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Review Article

In situ Gel: A Promising Ocular Drug Delivery System

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Abstract

The eye is a vital organ, faces challenges in drug delivery with traditional ophthalmic formulations due to the rapid loss of medications before reaching the cornea. This review explores novel drug delivery systems for ocular administration, emphasizing innovative dosage forms, i.e., *in situ* gels. This system aims to prolong drug contact time in the eyes, overcoming bioavailability issues associated with conventional delivery methods. The article further delves into *in situ* gelation approaches, highlighting pH-triggered, temperature-dependent, and ion-activated systems. It explores the use of excipients like polymers and solubilizing agents in the preparation of in-situ gels. The frequently used polymers and their applications in ocular drug delivery are detailed. Studies on the incorporation of nanoparticles in this gelling system for ocular drug delivery. Methodologies for evaluating *in situ* gels, including pH determination, rheological studies, drug content analysis, in vitro gelation, accelerated stability studies, and FTIR analysis, are presented. The advantages & applications of *in situ* gels are discussed, along with its limitations. The review concludes by emphasizing the benefits of novel ocular drug delivery systems, particularly *in situ* ophthalmic systems, which offer controlled and sustained drug release, and the future perspective of in *situ gel*. These advancements hold promise for more effective therapeutic outcomes in the field of ocular drug delivery.

Keywords: In situ gel, Polymer, Nanoparticles, Ocular barriers, Ocular drug delivery, Ophthalmic drug delivery

Introduction

The eye serves as the body's most crucial organ. Currently, 90% of available ophthalmic formulations consist of typical dosage forms. The primary challenge faced is the rapid loss of drugs before reaching the cornea due to nasolacrimal drainage (Lynch *et al.,* 2020). To increase the availability of drugs in the eyes, significant efforts are being dedicated to the development of new drug delivery systems for ocular administration. Recent research in this field has created systems that prolong the contact time of the drug in the eye. Innovative dosage forms such as in-situ gel, liposomes, niosomes, etc. are being explored (Shah *et al.,* 2022). The quick turnover of high tear fluids in traditional delivery systems leads to low bioavailability and a restricted therapeutic response, which expedites the removal of the medication from the eyes.

The focus of this review includes the materials and mechanisms of *in situ gel* formation and its use in ophthalmology, along with their methods of preparation and evaluation techniques. The study also includes novel drug delivery methods for ocular preparation (Fig. 1).

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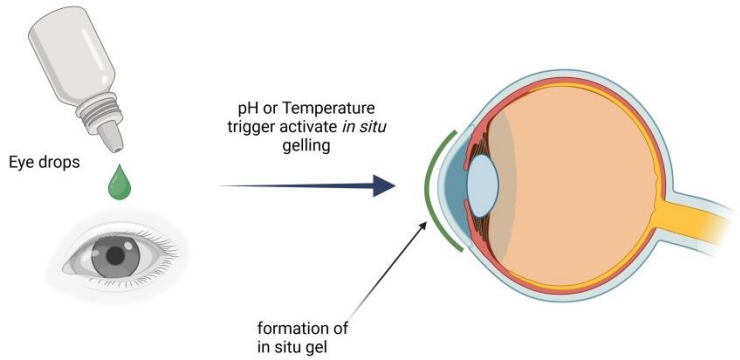

Figure 1. *In situ* gel: A promising ocular drug delivery

The eyes are the most important part of the body (Young, 2008). The ocular system is particularly intriguing due to its unique drug disposition characteristics. In the treatment of eye ailments, topical delivery is favoured over systemic delivery. Any medicine taken through the ocular route must first pass through the precorneal barriers (Srividya *et al.,* 2001). When a drug, in an appropriate dosage form, is instilled, it causes tear production, which lowers drug availability (Fang *et al.,* 2021). These limitations impose restrictions on controlled drug delivery to the eye. The creation of viscous gels can also extend precorneal drug retention. Microparticle/Nanoparticle suspensions or polymeric solutions may serve as bioadhesive systems (Almeida *et al.,* 2014). Furthermore, these systems offer better sustained release properties compared to drops. They are currently used in various eye diseases such as glaucoma, dry eye syndrome, and eye infections (Makwana *et al.,* 2016).

Studies in the field of *in situ* gel

In recent decades, a considerable number of innovative solutions that undergo *in situ* formation triggered by temperature, pH, and ions have been extensively documented in the literature. Each system exhibits its own unique merits and limitations.

Makwana *et al.* (2016) formulated a PH sensitive gel of ciprofloxacin using sodium alginate and HPMC as a viscosity enhancer without any additional excipient. The gel was subsequently evaluated for various parameters, including FT-IR studies, clarity, gelling capacity, rheological studies, measurement of pH, and in vitro dissolution studies. The percentage of ciprofloxacin in the formulation was determined to be 68%, and the gel exhibited stability, effectively prolonging the drug residence time in the eyes.

