




Original Article

Formulation, Characterization and in Vitro Evaluation of pH Triggered in-Situ Ocular Gelling System Containing Ofloxacin: An Antibacterial Study Against *Staphylococcus aureus*

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ABSTRACT

Background: Ocular drug delivery faces significant challenges due to anatomical barrier like cornea, conjunctiva, blood-aqueous barrier and physiological barriers like tear turnover, reflex blinking, nasolacrimal drainage. These factors cause rapid elimination of drugs, leading to less than 5% of topically applied drugs reaching the intraocular tissues. This leads to poor bioavailability of drug, thus reducing the desired therapeutic effect of the drug. One of the biggest challenges for ocular formulators is overcoming the protective barrier without causing harm to the permanent tissue.

Aim: The objective of this study was to develop, formulate and evaluate a pH-triggered in-situ ophthalmic gel for sustained ocular delivery of ofloxacin. Ofloxacin is a broad-spectrum fluoroquinolone antibiotic used for treating bacterial eye infections.

Method: pH-triggered in-situ ophthalmic gel formulations were prepared using varying concentration of carbopol 940P and hydroxy propyl methyl cellulose (HPMC E50 –LV). The formulations were evaluated for pH, clarity, viscosity, spreadability, drug content, in vitro drug release and antimicrobial activity.

Results: Formulation exhibited optimal characteristics with high drug content (96.8%), good spreadability, appropriate viscosity, and the highest cumulative drug release (92.3%) over 240 minutes. Fourier transform infrared spectroscopy (FTIR) and field emission scanning electron microscopy (FESEM) analysis confirmed the chemical stability and uniform gel matrix of the formulations. The in-situ gel formulations exhibited good antibacterial activity against *Staphylococcus aureus* with zone of inhibition (ZOI) 39 mm.

Conclusion: The results indicate that pH-sensitive in-situ gels have prolong ocular residence time and provide controlled drug release, thereby improving therapeutic efficacy and patient compliance.

Keywords: Ofloxacin, In-situ gel, Ophthalmic formulation, pH-triggered gel, Carbopol 940P, HPMC E50LV.

INTRODUCTION

For pharmaceutical scientists, one of the most fascinating and difficult areas is ocular medication delivery. Ocular drug delivery faces significant challenges due to anatomical barrier like cornea, conjunctiva, blood-aqueous barrier and physiological barriers like tear turnover, reflex blinking, nasolacrimal drainage. These factors cause rapid elimination of drugs, leading to less than 5% of topically applied drugs reaching the intraocular tissues. This leads to poor bioavailability of drug, thus reducing the desired therapeutic effect of the drug [1]. Ophthalmic in situ gels employ a variety of polymers and hydrogels are typically utilized. The viscosity of the solution will rise due to these polymers. For pharmaceutical scientists, one of the most fascinating and difficult areas is ocular medication delivery. The field has greatly improved during the past ten to twenty years [2]. Because of the delicate nature of the application site and its numerous restrictions, care must be taken when developing new products. The physiology of the eye states that this organ is impervious to outside

substances. It is challenging to formulate a medication that can pass through the protective layer of eye and reach the site of action with a high enough concentration [1,2]. Innovative drug delivery techniques sought to get past the biological barrier that can prevent effective drug administration into the eyes [3]. One of the biggest challenges for formulators during formulation is overcoming the protective barrier without causing harm to the permanent tissue. Common conditions that can be treated with topical medication delivery include glaucoma, trachoma, keratitis, conjunctivitis, and blepharitis [4]. Poor bioavailability, increased precorneal elimination, and considerable variability in efficacy are the main drawbacks of conventional formulations like solutions, suspensions, emulsions, ointments, etc. [5,6]. For ophthalmic chemotherapy, the most popular formulation is optical application due to its ease and safety.

MATERIALS AND METHODS

Chemicals

Ofloxacin was purchased from R.S. Scientific, Kolkata, India. Hydroxy propyl methyl cellulose (HPMC E50 –LV) and carbopol 940P were purchased from Sisco Research Laboratories, Mumbai, India. Citric acid was purchased from R.S. Scientific, Kolkata, India and tween 20 was purchased from Merck Life science PVT. Ltd, Mumbai, India. Disodium hydrogen phosphate was purchased from Loba Chemie Pvt.Ltd, Mumbai, India and sodium hydroxide was purchased from Qualikems Lifesciences Pvt.Ltd, Vadodra, India. Benzalkonium chloride was purchased from Loba Chemie Pvt.Ltd, Mumbai, India.

