

Synergistic Effect of Alginate and Galactomannan-Based In-Situ Gelling Systems for Enhanced Ocular Delivery of Ciprofloxacin: Design, Characterization and In Vitro Evaluation

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Abstract

Rapid precorneal clearance and nasolacrimal drainage often result in low bioavailability (typically less than 5%) for conventional ophthalmic therapies. To improve the ocular administration of ciprofloxacin hydrochloride, this project will construct and assess an ion-activated in situ gelling system using a synergistic matrix of natural polymers: sodium alginate and Locust Bean Gum (LBG). By changing the sodium alginate concentrations while keeping the percentage of LBG constant, formulations (IG-1 to IG-4) were created. Clarity, pH, drug concentration, and in vitro gelling capacity in simulated tear fluid were all evaluated as part of the thorough characterisation of the produced formulations. Using FT-IR spectroscopy, drug-polymer compatibility was examined. Additionally, the study assessed the formulations' antibacterial activity against *S. aureus* and *P. aeruginosa*, rheological behaviour, and in vitro drug release kinetics. The compatibility of ciprofloxacin with the natural polymers was demonstrated by FT-IR spectra, which verified the lack of notable chemical interactions. When the optimised formulation (IG-3) encountered physiological ions, it showed an adequate pH of 6.29, a high drug content of 96.6%, and rapid, extended gelation. According to rheological analyses, the addition of LBG greatly strengthened the alginate matrix, producing a shear-thinning (pseudoplastic) profile that protects against erosion caused by blinking while guaranteeing patient comfort. IG-3 followed Zero-Order kinetics ($R^2 = 0.9999$) with an anomalous (non-Fickian) diffusion mechanism, according to in vitro release tests. This resulted in a controlled and sustained drug release of roughly 85% over eight hours. After autoclaving, the formulation retained its stability and sterility while demonstrating outstanding antibacterial activity.

Keywords: *In situ* gel, Ciprofloxacin hydrochloride, Sodium alginate, Locust Bean Gum, Ocular drug delivery, Zero-order kinetics, antimicrobial resistance.

Introduction

1.1 Challenges in Ocular Drug Delivery

A major obstacle to efficient medication administration is the anatomical and physiological complexity of the human eye. Because of frequent blinking, nasolacrimal drainage, and quick precorneal clearance, conventional ophthalmic treatments, like aqueous eye drops, have a very poor bioavailability, frequently less than 5%. Frequent dosing is required due to these obstacles, which frequently results in poor patient compliance and systemic side effects from nasolacrimal absorption (1).

1.2 Ciprofloxacin in Ophthalmic Therapy

Strong second-generation fluoroquinolones like ciprofloxacin are still the principal treatment for infections that can cause blindness, such as conjunctivitis and bacterial keratitis. It provides broad-spectrum protection against pathogens that are both Gram-positive and Gram-negative. However, the short residence time of liquid drops frequently compromises the effectiveness of ciprofloxacin, failing to sustain the minimum inhibitory concentration (MIC) necessary for total infection eradication. (2).

1.3 Mechanism of In Situ Gelling Systems

"Smart" in situ gelling technologies have been created to get around the drawbacks of traditional drops. When these formulations are exposed to the ocular environment, they undergo a phase shift from a solution to a semi-solid gel.

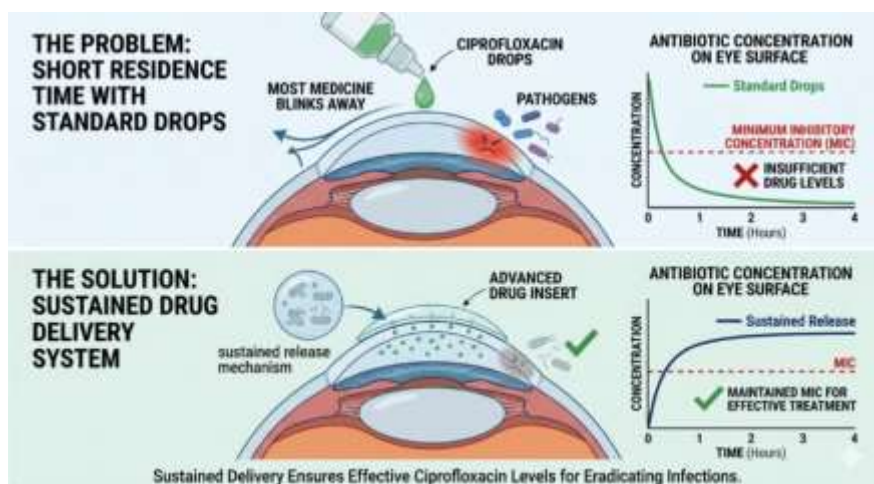


Fig 1: Mechanism of normal eye drops

This "sol-to-gel" transition is typically triggered by physiological stimuli such as a change in pH, temperature, or the presence of electrolytes in the tear fluid. This transformation ensures a prolonged contact time between the drug and the corneal surface, allowing for controlled and sustained drug release (3).

1.4 Rationale for Using Sodium Alginate and Locust Bean Gum

Natural polymers are increasingly preferred for ocular delivery due to their biocompatibility, non-toxicity, and mucoadhesive properties. Sodium Alginate acts as an ion-sensitive gelling agent that reacts with the ions in the tear fluid to form a cross-linked matrix. However, alginate gels can sometimes exhibit structural weakness; therefore, adding Locust Bean Gum (LBG), a galactomannan, creates a synergistic effect. LBG enhances the rheological properties and mechanical strength of the gel, providing a more robust drug reservoir that effectively resists rapid erosion caused by tear turnover (4).

