* gelation systems, including issues related to gel composition changes, degradation, and lack of control over gelation time. However, preformed gels may face challenges such as dilution by water and limitations in ophthalmic applications, resulting in less accurate dosing and potential vision disturbances.[10] These gels are applied externally before being delivered through a reservoir to prevent immediate gelation. Factors like pH, salinity, ions, hydrogen sulfide, temperature, as well as shear rate require careful consideration in their formulation.[11]

These gels are solutions or suspensions that solidify at a specific site upon interaction through body fluids or because of variations in physicochemical parameters or external stimuli.[12-14] This gel formation ensures SR of a drug, maintaining consistent drug levels in the body and prolonging drug retention on mucosal surfaces. These gels, with sol-

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to-gel conversion properties, are versatile for delivering bioactive molecules *via* various routes, including oral, buccal, transdermal, ocular, and others.[15-17] Their simple formulation reduces manufacturing complexity and costs. Gel formulations, particularly smart polymer gels, which adjust properties in response to environmental changes, have garnered significant interest in pharmaceutical research. Recent advancements in *in-situ* gels capitalize on physiological variations, making them a promising delivery of drug methods and a leading innovation in the field.[18-20]

Topical administration is preferred for eye medications because of its non-invasive nature and ease of use. However, achieving effective drug levels is challenging, necessitating sustained-release formulations to extend drug presence on the eye surface and minimize tear-related loss. Gel-based materials established in contact lenses, eye drops, and *in-situ* gel preparations have gained attention for their adaptability and usefulness in ophthalmology. This article discovers the part of *in-situ* gel-based materials in eye care, aiming to provide comprehensive insights into their applications and recent advancements to aid further research and development efforts.Top of Form

Ophthalmic Delivery of Drug

The pharmaceutical field of administering drugs to the eyes is rapidly expanding, particularly with the use of eye drops for conditions like macular degeneration, glaucoma, and dry eyes. However, delivering drugs to the eye faces unique challenges because of its constrained nature and constant movement. Traditional methods like eye drops, ointments, and injections often result in systemic side effects, low absorption rates, and poor patient compliance. The emergence of *in-situ* gel technology offers promising advancements in the ocular delivery of drug.[21, 22]

Current Challenges with Conventional Approaches

Traditional methods of delivering drugs to the eyes present challenges for patients and doctors alike. Eye drops, for example, have low bioavailability as much of the drug is lost before reaching its target.[23] The eye's natural tendency to expel foreign objects further limits the effective delivery of drug. Suboptimal bioavailability and poor patient adherence are common with traditional methods, leading to non-compliance.[24] Chronic conditions like glaucoma often require frequent, invasive injections, causing discomfort and infection risks. These limitations highlight the need for a more efficient and patient-friendly delivery of drug systems. This gelling technology offers a promising solution to these experiments.[25]

Need of Novel Approach (*In-situ* Based Ophthalmic Formulation)

The increasing prevalence of conditions like glaucoma, ocular keratitis, and diabetic retinopathy highlights the need for precise and efficient delivery of drugs. This gelling technology presents a superior alternative to traditional methods, offering controlled and prolonged drug application directly to the affected area.[26] Gel-forming polymers in *in-situ* gels protect the ocular surface, reducing the essential for recurrent injections as well as enhancing patient acquiescence. Advances in this technology, such as stimulus-responsive polymers and nanotechnology integration, enhance the delivery of drugs to specific ocular locations, improving bioavailability and extending release. The application of *in-situ* gel technology holds great promise for improving the management of ocular conditions and patient outcomes. Continued research is expected to yield more innovative and effective delivery of drug options.[26-28]

Advantages

In comparison to traditional ocular formulations, *in-situ* ocular gels present a range of benefits, positioning them as a promising and innovative method for delivering drugs to the eyes. Some key advantages include:

Prolonged residence time

Gel-like state ensures extended contact on the eye surface, enhancing drug absorption and therapeutic effects.

Improved bioavailability

Extended contact leads to enhanced drug absorption and controlled delivery, reducing the need for frequent administration.

