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Formulation and Evaluation of Ciprofloxacin Loaded Ocular Insitu Gel

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A B S T R A C T

The aim of this study was to develop an innovative delivery method for Ciprofloxacin, an ophthalmic drug, to enhance its limited effectiveness in the eye. A Ciprofloxacin gel was created using Carbopol 940, Sodium alginate, Xanthan gum, and HPMC K4M through a pH-triggered in situ gelling technique. The in situ gelling system, containing 0.5% W/V Ciprofloxacin, was successfully formulated to treat ocular infections such as conjunctivitis. The formulations were characterized based on appearance, color, pH, gelling capacity, rheological properties, and in vitro release in pH 7.4 phosphate buffer. All formulations were clear with pH ranging from 6.5 to 7.1. By optimizing the concentrations of Carbopol 940 and HPMC, superior gelling capacity and suitable gel strength under physiological conditions were achieved, allowing for easy instillation as eye drops. The cumulative percentage of drug release varied across formulations, with F4, F7, and F9 showing the highest release rates of 85%, 88%, and 81%, respectively, while F3 demonstrated significantly delayed drug release. Rheological characterization indicated that F3 exhibited better pseudoplastic behavior compared to other formulations. In vitro release studies revealed that increased polymer concentration slowed down drug release, whereas decreased polymer concentration accelerated it. FTIR analysis confirmed no interactions between the drug and polymers. The cost-effective methodology employed for the in situ gelling system provided sustained drug release over an 8-hour period. The hydrogel in situ formulations initially administered as a solution rapidly formed a hydrogel capable of withstanding shear forces in the cul-de-sac. This pH-triggered in situ gel of Ciprofloxacin offered sustained drug release compared to conventional ophthalmic solutions, resulting in prolonged residence time in the precorneal area, higher bioavailability, and reduced systemic side effects by preventing drainage through the nasolacrimal duct. The evaluated in situ gelling formulation demonstrated effective treatment of conjunctivitis with consistent drug release over the desired time period. Due to its ease of administration and extended ocular residence time without causing eye irritation, the pH-triggered in situ gelling technique presents a promising alternative to commercially available eye drops.

Keywords: hydrogel, in situ formulations, Ciprofloxacin, Carbopol 940, eye drops

A R T I C L E I N F O

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Contents

1. Introduction

Achieving and maintaining appropriate drug concentration at the target site within the eye has become a significant challenge in ophthalmic administration. To improve the duration of drug deposition for topical eye therapy, various ophthalmic delivery systems, including formulations, creams, gels, and polymeric implants, have been investigated. Eye drops typically suffer from poor absorption due to frequent washout during lacrimation [1-4]. Many formulations are administered as solutions or injections, but this issue can be addressed by developing medications that form a gel immediately upon ophthalmic application. Ciprofloxacin hydrochloride, a crystalline pale yellow powder, belongs to the fluoroquinolone group. It acts as an antimicrobial agent for treating corneal ulcers caused by bacterial strains, with its antimicrobial activity attributed to its interaction with the DNA gyrase enzyme, essential for microbial DNA replication. In situ gel formulations consist of polymers that transition from a solution to a gel phase in the cul-de-sac, enhancing patient acceptance due to changes in specific physicochemical properties such as pH, heat, and redox potential. Xanthan gum, a common thickening and suspending agent, is derived from Xanthomonas campestris, a single-cell species that produces xanthan gum through fermentation in cabbage, broccoli, and other leafy vegetables [5-7]. Xanthan gum serves as a suspension agent and an excellent thickener, even in small amounts, providing great consistency and cost-effectiveness. It is available in different grades to meet unique requirements for hydration, diffusion, and clarity. To support continuous drug delivery, Hydroxy Propyl Methyl Cellulose (HPMC) is incorporated as a viscosity enhancer [8-11]. HPMC is a semi-synthetic, stable, viscoelastic, non-ionic, non-toxic polymer that acts as a strong pharmaceutical carrier with high loading potential. These components collectively enhance the effectiveness and patient compliance of the ophthalmic delivery system[12-14].

2. Materials and Methods

Materials:

Ciprofloxacin was taken as a gift sample from Yarrow chemicals pvt Ltd, Carbopol, Sodium alginate, Xanthan Gum, HPMC E50LV and Benzalkonium chloride were purchased from SD Fine chemicals, Mumbai.

