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Development of an *In Situ* Gel Forming Solution for Controlled Ocular Delivery of Ciprofloxacin Hydrochloride

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ABSTRACT

Ciprofloxacin hydrochloride is a fluoroquinolone antibiotic, widely effective in the treatment of ophthalmic disorders like, corneal ulcers and conjunctivitis. In the present study, an attempt has been made to formulate ciprofloxacin hydrochloride as sustained release *in situ* gel systems utilizing the concept of ion- activated gelation using Gelrite alone and with sodium alginate in combination with HPMC E50 LV. Prepared formulations were evaluated for several parameters like drug polymer compatibility, viscosity, gelling and gel retention time, clarity, pH, drug content, antimicrobial efficacy, sterility and *in vitro* drug release. Among all the formulations, batches G3 containing 0.6 %w/v of Gelrite, A6 and A7 containing 1% w/w of sodium alginate with 0.5 and 0.75 % w/v of HPMC E50LV respectively were selected based on their gelling properties. The drug release of A6 extended upto 7 h and that of G3 and A7 extended upto 8 h. The formulations showed pseudo plastic behaviour after gelling. G3 showed better stability and clarity than the alginate formulations and was taken for further evaluations. It showed better antimicrobial efficacy when compared with standard. The mechanism of drug release from the best formulation was further evaluated. Hence the developed *in situ* system may be an alternative to conventional eye drops.

Keywords: Ciprofloxacin hydrochloride, *in situ* gel systems, Gelrite, Sodium alginate.

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INTRODUCTION

Conventional ophthalmic preparations result in poor ocular bioavailability due to many physiological and anatomical constraints. Drug solution draining away from the pre corneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently the ocular bioavailability of topically applied drugs. Due to these factors, typically less than 1% of the drug reaches the aqueous humor[1]. Many novel ocular drug delivery systems have been developed not only to prolong the contact time of the vehicle on the ocular surface, but also to slow down drug elimination thus increasing ocular bioavailability of drugs. The development of *in situ* gel systems has received considerable attention over the past few years to address the above problems. It has numerous advantages such as ease of administration and reduced frequency of administration, improved patient compliance and comfort when compared to inserts and ointments[2]. Such a system can be formulated as a liquid dosage form suitable to be administered by instillation into the eye, which upon exposure to physiological conditions, changes to the gel phase, thus increasing the pre-corneal residence time of the delivery system and enhancing ocular bioavailability[3]. *In situ* forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. There are some broadly defined mechanisms used for triggering the *in situ* gel formation of biomaterials: physiological stimuli (e.g; temperature and pH), physical changes in biomaterials (e.g., solvent exchange and swelling), chemical reactions (e.g., enzymatic, chemical and photo-initiated polymerization)[4-7]. Ciprofloxacin hydrochloride (CFX) is a fluroquinolone broad-spectrum antibiotic which is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division. It is used to treat ocular infections and ulcers in the cornea of the eye[8-10]. The aim of the present work was to formulate *in situ* gels of ciprofloxacin hydrochloride using the phase transition properties of Gelrite and sodium alginate which replaced with mono or divalent cations present in the tear fluid.

MATERIALS AND METHODS

Ciprofloxacin hydrochloride was obtained as a gift sample from Cadila Pharmaceuticals Ltd., Ahmedabad, India. Gelrite was procured from Sigma Chemicals. Sodium alginate was procured from Thomas Baker Chemicals Ltd., Mumbai. Hydroxy propyl methyl cellulose E50LV was

obtained from Orchid Pharmaceuticals, Chennai. All the materials and solvents used were of analytical grade.

Preformulation compatibility studies

To check for the evidence of any interaction between the drug and excipients used, solid admixtures were prepared by mixing the drug with optimized formulation excipients separately in the ratio of 1:1 and stored in air tight containers at 30 ± 2 ºC/65 ± 5 % RH. The solid admixtures were characterized using Fourier transform infrared (FTIR) spectroscopy.

FORMULATION OF OPHTHALMIC GEL

Various trial batches of ophthalmic gels were prepared using two different polymeric agents *viz*. Gelrite and sodium alginate. Drug was added only to those formulations which showed satisfactory gelling time.

