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Original Article

Formulation and Evaluation of Temperature Sensitive *in situ* Ocular Gel Drug Delivery System of Acetazolamide for the Treatment of Glaucoma

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ABSTRACT

Background: Conventional eye formulations are generally flushed away from the lacrimal area due to the rapid elimination of drugs from this region, with only a small amount being absorbed. The short-term precorneal contact time, coupled with corneal impermeability, leads to decreased bioavailability, necessitating repeated instillation of drops. Therefore, there is an urgent need for a system that can address these issues, maintain sustained drug action and enhance effectiveness. Numerous attempts have already been made to develop a system that can sustain drug release, with *in situ* gels being one promising approach. **Objectives:** This study aimed to formulate and evaluate a temperature-sensitive *in situ* ocular gel drug delivery system for Acetazolamide (ACZ) to treat glaucoma, providing prolonged drug release. **Materials and Methods:** A temperature-sensitive ophthalmic *in situ* gel of ACZ was prepared using a cold method and temperature-dependent polymers. The prepared gel was assessed for its appearance, clarity, pH, gelling ability, gelling temperature, sterility, viscosity, *ex vivo* permeation study, *in vitro* ocular irritancy test and *in vivo* pharmacodynamics study. **Results:** The *ex vivo* permeation study and *in vivo* pharmacodynamics study revealed that Formulation 3 exhibited the highest drug release. The formulation was found to be sterile. The *in vitro* ocular irritancy test (Hen's Egg Test-Chorioallantoic Membrane) confirmed that the formulation was non-irritating and the *in vivo* pharmacodynamics study on Wistar rats demonstrated that the formulation remained effective for an extended period. *In situ* gels extended the contact time and improved bioavailability, making them a promising approach for advanced drug delivery.

Keywords: Acetazolamide, *In situ* ocular gel, Glaucoma, Ophthalmic gels.

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INTRODUCTION

Glaucoma is a silent thief of vision, ranking as the second leading cause of vision impairment.[1] The disease can be managed through various medications and educational programs.[2] Late detection of disease leads to slow degradation of optic nerves.[3] It's a common eye ailment primarily caused by elevated intraocular pressure, which damages the optic nerve and ultimately results in vision loss.[4] Regular eye examinations are crucial.[5] These can be assessed using a tonometer, although sometimes the disease may go undetected in its early stages.[6]

The visual field test helps in early glaucoma detection due to wide fluctuations in intraocular pressure.[7] The eye continuously produces aqueous humor and intraocular pressure is regulated by the balance between its secretion and proper excretion. When the drainage angle does not function correctly, it creates pressure, leading to optic nerve damage. Other causes include eye infections, chemical injuries and eye inflammations.[8]

There are two types of glaucoma: Open-Angle Glaucoma, which occurs due to dysfunction in the drainage of aqueous humor through the trabecular meshwork, leading to increased intraocular pressure and optic nerve damage; and Angle-Closure Glaucoma, caused by the narrowing or blocking of the angle between the iris and cornea, which reduces drainage.[9,10]

Medications used for glaucoma include Adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, prostaglandin analogs, mitotic agents and hyperosmotic agents.[11] Other

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methods include laser trabeculoplasty, laser iridotomy and surgical operations. Micro-invasive techniques involve the insertion of intraocular pressure -lowering devices, such as the Hydrus microstent, drainage tube and implants, which function like tubes connected to a plate. Aqueous fluid collects into the plate and the body naturally absorbs it.[12,13]

Currently, various strategies are being used to treat glaucoma, such as eye drops. However, these drops have several disadvantages, including short-term precorneal contact time and corneal impermeability, leading to reduced bioavailability and the need for frequent administration. A promising system to overcome these drawbacks is *in situ* gels.[14,15]

The use of carbonic anhydrase inhibitors, such as ACZ, lowers intraocular pressure prior to surgery, delays the onset of blindness and treats symptoms of open-angle glaucoma. ACZ is now the most effective and widely used Carbonic Anhydrase Inhibitor (CAI) for the treatment of open-angle glaucoma. ACZ functions by inhibiting the Carbonic Anhydrase Enzyme (CAE), which has a role in transporting CO_2 from the tissues to the lungs and promoting the production of aqueous humor through ciliary processes. In order to achieve the intended reduction in intraocular pressure, it is necessary to take substantial oral doses of ACZ because CAE is widely distributed throughout the body.[16]