Kaur *et al.* (2000) formulated acetazolamide using water-soluble polymers. The goal of the study was to increase acetazolamide's bioavailability for ocular administration. The medication was added to an ocular delivery system that formed *in situ*. To improve drug absorption, EDTA, a penetration enhancer, was also used. The formulations underwent in vitro release testing. The formulations showed therapeutic efficacy in normotensive conscious rabbits, resulting in a significant drop in intraocular pressure (IOP).

Mohanty *et al.* (2018) developed a ciprofloxacin ocular preparation using three different methods: pH-triggered, temperature-induced, and ion exchange systems. In the pH-triggered system, Carbopol and HPMC were employed, while Pluronic F-127 and HPMC were used in the temperature-induced system, and Gelrite (Gellan Gum) was utilised in the ion exchange system. Citric acid was added to maintain solution isotonicity, and benzalkonium chloride served as a preservative. All three formulations underwent evaluation for accelerated studies, rheological studies, in vitro release studies, and antimicrobial studies. It reduced the frequency of administration.

Soliman *et al.* (2019) explored the versatile application of poloxamer in *in situ* drug delivery, leveraging its thermoresponsive gelling behaviour, biocompatibility, and sterilisation convenience. Poloxamer molecules, acting as surfactants, form micelles at the critical micelle concentration (CMC),

with PPO (Polypropylene Oxide) groups constituting the hydrophobic core and PEO (Polyethylene Oxide) groups comprising the micelle shell. Elevated temperatures enhance interactions among PPO groups, facilitating micelle formation and ultimately leading to gel formation upon micelle aggregation at a specific temperature.

The bioavailability problem with conventional ocular eye drops can be addressed by employing a gel system. These systems, when administered as eye drops, covert into the gel and provide high bioavailability of the drug (Mohanty *et al.,* 2018).

Upon phase transition, the resulting gel should exhibit sufficient strength, ensuring prolonged residence times in the eye. Its capability to provide prolonged drug release is decreasing the necessity for frequent administration. Depending on the approach used to induce the transition from a solution to a gel state on the eye surface, three distinct types of systems can be identified by Soliman *et al.* (2019).

Applications of *in situ* gel

1) *In situ* gels are utilised in the eyes for a variety of treatments because of their capacity to form a gel upon contact with the ocular surface. Because they offer continuous release of medication, these gels can increase patient compliance, decrease the frequency of doses, and improve drug bioavailability. Furthermore, they provide improved ocular surface retention (Wei *et al.,* 2020).
2) Oral Drug Delivery: The *in situ* gel developed for oral delivery of metformin HCl provided a sustained release of medicament (Wiwattanapatapee *et al.,* 2023). When these gels are exposed to gastrointestinal physiological circumstances, they can change from a solution or liquid state to a gel, which prolongs drug release and enhances therapeutic efficacy. *In situ* gel kept floating for 8 h, while slowly releasing the medicament with a cumulative % release of approximately 80% during 8 h (Wiwattanapatapee *et al.,* 2023).
3) Nasal drug delivery: Nanoparticle embedded *in situ* gel was developed for improved brain function of piribedil through nasal rout (Uppuluri *et al.,* 2021). Studies in rats demonstrated an increase in the relative bioavailability of drugs in the brain by approximately 6.4 times when compared to the plain intranasal suspension of the same drug.
4) Treatments for Periodontal Diseases: *In situ* gels are used in periodontal applications to deliver medications locally to the gums or periodontal pockets (Senarat *et al.,* 2021). When used to treat periodontal diseases, they can stick to the mucosal surfaces and release drugs over time.
5) Wound Healing: By administering medicinal agents straight to the site of injury, *in situ* gels can aid in healing through the use of L-proline nanoparticles and oxygen nanobubbles (Wiwattanapatapee *et al.,* 2023). They are capable of preventing external infections while facilitating wound healing.

Limitations of *in situ* gel

In-situ gel technology, like any other innovation, faces several limitations that must be considered:

1) Formulation viscosity plays a critical role; if it's too high, the gel can cause ocular irritation, whereas excessively low viscosity prevents adequate gelation and adhesion to the ocular surface, impacting sustained release capabilities (Dewan *et al.*, 2023).
2) In-situ gelation depends on specific triggers like temperature or pH; any deviation from these conditions can hinder gel formation and affect performance. The choice of polymers and additives influences the critical gelling temperature and, thus, the efficacy of the gel (Balu *et al.,* 2020).
3) The choice of polymer is crucial; it should be both biocompatible and degrade properly (Chowhan & Giri, 2020). Biocompatibility concerns may arise with some materials used in in-situ gels, potentially leading to irritation or toxicity. Hence, a careful evaluation is essential during the development phase to ensure safety, as different polymers can affect ocular tolerability differently.

