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REVIEW

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Revolutionizing ocular drug delivery: recent advancements in in situ gel technology

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Abstract

Background Ophthalmic in situ gel is a novel preparation. It can be instilled into the eye as a liquid but gels upon contact with the ocular surface, generating a sustained-release depot of the drug.

The main body of the abstract Among drug delivery modalities, ocular drug administration requires careful study and parameter assessment. This is because the eyes are sensitive and require careful care. Conventional ocular administration techniques quickly eliminate formulated compounds, minimizing epithelial interaction. This review covers polymers used in ocular medication delivery, their uses, and their drawbacks. The in situ gelling mechanism converts liquid formulations into gels under certain physiological or environmental conditions. When they contact the ocular surface, in situ ocular gels undergo this transformation for medication administration. Different mechanisms drive this change, depending on the gel's formulation and desired properties. Temperature-, pH-, and ion-induced gelation are common processes of in situ ocular gel formation. The medicine's physicochemical qualities, desired drug release kinetics, ocular environment, and patient comfort determine the mechanism. Researchers can create ocular gels that transport medications, improve bioavailability, and increase patient compliance by carefully formulating and understanding the in situ gelation mechanism. These polymers are useful in prodrug research and ocular penetration enhancement. The article thoroughly discusses polymeric systems and creates a viable ophthalmic drug delivery formulation.

Short conclusion In conclusion, in situ ocular gels advance ocular medication delivery. These gels overcome various difficulties of current delivery strategies for ocular therapeutics and provide a diverse and effective platform. In situ gelling, where the liquid formulation becomes a gel when it contacts ocular tissues, improves medication retention, bioavailability, and contact time.

Keywords In situ gel, Ocular drug delivery, Stimuli-responsive polymers, Bioavailability, Ocular residential time

Background

The topical route of administration is the most frequent one for ophthalmic medications since it is easy to apply, it does not involve any kind of invasive procedure, and it is available to all patients. Unfortunately, it is not possible for medications to achieve efficacious concentrations when they are just applied topically. In addition to this, their bioavailability needs to be increased so that the number of times they need to be administered, as well as the severity of the negative effects that come along with it, can be reduced. For this reason, throughout the course of the last several decades, a significant amount of focus has been placed on the possibility of producing prolonged-release forms that are able to increase the precorneal residence period while simultaneously reducing the amount of medication that is lost as a result of tear production. Gel-based materials are one of these forms that have been investigated as a potential perfect

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delivery mechanism due to the fact that they belong to a very adaptable class that has a wide variety of potential uses in ophthalmology. These components can be found in therapeutic contact lenses, eye drops that contain gel, formulations that gel in situ, intravitreal injections, and intravitreal injections. The purpose of this review is to discuss the many different in situ gel-based materials and the primary functions that they serve in the field of ophthalmology.

Main text

Structure of the eye

The human eye is extraordinary and complicated, as shown in (Fig. 1). Front and back compartments. First, the tear film, cornea, pupil, lens, and ciliary body. The latter has conjunctiva, sclera, choroid, retina, vitreous body, and optic nerve. Orbital glands and epithelial secretions control tear volume. Light enters the eye through the cornea (Sridhar 2018). It has epithelium, stroma, and endothelium layers. The epithelium has some tightly connected cells, the stroma is a dense water layer, and the endothelium keeps the cornea transparent (Boote et al. 2020).

Iris colour affects retinal light. Pupils are black circles in the iris. The clear lens focuses light onto the retina, while the pupil size fluctuates with light. Both pigmented and non-pigmented ciliary epithelia have stomas and muscle-filled ciliary bodies. Ciliary body capillaries connect the eye's front and back (Rupenthal and Daugherty 2019). The vitreous humour, a clear, avascular gel, separates the lens from the retina. Water, hyaluronic acid, ions, and collagen cushion the eye.

The conjunctiva covers the sclera and lines the eyelids. The outer epithelium, the substantia propria (containing nerves, lymphatic and blood arteries), and the submucosa (attached to the sclera) make up this mucous membrane (Boote et al. 2020).

Collagen and mucopolysaccharides form the cornea's sclera. The exterior retinal layers are fed by the choroid, an interstitial layer between the retina and sclera. The retina is a thin layer of neuronal and glial cells that lines the eye. Electrical impulses from the optic nerve are processed by the brain as visual data (Boote et al. 2020).

Ocular barriers

Capacity of Cul-de-sac

Figure 2 illustrates ophthalmic obstacles. The cul-de-sac between the lower eyelid's palpebral and bulbar conjunctiva prevents foreign substances from entering the eye and enlarges the upper eyelid crease. 30 µL is the maximum ocular cul-de-sac volume. When the lower eyelid returns to its usual position, the capacity is lowered to 70–80% of the swelling, and allergic reactions can also diminish the volume. The tiny volume of the cul-de-sac

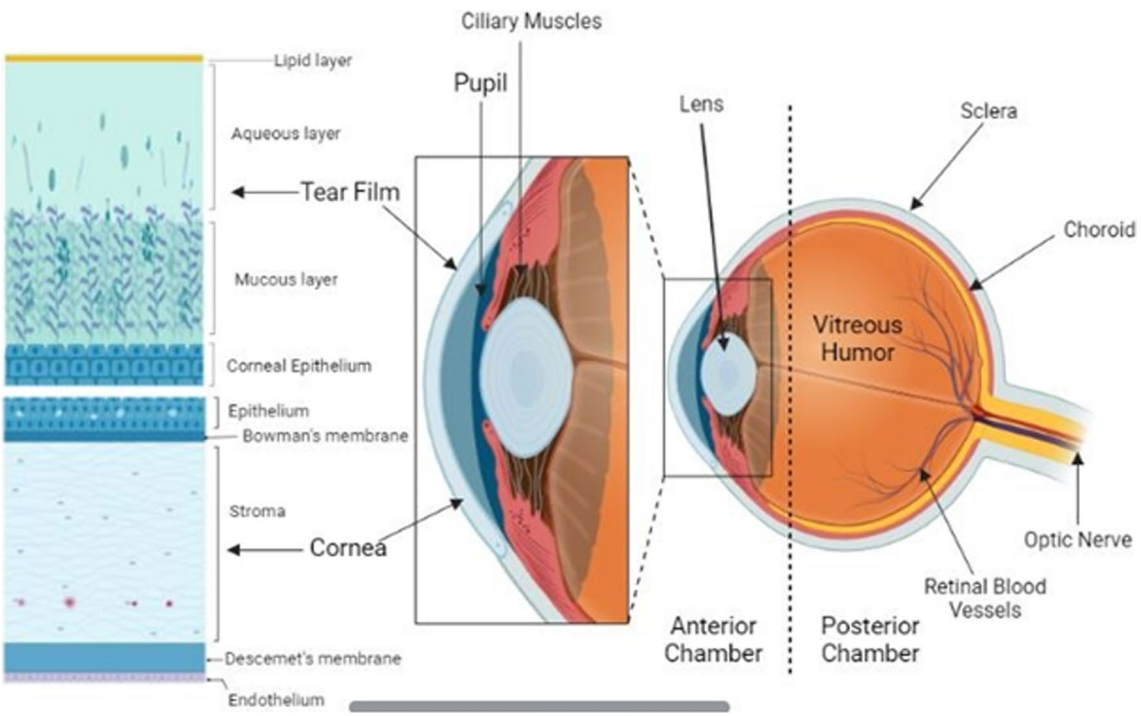

Fig. 1 Schematic diagram of the eye demonstrating the sclera, cornea, iris, ciliary body, choroid, retina, vitreous humour, and optic nerve as well as the inside and outside segments of the eye. A gel called vitreous humour fills the interior of the eye

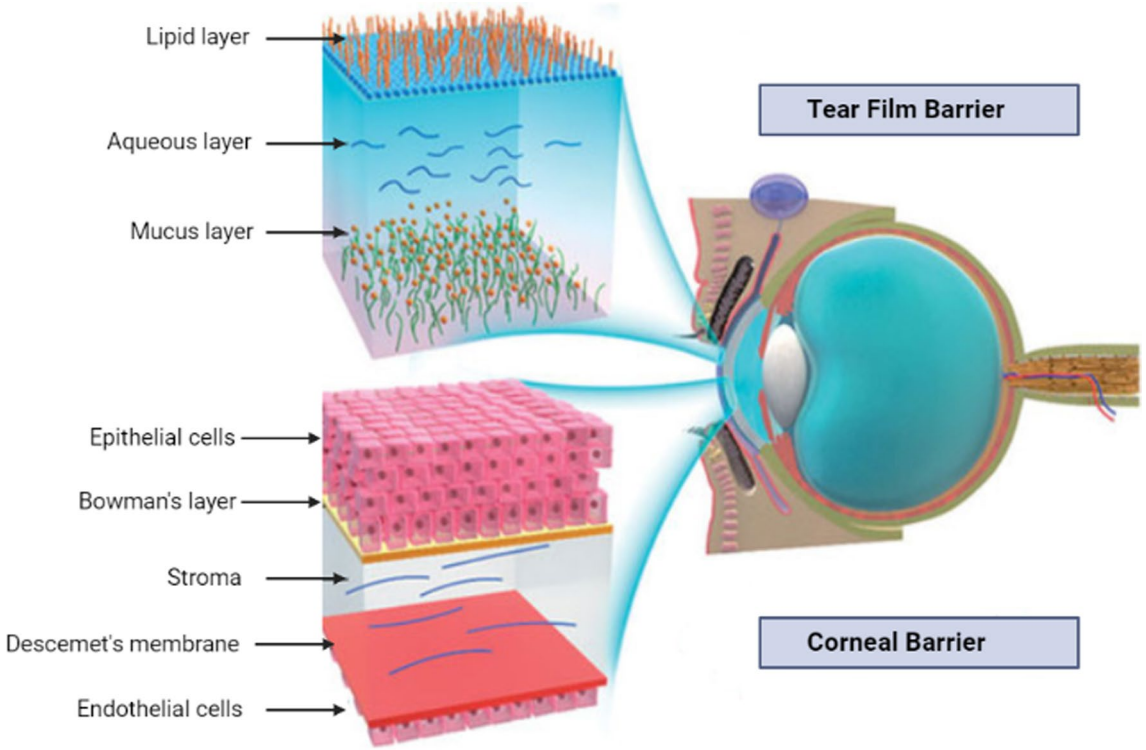

Fig. 2 Structure of ocular barriers. The figure represents two significant barriers for topical ocular medication delivery. Tear film barrier: rapid tear turnover and gel-like mucus. Corneal barrier: tight connections and five-layer structure

reduces drug concentration in the eye, decreasing its therapeutic efficacy (Bachu et al. 2018).

