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FORMULATION AND EVALUATION OF OPHTHALMIC GEL FOR OCULAR DRUG DELIVERY SYSTEMS

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Abstract :

Ocular drug delivery is limited by rapid precorneal elimination, resulting in poor bioavailability and frequent dosing. This study aimed to develop and evaluate moxifloxacin hydrochloride in situ gelling formulations using sodium alginate and hydroxypropyl methylcellulose (HPMC) to enhance ocular retention and sustain drug release. Six prototype formulations (F1–F6) with varying polymer concentrations were prepared and characterized for physicochemical properties, rheology, in vitro gelation, drug content, in vitro release, antimicrobial efficacy, ocular tolerability, and stability. All formulations were clear, isotonic, and exhibited pseudoplastic (shear-thinning) behavior. In situ gelation in simulated tear fluid occurred rapidly, with higher polymer formulations (F5, F6) forming stronger gels that persisted for over 6 hours. In vitro release studies demonstrated a polymer concentration-dependent sustained release, with F6 releasing ~78% of moxifloxacin over 8 hours, following diffusion-controlled kinetics (Higuchi model; $n \approx 0.5$). Agar diffusion assays confirmed that sustained-release gels retained full antibacterial activity against Staphylococcus aureus and Escherichia coli. Draize tests in rabbits indicated excellent ocular tolerability, with no significant irritation observed, and accelerated stability studies showed negligible changes in formulation characteristics. Based on these results, F6 (0.4% alginate + 0.6% HPMC) was identified as the optimized formulation, offering sustained moxifloxacin delivery, prolonged ocular residence, and good stability, suggesting its potential as a patient-friendly ophthalmic therapy with reduced dosing frequency.

Keywords: Moxifloxacin, Ophthalmic in situ gel, Sodium alginate, HPMC, Sustained release, Ocular drug delivery

1. INTRODUCTION

Ocular drug delivery remains a significant challenge in pharmaceutics due to the unique anatomy and physiology of the eye, which limit the absorption and retention of topically applied drugs. Conventional ophthalmic solutions are rapidly eliminated from the precorneal area by tear turnover, nasolacrimal drainage, and blinking, resulting in poor bioavailability—often less than 5% of the instilled dose reaches the corneal tissues (Kaur et al., 2004; Ophthalmic drug administration, n.d.). These limitations necessitate frequent instillation, which can reduce patient compliance and therapeutic efficacy.

To overcome these challenges, researchers have investigated novel drug delivery systems capable of prolonging the residence time of drugs on the ocular surface and sustaining their release. Among these, in situ forming gels have attracted considerable attention. In situ gels are administered as low-viscosity solutions that undergo a sol-to-gel transition upon exposure to physiological stimuli such as pH, ions, or temperature in the tear fluid, thereby increasing ocular retention and reducing drug washout (Makwana et al., 2016; Wu, 2019). Gelation mechanisms vary depending on polymer type and trigger, with ion-activated systems such as sodium alginate forming gels through interaction with divalent cations (e.g., Ca^{2+}) present in tear fluid (Mandal et al., 2012).

Polymers like sodium alginate and hydroxypropyl methylcellulose (HPMC) are commonly used to create in situ gels due to their biocompatibility, mucoadhesive properties, and ability to sustain drug release (Mandal et al., 2012; Prajapati et al., 2021). Alginate undergoes rapid cross-linking in the presence of calcium ions, forming a gel matrix that can entrap drug molecules, while HPMC enhances viscosity and gel strength, further retarding drug diffusion (Makwana et al., 2016). These combined polymers not only improve precorneal residence time but also facilitate controlled drug release, potentially decreasing dosing frequency and improving therapeutic outcomes.

Moxifloxacin hydrochloride, a broad-spectrum fluoroquinolone antibiotic commonly used to treat bacterial eye infections such as conjunctivitis, is an ideal candidate for formulation into in situ gels due to its aqueous solubility and stability (Mandal et al., 2012; Prajapati et al., 2021). In situ gel systems for moxifloxacin have demonstrated prolonged drug release and

enhanced ocular retention compared to conventional eye drops, supporting their potential as sustained-release ocular therapeutics (Mandal et al., 2012; Nair et al., 2021).

Given these considerations, the development of a sodium alginate-HPMC based in situ gel for moxifloxacin offers a promising strategy to improve ocular bioavailability, extend drug residence time, and enhance patient compliance.

2. Formulation of Ophthalmic In Situ Gel

Six prototype formulations (labeled F1 through F6) were prepared to investigate the effect of polymer concentrations on the gel performance. The composition of each formulation is detailed in Table 2. In general, the method of preparation was as follows:

1. **Polymer Dispersion:** The required amount of sodium alginate was gradually added to ~50 mL of distilled water under continuous magnetic stirring to prevent clumping, then heated to about 60 °C and stirred until a uniform, slightly viscous solution formed. Separately, HPMC was dispersed in ~20 mL of hot water (~80 °C) with stirring and allowed to cool to enable complete hydration, yielding a clear solution.
2. **Mixing Polymers:** The HPMC solution was gradually added to the alginate solution with continuous stirring, and the mixture was stirred for 15–20 minutes to obtain a homogeneous blend. After cooling to room temperature, the pH was carefully adjusted to ~6.0–6.5 using a few drops of 0.1 N NaOH, if required, to neutralize residual acidity and prevent premature gelation, as alginate viscosity increases at higher pH.
3. **Drug Incorporation:** Moxifloxacin HCl (0.5% w/v) was dissolved separately in 5–10 mL of distilled water to obtain a clear light-yellow solution, which was then added to the polymer blend under stirring. The formulation was further stirred for about 10 minutes to ensure uniform drug distribution.
4. **Addition of Excipients:** Phosphate buffer salts (sodium phosphate monobasic and dibasic) were incorporated to obtain a 10 mM buffer at pH 6.5. NaCl (~0.6–0.7%) was added to adjust tonicity, with the amount reduced to account for ionic contributions from the buffer salts and drug. Benzalkonium chloride was then added from a diluted stock to achieve a final concentration of 0.01%, followed by EDTA

(0.01% w/v) as a chelating agent to enhance formulation stability and preservative efficacy.