Preformulation Studies[15-17]:

Construction of calibration curve for Ciprofloxacin:

Calibration curves were constructed in 0.1N NaOH, pH 7.4 phosphate buffers.

Preparation of primary stock solution:

10mg of Ciprofloxacin was carefully weighed and dissolved in respective media, namely 0.1 NaOH, pH 7.4 phosphate buffer taken in 1oml volumetric flask and eventually made up to 1oml with respective media to achieve a concentration of 1mg/ml or 1000 g/ml.

Preparation of Secondary stock solution:

Calibration curve preparation in various solvent mediums: The medication was precisely weighed at 10 mg per 10ml. 1 ml of this solution is pipetted into a 10ml volumetric flask. The solution's volume was raised to 10ml. The solution was labelled a stock solution. Diluted stock solutions were made at concentrations of 0.2g/ml, 0.4g/ml, 0.6g/ml, 0.8g/ml, and 1.0g/ml. The above-prepared solutions were examined in a UV-Spectrophotometer at 291 nm in increasing order of concentration and absorbance was determined. The calibration curve was created by graphing absorbance versus Ciprofloxacin concentration. The regression equation was generated from the plot, which was employed in the current work for medication estimate.

FT-IR studies:

Fourier Transfer Infrared Spectroscopy is used to detect any potential incompatibilities between the medicine and the excipients. By using the pressed pellet method, the samples were fully mixed with a suitable diluting material, Potassium Bromide (KBr). The produced pellets were utilized for FTIR analysis [18-20]. Using an infrared spectrophotometer (BREUKER, ALPHA), the spectra of Ciprofloxacin and other excipients used in formulations was recorded.

Preparation of Ciprofloxacin ocular In situ gel:

- Initially, carbopal 934 was added to a small amount of cold distilled water with constant stirring or trituration on ice cold water until a clear solution was made. HPMCE50LV was then added and triturated thoroughly until a clear solution was formed, and the mixture was kept for 3 hours. This is the initial solution.
- Ciprofloxacin was added to cold distilled water and triturated until a clear solution was produced. This is the second option.
- The second solution was then put into the first solution and triturated before being placed into a Buffer pH 7.4 to produce gel.
- This is known as SOL-GEL formation.

Evaluation parameters:

1) Determination of visual appearance and clarity:

For the existence of any particle matter, the look and clarity were assessed visually on a white and black background.

2) pH:

One of the most critical parameters in ophthalmic formulation is pH. The effects of pH on solubility and stability are two crucial areas. The pH of an ophthalmic formulation should be such that it is stable at that ph while also causing no irritation to the patient following delivery of the formulation. The pH of ophthalmic formulations should be between 5 and 7.4. The pH of the developed formulations was determined using a control dynamics digital pH metre.

3) Drug content:

Diluting 1 mL of the formulation to 50 mL with pH 7.4 Phosphate Buffer yielded the drug content. A 5 mL sample was taken and diluted to 50 mL with synthetic tear fluid. A UV-Visible spectrophotometer was then used to measure the concentration of ciprofloxacin at 274 nm.

4) Rheological studies:

The viscosity of the implanted formulation is a significant component in influencing the drug's residence period in the eye. Nune's viscometer with spindle 4 was used to

determine the viscosity of produced mixtures. The sample's viscosity was determined at various angular velocities ranging from 20 to 200 rpm.

5) Gelling capacity:

In order to identify suitable compositions for use as in situ gelling systems, all prepared formulations underwent evaluation for their gelling capacity and viscosity. To determine the gelling capacity, a drop of each system was placed in a vial containing 2 ml of freshly prepared artificial tear fluid, which was equilibrated at 37°C. The gel formation was visually assessed, and the time for gelation and the time taken for the gel to dissolve were recorded. The flow behavior of the vehicle can be indicated using a "+" sign, which represents a liquid form that gels slowly and dissolves rapidly.

A flow behavior with a "++" sign indicates a liquid-gel like form, where the vehicle flows less readily. This indicates immediate gelation, which lasts for a few hours. A flow behavior with a "+++" sign indicates a gel form, where the sample is very difficult to flow. This also indicates immediate gelation, with the gel remaining for an extended period of time.