Drug loss by lacrimal fluid

Ocular solution drainage is a major precorneal challenge. Tears, solution drainage, and inadequate conjunctival absorption all cause drug loss. Protein binding and drug metabolism hinder medicine absorption (Ahmed et al. 2023). To keep eyes hydrated and keep foreign agents out, lacrimal fluid is constantly refreshed. Extending the formulation's residence period ensures pharmacological action (Agarwal et al. 2021).

Corneal barriers

The cornea shields and directs light to the retina (Mofidfar et al. 2021). Epithelium cells inhibit large molecules and hydrophilic medicinal agents. Hydrophilic thick stroma prevents lipophilic medicines (Varela-Fernández et al. 2020). The endothelium maintains corneal transparency and selectively lets hydrophilic drugs and macromolecules into the aqueous humour (Fig. 2). Drug ionization, molecular mass, charge, and hydrophobicity affect corneal penetration. Trans-corneal penetration inhibits tear-to-aqueous humour medication transfer (Ahmed et al. 2023).

Blood-ocular obstructions

Exogenous chemicals cannot reach the circulatory system because of the blood-retinal barrier (BRB) and the blood-aqueous barrier (BAB) (Mofidfar et al. 2021). BAB, which is found in the front of the eye, prevents the passage of many intraocular drugs but permits hydrophobic and smaller treatments (Lee et al. 2022). These drugs are eliminated from the body more quickly in the frontal region than hydrophilic and bigger drugs. Inulin clears more slowly than pilocarpine. In the back of the eye, BRB contains cells that make up the retinal pigment epithelium and endothelium. It shields the retina from toxins, water, and plasma (Bachu et al. 2018).

Ocular disorders

Cataract

Cataracts cause 40–60% of blindness worldwide. According to the National Programme for Control of Blindness and Visual Impairment, cataracts cause 62.6% of preventable blindness in India (Rupenthal and Daugherty 2019). Sunlight, diabetes, malnutrition, genetic predisposition, and smoking can induce cataracts (Chanet al. 2022). Crystalline proteins make the lens translucent and classify cataracts as cortical, nuclear, or posterior subcapsular. Cataracts are linked to changes in α, β, and crystalline

and their genes. Glycation, oxidative stress, and hydrophobic chemicals can raise calcium levels and lens crystalline protein buildup, causing cataracts. Hyperglycemia and hydroxyl radicals produce oxidative damage. Anti-cataract medicines may lessen the requirement for surgery (Dubald et al. 2018). These antioxidants chelate metal ions and scavenge free radicals. Curcumin, lanosterol, resveratrol, and metformin may treat cataracts.

Conjunctivitis

All ages, races, and genders suffer from conjunctivitis. It causes conjunctival oedema and might be infectious or non-infectious. Microbial infections produce infectious conjunctivitis, while irritants and allergens cause non-infectious. Conjunctivitis causes redness, irritation, excessive tearing, and ocular secretions. 40% of the globe has allergic conjunctivitis. Antibiotics or anti-inflammatories can be applied topically to treat conjunctivitis (Rupenthal and Daugherty 2019).

Diabetic retinopathy

Diabetes retinopathy affects both types of diabetes mellitus. 60% of type-2 diabetics and all type-1 diabetics have retinopathy after 20 years. Oxidative stress and inflammation induce diabetic retinopathy. After cataracts and corneal blindness, hyperglycemic disorders are the third leading cause of blindness worldwide (Sharma et al. 2021). Early detection and active blood glucose and blood pressure management can prevent it. Proliferative and non-proliferative diabetic retinopathy exist. Both can gradually destroy the retina. Laser photocoagulation and vitrectomy treat diabetic retinopathy, although they leave laser scars and provide only temporary relief. Interrupting inflammatory pathways with intravitreous corticosteroid injections or sustained-release implants can reduce macula swelling (Silva et al. 2021). Anti-VEGF medications (Ranibizumab and Aflibercept) minimize blood leakage and oedema (Fogli et al. 2018).

Retinoblastoma

Retinoblastoma is a cancerous retinal tumour that affects children under 5. Lack of treatments and a 99% death rate make retinoblastoma blinding. Retinoblastoma affects 1 in 20,000 live births, equally in both genders. Retinoblastoma is caused by a mutation in the tumour suppressor gene RB1 (Schaiquevich et al. 2022). Radiation, cryotherapy, systemic chemotherapy, and surgery can treat retinoblastoma. Recent research suggests treating retinoblastoma with proangiogenic hormones and blood vessel growth.

Fungal keratitis

Traumatized corneas get fungal keratitis, whereas healthy corneas do not. Candida tropicalis, Albicans, Krusei, Glabrata, and Parapsilosis can cause it. 40% of infectious keratitis cases occur in developing nations. Contact lenses, trauma, corneal surgery, corticosteroids, HIV positive, diabetes, and leprosy are risk factors for this illness (Masoumi et al. 2023). Fungal keratitis can slow wound healing, ulcerate the cornea, and inflame the corneal stroma, changing miRNA expression. Fungal keratitis can be treated with topical or oral antifungals or corneal surgery. Some surgeries did not restore eyesight. Fungal keratitis treatment trials are many. Nihal et al. developed a safer and more effective topical cubosome and mixed micelle sertaconazole nitrate formulation (Nihal et al. 2018).

Introduction to the ophthalmic drug delivery

Ophthalmic drug administration is a growing pharmaceutical specialty. It requires eyedrops to address macular degeneration, glaucoma, and dry eye condition. Since the eye is restricted, delivering drugs to it presents unique challenges (Conrady and Yeh 2021). Medication delivery must overcome eye barriers. These include the cornea, tear film, and blood-retina barrier. Since the eye movements are constant, it may be difficult to maintain drugs in place long enough for them to work. Eye drops, ointments, and injections have traditionally delivered ocular drugs (Shastri et al. 2023). These methods have systemic adverse effects, low absorption, and patient noncompliance. New in situ gel technology can revolutionize ocular medicine administration.

Current challenges with traditional ocular drug delivery approaches

Patients and doctors struggle with traditional ocular medication delivery. Eye drops, for example, have low bioavailability and lose a lot of medicine before reaching the intended site (Gote et al. 2019). The eye automatically expels foreign objects like eye drops, limiting how much medication can be given in a single dose.

Traditional ocular drug administration has poor bioavailability and patient compliance. Patients often forget to take their prescription or do it incorrectly, which increases medication loss and reduces treatment efficacy (Akhter et al. 2022). Eyedrops must be used often. Chronic ocular illnesses like glaucoma necessitate frequent, intrusive eye injections of medicine (Billowria et al. 2023). Treatment and control require these injections. This may increase the patient's stress, suffering, and risk of infection. These issues with conventional

medication administration to the ocular segments highlight the need for an effective, patient-friendly, and targeted system. In situ gel was created for this.

The promise of in situ technology intended for ophthalmic drug delivery

In situ gel technology could deliver drugs. Glaucoma, ocular keratitis, and diabetic retinopathy are increasing. Thus, focused and effective medication administration is more important than ever (Perminaite et al. 2021). In situ gel technology outperforms traditional pharmaceutical administration methods. Directly applying medicine to the afflicted area in a regulated and prolonged manner improves therapeutic results. In situ gels' gel-forming polymers protect the ocular surface, minimizing injections and improving patient compliance. In situ gel technology has dramatically improved ocular medication delivery. Stimulus-responsive polymers can change their properties in response to stimuli like temperature or pH to improve drug delivery to specific ocular locations (Campos et al. 2020). pH and temperature are examples. Nanotechnology and in situ gel technology have also led to improved bioavailability and extended-release ocular medication delivery methods.

The In situ gel technique for ocular medication administration holds great promise. It could improve ocular condition management and patient outcomes (Okur et al. 2020). We should expect more inventive and effective medicine delivery options as research continues.

Advantages of in situ gelling approach over conventional ocular formulations

In situ ocular gels offer several advantages over conventional ocular formulations, making them a promising and innovative approach to ocular drug delivery. Some of the key advantages include:

Extended residence time: One of the primary benefits of in situ ocular gels is their ability to transform from a liquid to a gel-like state upon contact with the ocular surface. This transformation leads to prolonged contact and increased residence time on the eye, which is crucial for effective drug absorption and sustained therapeutic action.

Enhanced bioavailability: The prolonged contact time provided by in situ ocular gels allows for improved drug absorption and bioavailability. The gel's sustained release of the drug enables a more controlled and prolonged delivery profile, reducing the need for frequent administration and optimizing therapeutic outcomes.

