A REVIEW ON IN-SITU GEL EYE DROPS: BRIDGING THE GAP BETWEEN CONVENTIONAL AND CONTROLLED OPTHALMIC THERAPY

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ABSTRACT: -

Ophthalmic drug delivery is often limited by rapid tear drainage, low drug absorption, and the need for frequent dosing. In-situ gel eye drops have emerged as a novel approach to address these challenges. These systems are designed to be administered as liquids that convert into gels upon contact with the eye, triggered by physiological factors such as temperature, pH, or ionic content. This transformation allows the formulation to stay longer on the ocular surface, leading to improved drug absorption and prolonged therapeutic effects. This review highlights the different types of in-situ gel systems, including temperature-sensitive, pH-responsive, and ion-activated formulations. It also discusses commonly used polymers, such as poloxamers, carbopol, gellan gum, and sodium alginate, which play a key role in gel formation. The advantages of in-situ gels—such as enhanced bioavailability, reduced dosing frequency, and better patient compliance—are reviewed, along with potential drawbacks like formulation complexity and polymer-related irritation. Recent developments in this field, including the use of nanoparticles and herbal ingredients in in-situ gels, are also explored. In conclusion, in-situ gel eye drops represent a promising and patient-friendly strategy for sustained ocular drug delivery and hold great potential for future therapeutic advancements.

Key Words: - In-situ gel, Ophthalmic drug delivery, Stimuli-responsive polymers, Nanoparticle, Therapeutic advancements

1. INTRODUCTION:

Ocular drug delivery systems provide numerous opportunities, but also complexities within its field. The eye is an isolated organ which makes it hard to study; drugs can only be administered on the ocular system for local action on the eye's superficial or interior membranes[1]. The eye is particularly interesting in regard to its placement characteristics of the drug. Ocular drug delivery remains complex to tackle for drug scientists [2]. This is due to the unique design of the eye which controls the drug molecule's access to the action site. The eye's anterior and posterior segments can be focused on for drug delivery [3]. Though over 90 percent of ocular marketed medications are available in the form of eye drops, they are not ideal when treating vision threatening diseases for the eyes [4]. Conventional systems such as suspensions, ointments, and eye drops predominately target the anterior segment eye diseases [5]. However, these formulations face the issue wherein the majority of the ophthalmic topical drugs are removed from the eye via tear dilution, tear turnover, and lachrymal drainage, thus greatly reducing the bioavailability of the drug in theeye [6].In addition, human cornea, endothelium, and the comprising epithelium, as well as the substantia propria, restrict the ocular entry of drug molecules, thus hindering drug bioavailability. Furthermore, both anatomical and physiological restrictions lead to poor ocular bioavailability; these factors include the relative impermeability of the corneal epithelial barrier, nasolacrimal drainage, and tear flow dynamics [7].The previously mentioned strategies including suspensions, solutions, and ointments do not provide the contemporary requirement for prolonged, constant rate delivery [8]. The primary reason is inadequate infusion residence time at the site of action, leading to low bioavailability. There have been numerous ophthalmic formulations, such as eye drops, suspensions, and ointments, and they all have their limitations [9]. Many attempts have been made to develop stable, sustained, and controlled release systems called in-situ gels [10].

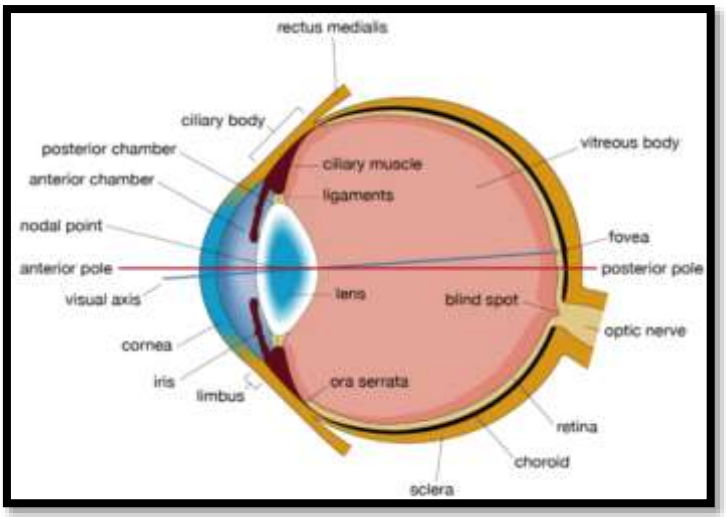

Figure 1: Structure of an Eye

1.1 In-Situ Gel:

In-situ gel forming systems are in a liquid aqueous solution state before administration, which are then transformed into gel under certain physiological conditions. These are delivery systems that can be instilled as eye drops and experience an immediate gelation when get in contact with the eye [11].