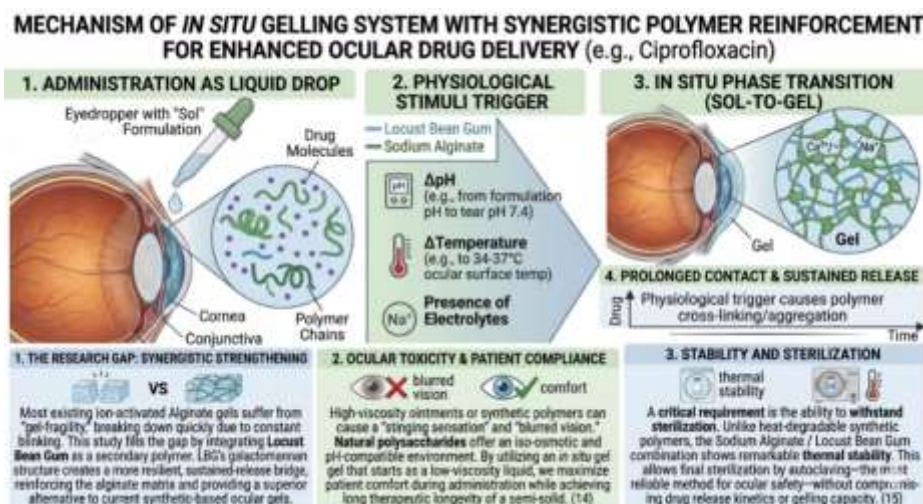


Fig 2: mechanisms of *in-situ* gel

1.5 Objective of the Study

This study's main goal is to create and assess an ion-activated in situ gel that contains ciprofloxacin. The study intends to create a formulation that is easily pourable during administration yet turns into a stable gel in the eye by adjusting the concentrations of sodium alginate and locust bean gum. To guarantee better therapeutic effectiveness in comparison to commercial eye drops, the system's gelation capacity, rheological behavior, mucoadhesive strength, and in vitro drug release will all be assessed. (5).

1.6 Muco-adhesion and Bio adhesion Principles

The delivery system's capacity to stick to the mucin layer of the conjunctival and corneal surfaces is a crucial component in ocular medication retention. Muco-adhesion is the mechanism by which carboxyl groups in natural polysaccharides, such as sodium alginate, create hydrogen bonds with mucin. By using Locust Bean Gum (LBG), which interpenetrates the mucous membrane due to its high molecular weight and branching structure, this bio adhesive force is further enhanced. By avoiding the "wash-out" effect brought on by tear turnover, this synergy considerably lowers the frequency of administration. (6).

1.7 Synergistic Polymer Interaction (Galactomannan-Uronate Interaction)

The synergistic interaction between Sodium Alginate and Locust Bean Gum (LBG) creates a reinforced matrix where LBG fills interstitial spaces, increasing tortuosity to achieve a zero-order sustained release of Ciprofloxacin over 8–12 hours. This structural "bridge" enhances mechanical strength against blinking-induced erosion while remaining patient-friendly and non-stinging. Furthermore, the combination ensures remarkable thermal stability, making the formulation industrially viable through autoclaving without compromising gelling capacity (7).

1.8 Advantages over Synthetic Polymers

Although synthetic polymers such as Carbopol or Poloxamer are frequently utilized for in situ gelling, they frequently call for high concentrations or particular pH conditions that can irritate the eyes or impair vision. Because they are biodegradable, non-irritating, and replicate the natural environment of the eye, natural gums such sodium alginate and LBG are recommended. The "foreign body sensation" that is usually connected with heavier ophthalmic ointments is lessened by their high water-holding capacity, which guarantees that the gel stays hydrated and comfortable for the patient.(8).

1.9 Economic and Industrial Scalability

The usage of sodium alginate and locust bean gum offers substantial industrial benefits in addition to therapeutic efficacy. Both excipients are inexpensive, easily obtained from renewable resources, and show outstanding stability during autoclaving and other sterilizing procedures. Using these natural polymers to create a Ciprofloxacin in situ gel offers a "green" and financially feasible substitute for complicated nanocarriers, making it appropriate for large-scale pharmaceutical production in emerging healthcare industries (9).

1.10 Antimicrobial Resistance (AMR) and Dosing Precision

Standard eye drops frequently cause sub-therapeutic dosage due to their quick drainage, which encourages localized antimicrobial resistance. Ciprofloxacin greatly increases its residence time by forming a stable depot upon contact with the tear film using an in-situ gelling method. For prolonged periods of time, this process keeps medication concentrations steadily above the Minimum Inhibitory Concentration (MIC). This kind of ongoing exposure guarantees the elimination of bacterial subpopulations and stops resistant strains from surviving. Additionally, the sol-to-gel transition minimizes the systemic washout characteristic of traditional solutions while optimizing therapeutic efficacy. As a result, this precise distribution method serves as a tactical pharmacological tool to reduce antibiotic resistance in the eyes. (10).