Improved patient compliance: Conventional ocular formulations often require frequent administration due to their rapid clearance from the eye. In situ ocular gels can reduce the frequency of administration, leading to improved patient compliance and convenience. Patients are more likely to adhere to their treatment regimen when they don't need to administer drops multiple times a day.

Reduced systemic absorption: In situ ocular gels minimize the risk of systemic absorption of the drug, as they are designed to stay localized on the ocular surface and within the eye. This is particularly important for drugs with potential systemic side effects, as it reduces the exposure of the rest of the body to the drug.

Precise drug delivery: The gelation mechanism of in situ gels can be fine-tuned to release drugs at a controlled rate. This precision allows for tailored drug delivery profiles, ensuring that therapeutic concentrations are maintained over a desired period while minimizing the risk of over- or under-dosing.

Protection of sensitive drugs: In situ ocular gels can provide protection to sensitive drugs from degradation and elimination. The gel matrix can act as a barrier against environmental factors, such as tear fluid or enzymes, that could otherwise degrade the drug before it reaches its intended target.

Enhanced therapeutic efficacy: The sustained drug release provided by in situ ocular gels can lead to enhanced therapeutic efficacy. This is particularly beneficial for treating chronic ocular conditions, where maintaining a consistent drug concentration is essential for managing the disease effectively.

Reduced frequency of application: Due to their prolonged release characteristics, in situ ocular gels often require less frequent application compared to conventional eye drops. This convenience can significantly improve the patient's quality of life and overall treatment experience.

Overall, the advantages of in situ ocular gels make them a promising platform for overcoming the limitations of conventional ocular formulations and improving the effectiveness of ocular drug delivery while enhancing patient comfort and adherence.

Role of in situ gelling approach to deliver the drug to inner compartments of the eye

The in situ gelling approach offers a promising solution to address the major challenge in ocular drug delivery, which is effectively delivering drugs to the inner parts of the eye where tight junctions create a barrier to drug penetration. Tight junctions between cells in ocular tissues, such as the cornea and conjunctiva, restrict the movement of molecules, including drugs, making it difficult to achieve therapeutic concentrations in the inner parts of the eye, such as the retina or the aqueous humour.

Researchers can address this difficulty by employing an in situ gelling technique, which offers the

advantages of prolonged drug exposure and improved drug penetration into the interior compartments of the eye. This technique demonstrates efficacy in addressing the challenge of drug delivery across tight junctions. In situ gelling formulations undergo a phase transition from a liquid state to a gel-like state when they come into contact with the ocular surface. The aforementioned alteration leads to an extended period of time during which the drug remains on the surface of the eye, hence enabling it to remain in close proximity to the tight junctions for an extended length. The viscoelastic nature of in situ gels facilitates their adherence to the ocular surface, including the cornea, conjunctiva, and adjacent tissues. The extended duration of contact enables enhanced interaction between the gel containing the drug and the ocular tissues, hence promoting improved drug permeation across tight junctions. In situ gels possess the capability to be formulated in a manner that facilitates the gradual release of the drug over a specific period. The present sustained release profile facilitates a consistent and regulated administration of the medication to the ocular regions, hence enabling the drug to surmount the obstacles presented by tight junctions. In situ gels have the capability to integrate penetration enhancers that facilitate the transportation of drugs over tight junctions. These enhancers have the ability to transiently disturb the integrity of tight junctions, thereby facilitating the translocation of the drug over these barriers and enabling its delivery to specific tissues. In situ gels have the capability to be produced with polymers and additives that are specifically designed to enhance medication delivery. The formulation can be modified to provide appropriate viscosity, mucoadhesive characteristics, and drug release kinetics in order to improve medication delivery to the interior compartments of the eye. In the context of ocular applications, in situ gels have the advantage of enabling direct application to the ocular surface, hence facilitating targeted drug administration to the desired site. This practise decreases the likelihood of systemic absorption and the potential adverse effects linked to the exposure of drugs to the entire system.

Researchers can efficiently boost medication delivery to the inner portions of the eye by leveraging the benefits of in situ gelling. This approach allows for the bypassing of tight junctions and facilitates the attainment of therapeutic drug concentrations in the targeted areas. The aforementioned methodology exhibits considerable promise in enhancing the management of diverse ocular ailments and disorders that impact the posterior segments of the ocular organ.

Mechanism of in situ gelling technology

In situ gel technology is a medicine delivery approach where a sol phase turns into a gel phase when it touches the body. The gel is given as a liquid and changes into a gel inside the eye, releasing the drug slowly (Okur et al. 2020). Ophthalmic medications benefit most from the technology's increased bioavailability and residence time at the target site. The gel stores active treatments and releases them slowly to maintain a steady medicine concentration (Rykowska et al. 2021). Polymers, lipids, and surfactants make the gel. These biocompatible, biodegradable, and medication-gelling ingredients are chosen.

In situ gel technology has fewer side effects, better patient compliance, and lower dosages than conventional drug delivery methods (Vigani et al. 2020). Ophthalmic medication distribution studies on it could revolutionize ocular disease treatment.

Sol–gel transition Organic substances like metal alkoxides or inorganic metal salts are often used as starting ingredients and called "sol."

The "sol–gel" technique hydrolyzes, polymerizes, or condenses the precursor to generate a colloidal solution or suspension. Complete polymerization and solvent loss cause the sol-to-gel phase transition (Vigani et al. 2020). Temperature, pH, and ionic activation can form in situ gelling systems. Liquid polymers that gel at the low critical solution temperature (LCST) are employed in tempstimulated in situ gelling (Fan et al. 2022).

Polymeric agents with basic or acidic functional moieties inside the chain molecule generate the pH-convinced in situ gel, which undergoes a sol–gel state modification when the pH rises. Ion-elicited systems, excessively investigated as osmotically induced in situ gelling systems, occur when monovalent or divalent cations in lacrimal solution, such as Na+, Ca^{+2}, and Mg^{+2}, transform the polymer from sol to gel. Photon polymerization and enzymatic cross-linking can initiate sol–gel conversion. This work focuses on temperature sensitivity, pH change, and ion exchange-driven in situ gels. Gels work in situ via these mechanisms (Ni et al. 2020).

The pH-triggered gelling method

pH fluctuations also cause in situ gel to develop. This mechanism gels when pH changes. At pH, the formulation is a free-flowing solution that coagulates when the tear fluid raises the pH to 7.4. After instilling pH4.4 into the tear film, the very fluid latex quickly turns into a thick gel. All pH-sensitive polymers have acidic or basic groups that receive or release protons depending on environmental pH. Polyelectrolytes have many ionizable groups. Hydrogel swelling increases with external pH if

the polymer contains weakly acidic (anionic) groups but decreases with weakly basic (cationic) groups.

Polymers utilized in the pH-responsive in situ gel system

Carbopol

Carbopol, a polyacrylic acid (PAA) polymer (Fig. 3), undergoes a sol–gel phase transition in an aqueous solution at a pH above its pK of roughly 5.5. PAA carboxylic groups receive and release protons at low and high pH. Due to the electrostatic repulsion of negatively charged groups, the PAA expands at high pH, releasing drug molecules into the environment.

The aforementioned variables display different traits, including higher numerical values and, in accordance, alkalinity. As a result of the negatively charged ions in poly (acrylic acid) (PAA) swelling at high pH conditions due to electrostatic repulsion, medicines are released into the surrounding media (Wu et al. 2019). This chemical is frequently used in the creation of ocular preparations with the goal of extending pre-corneal medication retention time. Comparing carbopol to other polymeric agents, it loses the benefit of having improved mucoadhesive properties. The interaction between polyacrylic acid and mucin, which occurs via four mechanisms—hydrogen bonding, electrostatic interaction, inter-diffusion, and hydrophobic interaction—is attributed to carbopol's mucoadhesive properties (Devasani et al. 2016). Despite having exceptional mucoadhesive properties, carbopol is severely constrained by its acidic nature, which can irritate and damage ocular tissues. As a result, new carbopol blends with various polymers, including HPMC and chitosan, were created in an attempt to address this issue.

Research progress in pH-sensitive in situ gelling system

This method has a great deal of potential for maintaining drug products stable and prolonging drug release. Wu et al. (2011) created pH-triggered gels with baicalin for continuous ocular drug distribution by combining carbopol 974P and HPMC E4M (0.6%, w/w) to thicken the gel. Methods for in vitro and in vivo testing, including gamma scintigraphic technique, microdialysis, rheometry, and confocal scanning light microscopy, were evaluated. According to the findings of the rheological study, the gel formation under biological conditions was significantly enhanced. Over the course of eight hours, the gel may continuously discharge the medication. Moreover, the C_{max} and AUC values were found to be 3.6 and 6.1 times greater than the control solution, respectively (Wu et al. 2011). The gel formation mechanism is characterized by a sol-to-gel phase transformation in response

