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IN-SITU OPHTHALMIC GELS: A SMART APPROACH TO OCULAR DRUG DELIVERY — A REVIEW

Snigdha S Babu[a*], Sanil Kumar R[b], Shaiju S Dharan[c], K.L.Krishna Kumar[d], Ashwini Badakundri[e] Shaikh Yasmin[f]

[a]Research Scholar, Department of Pharmacy, Annamalai University, Tamilnadu
[b]Assistant Professor, Department of Pharmacy, Annamalai University, Tamilnadu
[c]Principal, Ezhuthachan College of Pharmaceutical Sciences, Kerala
[d]Professor , Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore
[e]Assistant Professor, Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore
[f]Assistant Professor, Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore

**snigdhasatheesababu@gmail.com*

Abstract

The eye is the body's most delicate organ. Because of the eye's complex anatomy, small absorptive surface, low transparency of the cornea, lipophilicity of the corneal epithelium, pre-corneal loss (from nasolacrimal drainage), bonding of the drug with proteins in tear fluid, blinking, low conjunctival sac capacity, and ultimately poor ocular therapy, designing an ocular drug delivery system is the most difficult task for pharmaceutical scientists. This overview discusses the polymers utilised, research advancements in the field, and the in situ gelling mechanism, which turns liquid formulations into gels under specific physiological or environmental conditions. In situ ocular gels for drug delivery go through this change when they come into touch with the ocular surface. Various processes, contingent on the gel's composition and intended characteristics, are responsible for this transformation. In situ gelling enhances drug retention, bioavailability, and contact time by causing the liquid formulation to solidify into a gel upon contact with ocular tissues. Common methods of in situ ocular gel formation include temperature-, pH-, and ion-induced gelation. These gels offer a versatile and efficient platform while resolving a number of issues with the present ocular therapeutic administration methods.

Keywords: *in situ gel, ocular drug administration, nano particle laden insitu gelling approach*

1.Introduction

The ocular route of drug delivery presents unique challenges due to the eye's complex anatomy and protective mechanisms. Traditional ophthalmic formulations, like eye drops and ointments, frequently have quick precorneal clearance, low therapeutic effectiveness, and poor bioavailability. Because the corneal barrier is normally penetrated by less than 5% of the supplied amount, frequent dosing is required, which results in poor patient compliance. Advanced drug delivery methods, such as in situ ophthalmic gels, are being extensively investigated to get around these restrictions. The creation of in situ gelling drug delivery devices has drawn more interest from the scientific community throughout the past 10 years. Most of these systems have the unusual ability to gel into the body after being in a sol-state prior to injection. They are therefore distinguished by their simplicity of use, extended duration of residence, and prolonged release of the medication at the administration site, along with a decrease in the frequency of administration and an increase in patient comfort and compliance. The fact that these formulations can be taken by a variety of methods to produce a local or systemic effect of the medication loaded is one of the factors contributing to their enormous popularity.[1,2]

2.Insitu gelling system

The in situ gel system is a liquid preparation that may be injected into the eyes and turns into gel when exposed to the physiological environment. This lengthens the delivery system's precorneal residence period and improves the drug's ocular bioavailability. 2. Gel formation is dependent on variables such as changes in a particular physico-chemical parameter (temperature, pH, ion sensitivity), which allows the drug to be released gradually and under control.

In situ gel, nanosuspension, nanoparticulate system, liposomes, niosomes, dendrimers, ocular iontophoresis, collagen shield, minidisc, ocular film, implants, ocuserts, and more are examples of innovative dosage forms.

Environmentally sensitive polymers used in ophthalmic in-situ gelling will undergo structural changes in response to minor variations in environmental parameters such as pH, temperature, and ionic strength.When instilled into the eye, in-situ forming gels undergo fast gelation in the cul-de-saco of the eye to create viscoelastic gels in response to environmental changes the medications are then released gradually under physiological conditions [3].As a result, the gel's in-situ residence duration will be prolonged and the medication will be administered in a continuous way, improving bioavailability, reducing systemic absorption, and requiring fewer frequent doses, all of which increase patient compliance [4].