In-situ gel system is prepared as liquid formulation suitable to be instilled into the eyes of the patient which upon exposure to the physiological environment changes to gel outcomes in in-situ gel and, thus increasing the precorneal residence timing of the delivery system, and enhances the ocular bioavailability of the drug [12]. There are many factors on which preparation of gel is depended like change in a particular physio-chemical parameter (such as pH, temperature, ion-sensitive) by which the drug gets released in a sustained and controlled way [13]. These systems were innovated for drug content, clarity, pH, gelling capacity, viscosity, in vitro drug release studies, texture analysis, sterility testing, isotonicity evaluation, accelerated studies and irritancy test [14]. In this, drug and polymer incompatibilities are known with FT-IR Spectroscopy. In present-day study, Norfloxacin ophthalmic gel is prepared using polymers Carbopol-940, HPMC E4M, HPMC K4M and, HPMC-E50LVas a pH triggered gelling system to enhance contact time and controlled release, to decrease the frequency of administration and rise the therapeutic efficacy of the drug [15].

1.2In-Situ Gel Classification:

In-situ gel is classified based on their phase change (as shown in figure 2), they are as follows: -

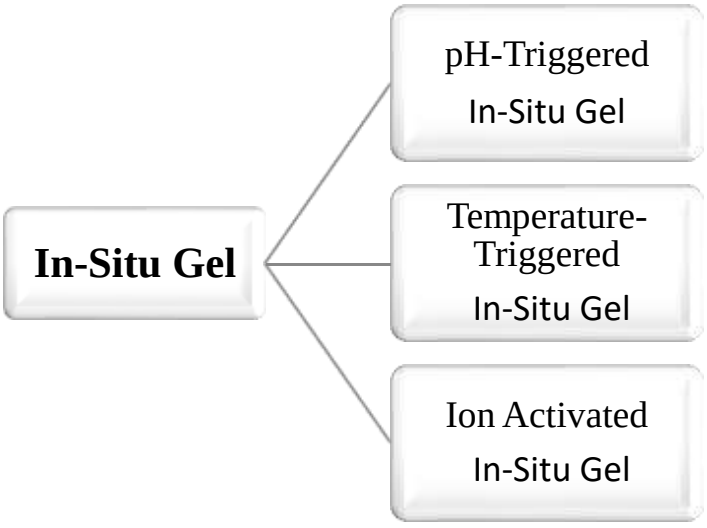

Figure 2: Classification of In-Situ Gels

A. pH Triggered In-Situ Gel:

- **pH sensitive polymers-** Some polymers consist of pH sensitive properties, where they transform from liquid to gel form when a change in pH takes place. For example, polymers such asalginate, polyacrylate, or methyl cellulose form a gel when the pH of the solution reaches a certain edge. Change in pH can cause changes in the bond between polymers, leading to the formation of gel [16].
- **Changes in environmental pH -** Some in-situ gels can form gels due to the changes in environmental pH. For example, in the acidic environment of the stomach, in-situ gelcomprising acidic polymers will experience a decline in pH and form a gel, which allows the drugs present in them to release [17].

B. Temperature Triggered In-Situ Gel:

- **Sol-gel transition -** Some polymers can experience sol-gel transition when change in temperatureoccur. At a particular temperature, polymers in liquid solution form a stable gel network. For example, Poly(N-isopropyl acrylamide acid) {PNIPAAm} is one of the most frequently used polymers in temperature-sensitive in situ gel system [18]. PNIPAAm forms gel at temperatures above a certain “gelling temperature” known as Critical Point of Solution (LCST) [19].

- **Gel formation by changes in ambient temperature -** Some in-situ gels are formed when subjected to environmental temperature changes. For example, in an application of injection in-situ gels may formed when the polymer solution which isadministered into the body experiences a drop in temperature due to the temperature of lower body, and thus forming a stable gel [20].

