



Thermosensitive in situ gels for ocular drug delivery: Advances in polymer-based formulations

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ABSTRACT

Ocular drug delivery presents significant challenges due to the unique anatomical and physiological barriers of the human eye, with the rapid precorneal elimination, limiting the bioavailability of conventional eye drops. Thermosensitive in situ gels have emerged as a promising delivery system to overcome these limitations by undergoing a reversible sol-to-gel transition upon contact with ocular surface temperature, which facilitates ease of administration as a liquid and subsequent transformation into a gel, thereby enhancing precorneal residence time, prolonging the drug release, and improving therapeutic efficacy. This review provides a comprehensive overview of thermos-responsive polymer-based ocular delivery systems, with a specific focus on poloxamers, poly(N-isopropylacrylamide), and cellulose derivatives. Particular attention is given to the physicochemical mechanisms of thermogelation, such as poloxamer micellization and micelle packing, as well as the role of auxiliary polymers in enhancing mucoadhesion, mechanical strength, and gel retention. Additionally, the review synthesizes findings from multiple experimental studies to highlight the critical formulation parameters essential for developing effective in situ gels, including sol-gel transition temperature and time, clarity, rheological behavior, gelling capacity, isotonicity, and ocular biocompatibility. By selecting an optimized thermosensitive in situ gel formulation with suitable characteristics, it becomes possible to develop effective delivery systems targeting both the anterior and posterior segments of the eye.

1. Introduction

The human eye is a complex and delicate organ essential for vision. By capturing light from the environment and converting it into neural signals, the eye transmits visual information to the brain through the optic nerve pathways, enabling the perception of sight. It consists of anterior and posterior segments, safeguarded by the orbit and eyelid sclera. The anterior segment includes the cornea, aqueous humour, iris, ciliary body, and crystalline lens, while the posterior segment comprises the retina and vitreous humour. The cornea, composed of epithelium, stroma, and endothelium, maintains structural integrity through the lamellar stroma but limits the diffusion of hydrophilic and hydrophobic molecules, resulting in low ocular bioavailability (1–7%) (Cholkar et al., 2013; Krishnaswami et al., 2018). This corneal epithelium forms the primary barrier to drug penetration due to tight junctions (zonula

occludens) in its apical layer, which seal the intercellular spaces and restrict paracellular transport. Additional structures such as desmosomes, adherens junctions, and hemidesmosomes provide mechanical strength, further limiting drug diffusion across the cornea (Mantelli et al., 2013). Ocular diseases are usually associated with one of the anterior or posterior segments. For instance, conjunctivitis, glaucoma, blepharitis, and cataracts are some of the diseases that affect the anterior segment of the eye, while diabetic retinopathy and age-related macular degeneration are known as posterior diseases (Wu et al., 2019).

Ocular drug delivery is challenging due to the complex anatomy of the eye and protective barriers that limit drug absorption and retention. Topical administration is preferred over systemic administration for treating anterior segment diseases. However, the barriers preventing less than 5% of the dose from reaching intraocular tissues are related to precorneal factors, such as blinking, tear drainage, lacrimation, and

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anatomical structure barriers. The lipophilic corneal epithelium blocks hydrophilic drugs, while the stroma limits the permeation of lipophilic ones, requiring drugs to be amphipathic for effective permeation through the cornea. Conjunctival vessels reduce bioavailability through systemic absorption, and scleral permeability varies with molecular size, structure, and charge (Gaudana et al., 2010). Another challenge is the low capacity of the cul-de-sac. Under normal conditions, the human conjunctival cul-de-sac holds 7–10 μL of fluid in the upright position and without blinking, which can be expanded up to $\sim 30 \mu\text{L}$ without overflow. However, most commercial eye drops have a volume of 25–70 μL , which far exceeds this capacity. As a result, 20–30 μL of the applied eye drop is immediately lost by overflow onto the skin. Moreover, the sudden increase in volume triggers reflex blinking, tearing, and accelerated nasolacrimal drainage, which dilutes the drug, lowering its concentration and its therapeutic activity (Ahmed et al., 2023; Santos et al., 2025; Van Santvliet and Ludwig, 2004). Furthermore, corneal absorption occurs more slowly compared to elimination processes such as drainage, dilution, and blinking, which limit drug absorption and reduce bioavailability (Mundada and Avari, 2009).

In order to overcome the poor bioavailability of more than 90% of marketed traditional eye drops, other ophthalmic products, such as ointments and ocular inserts are applied, can improve drug retention but often result in blurred vision and lower patient compliance. Systemic and invasive drug delivery methods, including intravitreal injections, are either inefficient or uncomfortable, which complicates effective ocular drug administration (Lanier et al., 2021). To overcome these limitations, researchers have explored advanced drug delivery systems, including prodrugs, permeation enhancers, and nanocarriers. A key strategy highlighted is the use of in situ gelling systems, which can improve precorneal retention and drug bioavailability, offering a promising solution for sustained drug delivery (Jumelle et al., 2020).

This review provides a comprehensive overview of in situ gel drug delivery systems, with a particular emphasis on thermosensitive polymers used for ocular applications. While previous reviews have largely concentrated on all in situ gel strategies such as pH- or ion-sensitive systems, our review distinguishes itself by focusing on different classes of thermo-responsive polymers, their structural features, micellization behaviour, sol–gel transition mechanisms, and the outlines of the formulation strategies for the preparation process. Additionally, it provides practical insights into advanced characterisation techniques, from rheological profiling and gelation kinetics to in vitro release and mucoadhesion studies. This review serves as an essential resource for researchers and formulators aiming to harness the full potential of thermosensitive in situ gels in ocular drug delivery.

2. Gels as drug delivery systems

Gels are semi-solid systems denser than liquids. Hydrogels comprise cross-linked hydrophilic polymers that absorb and retain water while maintaining a 3D structure. They include pre-formed hydrogels, which retain their form before application, and in situ gels, which transition from liquid to gel in response to physiological triggers (Bashir et al., 2021). The term "gel" originates from the Latin "gelu," meaning "frost" or "freeze," reflecting the transformation of a liquid into a solid-like, elastic material (Rathod and Mehta, 2015). Therefore, in situ gel drug delivery systems remain in a liquid state before administration and undergo gelation when exposed to physiological conditions (Chaudhary and Verma, 2014).

In recent years, in situ gelling systems have garnered significant attention as a novel approach to drug delivery. Their versatility allows for administration via multiple routes, allowing both local and systemic therapeutic effects. For example, they enhance nasal absorption, prolong buccal contact, and enable targeted gastrointestinal release via pH-sensitive hydrogels. Poloxamer-based gel systems have also improved the rectal, vaginal, and intravesical delivery due to their thermosensitive gelation. Furthermore, injectable PLGA-based gel systems offer

sustained release without the need for surgery (Vigani et al., 2020).

Across these routes, the main advantage of in situ gels lies in their sol-gel transition at the administration site, enabling sustained and controlled drug release. This transition increases the residence time of the formulation, improves drug bioavailability, enhances patient comfort through easy administration, and reduces dosing frequency. Moreover, the in situ gel systems utilize biocompatible and biodegradable natural or modifiable synthetic polymers, with some formulations specifically designed for adhesion to mucosal surfaces, enabling targeted, non-invasive drug delivery. (Mohanty et al., n.d.).

Among all applications, ophthalmic in situ gels have emerged as one of the most impactful examples, improving precorneal retention and enhancing ocular drug absorption and clinical efficacy throughout their response to physiological stimuli (temperature, ions, pH). For instance, thermosensitive in situ gels of betaxolol hydrochloride demonstrated ~ 2 -fold higher corneal area under curve (AUC) and mean residence time compared to the commercially available suspension eye drop approved by the Food and Drug Administration (FDA), Betoptic S[®], with higher drug levels at 4 hours, broader drug compatibility, and enhanced ocular retention (Wei et al., 2020).

3. Approaches of the gelling system

In situ gels can be formed through three primary mechanisms: physiological stimuli, physical changes, and chemical reactions.

1. Physiological stimuli include temperature-sensitive and pH-responsive polymers that undergo gelation when they encounter body conditions.
2. Physical changes, such as solvent exchange or swelling, alter the polymer structure, resulting in the formation of a gel.
3. Chemical reactions, including enzymatic or ionic cross-linking, induce gelation through molecular interactions. Photo-initiated polymerization, which occurs when light exposure activates polymerization, forms a gel and is commonly used for the in situ formation of biomaterials.