The in situ gel system is a liquid preparation that may be injected into the eyes and turns into gel when exposed to the physiological environment. This lengthens the delivery system's precorneal residence period and improves the drug's ocular bioavailability.[5] Gel formation is dependent on variables such as changes in a particular physico-chemical parameter (temperature, pH, ion sensitivity), which allows the drug to be released gradually and under control.

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Drug delivery systems that are in solution form before to being supplied to the body but go through gelation in situ thereafter to create a gel triggered by an external stimulus like pH, temperature, etc., and release the drug in a controlled or prolonged manner are known as in situ gel forming systems. Early in the 1980s, the unique idea of creating in situ gel was initially proposed.[7]

3.Polymers used in the formulation of in situ gels

A polymer is a macromolecule made up of structural units that repeat and are joined by covalent connections.[8]

3.1 Ideal characteristics of polymers

The following qualities should be present in the polymers used in in-situ gelling systems:

It ought to be biocompatible.

It need should be able to stick to mucus.

In order to provide reduced viscosity during blinking and stability of the tear film during fixation, the polymer should be able to decrease viscosity as the shear rate increases.

It ought to behave in a pseudoplastic manner.

It ought to be bearable.

It ought to be optically active.

It ought to affect the conduct of the tears.

Examples Polymers used in in-situ gels are Carbopol Poloxamer Sodium Alginate Gellan Gum Chitosan and Hydroxy Propyl Methyl Cellulose (HPMC) [9]

4. Mechanisms of in situ gelling technology

In situ gel technology is a method of administering medication in which a sol phase transforms into a gel phase upon contact with the body. When administered as a liquid, the gel transforms into a gel inside the eye, allowing the medication to be released gradually [10]. The technology's improved bioavailability and residence time at the target site are most advantageous for ophthalmic medicines. To keep the medication concentration constant, the gel holds onto active therapies and releases them gradually .[11]. The gel is composed of lipids, polymers, and surfactants. These chemicals are chosen because they are biocompatible, biodegradable, and medication-gelling.

Compared to traditional drug delivery systems, in situ gel technology provides fewer side effects, higher patient compliance, and lower dosages [12]. Research on the delivery of ophthalmic medications has the potential to transform the treatment of eye disorders.
Transition from sol-gel Often utilised as beginning ingredients, organic materials such as metal alkoides or inorganic metal salts are referred to as "sol."
The "sol–gel" method creates a colloidal solution or suspension by hydrolysing, polymerising, or condensing the precursor. The sol-to-gel phase transition is brought on by solvent loss and complete polymerisation [12].
In situ gelling systems can be formed via ionic activation, temperature, and pH. In temp-stimulated in situ gelling, liquid polymers that gel at the low critical solution temperature (LCST) are used [13].
The pH-convinced in situ gel is created by polymeric agents containing basic or acidic functional moieties inside the chain molecule; as the pH increases, the gel changes into a sol–gel state. Monovalent or divalent cations in lacrimal solution, such as Na+, Ca+2, and Mg+2, cause ion-elicited systems, which are overly studied as osmotically driven in situ gelling systems, to change the polymer from sol to gel. Sol–gel conversion can be started by enzymatic cross-linking and photon polymerisation.
This study focusses on ion exchange-driven in situ gels, temperature sensitivity, and pH changes. These mechanisms are how gels function in situ [14].

4.1The pH-triggered gelling method
In situ gel also forms as a result of pH variations. When the pH changes, this mechanism gels. When the tear fluid elevates the pH to 7.4, the formulation, which is a free-flowing solution at pH, coagulates. The extremely fluid latex rapidly solidifies into a thick gel after pH 4.4 is added to the tear film. Depending on the pH of the surrounding environment, the acidic or basic groups in all pH-sensitive polymers receive or release protons. There are numerous ionisable groups in polyelectrolytes. If the polymer contains weakly acidic (anionic) groups, hydrogel swelling rises with external pH; if it contains weakly basic (cationic) groups, hydrogel swelling falls.