C. Ion Activated In-Situ Gel:

- **Formation of ionic bonds -**Ionic bonds with certain ions can lead to the formation of gels through some polymers. For example, In in-situ gel systems, Gelatin is an oftenly used polymer in which stable cross-links between gelatin chains are formed using calcium ions,forming a strong gel [21].
- **Control of viscosity by ions -** The viscosity of the solution and aid in gel formation can be affected due to the addition of certain ions to a polymer solution. For example, To increase viscosity and form a stable alginate sodium or calcium ions are added to an alginate solution [22].

1.3 Role of In-Situ Gel in Eye Drop:

Table 1. Different types of In-Situ Gel with their mechanism

S. no.	Trigger Type	Common Polymers	Mechanism	Stimulus
1.	**pH Triggered**	Carbopol + HPMC	Sol remains liquid at low pH; gels when pH increases in the eye.	Tear pH (~7.4)
2.	**Temperature Triggered**	Poloxamer 407, Methyl Cellulose	Sol is liquid at room temperature and gel at body temperature.	Body Temperature
3.	**Ion Activated**	Gellan Gum, Alginat	Ions in tears cause cross-linking of polymer chains, forming a gel.	Ions in Tears

2. MATERIALS USED:

- **Active Pharmaceutical Ingredient (API) –** Primary therapeutic agent used for ocular disorders. Therapeutic agent selection is based on the targeted problem, such as infection, glaucoma, or inflammation [23].

Table 2. Drugs used for treating ocular disorders with examples

Drug Titles	Drug Uses	Particular Formulation
Brimonidine Tartrate	Antiglaucoma (α2 agonist)	pH-sensitive in-situ gels
Timolol Maleate	Antiglaucoma (beta-blocker)	Thermosensitive in-situ gels
Ciprofloxacin	Antibiotic (fluoroquinolone)	Ion-sensitivity in-situ gels
Ketorolac Tromethamine	NSAID for inflammation	Ion-sensitive / pH-sensitive

- **Gelling Agent (Polymer)**

A. <u>pH-sensitive Polymers:</u>

- These carriers gel when the pH shifts from acidic (the bottle) to about 7.4 when there is tear fluid.
- **Carbopol 934/940 (Carbomer)**, a derivative of polyacrylic acid, which is acidic in solution form, gels when the pH ranges from 6-7.4.
- **HPMC or HEC:** Are usually used in combination with carbopol for enhancing viscosity and feel [24].

B. Thermosensitive Polymers:

- Gels are formed when the temperature approaches the ocularsurface temperature, which is approximately 35-37 degrees Celcius [25].
- **Poloxamer 407 (Pluronic F127)** is the primary thermosensitive agent because it micellizes and develops a packable gel upon being heated.
- **Poloxamer 188:** Gelling temperature and viscosity of 407 are usually adjusted using 188.
- **Mechanism:** Gelation is achieved by rearrangement of micellar structures with rising temperature [26].

C. Ion-sensitive Polymers:

- Gels prepared in the presence of divalent cations such as Ca^{2+} and Mg^{2+} in tear fluid [27].
- **Gellan Gum (Gelrite)** is a polysaccharide anionic that forms a gel through ionic crosslinking.
- **Sodium Alginate** is another that also gels on the presence of Ca^{2+}.
- **Mechanism:** Matrix of gel is formed by crosslinking with ions [28]

➢ **Viscosity Enhancer/ Mucoadhesive Polymers-**This is used to control gel strength; and improve ocular comfort and residence time [29].

Table 3. Polymers used as viscosity enhancers

Polymer	Function(s)
Hydroxypropyl Methyl Cellulose (HPMC)	It enhances viscosity and tear film retention
Methylcellulose	Improve flow and gel consistency
Sodium carboxymethylcellulose	It enhances viscosity and muco-adhesion
Xanthan gum	Biocompatible mucoadhesive

➢ **Buffering Agent –**These are those agents that maintain physiological pH to safeguard patient comfort and drug stability [30].

Table 4. Buffers used in In-Situ Gel Eye Drop

Buffer	Role
Phosphate Buffer	Maintains neutral pH
Citrate Buffer	Occasionally used for weakly acidic drugs
Borate Buffer	Antimicrobial and stabilizing properties

➢ **Preservatives –**These agentsprevent Microbial growth in containers.