Enhanced patient adherence

Less frequent application compared to traditional formulations promotes patient compliance and convenience.

Reduced systemic exposure

Localized delivery minimizes systemic absorption, reducing the risk of systemic side effects.

Accurate delivery of drug

Gelation mechanism enables precise release, maintaining therapeutic levels while minimizing overdosing or underdosing.

Preservation of sensitive drugs

Gel matrix protects drugs from degradation, ensuring their effectiveness.

Improved therapeutic effectiveness

SR of drug enhances efficacy, particularly beneficial for chronic conditions.

Reduced application frequency

Less frequent application enhances patient's superiority of lifecycle as well as management involvement. Generally, *in-situ* ophthalmic gelled offer an auspicious solution to overcome the limitations of traditional ocular formulations, improving delivery of drug effectiveness and patient comfort.[28]

Pathway of *In-situ* Gelling Approach in Eye

These methods provide a hopeful solution for overcoming a significant challenge in the ocular delivery of drug-penetrating tight junctions (TJ) to reach the internal regions of the eye. TJ in ocular tissues restricts drug movement, making it challenging in the direction of accomplishing beneficial applications in areas like the retina or aqueous humor. These preparations gel on contact with the eye, prolonging drug exposure and facilitating interaction with tight junctions. These gels adhere to ocular surfaces, enhancing drug permeation and can be tailored for gradual drug release. Additionally, they can incorporate penetration enhancers to temporarily disrupt tight junction integrity, aiding drug translocation. *In-situ* gels allow direct, targeted drug application, reducing systemic absorption and associated side effects. Leveraging *in-situ* gelling benefits can enhance the delivery of drugs to the inner eye, promising better management of ocular conditions affecting posterior segments.[28]

Mechanism of this gelling technique

This technique is an innovative delivery of drug method wherever a liquid transforms into a gel upon contact with the body. This approach offers advantages in ophthalmic drugs by enhancing bioavailability as well as residence time at the targetinglocation.[28] The gel slowly releases the drug, maintaining consistent drug levels. Formulated with biocompatible ingredients like polymers, lipids, and surfactants, it reduces side effects and improves patient compliance compared to conventional methods. Research in this area holds promise for transforming the treatment of ocular diseases.[29,30]

The sol-gel conversion in *in-situ* gel technology utilizes organic substances such as metal alkoxides or inorganic metal salts, known as "sol." This technique involves hydrolyzing, polymerizing, or condensing the predecessor to create a colloidal preparation. The conversion from sol to gel arises through polymerization and solvent loss. Factors like temperature, pH, and ion exchange can trigger activation of *in-situ* gelling systems.[30] Temperature-stimulated system involves liquid polymers that gel at an LCST.[31] The pH-triggered *in-situ* gel utilizes polymeric agents with acidic or basic functional groups in the chain molecule, undergoing sol-gel state modification with a pH change. Ion-induced systems, particularly osmotically induced ones, occur when ions in the lacrimal solution cause polymer transformation from sol to gel. Sol-gel conversion can also be initiated through photon polymerization as well as enzymatic crosslinking. These mechanisms of temperature sensitivity, pH change, and ion exchange-driven gels offer a versatile and effective approach to the delivery of drugs within the body.[32] Figure 1 illustrates different mechanisms of *in-situ* gelling technology.