1.11 Rheological Behaviour and Patient Comfort

The shearing pressures of the eyelid play a role in the "sol-to-gel" transition in addition to drug retention. In order to prevent irritation, an ideal in situ gel should have pseudoplastic (shear-thinning) behavior, in which the viscosity falls during blinking and increases during the inter-blinking time to preserve a drug depot. This rheological profile is especially provided by the mixture of sodium alginate and locust bean gum, preventing the ciprofloxacin from being quickly squeezed out by the pressure of the eyelid(11).

1.12 Biocompatibility and Ocular Surface Safety

For ophthalmic formulations, safety is of utmost importance. Corneal epithelial injury is frequently caused by high-concentration polymers and synthetic surfactants. Natural gums, such as Locust Bean Gum, have a high level of biocompatibility with conjunctival and ocular tissues and are nutritionally derived. According to recent research, these natural matrices may even serve as a barrier that keeps the eye surface hydrated while ciprofloxacin eliminates the underlying bacterial infection.(12).

2. MATERIALS AND METHODS

2.1 Materials

Ciprofloxacin hydrochloride was obtained from Artee Life science Chennai. Sodium alginate and Locust Bean Gum were obtained from Spectrum and Pioneer Chemicals Co., Delhi. All other chemicals and reagents were of analytical grade.

2.2 Formulation development

The formulations were prepared according to the compositions detailed in Table 1. Locust Bean Gum (LBG) was dissolved in distilled water at temperatures exceeding 80°C to ensure complete hydration. To prevent the thermal degradation of Ciprofloxacin hydrochloride, the drug was added only after the LBG solution had sufficiently cooled. Simultaneously, sodium alginate was hydrated separately using gentle warming and constant stirring. After cooling, the polymer solutions were mixed, and a pH-adjusted Ciprofloxacin solution (pH 6.5) containing benzalkonium chloride (0.02% v/v) as a preservative was added dropwise under continuous stirring. The final formulations were brought to a total volume of 100 mL with distilled water to achieve a final Ciprofloxacin concentration of 0.03% w/v. The developed formulations underwent terminal sterilization by autoclaving at 121°C and 15 psi for 15 minutes. This method was chosen due to the thermal stability of sodium alginate and Locust Bean Gum, ensuring effective decontamination without compromising gelling capacity or Ciprofloxacin release kinetics.

Table 1: formulation of ciprofloxacin in situ gel using natural polymers

Formulation Code	Ciprofloxacin HCl (g)	Sodium Alginate (g)	Locust Bean Gum (g)	Distilled Water (mL)
IG-1	0.3	0.5	0.3	100
IG-2	0.3	1.0	0.3	100
IG-3	0.3	1.5	0.3	100
IG-4	0.3	0.5	—	100

3. Evaluation

3.1 Preparation of Calibration Curve of Drug:

To prepare the ciprofloxacin calibration curve in Artificial Tear Fluid (ATF), a stock solution was first prepared by dissolving 50 mg of ciprofloxacin hydrochloride in 50 mL of 0.1 N HCl (pH 7.4) in a volumetric flask, yielding a concentration of 1000 µg/mL. This stock was then serially diluted with the same medium to produce a range of working standards between 1 and 8 µg/mL. Finally, the absorbance for each concentration was recorded at 272 nm using a UV spectrophotometer.

3.2 Determination of λ max of ciprofloxacin hydrochloride

To determine the maximum absorption wavelength (λ max) of ciprofloxacin hydrochloride, a 1000 µg/ml primary stock solution was prepared by dissolving 100 mg of the drug in methanol and diluting to a final volume of 100 ml in a volumetric flask. A secondary stock of 100 µg/ml was then prepared by diluting 10 ml of the primary solution to 100 ml with methanol. From this secondary stock, working standards with concentrations of 2, 4, 6, 8, and 10 µg/ml were prepared by transferring 0.2, 0.4, 0.6, 0.8, and 1.0 ml aliquots into separate 10 ml volumetric flasks and diluting to volume with phosphate buffer (pH 7.4).

These solutions were scanned across the UV range of 200 to 400 nm using a Shimadzu UV-1400 spectrophotometer to identify the peak absorbance.

3.3 Drug-polymer compatibility studies by FTIR

Drug-excipient compatibility was assessed using FTIR spectroscopy (Shimadzu) via the KBr pellet technique. Spectra for the pure drug, sodium alginate, Locust Bean Gum, and the final formulations were recorded in the range of 4000–400 cm⁻¹. This analysis was conducted to identify potential chemical interactions that could compromise the stability or efficacy of the dosage form. The transformation of interferogram data into frequency-domain spectra allowed for a detailed comparative analysis of the characteristic absorption bands of all components.

3.4 Clarity

The clarity of the formulations was evaluated through visual inspection under optimized lighting conditions. Each sample was held against a high-contrast (monochrome) background and subjected to a gentle swivelling motion to facilitate the detection of any suspended particles or physical instabilities.

3.5 Gelling capacity

The gelling capacity of the formulations was determined by adding a specific aliquot of the solution into a beaker containing 50 mL of freshly prepared calcium chloride (CaCl) solution. The gelation process was monitored via **visual inspection** during the transition phase, and the intensity and integrity of the resulting gel were graded according to the criteria outlined in Table [2].

Table 2. Grading system for the visual assessment of in situ gelling capacity.