Formulations are initially in solution form before installation, but upon contact with various physiochemical parameters such as pH and temperature, they convert into a gel.[17] The advantages of *in situ* gels include sustained action, reducing the need for frequent eye drop administration, increasing patient comfort and suitability for unconscious patients.[18] However, the polymers used in these gel formulations should be well-tolerated by the eyes, Thermoreversible and able to convert into a gel at physiological stimuli.[19] Approaches used to prepare *in situ* gels include ion-activated *in situ* gels, where the positive ions of lacrimal fluid interact with the negative ions of polymers to form gels.[20] Temperature-sensitive *in situ* gels remain liquid before application but transform into a gel form at a certain physiological temperature (around 35-37°C). pH-triggered systems are typically liquid at a pH of approximately 4.2 but convert into a gel form as the pH increases (6.8-7.2).[21]

MATERIALS AND METHODS

ACZ and pharmaceutical-grade Poloxamer were purchased from Yarrow Pharmaceuticals Private Limited. Hydroxy propyl methyl cellulose (HPMC-K15M, K4M), Polyethylene glycol (PEG-400) and Benzalkonium chloride were procured from Otto Chemie Private Limited.

Methodology

Gel was prepared using the cold method. Poloxamer 407 was added to a specific quantity of distilled water and stirred on a mechanical stirrer at a speed of 50-100 rpm for 1-2 hr. The mixture was then stored in a refrigerator at 4°C±2°C for 24 hr to obtain a clear solution. In another beaker, ACZ was dispersed in PEG 400 solvent with constant stirring for 1 hr on a mechanical stirrer.

The following day, both solutions were combined with continuous stirring and HPMC- K15M, K4M was added while the solutions were continually mixed until a homogeneous solution was achieved. Afterward, the volume of distilled water was adjusted to 50 mL. Finally, Benzalkonium chloride was added and the solution was filtered using a 0.2 mm filter paper. The formulation composition is in Table 1.

Evaluation parameter of *in situ* gel

Visual Appearance and Clarity: The gels were visually inspected for their appearance.

Clarity: The clarity of the formed gel was assessed against both white and black backgrounds, as well as under fluorescent light, to check for any presence of particulate matter.

pH: pH plays a crucial role in maintaining stability and influencing the drug's solubility. For eye formulations, the pH should fall within the range of 6.5 -7.6. The pH was measured using a digital pH meter, which assesses the acidity and basicity of the formulation. The formulation should be prepared to remain stable within the eye's pH range.

Drug Content: A 1 mL sample of the prepared formulation was diluted in 100 mL of phosphate buffer and DMSO at a pH of 6.8. Absorbance was then measured at 300.5 nm using a UV spectrophotometer.

Gelling Capacity

This refers to the ability of the preparation to transform from a liquid (solution) state into a gel when administered in the eye. To assess this, stimulated tear fluid was first prepared by dissolving 0.2 g of sodium bicarbonate, 0.008 g of calcium chloride and 0.67 g of sodium chloride in 2 mL of distilled water, which was then equilibrated at 37°C. Subsequently, this freshly prepared 2 mL of simulated tear fluid was placed in a test tube. One drop of the prepared gel was added to it and the time taken for the solution to turn into a gel and subsequently dissolve was observed. Different symbols were used to represent the gelling capacity:

*Gel formed within a few seconds and dissolved immediately.

**Gel formed rapidly within a few seconds but remained for only a few minutes.

***Gel formed rapidly and remained for an extended period.

Gelation temperature

This is defined as the temperature at which the solution transforms into a gel. To determine the gelation temperature, 5-6 mL of *in situ*

Table 1: Formulation of Acetazolamide *in situ* gel.