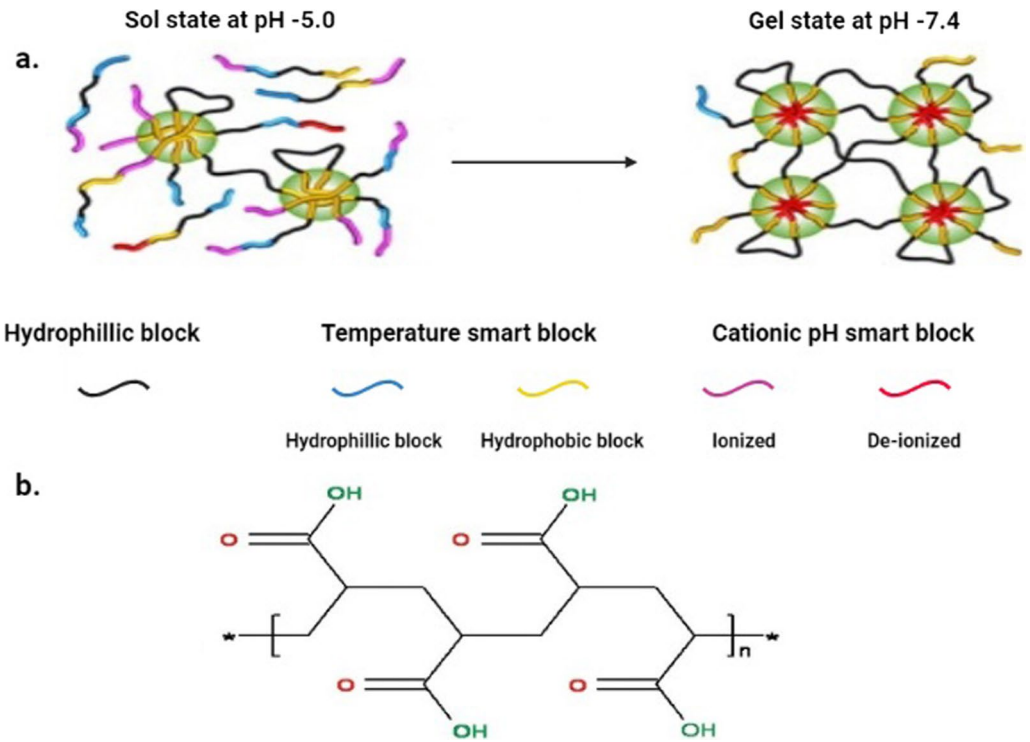

Fig. 3 Illustrating the effects of pH on carbopol gel formation. It shows a sol–gel phase transition in aqueous solution when the pH is increased. **a** Mechanism of pH triggered gelation. **b** Chemical structure of carbopol

to pH changes. Using polymeric agents that are pH-sensitive, also known as polyelectrolytes. (For example, the pH of the formulation is compared to the pH of the lacrimal fluid). Variations in the ionization state of the basic (ammonium) or acidic (carboxylic or phosphoric) groups present in the polyelectrolyte cause the sol–gel phase transition. The pKa values (3–10) and the molecular weight of the polymers determine the pH at which these groups ionize. The fluctuating ionization states of these groups influence the system's conformation, solubility, and expansion. Salt concentration, ionic strength, and temperature all have an effect on the gelling process and properties of certain pH-activated polymers. In another study, a group of researchers prepared ciprofloxacin-loaded bilosomes in situ gels for ocular delivery to minimize drug loss due to blinking reflex and nasolacrimal drainage. The goal of this study was to develop ciprofloxacin (CIP) loaded bilosomes (BLO) in situ gel for the improvement of therapeutic efficacy. The BLO was prepared by the thin-film hydration method and optimized by the Box – Behnken design. Cholesterol (CHO), surfactant (Span 60), and bile salt (sodium deoxycholate/SDC) were used as formulation factors. The optimized batch was then incorporated into the in situ gelling system using carbopol 934P and hydroxyl propyl methyl cellulose (HPMC K100M) gel base. The prepared in situ gelling system was evaluated for gelling capacity, viscosity, pH, in-vitro CIP release, ex-vivo permeation, and antimicrobial study. The prepared gel showed better gelling properties than conventional CIP gels with a viscosity of 145.85 cP in the gelling state. The formulation also exhibited sustained drug release and also showed better permeability than pure CIP (Alsaidan et al. 2022).

In situ gelling triggered by temperature

An interesting method for in situ gel generation involves the use of biopolymers whose transformation from sol to gel is prompted by temperature rises. Above the lower critical solution temperature, the temperature-sensitive smart polymers constrict and transition into a gel (Wei et al. 2020). The LCST is the temperature at which every component of a combination can be mixed in every possible quantity. This approach's ideal critical temperature is physiological and ambient; therefore, state change does not require any external heat sources other than body heat. This strategy aims to use poloxamer as a carrier for ocular medicine targeting by utilizing its in situ gel-forming characteristics (Luo et al. 2023). The phase conversion temperature of graft copolymers can be calculated using the temperature at which the meniscus first became immobile in each solution. These graft copolymers are a promising drug delivery system for long-term administration to the surface of the eye because of their bio-adhesive and thermos-gelling properties. The thermoresponsive approach that occurs above LCSTs according to the process of gel development starts as clear, homogeneous, freely flowing polymeric systems at temperatures below the LCST and changes to cloudy systems once they reach the LCST (Fig. 4). The turbidity of the solution is caused by buildup and enhanced light scattering, which follows the collapse of the polymeric chains. Phase separation separates the solution into a gel state and a solvent state, typically water, after the LCST. This is mostly due to an entropy consequence that, as the temperature rises, favours phase change.

Polymers used in the temperature-activated in situ gel system

Poloxamers

Poloxamers, triblock copolymers with hydrophobic propylene oxide and hydrophilic ethylene oxide domains, are amphiphilic (Wu et al. 2019). When their concentrations exceed 15% (w/w), the copolymers poloxamers or pluronics produce gels at physiological temperatures. Sol–gel phase change at increased temperatures was explained by several methods. These include polymer decomposition, micellar accumulation, and polymeric complex problems. Pluronic co-polymers come in a variety of grades and molecular masses (Almeida et al. 2013). L is for liquids, P for pastes, and F for flakes, depending on their physical properties. Poloxamers 338, 188, 407, and 237 are commonly used. Pluronic 407, also known as Poloxamer F-127, is a polypropylene oxide-polyethylene oxide copolymer. Its 70% ethylene oxide content makes this copolymer hydrophilic. F-127 is a co-polymer with a 12,000 Da molecular mass and a 1:2 PPO/PEO ratio. Non-toxic and less viscous below 4 °C. Poloxamer 407

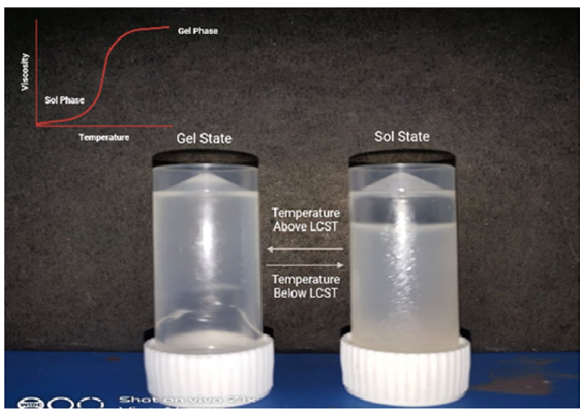

Fig. 4 Illustrating the effects of temperature on phase transition. It shows a sol–gel phase transition in aqueous solution when the temperature is increased above the lower critical solution temperature (LCST)

gels at body temperature. Hydrogen connections make F-127 more soluble in low-temperature water than in high-temperature water (Popescu et al. 2023).

Xyloglucan

A polysaccharide sourced from tamarind seeds is commonly referred to as tamarind seed polysaccharide (TSP). Upon partial degradation by β-galactosidase, it exhibits the ability to form thermally revocable gels in a diluted aqueous phase. The sol–gel conversion temperature exhibits variability in response to the extent of galactose degradation (Darge et al. 2019). The potential of TSP gels for drug delivery via various routes such as oral, ocular, intraperitoneal, and rectal has been described in the literature. The solubility of TSP in water is significant, and gelation is observed when the level of galactose removal surpasses 35%.

Cellulose

Cellulose is a linear chain of several hundred to over ten thousand β (1 → 4) connected d-glucose molecules. Methylcellulose, sodium carboxymethyl cellulose (NaCMC), hydroxyethyl cellulose, and hydroxypropyl methylcellulose, are among the cellulose derivatives commonly employed in topical ocular preparations (Rahman et al. 2021). At concentrations ranging from 1 to 10%, the aqueous solutions of these substances exhibit a liquid state at low temperatures but undergo gelation upon exposure to heat. Cellulose derivatives have the ability to exhibit a high phase transition temperature, which can be reduced through physical or chemical modification. The critical temperature range for MC lies between 45 to 50 °C, while for HPMC, it is between 70 to 90 °C (Joshi 2011). The inclusion of sodium chloride has been detected to reduce the gel-forming temperature of MC to a range of 33–34 °C. Similarly, the conversion temperature of HPMC may be dropped to approximately 40 °C by reducing the hydroxypropyl molar replacement.

Chitosan

It is an amino polysaccharide made from chitin through fractional depolymerization and deacetylation (Wu et al. 2019). Chitin is a natural material that comes from arthropods most of the time. For commercial reasons, most chitin comes from the shells of marine animals like crabs, lobster, shrimp, squid, and krill (Piekarska et al. 2023). Chitosan has been shown to have many uses in biological applications because it is biocompatible, biodegradable, sticks to mucous membranes, and has low immunogenicity. In recent years, there has been a lot of interest in temperature-sensitive gels made from chitosan and polyols like glycerol, sorbitol, and ethylene glycol. Thiolated Chitosan (TCS) is made by attaching thiol groups to the main amino groups of chitosan. People are very interested in the TCS drug delivery system because it sticks well to mucous membranes and keeps drugs in the body for a long time. The fact that TCS gels are in place is due to the formation of both intermolecular and intramolecular disulfide bonds, which happen when thiol groups are oxidized at biological pH.

Research progress in temperature-sensitive in situ gelling system

Bellotti et al. improved the use of pNIPAAm temperature-sensitive hydrogels for treating glaucoma by changing the amount of PEG and the molecular mass. They did this to try to lower the LCST of the ophthalmic gel and get it to form gel quickly after being given. They also made sure that the sol–gel change of the hydrogel was the same in cold conditions. (Bellotti et al. 2019) The in vitro drug release curve shows that the glaucoma drug brimonidine tartrate can be released repeatedly for 28 days.