Table 5. Preservatives used in In-Situ Gel Eye Drop

Preservative	Function(s)
Benzalkonium Chloride (BAK)	Most common ophthalmic preservative
EDTA (Disodium EDTA)	Chelates
Sodium Benzoate	Alternative preservative (less irritating)

- **Tonicity Adjusters –** These are used to ensure the formulation is isotonic with tears (~300 mOsm/kg) for comfort [31].

Table 6. Tonicity adjusters with their roles

Ingredient	Role
Sodium Chloride (NaCl)	Main tonicity agent
Potassium Chloride (KCl)	Maintain electrolyte balance
Dextrose	Alternative tonicity agent
Mannitol	Sometimes used for osmotic balance

- **Solvent –Purified Water**is used as the primary solvent for the entire formulation. It may contain little amount of co solvents such as (ethanol, propylene glycol etc.) if the drug is poorly water-soluble than this are used with caution in ophthalmic use.

3. METHODS OF PREPARATION:

3.1 Method of Preparation of pH-Triggered In-Situ Gel Eye Drops: -

1. Selection of Polymers:

- Use pH-sensitive polymers such as Carbopol 940(polyacrylic acid) as the main gelling agent.
- Use of viscosifier such as Hydroxypropyl methylcellulose (HPMC) is optional for enhancing consistency and clarity [32].

2. Preparation of Polymer Solution:

- Add Carbopol to distilled water with stirring until completely hydrated.
- Prepare a solution of HPMC in water, normally at an elevated temperature of about 60°C, then allow it to cool down [33].

3. Mixing of Solutions:

- Mix the two polymer solutions gently under stirring.
- Keep the pH of the solution at around 4.5–5.0 in order to prevent gelation, so the product remains in the liquid state during storage [34].

4. Addition of the API:

- Dissolve the drug e.g. timolol maleate, ciprofloxacin into the prepared gel base.
- Ensure that the drug will maintain stability under acidic pH.

5. Addition of Excipients:

- Add preservatives (e.g., benzalkonium chloride), stabilizing agents, and isotonic agents (e.g., sodium chloride), etc., as required [35].
- Ensure sterility during preparation.

6. pH Adjustment:

- The pH will be adjusted so that it remains in liquid form inside the container (around 4.5–5.0).
- On instillation to the eye (pH is about 7.4), gelation will occur due to increased ionization of Carbopol [36].

7. Sterilization:

- By sterile filtration 0.22-µm filter or aseptic processing.
- Filling in sterile eye drop bottles would be done under aseptic conditions [37].

8. Packaging and Storage:

- Store in sterile, light-resistant containers.
- Label as per directions for use.

3.2 Method of Preparation of Temperature-Triggered In-Situ Gel Eye Drops: -

1. Selection of Polymers:

- Consider using thermosensitive polymers like Poloxamer 407, also known as Pluronic F127, which turns into a gel at body temperature (around 35–37°C) [38].
- It’s often paired with Poloxamer 188 or thickening agents like Carbopol or HPMC to tweak the gel's strength and clarity [39].

2. Preparation of Polymer Solution (Cold Method):

- The cold method is a popular choice since Poloxamer dissolves more effectively at lower temperatures:
- Start by weighing out the necessary amount of Poloxamer 407 (usually between 15–25% w/v).
- Slowly mix it into cold distilled water (4–8°C) while stirring continuously.
- Let it chill in the fridge overnight (12–24 hours) to ensure it fully hydrates and dissolves [40].

3. Addition of Drug and Excipients:

- Dissolve your active pharmaceutical ingredient (API), like timolol or ketorolac, into the polymer solution.
- Then, add in preservatives (like benzalkonium chloride), stabilizers, and tonicity adjusters (such as sodium chloride).

4. pH Adjustment:

- Make sure to adjust the pH to a level that's suitable for eye use (around 6.5–7.4), depending on the drug's stability and comfort.

5. Sterilization:

- If compatible, sterilize using cold filtration with a 0.22 μm filter.
- Alternatively, you can prepare everything under aseptic conditions to keep it sterile.

6. Packaging:

- Fill sterile ophthalmic dropper bottles while maintaining aseptic conditions.
- Don't forget to label them properly for storage (usually in the fridge) and for patient use.

Mechanism:

At refrigerator temperatures (around 4–8°C), the formulation stays liquid. But once it's instilled into the eye (which is about 35°C), it transforms from a solution to a gel right there, which helps the drug stay in place longer [41].