Preformulation Studies: Drug Excipients Compatibility Studies:

Drug- excipient compatibility studies are conducted mainly to predict the potential incompatibility, and to provide justification for the selection of excipients in the formulation. An incompatibility may result in changes in physical, chemical, microbiological, or therapeutic properties of the dosage form.

Fourier transform infrared spectroscopy (FTIR) :

Infrared (IR) spectroscopy of pure drug and physical mixture of drug with polymers was carried out using FTIR instrument (Bruker Alpha II) to evaluate the interactions between drug and excipients, if any. The FTIR spectra of pure drug, HPMC E50 LV and carbopol 940P and physical mixture of drug-polymers were taken. The pure drug, polymer and physical mixture were separately mixed with infrared (IR) grade potassium bromide (KBr). This mixture was punched at a pressure of about 12 Psi under vacuum to form a disc, which was mounted in a suitable holder and scanned over a wave number range of 4000 to 400 cm⁻¹ [7].

Preparation artificial tear fluid:-

Simulated tear fluid (STF) was prepared according to the Indian Pharmacopoeia to mimic the natural tear environment for in vitro evaluation of the ophthalmic in-situ gel. The formulation consisted of 0.67 g of sodium chloride, 0.20 g of sodium bicarbonate, and 0.008 g of calcium chloride dihydrate, all dissolved in purified water to make a final volume of 100 ml. The ingredients were dissolved with continuous stirring, and the pH of the solution was adjusted to approximately 7.4 to match that of natural tears [8,9].

Preparation of pH triggered in-situ ophthalmic gel

Cold press method

This procedure involves dissolving the medication in an appropriate solvent together with several other excipients and water-soluble polymers.

The cold approach method was used to formulate ofloxacin in situ gel. The buffer salts was dissolved in 25 ml of purified water, then HPMC E50LV was added slowly. Carbopol 940P was dissolved in a separate solution using a magnetic stirrer and mixed with HPMC solution. Tween 20 and citric acid was added in the solution slowly with continuous stirring. After all the polymers were mixed properly and ofloxacin was dissolved in 10 ml of sodium hydroxide solution. The pH was then adjusted, followed by the addition of benzalkonium chloride. After that the drug solution was added to the polymer solution under the constant stirring until a uniform clear solution was obtained. The volume was adjusted to the required volume. All samples were then transferred into amber bottles and stored in room temperature. The formulation ingredients are presented in Table 1.

Table 1: Formulation ingredients of in-situ ophthalmic gel (Weights in mg)

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ofloxacin	10	10	10	10	10	10	10	10	10
Carbopol	250	250	250	180	180	180	100	100	100

940p									
HPMC E50 LV	750	500	380	750	500	380	750	500	380
Disodium hydrogen phosphate	562	562	562	562	562	562	562	562	562
Citric acid	203	203	203	203	203	203	203	203	203
Sodium hydroxide	80	80	80	80	80	80	80	80	80
Tween 20	qs	qs	qs	qs	qs	qs	qs	qs	qs
Benzalkonium chloride	qs	qs	qs	qs	qs	qs	qs	qs	qs
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs

Evaluation of in-situ ophthalmic gel:

pH detection: In ocular formulations, pH has an impact on the drug stability and solubility. It should be such that the patient won't experience any irritation during administration and that the formulation will be stable at that pH. The digital pH meter was used for the measurement [10].

Physical examination and clarity test: Physical evaluation or test of appearance and clarity is very important. It includes observation of colour, odour, and presence of suspended particulate matter. The clarity test should be performed against black and white background. Visual inspection of the formulations under light or against black and white backgrounds is frequently used to assess the clarity of the formulations both before and after gelling [11].

Viscosity studies: Viscosity of the formulation was determined by using a viscometer (Brookfield viscometer, Brookfield Corp., Canada) before and after gelation. For this study, spindle number 63 was used at 30 Revolutions Per Minute (RPM) where spindle factor 40 was used for the calculation (where Dial reading X Factor=Viscosity in centipoise, mPa.s). The ocular gelling system was taken in a beaker and the spindle was dipped in about 2 min and then reading was taken before and after gelation. The procedure was repeated 3 times for each formulation [12].

Drug content: Uniform distribution of active ingredient is important to achieve dose uniformity. The drug content was determined by diluting 1 ml of the formulation to 100 ml phosphate buffer. Aliquot of 1 ml was withdrawn and further diluted to 10 ml with solution. Ofloxacin concentration was then determined at 287 nm by using UV-Visible spectrophotometer (Shimadzu UV 1800) [13].