6) In-vitro diffusion study:

A release study was conducted on the in situ gel solution in a simulated tear fluid with a pH of 7.4. The study employed a Franz diffusion cell, where the formulation was placed in the donor compartment and freshly prepared simulated tear fluid was placed in the receptor compartment. A dialysis membrane with a pore size of 0.22 µm, previously soaked overnight in the dissolution medium, was positioned between the donor and receptor compartments. The entire setup was placed on a thermostatically controlled magnetic stirrer, maintaining the medium temperature at 37°C±0.5 °C.

At predetermined time intervals ranging from 1 hour to 8 hours, 1 mL of sample was withdrawn and replaced with an equal volume of fresh medium. The withdrawn samples were then diluted to a volume of 10mL in a volumetric flask using the respective solvent. These samples were subsequently analyzed using a UV spectrophotometer at specific wavelengths, with a reagent blank as reference. The drug content was calculated using an equation derived from a standard calibration curve, and the percentage of cumulative drug release (%CDR) was determined.

3. Results and Discussion

Characterization of Ciprofloxacin:

Physical appearance: Ciprofloxacin was appeared in solid in nature.

Melting point determination:

The melting point values reported for Ciprofloxacin in the range of 293℃ to 323℃.

Solubility:

Ciprofloxacin was soluble in buffer pH 7.4. Soluble in water (<1mg/ml), 100% ethanol, chloroform, methanol.

Calibration curve:

The wavelength of maximum absorbance (max) chosen for Phosphate Buffer with pH 7.4 for Ciprofloxacin was 274 nm. The displayed graph was discovered to be linear in the concentration range of 0 to 5g/ml and to fulfil Beer-Lambert's law in the same ranges. It is shown in fig.No. 1.

FTIR Spectroscopy:

The IR spectral investigations of the medication and its physical excipient mixes preserved their distinct absorption properties without interfering with one another. We may infer from this investigation that no unexpected chemical reactions occurred while doing this research. There is no interaction between the medication and the polymer. In the figure, the infrared spectra of pure drugs and physical mixes are depicted Fig no.2

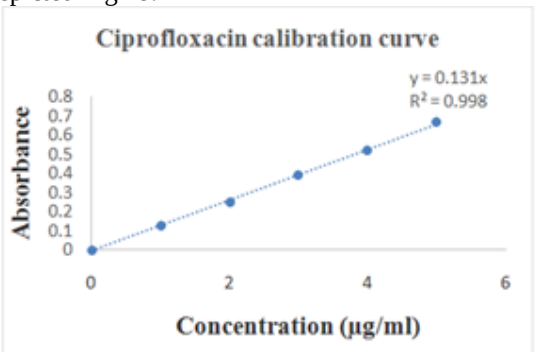

Figure No. 1 Calibration curve of Ciprofloxacin

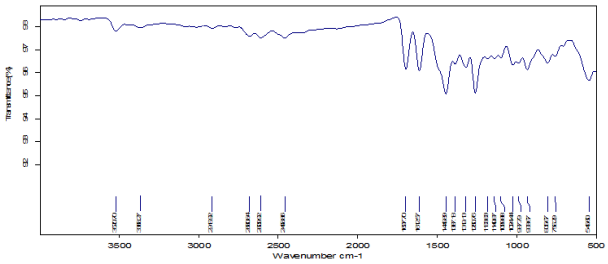

Fig No. 2: FTIR of pure drug (Ciprofloxacin)