3.3 Method of Preparation of Ion-Activated In-Situ Gel Eye Drops: -

1. Selection of Ion-Sensitive Polymers:

- Choose polymers that form a gel when they come into contact with ions, particularly calcium, found in tear fluid:

- Gellan gum (like Gelrite) – the most popular choice
- Alginate – sodium alginate is commonly used
- Carrageenan – not as frequently used

2. Preparation of Polymer Solution:

- Dissolve gellan gum or sodium alginate in hot distilled water (typically around 70–80°C) while stirring continuously.
- Let it cool with stirring until you achieve a clear solution [42].

3. Addition of Drug and Excipients:

- Mix the drug (API) (for instance, timolol maleate or pilocarpine) into the cooled polymer solution.
- Incorporate the necessary excipients:

- Preservatives (like benzalkonium chloride)
-Tonicity adjusters (such as sodium chloride)
- Stabilizers or buffering agents

4. pH Adjustment:

- Set the pH to around 6.5–7.4, which is ideal for both ocular comfort and drug stability.

5. Sterilization:

- Sterilize the solution using membrane filtration (with a 0.22 μm filter).

- If the polymer or drug is sensitive to heat, prepare it under aseptic conditions instead [43].

6. Packaging:

- Transfer the sterile formulation into sterile eye dropper bottles while maintaining aseptic conditions.
- Store at room temperature or according to the stability requirements of the formulation.

Mechanism:

The solution stays liquid in the container. When you apply it to the eye, divalent cations (like Ca^{2+}, Na^{+}, Mg^{2+}) in the tear fluid interact with the polymer (such as gellan gum), causing it to gel right where it's needed [44].

4. ADVANCEMENTS IN IN-SITU GEL:

In situ gelling could possibly turn into a great basis for ocular drug administration. This would rid the administration of some of the drawbacks encountered with conventional ocular drops and ointments. Further developments in in situ gel technology enabled the preparation of novel formulations that have more degrees of optimization regarding patient compliance and dose frequency [45].

The most important of these are probably mucoadhesive in-situ gels: these provide long-term adhesion to the surface of the eye, and allow for prolonged drug release and improved therapeutic effects. A further development is represented by stimuli-responsive in situ gels that release drugs in response to physiological triggers such as pH or temperature [46]. Broadly speaking, the in-situ gels technology seems to represent a promising new strategy for delivering ocular medicines and enhancing the clinical outcomes [47].

In-situ gelling systems are gaining traction as an exciting approach to delivering drugs in ophthalmology. They tackle issues like low bioavailability, quick drainage from the eye, and the hassle of frequent dosing. These innovative systems change from a liquid to a gel when applied, which helps keep the medication in the eye longer and allows for a steady release of the drug [48].

1. Stimuli-Responsive Polymers

Recent advancements have highlighted polymers that react to physiological changes, ensuring that gelation happens right where it's needed and that the drug is released over time:

- **Thermosensitive Polymers:** Pluronic F-127 is a temperature-sensitive polymer that shifts from a sol to a gel at body temperature, which helps it stay in the eye longer. Research has shown it works well for delivering sparfloxacin, with optimized versions providing a release that lasts up to 12 hours and aiding in the healing of eye infections [49].

- **pH-Sensitive Polymers:** Carbopol and hydroxypropyl methylcellulose (HPMC) are great for their ability to gel when they encounter the slightly acidic pH of the eye, allowing for controlled drug delivery.
- **Ion-Responsive Polymers:** Gellan gum is a standout ion-sensitive polymer that turns into a gel when it meets divalent cations found in tear fluid. Formulations with gellan gum have shown to release drugs over a longer period and improve how well the drug works in the eye [50].

2. Nanotechnology Integration

Bringing nanocarriers into in-situ gels has taken ocular drug delivery to the next level:

- **Bilosomes:** Bilosomes loaded with ciprofloxacin, when mixed into in-situ gels, have shown better antimicrobial effectiveness, improved penetration, and longer retention in the eye compared to traditional formulations [51].
- **Emulsomes:** Sparfloxacin emulsomes mixed into thermosensitive gels have demonstrated better drug permeability and longer retention in the eye, leading to better treatment results.