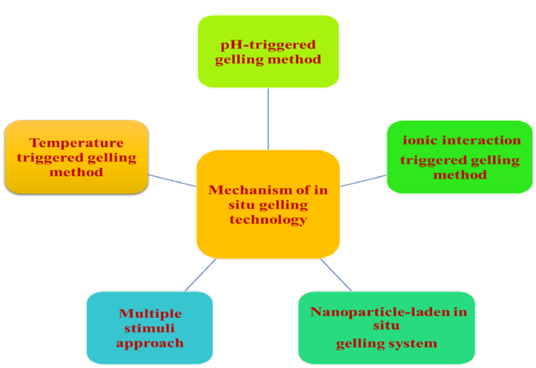

Figure 1: Different mechanism of *in-situ* gelling technology

The pH-triggered system

The pH fluctuations also play a part in the formation of *in-situ* gel, triggering gelation in response to pH changes. Under acidic pH conditions, the formulation remains a liquid solution but coalesces once the tear fluid increases the pH to 7.4. Upon instillation into the tear film with a pH of 4.4, the initially fluid latex rapidly converts keen on a dense gel. Polymers with pH sensitivity contain acidic or basic groups that either accept or release protons liable to the pH of the environment. Polyelectrolytes with multiple ionizable groups swell more at higher pH if anionic but less if cationic.

The temperature-triggered system

An effective technique for inducing gel formation includes using biopolymers that convert from sol to gel when the temperature rises. These temperature-sensitive smart polymers undergo gelation when the temperature exceeds the LCST.[33] The LCST is the temperature at which constituents of a combination can blend completely in any proportion. Importantly, the critical temperature for this technique is suitable for physiological and environmental conditions. Conversion is triggered solely by body heat. No external heating is required. This approach utilizes poloxamer as a carrier for ocular drugs, taking advantage of its *in-situ* gel-developing characteristics for targeted delivery of drugs in the direction of the eye.[34]

The phase alteration temperature of graft copolymers is determined by the temperature at which the meniscus first becomes immobile in each solution, which is crucial in this method. These copolymers offer potential as a DDS for prolonged ophthalmic administration owing to their bio-adhesive and thermos-gelling characteristics. During gel development above LCSTs, these copolymers initially appear as clear, and consistent, in addition to spontaneously flow polymeric methods at temperatures beneath the LCST. However, once the temperature reaches the LCST, the systems turn cloudy because of increased turbidity initiated by polymer chain collapse and aggregation, leading to heightened light scattering. Beyond LCST, phase parting splits the solution into gel and solvent states, driven by the rising temperature's entropy effect.[33,34]

The ionic-interaction triggered system

The shift from sol to gel can be initiated through anionic polysaccharides, which interact through divalent (Mg^{+2} and Ca^{+2}) and/or monovalent (Na^{+}) cations found in tear fluid, leading to increased polymer viscosity through crosslinking. As tear fluid dilutes viscous solutions, the concentration of cations, both divalent and monovalent, rises, consequently increasing polymer viscosity. This process extends drug retention in the eye, reduces lacrimal drainage, and improves drug bioavailability.

Multiple responsive-based systems

Combining different polymers with various gelling techniques has shown improved therapeutic effectiveness and patient acceptance. The maximum operational mode for ocular *in-situ* gelling currently involves using multiple stimuli-responsive approaches. Recent studies have explored applying the identical ophthalmic preparation through polymers reactive to pH, temperature, or ion changes. Strategies for precise drug-releasing controllers improve beneficial consequences. Multiple stimuli-responsive approaches encompass utilizing diverse triggers like temperature, pH, ions, and enzymes to convert the ocular formulation from liquid to gel upon application.[35]

- Dual-responsive gels combine polymers sensitive to temperature and pH variations, enabling phase conversion at body temperature and tear fluid pH. This enhances optical gelation, enhancing drug retention as well as release.
- The pH and enzyme double reactive gels responding the direction of pH changes as well as tear fluid enzymes, catalyzing gel formation. These systems mimic the dynamic nature of the biological environment.
- Ion and temperature double reactive gels use polymers delicate to ion concentration as well as temperature, targeting gelation in response to ocular conditions.
- Triple-responsive gels incorporate pH, temperature, and ion responsiveness for complex customization of the delivery of drug profiles.
- Sequentially responsive gels undergo pre-gelation because of pH changes and subsequent gelation at specific temperatures, offering intelligent drug administration.

The utilization of multiple stimuli-responsive gelling techniques offers tailored ophthalmic distribution of drugs, optimizing release kinetics, increasing bioavailability, and enhancing patient comfort and compliance. Yet, the intricate coordination of stimuli and the need for precise control over gelation and drug release pose challenges in system design and development.