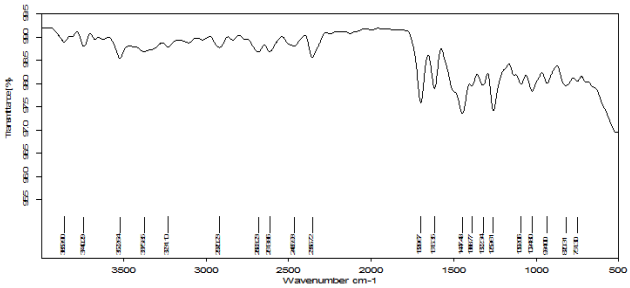

Fig. No.3: FTIR Spectra of Ciprofloxacin with HPMC

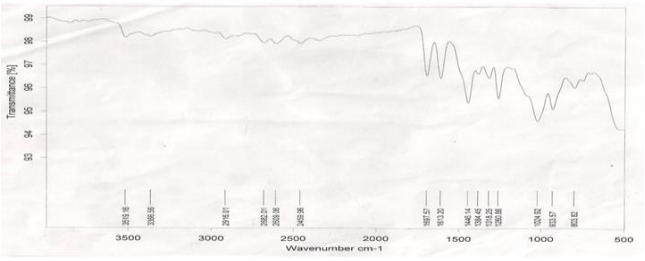

Fig No. 4: FTIR Spectra of Ciprofloxacin with Carbopol 934

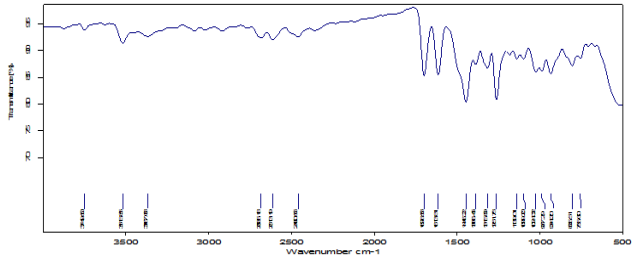

Fig No. 5: FTIR Spectra of Ciprofloxacin with xanthan gum

Fig No. 6-15: Formation of Insitu gel in pH 7.4 phosphate buffer of formulation (F6)

Ciprofloxacin ocular Insitu gel:

1) Visual Appearance and Clarity: The visual appearance and clarity of all formulations were determined to be good, and clarity was gained after overnight standing.

2) pH: The pH of all formulations was determined to be adequate, ranging from 6.5 to 7.1. The formulations were liquid and at the pH that was specified.

3) Drug content: The percent drug for formulations F1-F9 is shown in Table No. 7 below. The medication content was confirmed to be within permissible limits in all formulations.

4) Rheological studies:

The viscosity values obtained for formulas F1 - F9 using Nune's viscometer with spindle no. 4 at various angular viscosities are shown in Table No. 8.8. The rheological investigation findings indicated that the viscosity falls as the angular viscosity increases. A viscosity value in the range of 15-50 cps often enhances eye contact time substantially. Figure 8.16 depicts the rheological profile of Ciprofloxacin's developed in situ gelling system.

5) Gelling capacity:

When the formulations were added to the pH 7.4 Phosphate buffer, they all gelled instantly and lasted for a few hours. To promote continuous drug release locally, the in-situ produced gel should maintain its integrity for an extended length of time without dissolving or degrading.

6) In-vitro diffusion study:

Ciprofloxacin F1-F9 in-situ gelling formulations were submitted to 8-hour in vitro release experiments. The dissolving media for these in-vitro release tests was pH 7.4 phosphate buffer. The rate of release of the F3 formulation created with Carbopol 934P becomes more resistive as the polymer concentration increases. Tables 8.9, 8.10, and 8.11 depict the in-vitro drug release profile.