Sl.No.	Drug and Excipients	F1	F2	F3	F4
1.	Acetazolamide (mg)	150	150	150	150
2.	Poloxamer 407(g)	10	10	10	10
3.	HPMC K15M (mg)	100		150	
4.	HPMC K4M (mg)		100		150
5.	PEG 400 (mL)	8.75	8.75	8.75	8.75
6.	Benzalkonium chloride (mg)	10	10	10	10
7.	Purified Water (mL)	50	50	50	50

Table 2: Irritation score values.

Irritation score Inference	Inference
0-0.9	No irritancy
1-4.5	Weak irritancy
5-8.9	Moderate irritancy
9-21	Severe irritancy

gel was placed in a beaker. The beaker was then positioned on a heating mantle with a thermometer attached. As the temperature increased, the point at which the formulation converted into a gel and no longer flowed when the beaker was tilted to a 90° angle was recorded.

Rheological study

Viscosity plays a crucial role in understanding how long the drug will remain in contact with the ocular region and in retarding the settling of particles. Various polymers are employed to adjust the viscosity of formulations. It's important to maintain an appropriate viscosity level; it should neither be excessively high nor too low. The viscosity was measured at 25°C and 37°C using Brookfield viscometer and spindle number 62 at 100 rpm. The prepared formulation was first poured into a beaker and then the spindle's angular velocity was adjusted from 10 to 100 rpm. Viscosity was determined both before and after gelation.

Ex vivo permeation studies

This study was conducted using a Franz diffusion cell. In this study, goat corneas were removed from goat eyes procured from a slaughter house. The initial cornea obtained was rinsed with cold saline. The Franz diffusion cell comprises two compartments: the donor compartment, filled with 27 mL of phosphate buffer and DMSO solution and the receptor compartment, where the corneal membrane was placed. The corneal membrane was positioned on the receptor compartment in a way that allowed contact with the phosphate buffer and DMSO solution. A bead was placed in the solution within the receptor compartment. The temperature was maintained at 37±0.5°C and the speed was set at 50-60 rpm. 1 mL of the prepared *in situ* gel was applied to the corneal membrane, initiating the Franz diffusion process. At different time intervals (1, 2, 3 and 4 hr), 1 mL was withdrawn and replaced with 10 mL of phosphate and DMSO solution. The withdrawn sample 1 mL was diluted with 10 mL of phosphate and DMSO solution. Subsequently, it was analyzed at 300.5 nm using UV spectrophotometry and finally, the percentage of cumulative drug release (% CDR) was calculated.

In vitro ocular irritancy by Hen's egg test chorioallantoic membrane test: In this test, chicken eggs were utilized and eggs with physical damage were excluded. Three groups were created: one negative control group, one positive control group and one test group.

Positive Control: Eggs were treated with 0.9 % w/v NaCl (0.3 mL).

Negative Control: Eggs were treated with 1% sodium lauryl sulfate (0.3 mL), serving as an irritant for comparison.

Test Group

Eggs were treated with 0.3 mL of the test formulation. The eggs were initially placed in an incubator on a tray for approximately 14 days at a temperature of 37±0.5°C and a relative humidity of 58±2%. The eggs were rotated about 3-4 times a day. Upon confirmation of embryo growth, the following day, a hole was made on the upper side of the egg and the groups were treated with their respective solutions. Changes such as coagulation, lysis and hemorrhage were observed for 5 min.

The Formula for calculating the Irritation Score (IS) is presented below, followed by the corresponding values of the irritation score and their associated inferences, as shown in Table 2.

$$IS=(301-H)/300 *5+(301 -L)/300 *7+(301 -C)/300*9$$

Where,

H: Haemorrhage, L: Lysis of blood vessels, C: Coagulation.

Sterility test

Sterility testing was performed using soybean casein digest media. The test was conducted through the direct inoculation method. In this method, 1 mL of the *in situ* gel containing ACZ, our test solution, was transferred into 10 mL of soybean casein digest media using a sterile pipette. The test solution was thoroughly mixed with the soybean casein digest media and all steps were

carried out under laminar flow conditions. Subsequently, it was incubated in an incubator for a minimum of 14 days at 25±2°C.

