European Journal of Clinical Pharmacy
Print ISSN: 2385-409X **Online ISSN**: 3105-0409
Website: https://farmclin.com/

Original Research Article

Ophthalmic in-Situ Gel for Enhanced Drug Delivery: Formulation and Evaluation

Article History:

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Received: 29-11-2025
Revised: 10-12-2025
Accepted: 20-01-2026
Published: 08-02-2026

Abstract: This study aims to develop and evaluate a pH-triggered in-situ gel containing prednisolone and moxifloxacin to overcome the limitations of conventional eye drops, such as low bioavailability due to lacrimal drainage. The Formulation utilised Carbopol 940 as a crosslinked polyacrylic acid polymer and HPMC as a mucoadhesive agent to enhance viscosity. Buffering agents adjusted the pH to 6.5, enabling sol to gel transition upon contact with the ocular environment. Key Parameters such as clarity, pH, gelation temperature, spreadability and drug content were assessed. The optimized formulation demonstrated desirable transparency, gelation behaviour, and sustained drug release, offering improved stability, reduced irritation, and enhanced therapeutic efficacy compared to standard eye drops.

Keywords: pH Triggered, Improved Stability, Opthalmic insitu gel.

INTRODUCTION

The Eye is a complex organ with a unique anatomy and physiology. The Structure of the eye can be broadly classified into two segments: Anterior and Posterior Segments. Structural variation of each layer of ocular tissue can pose a significant barrier following drug administration by any route, i.e., topical, systemic, and periocular. One of the major limitations faced in ophthalmic delivery is the attainment and retention of optimum drug concentration at the site of action within the eye.

The eye drops have very poor bioavailability due to their rapid washout during lachrymation in eyes. Most of the systems are applied as solutions or suspensions. The rapid pre-corneal elimination observed with conventional ocular formulations ends in poor drug bio-availability. Ease of administration in case of highly viscous solution and gel forms retard its use and patient compliance. The blurred vision and the lachrymation are associated with the dosage form involving hydrogel.

These can be overcome by fabricating the drug as a formulation that undergoes transformation as insitu gel after administration in the eye. They undergo gelation after instillation due to pH changes occurring in the eye. It increases the pre-corneal residence time and better bioavailability of drug can be achieved by formulating in situ gel.It increases the pre corneal residence time and better bioavailability of the drug can be achieved by formulating as Insitu gel.

A major issue in ocular therapies is achieving adequate drug concentration at the site of action, which is hampered primarily by precorneal loss,

resulting in only a tiny proportion of the drug being absorbed ocularly. The effective dose can be adjusted by increasing the medication's retention period in the eye utilizing in situ gel-forming technologies. Ophthalmic medication delivery is a fascinating and hard venture.[1]

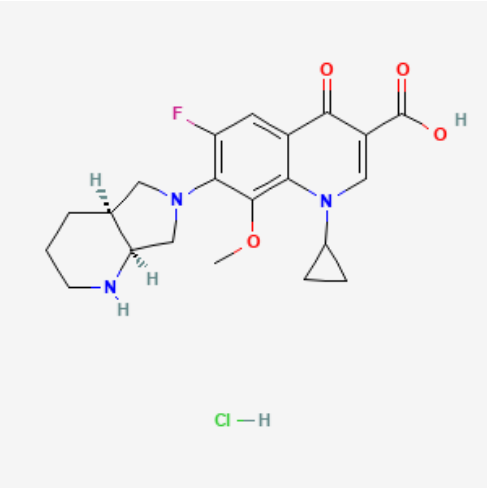
The eye's architecture, physiology, and biochemistry make it extremely resistant to external chemicals. The problem for the formulator is to evade the eye's protective defenses without causing irreversible tissue damage.[2]

Ophthalmic ointments improve medication bioavailability by increasing contact duration, reducing dilution by tears, and inhibiting nasolacrimal drainage. The main disadvantage of the ointment is that it causes blurred vision; thus, it should only be used at night or for treatment on the outside and edges of the eyelids. Suspension as an ocular delivery strategy is based on the concept that particles may stay in the conjunctival sac. Precorneal medication loss can be reduced by utilizing a diffusion-controlled, non-corrodible polymeric insert to delay drainage. The main downside of inserts is low patient acceptance due to complicated administration. The advancement of better, more sensitive diagnostic tools and treatment chemicals necessitates the development of more effective ocular delivery systems. In situ gel forming formulations provide a novel way to give medications to patients in a liquid dosage form while ensuring continuous drug release for the required duration.[3]