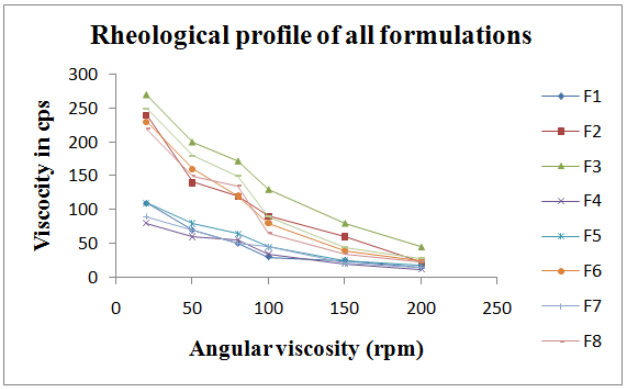

Figure No.16 : Rheological Profile of all formulations

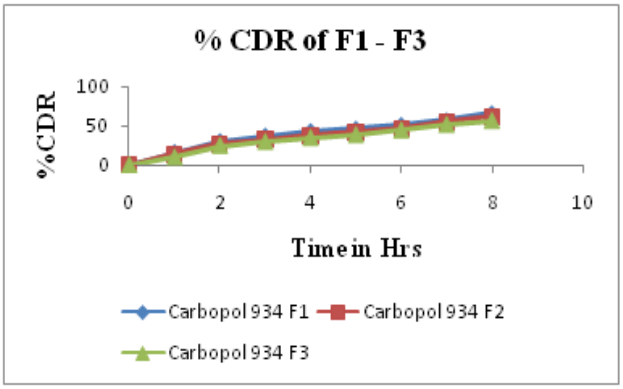

Figure No.17: % CDR of F1 – F3

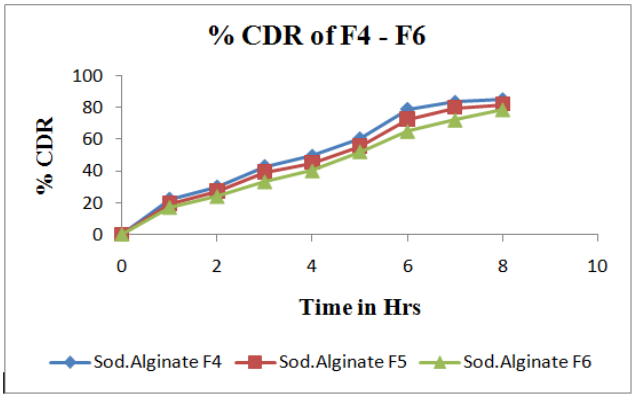

Figure No. 18 : % CDR of F4 – F6

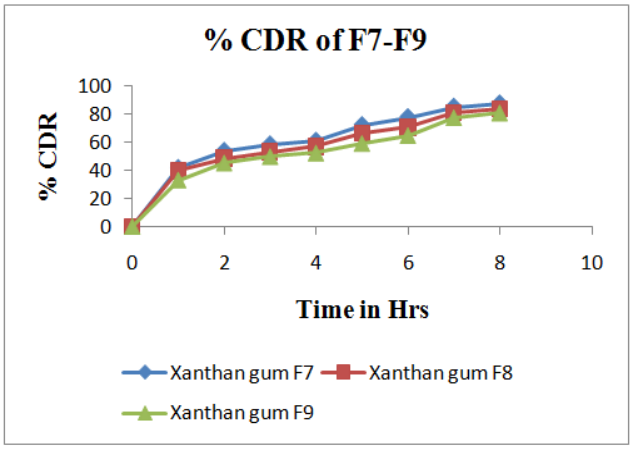

Figure No.19: % CDR of F7 – F9

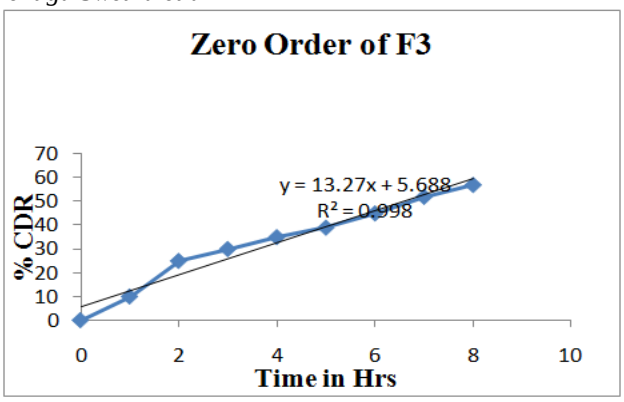

Figure No.20: Zero order kinetics of F3

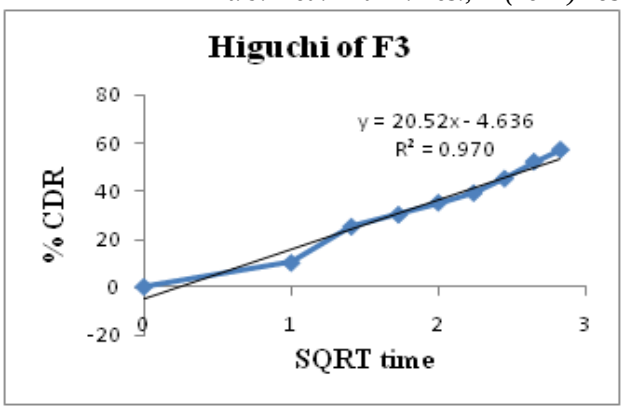

Figure No.8.22: Higuchi equation of F3

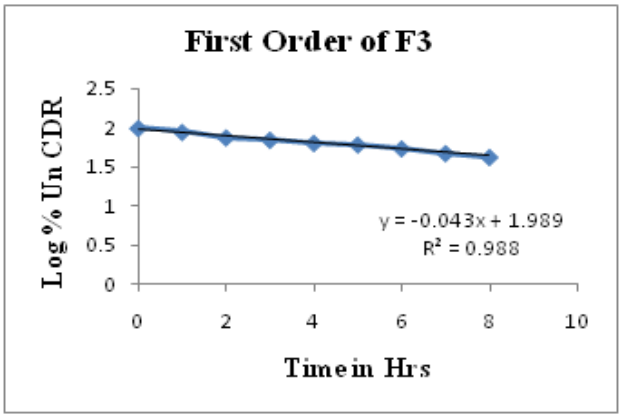

Figure No 21: First order kinetics of F3

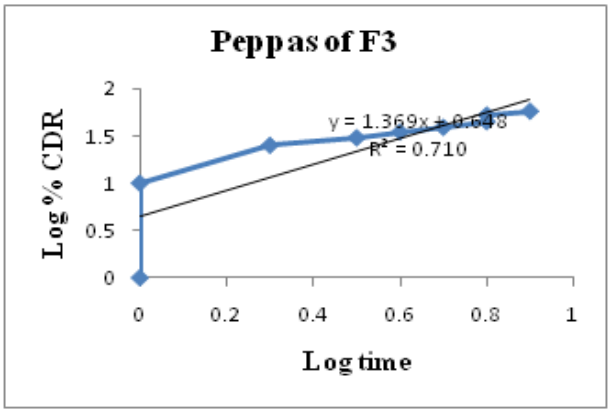

Figure No.8.23: Peppas equation of F3

Table No. 1Formulation table for Ciprofloxacin ocular In situ gel

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ciprofloxacin [mg]	250	250	250	250	250	250	250	250	250
Carbopol [mg]	500	1000	1500	-	-	-	-	-	-
Xanthangum[mg]	-	-	-	500	1000	1500	-	-	-
Sodium alginate [mg]	-	-	-	-	-	-	500	1000	1500
HPMC E50LV (mg)	30	30	30	30	30	30	30	30	30
Tween 20 (gm)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Benzalkonium chloride (mg)	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Distilled water [ml]	10	10	10	10	10	10	10	10	10