Osswald et al. (2017) prepared anti-VEGF (ranibizumab or aflibercept) microspheres by using poly (lactic-co-glycolic acid), and the prepared microspheres were then put into an injectable poly (N-isopropyl acrylamide)-based thermo-responsive hydrogel called drug delivery system (DDS). In vivo, a laser-induced rat model of choroidal neovascularization (CNV) was used to test how well the treatment worked. The CNV lesion area was evaluated and measured using fluorescein angiograms and a multi-Otsu thresholding method, respectively. Also, measures of the patient's intraocular pressure (IOP) and dark-adapted electroretinogram (ERG) were taken before and after the treatment. At 1, 2, 4, 8, and 12 weeks, these tests were done. During the study, the CNV lesions were much less serious in the anti-VEGF-loaded DDS group than in a control group of animals that did not get any treatment. This suggests that the DDS could be a big help in treating problems with the back of the eye (Osswald et al. 2017).

Jimenez et al. made a microsphere/temperature-responsive gel with sustained release properties to improve the ocular distribution of cysteamine, a reducing substance used to treat cystine crystals in cystinosis. The pNIPAAm-based temperature-responsive gel technology showed that a single drop of it released cysteamine over a 12-h period. After direct application, these results showed that cysteamine got to the eye in a good way, with a lot of drugs going into the cornea and not much going into the bloodstream (Jimenez et al. 2021).

In situ gelling triggered by ionic interaction

The sol–gel transition may be induced and polymer viscosity increased by anionic polysaccharides which crosslink with divalent (Mg^{2+} and Ca^{2+}) and/or monovalent (Na +) cations available in the tear fluid. The cation

concentration rises in direct amount to the rise in polymer viscosity. As a result, increasing tear creation to thin down viscous solutions would increase cation concentration and, in turn, polymer viscosity, extending the ocular retaining time of drugs, minimizing lacrimal drainage, and enhancing the bioavailability of drugs.

Polymers used in the ion-induced in situ gelling approach

Gellan gum

Gellan gum is a type of polysaccharide that can make ion-sensitive hydrogels work better. Linear anionic heteropolysaccharides are the type of material in question. Dubashynskaya et al. (2019) found that it is made up of a repeated tetrasaccharide element made of glucuronic acid, rhamnose, and glucose in a ratio of 1:1:2. The polymer is made up of functional groups like carboxylic and hydroxyl groups, which can interact with other polymers through electrical attraction and hydrogen bonding, among other things. Gelrite® is an easy-to-find product that gels when it comes in touch with either monovalent or divalent cations. When given as a liquid into the cul-de-sac, the cations Na^{+}, Mg^{2+}, and Ca^{2+} in the electrolytes of tear fluid have been shown to cause polymer gel to form (Chandra et al. 2022). When the right amount of calcium gluconate was added to gellan compositions, gellan calcium gluconate-STF gels were made that were much stronger than gellan-STF mixes that did not have calcium gluconate. Gelation can happen through either a process that is affected by temperature or one that is caused by cations. The likely process of gelation is the formation of double-helix junction zones, which then join together to form a three-dimensional framework by attaching hydrogen to water and linking with cations.

Alginate

It is also a polysaccharide with a straight structure that comes from certain types of bacteria and brown seaweeds. The substance in question is a block copolymer made up of R-l-guluronate (G) and a-d-mannuronate (M) monomers linked in a (1–4) structure. The polymer has both homopolymeric sequences of M and G and areas that look like the repeated structure of disaccharides (MG). When sodium alginate comes in touch with the Ca^{2+} in tears, calcium alginate is made. This is what causes sodium alginate to turn into a gel. The amount of -l-glucuronic acid and -d-mannuronic acid in the polymer determines how strong it is and how many holes it has. Alginate with a lot of guluronic acid gels better and needs less polymer to make a solid gel (Abka-Khajouei et al. 2022).

Pectin

Pectins are a group of polysaccharides characterized by a polymer backbone primarily composed of α-(1,4)- d -galacturonic acid residues. Slight methoxy pectins, characterized by a unit of esterification below 50%, exhibit the ability to undergo gelation in aqueous solutions when exposed to free Ca^{2+}, which facilitates cross-linking of the galacturonic acid chains. The water miscibility of pectin is a significant advantage, as it obviates the need for organic solvents in formulations (Gawkowska et al. 2018). A US patent has reported on the occurrence of in situ gelling of pectin persuaded by Ca^{2+} in the tear fluid. Furthermore, the utilization of pectin-founded in situ gel has been observed to extend the time of drug release from various preparations, including acetaminophen, cimetidine, and theophylline.

Research development in ionic interaction In situ gelling system

Alginic acid and gellan gum are examples of commonly used polysaccharides that are activated by ions. Pseudomonas elodea produces deacetylated anionic extracellular polysaccharide gellan gum, which is composed of repeated units of -D-glucuronic acid, -L-rhamnose, and two -D-glucuronic acid residues. This polymer is composed of double helices in an aqueous solution at room temperature, which is held together by mild van der Waals forces. Upon interaction with the cations of the tear fluid, these helices assemble, causing the polymer to cross-link and form a complex with the cations in addition to hydrogen bonds with the water. Several in situ gelation techniques that are ion-stimulated have been described previously (Salunke and Patil 2016). Elmowafy et al. (2019) demonstrated that the in situ gelling technique is non-irritating and demonstrates the viability of in situ gel for buccal delivery. Using deacetylated gellan gum, Zhu et al. (2015) invented ion-activated ketotifen preparations for ophthalmic administration. According to Zhu et al. (2015), deacetylated gellan gum enhanced the capacity to prolong ocular residence time. Comparing equivalent doses of in situ formulations to conventional or regular ocular solutions, the in situ formulations exhibited significantly longer durations of action. In the production of bio-adhesive and ion-subtle hydrogels, the incorporation of weakly water-soluble medication is extremely challenging. Cyclodextrins are an example of a pharmaceutical excipient used to aid in the formulation of drugs with minimal solubility in water. The incorporation of hydroxypropyl-cyclodextrin into the in situ-produced gel resulted in enhanced fluconazole release and enhanced control. In situ ocular gel of brinzolamide was produced with gellan gum in addition to dimethyl

sulfoxide, polyoxyl 35, castor oil, and polysorbate 80 and it was discovered that brinzolamide demonstrates greater therapeutic efficacy and a longer intraocular pressure-lowering effect in an in situ gel formulation than in conventional eye drops and tablets (Bhalerao et al. 2020).

Multiple stimuli approachable in situ gelation

The utilization of a mixture of polymers by using diverse gelling approaches, which have established better therapeutic value and patient acceptance. The multiple stimuli-responsive methods are the greatest effective method for ocular in situ gelling at the moment. Numerous studies using the same ophthalmic formulation with pH-responsive polymers, thermos-responsive polymeric agents, or ion-activated polymeric agents have been published recently (Agrawal et al. 2020).

Multiple stimuli-responsive in situ gelling approaches for ocular drug delivery involve utilizing various triggers to induce the transformation of a liquid ocular formulation into a gel-like state upon application to the eye. These stimuli can include changes in temperature, pH, ions, enzymes, and other environmental factors. By designing formulations that respond to multiple stimuli, researchers aim to achieve precise control over drug release and enhance therapeutic outcomes. Here are some examples of multiple stimuli-responsive in situ gelling approaches for ocular drug delivery:

Dual-responsive gels: Formulations can react to temperature and pH changes. A gel made of thermoresponsive and pH-sensitive polymers can phase transition when exposed to body temperature and tears. This dual-responsive method triggers ocular gelation, improving medication retention and release.

pH and enzyme dual-responsive gels: Some formulations can respond to pH and tear fluid enzymes. These enzymes catalyze gel-forming processes. Dual-responsive ocular medication delivery systems replicate the biological environment with a dynamic and adaptive mechanism.

Ion and temperature dual-responsive gels: Ion-sensitive and thermoresponsive polymers can respond to ocular temperature and tear fluid ionic composition. This method targets gelation by ion concentration and temperature, tailoring medication delivery.

Triple-responsive gels: Some formulations use pH, temperature, and ion concentration. These complex formulations allow complicated medication delivery profile customization due to better gelation and drug release control.

Sequentially responsive gels: These gels respond to stimuli sequentially. A formulation may first pregelate due to pH changes, then gel at temperature. This sequential technique is smart and versatile for drug administration.

Multiple stimuli-responsive in situ gelling methods could offer personalized and targeted ocular drugs. These formulations optimize drug release kinetics, bioavailability, patient comfort, and compliance by leveraging the complex interaction of visual triggers. However, due to complex stimulus interactions and the necessity for accurate gelation and drug release dynamics, designing and developing such systems is difficult.