4) Certain permeation enhancers used in formulations can potentially lead to ocular toxicity if not carefully controlled. The optimal concentration for permeation enhancer was reported to be 20% when studied with other parameters like entrapment efficiency (Shukr *et al.,* 2021). They may increase corneal hydration levels and affect blinking frequency, underscoring the need for cautious application

Nanoparticles incorporated *in situ* gels

Nanoparticles have been incorporated into in situ gel systems to enhance drug permeation and drug bioavailability at the ocular surface while using the benefits of in situ gelling systems to improve precorneal retention (Chaudhari *et al.,* 2022). The general scheme is illustrated in Fig. 2.

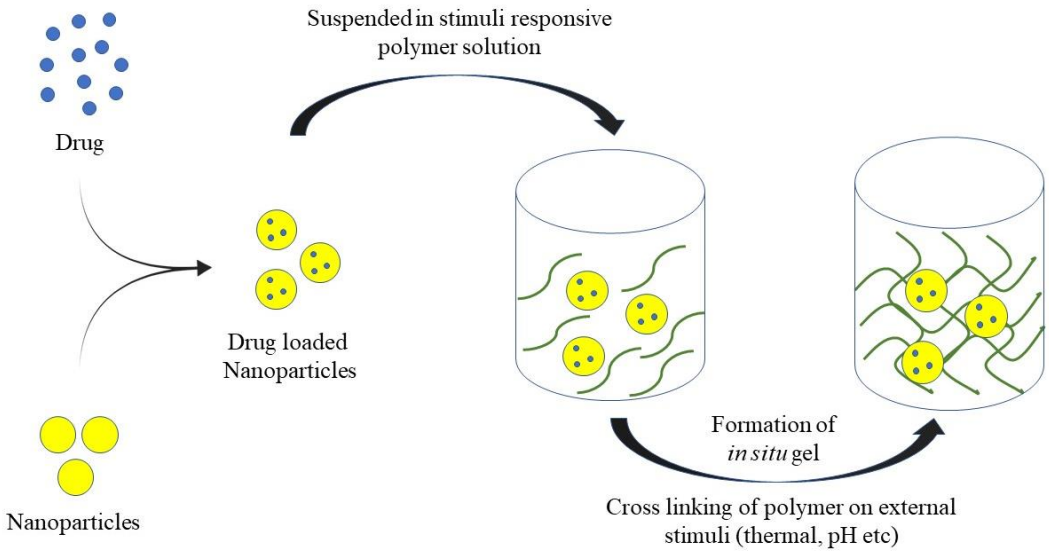

Figure 2: Scheme of formulation of drug-loaded nanoparticle embedded *in situ* gel

Ciprofloxacin-containing nanostructured lipid carriers were prepared and loaded into an *in situ* gel system for enhanced and sustained antibacterial activity in bacterial endophthalmitis treatment (Youssef *et al.,* 2020). Nanoparticles were prepared by the hot homogenization method and optimised for physicochemical characteristics and stability. The optimised ciprofloxacin loaded nanoparticles were incorporated into gellan gum as the gelling agent to make the final formulation.

The PLGA nanoparticles containing pioglitazone were prepared in an *in situ* gel using Poloxamer 407 and HPMC K4M for the treatment of dry eye disease (Laddha & Kshirsagar, 2021). The composition and process parameters of the nanoparticles and *in situ* gel were optimised using a 3^2-factorial design. The particles were observed to be spherical in SEM studies, indicating their non-scratching characteristic. XRD and DSC studies confirmed the molecular dispersion of the drug in the polymer. In vitro drug release studies demonstrated a more sustained release of the drug. The formulation was found to be non-irritant in histology studies on goat eye corneas.

Loteprednol Etabonate (LE) lyotropic liquid crystalline nanoparticles (LCNP) were formulated into an in situ ocular gel to solve the drawbacks of conventional drug delivery systems, such as low penetration, retention, and bioavailability through the corneal surface (Priya *et al.*, 2023). The LE-loaded LCNP formulation was incorporated into in situ gelling systems to develop and characterise a temperature-sensitive and ion-activated in situ ocular gel using Poloxamer 407 (P407) and Gellan gum (GG). Rheological studies demonstrated that the viscosity of the LE-LCNP P407 and LE-LCNP GG in situ ocular gel formulations was 4.7 and 3.9 times higher than that of the marketed LE suspension, respectively, at 25°C. The higher viscous characteristics of the LE-loaded LCNP in situ ocular gel resulted in improved ocular retention, efficacy, and patient compliance. The ex-vivo corneal

permeation study showed that the LE-LCNP P407 and LE-LCNP GG in situ ocular gels had 7- and 2.5-times higher ocular permeation compared to the marketed LE suspension, respectively.