Table:2 Calibration curve of Ciprofloxacin in pH 7.4 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
1	0.13
2	0.25
3	0.39
4	0.52
5	0.67

Table No.7: pH, Drug content and Gelling capacity studies of Ciprofloxacin ocular insitu gel

Formulation code	pH	Drug content (%)	Gelling capacity
F1	6.7	95.76	++
F2	6.8	96.30	++
F3	7.1	99.81	+++
F4	6.6	94.14	++
F5	6.5	95.12	++

F6	6.8	97.85	+
F7	6.9	93.66	++
F8	7.1	94.74	++
F9	6.8	97.25	++

Table No.8: Rheological studies of Ciprofloxacin ocular insitu gel

Formulation code	**Angular velocity (rpm)**					
	20	**50**	**80**	**100**	**150**	**200**
F1	110	70	50	30	25	15
F2	240	140	120	90	60	22
F3	270	200	172	130	80	45
F4	80	60	55	35	20	12
F5	110	80	65	45	25	18
F6	230	160	120	80	40	25
F7	90	70	50	45	20	14
F8	220	150	135	65	35	23
F9	250	180	150	90	45	28

Table No.9: % CDR of formulation F1 – F3 made with Carbopol 934

Time in Hrs	Carbapol 934		
	F1	F2	F3
0	0	0	0
1	16	14	10
2	30	27	25
3	37	33	30
4	43	38	35
5	46	42	39
6	51	47	45
7	57	55	52
8	66.2	62	57

Table No.10: % CDR of formulation F4 – F6 made with Sodium alginate

Time in Hrs	Sod. Alginate		
	F4	F5	F6
0	0	0	0
1	22.24	19.27	17.12
2	29.94	27.25	24.03
3	42.82	39.28	33.33
4	49.35	45.13	40.23
5	60.32	55.42	52.29
6	78.92	72.56	65.17
7	83.37	80.15	72.34
8	85	82	79