Nanoparticle-laden system

In recent years, nanoparticles (NP) have gained popularity for their ability to efficiently deliver drugs to targeted sites, ensuring optimal therapeutic effects. These nanoparticles, typically ranging from 10 to a few nanometers in size, either dissolve or encapsulate drugs within a polymeric matrix. They have revealed considerable promise in the ophthalmic distribution of drugs. Various methods are available for producing these nanoparticles, with one common approach involving dissolving the polymer in an organic solvent. The drug substance is then distributed in this polymer solution in the direction of making a W/O emulsion, which is further emulsified in an aqueous solution. However, it's important to highlight that the use of organic solvents in this process may pose health risks.[36]

The USFDA have imposed restrictions on the quantity of organic solvents allowed in injectable colloidal methods. However, for producing PNP, commonly utilized methods include the salting out technique and supercritical fluids. Two approaches for drug encapsulation in NP: throughout NP development or by adding NP to a drug solution. The former method is more efficient as it captures a significant amount of drug during incorporation. Subsequently, these drug-containing nanoparticles are combined with a gel base for ocular therapy. Innovative therapeutic delivery relies on effective gelling preparations, utilizing lipid-centered nano-carriers and nano-suspensions to enhance the absorption of ocular therapeutics.[36]

Advantages of system

Ophthalmic *in-situ* nano-gels enhance drug bioavailability for eye ailments, surpassing other delivery methods. Their small nanoparticle size facilitates drug penetration into ocular tissues, leading to increased drug concentrations at the targeting location. Furthermore, these nano-gels are effectively regulating releasing of drugs, ensuring a slow and SR compared to rapid removal by ocular drops. This feature is particularly beneficial for chronic eye conditions requiring continuous drug resources. These gels are user-friendly as well as non-invasive, promoting patient and physician acceptance. Their biocompatibility and biodegradability help prevent adverse reactions and toxicity. In summary, ocular *in-situ* nano-gels hold promise for improving the delivery of drugs for eye disorders, with ongoing nanotechnology research offering the potential for further advancements.**Top of Form**

Drawbacks and challenges in system

Like any delivery of drug method, ophthalmic *in-situ* nano-gels have limitations. One major challenge is their stability, as they often have a short shelf life and are prone to damage. Their effectiveness is also influenced by their size and shape, needing to be small enough to penetrate the cornea but large enough to avoid easy elimination. Regulating drug release from nano-gels is crucial for maintaining efficacy, requiring careful planning and testing. Additionally, the complexity of these nano-gels makes regulatory approval difficult, especially for smaller companies facing lengthy clearance processes. Despite these challenges, ocular *in-situ* nano-gels show promise for treating various eye conditions, and further research could improve their safety and effectiveness.

Polymers Utilized in This Technology

Polymers in pH-triggered system

- *Carbopol*

Carbopol, a polymer derived from poly-acrylic acid (PAA), undergoes a sol-gel conversion in an aqueous solution when the pH surpasses its pK value of approximately 5.5. At low and high pH levels, PAA's carboxylic groups accept and release protons, respectively. This expansion of PAA at high pH, driven by electrostatic repulsion of negatively charged groups, leads to drug molecule release. Carbopol's use in ocular preparations aims to extend pre-corneal drug retention, albeit lacking enhanced mucoadhesive properties compared to other polymers. While its muco-adhesive properties are attributed to interactions with mucin, such as hydrogen bonding, electrostatic interface, inter-diffusion, and hydrophobic interface, Carbopol's acidic nature may cause ocular tissue irritation. To mitigate this, novel blends of Carbopol with polymers like HPMC and chitosan have been developed.[37,38]