Spreadability: The apparatus consists of a wooden block with a ground glass slide placed on it. On this ground slide, every formulation weighing roughly 2 g was positioned and examined. After that, a second slide with dimensions similar to the fixed glass slide was placed and the gel preparation was sandwiched between them. An attached hook was given to the second slide. To create a homogenous gel coating between the two slides and release any trapped air, 1 g weight was attached to the hook and the time (second) required by the top slide to cover a distance (cm) was noted. The procedure was repeated 3 times for each formulation [14,15].

Spreadability was calculated using the following formula:

$$S = \frac{M \times L}{T}$$

Where, S= Spreadability, M= Weight in the pan (tied with the upper slide) , L= Length moved by the glass slide , T= Time in seconds needed to separate the top slide from the bottom slide.

In-vitro drug release study: The drug release from the prepared formulation was studied by Franz diffusion cell (Labindia-8000) using cellophane membrane soaked overnight in the receptor medium pH 6.8. The diffusion medium was filled in the receptor compartment and it was stirred at 50 RPM at $37 \pm 0.5^\circ$ C. One end of the diffusion tube was covered by a cellophane membrane. The 1 ml formulation was spread on the cellophane membrane and membrane was placed such that

it just touches the diffusion medium present in receptor compartment. The drug samples were withdrawn at the interval of 30 min for the period of 4 hrs from diffusion medium and analysed by a UV spectrophotometer at 287 nm [15].

Antibacterial activity study: Antibacterial activity study was determined by the agar well diffusion method. Standard solution of streptomycin in phosphate buffer pH 6.8 and the developed formulations diluted suitably with phosphate buffer, pH 6.8 (test samples) were poured into agar well previously seeded with test organism *Staphylococcus aureus*. After allowing diffusion of the solutions for 2 h, the agar plates were incubated at 37°C for 48 hrs. The zone of inhibition (ZOI) was measured for standard, control and samples. [16].

Field emission scanning electron microscopy (FESEM)

FESEM analysis was carried out to study the surface morphology of the optimized in-situ ocular gelling system. The sample was dried and mounted on an aluminium stub using double-sided adhesive carbon tape, followed by gold sputter-coating to make it conductive. The sample was then scanned under high vacuum using a FESEM instrument at various magnifications (Sigma-300 Zeiss) [16].