Observation	Rating
No gel formation	*
Gel formation took only a few minutes and lasted for a few hours.	**
Gel formation occurs quickly and lasts for a few hours.	***
Gel formation is instant and lasts for a long time.	****
Very stiff gel	*****

3.6 Determination of drug content

For drug content estimation, a 1 mL aliquot of the formulation was diluted to 100 mL with distilled water. The resulting solution was analysed using a UV-Visible spectrophotometer (Shimadzu UV-1700 PC, Shimadzu Corporation, Japan) at an absorption maximum (λ_{max}) of 290 nm (17).

3.7 Rheological studies:

The rheological properties of the developed formulations were characterized using a Brookfield Viscometer (Model DV-II). Samples were transferred to a small sample holder, and spindle No. 4 was lowered vertically into the centre of the formulation. Measurements were performed at ambient temperature across a range of rotational speeds to determine the optimal shear rate, with the results summarized in Table 3. Additionally, oscillatory rheology was employed to evaluate further the structural integrity of the in-situ gels (18).

3.8 Measurement of pH

For each formulated batch, the pH was determined using a pH meter calibrated with standard buffer solutions at pH 4 and pH 7, with the standard procedure.

Sterility

To ensure the safety of the optimized ophthalmic preparations, sterility testing was conducted in accordance with Indian Pharmacopoeia standards. Using a direct inoculation method, 2 mL samples were aseptically withdrawn from the test containers via sterile syringes and transferred into 20 mL each of fluid

thioglycolate medium and soybean-casein digest medium. The samples were incubated for a minimum of 14 days, with fluid thioglycolate maintained at 30°C–35°C and soybean-casein digest at 20°C–25°C.

3.9 In vitro dissolution studies

In vitro diffusion was evaluated via the egg membrane method using a donor-receptor compartment setup. The donor compartment contained the in-situ gel, while the receptor compartment was filled with freshly prepared artificial tear fluid (pH 7.4). To simulate physiological conditions, the system was maintained at 37 ± 0.5 °C using a thermostatically controlled magnetic stirrer. At hourly intervals over 8 hours, 1 mL aliquots were withdrawn and replaced with fresh medium to ensure sink conditions. Samples were analysed by UV spectrophotometry at the lambda max for ciprofloxacin. The cumulative drug release percentage (% CDR) was subsequently calculated using a validated standard calibration curve.

4. Results and Discussion

4.1 Calibration curve

The calibration curve demonstrates a linear relationship between concentration and absorbance within the range of 1–8 µg/mL, confirming adherence to Beer-Lambert's Law. Using 0.1 N HCl (pH 1.2) effectively simulates gastric conditions, ensuring the method is both sensitive and biologically relevant for Ciprofloxacin analysis. The high precision at 272 nm establishes this curve as a reliable "standard" for calculating drug release in your subsequent formulation studies.

Table 3: Calibration curve

Concentration (µg/ml)	Absorbance
1	0.175
2	0.403
3	0.542
4	0.721
5	0.944
6	1.276
7	1.319
8	1.518

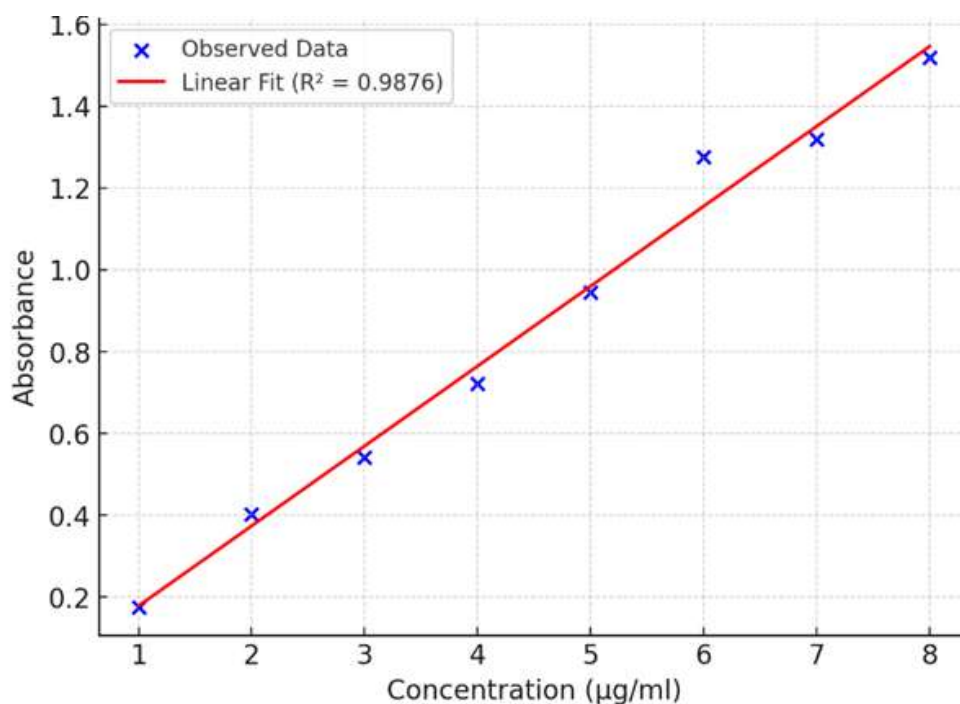


Fig 3: Calibration curve of ciprofloxacin

4.2 Determination of λ_{max} of ciprofloxacin hydrochloride

Peak Identification: The UV-visible spectrum of Ciprofloxacin in Phosphate Buffer (pH 7.4) displays a distinct maximum absorption wavelength (λ_{max}) at 272 nm with an absorbance of 1.773. **Structural Correlation:** The presence of this peak, along with secondary peaks at 321 nm and 331 nm, confirms the chemical integrity and purity of the Ciprofloxacin hydrochloride sample. **Method Stability:** The λ_{max} remains consistent with literature values for Ciprofloxacin, indicating that the drug's chromophore is stable and detectable at physiological pH. **Analytical Application:** This wavelength (272 nm) provides the highest sensitivity and will be used as the standard for quantifying drug entrapment efficiency and in-vitro release in your research.