4.2 In situ gelling triggered by temperature
Using biopolymers, whose conversion from sol to gel is triggered by temperature increases, is an intriguing technique for in situ gel creation. The temperature-sensitive smart polymers constrict and turn into a gel above the lower critical solution temperature[15]. The temperature at which all of a combination's ingredients can be combined in any amount is known as the LCST. The optimal critical temperature for this method is physiological and ambient, thus body heat alone is sufficient for state transition. Using poloxamer's in situ gel-forming properties, this approach seeks to use it as a carrier for ocular medication targeting [16].

4.3 In situ gelling triggered by ionic interaction
Through cross linking with divalent (Mg2+ and Ca2+) and/or monovalent (Na +) cations present in the tear fluid, anionic polysaccharides can trigger the sol–gel transition and enhance the viscosity of the polymer. The increase in polymer viscosity is directly correlated with an increase in cation concentration. Consequently, boosting tear production to thin viscous solutions would raise cation concentration and, consequently, polymer viscosity, prolonging the duration of medication retention in the eyes, reducing lacrimal drainage, and improving drug bioavailability.

5. Nanoparticle-laden in situ gelling system
The idea of nanoparticles has become more and more popular in recent decades. To deliver drugs to their target locations at therapeutically suitable rates and dosing regimens, a variety of polymeric nanoparticles are employed . Ten to a few nanometres is the size range of nanoparticles [17]. A polymeric matrix encapsulates the medicine once it has been dissolved. Drug delivery that targets the eyes has shown a lot of promise with nanoparticles. Polymeric nanoparticles can be produced using a variety of useful techniques. The polymer is dissolved using the organic solvent. The drug material is broken up or distributed in a polymer solution before being emulsified in an aqueous solution to produce a water-in-oil (W/O) emulsion. After that, the organic solvent is expelled by continuously raising the temperature while applying pressure.
Human health may be at risk if an organic solvent is used during the solvent evaporation procedure.
The overall number of organic solvents allowed in injectable colloidal systems is limited by the US Food and Drug Administration. However, supercritical fluids and the salting out process are commonly used to create polymeric nanoparticles. There are two methods for encapsulating drugs in nanoparticles: either integrating the drug during the nanoparticle's formation or adding the nanoparticles to a drug solution. The integration process is more successful because it caught a significant amount of drug[17].

5.1.Advantages of nanoparticle-laden in situ gelling approach
For eye conditions, ocular in situ nanogels are superior to alternative drug delivery techniques. They increase the bioavailability of medications. The tiny size of the gel's nanoparticles facilitates drug penetration into ocular tissues, raising drug concentrations at the intended location.
Drug release is also controlled via ocular in situ nanogels.
Unlike ocular drops, which may eliminate medicines fast, ocular in situ nano-gels release pharmaceuticals gradually, extending the therapeutic concentration at a selected area.

Chronic eye conditions necessitate a continuous supply of medications.
Both patients and physicians can easily employ ophthalmic in situ nanogels because they are noninvasive. They avoid toxicity and unpleasant reactions because they are biocompatible and biodegradable.
One intriguing method of treating eye conditions with medication is the use of ocular in situ nanogels. As research advances, nanotechnology for the delivery of ophthalmic medications may get better.

5.2 Research progress of nanoparticle-laden in situ gelling approach

A brimonidine tartrate niosomal in situ gel ocular administration device was created by Hasansathali et al. The study's goal was to create brimonidine tartrate niosomal in situ gels for the treatment of glaucoma. Different ratios of span series and cholesterol were used to produce niosomes. The longest duration of drug release and the maximum entrapment efficiency were seen in Span 60 (S/C 2:1) niosomes. To keep the drug localised for a long time, HPMC K 15 M and carbopol 940 were used to manufacture insitu gelling of niosomal drops. When the niosomal formulation was injected into the eye, it changed into a gel.. Every gel formulation demonstrated a regulated drug release pattern and pseudo-plastic rheological behaviour. [18]