RESULTS AND DISCUSSION

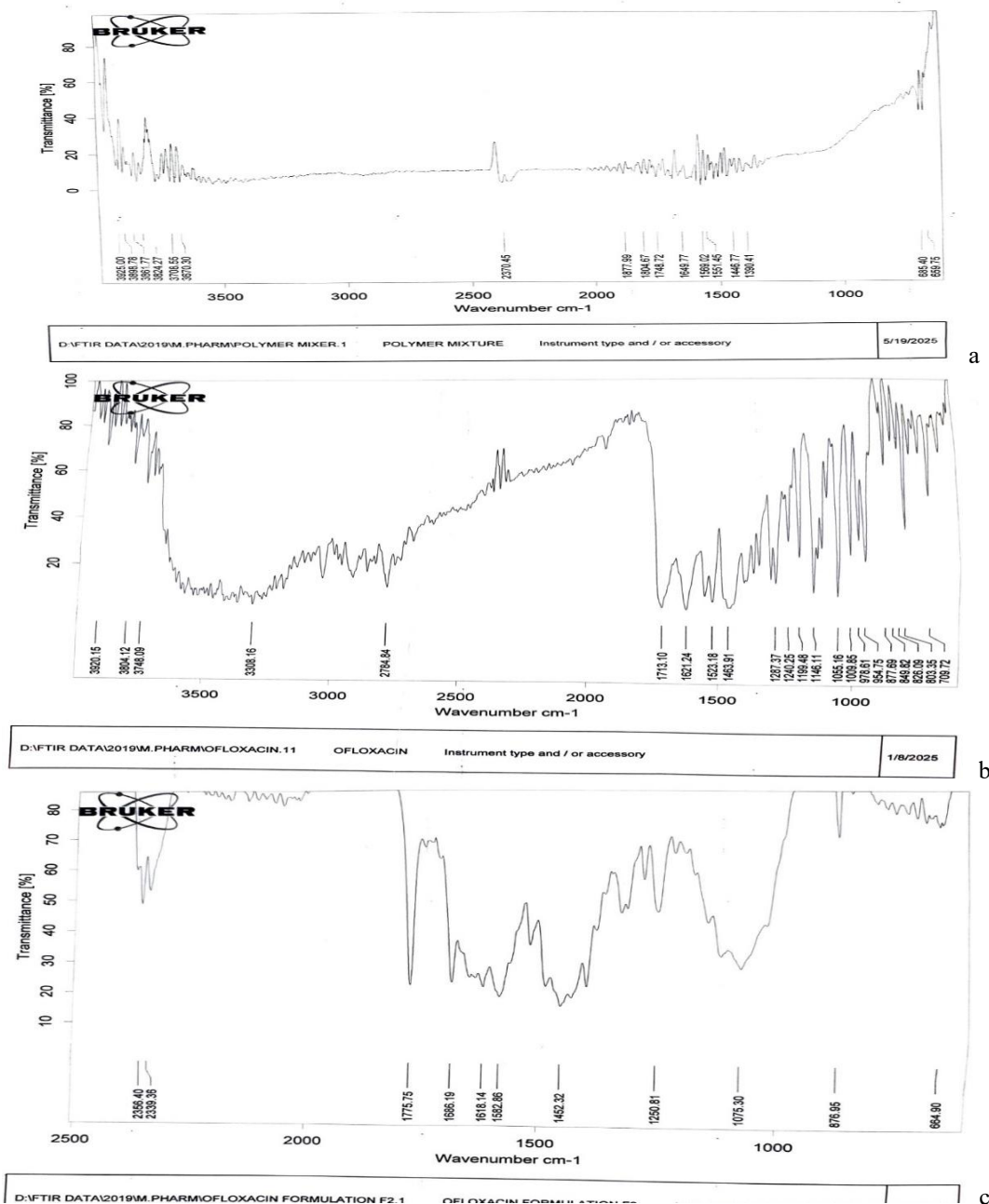


Figure 1 : a. FTIR spectrum of ofloxacin b. FTIR spectrum of polymer mixture HPMC E50 LV and carbopol 940P c. FTIR spectrum of in-situ gel formulation containing ofloxacin

The FTIR spectrum of pure ofloxacin showed characteristic peaks corresponding to its functional groups. A broad peak observed around 3308.16 cm^{-1} is attributed to the O–H and N–H stretching vibrations, indicating the presence of hydroxyl and amine groups. A strong peak at 1713.10 cm^{-1} corresponds to the C=O stretching of the carboxylic or ketone group. The peaks at 1621.24 cm^{-1} and 1523.18 cm^{-1} represent C=C or C=N stretching vibrations, typically seen in aromatic rings or heterocyclic. Additional bands in the region of 1282.37 to 703.72 cm^{-1} represent C–F, C–N, and C–H bending vibrations in the fingerprint region, confirming the structural identity of ofloxacin (Figure 1a).

The FTIR spectrum of the polymer mixture comprising carbopol 940P and HPMC E50LV was analyzed to assess potential interactions between the polymers used in the in-situ gel formulation. A broad absorption band observed between 3925–3670 cm^{-1} corresponds to O–H stretching vibrations, indicating the presence of abundant hydroxyl groups and hydrogen bonding, typical of hydrophilic polymers like HPMC and carbopol. Sharp peaks in the region of 1746–1699 cm^{-1} are attributed to C=O stretching vibrations from the carboxylic acid groups of carbopol. The absorption bands appearing at 1551 cm^{-1} , 1496 cm^{-1} , and 1390 cm^{-1} correspond to asymmetric and symmetric COO^- stretching, suggesting partial neutralization of carbopol with sodium hydroxide in the formulation process. Additionally, small but distinct peaks were noted at 1246 cm^{-1} and 1048 cm^{-1} , which may represent C–O stretching vibrations typical of ether linkages in HPMC. The absence of any new peaks or significant shifts in functional group regions indicates that no chemical interaction occurred between carbopol and HPMC. The retention of characteristic peaks from both polymers confirms their physical compatibility, making them suitable excipients for the development of a stable pH-sensitive ophthalmic in-situ gel formulation (Figure 1b).

The FTIR spectrum of the in-situ gel formulation showed the presence of characteristic peaks of ofloxacin. The peak at 1618.14 cm^{-1} corresponds to C=N or aromatic stretching, while 1452.32 cm^{-1} confirms aromatic ring vibrations. Other significant peaks, such as at 1075.30 cm^{-1} , indicate C–O and C–F stretching, consistent with the drug structure. Key absorption peaks included broad bands at 3500–3300 cm^{-1} corresponding to O–H and N–H stretching (indicating hydrogen bonding), a strong peak at 1724 cm^{-1} due to C=O stretching of the carboxylic acid group, a peak at 1628 cm^{-1} for the ketone group in the quinolone ring, C=C stretching vibrations between 1450–1500 cm^{-1} representing the aromatic system, and peaks in the range of 1050–1250 cm^{-1} due to C–F stretching, indicative of the fluorinated moiety of ofloxacin. These peaks in the formulation were preserved with only minor shifts, suggesting physical entrapment of the drug within the polymer matrix rather than chemical bonding. No major shifts, disappearance, or emergence of new peaks were observed when compared to the spectra of pure drug and physical mixture. This indicates that ofloxacin remains chemically stable and intact in the formulation, with no evidence of interaction between the drug and excipients (Figure 1c). These results demonstrate the chemical compatibility and stability of ofloxacin within the gel matrix, validating the structural integrity of formulations and supporting its potential as a stable and effective ophthalmic drug delivery system [17].