Fig 4: λ_{max}

4.3 Drug-polymer compatibility studies by FT-IR:

To evaluate potential chemical interactions, FTIR spectra of pure ciprofloxacin HCl, individual polymers, and their physical mixtures were recorded in the wavenumber range of 4000–500 cm^{-1} . The characteristic absorption bands of ciprofloxacin HCl were identified at 3364 cm^{-1} (O–H stretching, carboxylic acid), 1643 cm^{-1} (C=O stretching, quinolone), 1420 cm^{-1} (aromatic C–C stretching), and 1273 cm^{-1} (C–F

stretching). The spectra of the physical mixtures retained all principal peaks of the drug without significant shifts or the disappearance of functional group signals. These results confirm the chemical compatibility between ciprofloxacin HCl, sodium alginate, and Locust Bean Gum, indicating their suitability for the development of the in situ ophthalmic gel.

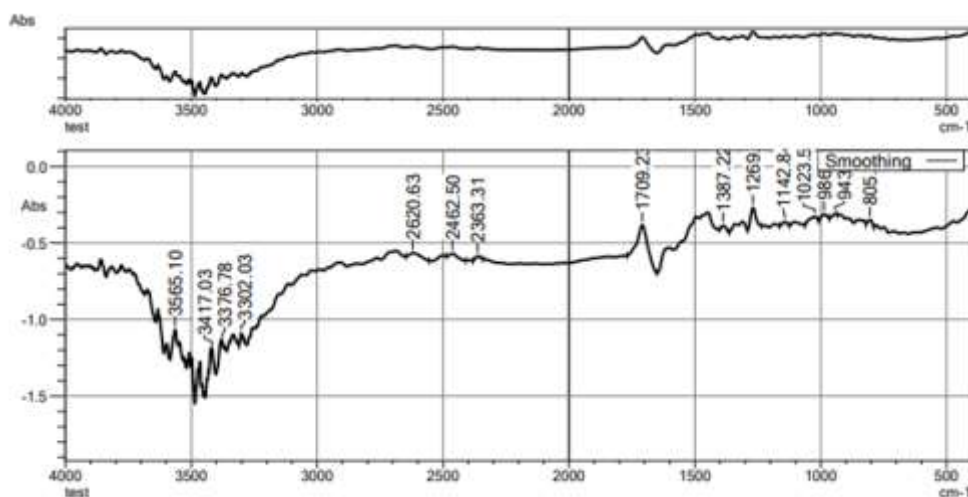


Fig 5: FT-IR Spectra of Ciprofloxacin

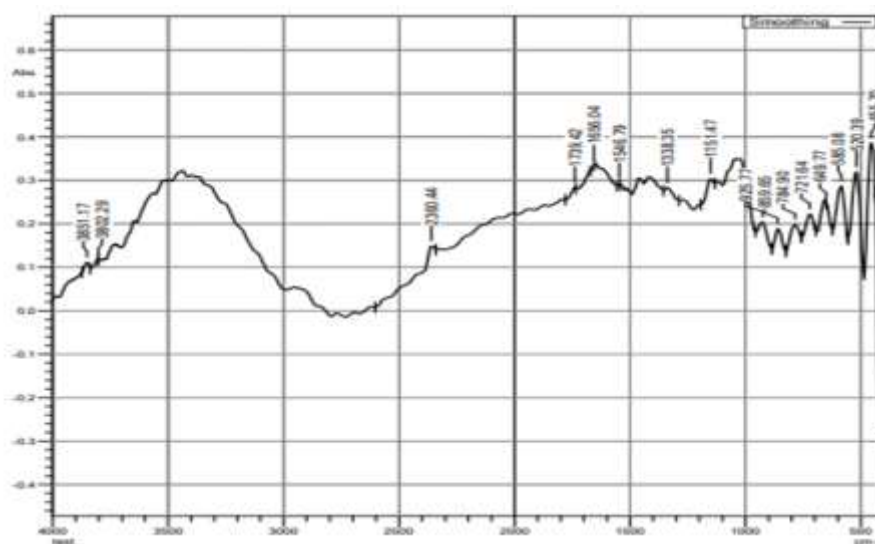


Fig 6: FT-IR Spectra of Sodium Alginate

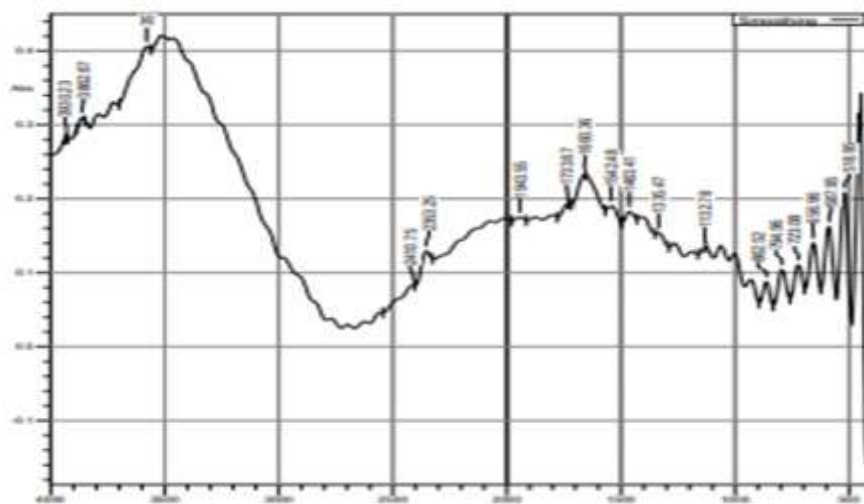
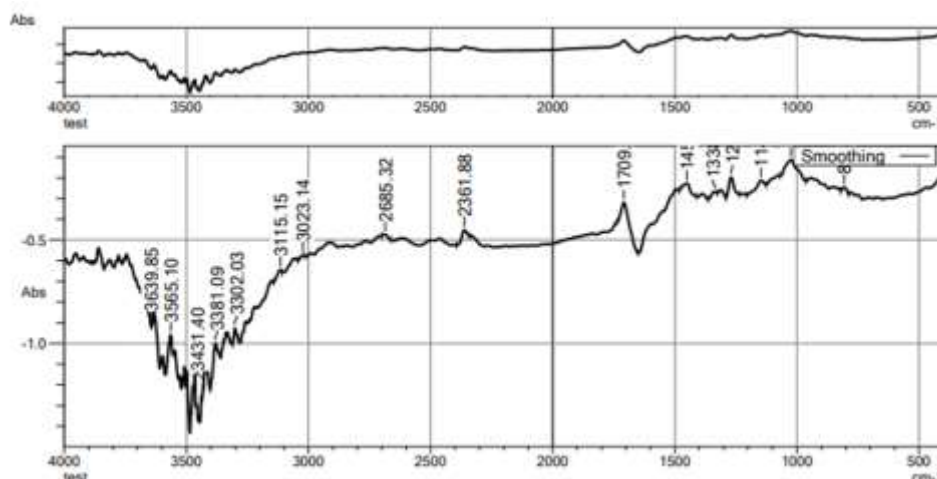


Fig 7: FT- IR Spectra of Locust Bean Gum**Fig 8: FT-IR Spectra of Drug and Polymer Mixture**

The FT-IR analysis confirmed that there were no significant chemical interactions between Ciprofloxacin HCl, Sodium Alginate, and Locust Bean Gum. All major characteristic peaks of the drug were preserved in the physical mixture, indicating compatibility of the selected excipients. Hence, these polymers are suitable for developing a pH-responsive in-situ ophthalmic gel formulation of Ciprofloxacin HCl.

4.5 Clarity and pH