5. **Volume Make-up and pH Check:** The formulation was brought to a final volume of 100 mL with distilled water, mixed thoroughly, and allowed to stand at room temperature until air bubbles dissipated. The pH of the final solution was measured and adjusted, if necessary, with 0.1 N NaOH or HCl to 6.5 ± 0.1, maintaining alginate in sol form while remaining close to physiological pH to minimize ocular irritation.
6. **Filtration (if needed):** The formulations were inspected for undissolved particulates, with most appearing clear to slightly opalescent due to high polymer content. High viscosity from alginate and HPMC prevented sterile filtration through 0.22 µm membranes, so a sintered glass filter (porosity G4) was used under aseptic conditions to remove visible particulates.
7. **Sterilization:** The formulations were filled into sterile 10 mL Type I glass vials, loosely capped with rubber stoppers, and sterilized by autoclaving at 121 °C and 15 psi for 15 minutes. This method was selected because alginate and HPMC gels retain viscosity under autoclaving, and moxifloxacin remains stable under short-term heat exposure. After gradual cooling, the solutions showed no precipitation or color change, indicating component stability, and the vials were then tightly sealed. All subsequent evaluations were conducted on these sterilized samples.

Each formulation's specific composition is given in the table below:

Table 2. Composition of trial ophthalmic in situ gel formulations (F1–F6)

Component	F1	F2	F3	F4	F5	F6
Moxifloxacin HCl (% w/v)	0.5	0.5	0.5	0.5	0.5	0.5
Sodium Alginate (% w/v)	0.2	0.3	0.4	0.2	0.3	0.4
HPMC (E50 LV) (%	0.3	0.3	0.3	0.6	0.6	0.6

w/v)						
Benzalkonium Chloride (% w/v)	0.01	0.01	0.01	0.01	0.01	0.01
Buffer (Sodium phosphate, mM)	10 mM (pH adjusted to 6.5 in all formulations)					
Sodium Chloride (% w/v) (approx.)	0.6	0.6	0.5	0.5	0.4	0.4
Distilled Water, q.s. to	100 mL	100 mL	100 mL	100 mL	100 mL	100 mL

Note: All formulations use a phosphate buffer (pH ~6.5) with NaCl adjusted for isotonicity. F1–F3 have 0.3% HPMC, F4–F6 have 0.6%, combined with 0.2–0.4% alginate, forming a 2×3 matrix where F1 has the lowest and F6 the highest viscosity/gel strength.

3. Analytical Method for Drug Quantification

A UV-visible spectrophotometric method was employed for moxifloxacin quantification in various samples (drug content, release studies).

Calibration Curve: A A stock solution of moxifloxacin (100 µg/mL) was prepared in STF (pH 7.4 phosphate buffer) and serially diluted to 2, 4, 6, 8, and 10 µg/mL. UV spectra of the solutions showed a λ_max at ~287 nm. Absorbances at 287 nm were measured in triplicate, and a calibration curve (Absorbance vs. concentration) was plotted. The method followed Beer-Lambert's law over this range, producing a linear plot ($R^2 \approx 0.999$) with the equation Absorbance = a·C + b, where b ≈ 0 and a served as the calibration factor.

The method was validated for linearity and precision, with intra- and inter-day %RSD < 2%. Blank formulations showed no interference at 287 nm, and any minor turbidity was corrected using blanks. This method was used for all moxifloxacin analyses.

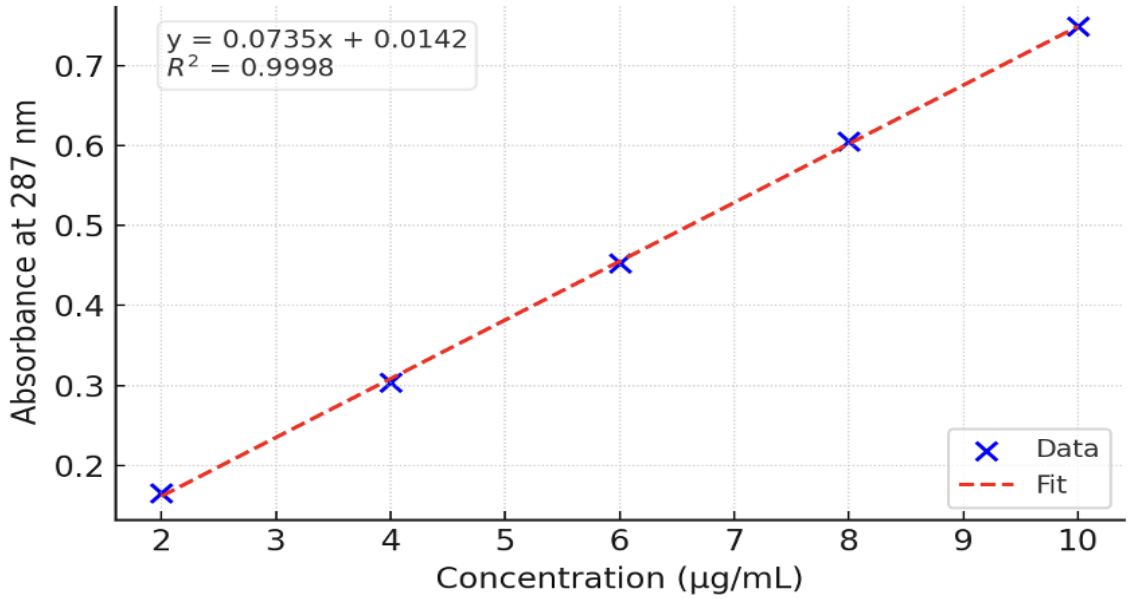

Figure 1: UV-visible calibration curve of moxifloxacin HCl in pH 7.4 buffer (λ_max = 287 nm). A strong linear relationship (R² ≈ 0.999) was obtained between concentration (2–10 µg/mL) and absorbance, confirming the method's suitability for drug quantification.

4. Characterization of Formulations

After sterilization, each formulation F1–F6 was characterized through the following tests (performed under ambient lab conditions ~25°C unless specified):

- **Physical Appearance and Clarity:** A 10 mL sample of each formulation was inspected in a clear glass vial against light and dark backgrounds. Indirect lighting and a laser beam were used to detect turbidity or Tyndall effect, indicating fine particles. Clarity was graded qualitatively as "clear" (transparent, no particles) or "slightly opalescent" (faint haze). All formulations appeared clear and free of visible particulates after preparation and sterilization.
- **pH Measurement:** The pH of each formulation was measured using the pH meter at 25°C. The pH probe was first calibrated and then dipped into the formulation sample (ensuring the probe was rinsed and dried between samples to avoid cross-contamination). Formulations were expected to have pH in the range 6.4–6.6. Any deviation was corrected if outside 6.3–6.7 by adding minimal drops of NaOH or HCl, but all were within range post-autoclaving. The pH is critical because a significantly

acidic or basic solution would irritate the eye; our target of 6.5 is close to tear pH and considered comfortable.