In vivo pharmacodynamic studies

In vivo pharmacodynamic studies were conducted on male Wistar rats weighing 150-250 g. A total of 24 rats were used and divided into 4 groups. The experimental protocol of the study was approved by the Institutional Animal Ethics Committee (KUDOPS/172).

Group 1

This group served as the normal control and the rats were given distilled water for 14 days.

Group 2

Considered the positive control, rats in this group were anesthetized with 2 drops of lidocaine hydrochloride I.P (a 2% solution of lidocaine). Glaucoma was induced by injecting alpha-chymotrypsin (0.05 mL) into the intra vitreous region of the eye. After 2-3 days of injection, 1-2 drops of dexamethasone eyedrops were administered to prevent inflammation. Intraocular pressure was measured using a Schiotz tonometer.

Group 3

This group served as the standard control (using a marketed formulation). Rats were anesthetized with 2 drops of lidocaine hydrochloride I.P (a 2% solution of lidocaine). Glaucoma was induced as in Group 2. After 2-3 days of injection, 1-2 drops of dexamethasone eye drops were administered to prevent inflammation. Intraocular pressure was measured using a Schiotz tonometer and the eye was treated with the marketed formulation, Dorzolamide eye drops "DORZOX" (50 µL).

Group 4

Rats in this group were administered the prepared *in situ* gel of ACZ. They were anesthetized with 2 drops of lidocaine hydrochloride I.P (a 2% solution of lidocaine). Glaucoma was induced as in the previous groups. After 2-3 days of injection, 1-2 drops of dexamethasone eye drops were given to prevent inflammation. Intraocular pressure was measured with a Schiotz tonometer. Once the intraocular pressure was stabilized, pharmacodynamic studies were initiated by treating the eye with the selected *in situ* gel formulation (50 µL).

RESULTS

IR Spectra

FTIR studies confirmed the compatibility of the drug, ACZ, with the *in situ* gel polymers, as no additional peaks were observed in the spectra. This indicates the absence of chemical interactions between the drug and the polymers. The FTIR spectra of the drug ACZ and the physical mixture of ACZ and polymers are given in Figure 1.

Clarity: All the formulated gels were examined for the presence of particulate matter. The results are presented in Table 3.

pH: The pH of all the prepared formulations fell within an acceptable range. Each formulation had a pH between 6.5 and 7.6, which is within the acceptable range for ocular use and ensures it will not cause irritation upon administration. The results are provided in Table 3.

Drug content: The drug content in all the formulations ranged between 80% and 90%. The results are displayed in Table 3.

Gelling capacity

Gelling capacity was determined visually and the results are presented in Table 3. All formulations exhibited rapid gelation that remained effective for an extended duration. Among the obtained values, formulations F3 and F4 demonstrated rapid gelation and prolonged retention. It is evident that when the gels are introduced into the cul-de-sac, it undergoes immediate gelation and maintains its form for an extended period.

Gelation temperature

The gelation temperature for the prepared formulations was within the range of 36-38°C, as depicted in Table 3.

*Gel formed within a few seconds and disappeared immediately.

**Gel formed rapidly in a few seconds but remained for only a few minutes.

***Gel formed rapidly and also remained for an extended period.

*Gel formed within a few seconds and dissolved immediately. **Gel formed rapidly within a few seconds but remained for only a few minutes. ***Gel formed rapidly and remained for an extended period.

Rheological studies

As shown in Figure 2, the viscosity values were obtained using a Brookfield viscometer. An increase in spindle angular velocity resulted in a decrease in the gel's viscosity. The viscosity of the formulation was directly proportional to the polymeric content. With an increase in HPMC- K15M, K4M concentration, the viscosity of the *in situ* gel also increased. The addition of HPMC-K15M, K4M assisted Poloxamer 407 in forming a robust structural arrangement, enhancing viscosity and enabling the formulation to withstand shear forces during blinking. These rheological graphs demonstrated the pseudoplastic flow nature of the fluid. The formulations exhibited optimal viscosity, facilitating the convenient installation of the gel.