Using Gelrite as gelling agent

Gelrite was dissolved in 75 ml of distilled deionized water, and this solution was heated to about 85°C for 15 min, then beaker was cooled with stirring. After cooling, benzalkonium chloride and drug solution were added to the polymer solution and volume was made up to 100 ml with distilled deionized water. Aseptic conditions were maintained (by Laminar air flow system) throughout the formulation process and the formulations, in their final pack were subjected to terminal sterilization by autoclaving at 121°C and 15 psi for 20 min. Five different concentrations of the polymers were tried to get the formulations G1 to G5. The composition of the batches is shown in table 1.

Table 1: Formulation chart for Gelrite batch

Ingredients	Formulation code				
	G1	G2	G3	G4	G5
CFX (mg)	-	-	300	-	-
Gelrite (% w/v)	0.3	0.45	0.6	0.75	0.9
Benzalkonium chloride (% w/v)	0.02	0.02	0.02	0.02	0.02
Distilled water (qs to 100 ml)	qs	qs	qs	qs	qs

CFX: Ciprofloxacin hydrochloride

Using sodium alginate as gelling agent

The alginate solution was prepared by dispersing the required amount in 75 ml distilled deionized water with continuous stirring until completely dissolved. The alginate/HPMC solutions were prepared by dispersing the required amount of HPMC in the desired concentration of alginate with continuous stirring until completely dissolved. Benzalkonium chloride and drug solution were added to the polymer solution and volume was made up to 100 ml with distilled deionized water. Aseptic conditions were maintained (by Laminar air flow system) throughout

the formulation process and the formulations in their final pack were subjected to terminal sterilization by autoclaving at 121°C and 15 psi for 20 min. Eleven different concentrations of sodium alginate were tried with varying concentration of HPMC E50LV to get the formulation A1 to A11. The composition of the batches is shown in table 2.

Table 2: Formulation chart for sodium alginate batch

Ingredients	Formulation code										
	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11
CFX (mg)	-	-	-	300	-	300	300	-	-	-	-
Sodium alginate (%w/v)	0.75	0.75	0.75	0.75	0.75	1.0	1.0	1.0	1.0	1.0	1.25
HPMC E50LV	0.4	0.7	1.0	1.3	1.6	0.4	0.7	1.0	1.3	1.6	0.4
Benzalkonium chloride (% w/v)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Dis. water (qs to 100 ml)	qs	qs	qs	Qs	qs	qs	qs	qs	qs	qs	qs

CFX: Ciprofloxacin hydrochloride

***In vitro* evaluation of formulation**

Gelling time

The gelling time was determined by mixing the formulation with freshly prepared simulated tear fluid in a proportion of 25:7. The results were assessed visually. The time taken for gel to form and the time taken for it to dissolve was noted.

pH and clarity of the solution

pH of the formulation was determined using digital pH meter. The formulations were inspected under fluorescent light against a white and black background in well-lit cabinet for appearance and clarity.

Drug content estimation

Drug content in the ophthalmic gels was estimated by calibration curve method using UV – visible spectrophotometer.

***Ex vivo* corneal permeation studies**

Goat cornea was used in the present investigation to study the permeation across the corneal membrane. The study was carried out by using Franz-diffusion cell in such a way that cornea side continuously remained in intimate contact with formulation in the donor compartment. The receptor compartment was filled with simulated tear fluid pH 7.4 maintained at 34 º C ± 0.5º C. The receptor medium was stirred on a magnetic stirrer. The samples were withdrawn at different time intervals and analyzed for drug content. Receptor medium was replenished with an equal volume of simulated tear fluid (pH 7.4) at each time interval.

Rheological study

The viscosity measurements were performed using Brookfield DV-e viscometer. The viscosity of the formulation before gelling was carried out using LV-2 spindle. The developed formulation was placed in the adaptor of the viscometer and RPM was increased gradually from 6 to 100 rpm and then the hierarchy of RPM was reversed. The average of the two readings was used to calculate the viscosity. By adding simulated tear fluid, the formulation was converted into a gel form and the viscosity was determined as specified above using LV-3 spindle.

Test for sterility[11]

Tests for sterility were performed on the formulations for aerobic, anaerobic bacteria and fungi by using malternate thioglycollate medium and soyabean casein digest medium. As per IP procedure two containers were selected for sterility test. In each test, three sterile test tubes were used in the study and labelled as 'negative control', 'test' and 'positive control'.

Test for aerobic bacteria

20 ml of sterile alternate thioglycollate medium was transferred to each of the three tubes aseptically. The tube labeled as positive control was inoculated with viable aerobic microorganism *Bacillus subtilis* (ATCC No. 6633) aseptically. 2.5 ml of the ophthalmic preparation was added to the tube labeled as test. All three tubes were incubated at 30-35ºC for not less than 7 days.