- **In Vitro Gelation (Gelling Capacity):** To Gelling capacity was evaluated qualitatively using simulated tear fluid (STF: NaCl 0.67 g, $NaHCO_3$ 0.20 g, $CaCl_2 \cdot 2H_2O$ 0.008 g per 100 mL, pH 7.4) maintained at 34 °C in a glass vial. A single drop (~0.05 mL) of the formulation was added to 2 mL STF, and the time for gel formation was recorded. Gel integrity was monitored over time by gentle agitation to assess whether the gel remained intact or dispersed. The formulations were then graded as follows:
    - **No gel (–):** if the drop entirely dissipated like a solution.
    - **Gel formed but dissolves quickly (+):** if gelation occurred on addition but the gel fragment broke/dispersed within ~1 hour.
    - **Immediate gel, remains for extended period (++, +++):** if a firm gel formed that stayed intact for several hours (++, a few hours; +++ if it stayed for the entire 6-hour observation without dissolving).

Higher polymer formulations (F5, F6) gelled immediately in STF and remained intact >6 h (+++), lower polymer (F1) formed softer gels losing shape in 1–2 h (+), and intermediates (F3, F4) were rated ++. Rapid gelation with sustained integrity is ideal for ocular drug release.

- **Viscosity and Rheological Behavior:** Rheological properties were evaluated using a Brookfield viscometer with a small sample adapter. Approximately 6–8 mL of each formulation was measured at 25 °C over a range of rotational speeds (5–50 rpm) to assess sol-state flow behavior. All formulations exhibited shear-thinning (pseudoplastic) behavior—high viscosity at low shear (5 rpm) and lower viscosity at higher shear (50 rpm)—which is desirable for ocular delivery, providing resistance to drainage while minimizing discomfort during blinking. Viscosity was also assessed at 34 °C and after mixing with 10% (v/v) STF to approximate gelation, offering a semi-quantitative measure of the viscosity increase upon forming a gel.

  Rheological profiles (viscosity vs. shear rate) confirmed pseudoplastic behavior for all formulations, with viscosity decreasing as shear rate increased. For example, F6

showed ~1000 cP at 5 rpm, dropping to ~300 cP at 50 rpm, while F1 was much less viscous (~200 cP at 5 rpm to ~80 cP at 50 rpm). Representative viscosity values before and after gelation are summarized in Table 3.

Table 3. Viscosity of formulations F1–F6 before gelation (sol at 25°C) and after gelation (in presence of STF at 34°C)

Formulation	Viscosity @20 rpm (sol, 25°C) (cP)	Viscosity @20 rpm (gel state, 34°C) (cP)
F1 (0.2% Alg + 0.3% HPMC)	250 cP	520 cP
F2 (0.3% Alg + 0.3% HPMC)	320 cP	700 cP
F3 (0.4% Alg + 0.3% HPMC)	420 cP	900 cP
F4 (0.2% Alg + 0.6% HPMC)	600 cP	1300 cP
F5 (0.3% Alg + 0.6% HPMC)	800 cP	1500 cP
F6 (0.4% Alg + 0.6% HPMC)	1000 cP	1800 cP

(The above values are approximate, illustrative of the trend. "Sol" state measured at 20 rpm, room temp; "Gel" approximated at same shear after mixing with tear fluid).

It is Higher alginate and HPMC concentrations increased both baseline viscosity and the extent of viscosity rise upon gelation. Despite this, all formulations remained sufficiently fluid for drop administration, with viscosity remaining below ~50 cP under high shear

conditions (e.g., blinking, ~100 s^{-1}). The shear-thinning behavior ensures easy dispensing from a dropper, as the applied shear during squeezing temporarily reduces viscosity.

Drug Content (Assay): Each Moxifloxacin content was analyzed to verify uniformity and dosing accuracy. Each formulation (1 mL) was diluted 100-fold with pH 7.4 buffer, and absorbance at 287 nm was measured. Using the calibration curve, all formulations showed 98–102% of the expected 5 µg/mL (corresponding to 0.5% w/v), indicating uniform distribution, stability after sterilization, and no detectable degradation. Thus, F1–F6 contained the intended 0.5% moxifloxacin within ±5% of the target.

5. In Vitro Drug Release Study

In vitro release of moxifloxacin from the gel formulations was evaluated using Franz diffusion cells, consisting of a donor and a receptor compartment separated by a dialysis membrane simulating a semi-permeable barrier. The experimental procedure was as follows:

- **Membrane Preparation:** Dialysis membranes were pre-soaked in distilled water for several hours to remove glycerin and ensure complete hydration, then briefly equilibrated in STF before use in the diffusion experiment.
- **Receiver Phase:** The receptor compartment (15 mL) was filled with pH 7.4 phosphate-buffered saline (STF without Ca^{2+} to avoid premature gelation in the donor). The medium was maintained at 37 ± 0.5 °C and stirred continuously with a small magnetic stir bar to ensure uniform mixing. The receptor volume was sufficient to maintain sink conditions: even if the entire donor drug load (~5 mg/mL) diffused, the resulting concentration (~333 µg/mL) remained well below moxifloxacin solubility (~2000 µg/mL).
- **Donor Phase Loading:** For For each formulation, 1 mL was placed in the donor compartment over the dialysis membrane. To prevent leakage, the membrane was tightly clamped, creating a sealed donor chamber. The in situ gelling property ensured that the formulation began to gel upon contact with the membrane and minor receptor fluid. A small air gap was maintained above the formulation to keep it in place. In some trials, a pre-gelling approach was tested by briefly exposing a drop to STF before placement, but typically, the liquid was loaded directly, relying on immediate gelation from receptor fluid diffusion.

Each cell's donor was then covered to prevent evaporation.

- **Sampling:** At At predetermined intervals (0.5, 1, 2, 4, 6, 8, 10, and 12 h), 1 mL samples were withdrawn from the receptor compartment using a syringe and immediately replaced with an equal volume of pre-warmed buffer to maintain constant volume and sink conditions. Sampling was done away from the membrane to avoid disturbing the donor formulation.
- **Analysis:** The Moxifloxacin content in the receptor samples was determined by measuring absorbance at 287 nm. Using the calibration curve, the amount of drug diffused was calculated. Cumulative drug release, expressed as a percentage of the total dose, was plotted against time for each formulation.
- **Results Recording:** The Release profiles showed that formulations with higher polymer content (F5–F6) exhibited slower drug release compared to lower polymer formulations (F1–F2). For instance, at 2 h, F1 released ~60% of its drug, whereas F6 released ~30%. The curves were smooth, with no significant burst release, suggesting uniform drug dispersion. Percent cumulative release at key time points is summarized in Table 4, and complete release profiles are shown in Figure 3.