Visual appearance and clarity was checked under fluorescent light against a black and white background for presence of any particulate matter. No particulate matter was seen against black or white background.

The pH of the in-situ gelling system after addition of all ingredients was measured using digital pH meter. All the formulations showed pH values within the range of 5.78 to 6.90, which could be considered suitable for ocular application. Importantly, the pH values of the formulations fall within a range where carbopol undergoes a sol-to-gel transition due to ionization of its carboxylic groups, enabling in-situ gel formation upon contact with the lacrimal fluid (Table2).

Table 2: pH of in-situ gel formulations:

Formulation code	pH of formulations (sol from)	pH of formulations (gel from)
F1	5.98	6.9
F2	6.63	6.6
F3	6.1	6.8
F4	6.14	6.7
F5	5.78	7.2
F6	6.3	6.9
F7	6.5	7.3
F8	6.9	6.4
F9	6.21	6.6

The spreadability values of formulations ranged from 5.28 to 6.63 gm.cm/sec, indicating the ease of flow and consistency among formulations. Formulations exhibited the highest spreadability (6.31 gm.cm/sec), suggesting they spread more easily in less time over a moderate distance. Formulations with lower spreadability (5.28 gm.cm/sec), indicating a slightly thicker or more viscous gel which requires more time to spread the same length. Formulations with higher spreadability are expected to provide better patient comfort due to easier application and uniform spreading on the eye surface, which

can also influence the drug release and absorption (Table 3). Formulation (F3) showed a spreadability value of 5.28 gm.cm/sec, adequate to ensure ease of application and uniform ocular coverage. This parameter is particularly important for patient compliance and comfort, as it ensures the gel spreads well without causing irritation or blurred vision. The smooth consistency ensures even drug distribution across the ocular surface, enhancing therapeutic performance. The optimal spreadability also suggests that upon instillation, the formulation can rapidly form a uniform film over the corneal surface, promoting enhanced contact with the target tissue and reducing variability in drug delivery due to blinking or tear flow [18].

Table 3: Spreadability of in-situ gel formulations

Formulation	M (weight in g at upper slide)	T (time in seconds)	L (length moved in cm)	Spreadability (gm.cm/sec)
F1	6.8	9	7.5	5.67
F2	6.8	8	7.8	6.63
F3	6.8	9	7	5.28
F4	6.8	7	6.5	6.31
F5	6.8	8	7	5.95
F6	6.8	8	7.5	6.38
F7	6.8	8	7.5	6.38
F8	6.8	8	7.8	6.63
F9	6.8	7	6.5	6.31

The viscosity of all formulations was evaluated at pH 6.6 and pH 7.4 to assess the sol-to-gel transition behavior of the in-situ ocular gelling system. A notable increase in viscosity was observed when the pH changed from 6.6 to 7.4 across all formulations, confirming the pH-sensitive gelling property.

Formulation F1 exhibited the lowest mean viscosity 52 cPs at pH 6.6 and 133.33 cPs at pH 7.4, while F5 demonstrated the highest viscosity 70.66 cPs at pH 6.6 and 232 cPs at pH 7.4, indicating a more robust gel formation (Table 4).

Formulation (F3) exhibited a viscosity of 160 cPs, indicating a successful sol-to-gel transition suitable for ocular retention. This rheological behaviour ensures that the gel remains in the conjunctival sac of the eye long enough for effective drug absorption. Importantly, the formulation maintained a shear-thinning behaviour, allowing easy blinking and comfort post-administration. An ideal viscosity in ocular gels reduces drainage and enhances corneal contact time, crucial for drugs like ofloxacin that require sustained antimicrobial action. The observed moderate viscosity also supports patient compliance, avoiding issues like blurring or sticky residue post-instillation. This makes the formulation strong candidate for prolonged ocular retention without interfering with vision or causing discomfort [18].