Table No.11 % CDR of formulation F7 – F9 made with Xanthan gum

Time in Hrs	Xanthan gum		
	F7	F8	F9
0	0	0	0
1	42.17	39.72	33.15
2	54.28	48.84	45.32
3	58.96	53.37	49.88
4	61.48	57.12	52.42
5	72.59	66.56	59.17
6	78.23	70.93	64.92
7	85.68	81.24	77.67
8	88	84	81

Table No. 12: Drug release kinetics of formulation F3

Time in Hrs	Sqrt time	Log time	% CDR	Un CDR	log% un CDR	Log % CDR
0	0	0	0	100	2	0
1	1.00	0.0	10	90	1.95	1.00
2	1.41	0.3	25	75	1.88	1.40
3	1.73	0.5	30	70	1.85	1.48
4	2.00	0.6	35	65	1.81	1.54
5	2.24	0.7	39	61	1.79	1.59
6	2.45	0.8	45	55	1.74	1.65
7	2.65	1	52	48	1.68	1
8	2.83	0.9	57	43	1.63	1.76

Table No. 13*: In vitro* release kinetics of F3 Formulation

Formulation code	Zero order		First order		Higuchi model		Korsmeyer-peppas		Release Mechanism transport
	Slope	R^2	Slope	R^2	Slope	R^2	n	R^2	
F3	13.271	0.998	-0.043	0.988	20.52	0.970	1.369	0.710	Super Case II transport

According to the data analysis, the drug release followed zero order kinetics, as the greatest linearity of R2 achieved was close to one for the entire manufactured nasal in situ gel as plot between time vs percent cumulative drug releases.

Discussion

The study aimed to develop a novel method for delivering Ciprofloxacin, an ophthalmic drug, to enhance its effectiveness in the eye. A Ciprofloxacin gel was formulated using Carbopol 940, Sodium alginate, Xanthan gum, and HPMC K4M through a pH-triggered in situ gelling technique. This system, containing 0.5% W/V Ciprofloxacin, was designed to treat ocular infections like conjunctivitis. The formulations were characterized by their appearance, color, pH, gelling capacity, rheological properties, and in vitro release in pH 7.4 phosphate buffer. All formulations were clear with pH values ranging from 6.5 to 7.1. Optimization of Carbopol 940 and HPMC concentrations resulted in superior gelling capacity, making the gels suitable for easy instillation as eye drops under physiological conditions. The cumulative percentage of drug release varied across formulations, with F4, F7, and F9 showing the highest release rates of 85%, 88%, and 81%, respectively, while F3 exhibited significantly delayed release. Rheological characterization indicated that F3 demonstrated better pseudoplastic behavior. In vitro release studies revealed that higher polymer concentrations slowed drug release, while lower concentrations accelerated it. FTIR analysis confirmed no interactions between the drug and polymers. The methodology for the in situ gelling system was cost-effective and provided sustained drug release over an 8-hour period. These hydrogel formulations, initially administered as solutions, rapidly formed hydrogels capable of withstanding shear forces in the cul-de-sac. The pH-triggered in situ gel of Ciprofloxacin showed sustained drug release compared to conventional ophthalmic solutions, offering a viable alternative to traditional eye drops by prolonging drug release. The prolonged residence time of the in situ gelling system in the precorneal area resulted in higher bioavailability and reduced systemic side effects by preventing drainage through the nasolacrimal duct. This formulation effectively treated conjunctivitis with consistent drug release over the desired period. The evaluated in situ gelling formulation shows potential for ophthalmic use due to its ease of administration and extended ocular residence time without causing eye irritation.

4. Conclusion

The development of a pH-triggered in situ gelling system for Ciprofloxacin demonstrates a promising approach to enhance the effectiveness of ophthalmic drug delivery. The optimized formulations provided sustained drug release, improved bioavailability, and reduced systemic side effects compared to conventional eye drops. This technique offers a viable alternative to traditional ophthalmic solutions by ensuring prolonged residence time in the eye, making it an effective treatment option for ocular infections such as conjunctivitis. The in situ gelling system's ease of administration and potential to extend ocular residence time without causing irritation highlight its promise for future ophthalmic applications.

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