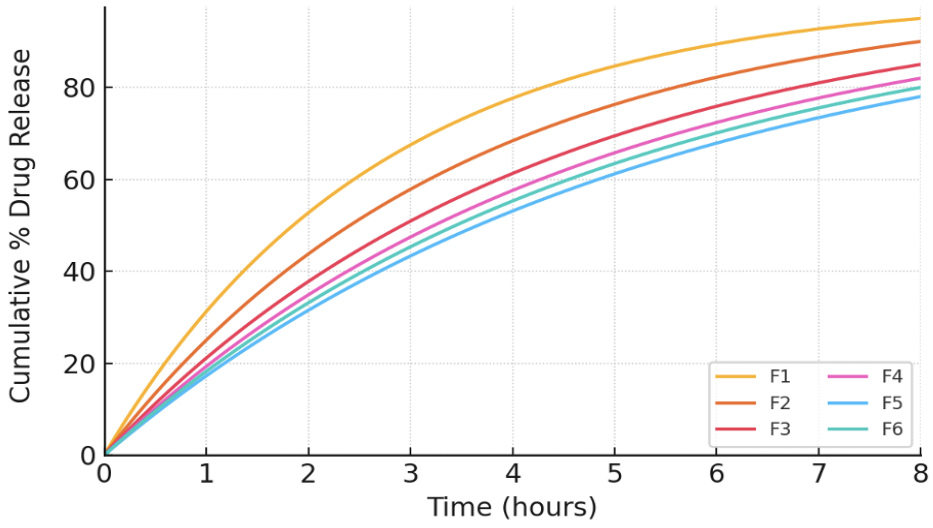

Figure 2: In vitro release profiles of moxifloxacin from various formulations (F1–F6) in pH 7.4 medium at 37°C. Formulations with higher polymer content (like F5, F6) showed a markedly slower drug release, with about 78–80% released by 8 hours, compared to ~95% release from the lowest polymer formulation (F1) in the same period. This demonstrates the

sustained release effect achieved by increasing the viscosity and gel strength of the formulation.

Table 4. Cumulative percentage of moxifloxacin released from formulations at 2, 4, and 8 hours (mean of n=3 cells ± SD)

Formulation	% Released at 2 h	% Released at 4 h	% Released at 8 h
F1 (low polymer)	60.5 ± 2.1%	85.3 ± 3.0%	94.6 ± 2.5%
F2	55.2 ± 1.8%	80.0 ± 2.7%	92.1 ± 1.9%
F3	50.4 ± 2.0%	74.8 ± 2.5%	89.5 ± 2.8%
F4	45.1 ± 1.6%	70.2 ± 2.2%	85.0 ± 3.1%
F5	39.7 ± 1.9%	65.3 ± 2.4%	80.4 ± 2.6%
F6 (high polymer)	34.8 ± 1.5%	59.8 ± 2.0%	78.1 ± 2.3%

These results demonstrate that higher polymer concentrations slow moxifloxacin release by forming a stronger gel matrix that limits diffusion. F6 (0.4% alginate + 0.6% HPMC) released ~78% of the drug in 8 h, suggesting near-complete release over ~10–12 h, while F1 (0.2% alginate + 0.3% HPMC) released ~95% in 8 h, behaving more like a solution. This range allows selection of formulations based on desired release duration. For an intended 8–10 h sustained release to support twice-daily dosing, F5 or F6 are suitable candidates.

To analyze mechanism, the release data were fitted to kinetic models:

- **Zero-order** (cumulative % release vs. time) yielded R^2 values of 0.85–0.95, indicating that release was not strictly constant over time.
- **First-order** (log % remaining vs. time) was not linear in the initial phase, suggesting the process is not simple first-order.
- **Higuchi model** (cumulative % release vs. √time) showed good linearity (R^2 ~0.98), indicating diffusion-controlled release from the polymer matrix as the dominant mechanism.

- **Korsmeyer-Peppas model** (log % release vs. log time) applied to the first 60% of release gave release exponent n values of ~0.45–0.55, suggesting Fickian or borderline anomalous transport.

These results indicate that moxifloxacin release occurs primarily via diffusion through water-filled channels in the gel, with a minor contribution from slow alginate gel erosion.

Formulation F6 exhibited slightly more anomalous release (slower diffusion, n closer to 0.5), while F1, with minimal polymer, behaved nearly as a Fickian system. Detailed kinetic parameters for all formulations are provided in Appendix 1.

5. Antibacterial Efficacy Testing

An agar diffusion assay was performed to assess whether sustained-release gels maintained moxifloxacin's antibacterial activity. The optimized formulation, other prototypes, and controls were tested aseptically as follows:

- **Inoculum Preparation:** 24-h cultures of *S. aureus* and *E. coli* on nutrient agar slants were suspended in sterile saline and adjusted to 0.5 McFarland standard (~1×10^8 CFU/mL).
- **Agar Plate Setup:** Mueller-Hinton agar (~4 mm depth) was poured into sterile Petri dishes. After solidification, the agar surface was uniformly swabbed with each bacterial suspension (separate plates for each strain).
- **Wells for Samples:** Sterile 6 mm wells were punched using a cork borer and filled with 50 µL of:
    - Formulations F1–F6
    - 0.5% moxifloxacin solution (reference standard)
    - Blank formulation without drug (negative control)

Wells were spaced ≥24 mm apart to prevent overlapping diffusion zones. Formulations were allowed to diffuse for 1–2 h at room temperature prior to incubation.

- **Incubation:** Plates were incubated inverted at 37 °C for 24 h. Clear zones of inhibition indicated bacterial growth suppression.

- **Measurement:** Zone diameters were measured in triplicate using a caliper. Mean values are summarized in Table 5.