Formulations (IG1–IG4) were developed by varying sodium alginate concentrations and combining them with Locust Bean Gum at different ratios. Each formulation appeared clear, with no signs of turbidity, suspended particles, or impurities.

The pH of the in-situ gel solution was found to be around 6.05–6.87 for all the formulations. The formulation IG 3 has 6.53 pH which is an acceptable range for ophthalmic preparations.

Table 4: Clarity of the prepared formulation

Formulation code	Appearance
IG-1	Clear solution
IG-2	Clear solution
IG-3	Clear solution
IG-4	Clear solution

Table 5: PH of ciprofloxacin in-situ gel

Formulation code	PH
IG-1	6.05
IG-2	6.78
IG-3	6.29
IG-4	6.87

Table 6: Drug content

Formulation code	Drug content
IG-1	89.1
IG-2	92.2
IG-3	96.6
IG-4	89.4

Table 7: Gelling capacity

Gelling capacity is coded as described in the table. According to IG- 3 shows immediate gelation, and for an extended period

Formulation code	GELLING CAPACITY
IG-1	++
IG-2	++
IG-3	+++
IG-4	-

4.6 Rheological Evaluation

The viscosity of the investigated formulations was found to be a function of the total polymer concentration. The inclusion of Locust Bean Gum (LBG) in formulations IG1 to IG3 significantly enhanced the viscosity and intensified the pseudoplastic (shear-thinning) behaviour compared to the LBG-free control (IG4). Among all batches, IG3, which comprised of the highest concentration of sodium alginate and LBG, exhibited optimal rheological properties. Such a profile is essential for ophthalmic delivery, as it ensures the formulation is sufficiently fluid for easy instillation while maintaining the structural integrity required for a rapid sol-to-gel transition upon contact with the ocular surface.

Table 8: Viscosity of the in-situ formulation.