These mechanisms enable controlled and sustained drug delivery, enhancing therapeutic efficacy and patient compliance (Bakliwal and Pawar, 2010; Singh and Lee, 2014).

4. Ophthalmic in situ gel drug delivery system

Developing in situ gel systems represents a significant advancement in ocular drug delivery. These systems address the limitations of conventional eye drops by extending drug retention, ensuring sustained release, enhancing bioavailability, and enhancing therapeutic effectiveness. The liquid formulations transition into gels upon contact with the eye, offering a simple, cost-effective approach with accurate dosing while preventing drug leakage into surrounding tissues (Ahmed et al., 2024). Compared to traditional formulations, in situ gel technology enables precise and prolonged drug release, reducing the need for frequent dosing and improving patient compliance. For instance, a recent study found that traditional Ganciclovir eye drops typically exhibit a short ocular residence time of less than 5 minutes, whereas the in situ gel formulation sustained drug presence on the ocular surface for up to 12 hours. Moreover, pharmacokinetic evaluations demonstrated that the in situ gel achieved significantly higher peak drug concentrations and a greater AUC, reflecting enhanced ocular absorption and prolonged therapeutic levels compared to conventional eye drops (Paul et al., 2025). Another study found that levofloxacin in situ gel retention time was up to 12 hours in rabbit eyes, compared to 4 hours for commercial Levoxin[®] eye drops (Saher et al., 2016).

The gel-forming polymers protect the ocular surface and enhance drug penetration into deeper eye segments through their viscoelastic properties, which allow them to adhere and spread evenly across the eye

Table 1

Physiological parameters of the human eye relevant to ocular drug delivery.

Parameter	Values	Ref.
Tear pH	7.45	(Conditions and Flattau, 1991)
Tear film volume	3 μ L in volume that covers the outer mucosal surfaces of the eye.	(Dartt and Willcox, 2013)
Tear film thickness	Unique thin fluid layer approximately 3 mm thick.	(Dartt and Willcox, 2013)
Normal tear secretion	1-2 μ L/min	(Van Haeringen, 1981)
The precorneal film	Complex layer of fluid with a thickness of 5-10 μ M.	(Van Haeringen, 1981)
Ocular surface temperature	Typically ranges from 31 to 37°C	(Shah and Galor, 2021)
Tear Osmolarity	302 $\pm$ 9.7 mOsm/L	(Bron and Willshire, 2021)
The Cul-de-sac capacity	Approximately 30 μ L	(Singh et al., 2020)
Tear fluid ion concentration	Na ⁺ :120-165 mM, Mg ²⁺ : 0.5-1.1 mM, Ca ²⁺ :0.4-1.1 mM, Cl ⁻ :118-135 mM, K ⁺ :15-42 mM, HCO ₃ ⁻ : 20 - 42 mM.	(Tseng et al., 2018)

surface, prolonging the drug-tissue interaction time and facilitating better absorption across ocular barriers. Researchers can optimize drug targeting by utilizing stimulus-responsive polymers that respond to changes in temperature, pH, or ion concentration. Furthermore, their formulation may be enhanced using penetration enhancers, mucoadhesive substances, and controlled-release systems to guarantee consistent and effective drug delivery. Ultimately, in situ gelling technology presents considerable potential for advancing the management of ocular diseases by improving drug penetration and ensuring more effective treatment for conditions impacting both the anterior and posterior segments (Paul et al., 2023). Table 1 highlights the physiological characteristics of the eye, such as tear volume, pH, and osmolarity, which play a crucial role in influencing the performance of ocular drug delivery systems.

5. Mechanisms of ocular drug delivery systems

The liquid-gel phase transition varies based on the specific polymer used and its mechanism for initiating the transition to the gel phase in the eye, influenced by changes in temperature, pH, and ion sensitivity. Polymers are essential components of most drug delivery systems. Recently, these materials have gained significant attention in drug delivery research as stimuli-responsive polymers. The following section provides a detailed discussion of these intelligent polymers that exhibit in situ gelation induced by temperature, pH, and ions.

Table 2

Summary of pH-sensitive in situ gel formulations for ocular drug delivery.

Model Drug	Polymers	Major findings	Ref.
Dorzolamide	Carbopol®+ HPMC	Optimized gel with mucoadhesive properties, prolonged precorneal residence time, improved bioavailability, and efficacy for glaucoma.	(Kouchak et al., 2019)
Baicalin	Carbopol®+ HPMC	Rapid gelation, enhanced residence time, sustained release (8h), and improved ocular bioavailability.	(Wu et al., 2011)
Vinpocetine	Carbopol®+ HPMC	Superior systemic absorption for brain targeting, prolonged ocular residence time, and improved pharmacokinetic profile compared to ointment.	(Ma et al., 2020)
Besifloxacin HCl	Carbopol®934 + HPMC K100	Sustained antibacterial activity (8h), no ocular irritation, with over 3 months of stability at room temperature.	(Waghulde and Saudagar, 2018)
Norfloxacin	Chitosan + Carbopol®934P	Prolonged release, excellent antibacterial activity, significant mucoadhesive strength, and absence of ocular irritancy.	(Upadhayay et al., 2016)
Ketorolac Tromethamine	Chitosan + Carbopol®940	Sustained release, enhanced healing of ocular ulcers, with no ocular irritation in in vivo evaluations.	(Zaki et al., 2011)
Bupivacaine HCl	Chitosan + HPMC	pH- and temperature-responsive gelation, sustained release (6h), immediate anaesthetic effect, and enhanced ocular bioavailability.	(Popa et al., 2021)

5.1. pH-triggered in situ gel

pH-sensitive polymers play a crucial role in drug delivery by controlling drug release through pH-dependent swelling mechanisms. These polymers, known as polyelectrolytes, contain ionizable acidic or basic groups that respond to environmental pH changes by either accepting or releasing protons. Weakly acidic polymers swell as the pH increases, while weakly basic ones contract. This mechanism is particularly useful in ophthalmic formulations, where buffers help maintain the pH stability and enhance patient comfort by reducing irritation and ensuring compatibility with the natural tear fluid. Table 2 presents various studies that have investigated pH-sensitive in situ gels formulated with polymers such as Carbopol® and chitosan, demonstrating their ability to prolong ocular residence time and enhance bioavailability. These polymers gel when exposed to the natural eye pH (7.4), improving the drug retention and sustained release (Kumar et al., 2013). Chitosan, a biocompatible and well-tolerated, pH-responsive polymer, remains liquid until a pH of 6.2 and transforms into a gel at a pH of 7.4. Gelation is driven by the deprotonation of amino groups, leading to hydrogen bonding and ionic interactions with negatively charged mucin components, such as sialic acid. The gelation time depends on the chitosan degree of deacetylation; greater deacetylation results in improved gelation due to increased hydrophobic groups (Irimia et al., 2018).

5.2. Ion-induced in situ gel

Anionic polysaccharides, such as gellan gum and alginic acid, undergo a sol-to-gel transition when crosslinked with monovalent (Na⁺) and divalent (Mg²⁺, Ca²⁺) cations present in lacrimal fluid, increasing polymer viscosity. This viscosity enhancement is directly influenced by cation concentration; thus, increased tear production, while diluting the formulation, also raises the availability of cations, further promoting gel formation. Consequently, the ocular retention time of the drug is prolonged, reducing nasolacrimal drainage and improving drug bioavailability, making ion-activated polysaccharides effective carriers for sustained ophthalmic drug delivery (Al-Kinani et al., 2018). Table 3 summarizes various studies that have developed ion-activated in situ gels using polymers such as gellan gum and sodium alginate. Gellan gum is a naturally derived anionic exopolysaccharide known for its biocompatibility, non-toxicity, and biodegradability. It exhibits ion-sensitive gelation behavior, forming gels in the presence of physiological cations such as potassium, calcium, and magnesium (Zhou et al., 2022). Sodium alginate is another natural, hydrophilic, linear polysaccharide known as a gel-forming mucoadhesive polymer, which undergoes rapid gelation upon contact with lacrimal fluid through ionic crosslinking with divalent cations (Ca²⁺), forming calcium alginate (Makwana et al., 2016).

Table 3

Summary of ion-activated in situ gel formulations for ocular drug delivery.