Polymer-based delivery systems can extend medication formulations' absorption time. Recently, there has been a growing interest in water-soluble polymers that can form gels when applied to the delivery site. In situ gelling polymers offer a significant benefit over other polymers as they can be delivered in liquid form to the location of drug absorption, unlike strong gels. Drag absorption causes a strong gel to form, which can extend the active substance's residence period.[4]To overcome the low bioavailability and therapeutic responsiveness of conventional ophthalmic solutions due to rapid precorneal elimination, a gel system can be used as drops put into the eye and undergo a sol-gel process.[5] Topical administration is favored for treating most ocular diseases, as systemically delivered medications only reach the eye with a small percentage of their complete dose from the circulatory system.

The blood-retinal barrier (BRB) hinders delivery of this fraction to the interior of the eye.

Moxifloxacin is a fluoroquinolone antibiotic used to treat various bacterial infections.[6] It works by stopping the activity of bacterial enzymes, DNA gyrase and topoisomerase IV, essential for replication and repair of bacterial DNA. This action kills bacteria, thus preventing the spread of infection.



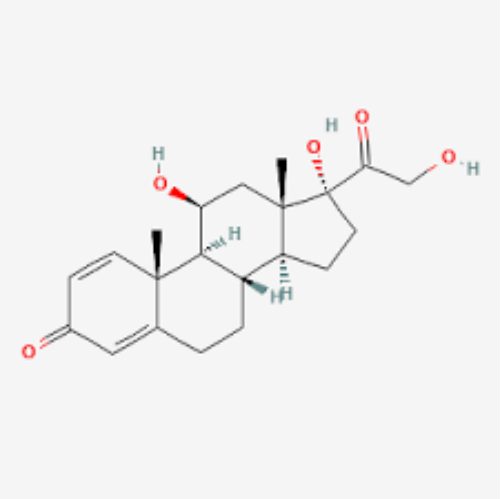
With broad-spectrum protection against both Gram-positive and Gram-negative bacteria, it comes in eye drop form, usually as a 0.5% moxifloxacin hydrochloride solution. For many eye infections, moxifloxacin is the recommended treatment due to its low resistance rate and increased antibacterial efficacy.

Eye drops containing moxifloxacin are frequently given for bacterial conjunctivitis, keratitis, and blepharitis. It functions by blocking the bacterial enzymes topoisomerase IV and DNA gyrase, which are necessary for bacterial DNA replication and repair. It works even against some resistant bacteria that might not react to previous antibiotics because of its dual method of action.

Prophylactic usage of moxifloxacin before and after eye procedures, such as cataract surgery, to avoid postoperative infections such endophthalmitis is another significant application of the antibiotic in ophthalmology. It is perfect for this because of its quick beginning of action and superior ocular penetration. Additionally, moxifloxacin is safe for sensitive eyes because it is usually well tolerated and doesn't need to be compounded with preservatives in

some forms.

Prednisolone is a glucocorticoid used to treat adrenocortical insufficiency, inflammatory conditions, and some cancers.



A synthetic corticosteroid called prednisolone is frequently used in ophthalmology to treat eye irritation and allergic responses. Usually used as eye drops, it comes in a variety of ophthalmic forms, including prednisolone acetate and prednisolone sodium phosphate. These formulations aid in the drug's direct delivery to the ocular tissues that are impacted, providing quick relief from inflammation-related symptoms like redness, swelling, discomfort, and itching.

Prednisolone is frequently used in clinical practice to treat ailments including as keratitis, episcleritis, uveitis, iritis, and allergic conjunctivitis, especially when these disorders are not infectious in nature. Prednisolone helps stop tissue damage and encourages healing in inflammatory ocular structures by inhibiting the immune system and lowering the release of inflammatory mediators.

In order to manage post-operative inflammation and lower the risk of problems like scarring or graft rejection, it is also commonly administered following eye procedures like cataract extraction or corneal transplantation.

Prednisolone eye drops are helpful, but long-term or improper use can cause side effects such increased intraocular pressure, which can cause glaucoma, delayed wound healing, and an increased risk of infection. As a result, it is usually advised to use it for brief periods of time under the guidance of an eye professional and to be regularly monitored if used for longer.