Table 4: Viscosity of in-situ gel formulations

Formulation	Spindle Factor	Dial Reading at pH 6.6	Viscosity at pH 6.6 (cPs)	Mean Viscosity at pH 6.6 (cPs)	Dial Reading at pH 7.4	Viscosity at pH 7.4 (cPs)	Mean Viscosity at pH 7.4 (cPs)
F1	40	1	40		3.2	128	
		1.6	64	52	3.1	124	133.33
		1.3	52		3.7	148	
F2	40	1.1	44		5.0	200	
		1.2	48	53.33	3.6	144	160
		1.7	68		3.4	136	
F3	40	1.5	60		4.1	164	
		1.4	56	58.66	3.8	152	160
		1.5	60		4.1	164	
F4	40	1.6	64		4.5	180	
		1.5	60	61.33	4.3	172	173.33
		1.5	60		4.2	168	
F5	40	1.7	68		6.1	244	
		1.8	72	70.66	5.4	216	232
		1.8	72		5.9	236	
F6	40	1.2	48		5.2	208	
		1.4	56	56	3.6	144	174.66
		1.6	64		4.3	172	

F7	40	1.1	44		5.6	224	
		2.1	84	62.66	4.6	184	188
		1.5	60		3.9	156	
F8	40	1.3	52		6.1	244	
		1.6	64	62.66	5.2	208	218.66
		1.8	72		5.1	204	
F9	40	1.9	76		6.1	244	
		1.3	52	65.33	5.5	220	229.33
		1.7	68		5.6	224	

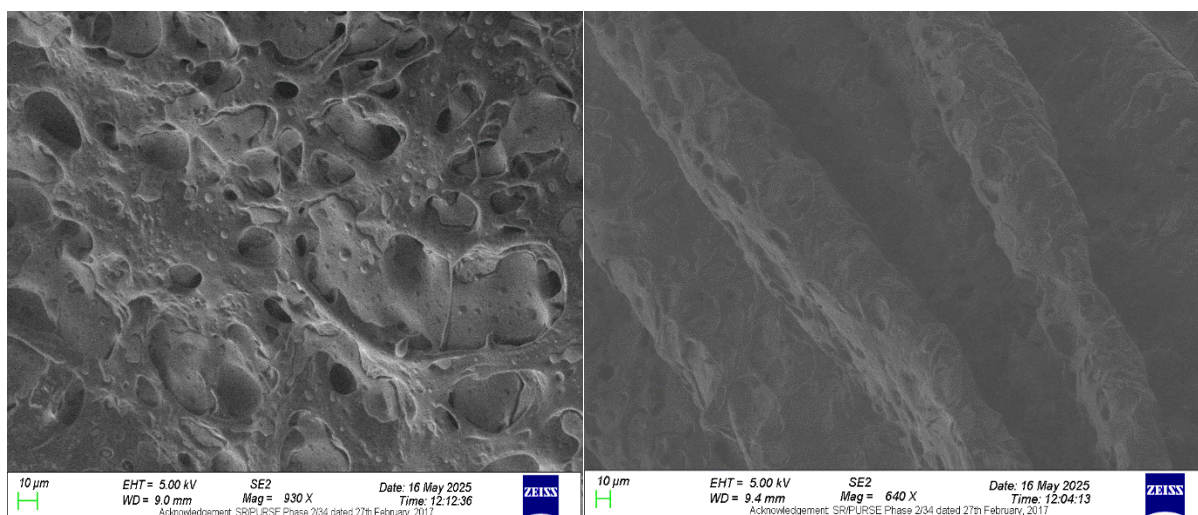


Figure 2: Field emission scanning electron microscopy (FESEM) of in-situ gel formulations

The series of FESEM images revealed the surface morphology of in-situ gel formulations, to analyse the microstructural characteristics in response to pH-triggered gelation. These high-resolution micrographs revealed the gel matrix architecture and morphological changes associated with in-situ gel formation. At physiological pH 7.4, a denser and more entangled network was observed, signifying the transition to a gel phase. This transition is crucial for prolonged ocular retention and controlled drug release. The images also exhibit smooth and interconnected polymeric textures, suggesting uniform gel formation and good miscibility of the polymers used (Figure 2). The FESEM analysis supports the successful pH-responsive gelation behaviour of formulation (F3), validating its potential as a stable in-situ ocular gelling system for sustained delivery of ofloxacin [19].