An *in situ* gelling system based on PLGA nanoparticles (NPs) has been developed and optimised for the administration of riluzole (RLZ) as a neuroprotective drug for the treatment of glaucoma (Esteruelas *et al.,* 2022). These RLZ NPs have been found to possess suitable physicochemical characteristics, enabling them to penetrate various ocular tissues, specifically across the blood-retinal barrier (BRB), to progressively release RLZ. In vitro and in vivo studies indicated that RLZ NPs are non-irritant and locate in the posterior ocular segment within 24 hours. Additionally, an *in situ* ionic gelling formulation composed of Gellan gum (GG), hydroxypropyl methylcellulose (HPMC), and hyaluronic acid (HA) was optimised to enhance eye hydration, particularly for glaucomatous dry eye patients, and improve the comfort of eye drops. The RLZ NPs gel was able to increase the ocular retention of RLZ NPs. Furthermore, it exhibited suitable rheological and viscosity characteristics, preventing blurry vision while maintaining high mucoadhesive strength. Thus, RLZ-loaded NPs have been developed and dispersed in an *in situ* ionic gelling system capable of reaching posterior ocular tissues.

An antimicrobial in situ-forming gel containing silver nanoparticles was developed for oromucosal delivery, utilising smart polymers like thermosensitive Pluronic® F-127, methylcellulose, and pH-sensitive Noveon® AA-1 (Rohaþová *et al.,* 2024). The formulations underwent various evaluations critical for oromucosal gels, and the most optimum composition was identified. This gel forms rapidly at physiological pH and temperature, with viscosity, adhesiveness, and rigidity increasing with temperature. The gel released almost all the nanoparticles within 40 minutes through erosion and dissolution. Stability is attributed to the initial electrostatic and steric stabilisation of the organic material and the gel structure at physiological temperature. The selected formulation demonstrated antibacterial activity against E. coli and S. aureus.

Materials used for preparing *in situ* gel

A particular ingredient must be used in the creation of *in situ* gels to obtain the appropriate gelation characteristics.

Polymers

In the context of medication delivery, a polymer is a big molecule made up of structural units that repeat and are usually joined by covalent connections. Because polymers can regulate drug release, increase bioavailability, and boost therapeutic efficacy, they are essential components of drug delivery systems (Konatham *et al.,* 2021). Polymers are frequently utilised to create sustained-release systems for *in situ* ocular drug administration, which allow medications to be administered to the eye over an extended period of time. This system can reduce side effects, increase patient compliance, and extend the duration that medications remain on the surface of the eyes (B. *et al.,* 2010).

Polymers are categorised according to their place of origin into two categories:

1) Natural polymers like xanthan gum, xyloglucan, alginic acid, carrageenan, chitosan, gum arabic, gellan gum, pectin, sodium hyaluronate, etc.

2) Semi-synthetic polymers (like polyacrylic acid, hydroxypropyl methylcellulose, methylcellulose, cellulose acetate phthalate, and poly (lactic-co-glycolic acid) poloxamers) (B. *et al.,* 2010).

Examples of frequently used polymers for *in situ* ocular preparation are as follows:

1) Carbopol 934P:

Carbopol (Fig. 3) is a cross-linked polyacrylic acid derivative with a high molecular weight and high mucoadhesive properties, also known as acrylic acid polymer or carbomer. This polymer,is sensitive to pH. When the pH is increased above its pKa value of around 5.5, it exhibits *the sol to gel* transition in an aqueous solution. The acidic nature of Carbopol may irritate the eyes as its concentration rises.

Cellulose addition will lower the concentration of polymers and enhance the gelling property (Srividya *et al.,* 2001).

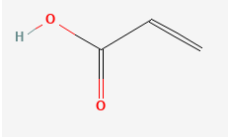

Figure 3. Acrylic acid *(PubChem Compound Summary for CID 6581, Retrieved March 18, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Acrylic-acid)*

2) Cellulose Acetate Phthalate:

Cellulose Acetate Phthalate (Fig. 4) shows a buffer capacity enough to gel successfully in the eye's cul-de-sac with cellulose acetate phthalate & derivatives. The very fluid latex transforms into viscous gel nearly instantly upon the formulation's instillation into the eyes, resulting in a pH shift of around 2.8 units. Because latex is a free-running solution at pH 4.4, it becomes gel when the pH is elevated to pH 7.3 by tear fluid. Cellulose acetate phthalate latex is a polymer with potentially beneficial features for prolonged medication administration to the eye (Makwana *et al.,* 2016).