Moxifloxacin and Prednisolone is primarily used to manage bacterial eye infections and belongs to the group of antibiotics and corticosteroids. This medicine combination is useful in reducing inflammation associated with these infections.

In situ gelling systems consist of polymer that exhibit sol-to-gel phase transitions in the cul-de-sac which improves patient compliance due to change in specific physico-chemical parameters like pH, temperature and ionic strength in the environment The sol-to-gel phase transition on the eye surface depending on the different methods employed which consist of thermo-sensitive, ion-activated and electric-sensitive, magnetic field-sensitive, ultrasonic-sensitive and chemical material-sensitive varieties. But above them the most commonly methods are as follows:

1.pH-triggered system
2.Temperature dependent system and
3.Ion activated system

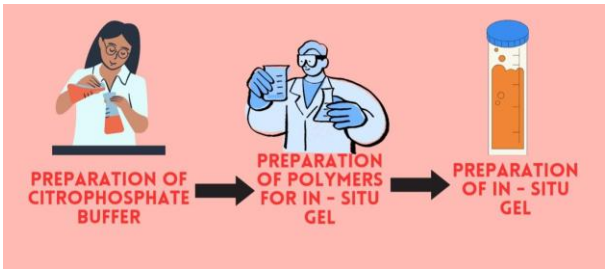
Carbopol® is a pH-sensitive polymer that is in a liquid form at a pH lower than 5.5, and is able to form a semi-solid gel above this pH. The sol-gel transition occurs with the formation of a three dimensional (3D) network swollen in aqueous solution due to electrostatic repulsion and osmotic forces within the polymer backbone Carbopol®-HPMC *in situ* gels have been developed to deliver puerarin [30], baicalin [31], pefloxacin [32] and timolol and brimonidine simultaneously [33]. Compared to standard solutions, higher drug concentrations were delivered in ocular tissues by these *in situ* gels, showing their ability to increase precorneal retention time

MATERIALS AND METHOD:

Moxifloxacin hydrochloride was obtained from Dr. Reddy's laboratories.

- The right vehicle must be chosen before the in situ gelling system is prepared.
- As a result, polymer dispersions were made in several buffer solutions, such as citrophosphate buffer, acetate buffer I.P. (pH 4.0, 5.0), Phosphate buffer I.P. (pH 6.0) and I.P. (pH 5.0, 6.0).
- Considering the visual look and solubility at the targeted dose level of 0.5%, w/v;

The pH 5.0 citrophosphate buffer was selected because it produced clear solutions, however others had tiny fibers or precipitates.



PREPARATION OF CITROPHOSPHATE BUFFER:
75ml of citrophosphate buffer pH 6.5 was prepared in distilled water by mixing 1.125gm disodium hydrogen phosphate and 0.407gm citric acid.

Preparation of pH-induced in Situ Gelling System :

❖PH sensitive polymers like carbomers form gel upon change in their environment (pH).

❖Carbopol 934P is a polyacrylic acid, which undergoes sol-to-gel transition in aqueous solution when the pH is raised above its pKa value
of about 5.5. Hence, carbopol 934P was selected for preparation of pH
induced insitu gelling system.

❖ The intended work was divided into two parts so as to optimize the
polymer concentration:
1.Optimization of polymers concentration.
2.Incorporation of active ingredients in optimized polymer ratio.

Optimization of Carbopol for In Situ Gelling Capacity :
Carbopol 934P in various concentrations (0.1 to 0.5% w/v), was uniformly dispersed in beakers containing required quantity of citrophosphate buffer (pH 5.0), and allowed to hydrate overnight. Subsequently, stirring was done by magnetic stirrer.

❖ These solutions were evaluated for clarity, gelling capacity and viscosity at nonphysiological (pH 5.0) conditions. The results were considered while selecting an optimum polymer concentration.

Optimization of Carbopol and HPMC Combination for In Situ Gelling System:

- When applied to the eye, carbopol does not form a hard gel at lower concentrations and instead generates low viscosity solutions.
- However, a high concentration turns the solution extremely acidic, making it difficult for the tear fluid's buffering activity to neutralize.
- Adding an appropriate viscosity-enhancing polymer, like hydroxypropyl methylcellulose (HPMC), can lower the carbopol concentration without affecting the system's overall rheological behavior or in situ gelling capabilities. HPMC K4M (4000-5600 cps) was thus utilized in the formulation.