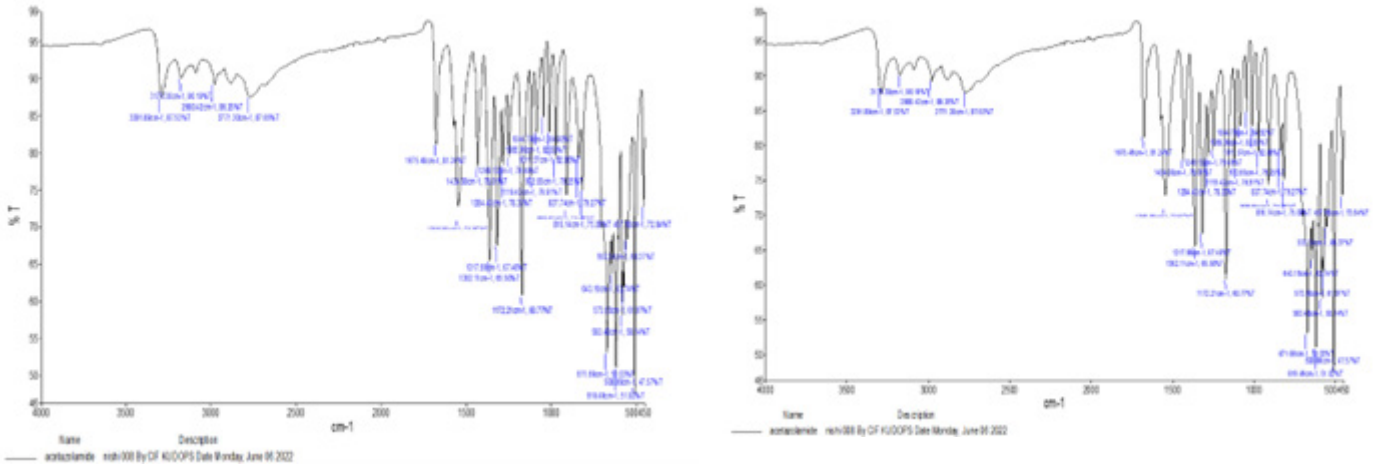

Figure 1: IR Spectra of pure drug Acetazolamide (A), IR spectra of drug and polymers (B).

Table 3: Results of clarity test, pH, Drug content, gelling capacity, gelation temperature.

Formulation code	Clarity	pH	Drug Content	Gelling capacity	Gelation temperature
F1	Gel was Clear.	6.6	81.6%	**	37°C
F2	Gel was Clear.	6.5	83.0%	**	36°C
F3	Gel was Clear.	6.7	84.0%	***	37°C
F4	Gel was Clear.	6.8	80.1%	***	38°C

Sterility test

No turbidity was observed, indicating the absence of microbial growth after at least 14 days of incubation at 25±2°C, confirming the sterility of the preparation.

Ex vivo permeation study

This study was conducted on formulations (F1, F2, F3 and F4) using a Franz diffusion cell. The experiment spanned 4 hr at 50-60 rpm, with the temperature maintained at 37±0.5°C. Samples were collected at 1 hr intervals. The drug permeation ranged from 49.0 % to 53.0%. The release profile can be seen in Figure 3.

In vitro ocular irritancy by Hen's egg test chorioallantoic membrane test

The eggs treated with 1 % w/v SLS (the effect of SLS, used as the positive control, that induced irritation and hemorrhage on the membrane), which served as the negative control, exhibited irritation, as indicated by the presence of redness and ruptured vessels. Eggs treated with 0.9 % w/v NaCl and the test formulations did not show any signs of irritation when compared to the negative control group, as depicted in Table 4. Images from the Hen's egg test chorioallantoic membrane tests is provided in Figure 4.

In vivo pharmacodynamic studies

In vivo pharmacodynamic studies were done on male Wistar rats weighing 150-250 g and on 24 rats which were divided into 4 groups. The experimental protocol of the study was sanctioned by the institutional animal ethics committee (KUDOPS/172).

Group 1: Considered as normal control.

Group 2: Considered as positive control.