Model Drug	Polymers	Major finding	Ref.
Posaconazole	Gellan gum	Superior antifungal activity compared to itraconazole, sustained release, 70% corneal retention, and non-irritant profile.	(Khare et al., 2022)
Monocaprin	Gellan gum + Sodium alginate	Enhanced corneal permeation, sustained release, ideal viscosity, and non-irritant profile for ocular application.	(Giri et al., 2023)
Moxifloxacin	Gellan gum + Sodium alginate + HPMC	Sustained drug release over 10 hours, higher ocular bioavailability compared to commercial eye drops, with no observed ocular irritation.	(Nair et al., 2021)
Acyclovir	Gellan gum + Carboxymethyl cellulose	Sustained drug release for up to 6 hours, enhanced mucoadhesion, and a non-irritant profile.	(Chowhan et al., 2023)
Tobramycin	Sodium alginate	Gelation upon contact ocular surface, sustained drug release, enhanced ocular residence time, and improved patient compliance.	(S et al., 2023)
Ketoconazole	Sodium alginate + HPMC + HP-β-CD	47-fold increase in corneal bioavailability and enhanced permeability and antifungal activity, with a non-irritant profile.	(Xia et al., 2024)
Acyclovir	κ-Carrageenan	Sustained drug release (80% over 6 hours), 2.16-fold increase in corneal permeability, and non-irritant profile in rabbit models.	(Li et al., 2018)

5.3. Temperature-triggered in situ gel

Temperature-triggered in situ gel systems undergo a sol-gel transition in response to temperature changes, utilizing temperature-sensitive polymers that lead to sustained drug release. In ocular drug delivery, these polymers are employed in a liquid state at room temperature (20–25°C) and form a gel upon exposure to body temperature (35–37°C), enabling localized and controlled drug release. This property is advantageous for minimizing systemic side effects and enhancing patient compliance (Devasani et al., n.d.).

Thermo-responsive hydrogels are classified into two types based on their critical solution temperature (CST): the lower critical solution temperature (LCST) and the upper critical solution temperature (UCST) types. LCST-type hydrogels include both hydrophilic and hydrophobic groups that gel when temperatures rise above 32–37°C. This process is driven by entropy, as higher temperatures interfere with polymer-water interactions, resulting in dehydration and aggregation. In comparison, UCST-type hydrogels, composed mainly of hydrophilic polymers, gel upon cooling below 25–35°C due to enthalpy-driven interactions, such as hydrogen bonding, while they dissolve at higher temperatures (Moon et al., 2024).

Thermosensitive hydrogels are categorized into positive, negative, and temperature-sensitive systems (Pasparakis and Tsitsilianis, 2020; Peppas et al., 2000):

1. Positive temperature-sensitive hydrogels: The polymers exhibit a UCST, meaning they are insoluble at low temperatures and become soluble as the temperature increases, driven by favorable enthalpic interactions.

2. Negative temperature-sensitive hydrogels: The polymers exhibit an LCST, meaning they are soluble in water at lower temperatures but undergo phase and shrink when heated above this temperature,

Table 4

Summary of temperature-triggered in situ gel formulations for ocular drug delivery.

Model Drug	Polymers	Major finding	Ref.
Timolol Maleate	Poly(N-isopropylacrylamide) + Chitosan	A thermosensitive in situ gel (LCST 32 °C), doubled aqueous humor drug level, extended intra-ocular pressure (IOP) reduction over 12h, and low cytotoxicity.	(Cao et al., 2007)
Metronidazole	Poloxamer 407 + Poloxamer 188 + Polycarbophil	Gelation temperature at 32°C. Polycarbophil enhanced the mucoadhesive properties, resulting in a prolonged ocular residence time.	(Hirun et al., 2022)
Dexamethasone Sodium Phosphate + Tobramycin Sulfate	Poloxamer 407 + HPMC K4M	The optimized gel demonstrated sustained drug release, prolonged residence time, improved corneal penetration, and enhanced bioavailability.	(Patel et al., 2016)
Ofloxacin	Poloxamer 407 + Chitosan	Suitable gelation temperature between 30–34°C, pseudoplastic behavior, with a sustained drug release, and enhanced mucoadhesive properties.	(Karatas et al., n.d.)
Ketoconazole	Poloxamer 407 + HPMC + Sodium Alginate + Sodium CMC	Gelation temperature at 34.67 °C with a rapid gelation time, enhanced solubility and release of ketoconazole, and over three months of stability.	(Chaiwut et al., 2025)
Moxifloxacin Hydrochloride	Pluronic® F127 + Gellan Gum + Carbopol®	Multifactorial gelation mechanism triggered by temperature, pH, and ion changes, an appropriate viscosity, sustained drug release, and no irritation.	(Gupta et al., 2018)
Cannabidiol	Hydroxypropyl Cellulose	Suitable rheological behavior, mucoadhesion, and prolonged in vivo residence time on ocular surface, thereby improving therapeutic outcomes.	(Kamenova et al., 2023)

primarily due to increased entropy and disrupted hydrogen bonding. Poly(N-isopropylacrylamide) is a prime example of a negative temperature-sensitive polymer.

3. Thermo-reversible polymers undergo reversible sol-gel transitions with changing temperature. A typical ocular example is Pluronic®.

Temperature-sensitive hydrogels, particularly those with LCST, exhibit unique properties as their solubility decreases with increasing temperature. LCST polymers display inverse temperature dependence, causing them to shrink above their LCST. This shrinking is due to enhanced hydrophobic interactions among hydrophobic segments and weakened hydrogen bonding between hydrophilic segments and water molecules. The LCST of a hydrogel can be adjusted by modifying the ratio of hydrophilic to hydrophobic segments, such as creating copolymers of hydrophobic N-isopropylacrylamide (NIPAAm) and hydrophilic monomers like acrylic acid. In contrast, poloxamers, which are poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) block copolymers, demonstrate thermally reversible gelation, transitioning from a sol to a gel state upon heating due to the aggregation of hydrophobic polypropylene oxide (PPO) segments. The polymer balance between hydrophobic and hydrophilic segments influences this behavior (Qiu & Park, 2001). Several studies have focused on the development of thermosensitive polymers for ocular in situ gel formulations, utilizing them either alone or in combination with other gelation mechanisms, as summarized in Table 4.

6. Polymers used in temperature-triggered in-situ gel systems

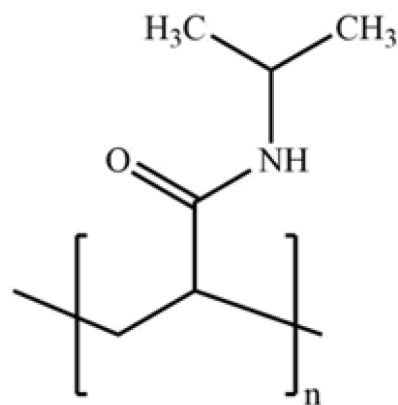
6.1. Poly(N-isopropylacrylamide)

Poly(N-isopropylacrylamide) (PNIPAAm), chemical formula $(C_6H_{11}NO)_n$ (Fig. 1), is a macromolecule that exhibits a unique thermos-responsive behavior with an LCST near physiological levels ($\sim 32^\circ\text{C}$). This property enables PNIPAAm-based drug delivery systems to remain soluble at room temperature and form gels at body temperature, allowing for the targeted and controlled release of drugs. Through chemical modifications and copolymerization, PNIPAAm systems are tailored for enhanced biocompatibility, stability, and functionality, making them valuable platforms for innovative stimuli-responsive systems (Throat and Bhattacharya, 2024). PNIPAAm-based hydrogels can be prepared via physical crosslinking (e.g., ionic interactions, hydrogen bonding, freeze–thaw methods), which offers reversibility, biocompatibility, and self-healing, though often with limited mechanical strength. To enhance stability, chemical crosslinking methods, such as free radical polymerization, are employed, resulting in stronger networks. Combining PNIPAAm with other polymers improves mechanical properties and responsiveness, making these hydrogels promising for a drug delivery system (Ansari et al., 2022). For instance, incorporating poly(acrylamide) into PNIPAAm hydrogels significantly improved the mechanical strength and thermal responsiveness, enhanced drug loading capacity, and controlled release behavior (Santhamoorthy et al., 2022).

PNIPAAm exhibits good biocompatibility with low cytotoxicity as demonstrated by intravitreal injection of 50% PNIPAAm in rabbit eyes, which showed good ocular tolerance with no long-term toxicity. Mild, transient inflammation resolved within three months, confirming the safety of a thermoresponsive bioadhesive for retinal therapies (Lima et al., 2016).