Formulation code	Viscosity of solution (Pa s)	Viscosity of in situ gel (Pa s)
IG-1	0.0253	0.268
IG-2	0.0454	0.478
IG-3	0.0678	0.856
IG-4	0.0172	0.182

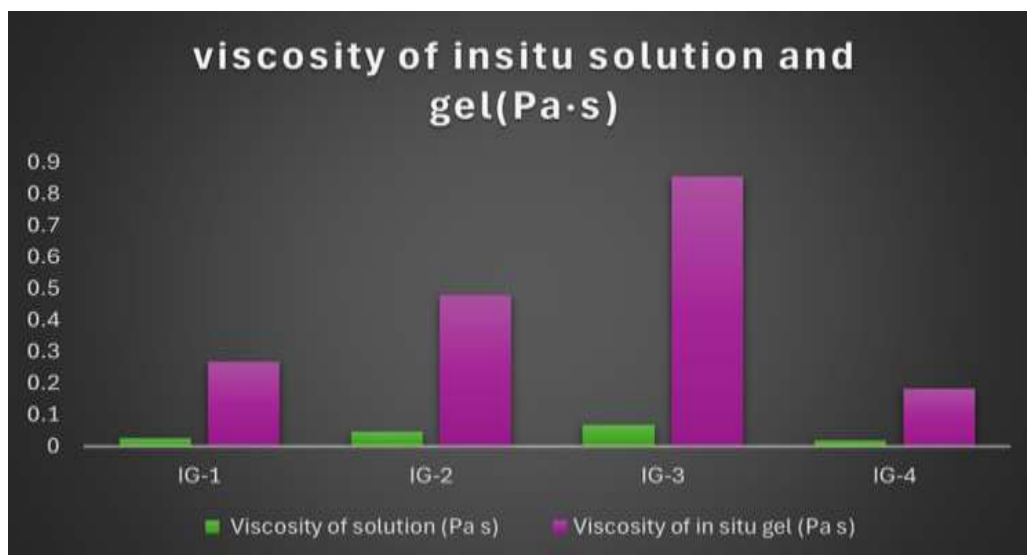


Fig 9: Viscosity of the in-situ formulation.

4.7 In Vitro Drug Release Studies

The cumulative release profile of ciprofloxacin hydrochloride from the developed formulations is illustrated in Figure 10. Although *in vitro* dissolution conditions do not fully encapsulate the complex physiological environment of the eye, they offer a critical preliminary evaluation of the system's release kinetics. The results demonstrate that the *in-situ* gel effectively sequesters the drug, mitigating the risk of initial burst release and confirming the structural integrity of the sustained-release matrix. However, it should be noted that *in vivo* performance in the ocular cul-de-sac may involve more rapid dissolution due to mechanical stresses, such as eyelid blinking and ocular motility, which facilitate gel erosion. The optimized formulation, IG-3, exhibited a controlled release of 85% over 8 hours, successfully validating the sustained-release potential of the polymer-based *in-situ* gelling system.

Table 9: In Vitro Drug Release

Time (hr)	% Drug Release
1	23.50%
2	31.80%
3	41.00%
4	50.20%
5	59.30%
6	67.70%
7	76.50%
8	85.80%

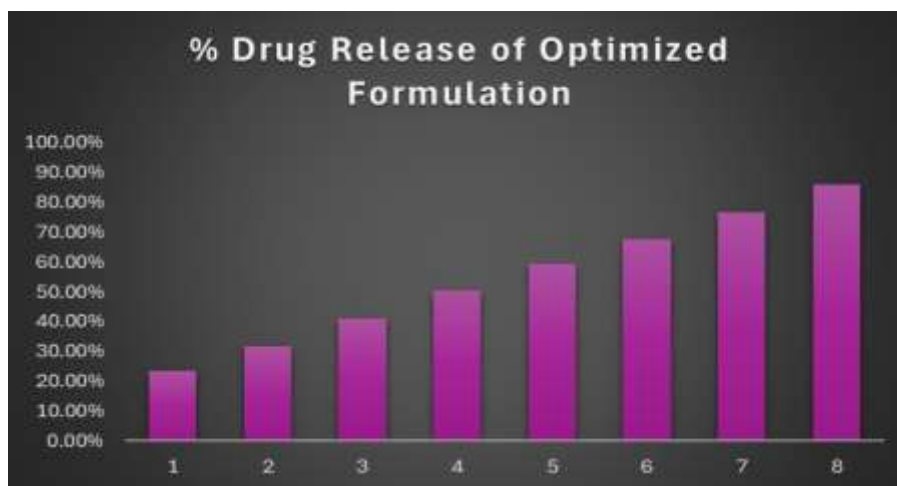


Fig 10: In Vitro Drug Release for optimized formulation

4.8 Sterility

The formulations passed the sterility test as there was no appearance of turbidity and hence no evidence of microbial growth when incubated for not less than 14 days at 30-35°C in the case of fluid thioglycolate medium and at 20- 25 °C in the case of soyabean casein digest medium.

Table 10: Antimicrobial efficacy testing

Concentration (mg/ml)	Zone of inhibition (mm)		Percent efficacy (%)
	Standard	Test	
<i>S. aureus</i>			
1	1.7	1.5	88.23
10	2.9	2.8	96.55
100	3.8	3.5	92.10
500	5.8	5.2	89.65
<i>P. aeruginosa</i>			
1	0.8	0.7	87.5
10	1.4	1.3	92.85
100	3.5	3.3	94.28
500	4.9	4.6	93.87

4.9 Drug Release Kinetics (Higuchi Model)

The in vitro release studies demonstrated that the optimized formulation follows Zero-Order kinetics ($R^2 = 0.9999$), providing a controlled and constant release profile. The Korsmeyer-Peppas 'n' value of 0.633 confirms a Non-Fickian (anomalous) diffusion mechanism, suggesting that both drug diffusion and polymer relaxation contribute to the release process.