Test for anaerobic bacteria

20 ml of sterile alternate thioglycollate medium was transferred to each of the three tubes aseptically. The tube labeled as positive control was inoculated with viable anaerobic microorganism *Bacteriodes vulgatus* (ATCC No. 8482) aseptically. 2.5 ml of the ophthalmic preparation was added to the tube labeled as test. All three tubes were incubated at 30-35ºC for not less than 7 days.

Test for fungi

20 ml of sterile soyabean casein digest medium was transferred to each of the three tubes aseptically. The tube labeled as positive control was inoculated with *Candida albicans* (ATCC No. 10231) aseptically. 2.5 ml of the ophthalmic preparation was added to the tube labeled as test. All three tubes were incubated at 20-25ºC for not less than 7 days.

Stability studies

To assess the stability of drug and formulation, accelerated stability studies were performed on A6, A7 and G3 formulations for 60 days at 30 ± 2°C, 65 ± 5% RH and 40 ± 2°C, 75 ± 5% RH. Required amount of samples were taken at the end of 30 days and 60 days and evaluated for their gelling capacity, gel retention, drug content, pH, clarity and drug release profile.

Antimicrobial studies[12,13]

This test was carried out by the agar diffusion test using the cup-plate technique. Cups were bored into sterile nutrient agar plates previously seeded with *Staphylococcus aureus* (ATCC 25923). Marketed ciprofloxacin eye drops and the developed formulation G3 were poured into these cups and the solutions were allowed to diffuse for 2 h after which the agar plates were incubated at 37 ± 0.5ºC for 24 h. The zone of inhibition was measured around each cup and compared with that of control. Both positive and negative controls were maintained.

Drug release kinetics[14,15]

The interpretation of the release profile was carried out using different kinetic models, namely, Zero order, Higuchi and Korsmeyer- Peppas.

Ocular irritancy studies[16,17]

Ocular irritation study was performed on optimized formulation G3 after due permission from Institutional animal Ethics Committee. Three male albino rabbits (A, B, C) each weighing about 2 to 3 kg were taken and as per Draize's test, sterile G3 formulation (0.1 ml) was instilled in to cul-de-sac and irritancy was tested at the time interval of 1, 24, 48, 72 hours and 1 week after administration. The rabbits were observed periodically for redness, swelling and watering of the eyes.

Comparison of most satisfactory formulation with marketed formulation

The *in vitro* drug release profile of the best formulation of *in situ* gel i.e., G3 was compared with that of the marketed ciprofloxacin eye drops.

RESULTS AND DISCUSSION

Five formulations of *in situ* gelling systems of varying compositions of Gelrite and ten formulations of varying compositions of sodium alginate were prepared. The prepared *in situ* gels were evaluated for clarity, pH, gelling capacity, drug content, rheological study, *ex vivo* corneal diffusion study, sterility and antimicrobial efficacy.

Preformulation studies

FT-IR spectra of pure drug and mixture of drug and polymers is shown in figure 1. It was observed that there were no significant changes in the characteristic peaks of drug in drug-polymer mixture, thus indicating compatibility between drug and the polymers.