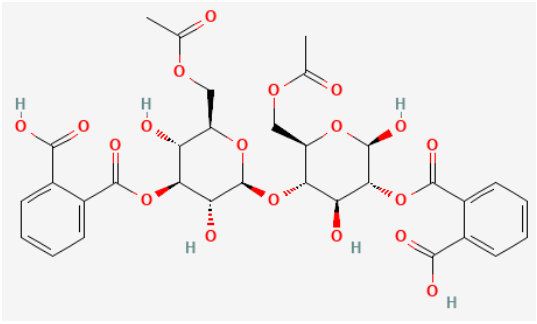

Figure 4.Cellulose acetate phthalate.*(PubChem Compound Summary for CID 53315792, Retrieved March 18, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Cellulose-acetate-phthalate)*

3) Chitosan:

Chitosan is an amino polysaccharide (Fig. 5). It is a cationic, pH-dependent, biodegradable, biocompatible, and temperature-sensitive polymer. Because of its electrostatic interaction with charged mucosal surfaces, it possesses exceptional mucoadhesive characteristics and antibacterial properties (Gupta *et al.,* 2010). Chitosans can interact with ions of opposite charges in a typical pH range of 4–6, leading to gelation (Sacco *et al.,* 2018).

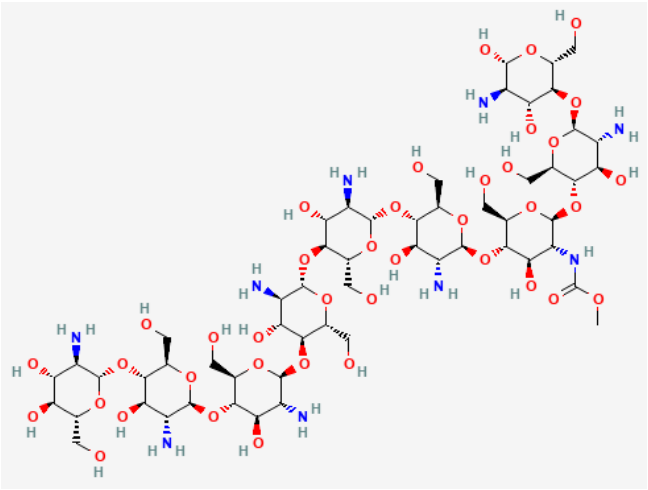

Figure 5. Chitosan (*PubChem Compound Summary for CID 71853,.Retrieved March 18, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/Chitosan.)*

5) Poloxamers:

Pluronics®, a commercial name for poloxamers (Fig. 6), is used in thermosensitive *in situ* gels that are known for their exceptional thermal setting properties, which extend the duration that medications remain effective. The two segments of these water-soluble tri-block copolymers are polyethylene oxide (PEO) and polypropylene oxide (PPO). The most widely used poloxamer in the pharmaceutical industry, Pluronic F127, is chosen because it can create clear, colorless gels. Pluronic F127, which is composed of 70% PEO and 30% PPO, functions as a useful polymer in *in situ* gel compositions. Pluronic F127-g-poly (acrylic acid), a copolymer, has been used as an *in situ* gelling agent to increase bioavailability and lengthen the duration of drug residence in ocular applications (Soliman *et al.,* 2019; Boddu *et al.,* 2015).

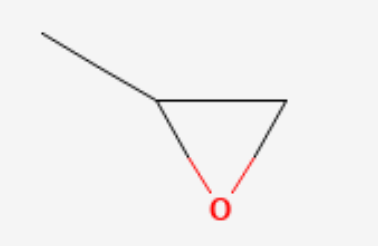

Figure 6. Poloxamer*(PubChem Compound Summary for CID 24751 (from https://pubchem.ncbi.nlm.nih.gov/compound/Poloxamer. Retrieved March 18, 2024)*

6) Gellan gum:

Gellan gum (Fig. 7) is a polysaccharide obtained by the fermentation of *Pseudomonas elodea* (Lin *et al.,* 2023). It is commercially known as Gelrite™. It is a water-soluble, hetero-anionic polysaccharide that exhibits temperature-dependent characteristics. It is thermally stable. Like alginate, gellan gum can gel when it comes into contact with divalent or monovalent metal cations (like Ca^{2+} or Mg^{2+}) or monovalent cations (like Na^{+} or K^{+}). Double-helical junction zones are formed during the gelation process, and these segments then aggregate to form three-dimensional networks by complexing with cations and forming hydrogen bonds with water. It is noteworthy as one of the polymers that is used most frequently in the manufacture of *in situ* gels (B. *et al.,* 2010). The gellan gum *in situ* gel exhibited significantly better stability compared to commercially available brinzolamide eye drops (Azopt®) (Yu *et al.,* 2015).