Group 3: Considered as standard control (Marketed formulation)

Group 4: Given prepared *in situ* gel of Acetazolamide. (F3)

It was observed that with the marketed formulation DORZOX, intraocular pressure started to decrease on the 4th day, but there was a subsequent increase in intraocular pressure, which may be attributed to the drug's elimination. Therefore, it was evident that sustainability was not achieved with the marketed formulation and frequent administration of eye drops was necessary. The maximum decrease shown by the marketed formulation was 17.650±2.952 mm Hg. However, in the case of the test formulation F3, the maximum decrease was 14.783±2.189 mm Hg, as shown in Figure 5. Intraocular pressure started to decrease on the 5th day but maintained a sustained effect. This suggests that sustainability was achieved with the prepared *in situ* gel, resulting in a prolonged effect and increased corneal residence.

The mean pharmacokinetic parameters of ACZ *in situ* gel and the marketed DORZOX eye drops were as follows: Δ intraocular pressure max value for ACZ was 25.50, while that of the marketed product was 25.00. The T_{max} values were different; for the marketed formulation, the decrease was observed on the 4th day, but for ACZ *in situ* gel, it occurred on the 5th day. The AUC value for ACZ

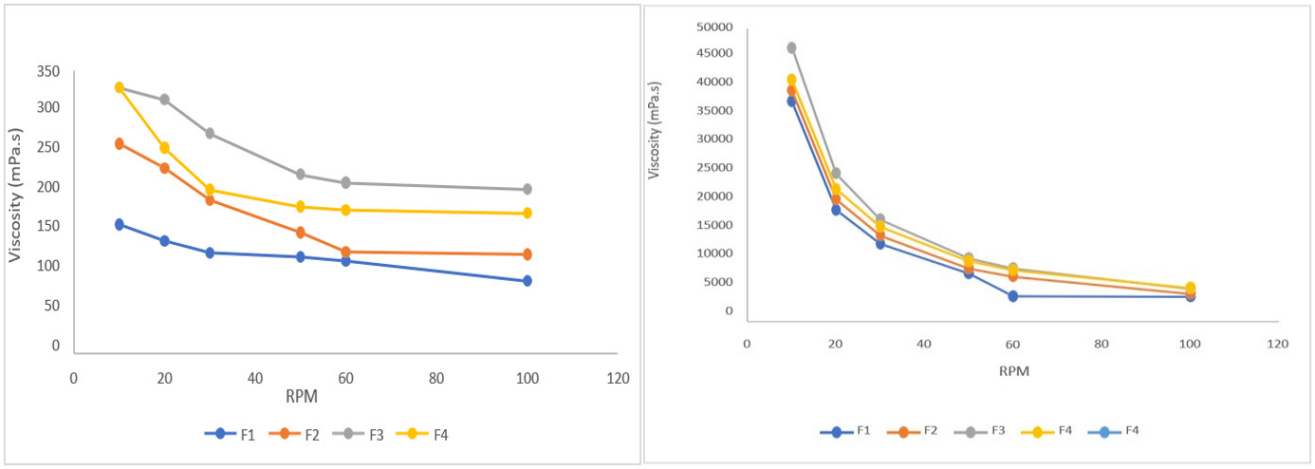

Figure 2: Viscosity of temperature sensitive *in situ* gel before gelation and after gelation. *mPa.s-millipascal-second

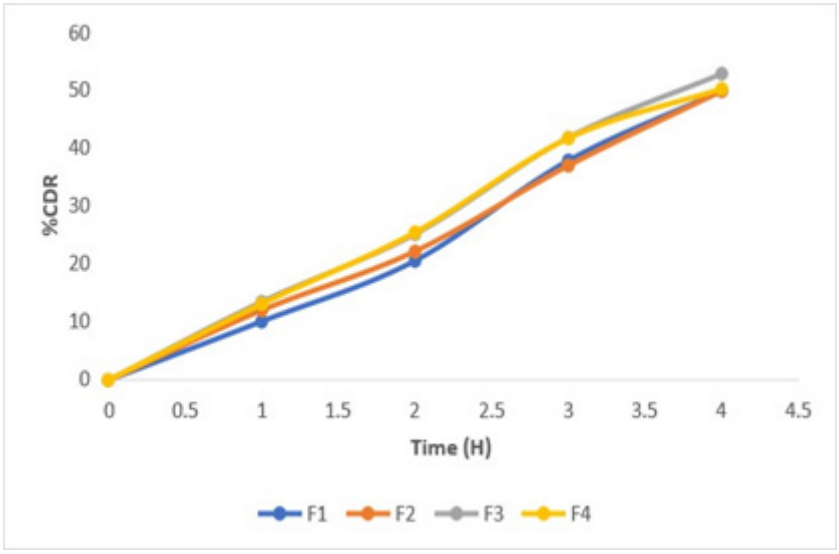

Figure 3: Graph of *ex vivo* permeation studies.