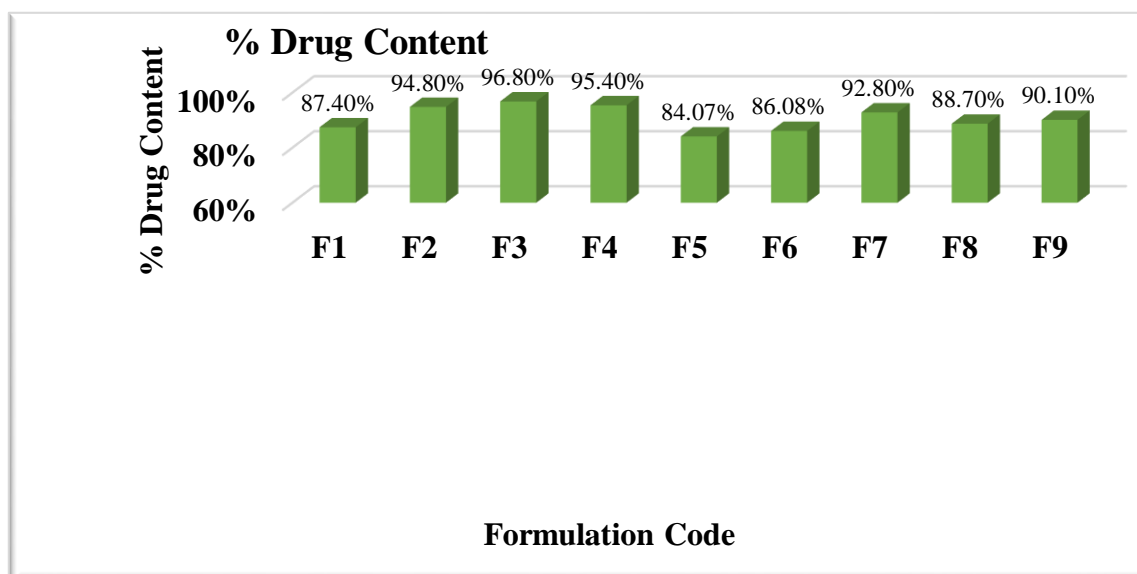


Figure 3: Drug content of in-situ gel formulations

Formulation (F3) exhibited the highest drug content at 96.8%, reflecting uniform dispersion and effective drug loading within the polymer matrix (Figure 3). This parameter is essential for ensuring dosage accuracy in ophthalmic delivery, where a small volume is administered. The high drug content of formulation (F3) indicates a robust preparation method with minimal drug loss during formulation, ensuring therapeutic efficacy over the intended shelf life. Additionally, it demonstrates the stability of ofloxacin in the gel environment without degradation or precipitation. High drug content also minimizes dose variability between units, ensuring reproducibility and reliability in therapy.

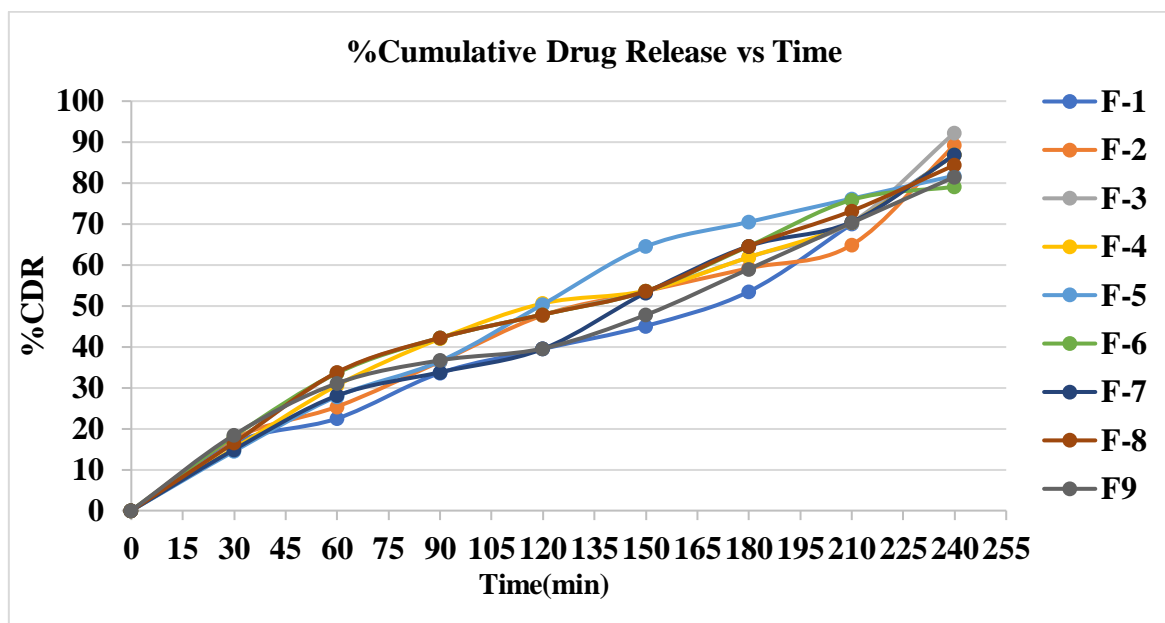


Figure 4: In- vitro drug release study of various gel formulations

The in vitro release profiles of formulations (F1- F9) showed sustained release of ofloxacin over 240 minutes (Figure 4). An initial slow release was observed, followed by a steady increase, indicating proper gel formation and controlled drug diffusion. Formulation F3 exhibited the highest drug release (92.3%), while formulation (F6) had the lowest (79.1%), likely due to differences in polymer concentration affecting gel viscosity. Most formulations released over 80% of the drug by 240 minutes, demonstrating effective sustained release.