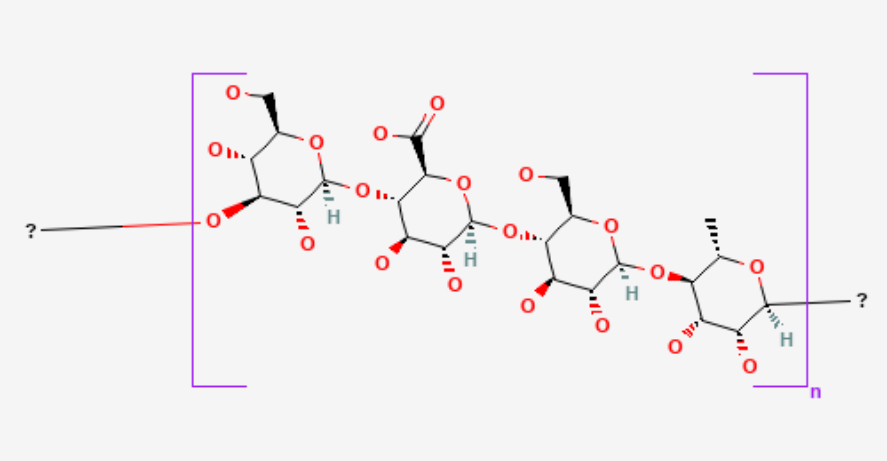

Figure 7. GELLAN GUM *[PubChem Substance Record for SID 472396449, (LOW ACYL), [Source: FDA Global Substance Registration System (GSRS) from https://pubchem.ncbi.nlm.nih.gov/substance/472396449 Retrieved March 18, 2024.]*

Solubilizing agent

A solubilizing agent is a material that improves a drug's solubility in a certain formulation. Solubilizing compounds are essential for increasing the solubility and bioavailability of pharmaceuticals in the

setting of *in situ* ocular drug administration (Moghimipour *et al.*, 2017). This helps to ensure that the drugs can be transported to the targeted ocular tissues efficiently. These substances can be especially helpful when handling medications that are hydrophobic or have low water solubility.

One popular class of solubilizing chemicals utilised in ocular formulations is surfactants. They can interact with lipids and water because they have both hydrophilic and hydrophobic areas. This helps solubilize medications that are hydrophobic. Surfactants have the ability to encapsulate drugs in micelles or other structures, thereby increasing their solubility. For instance, a hydrophobic medication is used to treat a particular eye ailment. The drug's solubility in the eye drops can be improved by incorporating a surfactant, like cremophor or polysorbate 80, into the formulation (Al-Mahallawi *et al.,* 2021). This guarantees that the medication is evenly distributed within the tear film at the time of instillation, resulting in enhanced absorption and therapeutic effectiveness.

Various approaches for making *in situ* gelation

pH-Triggered Systems:

Using pH-sensitive polymers with basic or acidic groups, the in-situ gelling technique forms gels at a pH of 7.4.

Mechanism: Polyelectrolytes, or polymers that react to pH variations, are used in ocular formulations. Depending on changes in the pH of the surrounding medium, namely between the pH during production and the pH of lacrimal fluid, these polymers go through a sol-gel transition. Alterations in the ionisation state of weakly basic (ammonium) or weakly acidic (carboxylic or phosphoric) groups within the polyelectrolyte affect this transition. These groups' pKa values, which range from 3 to 10, and the molecular weights of the polymers dictate the pH at which they ionize. A change in ionisation causes modifications to the system's swelling, solubility, and conformation. Certain pH-responsive polymers' gelling methods and properties are influenced by temperature, ionic strength, and salt content, among other things (Al-Kinani *et al.,* 2018).

Temperature-Dependent Systems:

One popular kind of stimuli-responsive gel that may be easily inserted into the eye without causing discomfort or blurriness is temperature-sensitive in-situ gel. At 35 °C, the precorneal temperature, it turns into gel.

Mechanism: At temperatures below the lower critical solution temperature (LCST), thermo-responsive systems that experience a phase shift begin as transparent, homogeneous, and freely flowing polymeric solutions. The solution becomes hazy as the temperature approaches the LCST because of the polymeric chains breaking, aggregating, and increasing light scattering. Phase separation takes place beyond the LCST, separating the solution into a gel phase and a solvent phase—typically water. The primary force behind this separation is the entropy effect, which favours phase separation as temperature rises. Achieving the intended LCST requires adjusting a number of variables, such as adjustment of salt or by varying PH (Al-Kinani *et al.,* 2018).