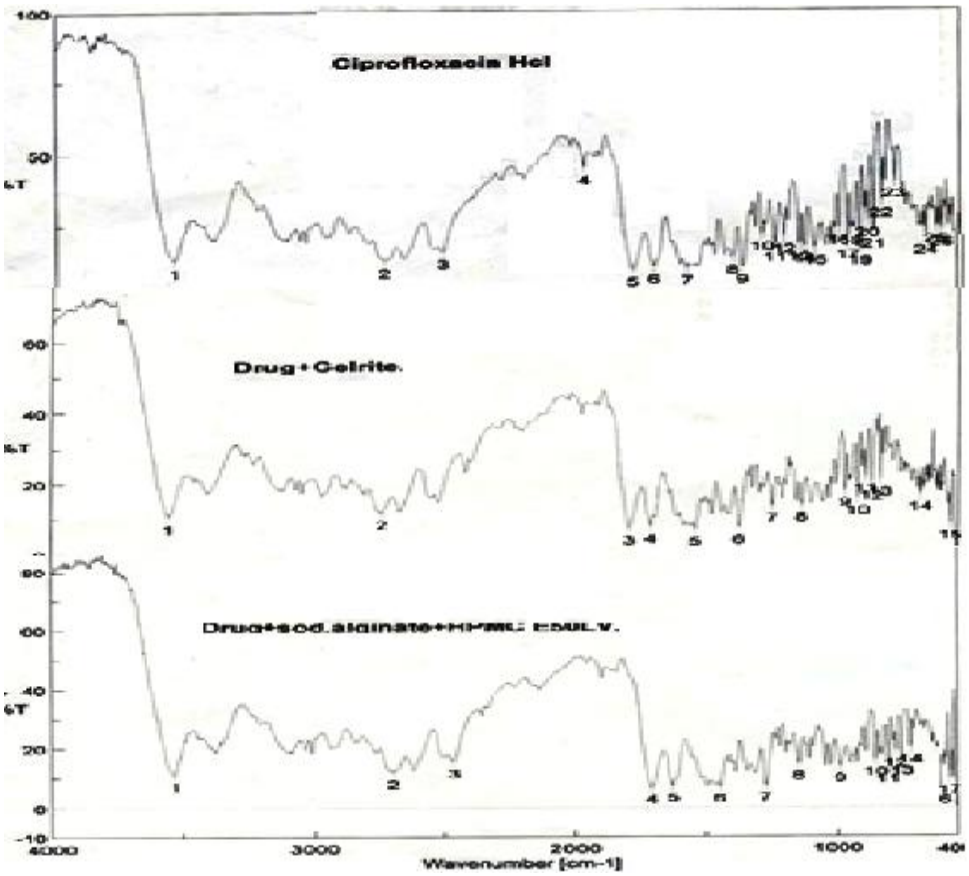

Figure 1: FTIR spectra of pure drug with Gelrite, sodium alginate + HPMC E50LV

Gelling time

The viscosity and gelling capacity plays an important role in *in situ* gelling systems. The gelling capacity and time of various formulations is given in table 3. The study indicated that G4, G5, A8, A9 and A10 converted to gel form even before dilution with tear fluid and hence these formulations were not suitable for ophthalmic use. G3, A4, A6, and A7 formulations showed satisfactory gelling time and capacity. Hence these formulations were selected and drug was added to it.

pH and clarity of the solution

The G3 formulation was found to be clear and transparent whereas formulations A6 and A7 was pale yellow in colour and less transparent. The pH of all the formulations was found to be in the range of 6.1 to 6.5 which is optimum for an ophthalmic formulation. The results are shown in table 4.

Table 3: Gelling capacity of various formulations

Formulation code	Gelling capacity	Gel retention time (h)
G1	+	-
G2	++	4.12

G3	+++	7.98
G4	O.V.	-
G5	O.V.	-
A1	++	1.9
A2	++	3.3
A3	++	4.3
A4	++	5.41
A5	O.V.	-
A6	+++	7.21
A7	+++	8.23
A8	O.V.	-
A9	O.V.	-
A10	O.V.	-
A11	O.V.	-

+ : weak gelling and gel not retained; ++ : instant gelling and gel retained for few hours;

+++ : instant gelling and gel retained for extended period of time; O.V.: outside viscous.

Table 4: Data for pH, clarity and drug content of formulations

Formula code	Appearance	Clarity	pH	Drug content (%)*
G3	Transparent, colorless	Transparent	6.53	98.7 ± 0.224
A4	Pale yellow	Satisfactory	6.05	98.79 ± 0.213
A6	Pale yellow	Satisfactory	6.23	99.8 ± 0.243
A7	Pale yellow	Satisfactory	6.10	99.03 ± 0.189

* values are expressed as mean ± SD, n=3

Drug content estimation

The drug content was found to be in the range of 98.7 % to 99.80 % which indicated a uniform distribution of drug in the formulations and results are presented in table 4.

***Ex vivo* corneal permeation studies**

The release profile of the formulations is shown in figure 2. The release of the drug from the formulation G3 was found to be 97.93 % after 8 h whereas for A4, A6 &A7 the drug release was extended for about 5, 7 and 8 h respectively. A4 showed a drug release of 98.47 % at the end of 5h and A6 and A7 showed a release of 95.57 % and 97.08 % of ciprofloxacin respectively at the end of 8 h. Amongst the three formulations of sodium alginate batch the drug release was found to be good in A6 which showed a release upto 7 h and A7 which showed a release up to 8 h which may be due to the presence of higher conc. of sodium alginate along with HPMC E50LV. Hence G3, A6 and A7 were selected for further studies.