Research progress in multiple stimuli-triggered in situ gelling system

Khan et al. (2015) designed and studied a new gelling method for sustained release in ocular drug distribution involving sparfloxacin encapsulated in methylcellulose and sodium alginate that is pH- and ion-triggered. At pH 4.7, the preparation was in the sol phase, but when the pH was increased to 7.4, it rapidly changed to the gel state. In contrast to ocular droplets, the sparfloxacin release from ocular in situ preparations was sustained for 24 h. The ex-vivo corneal penetration investigation of prepared in situ gel on goat eye revealed significantly higher permeability than conventional eye drops. Yu et al. (2017) designed a nepafenac in situ gel by combining poloxamer and carboxymethyl chitosan. When the pH and temperature were altered at a very low concentration, the PEO-PPO-PEO block copolymer underwent a modifiable sol–gel transformation. The cell counting kit-8 method demonstrated that at lower concentrations, the preparation was not toxic to corneal epithelial cells. The hydrogel release of nepafenac was sustained in the poloxamer-CMC/NP formulation. At 35^0C and a pH of 7.4, the maximal rate of release was observed. Sodium alginate and methylcellulose are Ion and pH-elicited multiple stimuli in situ formulations that exhibited rapid gelation upon increasing the pH to 7.4 and sustained sparfloxacin release over a 24-h period (Yu et al. 2017). Chitosan and gellan gum encapsulated timolol maleate in situ ocular gel acted as multiple stimuli-responsive, exhibiting enhanced drug penetration through the cornea and retaining the therapeutic concentration of the drug at the corneal site for an extended period.

Nanoparticle-laden in situ gelling system

In recent decades, the concept of nanoparticles has gained in popularity. Various polymeric nanoparticles are used to deliver medications to their target sites at therapeutically appropriate rates and dosing schedules (Fig. 5). Nanoparticles range in size from 10 to a few nanometers (Pilipenko et al. 2021). The drug is dissolved and encapsulated in a polymeric matrix. Nanoparticles have shown great promise in the delivery of

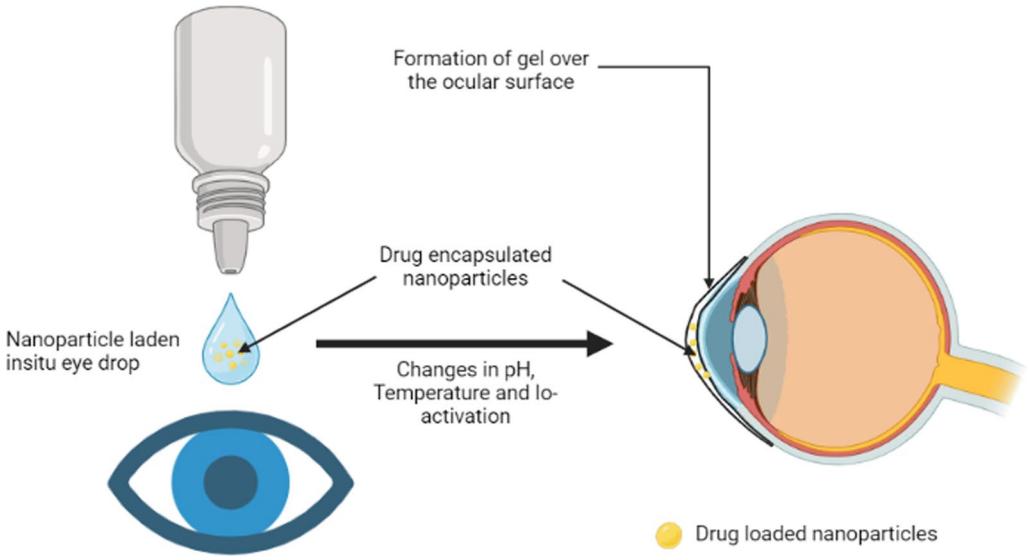

Fig. 5 In situ gel formation on the ocular surface. When administered into the eye, the formulation, which contains nanoparticles dispersed in the liquid phase, quickly transforms into gel in the cul-de-sac of the eye in response to environmental changes like pH, temperature, and ions before slowly releasing the medication under physiological conditions

ocular-targeted medications. For the production of polymeric nanoparticles, a number of applicable methods exist. The organic solvent is used to dissolve the polymer. To create a water-in-oil (W/O) emulsion, the drug substance is fragmented or disseminated in a polymer solution and then emulsified in an aqueous solution. The organic solvent is then ejected by consistently agitating or increasing the temperature under pressure. The use of an organic solvent during the solvent evaporation process could be hazardous to human health.

The U.S. Food and Drug Administration imposed limits on the total amount of organic solvents permitted in injectable colloidal systems. For the creation of polymeric nanoparticles, however, the salting out method and supercritical fluids are frequently employed. Drug encapsulation in nanoparticles can be accomplished in one of two ways: either by integrating the drug during nanoparticle development or by incorporating the nanoparticles into a solution of the drug. Due to the fact that the incorporation procedure captured a substantial amount of medication, it is more effective than the latter method (Pilipenko et al. 2021). The nanoparticles containing the substance are then combined with the gel base for eye therapy. In situ gel formulations in innovative therapeutic agent distribution systems as colloidal transporters, such as lipid-centred Nano-carriers and nanosuspensions, have been proven to be the most effective method, resulting in an increase in the absorption of ocular therapeutics.

Research progress in the nanoparticle-laden in situ gelling system

Liu et al. (2016) created a curcumin-loaded ophthalmic nano-gel using cationic nanostructured phospholipid carriers and a temperature-sensitive gelling agent. Researchers examined preocular retention, in vitro release, corneal penetration, and ophthalmic irritation. Microdialysis assessed drug pharmacokinetics in aqueous humour. Curcumin nano-gel had a higher AUC than curcumin ocular drops, indicating improved bioavailability. The nonirritating optimized in situ gelling ocular insert had a significantly delayed T_{max}, greater C_{max}, and improved bioavailability. Al-Khateb et al. (2016) created microsphere-encapsulated ofloxacin ion-triggered in situ gel. In rabbit research, in situ gel with ofloxacin microspheres had higher bioavailability than commercial eye treatments. Ofloxacin-encapsulated microspheres in in situ gel formulation have a longer duration of action, reducing the requirement for repeated administration and improving patient compliance (Al-Khateb et al. 2016). Pandurangan et al. created an SLN-filled in situ gel encapsulating voriconazole for ocular delivery. Paradkar et al. created an in situ gel with natamycin-containing niosomes using Poloxamer 407 and HPMC K4M. The bioadhesive Natamycin niosomal in situ gel formulation showed a longer corneal retention time and a 24-h drug release time than existing products. The formulation also increased transcorneal permeability. To make ofloxacin-loaded nanocarriers, chitosan was a polymer

matrix and STTP was an anionic cross-linker. Chitosan nanoparticulate in situ gel outperformed commercial ophthalmic treatments. In situ gelling increased levofloxacin nanoparticle ocular retention. Gupta et al. used PLGA to introduce levofloxacin nanoparticles to chitosan in situ gels. Gamma scintigraphy measured rabbit eye residential time (Al-Khateb et al. 2016). The nanoparticle-laden in situ gel preparations stayed on the eye longer than commercial versions. A comparable group reported that sparfloxacin nanoparticle-laden in situ gelling showed excellent sustained release. Poloxamer 407 and 188-encapsulated Loteprednol temperature-sensitive-nano emulsion was compared to the commercial formulation. In situ gel improved mean residential time and bioavailability by 2.54 times compared to standard formulations (Pandurangan et al. 2016).

Advantages of nanoparticle-laden in situ gelling approach

Ocular in situ nano-gels offer advantages over other medication delivery methods for eye disorders. They boost medication bioavailability. The gel's nanoparticles' small size helps drugs penetrate ocular tissues, increasing drug concentrations at the target site.

Ocular in situ nano-gels also regulate drug release. Ocular in situ nano-gels release drugs slowly, prolonging the therapeutic concentration at a chosen spot, unlike ocular drops, which may remove therapies quickly. Chronic eye problems require a long-term medication supply.

Ophthalmic in situ nano-gels are noninvasive and easy to use for patients and doctors. Biocompatible and biodegradable, they prevent unpleasant reactions and toxicity.

Ocular In situ nano-gels are a promising medicine delivery technique for eye disorders. Nanotechnology for ocular medicine delivery may improve as research continues.

Drawbacks & challenges of nanoparticle laden in situ gelling system

Ophthalmic in situ nano-gels have drawbacks like any medication delivery technique. Nano-gel stability is a major issue. Gels have a short shelf life and are easily damaged. Nano-gel size and shape also affect efficiency. They must be small enough to pierce the cornea and reach the target cells, but not too small to be removed from the eye.

Regulating nano-gel medication release is another issue. To maintain pharmacological efficacy, extended-release is important. Monitoring the release pace requires careful planning and testing.

Finally, ocular in situ nano-gels are complicated, making regulatory approval difficult. Smaller enterprises may find the clearance process lengthy and exclusive.

Despite these obstacles, ocular in situ nano-gels have enormous potential as drug delivery methods for treating several eye conditions. Further research and expansion can overcome these limits and improve technology to treat patients safely and effectively.

Recent advancements in in situ gelling technology for ophthalmic drug delivery

In situ gelling could revolutionize ocular drug administration. This method solves the issues with eye drops and ointments for ocular medicine administration.

The ocular surface turns in situ gels into a gel. They're temperature-sensitive. This extends drug release and bioavailability.

Recent advances in in situ gel technology have enabled the production of novel preparations with even more benefits, such as improved patient compliance and reduced dose frequency.

One of the most important advancements is the production of mucoadhesive in situ gels, which stick to the eye surface for a long time and allow for sustained drug release and improved therapeutic benefits. Another advancement is using in situ gels that release medication in response to physiological cues like pH or temperature. In general, in situ gel technology offers promising new ways to deliver ocular medicines and improve patient outcomes.

Advantages of in situ gel technology over other ocular drug delivery methods

The In situ gel technique for ocular drug delivery is popular due to its many benefits. The In situ gel technique provides sustained medication release. One of the technology's key advantages. This prolonged release keeps the medicine in the ocular tissue longer, improving therapy.

In situ gel reduces administration frequency, another benefit. Because the active therapeutics are supplied over a longer period of time, frequent drug delivery, which can be difficult for patients and increase treatment non-compliance, is eliminated. Patients choose in situ gel technology since it is painless and noninvasive.