6.2. Cellulose derivatives

Cellulose derivatives, such as methylcellulose (MC), hydroxypropylmethyl cellulose (HPMC), and hydroxyethylcellulose (HEC), are widely used in ocular applications due to their water-soluble, biocompatible, and reversible thermosensitive properties, which are attributed to their amphiphilic nature with hydrophilic/hydrophobic segments within the polymer. This dual character is strategically exploited in in



Poly(N-isopropylacrylamide)

Fig. 1. Poly(N-isopropylacrylamide) chemical structure.

situ gel systems to enable temperature-triggered gelation at physiological conditions, particularly for ocular drug delivery. As the temperature increases, cellulose derivatives undergo gelation through the exclusion of water from regions rich in methoxy ($-\text{OCH}_3$) groups, leading to dehydration, reduced water attraction, and enhanced hydrophobicity (Silva et al., 2008).

MC is an amphiphilic LCST polymer that transitions from Newtonian to non-Newtonian flow as temperature increases, due to hydrophobic interactions (Nasatto et al., 2015). The results of a notable example involve incorporating Tranilast Solid Nanoparticles with MC, demonstrating that formulations containing MC significantly prolonged pre-corneal and pre-conjunctival contact time, resulting in higher drug concentrations in the cornea and conjunctiva compared to formulations without MC (Nagai et al., 2020b).

For ocular delivery of ketorolac tromethamine, Bain et al. modified MC with fructose and sodium citrate to reduce the gelation temperature from $\sim 59^\circ\text{C}$ to 32°C . Despite being a single-polymer system, it achieved prolonged drug release (9 h) versus the MC-HPMC blend (4 h), highlighting the potential of optimized single polymers for effective thermogelling and sustained release (Bain et al., 2009). In contrast, Bhowmik et al. found that a combination of MC and HPMC resulted in increased viscosity and mucoadhesiveness, supporting gel stability and retention, while the addition of oral rehydration salts helped lower the gelation temperature to near-physiological levels (Bhowmik et al., 2011).

Researchers have investigated cellulose derivatives combined with other stimuli-responsive polymers, such as Carbopol®, to enhance the stability, bioavailability, and sustained drug release of in situ gel formulations. For instance, a combination of HPMC and Carbopol® showed satisfactory sustained drug release for up to 8 h, a pseudoplastic behavior with viscosity decreasing under higher shear rates, while formulating Norfloxacin in situ gels for conjunctivitis treatment (Patil et al., n.d.). Similarly, a Sinomenine Hydrochloride gel using Carbopol®940 and HPMC for uveitis treatment demonstrated improved bioavailability, sustained release, and effective therapeutic outcomes in rabbit models (Song et al., 2013). Also, Sultana et al. used a combination of MC and Carbopol® to enhance the residence time and prolong the release of pefloxacin mesylate compared to conventional eye drops (Sultana et al., 2006).

On the other hand, Dasankoppa et al. developed the use of cellulose derivatives combined with ion-sensitive polymers, gellan gum, and MC, to enhance the residence time and bioavailability of Ofloxacin. The system exhibited pseudoplastic flow behavior and sustained drug release over 8 h, with safety confirmed through ocular toxicity studies on

rabbits (Dasankoppa et al., 2017). Another innovative combination, gellan gum and HEC, was used to administer phenylephrine and tropicamide. This formulation demonstrated rapid gelation upon contact with simulated tear fluid (STF) and exhibited appropriate viscosity for ocular application (Destruel et al., 2020).

6.3. Poloxamers (Pluronic®)

Poloxamers, also known as Pluronics®, a trademark of BASF Corporation, are a class of water-soluble, non-ionic, amphiphilic triblock copolymers composed of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) (PEOn–PPOn–PEOn) sequences as shown in Fig. 2. The hydrophilic PEO blocks form the outer blocks, and the hydrophobic PPO segments create the central hydrophobic core. The hydrophobic core interacts with solubilized substances through van der Waals forces, while the hydrophilic blocks enhance water solubility through hydrogen bonding interactions with water molecules. This dual nature makes Poloxamers soluble in both aqueous and nonpolar organic solvents, rendering them valuable in drug delivery formulations (Almeida et al., 2014).

Poloxamers are known for their ability to undergo thermal gelation at physiological temperatures, ranging from 25°C to 37°C. This property facilitates the convenient administration of ocular in situ gel formulations as liquid drops that gel upon reaching body temperature, thereby enhancing drug bioavailability and therapeutic effect through prolonged ocular residence time (Ludwig, 2005).

6.3.1. Poloxamer micellization

The amphiphilic structure of poloxamers enables them to undergo a micellization process, where self-assembly into micelles is highly dependent on the critical micelle concentration (CMC). As shown in Fig. 3, at low concentrations, the polymers remain dispersed as individual units within the medium. However, when the concentration reaches the CMC, they begin to organize into a more ordered structure driven by hydrophobic interactions between the hydrophobic PPO blocks, which come together and conceal themselves inside small spherical structures called micelles, while the hydrophilic PEO blocks remain on the outside, in contact with water (Perumal et al., 2022).

The micellization process is endothermic, meaning that increasing the temperature promotes the interactions between the hydrophobic PPO blocks, leading to a decreased CMC and initiating the gelation process, which progresses through the entanglement of micelles to form a stable, viscous network (Destruel et al., 2017), as well as well-organized micellar structures, which can encapsulate and deliver hydrophobic drugs efficiently (Frey and Lee, 2007).

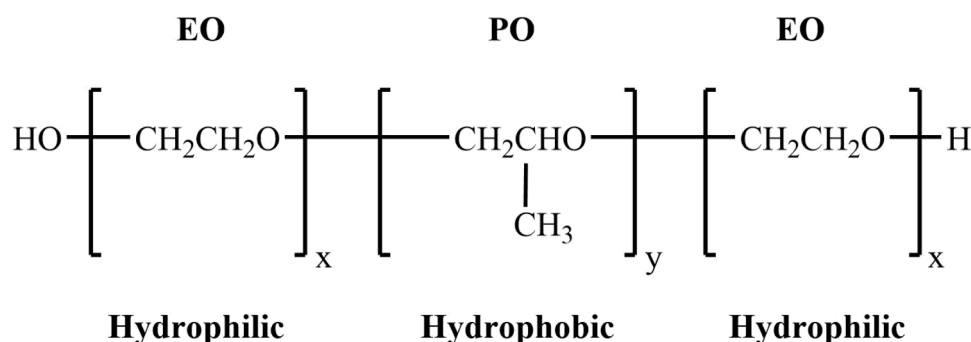
In addition to the crucial role of temperature in micelle formation, other factors, such as polymer concentration and the presence of

additives, also significantly influence micellization behavior, structural characteristics, stability, and drug-loading capacity of the system, all of which are critical considerations for designing efficient drug delivery systems (Torchilin, 2001). For instance, a study investigated the impact of polymer concentration on micelle formation and stability using a Poloxamer 407/TPGS system for gambogic acid delivery, and demonstrated that increasing the polymer concentration reduced the CMC, facilitating micelle formation, and resulting in more stable carriers that can hold more drug and stay intact even when diluted in the bloodstream (Saxena and Hussain, 2012). Furthermore, additives such as preservatives or cosolvents can influence poloxamer micelle properties by altering their size, internal structure, and stability. A study using phenol and benzyl alcohol with P188 demonstrated that such additives promote micellization at lower concentrations, modify micelle dimensions, and may even induce phase separation at higher levels (Ford et al., 2023).

Poloxamer-based micelles offer several advantages, making them a promising platform for ophthalmic drug delivery. Their small size facilitates penetration through ocular barriers, enhancing drug delivery to targeted eye tissues. Additionally, poloxamer micelles can prolong drug retention time on the ocular surface, thereby reducing the frequency of administration (Li et al., n.d.). Moreover, the micelle-forming ability of poloxamers enables the effective encapsulation and protection of poorly water-soluble drugs within their hydrophobic core, thereby enhancing the drug solubility and stability. The hydrophilic shell contributes to colloidal stability in biological fluids, collectively improving the bioavailability of therapeutic agents (Jones and Leroux, 1999; Kwon and Kataoka, 1995). For instance, a research group successfully encapsulated the hydrophobic anticancer drug Etoposide using poloxamer 407, achieving high encapsulation efficiency and sustained drug release (Soni and Yadav, 2014). In a separate study, Basak and Bandyopadhyay examined the effects of temperature, pH, and drug hydrophobicity on the behavior of Pluronic® F127 micelles loaded with hydrophobic drugs. They observed that lower temperatures increased micelle size and polydispersity due to greater core hydration, while higher drug loading reduced the critical micelle temperature (CMT). At pH 11.36, drug ionization triggered micelle rupture and release, highlighting temperature and pH as critical factors in modulating drug release from these systems (Basak and Bandyopadhyay, 2013).