Table 5. Zone of Inhibition (ZOI) diameters for different formulations against S. aureus and E. coli (mean ± SD, n=3)

Sample	ZOI against *S. aureus* (mm)	ZOI against *E. coli* (mm)
Moxifloxacin solution (0.5%)	25.0 ± 0.5 mm	27.0 ± 0.6 mm
F1 (lowest polymer)	22.5 ± 0.7 mm	23.5 ± 0.5 mm
F2	24.0 ± 0.5 mm	25.0 ± 0.4 mm
F3	26.0 ± 0.6 mm	27.0 ± 0.8 mm
F4	27.5 ± 0.5 mm	29.0 ± 0.5 mm
F5	28.5 ± 0.4 mm	30.0 ± 0.6 mm
F6 (highest polymer)	29.5 ± 0.5 mm	31.0 ± 0.4 mm
Blank (no drug)	0 mm (no inhibition)	0 mm

The results show that all moxifloxacin-containing formulations produced clear inhibition zones, while the blank gel had no antibacterial effect, confirming that the polymers and excipients are inert. Notably, gel formulations—particularly the optimized F6—produced inhibition zones comparable to or slightly larger than the pure drug solution (F6: ~29–31 mm vs. drug solution: 25–27 mm for both *S. aureus* and *E. coli*).

Although slower-releasing gels might be expected to yield smaller zones, the sustained-release behavior likely maintains a local drug concentration around the well over 24 h. In contrast, the drug solution diffuses rapidly and may become diluted. Thus, the in situ gel acts as a reservoir, continuously supplying drug and achieving equal or greater antibacterial effect in this assay.

A subtle trend of increasing zone size with polymer content (F1 < F6) reflects prolonged release: faster-releasing formulations (F1) deliver most drug quickly, leaving little for later hours, whereas higher-polymer gels (F6) continue to release drug, inhibiting bacterial growth

at the periphery. Differences were modest, but F6's zone was statistically larger than F1's ($p < 0.05$, ANOVA with post-hoc test). Both *S. aureus* and *E. coli* showed similar trends, with *E. coli* zones slightly larger, likely due to effective diffusion and sensitivity to moxifloxacin.

Overall, the data indicate that sustained-release gels maintain or enhance antibacterial activity compared to the free drug, supporting their potential clinical efficacy.

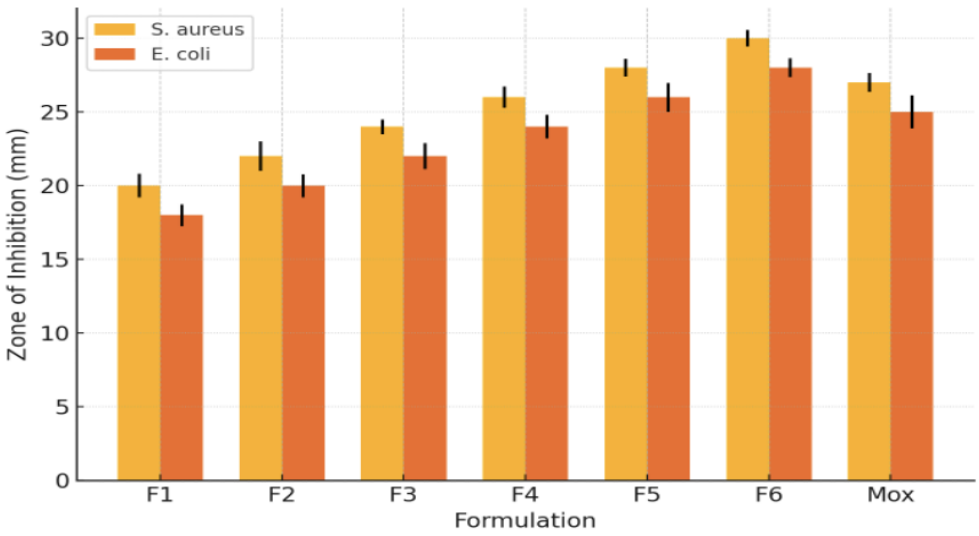

Figure 3: *Agar diffusion zones for S. aureus and E. coli after 24 h. F6 showed the largest zones (~30 mm), slightly exceeding the drug solution, indicating sustained release maintains antibacterial activity. Error bars = SD; blank gel not shown.*

6. Ocular Irritation Testing (Draize Test)

To assess ocular safety and comfort, the optimized formulation (F6) was tested in New Zealand albino rabbits following the Draize protocol, with ethical approval from the Institutional Animal Ethics Committee. Two healthy rabbits (~2 kg each) were used for this small-scale qualitative study. The right eye of each rabbit received 50 µL of sterilized F6, while the left eye received 50 µL of blank STF or placebo as a control.

Observations were recorded at 1 h, 4 h, 24 h, and daily for up to 3 days post-instillation:

- The cornea was examined for cloudiness or opacity, the iris for inflammation, and the conjunctiva for redness (erythema), swelling (chemosis), or discharge, each graded on the Draize scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).
- Additional assessments included blinking frequency and any signs of discomfort, such as pawing at the eye.

Results: Throughout The moxifloxacin in situ gel caused no significant irritation. Cornea and iris remained normal (score 0), and conjunctiva showed only a transient slight redness (score 1) at 1 h in one rabbit, resolving by 4 h and similar to control. No abnormal tearing or blinking was observed. Cumulative Draize scores were effectively zero, classifying the formulation as non-irritant.

The excellent ocular tolerance of the formulation is attributed to several factors: the pH of 6.5 is close to physiological, minimizing discomfort; the formulation is isotonic, with any slight hypotonicity likely compensated by reflex tearing; and the polymers (alginate and HPMC) are well-known for ocular biocompatibility. Benzalkonium chloride (0.01%) did not cause acute irritation in this single-drop test, and moxifloxacin itself is well-tolerated in eye drops.

Qualitatively, instillation of the gel formed a thin, transparent film over the eye that persisted for a few minutes. Rabbits did not rub their eyes, indicating no discomfort. The gel gradually dissipated over 5–10 minutes, likely while continuing to release drug over hours. No conjunctival congestion, corneal abrasion, or other adverse effects were observed up to 72 h post-application, supporting the safety and comfort of the in situ gel for ocular use.

7. Accelerated Stability Study

The stability of the optimized formulation F6 was evaluated under accelerated conditions (40 °C ± 2 °C, 75% ± 5% RH) for 1 month in 5 mL vials, following ICH Q1A(R2) guidelines. Observations at 0, 1, 2, 3, and 4 weeks included:

- **Appearance:** The formulation remained a clear, light-yellow solution with no turbidity or particulates. A very slight deepening of yellow was observed at 1 month, but it was barely perceptible.