To treat glaucoma, Bhalerao et al. [19] developed an in situ gelling ocular drug delivery device. Based on the idea of ion-activated in situ gelation, they report the development and testing of an ocular delivery system for the antiglaucoma drug dorzolamide hydrochloride. Together with HPC (hydroxypropyl cellulose), which increased viscosity, sodium alginate was utilised as the gelling agent. According to in vitro release experiments, the medication was better retained by the alginate/HPC solution than by either alginate or HPC solutions alone. The formulation offered sustained release, stability, and therapeutic efficacy.[19]
To treat glaucoma, Darwhekar et al. created and refined an in situ gel containing timolol maleate and dorzolamide hydrochloride. In order to increase contact time, achieve controlled release, reduce the frequency of administration, and increase the therapeutic efficacy of the drug, an in situ gel was prepared using different concentrations of HPMC (0.5, 1.0, 1.5% w/v) (Methocel K15M) as a viscosity-enhancing agent in conjunction with different concentrations of Pluronic F-127 (15–20% w/v) as a temperature-induced gelling system.[20]
For ocular administration, Pandurangan et al. developed an SLN-filled in situ gel that encapsulated voriconazolen the present investigation, solid lipid nanoparticles (SLNs)-loaded in situ gel with voriconazole drug was formulated.Film hydration technique was used to prepared SLNs from lecithin and cholesterol.The in situ gels were prepared using viscosity-enhancing polymers such as Carbopol and (hydroxypropyl)methyl cellulose (HPMC). Formulated SLN in situ gel formulations were characterized.The results revealed that there was no ocular damage to the cornea, conjunctiva, or iris. Stability studies were carried out on the F6 formulation for 3 months, which showed that the formulation had good stability. These results indicate that the studied SLNs-loaded in situ gel is a promising vehicle for ocular delivery.[23]
By altering the molecular mass and PEG content, Bellotti et al. enhanced the application of pNIPAAm temperature-sensitive hydrogels for the treatment of glaucoma. In order to prevent the gelled drop from turning back into liquid in cold or windy conditions and to guarantee rapid gelation after delivery, they adjusted the sol-to-gel transition temperature and de-swelling kinetics of pNIPAAm gels. By altering the amount of poly(ethylene glycol) in the water phase and its molecular weight, it was possible to successfully reduce the gel LCST, accelerate the gelation kinetics, and create a viscosity that was appropriate for administration as an eye drop. With typical drug concentration profiles of the old and new formulations showing similar anti-glaucoma release kinetics, their data indicate that drug release is unaffected by these modifications.[24]

Study (Author)	**Drug Used**	Polymers / Materials Used	**Major finding**
Hasansathali et al.	Brimonidine Tartrate	Niosomes (Span series & cholesterol), HPMC K 15 M, Carbopol 940	Span 60 (S/C 2:1) niosomes showed highest entrapment & prolonged release; in situ gel formed in the eye with controlled release and pseudo-plastic behavior.
Bhalerao et al.	Dorzolamide Hydrochloride	Sodium Alginate (ion-activated), Hydroxypropyl Cellulose (HPC)	Alginate/HPC combination enhanced viscosity and drug retention; provided sustained release, stability, and therapeutic efficacy.

Study (Author)	**Drug Used**	Polymers / Materials Used	**Major finding**
Darwhekar et al.	Timolol Maleate, Dorzolamide Hydrochloride	HPMC (Methocel K15M) (0.5–1.5% w/v), Pluronic F-127 (15–20% w/v)	Achieved controlled release, increased ocular contact time, reduced dosing frequency, and improved therapeutic effect using thermoresponsive in situ gel.
Bellotti et al.	Not specified (anti-glaucoma agents)	pNIPAAm hydrogel, Polyethylene Glycol (PEG)	Modified PEG content and molecular weight to lower LCST, enhance gelation kinetics, and maintain drug release profile in various environmental conditions.
Pandurangan et al	voriconazole	Carbopol, lecithin and (hydroxypropyl)methyl cellulose (HPMC)	SLN-loaded in situ gel was safe for ocular tissues (cornea, conjunctiva, iris); showed good 3-month stability and promising potential for ocular delivery.