Ion-Activated Systems:

Ion-activated systems undergo conversion due to changes in ionic concentration. They crosslink with the cation present in the tear film and form gel.

Mechanism: A sol-gel transition and an increase in polymer viscosity can be caused by crosslinking anionic polysaccharides with (Na+) and/or (Mg2+ and Ca2+) cations available in lacrimal fluid. There is a clear correlation between the concentration of cations and the increase in polymer viscosity . As a result, increasing tear production in an effort to dilute the viscous solutions would raise the concentration of cations. Consequently, this would lead to an increase in polymer viscosity, which would prolong the duration of drug retention in the eyes, decrease nasolacrimal drainage, and improve drug bioavailability (Al-Kinani *et al.,* 2018).

Method of Preparation of *in situ* gel

The required quantity of polymers and co-polymers is dispersed in water to generate the polymeric solution. The final solution contained preservatives like benzalkonium chloride, buffering agents such as NaOH and citric acid to adjust the solution to the required PH, and osmolality agents such as NaCl to maintain the osmotic pressure according to the eye. The final volume of the resultant *in situ* gel eye drop is maintained using the distilled water (Sravya *et al.,* 2022) (Geetha *et al.,* 2023). These formulations with stimuli-responsive polymers are sensitive to pH, temperature, and ion concentration form gel instantaneously upon ocular instillation. Combining multiple stimuli-responsive polymers in one formulation may improve gelation results.

Evaluation of *in situ* gel

Visual Appearance and Clarity: To detect the presence of any particle matter, visual appearance and clarity were assessed using fluorescent light against a white and black background. In order to assess clarity, the formulation must be visually assessed against a backdrop of black and white in appropriate lighting. Generally applied to liquid forms (suspensions excepted), it is thoroughly documented in Pharmacopoeia. *In situ* gels and eye drops are covered by this examination prior to and following gelling (Gupta *et al.,* 2010).

pH: Following the addition of each ingredient, the created in-situ gelling system's pH has been determined using a pH measuring device. The freezing-point depression method is a useful tool for measuring osmolality. Potentiometric analysis is the most common technique used to calculate pH. When applied topically, the acceptable ranges for pH and osmolality are 3–8 and 250–450 mOsm/kg, respectively (Mandal *et al.,* 2012).

Rheological Studies: Determining the length of time a drug remains in the eye is crucial taking into account the injected formulation's viscosity (Mandal *et al.,* 2012). The ready-made mixtures were left to gel at physiological PH, and a Brookfield viscometer was used to determine the viscosity after that. The flow pattern examined by plotting the shear rate vs. shear stress graph. A drug's bioavailability and comfort level following injection can both be impacted by the rheological parameter. Tears quickly lose their fluids or solutes, resulting in a brief period of contact with the eye, high drainage rates, and improved drug bioavailability. Increases in viscosity are possible, but they may be uncomfortable because vision problems, a feeling of a foreign body, and harm to the ocular epithelia as a result of an increase in reflex tears and blinks caused by shear stress during blinking lead to quicker elimination (Ceulemans & Ludwig, 2002).

Drug Content Analysis: A spectrophotometric approach used to analyse the drug content of manufactured in-situ gelling solutions. Pipetting 0.1 ml of each optimised formulation and diluting it with up to 100 ml of Simulated Tear Fluid (pH 7.4). The absorption was measured with a UV-Visible spectrophotometer at 275 nm (Ganguly & Dash, 2004).

In vitro gelation: The formulations combining sodium alginate and HPMC had a gelling capability of Assessed. To execute the procedure, a drop of polymeric solution was added to vials holding one millilitre of Simulated Tear Fluid to equilibrate at 340 degrees Celsius. The gel formation then visually evaluated (Gupta *et al.,* 2010).

Studies on Accelerated Stability: The stability testing done on the optimised sterile formulation. Glass vials containing sterile, optimized ocular formulations were filled, sealed, and fastened with grey butyl rubber closures. An aluminium bottle. A few sterile formulations were kept at room temperature, 4±1 °C. 27.11 °C, drug content evaluated at periodic intervals, clarity, PH, rheology, in vitro drug release, and sterility (Geetha *et al.,* 2023).

FTIR Study: The technique known as Fourier Transform Infrared Spectroscopy, or FTIR, is used to examine the chemical makeup of various materials (Gupta *et al.,* 2010). FTIR is useful for analysing the molecular structure and content of ocular gels in situ during assessment. Sample preparation, equipment setup, sample placement, infrared exposure data collection, and spectrum analysis are all

steps in the process. The findings help evaluate the formulation and comprehend the properties of the in situ ocular gel by providing insights into its chemical composition, interactions, and features (Chavda, 2016).