6.3.2. Poloxamer types

The physical form of poloxamers, ranging from liquid to paste to solid, depends primarily on their molecular weight (1,100–14,000 Da), while their hydrophilic-lipophilic balance (HLB) is determined by the ratio of PEO/PPO (1:9 to 8:2). This ratio directly affects their solubility, micellization behaviour and biological interactions (Russo & Villa, 2019). These properties make poloxamers, particularly Poloxamer 188



Poloxamer general structure

Fig. 2. Poloxamer chemical structure.

Thermoresponsive Micellization of Poloxamers

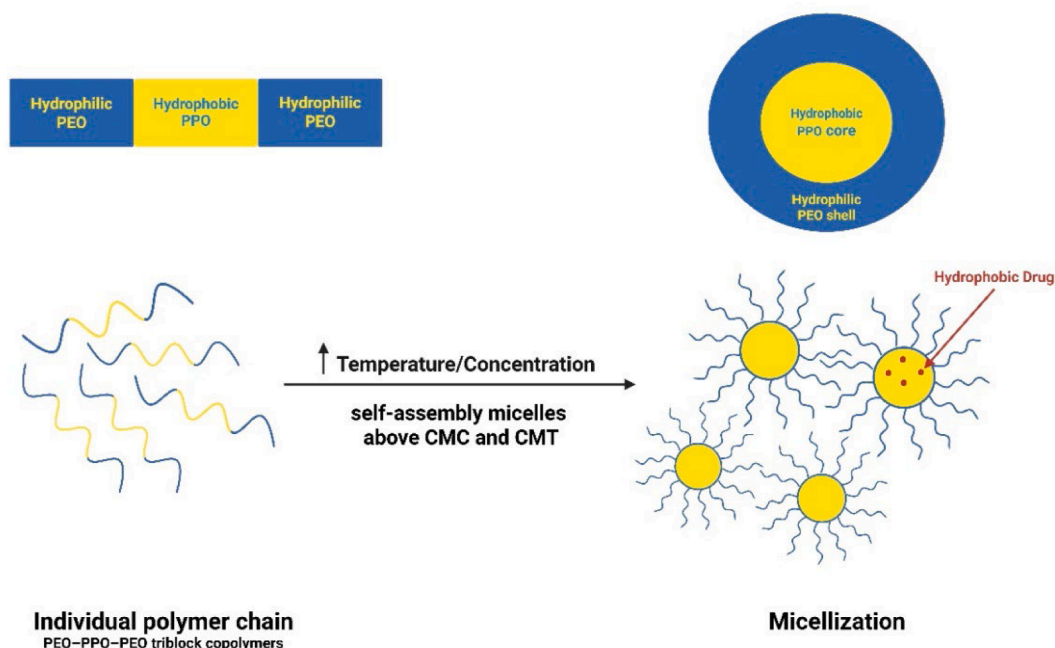


Fig. 3. Poloxamer micellization process (created by BioRender.com).

and Poloxamer 407, highly suitable for in situ gel systems and advanced drug delivery applications. Both are among the few U.S. FDA-approved poloxamers, valued for their excellent biocompatibility, amphiphilic nature, and safety in pharmaceutical formulations (Khaliq et al., 2023; Nugraha et al., 2023).

Poloxamer 188 (P188), also known as Pluronic®F68 or Kolliphor® P188, is a non-ionic copolymer comprised of a central hydrophobic PPO block flanked by hydrophilic PEO chains, with a molecular weight of approximately 8,400 Da, 80% PEO content, and a high hydrophilic-lipophilic balance (HLB of ~29) (Chen et al., 2022; Crabtree et al., n. d.). Poloxamer 407, also known as Pluronic®F127, is one of the most commonly used poloxamers in formulating ophthalmic in situ gel systems, recognized for its sustained release capabilities, particularly for lipophilic drugs. This non-ionic, amphiphilic copolymer has a molecular weight of approximately 12,000 Da and a PPO/PEO ratio of 1:2. Its high ethylene oxide content (approximately 70%) imparts hydrophilicity. In contrast, the propylene oxide segments contribute to hydrophobicity, enabling temperature-sensitive sol-gel transitions (Paul et al., 2023). At low temperatures, P407 stays a low-viscosity solution but transitions to a gel near physiological temperature (33–37°C), making it an ideal candidate for thermogelling in situ systems. The gelation temperature and properties can be adjusted by polymer concentration (typically 25–30% w/v), as well as the presence of salts, other polymers, and modifications to pH or ionic strength (Kurniawansyah et al., 2021).

Qi et al. found that P407 at a concentration of 18% or higher transforms from a liquid to a gel at room temperature, and dilution by tear fluid results in the loss of its gel-forming ability; thus, 25% P407 is recommended to ensure proper gelation (Qi et al., 2007). However, Edsman et al. demonstrated that increasing poloxamer concentration enhances gel strength and prolongs ocular residence time, lowering the gelation temperature to room temperature. Therefore, P407 may require combining other polymers or excipients to ensure reliable gelation and sustained drug release in vivo (Edsman et al., 1998).

The combination of P407 and P188 has emerged as a rational strategy in the design of ocular thermosensitive in situ gels, where P188, due to its higher hydrophilicity, acts as a thermo-responsive modifier by raising the gelation temperature and modulating micellar interactions. A study on P407-based diclofenac sodium in situ gels demonstrated that

increasing P407 lowered the sol-gel transition temperature, while P188 increased it within an optimal range. The optimized, clear, pseudoplastic, and easily administrable formulation comprises 20% P407 and 11% P188 (Asasutjarit et al., 2011). However, different concentrations of the same combination were used to develop a chloramphenicol-loaded ocular gel: 20.5% (w/v) P407 and 5.0% (w/v) P188. The ratio of P407/P188 played a critical role in modulating the gelation temperature. P407, which contains a higher proportion of hydrophobic PPO blocks (3:7 PPO: PEO), tends to lower the gelation temperature, whereas the more hydrophilic P188 (2:8 PPO:PEO) increases it. This formulation also enhanced the antimicrobial efficacy and prolonged the ocular retention of chloramphenicol-chitosan nanoparticles incorporated into a thermosensitive in situ gel (Huang et al., 2023). Similarly, in a betaxolol hydrochloride-loaded in situ hydrogel formulation, the researchers added P188 to P407 to adjust the gelling temperature by altering the hydrophilic-lipophilic balance of the system, which stabilized the gelation temperature, enhanced rheological properties, improved bioavailability, and therapeutic outcomes, while minimizing irritation (Huang et al., 2016).

Beyond thermosensitive poloxamer systems, some studies have explored dual-responsive formulations by incorporating poloxamers with pH-sensitive polymers or ion-sensitive polymers to enhance mucoadhesion and extend ocular residence time. For instance, Gratieri et al. found that adding chitosan to the P407 in situ gel formula improved mucoadhesiveness and mechanical properties, enhanced viscoelasticity and adhesion to the ocular mucosa, and confirmed significantly increased retention on the ocular surface, with 50–60% of the instilled formulation remaining after 10 minutes, compared to just 15% from conventional aqueous solutions (Gratieri et al., 2010). Similarly, the addition of Carbopol® to the in situ gel formula of P407 and Tween 80 fluconazole-loaded in situ gel system enhanced the gel mucoadhesive strength and retention time on the ocular surface, with a suitable sol-gel transition temperature of $30.6 \pm 1.2^\circ\text{C}$, excellent transparency, and pseudoplastic flow, making it appropriate for ocular administration (Lihong et al., 2014). Furthermore, Lin et al. used pilocarpine as a model drug to prove that the synergistic blend of alginate and Pluronic®F127 enhanced the gel strength, prolonged the drug release, and significantly improved the in vivo ocular bioavailability

(Lin et al., 2004).