3. Biodegradable and Biocompatible Polymers

Using natural polymers ensures that the gels are biocompatible and reduce irritation in the eye:

- **Chitosan:** Researchers have really delved into chitosan-based in-situ gels for delivering drugs to the eyes, thanks to their impressive mucoadhesive qualities and ability to break down naturally. These gels not only ensure a steady release of medication but also boost how well the drugs work in the eye [52].

4. Enhanced Therapeutic Efficacy

In-situ gels have been specifically designed for the gradual release of different eye medications:

- **Anti-Glaucoma Agents:** Gels that include brinzolamide have been found to keep intraocular pressure down for longer and make it easier for patients to stick to their treatment compared to regular eye drops [53].
- **Antibiotics and Anti-Inflammatory Drugs:** When ciprofloxacin and corticosteroids are formulated into in-situ gels, they show better therapeutic results and require less frequent dosing, which helps patients stay on track with their treatment [54].

5. Clinical Translation and Regulatory Approvals

Several in-situ gel formulations are making strides toward being used in clinical settings:

- **Clinical Trials:** There have been promising results from Phase I and II clinical trials for these in-situ gel formulations, showing they are safe and effective for people.
- **Regulatory Approvals:** A few of these formulations have already gained regulatory approval in different areas, setting the stage for them to be available commercially [55].

5. PATENTS PUBLISHED:

Patent no.	Publication Year	Inventors	Key Findings	Reference
US2002/0114778A1	2002	Xia E, Smerbeck RV	Established an in-situ gel ophthalmic drug delivery system using deacetylated gellan gum for cataract anticipation.	Research Progress of In-situ Gelling Ophthalmic Drug Delivery System
US 6511660B1	2003	Lin HR, Sung KC	Developed ophthalmic drug delivery formulation and methods for making the same using Carbopol and pluronic.	Research Progress of In-situ Gelling Ophthalmic Drug Delivery System
US 6703039B2	2004	Xia E, Smerbeck RV	Developed a rescindable gelling system for ocular drug delivery using a block copolymer of propylene oxide and ethylene oxide by means of HPMC.	Patent Link
WO 2011018800A3	2011	Chandavarkar NM, Jindal KC, Malayandi R	Presented an in-situ gel forming solution for ocular drug delivery consisting a combination of natural polysaccharide with a thermo-reversible polymer.	Patent Link
US 20110082221A1	2011	Claire Haug	Introduced in-situ gelling system as sustained delivery for the frontal of the eye, exploiting a reversible gelling system for ocular drug delivery.	Patent Link
US 2011/0082128A1	2011	Not Specified	Established an in-situ gel ophthalmic drug delivery system using deacetylated gellan gum	Research Progress of In-situ Gelling Ophthalmic Drug Delivery System

			for cataract anticipation.	
US 8343471B2	2013	Banerjee R, Carvalho E	Developed nanoparticulate in-situ gels of TPGS, gellan, and PVA as vitreous humor alternates.	Patent Link
US 9757330B2	2017	Not specified	Delivered a recipe for in-situ gel, and implant, drug delivery system formed thereby.	Patent Link
US 10226417B2	2019	Not specified	Developed drug delivery systems and applications, including ophthalmic applications.	Patent Link
US 11576973B2	2023	IVIEW Therapeutics, Inc.	Developed aqueous formulations comprising an anti-infection agent, a biocompatible polysaccharide, an osmotic pressure regulator, a pH regulator, and water, where in a gel containing the therapeutic agent is formed in-situ upon instillation on to the skin and body cavity of a patient.	Patent Link

6. CONCLUSION: -

In-situ gel eye drops represent a significant innovation in ophthalmic drug delivery, offering solutions to the major limitations of conventional eye formulations. By transforming from a liquid to a gel upon contact with the eye's natural environment, these systems enhance drug retention, minimize the need for frequent dosing, and improve overall treatment effectiveness. The adaptability of in-situ gels—whether triggered by temperature, pH, or ionic changes—makes them suitable for various therapeutic applications. Despite the benefits, certain challenges such as polymer selection, formulation stability, and patient sensitivity must be carefully addressed during development. Continued research and the integration of new technologies, including nanocarriers and natural bioactives, hold great promise for the advancement of safer, more efficient, and more targeted ocular therapies.

With ongoing progress, in-situ gel systems are likely to become a preferred choice in modern eye care.

7. DECLARATION OF INTEREST

Author declares no conflict of interests.

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