Sterility Testing: This procedure carried out to identify the existence of living microorganisms in the sample. The samples underwent sterilisation using UV radiation. A Soyabean Casein Digest Medium sterilised through autoclaving at 121 °C for 15 minutes under 15 lbs of pressure. Subsequently, the sterilised preparations were introduced into bottles containing the nutrient medium and allowed to incubate for 7 days to monitor microbial growth (Sheshala *et al.,* 2019).

Future perspectives for *in situ* gel

In-situ gel technology is an innovative drug delivery system that employs *sol to gel* transitions upon administration, enabling controlled and sustained drug release (Dewan *et al.,* 2023). These gels are made from crosslinked polymer networks and have numerous applications in drug delivery and disease treatment. However, further research is needed to address issues such as drug degradation. The technology can be customised to meet individual patient needs, enhancing patient compliance. Additionally, it can carry multiple drugs simultaneously, potentially transforming the treatment of complex diseases. Future uses of *in situ* gels include the delivery of proteins, peptides, and drug molecules, protecting them from degradation by providing targeted and localised release (Chowhan & Giri, 2020).

The *in situ* gelling system for ocular drug delivery is a well-studied strategy that can prolong precorneal residence time and provide sustained drug release, improving ocular bioavailability and therapeutic efficacy while reducing systemic absorption and toxicity. Exploring the integration of different drug delivery approaches, such as nanoparticles loaded into *in situ* gels, is an attractive strategy for enhancing ocular drug delivery.

Given the eye's sensitivity, safety is a crucial parameter for ocular formulations. Most studies reviewed indicate that *in situ* gels do not cause significant cytotoxicity or irritation. However, further research is needed to assess the potential toxicity of repeated and long-term use, as well as the materials used in nanoparticle-based systems. Increased viscosity in in-situ gels can cause issues like blurred vision and discomfort, leading to faster elimination due to reflex tears and blinking. Therefore, careful control of viscosity is essential during formulation design and optimisation to mitigate these limitations (Dewan *et al.,* 2023).

Future strategies should focus on developing formulas with multiple ingredients, such as traditional Chinese medicine, which uses a multi-target approach. Additionally, there is an expectation for new and more reliable in-situ forming polymers responsive to biochemical markers associated with eye diseases. Improved ocular permeation over longer durations would provide sufficient contact time for managing ocular diseases. The simple and economical preparation methods will facilitate industrial scale-up. These formulations can be further processed for large-scale batches and pharmacological evaluation through in-vivo studies.

The future of *in situ* gels is promising, with potential for innovative drug delivery solutions and applications across various industries, including cancer and ulcer treatment. *In situ* gels can also be utilised as templates for tissue engineering and cell transplantation by releasing growth factors and other bioactive molecules in a controlled manner to promote tissue regeneration. Combining *in situ* gels with 3D printing technology could lead to patient-specific drug delivery systems (Ding *et al.,* 2023). Different types of stimuli-responsive gels, such as temperature, pH, and ionic, can be developed for remote drug release control. Incorporating in-situ gels into implantable devices like wound dressings can provide sustained drug release at target sites. The in-situ gel system is a dynamic field with ongoing research, and further technological advancements may lead to new applications beyond those currently envisioned.

Conclusion

Novel drug delivery has the benefit of enhancing drug bioavailability and surrounding ocular barriers to ensure more effective therapeutic outcomes. The controlled and sustained release offered by these systems stands out, allowing for prolonged therapeutic effects and minimising the need for frequent administrations. Improved patient compliance is another noteworthy advantage, as the convenience of less frequent dosing and reduced side effects contribute to better treatment adherence. The present review article discusses *in situ* gel formulations that hold significant promise for ocular drug delivery due to their ability to overcome various challenges associated with conventional eye drops. The materials used specially the polymers used for making in situ gel were discussed. The method of preparation outlined in this article provides a systematic approach to developing *in situ* gels, ensuring uniformity and reproducibility in formulations. Evaluation of various parameters such as visual appearance, pH, rheology, drug content, gelation, stability, FTIR analysis, and sterility testing confirms the quality and reliability of the formulations. Further research and development in this area is warranted to explore new formulations and optimise existing ones for enhanced therapeutic outcomes in ocular treatments. Within the realm of novel ocular drug delivery systems, *in situ* ocular systems present unique advantages. Their transformation capabilities enable the transformation of solutions into gels upon exposure to physiological conditions, ensuring prolonged drug retention. The ease of administration, coupled with the ability to form a gel *in situ*, makes these systems user-friendly and convenient for patients.

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Conflict of Interest:

All authors are declared no conflict of interest.

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