7. Preparation and pharmaceutical evaluation of thermosensitive ophthalmic in situ gel formulations

7.1. Preparation of thermoreversible formulation

The cold method is the most common technique for preparing poloxamer gels, which involves dispersing the poloxamer in cold water (between 5°C and 10°C) under continuous stirring to ensure a homogeneous solution. The system remains liquid as long as the temperature is below the gelation threshold. As the temperature rises to physiological levels, gelation occurs in situ. Sathyanarayana et al. used the cold method in developing thermosensitive ophthalmic in situ gels of Bimatoprost using P407/P188 with HPMC (Sathyanarayana et al., 2020). Moreover, a thermosensitive ophthalmic formulation of flurbiprofen was developed by preparing solid dispersions of flurbiprofen with P407 using the melt method, followed by dispersing the polymer mixture (P407/P188/bioadhesive polymers) into cold water (Adisanoğlu & Özgüney, 2024). However, traditional methods for preparing poloxamer gels, such as the hot or cold process, can be energy-intensive and challenging to scale. In contrast, hot-melt extrusion was demonstrated to provide a solvent-free, continuous alternative for producing homogeneous P407/P188 gels loaded with ketoprofen, exhibiting suitable gelation temperatures (Mendonsa et al., 2018).

PNIPAAm hydrogels are commonly synthesized via free radical polymerization (FRP), controlled/living radical polymerization (CLRP), and graft copolymerization (GCoP). FRP is a straightforward method that utilizes initiators like ammonium persulfate to polymerize NIPAM with cross-linkers. While CLRP includes reversible addition–fragmentation chain transfer and offers better control over molecular weight. In GCoP, grafting PNIPAAm onto polymers like chitosan to enhance biocompatibility (Narayana et al., 2025). For example, CS-g-PNIPAM copolymers are synthesized by polymerizing NIPAM in acetic acid with chitosan at 60 °C, followed by purification to remove unreacted PNIPAAm (Babelyte et al., 2023).

7.2. pH and clarity

Maintaining a physiological pH and optical clarity is essential for ocular formulations to ensure patient comfort and minimize irritation. As mentioned in Table 1, human tear pH is approximately 7.45, fluctuating between 7.14 and 7.82 due to diurnal and seasonal variations (Chang and Purt, 2025). Formulation studies have consistently aimed to align with this range to ensure both safety and therapeutic efficacy. For instance, HPMC-based hydrogel formulations demonstrated pH within the acceptable range of 6.5 to 7.5, effectively maintaining ocular comfort, while also exhibiting a clear and transparent appearance (Kurniawansyah et al., 2018). Similarly, Perminaitė et al. highlighted the importance of pH and clarity compatibility in ocular formulations, with their formulations containing Lithuanian royal jelly achieving a refractive index close to that of the cornea, thereby preserving visual quality (Perminaitė et al., 2021).

7.3. Sol–gel transition temperature measurements:

The gelation temperature of in situ gel systems is a critical parameter that influences their performance upon administration. This subchapter summarizes the common methods employed in different literatures to determine the sol–gel transition temperature. The techniques described below represent standard, widely accepted procedures for assessing the sol–gel temperature measurement.

As reported in a previous study, the gelation temperature of an acetazolamide ocular in situ gel formulation was evaluated by placing the formulation in a beaker submerged in a low-temperature water bath, with continuous stirring using a magnetic bead. The temperature was

gradually increased at a constant rate (e.g., 2°C/min), and the gelation point was identified at which the magnetic bead ceased movement, indicating a rise in viscosity and the formation of a structured gel matrix (Ali et al., 2023). In contrast, Gugleva et al. described the test tube inversion method as a simple and visually appealing approach for measuring the transition temperature. This method involves placing 2 mL of the formulation in a small vial and immersing it in a thermostatically controlled water bath. The vial is tilted at regular intervals as the temperature increases gradually, typically at a rate of 0.5°C/min. The gelation temperature is defined as the minimum temperature at which the formulation ceases to flow upon inversion (Gugleva et al., 2022). For a more quantitative assessment, a research study has reported that using a Brookfield viscometer equipped with a temperature-controlled jacket can be employed. The sample is subjected to a controlled increase in temperature (3 to 40°C) while maintaining a constant shear rate (e.g., 10 rpm). The gelation temperature is defined by a sudden increase in viscosity, reflecting the system transition to a gel phase (Kerdmanee et al., 2022). In addition, Wu et al. measured the LCST of a thermosensitive in situ microgel system comprising hyaluronic acid grafted with PNIPAAm using a UV–visible spectrophotometer by tracking optical transmittance at 600 nm during a controlled temperature range from 25°C to 40°C at a rate of 0.5°C/min. This method reliably characterized the sol–gel transition behavior of PNIPAAm-based microgels, which exhibited an LCST of 32.7 °C, facilitating a sol–gel transition upon contact with the ocular surface (Wu et al., 2013).

7.4. Sol–gel transition time measurements

The gelation time reflects the ability of the formulation to undergo a sol–gel transition upon exposure to physiological temperatures. In this section, the following methodologies reflect established experimental standards and are provided as representative examples of the techniques used to accurately determine gelation time for ophthalmic in situ gel formulations.

The gelation time of a ketorolac tromethamine ocular thermos-responsive in situ gel using P407/P188 was reported in the literature to be measured by placing a few drops of the formulation into an aluminum pan set on a hot plate at 35°C. The pan was then tilted to a 90° angle, and gelation was deemed complete when the initially free-flowing solution transformed into a non-flowing gel, as indicated by the absence of meniscus movement (M A Fathalla et al., 2017). Alternatively, Obiedallah et al. employed the tube inversion method to assess gelation time in their development of an ocular thermos-responsive acetazolamide microsponges in situ gel using P407, where 2 ml of the gel, initially stored at 4°C, was transferred into a test tube and placed in a water bath maintained at 35 ± 1°C. The tube was periodically inverted, and the gelation time was recorded as the moment the gel ceased to flow upon inversion (Obiedallah et al., 2018). Similarly, a previous study has assessed the gelation time of a PNIPAAm-grafted MC hydrogel using a standard tube inversion method, and showed a rapid sol-to-gel and gel-to-sol transition, completing gelation within approximately one minute at physiological temperature (Liu et al., 2004).

7.5. Gelling capacity

An optimal gelling capacity is essential for in situ gel formulations to ensure a rapid sol-to-gel transition upon administration and to maintain gel integrity over time. Gupta et al. formulated a sodium alginate-based in situ gel of moxifloxacin hydrochloride, where gelling capacity was evaluated by placing a drop of the formulation into 2 mL of simulated tear fluid and visually observing the gel formation. The optimized formulation demonstrated immediate gelation that lasted for several hours (Mandal et al., 2012). Similarly, a gellan gum–sodium alginate in situ gel of monocaprin showed pH-dependent gelation (pH 7.2–7.4) at 37°C ± 0.5, with the selected formulation demonstrating both immediate and sustained gelation, thereby supporting its potential for

prolonged ocular retention (Giri et al., 2023).

7.6. Isotonicity

The tear osmolality, as mentioned in Table 1, is another important parameter for preventing irritation and maintaining ocular tissue integrity in ocular formulations. Several studies have explored methods to assess and achieve isotonicity in ophthalmic preparations. For example, Kurniawansyah et al. examined ophthalmic in situ gel formulations containing chloramphenicol with P407/HBMC designed to enhance ocular drug retention and minimize irritation. The isotonicity assessment was conducted using a blood cell morphology test, in which the formulations demonstrated normal erythrocyte morphology comparable to that of the isotonic control, indicating suitable isotonicity. Furthermore, the Draize irritation test on rabbit eyes showed no signs of irritation affecting the cornea, iris, conjunctiva, or causing edema, confirming the ocular safety of these formulations (I. Kurniawansyah et al., 2021). On the other hand, Kotreka et al used the freezing point depression method with a cryoscopic osmometer to measure the osmolality of a developed ion-activated in situ gel-forming estradiol eye drop formulation. To achieve physiological isotonicity, mannitol was employed as a tonicity agent. The osmolality values were within the acceptable physiological range (275–325 mOsm/kg), confirming the isotonic nature and maintaining ocular comfort, while minimizing the potential for irritation upon administration (Kotreka et al., 2017).