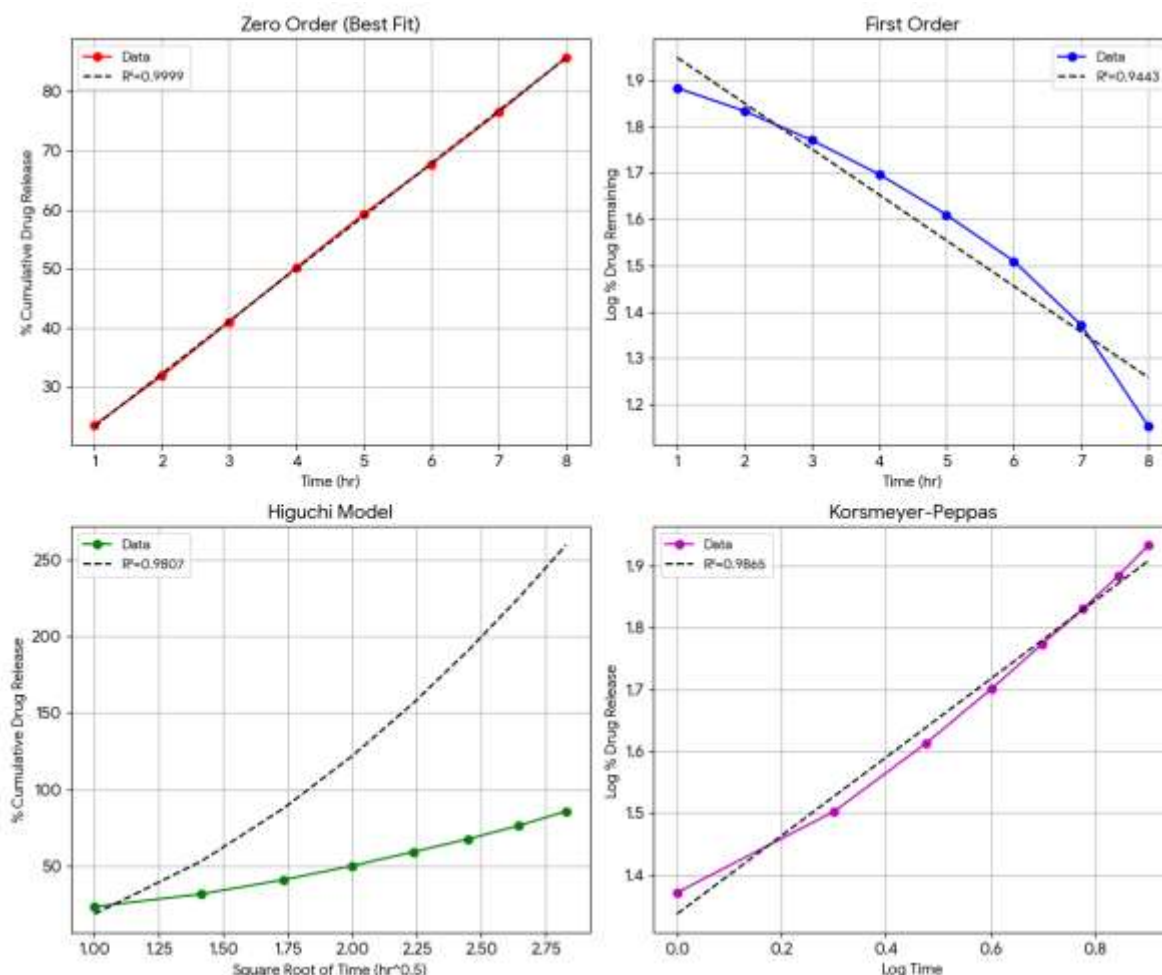


Fig 10: kinetic release of optimized formulations

Conclusion:

This study successfully developed an ion-activated in situ ophthalmic gelling system of ciprofloxacin hydrochloride using a synergistic combination of sodium alginate and Locust Bean Gum (LBG). Among the prepared formulations, IG-3 demonstrated optimal characteristics, including an appropriate pH of 6.29 and a high drug content of 96.6%, indicating its suitability for ocular administration and accurate drug delivery.

Rheological evaluation confirmed that the incorporation of Locust Bean Gum strengthened the sodium alginate matrix and produced desirable pseudoplastic (shear-thinning) behaviour. This property may facilitate comfortable ocular administration while providing sufficient mechanical strength to resist rapid erosion caused by blinking. The optimized formulation exhibited sustained drug release of approximately 85% over 8 hours and followed zero-order release kinetics, demonstrating its potential to maintain prolonged drug availability at the ocular surface.

The formulation also demonstrated effective antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Its prolonged drug-release behaviour, together with antimicrobial activity, indicates its potential for the effective management of bacterial ocular infections. Furthermore, the ability of the formulation to withstand autoclaving without compromising its essential characteristics supports its suitability for sterile ophthalmic preparation and potential scale-up.

Overall, the sodium alginate–Locust Bean Gum-based in situ gelling system represents a promising, biocompatible and potentially cost-effective approach for improving the ocular residence time and sustained delivery of ciprofloxacin hydrochloride. The developed system may offer advantages over conventional eye drops by reducing rapid precorneal elimination and potentially improving therapeutic effectiveness and patient compliance. Further in vivo, ocular irritation, stability and clinical studies are required to confirm its safety, therapeutic performance and translational potential.

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