Table 1 :Research progress of nanoparticle-laden in situ gelling approach

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

The in situ gel method effectively dispersed eye medications in clinical trials. A group of scientists made an in situ gel using the glaucoma medication timolol maleate and contrasted it with conventional eye drops. Compared to conventional eye drops, the in situ gel maintained therapeutic concentrations for a longer period of time by sustaining the release of the therapeutic ingredient. This lowers dosing frequency and increases patient adherence. In situ gels were investigated for the treatment of dry eye condition. Results indicated that the in situ gel exhibited a sustained drug release profile similar to eye drops, enhancing clinical efficacy. The gel formulation contained cyclosporine. These studies demonstrate how in situ gel technology can enhance patient adherence and aid in the distribution of ocular pharmaceutical components. As research advances, it is anticipated that the way ocular medications are delivered to patients with different ocular disorders will improve.

7.Potential future developments in in situ gelling technology

For the distribution of ocular medications, the in situ gel approach appears to be promising. Still, there is potential for development. In situ gel compositions could be improved via nanotechnology. Drug solubility, stability, uptake, and ocular tissue delivery can all be enhanced by nanoparticles. Another area of interest is stimuli-triggered in situ gels. The gels dispense medications in a precise and regulated way in response to stimuli like pH and temperature. This approach lessens adverse effects and enhances medication delivery.

Biodegradable materials for in situ hydrogels are also being researched by researchers. Elimination procedures may be eliminated and patient comfort may be enhanced by the gel's gradual absorption by the body. In situ gelling techniques are generally encouraging and have the potential to enhance the administration of ocular medications.

8.Clinical application of in-situ ophthalmic gels

To date, some of in-situ gel formulations have been commercially available for ocular drug delivery .For instance, Timoptic-XE® ,containing timolol maleate (0.25% and 0.5%) in gellan gum has been available on market since 1994 ,which is applied topically on the eye to treat glaucoma. Furthermore, some of the patents on in-situ gel for ocular delivery system have been issued in the last decades, and are being summarized in table 2

Product Name	Drug Used	Polymer	Manufacturer
Pilopine HS®	Pilocarpine hydrochloride (4%)	Carbopol 940 / pH-triggered	Alcon Laboratories, USA
Akten®	Lidocaine hydrochloride (3.5%)	Lidocaine hydrochloride (3.5%)	Akorn Inc., USA
Akorn Inc., USA	Interleukin-2 (IL-2)	ReGel® (Thermo-sensitive depot)	Macromed

Product Name	Drug Used	Polymer	Manufacturer
Besivance®	Besifloxacin (0.6%)	DuraSite® (Mucoadhesive polymer)	Bausch & Lomb

Table 2 : Marketed In Situ Ophthalmic Gel Products

9.**CONCLUSION**

The safety of ophthalmic formulations is crucial since the eye is the most vital and delicate organ in the body. The majority of the cytotoxicity and irritability research that was part of this study demonstrated that the use of in-situ gel did not result in any appreciable changes or indications of toxicity.

To assess the potential toxicity resulting from repeated and prolonged applications and materials for the creation of nanoparticles in nano-gel systems, more research is necessary.

Furthermore, the higher viscosity of in-situ gel may result in certain drawbacks, such as obscured vision and patient discomfort, which could speed up elimination because of reflex tears and blinks.

Therefore, in order to minimise the restrictions to a manageable level, essential control of the viscosity should be taken into account throughout the design and optimisation of the in-situgel formulation.

Only a small number of medications in the form of in-situ gel are presently being used in clinical settings, despite the great potential of in-situ gel in ocular drug delivery. As a result, more research should be done to investigate this drug delivery method for the therapeutic use of more eye medications.

Currently, the majority of ophthalmic in-situ gels were created exclusively for formulations with a single active component.

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