Table 4: Irritation score value of Hen's egg test chorioallantoic membrane test.

Test compound	Mean irritation score	Inference
0.9 % w/v NaCl	0.08	No irritancy
1 % w/v SLS	14.56	Severe irritancy
Test formulation 3	0.09	No irritancy

gel was 127.343, while the marketed DORZOX formulation had an AUC of 117.023, as shown in Figure 5. These results indicate the higher therapeutic efficiency of ACZ *in situ* thermosensitive gelling system represented by F3 over the marketed eye drops."

DISCUSSION

In this study, we aimed to formulate a temperature-sensitive *in situ* ocular gel of ACZ using Poloxamer 407, HPMC K4M and HPMC K100M-based vehicles. The objective was to prevent nasolacrimal drainage, improve bioavailability and reduce dosing frequency. These gels remain in liquid form at room temperature and undergo gelation at body temperature. The gel was prepared using the cold method. IR studies confirmed that there was no physical or chemical incompatibility between the drug and the polymers.

The developed ocular *in situ* gel demonstrated superiority compared to standard medication. The *in situ* gel formulations were evaluated for various parameters, including appearance, clarity, gelation temperature, gelation time, pH, *ex vivo* release, *in vitro* ocular irritancy tested using the Hen's egg test chorioallantoic membrane method and *in vivo* pharmacodynamic studies. All these parameters met acceptable standards. The gels were clear with no particulate matter. The pH of all formulations fell within the range of 6.5-7.6, which is suitable for ocular use. All formulations exhibited rapid gelation, which persisted for an extended duration. The drug content in all formulations ranged between 80-90%. Rheological studies revealed that an increase in HPMC- K15M, K4M concentration led to an increase in the

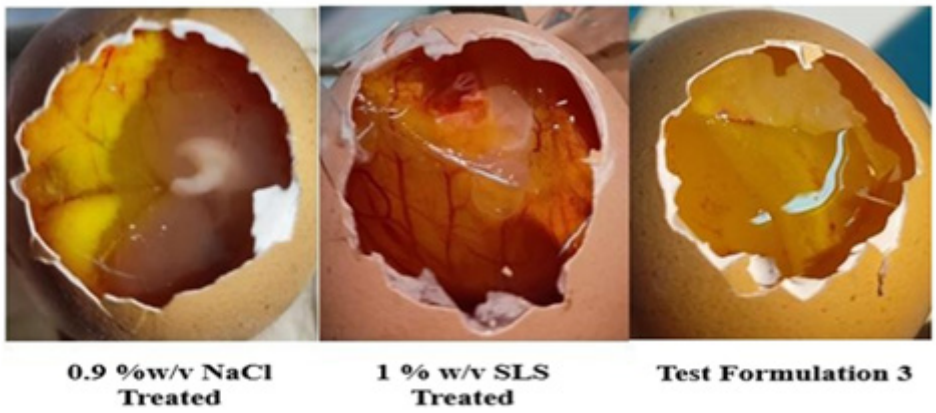

Figure 4: Hen's egg test chorioallantoic membrane test for optimized formulation.