Polymers in temperature-triggered system

- *Poloxamers*

Poloxamers, also known as pluronic copolymers, are amphiphilic tri-block copolymers containing of hydrophobic propylene oxide and hydrophilic ethylene oxide segments. When their concentration exceeds 15% (w/w), these copolymers form gels at physiological temperatures because of mechanisms like polymer decomposition and micellar accumulation. Different grades of Poloxamers are available, such as L for liquids, P for pastes, and F for flakes, with frequently utilized varieties including Poloxamers 338, 188, 407, and 237. Poloxamer 407, or F-127, with 70% ethylene oxide content, is hydrophilic, non-toxic, as well as lesser gelatinous beneath 4°C. Notably, F-127 undergoes gelation at body temperature because of hydrogen bonds and higher solubility in lower-temperature of water compared to higher-temperature water.[38-40]

- *Xyloglucan*

Tamarind seed polysaccharide (TSP), sourced from tamarind seeds, forms reversible gels in diluted aqueous solutions when partially broken down by β-galactosidase. The temperature triggering the sol-gel conversion rest on the degree of galactose degradation. TSP gels show promise for delivery of drug via oral, ocular, intraperitoneal, and rectal routes because of their solubility in water, with gelation occurring when over 35% of galactose is removed.[41]

- *Cellulose*

Cellulose and its derivatives, like methylcellulose and hydroxypropyl methylcellulose, are commonly utilized in ocular preparations. These derivatives convert from a liquid to a gel state once exposed to heat, with critical temperature ranges varying based on the specific derivative. For example, methylcellulose gels at temperatures between 45 to 50°C, while hydroxypropyl methylcellulose gels between 70 to 90 °C. Adjustments such as the addition of sodium chloride can modify the gel-forming temperature, making it lower.[42, 43]

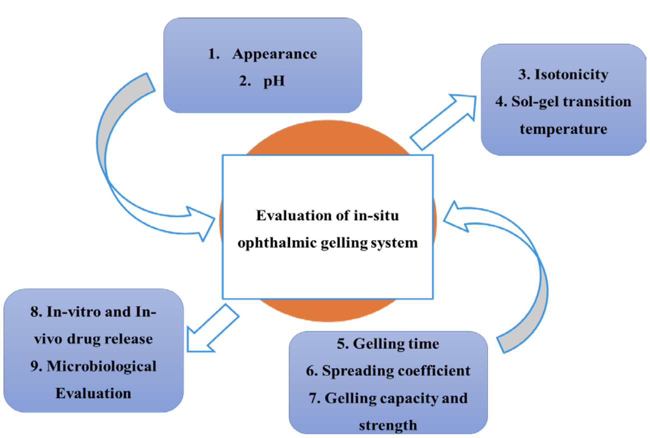

Figure 2: Evaluation of *in-situ* gel

- *Chitosan*

Chitosan, derived from chitin found in marine animal shells, is a natural polysaccharide known for its biocompatibility and biodegradability. It has gained prominence for its affinity in the direction of self-lubricating membranes as well as minimal immunogenicity. Current focus temperature-sensitive gels with chitosan and polyols similar to glycerol, sorbitol, and ethylene glycol. Thiolated Chitosan (TCS), created by adding thiol groups to chitosan's primary amino groups, is recognized for its strong adhesion to mucous membranes, allowing sustained drug retention. Gelation in TCS occurs through the formation of disulfide bonds, both between and within molecules, upon oxidation of thiol groups at physiological pH levels.[37, 44]

Polymers in ionic-interaction

- *Gellan gum*

Gellan gum, an ion-sensitive hydrogel enhancer, is a linear anionic hetero-polysaccharide consisting of glucuronic acid, rhamnose, as well as glucose in specific ratios. It contains COOH- and –OH groups, allowing interaction utilizingsupplementary polymers done electrical attraction as well as H-bonding. Gelrite®, a commercially available product, forms gels upon exposure to monovalent or divalent cations like Na^{+}, Mg^{+2}, and Ca^{+2} present in tear fluid electrolytes. The introduction of calcium gluconate enhances the strength of gellan-STF gels, possibly through the establishment of double-helix connection regions that aggregate into a 3-Dbackgroundthrough interacting with H_2O and cations.[45, 46]