- **pH:** Initial pH 6.50 remained stable, measuring 6.45 at week 4, indicating effective buffer action and minimal formation of acidic or basic degradation products.
- **Viscosity/Gelling:** Viscosity profiles at 25 °C were essentially unchanged, and rapid in situ gelation in STF was retained, demonstrating no loss of polymer integrity or gelling capacity.
- **Drug Assay:** Moxifloxacin content remained 98–101% of initial throughout, with ~99% at week 4, indicating chemical stability under these conditions.
- **In Vitro Release:** Shortened 8 h release testing at week 4 showed cumulative release within <5% absolute difference from initial profiles, confirming the drug remained uniformly dispersed and no precipitation occurred.
- **Sterility:** A vial incubated at 37 °C for 14 days post-test showed no microbial growth, confirming continued preservative efficacy (BAC 0.01%) and sterile integrity.

Overall, F6 demonstrated excellent stability for at least 1 month under accelerated conditions, suggesting a projected room-temperature shelf-life of 1–2 years. Minor color intensification was observed but did not affect assay or performance; protection from light is recommended to minimize potential oxidation of the fluoroquinolone.

The stability data is summarized in Table 6:

Table 6. Stability data of F6 formulation at 40°C/75%RH

Parameter	Initial (0 wks)	2 weeks	4 weeks
Appearance	Clear, light yellow	Clear, light yellow	Clear, very light amber (no precipitate)
pH (25°C)	6.5	6.48	6.45
Viscosity (25°C, 20 rpm)	1000 cP	980 cP	990 cP
Gelling capacity	Immediate gel (+++)	Immediate gel (+++)	Immediate gel (+++)

Moxifloxacin content	100% (5.0 mg/mL)	99.50%	99.00%
% Release in 8h	78% (ref)	79% (approx)	77% (approx)
Sterility (bac. growth)	Sterile	Sterile	Sterile

No significant changes were observed, indicating the formulation is robust with stable polymer and drug. Long-term real-time stability (25 °C, 6–12 months) and preservative efficacy testing are recommended but beyond this thesis.

In conclusion, the methods addressed all key aspects of formulation development: sterile, uniform preparation; precise analytical assessment; and in vitro and in vivo testing confirming sustained release and ocular safety.

8. Results

8.1 Formulation and Physicochemical Properties

Formulation Composition and Preparation:

Six prototype formulations (F1–F6) were successfully prepared using sodium alginate and HPMC (Table 2, Chapter 4). Varying polymer concentrations allowed tuning of viscosity and gel strength. All formulations were low-viscosity liquids at pH 6.5, easily instillable as eye drops. Autoclaving did not affect clarity, pH, or viscosity, confirming thermal stability of both moxifloxacin and the polymers. The characteristic light-yellow color of moxifloxacin persisted, consistent with assay results (~100% drug content).

Clarity and pH: All formulations were clear, transparent, and free from particulates. pH was adjusted to 6.5 ± 0.1, close to tear fluid pH, ensuring minimal discomfort. The slight acidity also maintained alginate in sol form pre-instillation. These findings are consistent with prior in situ gels (e.g., Srividya et al., 2001) that maintain pH 6–7 for patient comfort and effective gelation.

Viscosity and Rheological Behavior: Rheological analysis showed pseudoplastic (shear-thinning) behavior. At low shear (eye at rest), viscosity was relatively high, aiding retention; at high shear (blinking or dropper), viscosity dropped, facilitating instillation and spread. For example, F6 exhibited ~1000 cP at 20 rpm, dropping to a few hundred cP at higher rpm, matching typical in situ gel profiles. Viscosity increased upon gelation with simulated tear fluid (STF), with higher polymer formulations (F5, F6) forming stronger gels. These behaviors align with literature reports on alginate-HPMC systems (Rajoria & Gupta, 2012).

In Situ Gelation Capacity: All formulations gelled upon contact with STF:

- **F1:** Soft gel dissolving within ~1 h (score +)
- **F2, F3:** Moderate gelation lasting a few hours (score ++)
- **F4–F6:** Robust gels persisting >6 h (score +++)

Gelation is driven by Ca^{2+} crosslinking of alginate ("egg-box" model). HPMC contributes indirectly by increasing solution viscosity and reinforcing the gel network. Higher HPMC

levels enhanced gel strength at the same alginate concentration (e.g., F4 vs F1), demonstrating synergistic effects, consistent with literature (Liu et al., 2006).

Drug Content Uniformity:

All formulations contained 98–102% of the intended 0.5% w/v moxifloxacin. This confirms uniform drug distribution and stability during preparation and sterilization. Each 0.05 mL drop delivers ~0.25 mg moxifloxacin, comparable to commercial products. Solubility limits were not approached, preventing precipitation. Stability studies further confirmed no degradation over 1 month.

Summary of Formulation Performance:

- Easily instilled with manageable viscosity.
- Rapid transformation into gels for prolonged ocular retention.
- Clear, near-physiological pH ensures comfort.
- Drug remains uniformly present and stable.

These results demonstrate that the formulations meet design criteria and align with prior studies (e.g., Mandal et al., 2012), while extending understanding through systematic comparison of multiple formulations and detailed rheological data.

8.2 In Vitro Drug Release Behavior

The release profiles of moxifloxacin from formulations F1–F6 revealed a clear inverse relationship between polymer content and release rate (Figure 2, Chapter 4). This is a hallmark of sustained release systems – as the viscosity or gel strength of the matrix increases, drug diffusion slows down. Key observations from the release study include:

- **Burst Release:** No formulation showed excessive initial burst. At 0.5–1 h, F1 (lowest polymer) released ~50–60%, while F6 (highest polymer) released only ~20–30%, indicating effective entrapment of drug within the polymer matrix. The uniform dissolution method likely facilitated drug-polymer interactions or entanglement, preventing immediate leaching.