PROCEDURE:

- In order to choose the best polymer combination, several formulations were created using different grades of HPMC combined with carbopol.
- Equal amounts of buffer solutions were put into beakers, and HPMC K4M (0.2 to 0.6% w/v) was spread out while being constantly stirred.
- Carbopol 934P was added to all of the solutions in amounts ranging from 0.3 to 0.5% w/v and put aside to stay hydrated throughout the night.
- To achieve uniformity, the liquids were then agitated using a magnetic stirrer.
- Several solutions were examined for their ability to gel, clarity, and viscosity using a Brookfield viscometer in non-physiological (pH 5.0) circumstances.

INGREDIENTS (Qty in g)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Moxifloxacin	0.5	0.5	0.5	0.5	0.5	0.5
Prednisolone	0.5	0.5	0.5	0.5	0.5	0.5
HPMC k4M	0.1	0.1	0.1	0.1	0.1	0.1
Carbopol	0.3	0.4	0.5	0.3	0.4	0.5

Benzalkonium Chloride	0.01	0.01	0.01	0.01	0.01	0.01
Citric Acid	0.405	0.405	0.405	0.405	0.405	0.405

EVALUATION PARAMETERS

Clarity
Ophthalmic preparations must have excellent clarity. The formulations were visually inspected on a white and black background to detect particles.

pH:
The preparation to be administered to the eye should not irritate the eye. To match the pH of lacrimal fluid, the pH of the in-situ gelling solution after adding all materials was measured using a digital pH meter.

Drug Content Uniformity :
After shaking the vials (n=3) for 2-3 minutes, 1 ml of the product was transferred to a 100 ml volumetric flask and diluted with simulated tear fluid pH 7.4. An aliquot of material was taken and diluted to 10 ml with the same synthetic tear fluid pH 7.4. The concentration of Moxifloxacin HCl was measured at 287 nm using a UV-Visible spectrophotometer.

In Vitro Gelation Studies :
- The gelling capacity of a system containing carbopol 934P and HPMC K4M was assessed.
- To test the gel, a drop of system was added to vials filled with 1 ml of freshly manufactured and equilibrated simulated tear fluid at 37 0C. The gel was then visually assessed.
- Formation and time taken is then recorded for taking the gel to gel and disintegrate.
- Simulated tear fluid (STF) was composed of sodium chloride (0.670 g) and sodium bicarbonate (0.200 g).
- Calcium chloride dihydrate and double distilled water, 100.0 g each. Physiological pH (7.4 0.2) was adjusted by adding the appropriate amount of 0.1 N HCl.

Measurement of Gel Strength :
- The gel sample of 50g was placed in a 100 ml graduated cylinder and gelled with 0.5N NaOH at pH 7.4 at 37°C. The gel strength measurement instrument was allowed to penetrate the in-situ ophthalmic gel.
- The gels' strength, or viscosity at physiological pH, was measured by sinking the device 5cm through the prepared gel in seconds.

RHEOLOGICAL STUDIES :
The viscosity of the implanted formulation affects the drug's residence period in the eye. The rheological investigations of the formulations were conducted using a Brookfield viscometer (RVDV II+ Pro model) with a sample adaptor and spindle number (SC4-21). The angular velocity was gradually increased from 0.5 to 100 rpm. Then the angular velocity hierarchy was inverted (from 100 to 10 rpm). Viscosity was calculated by taking the average of two readings. To raise the pH of the formulations from 5.0 to 7.4, add 0.5 N sodium hydroxide solution while increasing the temperature from 25 to 37 0C. The viscosity of the samples was measured before and after gellification.

INVITRO RELEASE STUDIES
- The diffusion technique was used to estimate the in vitro release rate of Moxifloxacin Hydrochloride for ocular drug availability in a sol gel system.
- 1 ml of the formulation was placed in the donor compartment over a dialysis membrane, which was then cleaned and immersed in diffusion medium for 24 hours.
- The donor compartment was immersed in the calibrated receptor compartment, which had 25.38 ml of synthetic tear fluid (7.4). The diffusion medium (receptor compartment) was kept at 37±0.5ºC and stirred continuously at 22 rpm with a magnetic stirrer.
- Every hour during 8 hours, 1 ml aliquots were taken from the diffusion medium and replaced with the equal amount of fresh medium.
- The samples were analyzed for Moxifloxacin Hydrochloride at 287nm using a Shimadzu Double Beam UV-Visible spectrophotometer.
- The study compared medicines released from developed formulations to marketed eye drops.