Formulation (F3) showed the highest cumulative drug release (92.3% at 240 minutes), which is a critical attribute for ensuring prolonged therapeutic levels at the site of action. This superior release is attributed to the balanced concentration of carbopol and HPMC, forming a gel matrix that controls the drug diffusion effectively. The release pattern observed follows a sustained release profile, which is often desirable in ocular drug delivery to maintain consistent drug levels without fluctuations. This extended release profile helps reduce dosing frequency, improve adherence, and minimize systemic absorption via the nasolacrimal duct. Furthermore, the diffusion profile of formulation (F3) suggests a highly efficient delivery system for hydrophilic drugs like ofloxacin. [20].



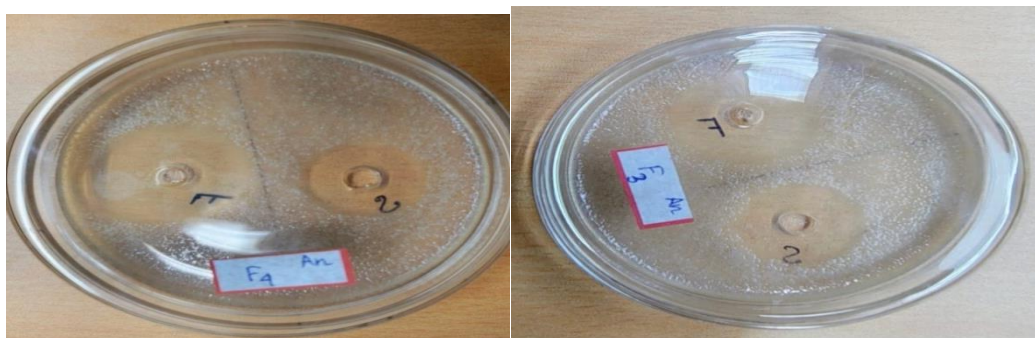


Figure 5: Zone of inhibition (ZOI) of various in-situ gel formulations

Antimicrobial activity of formulated in situ gel was performed against *Staphylococcus aureus*. The in-situ gel formulations exhibited good antibacterial activity against *Staphylococcus aureus* with zone of inhibition (ZOI) 39 mm (Figure 5) which was compared with ZOI exhibited by positive control. The formulation exhibits antimicrobial activity due to presence of ofloxacin.

The formulation and evaluation of a pH-triggered in-situ ophthalmic gel of ofloxacin aimed to address the limitations of conventional eye drops by improving precorneal retention, enabling sustained drug release, and enhancing patient compliance. A trial and error approach was adopted to optimize the concentrations of carbopol 940P and HPMC E50LV as gelling agents. A total of nine formulations (F1–F9) were prepared and evaluated for their physicochemical and pharmacological properties. Among these, formulation (F3) exhibited the most favourable results in terms of clarity, gelling capacity, viscosity, drug content, in vitro drug release, and antimicrobial activity. Based on the research results, the formulation (F3) that exhibited a pH close to physiological levels while ensuring effective drug delivery and release is commonly identified as a pH-triggered in-situ ocular gelling system.

CONCLUSION

The present research work was successfully developed and evaluated a pH-sensitive in-situ ophthalmic gel of ofloxacin using carbopol 940P and HPMC E50LV as gelling agents. The primary objective was to enhance ocular drug delivery by increasing precorneal residence time and providing sustained drug release. Formulation (F3) demonstrated the most promising results, with optimal pH, viscosity, drug content, spreadability, antibacterial activity, and the highest in vitro drug release (92.35% at 240 minutes).

The pH-triggered sol-to-gel transition of the formulation ensures patient comfort and effective drug retention at the site of action. Furthermore, the FESEM analysis confirmed the formation of a stable and uniform gel matrix. Overall, the findings indicate that the in-situ ocular gelling system, particularly F3, has strong potential to improve therapeutic outcomes, reduce dosing frequency, and enhance patient compliance. This formulation represents a promising alternative to conventional ophthalmic preparations for the effective treatment of ocular infections.

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CONFLICT OF INTERESTS

The authors report no conflicts of interest in this research work.

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