- *Alginate*

Alginate, from bacteria and brown seaweeds, contains R-l-guluronate (G) and a-d-mannuronate (M) monomers. Interaction with Ca^{+2} forms calcium alginate gel. Gel strength and porosity depend on guluronic acid content, with higher proportions enhancing gelation efficiency.[47]

- *Pectin*

Pectins, a group of polysaccharides, primarily consist of α-(1,4)-d-galacturonic acid (GA) residues in their polymer backbone. Slightly methoxy pectins, with esterification units below 50%, can gel in water when exposed to free Ca^{+2}, leading to crosslinking of GA chains. Pectin's solubility in H_2O eliminates the requirement for organic solvents in preparations. In tear fluid, Ca^{+2} induces *in-situ* gelling of pectin, as documented in a USA patent. Pectin-based formulations have been shown in the direction of extending drug-releasing time in various preparations, such as acetaminophen, cimetidine, and theophylline.[48]

Evaluation of in-situ ophthalmic gelling method

Figure 2 provides detailed information regarding the assessment of *in-situ* ophthalmic gelling methods.

Recent studies in this gelling system:

Table 1 illustrates the investigation evolvement update in the *in-situ* gelling method.

Table 1: Research devolvement of *in-situ* gelling system[49,50]

Authors	*Outcomes*
pH triggered system	
Wu *et al*. 2011	Baicalin-loaded pH-responsive gels for sustained ocular drug release employed a blend of carbopol 974P and HPMC E4M (0.6%, w/w). Rheological analysis indicated significant gel enhancement under physiological conditions, with continuous drug release observed over eight hours. Notably, Cmax and AUC values were 3.6 and 6.1 times higher, respectively, equated in the direction of the control solution.Top of FormTop of Form
Alsaidan *et al*. 2022	Researchers developed *in-situ* gels loaded with ciprofloxacin-containing bilosomes for ocular delivery, aiming to reduce drug loss from blinking reflex and nasolacrimal drainage. Bilosomes were optimized using cholesterol, Span 60, and sodium deoxycholate, then integrated into a gel base of carbopol 934P and HPMC K100M. The resulting gel showed superior gelling properties, viscosity of 145.85 cP, sustained release, improved permeability, and enhanced antimicrobial efficacy compared to conventional ciprofloxacin gels.Top of Form
Suryawanshi and Panda (2023)	Researchers developed a pH-sensitive polymeric material using a cost-effective microwave irradiation process with KPS as the redox initiator, offering an environmentally friendly approach. Batch BSM-4 exhibited 464% grafting and 107.23% GE. Comprehensive analyses, including FTIR, DSC, H-NMR, and XRD, confirmed the grafting procedure completion and revealed alterations in functional groups. BSM-4 demonstrated the safety and efficacy of the BSM polymeric network for oral delivery of BCS class II and IV drugs. Toxicity studies indicated the non-toxic nature of the developed polymeric network, suggesting its potential for various oral deliveries of drug methods.Top of Form
Temperature triggered system	
Bellotti *et al* 2019	Improvements were made to temperature-sensitive hydrogels containing pNIPAAm for treating glaucoma by adjusting PEG quantity and molecular weight. The aim was to lower the LCST of the eye gel for faster gel formation upon application and ensure consistent sol-gel conversion in cold conditions. In vitro testing showed repeated release of the glaucoma drug brimonidine tartrate over 28 days.
Oswald *et al* 2017	Microspheres containing anti-VEGF agents (ranibizumab or aflibercept) were formulated utilizing poly(lactic-co-glycolic acid) and incorporated into an injectable thermo-responsive hydrogel based on poly(N-isopropyl acrylamide) to create a DDS. The efficacy of this treatment was evaluated in vivo utilizing a rat model with laser-induced CNV. CNV lesion areas were evaluated using fluorescein angiograms with a multi-Otsu thresholding method, IOP and ERG were monitored before in addition to after management at various intervals. Results showed significantly reduced CNV lesions in the group treated with the anti-VEGF-loaded DDS compared to an untreated control group, indicating promising potential for addressing posterior segment eye conditions.