RESULTS

Clarity
Appearance and clarity by visual observation against a white and black background was evaluated.

pH
The clarity of all formulations was found to be satisfactory. The formulations were light yellow in colour. Terminal sterilization with autoclaving had no effect on the physicochemical properties of the formulations. PH of the formulations did not vary considerably.

Drug Content Uniformity :
The drug content was found to be in the acceptable range for all the formulations. Percent drug content for all nine formulations was in the range of 97.84-100.11% indicating uniform distribution of the drug.

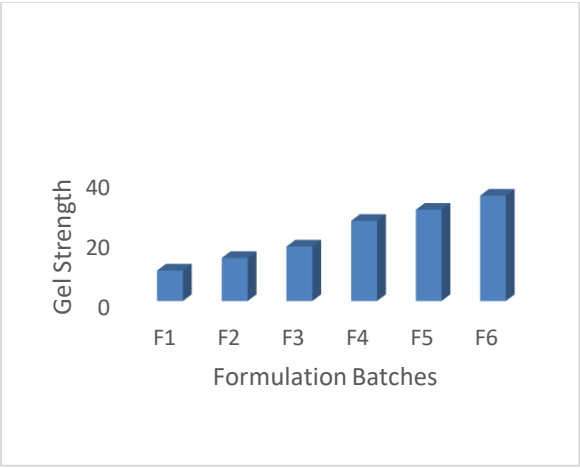
S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Visual appearance	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent
2	Clarity	Clear	Clear	Clear	Clear	Clear	Clear
3	pH	5.9	6.7	6.54	6.48	6.62	6.62
4	Gelling capacity	+	++	++	+	++	++

Invitro Gelation studies
F1, F2 and F3 exhibited very weak gelation.
F4 and F5 showed more suitable gelling capacity, which completed the gelation immediately and remained for few hours, compared with the F6, F7, F8, and F9, which gelled instantaneously but remained for extended period of time.

These can also be reflected in the viscosity F9 had greater viscosity, which would cause the gel difficult to spread out on cornea and would make vision blurring.

Measurement of Gel Strength:
At the physiological pH condition (pH 7.4) the viscosity of formulations were increased with increase in polymer concentrations and that causes increase in gel strength.

The gel strength increases from F1-F9 batches.
The highest gel strength was exhibited by the F9 batch that contain Carbopol 934P 0.5% and HPMC K4M 0.5% and lowest gel strength was exhibited by the F1 batch that contains lowest concentration of both the polymer.



Rheological studies:
Dynamic viscosity of formulations was measured as the change of shear rate under non-physiological (pH 5) and physiological (pH 7.4) conditions to investigate the rheology of these formulations.

At pH 5.0 the formulations were in a liquid state and exhibited low viscosity.
An increase in the pH to 7.4 caused the solutions to transform into gels with high viscosity. The formulations exhibited pseudo plastic rheology.

Invitro release studies :
F1-F3 formulations exhibited good release at 6 hr and with slight increase up to8hr i.e. they exhibited sustained release effects and this could be due to increase in HPMC concentration.

F4, F5, and F6 showed 95.27%, 93.91%, and 90.54% drug release. 89.01% and 86.38% of the drug was released from F7 and F8.

This more sustained release was seen due to higher concentration of both carbopol (0.5% w/v) and HPMCK4M. F9 showed least drug release (84.85%). 97.79% of drug was released in 3h from marketed eye drop The developed formulations obviously performed the marketed eye drop by releasing drug over a long period of time and lead to prolonged therapeutic activity.

CONCLUSION

The optimized formulation (F6) contained 0.4% w/v Carbopol 934P and 0.5% w/v HPMC K4M, wherein Carbopol caused initial fast release of the drug due to its hydrophilic nature. Later on, hydroxypropyl methylcellulose imparted sustained release property to the gel formed in situ. The in situ gelling system is likely to achieve good patient acceptance because it is easy to instill and gradually erodes by dissolution of the gel, avoiding the need for removal. Hence, it can be concluded that in situ gels are a viable alternative to conventional eye drops by providing sustained release of the medicament, resulting in decreased frequency of administration and leading to better patient acceptance.

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