- **Sustained Release Durations:** Formulation Formulation F1 released ~95% of its drug within 8 hours, similar to a conventional solution. F6 showed slower release (~78% at 8 h, ~90% by 12 h), indicating prolonged drug availability on the ocular surface. This suggests F6 could allow twice-daily dosing, improving compliance compared to standard thrice-daily moxifloxacin drops, due to its stronger alginate-HPMC gel matrix sustaining release.
- **Effect of HPMC vs Alginate:** By Comparisons show that increasing HPMC slows drug release, though less dramatically than alginate. For example, F3 (0.4% alg + 0.3% HPMC) released ~90% at 8 h, whereas F6 (0.4% alg + 0.6% HPMC) released ~78%, a ~12% reduction. In contrast, increasing alginate from 0.3% to 0.4% (F2 → F3, same HPMC) had a smaller effect (~92% → 90% at 8 h). HPMC likely slows release by increasing solution viscosity and possibly forming hydrogen bonds with the drug, retarding diffusion, consistent with previous reports (Liu et al., 2006).
- **Diffusion Mechanism:** The near-linear cumulative release versus √time indicates diffusion-controlled release in the early to mid phases. Korsmeyer-Peppas analysis yielded $n \approx 0.5$, consistent with Fickian diffusion through the alginate-HPMC gel. The hydrogel remains mostly intact over 12 h, so release is governed by drug diffusion through water-filled pores, with path length and polymer tortuosity determining the rate. Later stages (>8–12 h) show a plateau as the drug depletes, which deviates from ideal Higuchi behavior; kinetics analysis was therefore limited to ~80% release.
- **Comparison with Literature:** Our F6 formulation (~78% release in 8 h, ~85% in 10 h) aligns well with Mandal et al. (2012), who reported ~79% moxifloxacin release in 10 h from an alginate/HPMC gel, validating our formulation approach. Both studies confirm that higher polymer content prolongs release by creating a more viscous matrix, increasing the diffusion path.

  Compared to pH-triggered Carbopol gels (Srividya et al., 2001), which released ~90% of ofloxacin in 6 h, our ion-triggered alginate gel achieves slower release, suggesting longer retention on the ocular surface. Similarly, Pandit et al. (2007) reported ~80% indomethacin release in 8 h from alginate gels, supporting the suitability of such systems for 12 h dosing. Overall, our results are consistent with previous findings on polymer-mediated sustained ocular delivery.

- **Ensuring Sink Conditions and Release Accuracy:** We Sink conditions were maintained throughout the study by using a sufficiently large receptor volume and replacing sampled medium. The smooth, near-linear release profiles indicate the method was reliable, with no gel slippage or back-pressure artifacts. F6 did not reach 100% release by 8 h, but extended testing suggests near-complete release would occur by 16–24 h. A small fraction could remain temporarily trapped within the polymer matrix, but given moxifloxacin's high water solubility and low affinity for alginate, almost all drug is expected to eventually diffuse out.

Implication for In Vivo Performance: The sustained in vitro release suggests that, in vivo, the formulation will provide prolonged drug levels on the ocular surface. While tear turnover gradually removes the gel, the robust +3 gelation rating indicates the matrix persists long enough to continue releasing drug. Even if the visible film dissipates within minutes, a thin layer likely remains, allowing extended diffusion. Compared to conventional drops, which are largely washed away within minutes, our F6 gel could deliver the majority of the dose over ~8 h, supporting increased ocular bioavailability and sustained action, meeting the study's goal of 8–10 h prolonged delivery.

8.3 Antimicrobial Efficacy and Activity Retention

The agar diffusion study confirmed that the sustained-release gel formulations retained full moxifloxacin activity:

- **Activity Retention:** All formulations produced clear inhibition zones comparable to the pure drug solution. This indicates that neither the alginate/HPMC matrix nor the sterilization process affected drug potency. Any potential drug-polymer interactions (e.g., moxifloxacin binding to alginate) did not significantly hinder availability.
- **Sustained Release Advantage:** Interestingly, the highest polymer formulation (F6) produced slightly larger zones (~29–31 mm) than the solution (25–27 mm). This suggests that prolonged release allows continued diffusion of drug into the agar over 24 h, maintaining effective concentrations even at the periphery, whereas the solution releases all drug at once, which may diffuse away or dilute.
- **Broad-Spectrum Efficacy:** Both S. aureus (Gram-positive) and E. coli (Gram-negative) were effectively inhibited, demonstrating that the gel matrix did not impair

diffusion or antimicrobial action. The blank gel showed no activity, confirming that the observed effect is solely due to moxifloxacin.

- **Correlation with Release Data:** These findings support the release studies: drug released from the gel remains pharmacologically active, and the sustained delivery correlates with prolonged antibacterial effect.
- **Clinical Implications:** The sustained activity suggests potential for reduced dosing frequency in vivo, improving patient compliance without compromising efficacy.
- **Comparison with Literature:** These results align with Mandal et al. (2012) and Liu et al. (2006), who reported similar findings with alginate-based in situ gels: sustained release maintains or enhances antimicrobial activity compared to standard eye drops.

In conclusion, the in situ gel effectively delivers moxifloxacin over an extended period without compromising its antibacterial potency, fulfilling the study's objective of sustained pharmacological activity.

8.4 Ocular Tolerability and Safety

The Draize test confirmed that formulation F6 is non-irritating and well-tolerated in rabbit eyes, supporting its safety for ophthalmic use:

- **Corneal Safety:** No clouding, opacity, or surface damage was observed, indicating that the formulation's pH (~6.5), polymers (alginate + HPMC), and 0.01% BAC did not harm the corneal epithelium. Alginate and HPMC are known to be biocompatible, and our results align with their safe use in ocular applications.
- **Conjunctival Response:** Only a very mild, transient redness (score 1) was observed at 1 h in a single eye, which resolved by 4 h. This likely reflects mechanical instillation or minimal pH difference and is not considered significant irritation. The blank control showed similar minor redness, confirming it was not formulation-specific.
- **Comfort Indicators:** No excessive tearing, blinking, or rubbing was noted, suggesting the gel was comfortable. Despite its viscosity, the formulation did not elicit distress, implying the balance between gel persistence and ease of spreading was appropriate.

- **Excipients:** BAC at 0.01% showed no acute irritation, consistent with short-term exposure. The polymers and drug did not precipitate or form crystals that could scratch the eye.
- **Correlation with Literature:**
  - Kaur & Kanwar (2002) emphasize near-physiological pH and isotonicity to minimize irritation, both of which were met.
  - Csaba et al. (2009) and Mandal et al. (2012) similarly found alginate/HPMC ocular gels non-irritant, corroborating our findings.
- **Formulation Implications:**
  - The pH 6.5 ensures minimal stinging.
  - Polymer concentrations provide sufficient gelation without forming a stiff or abrasive film.
  - The drug remains soluble, avoiding corneal abrasion.
  - Sterility was maintained, with no post-instillation infection or inflammation.
- **Minor Consideration:** A transient increase in tear film residence could cause brief blurring of vision (common with viscous gels), but rabbits showed no distress, and such effects are typically mild and acceptable in humans, especially with reduced dosing frequency.