7.7. Rheological properties

Rheological behavior significantly influences the in vivo performance of in situ gels. Excessively viscous formulations may cause discomfort and leave residue on the eyelid, while low-viscosity gels risk rapid elimination by tear fluid. Poloxamer-based in situ gels typically exhibit pseudoplastic (shear-thinning) behavior, characterized by a decrease in viscosity with increasing shear rate, such as during blinking, which results in enhanced patient comfort and improves corneal residence time. As non-Newtonian systems, these gels undergo sol-gel

transitions triggered by physiological stimuli, further supporting their utility in ocular drug delivery, as shown in Fig. 4 (Dasankoppa et al., 2017; Kerem Polat, 2022). Alsheikh et al. investigated the rheological properties of an ophthalmic in situ gel containing P407 and P188. Flow curve analysis revealed that at room temperature, the formulation behaved as a Newtonian fluid, facilitating easy instillation. However, at an ocular surface temperature, the gel exhibited pseudoplastic behavior, with viscosity decreasing as the shear stress increased. This property is beneficial during blinking or rapid eye movement, enhancing the spread ability of the formulation over the corneal surface, which improves patient comfort and drug residence time (Alsheikh et al., 2024).

In the study by Bellotti et al., PNIPAAm hydrogels exhibited Newtonian flow at room temperature, as confirmed by rheological measurements performed using a rheometer, which allowed the easy instillation. Upon reaching ocular temperature, the formulations rapidly gelled, enhancing retention. The viscosity remained stable under environmental conditions, supporting their suitability for ocular use (Bellotti et al., 2019).

7.8. Safety and ocular compatibility of in situ gel systems

Poloxamers, particularly P407 and P188, are FDA-approved excipients widely used in ophthalmic drug delivery due to their excellent biocompatibility and thermos-responsive properties (Dumortier et al., 2006, p. 407; Giuliano et al., 2018; Mfoafo et al., 2022). Their safety and suitability have been extensively demonstrated in the literature through in vitro, in vivo, and ex vivo studies. The safety of ketorolac tromethamine-loaded in situ gels based on P407/P188 was confirmed using in vitro assays. The Hen Egg Test-Chorioallantoic Membrane test showed no irritation, indicating good ocular tolerability, while the Bovine Corneal Opacity and Permeability assay revealed no significant changes in corneal opacity or permeability. Additionally, the 3-(4, 5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide colorimetric assay (MTT) cytotoxicity results also demonstrated high cell viability, supporting the non-toxic nature of the formulation (M A Fathalla et al., 2017). In vivo testing of a dorzolamide hydrochloride in situ gel with

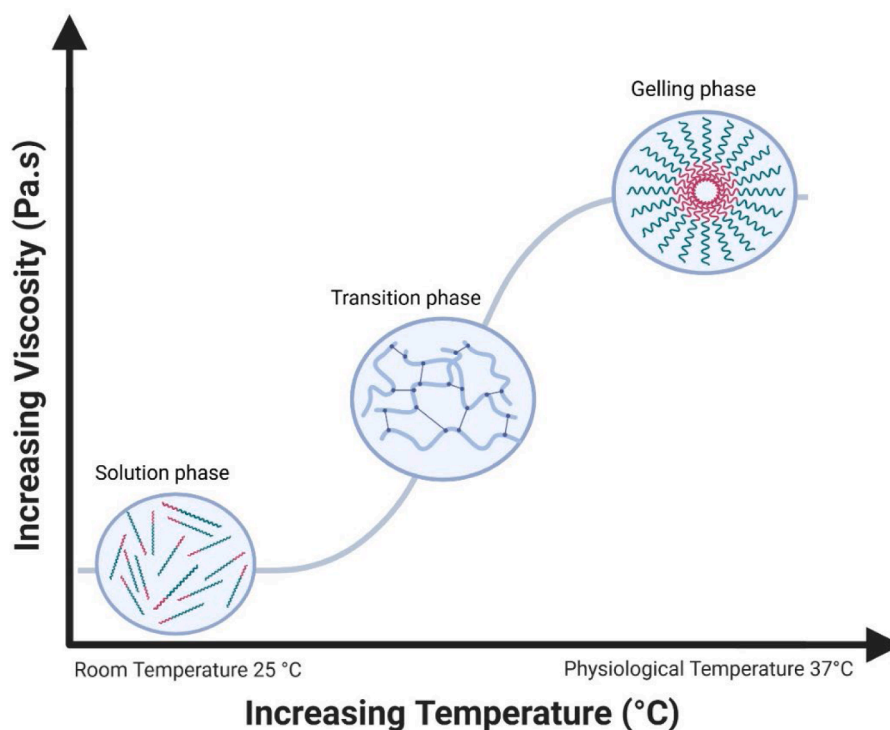


Fig. 4. Viscosity-Temperature relation of thermosensitive ocular in situ gel (created by BioRender.com).

HPMC/P407 in rabbit eyes demonstrated sustained intraocular pressure reduction, highlighting prolonged drug release and improved bioavailability. Ex vivo permeation studies across goat corneas indicated effective drug release for up to 5 hours. Histopathological analysis revealed no signs of inflammation or tissue damage, confirming the safety and biocompatibility of the formulation (Barse et al., 2016). Another study developed an ocular drug delivery system by incorporating oxytetracycline-loaded nanoparticles formulated from a gelatin and polyacrylic acid polyelectrolyte complex, into a P407-based thermos-responsive in situ gel. The in vivo tests in rabbits using the Draize test and histological analysis indicated excellent ocular tolerance and intact tissue architecture, supporting the compatibility of the formulation (Abbas et al., 2022).

Turturro et al. investigated the intravitreal injection of a cross-linked PNIPAAm-based hydrogel containing PEG diacrylate, which gelled without affecting retinal function. Electroretinography showed no significant changes compared to baseline, and histological analysis revealed no inflammation or structural damage to retinal tissues, supporting the biocompatibility and safety of PNIPAAm hydrogels (Turturro et al., 2011). Moreover, cytocompatibility of PNIPAAm hydrogels was confirmed using human conjunctival epithelial cell viability assay. After 48 hours of exposure, live/dead staining revealed high cell viability ($\geq 80\%$), indicating minimal cytotoxicity and highlighting the biocompatibility of PNIPAAm for prolonged drug delivery (Bellotti et al., 2019).

These studies highlight the wide range of experimental models applied for ocular safety assessment, including cell-based assays, non-animal tests, ex vivo corneal models, and in vivo evaluations (Fig. 5).

7.9. Drug release profile

Drug release from poloxamer-based in-situ gels occurs mainly by diffusion and gel erosion, depending on the physicochemical properties of the drug. Hydrophilic drugs diffuse rapidly through the aqueous channels, whereas hydrophobic or high-molecular-weight drugs rely on gel erosion. The gel microstructure and conditions, such as dissolution medium and temperature, significantly influence the release behavior, highlighting the importance of designing in vitro experiments that closely replicate in vivo conditions. To overcome the rapid erosion and short residence time of poloxamer systems, several formulation strategies have been developed to enhance and sustain drug release. One of these includes physical blending with polymers like hyaluronic acid, chitosan, cellulose derivatives, alginates, and salts to improve gel strength, reduce porosity, and enhance mucoadhesion (Abdeltawab et al., 2020). A study supported this finding, where the addition of chitosan to a thermosensitive in situ gel using P407 increased mechanical strength and exhibited a high mucoadhesive force. In vivo gamma

scintigraphy in human volunteers showed that over 50% of the instilled dose remained on the ocular surface after 10 minutes, approximately four times longer than a standard solution, indicating prolonged pre-corneal residence and sustained drug release (Gratieri et al., 2010). Moreover, Sathyanarayana et al. formulated an in situ gel for glaucoma treatment using HPMC K4M with P407/P188. The Franz diffusion cell method was employed to evaluate the release of Bimatoprost, where the gel formulation was placed inside a dialysis bag and immersed in simulated tear fluid at $34 \pm 0.5^\circ\text{C}$ to mimic ocular conditions, with samples withdrawn at specified time intervals and analyzed via UV-visible spectrophotometry (Sathyanarayana et al., 2020).

A comparative study evaluating the release of [^3H]-epinephrine from thermos-responsive copolymers, a linear random copolymer (PAAc-co-PNIPAAm) and a graft copolymer (PAAc-g-PNIPAAm), demonstrated that the graft copolymer provided a more sustained release of the drug, due to its higher water content and enhanced capillary structure. The drug release followed a diffusion-controlled mechanism ($n \approx 0.5\text{--}0.6$), supporting the potential of graft copolymers for sustained ocular delivery systems (Prasannan et al., 2014).

7.10. Permeability

Drug permeation through the cornea is commonly assessed ex vivo using goat, rabbit, bovine, or pig eyes. Goat corneas are favored for their availability, ethical acceptability, and similarity in size to human eyes, while porcine corneas (0.67 mm) closely resemble human cornea thickness (0.52 mm). Franz diffusion cells are typically utilized with setups that ensure constant contact between the corneal surface and the formulation in the donor chamber, with the receptor chamber maintained at pH 7.4 and $34 \pm 0.5^\circ\text{C}$. Samples collected at intervals are analyzed via UV-Vis, HPLC, or chromatography to evaluate the permeation and disintegration rates (Dewan et al., 2023).