In situ gel technology also makes hydrophilic and hydrophobic drugs easy to distribute. It reduces glaucoma, macular degeneration, and dry eye syndrome due to its flexibility.

In situ gel technology could revolutionize ocular medicine delivery because it is better than current methods.

Clinical studies and results using in situ gel technology for ocular drug delivery

In clinical trials, the in situ gel technique distributed ophthalmic medicines well. A team of researchers created an in situ gel containing timolol maleate, a glaucoma treatment, and compared it to standard ocular drops. The in situ gel sustained therapeutic agent release, maintaining therapeutic concentrations longer than standard eye drops. This improves patient adherence and reduces dosage frequency. In situ gels were studied for dry eye syndrome management. The gel formulation contained cyclosporine, and results showed that the in situ gel had a prolonged drug release profile like eye drops, improving clinical efficacy. These studies show that in situ gel technology can help distribute ocular medicinal ingredients and improve patient adherence. Ocular medicine delivery is expected to improve for people with various ocular conditions as research continues.

Potential future developments in in situ gelling technology

The In situ gel technique for ocular medication distribution seems promising. However, there is room for improvement. Nanotechnology could advance in situ gel compositions. Nanoparticles can improve drug solubility, stability, uptake, and ocular tissue delivery. Stimuli-triggered in situ gels are another focus. The gels respond to stimuli like temperature and pH to distribute medications in a controlled and targeted manner. This method improves medicine delivery and reduces side effects. Researchers are also studying biodegradable materials for in situ hydrogels. The gel's slow absorption by the body may improve patient comfort and eliminate elimination procedures. In general, in situ gelling strategies for delivering therapeutic compounds to the eye are promising and could improve ocular medication delivery.

Comparison of in situ gel technology to other ocular drug delivery methods

Drug administration to the eye has numerous methods. Due to its unique properties and advantages over conventional methods, in situ gel technology may be effective for drug delivery. The in situ gel technology's sustained release of pharmaceuticals keeps the medication in the eye longer, improving its efficacy. The In situ gel technique has this major advantage.

In contrast to eye drops, in situ gel technology releases medicine more slowly. This reduces medicine administration frequency. Its improved bioavailability means more drug is administered to the area that needs them, increasing its therapeutic efficacy.

Eye drops, on the other hand, are swiftly eliminated from the eye, reducing their efficacy.

Ocular implants are another approach to sustaining drug release. However, insertion and removal of the ocular inserts may cause discomfort, which may lead to non-compliance.

In conclusion, in situ gel technology offers sustained drug release, improved bioavailability, and less medication administration, making it a potential option for ocular drug delivery. In situ gelling is faster and less unpleasant than other topical pharmaceutical administration procedures.

Conclusion

In conclusion, in situ gel technology for ocular medication delivery may reduce the shortcomings of current drug delivery systems. In situ gels improve bioavailability, prolong drug release, and reduce dose frequency. Benefits boost patient acceptance and clinical outcomes.

Despite significant advances in this area, problems remain. In situ gelling procedures that maintain optimal medication concentration levels for long periods are a major challenge. Optimizing formulation parameters for in situ gel stability and safety is another challenge.

In situ gel technology for ophthalmic medication administration could develop stimuli-responsive devices that react to changes in the ocular environment. Nanotechnology and other advanced medication delivery methods can improve in situ gel efficacy and safety.

In situ formulation technology could transform ophthalmic medicine distribution and improve the quality of life for many ocular disease patients. As research progresses, in situ gels may become the preferred ocular drug delivery method.

Abbreviations

BRB	Blood-retinal barrier
BAB	Blood-aqueous barrier
Anti-VEGF	Anti-Vascular endothelial growth factor
miRNA	Micro RNA
LCST	Lower critical solution temperature
HPMC	Hydroxypropyl methylcellulose
C_{max}	Maximum plasma concentration
T_{max}	Maximum time to reach C_{max}
AUC	Area under the curve
PAA	Poly (acrylic acid)
PPO	Poly(propylene oxide)
PEO	Poly(ethylene oxide)
TSP	Tamarind seed polysaccharide
NaCMC	Sodium carboxymethyl cellulose
MC	Methylcellulose
DDS	Drug delivery systems
TCS	Thiolated Chitosan
PEG	Polyethylene glycol
pNIPAAm	Poly(*N*-isopropylacrylamide)
CNV	Choroidal neovascularization
SLN	Solid lipid nanoparticle
STTP	Sodium tripolyphosphate

IOP Intraocular pressure
PVA Polyvinyl alcohol

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All the research studies have been duly cited and we have all the open access rights to access these studies.

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No, the authors declare that they have no competing interests.

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References

Abka-Khajouei R, Tounsi L, Shahabi N, Patel AK, Abdelkafi S, Michaud P (2022) Structures, properties and applications of alginates. Mar Drugs 20(6):364
Agrawal M, Saraf S, Saraf S, Dubey SK, Puri A, Gupta U, Kesharwani P, Ravichandiran V, Kumar P, Naidu VGM, Murty US, Ajazuddin AA (2020) Stimuli-responsive In situ gelling system for nose-to-brain drug delivery. J Control Release 327:235–265. https://doi.org/10.1016/j.jconrel.2020.07.044
Agarwal P, Craig JP, Rupenthal ID (2021) Formulation considerations for the management of dry eye disease. Pharmaceutics 13(2):207. https://doi.org/10.3390/pharmaceutics13020207
Ahmed S, Amin MM, Sayed S (2023) Ocular drug delivery: a comprehensive review. AAPS PharmSciTech 24:66
Akhter MH, Ahmad I, Alshahrani MY, Al-Harbi AI, Khalilullah H, Afzal O, Altamimi ASA, Najib Ullah SNM, Ojha A, Karim S (2022) Drug delivery challenges and current progress in nanocarrier-based ocular therapeutic system. Gels 8(2):82. https://doi.org/10.3390/gels8020082
Al-Khateb K, Ozhmukhametova EK, Mussin MN (2016) In situ gelling systems based on Pluronic F127/Pluronic F68 formulations for ocular drug delivery. Int J Pharm 502(1–2):70–79
Almeida H, Amaral MH, Lobao P, Sousa Lobo JM (2013) Applications of poloxamers in ophthalmic pharmaceutical formulations: an overview. Expert Opin Drug Deliv 10(9):1223–1237
Alsaidan OA, Zafar A, Yasir M, Alzarea SI, Alqinyah M, Khalid M (2022) Development of ciprofloxacin-loaded bilosomes in-situ gel for ocular delivery: optimization, in-vitro characterization, ex-vivo permeation, and antimicrobial study. Gels 8(11):687. https://doi.org/10.3390/gels8110687
Bachu RD, Chowdhury P, Al-Saedi ZHF, Karla PK, Boddu SHS (2018) Ocular drug delivery barriers-role of nanocarriers in the treatment of anterior segment ocular diseases. Pharmaceutics 10(1):28
Bellotti E, Fedorchak MV, Velankar S, Little SR (2019) Tuning of thermoresponsive pNIPAAm hydrogels for the topical retention of controlled release ocular therapeutics. J Mater Chem B 7(8):1276–1283
Bhalerao H, Koteshwara KB, Chandran S (2020) Brinzolamide dimethyl sulfoxide in situ gelling ophthalmic solution: formulation optimisation and in vitro and in vivo evaluation. AAPS PharmSciTech 21(2):69. https://doi.org/10.1208/s12249-019-1555-0
Billowria K, Sandhu NK, Singh B (2023) Topical advances in mucoadhesive ocular drug delivery system. Curr Drug Deliv 20(8):1127–1140. https://doi.org/10.2174/1567201819666221010122413
Boote C, Sigal IA, Grytz R, Hua Y, Nguyen TD, Girard MJA (2020) Scleral structure and biomechanics. Prog Retin Eye Res 74:100773. https://doi.org/10.1016/j.preteyeres.2019.100773
Campos PM, Petrilli R, Lopez RFV (2020) The prominence of the dosage form design to treat ocular diseases. Int J Pharm 30(586):119577. https://doi.org/10.1016/j.ijpharm.2020.119577
Chan HN, Zhang XJ, Ling XT, Bui CH, Wang YM, Ip P, Chu WK, Chen LJ, Tham CC, Yam JC, Pang CP (2022) Vitamin D and ocular diseases: a systematic review. Int J Mol Sci 23(8):4226
Chandra NS, Gorantla S, Priya S, Singhvi G (2022) Insight on updates in polysaccharides for ocular drug delivery. Carbohydr Polym 297:120014
Conrady CD, Yeh S (2021) A review of ocular drug delivery platforms and drugs for infectious and noninfectious uveitis: the past, present, and future. Pharmaceutics 13(8):1224
Darge HF, Andrgie AT, Tsai HC, Lai JY (2019) Polysaccharide and polypeptide based injectable thermo-sensitive hydrogels for local biomedical applications. Int J Biol Macromol 133:545–563
Devasani SR, Dev A, Rathod S, Deshmukh G (2016) An overview of in situ gelling systems. Pharm Biol Eval 3(1):60–69
Dubald M, Bourgeois S, Andrieu V, Fessi H (2018) Ophthalmic drug delivery systems for antibiotherapy—a review. Pharmaceutics 10(1):10
Dubashynskaya N, Poshina D, Raik S, Urtti A, Skorik YA (2019) Polysaccharides in ocular drug delivery. Pharmaceutics 12(1):22
Elmowafy E, Cespi M, Bonacucina G, Soliman ME (2019) In situ composite ion-triggered gellan gum gel incorporating amino methacrylate copolymer microparticles: a therapeutic modality for buccal applicability. Pharm Dev Technol 24(10):1258–1271
Fan R, Cheng Y, Wang R, Zhang T, Zhang H, Li J, Song S, Zheng A (2022) Thermosensitive hydrogels and advances in their application in disease therapy. Polymers (basel) 14(12):2379. https://doi.org/10.3390/polym14122379
Fogli S, Del Re M, Rofi E, Posarelli C, Figus M, Danesi R (2018) Clinical pharmacology of intravitreal anti-VEGF drugs. Eye (lond) 32(6):1010–1020
Gawkowska D, Cybulska J, Zdunek A (2018) Structure-related gelling of pectins and linking with other natural compounds: a review. Polymers (basel) 10(7):762
Gote V, Sikder S, Sicotte J, Pal D (2019) Ocular drug delivery: present innovations and future challenges. J Pharmacol Exp Ther 370(3):602–624
Jimenez J, Washington MA, Resnick JL, Nischal KK, Fedorchak MV (2021) A sustained release cysteamine microsphere/thermoresponsive gel eyedrop for corneal cystinosis improve drug stability. Drug Deliv Transl Res 11(5):2224–2238
Joshi SC (2011) Sol-gel behavior of hydroxypropyl methylcellulose (HPMC) in ionic media including drug release. Materials (basel) 4(10):1861–1905
Khan N, Aqil M, Imam SS, Ali A (2015) Development and evaluation of a novel in situ gel of sparfloxacin for sustained ocular drug delivery: in vitro and ex vivo characterization. Pharm Dev Technol 20(6):662–669
Lee YR, Son M, Kim YS, Kim JS, Kim CH, Jung SH (2022) Evaluation of a rapid and simple method for assessing retinal vessel structures in adult zebrafish. Int J Mol Sci 23(23):15069. https://doi.org/10.3390/ijms232315069
Liu H, Liu J, Qi C, Fang Y, Zhang L, Zhuo R, Jiang X (2016) Thermosensitive injectable in-situ forming carboxymethyl chitin hydrogel for three-dimensional cell culture. Acta Biomaterialia 35:228–237. https://doi.org/10.1016/j.actbio.2016.02.028
Luo J, Zhao X, Guo B, Han Y (2023) Preparation, thermal response mechanisms and biomedical applications of thermosensitive hydrogels for drug delivery. Expert Opin Drug Deliv 20(5):641–672. https://doi.org/10.1080/17425247.2023.2217377
Masoumi A, Soleimani M, Azizkhani M, Izadi A, Cheraqpour K, Tabatabaei SA, Khodavaisy S, Aminzadeh M (2023) Clinical features, risk factors, and