Jimenez *et al* 2021	A novel microsphere/temperature-responsive gel system was created to improve the delivery of cysteamine, a treatment for cystinosis. The gel, made from pNIPAAm, enabled SR of cysteamine over 12 hours with a single application. Direct application to the eye showed efficient delivery to the cornea while reducing systemic absorption.
Ionic interaction system	
Elmowafy *et al*. 2019	The *in-situ* gelling method demonstrated non-irritating properties and validated its potential for buccal delivery.
Zhu *et al*. 2015	Novel ophthalmic ketotifen formulations were created using de-acetylated gellan gum to prolong ocular residence time. Compared to conventional solutions, these formulations showed significantly longer effectiveness. However, incorporating poorly water-soluble drugs into bio-adhesive, ion-sensitive hydrogels presents challenges.
Bhalerao *et al* 2020	Cyclodextrins are utilized in pharmaceuticals to aid in formulating poorly water-soluble drugs. Adding hydroxypropyl-cyclodextrin to the *in-situ* gel improved the release of fluconazole. An *in-situ* ocular gel containing gellan gum, along with dimethyl sulfoxide, polyoxyl 35, castor oil, and polysorbate 80, was developed for brinzolamide. Brinzolamide showed enhanced therapeutic effectiveness and sustained reduction in intraocular pressure when formulated in the *in-situ* gel compared to traditional eye drops and tablets.
Multiple stimulated triggered system	
Khan *et al*. 2015	A novel mode for ocular delivery of drug was developed, using sparfloxacin incorporated in a blend of MC and SA, triggered by both pH and ions. The formulation remained soluble at pH 4.7 but gelled rapidly at pH 7.4. Unlike conventional eye drops, sparfloxacin release from the *in-situ* ocular preparation was extended for 24 hours. Ex-vivo testing on goat eyes showed notably enhanced corneal penetration with the prepared *in-situ* gel compared to regular eye drops.
Yu *et al*. 2017	A new *in-situ* gel for nepafenac was created by blending poloxamer and carboxymethyl chitosan, which exhibited adjustable sol–gel transformation characteristics in reactionin the direction of pH and temperature variations. The formulation was found to be non-toxic to corneal epithelial cells at lower concentrations. Nepafenac release from the gel showed SR characteristics, with maximum release observed at 35ºC and pH 7.4. Additionally, *in-situ* formulations containing sodium alginate and methylcellulose, triggered by both ions and pH, demonstrated rapid gelation at pH 7.4 and sustained Sparfloxacin released completed 24 hours.
Nanoparticle-laden system	
Liu *et al*. 2016	Researchers created a Curcumin-loaded nano-gel for ophthalmic use, employing cationic nanostructured phospholipid carriers and a temperature-sensitive gelling agent. The Curcumin nano-gel showed enhanced bioavailability compared to Curcumin ocular drops, with the optimized *in-situ* gelling ocular insert demonstrating improved pharmacokinetic parameters and nonirritating properties.

Al-Khateb *et al*. 2016	A new *in-situ* gel activated by ions and incorporating ofloxacin microspheres, demonstrated higher bioavailability in rabbit studies compared to standard eye treatments. This formulation extended drug action, reducing the necessity for frequent administration and enhancing patient adherence.
Pandurangan *et al*. 2016	Nanoparticle-enriched *in-situ* gel formulations showed prolonged eye retention compared to commercial equivalents. Similarly, sparfloxacin-loaded *in-situ* gels with nanoparticles exhibited remarkable SR. A temperature-sensitive nanoemulsion containing Loteprednol in Poloxamer 407 and 188 outperformed commercial products, boosting MRT and bioavailability by 2.54-fold.