Poloxamers have been shown to enhance drug permeability, as evidenced by in situ gels of tetrahydrozoline hydrochloride formulated with P407/P188. Ex vivo trans corneal permeation studies using goat corneas in Franz diffusion cells showed enhanced drug permeation compared to conventional eye drops. This enhancement is attributed to the sustained drug release and prolonged contact with the ocular surface, promoting better corneal absorption (Okur et al., 2020). Interestingly, Gratieri et al. reported that chitosan alone enhanced ocular permeability more effectively than when combined with poloxamer, specifically chitosan solutions delivered a greater amount of fluconazole compared to the P407/chitosan in situ gel formula. Ex vivo permeation studies using porcine corneas in Franz diffusion cells, with drug permeation quantified over time, demonstrated that both formulations significantly sustained drug release and enhanced fluconazole permeation compared to an aqueous solution, with the chitosan solution

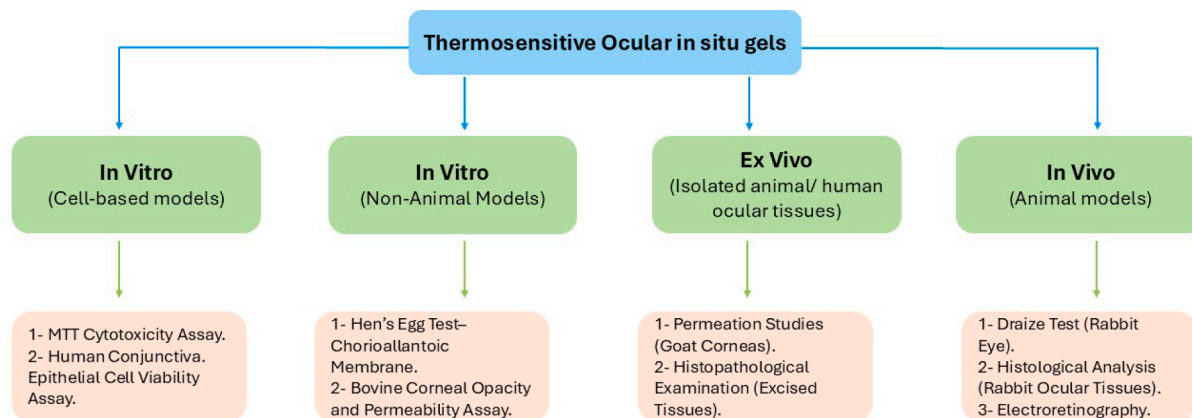


Fig. 5. Summary of safety and ocular compatibility evaluation methods.

exhibiting the highest permeation flux (Gratieri et al., 2011). Incorporating excipients such as HPMC and HA improved drug penetration by increasing the viscosity and mucoadhesiveness of the thermos-responsive ophthalmic in situ gel using the P407 formula. Ex vivo permeability conducted with porcine corneas in Franz diffusion cells showed that formulations containing HPMC and HA improved gelation, provided stronger mucoadhesion, and significantly enhanced drug permeation compared to P407 alone (Chen et al., 2023).

Strategies like incorporating solid dispersions or nanoparticles into poloxamer-based in situ gels have shown promise in enhancing ocular drug permeability. Yadav et al. investigated a thermosensitive in situ gel incorporating drug-loaded nanoparticles using P407, observing enhanced permeability compared to conventional formulations. This enhancement was primarily attributed to the nanoscale size particles, which improved interaction with ocular tissues and promoted deeper penetration. Ex vivo trans-scleral permeation studies using goat eyes demonstrated higher drug flux from the nanoparticle-loaded gel, highlighting the synergistic effect of nanosize and mucoadhesive properties of the gel, sustained-release properties, and enhanced drug permeability (Üstündağ Okur et al., 2019). Zhang et al. formulated a thermosensitive in-situ gel using solid dispersion for the ocular delivery of poorly soluble drugs, such as disulfiram. The permeability assessment using rabbit corneas demonstrated a significant increase in cumulative permeation and a higher permeation rate for disulfiram solid dispersions with P188. This enhancement was attributed to the synergistic effect of the solid dispersion technique in increasing solubility and the prolonged residence time from the thermosensitive gel, resulting in improved corneal absorption (Zhang et al., 2018).

In an ex vivo study using Franz diffusion cells and excised rabbit corneas, the cysteamine-loaded PLGA microsphere embedded in a thermos-responsive PNIPAAm-PEG hydrogel significantly enhanced corneal permeation compared to conventional eye drops. The formulation provided sustained and consistent drug flux due to prolonged ocular residence and controlled microsphere release, thereby improving permeability, reducing dosing frequency, and maintaining therapeutic levels for the treatment of corneal cystinosis (Jimenez et al., 2021).

Overall, incorporating biocompatible, mucosal-adherent, and pseudoplastic polymers within these in situ gel systems further sustains drug release, increases ocular bioavailability compared with conventional formulations, and represents an effective strategy to overcome the intrinsic permeability barriers of the eye and substantially improve drug delivery to the anterior segment (Nagai et al., 2020a; Pandhare et al., 2020).

8. Challenges and future directions

The emergence of ophthalmic in situ gels represents a shift toward smarter and more adaptive drug-delivery systems capable of prolonging precorneal residence time, sustaining drug release, improving bioavailability, and reducing systemic absorption and dosing frequency. Collectively, these properties enhance both therapeutic efficacy and patient compliance.

Despite this significant progress, several challenges continue to limit the broader translation of ophthalmic in situ gels. The eye sensitivity necessitates a strict assessment of long-term safety, as repeated exposure may induce irritation, inflammation, or alterations in ocular surface homeostasis. Stability issues, including polymer degradation, phase separation, drug-polymer interactions, and rheological drift, can compromise performance and shelf-life, underscoring the need for optimized compositions, stabilizers, and robust preservation strategies. Patient-related barriers such as transient blurred vision, discomfort, and difficulties in administration, as well as the limited ability of current systems to deliver drugs to the posterior segment, further constrain clinical applicability. Manufacturing and regulatory challenges also persist. Maintaining sterility, scaling up complex multi-polymer or nano-gel systems remain substantial obstacles to industrial translation.

Future research is expected to advance toward biodegradable and highly biocompatible smart polymers, multi-stimuli-responsive and disease-responsive systems, and nanoengineered in situ gels capable of targeted posterior-segment delivery. Additionally, the incorporation of imaging-compatible gels enabling real-time monitoring of gel distribution and drug release holds promise for improving clinical outcomes. Continued interdisciplinary collaboration between material scientists, formulation researchers, and clinicians will be essential for overcoming current limitations and accelerating the development of clinically translatable in situ gel technologies (Patil et al., 2024; Vivak Bhati and Deepak Marathia, 2025; Waghmode et al., 2024).

9. Conclusion

This review highlights the increasing potential of thermosensitive in situ gels as advanced ocular drug delivery systems that can address the limitations of traditional eye drops. By gathering and critically analyzing a broad array of studies, the ideal thermosensitive gels exhibit a sol-gel transition temperature close to physiological conditions (typically between 30–35 °C), rapid gelation upon instillation, appropriate gelation time (within 30–60 seconds), and suitable viscosity to ensure retention without causing blurred vision or discomfort. The addition of thermosensitive polymers, such as poloxamers, PNIPAAm, and cellulose derivatives or mucoadhesive agents, further enhances mechanical strength, bioavailability, and sustained release. Ultimately, thermosensitive in situ gels represent a powerful drug delivery system for achieving controlled ocular drug delivery, enhancing patient compliance, and improving overall therapeutic effects.

CRedit authorship contribution statement

Raghad Alsheikh: Writing – original draft, Methodology, Investigation, Data curation. **Dániel Nemes:** Writing – review & editing, Supervision, Conceptualization. **Pálma Fehér:** Writing – review & editing, Formal analysis. **Zoltán Ujhelyi:** Visualization, Methodology, Formal analysis. **Ádám Haimhoffer:** Validation, Conceptualization. **Ádám Papp:** Writing – review & editing, Data curation. **Ildikó Bácskay:** Validation, Supervision, Conceptualization.

Data availability

No data was used for the research described in the article.

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