management of candida keratitis. Ocul Immunol Inflamm 4:1–6. https://doi.org/10.1080/09273948.2023.2203752
Mofidfar M, Abdi B, Ahadian S, Mostafavi E, Desai TA, Abbasi F, Sun Y, Manche EE, Ta CN, Flowers CW (2021) Drug delivery to the anterior segment of the eye: a review of current and future treatment strategies. Int J Pharm 607:120924. https://doi.org/10.1016/j.ijpharm.2021.120924
Ni X, Guo Q, Zou Y, Xuan Y, Mohammad IS, Ding Q, Hu H (2020) Preparation and characterization of bear bile-loaded pH sensitive in-situ gel eye drops for ocular drug delivery. Iran J Basic Med Sci 23(7):922–929
Nihal FY, Sally AAH, Abdelhalim IE (2018) Corneal targeted Sertaconazole nitrate loaded cubosomes: preparation, statistical optimization, in vitro characterization, ex vivo permeation and in vivo studies. Int J Pharm 553(1–2):386–397
Okur NÜ, Yağcılar AP, Siafaka PI (2020) Promising polymeric drug carriers for local delivery: the case of in situ gels. Curr Drug Deliv 17(8):675–693. https://doi.org/10.2174/1567201817666200608145748
Osswald CR, Guthrie MJ, Avila A, Valio JJ, Mieler WF, Kang-Mieler JJ (2017) In vivo efficacy of an injectable microsphere-hydrogel ocular drug delivery system. Curr Eye Res 42(9):1293–1301
Pandurangan DK, Bodagala P, Palanirajan VK, Govindaraj S (2016) Formulation and evaluation of voriconazole ophthalmic solid lipid nanoparticles in situ gel. Int J Pharm Investig 6(1):56–62
Perminaite K, Marksa M, Stanciauskaitė M, Juknius T, Grigonis A, Ramanauskiene K (2021) Formulation of ocular in situ gels with Lithuanian Royal Jelly and their biopharmaceutical evaluation in vitro. Molecules 26(12):3552. https://doi.org/10.3390/molecules26123552
Piekarska K, Sikora M, Owczarek M, Jóźwik-Pruska J, Wiśniewska-Wrona M (2023) Chitin and chitosan as polymers of the future—obtaining, modification, life cycle assessment and main directions of application. Polymers 15(4):793
Pilipenko I, Korzhikov-Vlakh V, Valtari A, Anufrikov Y, Kalinin S, Ruponen M, Krasavin M, Urtti A, Tennikova T (2021) Mucoadhesive properties of nanogels based on stimuli-sensitive glycosaminoglycan-graft-pNIPAAm copolymers. Int J Biol Macromol 186:864–872. https://doi.org/10.1016/j.ijbiomac.2021.07.070
Popescu I, Constantin M, Bercea M, Coşman BP, Suflet DM, Fundueanu G (2023) Poloxamer/carboxymethyl pullulan aqueous systems-miscibility and thermogelation studies using viscometry, rheology and dynamic light scattering. Polymers (Basel) 15(8):1909. https://doi.org/10.3390/polym15081909
Rahman MS, Hasan MS, Nitai AS, Nam S, Karmakar AK, Ahsan MS, Shiddiky MJA, Ahmed MB (2021) Recent developments of carboxymethyl cellulose. Polymers (basel) 13(8):1345
Rupenthal ID, Daugherty AL (2019) Ocular drugs and drug delivery systems—current trends and future perspectives. Drug Discov Today 24(8):1425–1426
Rykowska I, Nowak I, Nowak R (2021) Soft Contact lenses as drug delivery systems: a review. Molecules 26(18):5577. https://doi.org/10.3390/molecules26185577
Salunke RS, Patil BS (2016) Ion activated in situ gel of gellan gum containing salbutamol sulphate for nasal administration. Int J Biol Macromol 87:41–47
Schaiquevich P, Francis JH, Cancela MB, Carcaboso AM, Chantada GL, Abramson DH (2022) Treatment of retinoblastoma: what is the latest and what is the future. Front Oncol 12:822330
Sharma DS, Wadhwa S, Gulati M, Kadukkattil Ramanunny A, Awasthi A, Singh SK, Khursheed R, Corrie L, Chitranshi N, Gupta VK, Vishwas S (2021) Recent advances in intraocular and novel drug delivery systems for the treatment of diabetic retinopathy. Expert Opin Drug Deliv 18(5):553–576
Shastri DH, Silva AC, Almeida H (2023) Ocular delivery of therapeutic proteins: a review. Pharmaceutics 15(1):205. https://doi.org/10.3390/pharmaceutics15010205
Silva M, Peng T, Zhao X, Li S, Farhan M, Zheng W (2021) Recent trends in drug-delivery systems for the treatment of diabetic retinopathy and associated fibrosis. Adv Drug Deliv Rev 173:439–460
Sridhar MS (2018) Anatomy of cornea and ocular surface. Indian J Ophthalmol 66(2):190–194. https://doi.org/10.4103/ijo.IJO_646_17
Varela-Fernández R, Díaz-Tomé V, Luaces-Rodríguez A, Conde-Penedo A, García-Otero X, Luzardo-Álvarez A, Fernández-Ferreiro A, Otero-Espinar FJ (2020) Drug delivery to the posterior segment of the eye: biopharmaceutic and pharmacokinetic considerations. Pharmaceutics 12(3):269. https://doi.org/10.3390/pharmaceutics12030269
Vigani B, Rossi S, Sandri G, Bonferoni MC, Caramella CM, Ferrari F (2020) Recent advances in the development of in situ gelling drug delivery systems for non-parenteral administration routes. Pharmaceutics 12(9):859. https://doi.org/10.3390/pharmaceutics12090859
Wei Y, Li C, Zhu Q, Zhang X, Guan J, Mao S (2020) Comparison of thermosensitive in situ gels and drug-resin complex for ocular drug delivery: in vitro drug release and in vivo tissue distribution. Int J Pharm 578:119184. https://doi.org/10.1016/j.ijpharm.2020.119184
Wu H, Liu Z, Peng J, Li L, Li N, Li J (2011) Design and evaluation of baicalin-containing in situ pH-triggered gelling system for sustained ophthalmic drug delivery. Int J Pharm 410(1–2):31–40
Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, Lu J, Li J, Du S, Liu Z (2019) Research progress of in-situ gelling ophthalmic drug delivery system. Asian J Pharm Sci 14(1):1–15
Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, Jun Lu, Li J, Shouying Du, Liu Z (2019) Research progress of in-situ gelling ophthalmic drug delivery system. Asian J Pharm Sci 14(1):1–15
Yu S, Zhang X, Tan G (2017) A novel pH-induced thermosensitive hydrogel composed of carboxymethyl chitosan and poloxamer cross-linked by glutaraldehyde for ophthalmic drug delivery. Carbohydr Polym 155:208–217
Zhu L, Ao J, Li P (2015) A novel in situ gel base of deacetylase gellan gum for sustained ophthalmic drug delivery of ketotifen: in vitro and in vivo evaluation. Drug Des Devel Ther 9:3943–3949

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