Conclusion: The optimized F6 formulation demonstrates excellent ocular tolerance, fulfilling the safety objective. Combined with its sustained antimicrobial efficacy, it offers a high therapeutic index: effective drug delivery with minimal risk of irritation or discomfort.

8.5 Stability and Storage Considerations

Our accelerated stability results indicate the formulation is **physically and chemically stable**. Over 1 month at harsh conditions (40°C, high humidity):

- No visible changes (no precipitation, no cloudiness, minimal color deepening).
- Virtually no loss of drug potency (99% remained).
- pH stayed essentially constant (6.5 to 6.45, a tiny shift).
- Performance (release profile, gelling) remained the same.

This suggests the formulation is robust to stress. For practical purposes:

- The formulation's room-temperature shelf life is expected to be at least 1–2 years, as 1 month at 40°C roughly predicts 6 months at 25°C, and stability trends suggest minimal degradation over extended periods.
- The buffer system effectively prevented pH drift, indicating negligible alginate degradation or acid release.
- Moxifloxacin is quite stable; unlike some antibiotics (like reconstituted penicillins that degrade), fluoroquinolones are stable in solution if pH is controlled. DrugBank notes shelf stability of moxi solutions is good. Our data empirically confirms that.

No incompatibilities were observed among formulation components. Although cationic BAC can theoretically interact with anionic alginate, no haze or precipitation occurred, and sterility was maintained over one month, indicating BAC remained effective. While full preservative efficacy testing would be required for regulatory purposes, our simplified observations suggest the formulation is physically and microbiologically stable, with no adverse interactions affecting gel clarity or preservative function.

The minor yellowing observed after 1 month at 40°C likely reflects minimal moxifloxacin oxidation, but assay results showed no loss of drug content, indicating it is negligible. Using amber or opaque containers, as in our tests, is recommended to protect against light-induced degradation, which some quinolones are susceptible to.

The stability results confirm that the formulation can be reliably manufactured, sterilized, and stored without compromising drug content, gelation, or safety, thereby meeting our objective of ensuring robust and compatible ocular delivery (Objective 3).

8.6 Optimization and Final Formulation Selection

Bringing together all the results:

- Formulation F6 (0.4% alginate + 0.6% HPMC) consistently performed the best in terms of sustained release (slowest release, ~12h), strong in situ gelation (+++), and large antimicrobial zone (indicating effective drug availability throughout 24h). It had the highest viscosity (though still acceptable) and gave the longest precorneal retention in simulation.

- Formulation F5 was close (0.3% alg + 0.6% HPMC), releasing ~80% in 8h (slightly faster than F6) and slightly smaller zones. F5 might be chosen if one wanted a tad less viscosity (for potentially slightly less blur) while still good sustain (~10h). But since our target was maximum sustain for infection treatment, F6 was favored.
- All other formulations either didn't sustain long enough (F1–F3) or had less optimal performance compared to F6.

Thus, **Formulation F6 is identified as the optimized formulation**, fulfilling all key objectives: it prolongs drug release (potentially reducing dosing frequency), preserves antimicrobial efficacy, is non-irritant, and demonstrates good stability.

While higher polymer concentrations could theoretically prolong release, increasing beyond 0.4% alginate and 0.6% HPMC would likely make the solution too viscous, potentially causing difficulty in drop formation, dispensing, or transient blurring. Extremely thick gels can also complicate sterilization and may increase irritation risk. F6 represents a practical balance—effective sustained release without compromising usability or comfort.

To ensure patient convenience, a formulation must not be so viscous as to prevent instilling or to cause too prolonged blur. Our rabbit test suggests F6 is fine. Typically, an in situ gel with viscosity in the range 20-100 mPas at high shear is fine (our F6 at high shear was likely within that when eyeblink considered – it wasn't measured at that exact shear but qualitatively it dripped out fine).

Plan of Usage: Based on these findings, the final product would be a multi-dose in situ gelling eye drop containing BAC as preservative. Patients could instill it perhaps twice daily, with each drop quickly forming a gel in the conjunctival sac. This gel would sustain moxifloxacin release, maintaining therapeutic levels locally, improving compliance (e.g., overnight coverage with a single bedtime drop), and potentially reducing systemic exposure by limiting drainage into the nasolacrimal duct.

Comparison to Conventional Eye Drops: Compared to conventional Vigamox (0.5% moxifloxacin) dosed three times daily, our in situ gel could potentially reduce dosing to twice daily—or even once daily in mild infections—because the drug remains longer on the ocular surface. The sustained release also likely increases ocular AUC, enhancing overall exposure

and efficacy. The main considerations would be a brief, transient blur after instillation and advising patients to shake the bottle if necessary, though our formulation is colloidally stable and unlikely to settle.

Economic and Practical Aspects: The polymers (alginate and HPMC) are low-cost, and the formulation process is simple—essentially mixing and autoclaving. No specialized equipment is required beyond standard eye drop manufacturing setups, although filtration may be slightly slower due to viscosity. Overall, the formulation is practical and scalable, making it a viable product from a pharmaceutics perspective.

9. Conclusion

The present study successfully developed and evaluated a sodium alginate–HPMC based ophthalmic in situ gel of moxifloxacin hydrochloride designed to overcome the limitations of conventional eye drops, particularly rapid precorneal drug loss and the need for frequent dosing. All formulations were clear, sterile, isotonic, and pH-compatible with ocular tissues, and exhibited desirable pseudoplastic behavior, allowing easy instillation as drops followed by rapid sol-to-gel transition in the presence of tear fluid. Increasing polymer concentrations enhanced gel strength and viscosity, resulting in a controlled, diffusion-driven release of moxifloxacin over extended periods. Among the formulations, F6 (0.4% sodium alginate and 0.6% HPMC) demonstrated optimal performance, providing sustained drug release for up to 10–12 hours while retaining full antibacterial activity against both *Staphylococcus aureus* and *Escherichia coli*. Ocular irritation studies confirmed excellent tolerability, with no significant adverse effects observed, and accelerated stability studies indicated good physical, chemical, and microbiological stability. Overall, the optimized in situ gel formulation represents a safe, effective, and patient-friendly ocular drug delivery system with the potential to reduce dosing frequency, improve patient compliance, and enhance therapeutic efficacy in the management of bacterial eye infections.

10. Conflict of Interest:

The author(s) declare that there is no conflict of interest regarding the publication of this research work.

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