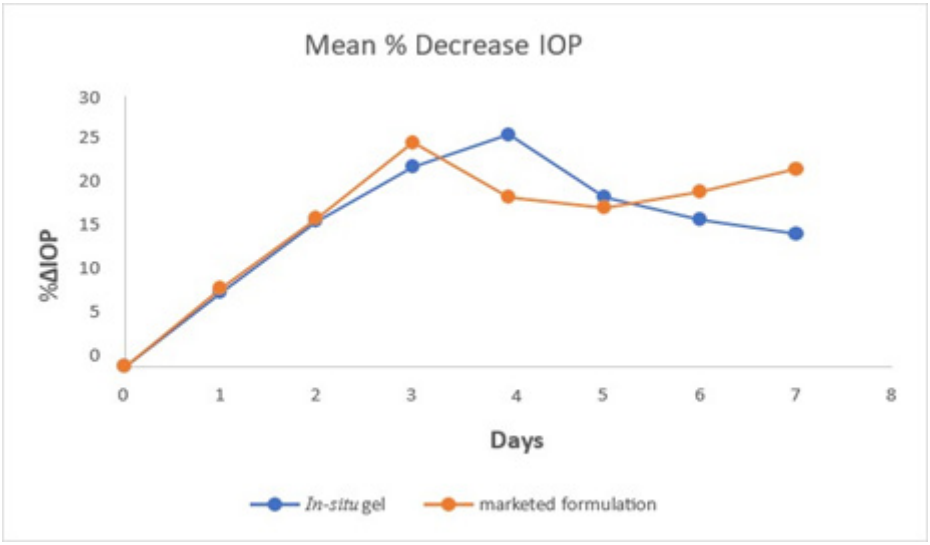

Figure 5: Comparative *in vivo* intraocular pressure lowering activity of marketed and *in situ* gel formulation shown by Graph.

viscosity of the *in situ* gel. Sterility tests showed no microbial growth in the gels. The drug permeation for all gels ranged from 49.0-53.0%. Among the formulations, F3 was optimized as the best, showing the highest drug release. It was clear, had a gelation temperature of 37°C with a gelation time of a few seconds and a pH within the range of 6.7. Hen's egg test chorioallantoic membrane studies demonstrated that the prepared *in situ* gel did not cause irritation.

In situ ocular gel provided sustained drug delivery and effectively addressed the limitations of traditional ocular dosage forms. This innovative technique has garnered significant attention from researchers due to its numerous advantages.

CONCLUSION

According to the study's findings, ACZ gel that has been manufactured *in situ* provides a better option than prescription drugs. Numerous analyses of this research project's excipient and methodology selections have shown that they were result-oriented in the fabrication of *in situ* gel. The commonly utilised ocular formulations at the moment are linked to a number of undesirable side effects. Therefore, more research on the drug's molecular mode of action in diverse eye illnesses is warranted given the new formulation of *in situ* gel. The outcomes showed that the gel that was made functioned better than the formulation that was sold. It may function as a more potent substitute for conventional drugs. Moreover, more investigation is required to create various dosage forms of ACZ-incorporated *in situ* gel that have lower toxicity and more useful therapeutic applications.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AUC: Area under the curve; **CAI:** Carbonic anhydrase inhibitor; **CAE:** Carbonic anhydrase enzyme; **ºC:** Degree Celsius; **cps:** Centipoise; **FTIR:** Fourier transform infra-red; **g:** Gram; **H:** Haemorrhage; **hr:** Hours; **L:** Lysis of blood vessels; **mg:** Milligram; **min:** Minutes; **mL:** Milliliter; **mPa.s:** Millipascal-second; **NaCl:** Sodium chloride; **nm:** Nanometer; **rpm:** Revolutions per minute; **RBCs:** Red blood cells; **SLS:** Sodium lauryl sulfate; **STF:** Simulated tear fluid; **µL:** Microliter.

SUMMARY

This study aimed to formulate a temperature-sensitive *in situ* ocular gel using varying concentrations of HPMC K15M and HPMC K4M, with HPMC serving as a viscosity enhancer. The prepared gel was subjected to various evaluations, including clarity, pH, viscosity, drug content, gelling capacity, gelation temperature, *ex vivo* permeation study, *in vitro* ocular irritancy tested via the Hen's Egg Test Chorioallantoic Membrane method, sterility test, rheological studies and *in vivo* pharmacodynamic studies. The results showed that the gel achieved sustained release compared to the marketed formulation (DORZOX) and effectively addressed the disadvantages associated with traditional ocular dosage forms.

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