Table 2: A summary of the reported drugs and polymers utilized in this system[51-56]

Drug	*Polymer Utilized*	*Route of Administration*	*Reference*
Doxorubicin	Human serum albumin and tartaric acid derivative	Parenteral	51
Paracetamol and Ambroxo	Pectin	Oral	52
Pheniramine maleate and albumin FITC	Polymethacrylic acid	Parenteral	53
Recombinant human interleukin-2	Dextran	Parenteral	54
Testosterone	PLA and PLGA	Parenteral	55
Theophylline	Gellan Gum	Oral	56

Table 3: Summary of the marketed products of *in-situ* system[57-62]

Company name	*Product name*	*Drug utilized*	*Reference*
akten	Akten™	Lidocaine Hydrochloride	57
Alkon Laboratories	Pilopine HS	Pilocarpine Hydrochloride	58
Insite vision	Azasite	Azithromycin	59
Macromed	Cytoryn	Interleukin-2 (IL-2)	60
Macromed	Regel Depot Technology	Human Growth Hormone	61
Merck Pvt. Ltd.	Timoptic-XE	Timolol Maleate	62
Spectrum Thea Pharmaceuticals	Virgan	Ganciclovir	58

Table 2 and 3 presented an overview of the reported drug and polymer combinations in gelling method, in addition to a summary of commercially available products using the *in-situ* system.

Future perspectives

The *in-situ* gel method for distributing ophthalmic drugs shows promise, although there are areas where enhancements can be made.[63-65] Nanotechnology presents opportunities for advancing the compositions of *in-situ* gels, with nanoparticles offering benefits such as improved drug solubility, stability, uptake, and delivery to ocular tissues.[66-68] Another area of focus is stimuli-responsive *in-situ* gels, which react to factors like temperature and pH to enable controlled and targeted drug distribution, thereby enhancing delivery efficacy and minimizing side effects.[69-72] Additionally, researchers are investigating the use of biodegradable materials for *in-situ* hydrogels, which could improve patient comfort by enabling slow absorption in the body and potentially eliminating the need for elimination procedures.[73] Overall, strategies involving this system hold promise for enhancing the delivery of therapeutic compounds to the eye and improving ocular drug distribution.[74-76]

There are various methods for administering drugs in the direction of the eye, but *in-situ* gel technology stands out because of its exclusive properties as well as benefits compared to traditional approaches.[77] One notable benefit of this gelling technique is its ability to sustain the release of pharmaceuticals, so outspreading the existence of the drug in the eye in addition to improving its effectiveness. Unlike eye drops, which are speedily expelled from the eye, *in-situ* gel technology releases drugs at a slower rate, reducing the frequency of drug administration.[78-80] This slower release also improves the bioavailability of the drug, ensuring that more drugs reach the targeted area, thereby enhancing its therapeutic effects. In contrast, ocular implants offer SR of drug but may cause discomfort during insertion and removal, potentially leading to non-compliance.[81-84] In essence, *in-situ* gel expertise suggestions SR of a drug, enhanced bioavailability, as well as decreased frequency of drug administration, presenting a favorable alternative for delivering drugs to the eyes. Moreover, it provides quicker and more comfortable administration compared in the direction of supplementary topical DDS.

CONCLUSION

In summary, the application of *in-situ* gel technology in the ocular delivery of drugs holds promise for mitigating the limitations of existing DDSs. These gels contribute to enhanced bioavailability, extended drug release, and reduced dosing frequency, thereby improving patient acceptance and clinical outcomes. Notwithstanding notable advancements in this field, challenges persist, particularly in maintaining optimal drug concentrations over prolonged periods through *in-situ* gelling procedures. Additionally, optimizing formulation parameters for the stability and safety of *in-situ* gels remains a significant hurdle. The potential development of stimuli-responsive devices within *in-situ* gel technology that can adapt to changes in the ocular environment presents an ongoing area of exploration. Advanced delivery of drug methods, including nanotechnology, offers avenues for enhancing the efficacy and safety of this gelling system. The continued progress of research in *in-situ* formulation technology has the potential to revolutionize the distribution of ophthalmic drugs and enhance the quality of life for individuals with ocular diseases. With ongoing advancements, *in-situ* gels may emerge as the favorite method for the ocular delivery of drugs.

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