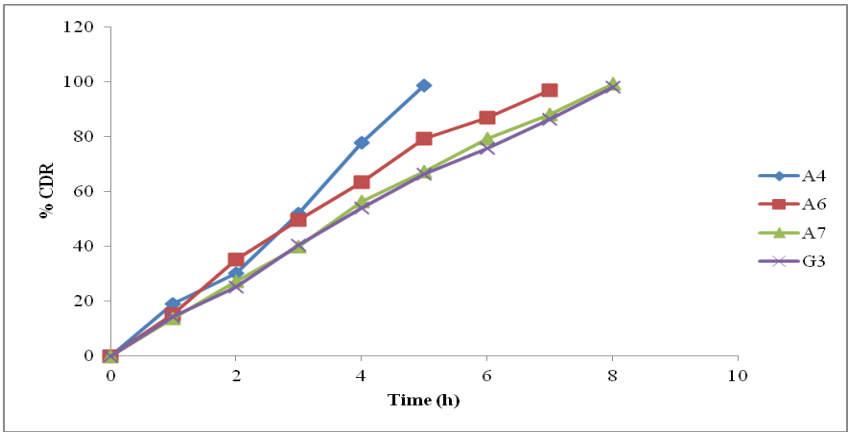

Figure 2: Drug release profile of G3, A4, A6 and A7 formulations

Rheological study

The batches G3, A6 and A7 were evaluated for their rheological profile both before and after gelling state. In both these conditions, a decrease in viscosity was found with an increase of RPM. The formulations exhibited pseudoplastic flow, as shown by shear thinning and a decrease in viscosity with increased RPM. This could give comfort to the patient without interrupting in the blinking of eye. Results are shown in and figure 3.

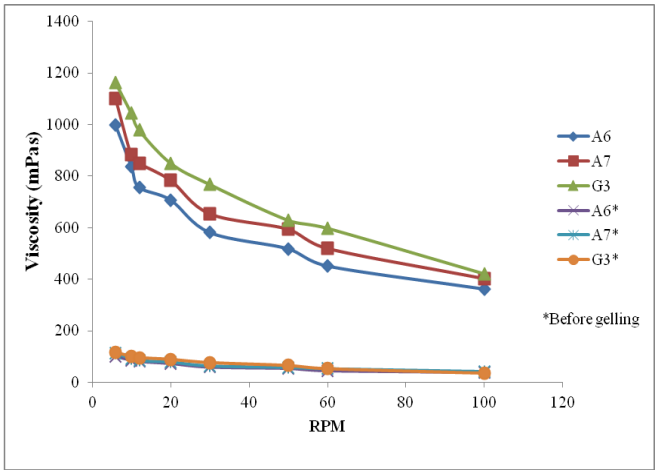

Figure 3: Rheological profile of G3, A6 and A7 formulations before and after gelling

Test for sterility

The formulations G3, A6 and A7 passed the test for sterility. There was no evidence of microbial growth till 7 days when incubated appropriately.

Stability studies

The results showed that batch G3, A6 and A7 did not show any significant changes in the parameters evaluated. Release profiles were similar to that of initial. It was also observed that the gelling capacity was not affected when stored. However due to the pale yellow to yellow-brown colour of sodium alginate batch, Gelrite was chosen as the polymer for *in situ* gelling. G3 was

selected for further evaluation since it gave a clear transparent gel. The data is shown in tables 5 and figure 4, 5 and 6.

Table 5: *In vitro* evaluation parameters of G3, A6 and A7 during stability studies

Formula code	Gelling capacity	Gel retention time (h)	Drug content* (%)	pH	Clarity/ Appearance
G3	Instantaneous	7.98	98.1 ± 0.472	6.53	Transparent
G3 A	Instantaneous	7.83	98.23 ± 0.208	6.59	Transparent
G3 B	Instantaneous	7.79	98.10 ± 0.264	6.68	Transparent
G3 C	Instantaneous	7.78	98.13 ± 0.152	6.82	Transparent
G3 D	Instantaneous	7.52	97.90 ± 0.251	6.87	Transparent
A6	Instantaneous	7.32	99.3 ± 0.171	6.23	Satisfactory/ Pale yellow
A6 A	Instantaneous	7.30	99.24 ± 0.130	6.32	Satisfactory/ Yellow-brown
A6 B	Instantaneous	7.30	99.19 ± 0.226	6.59	Satisfactory/ Yellow-brown
A6 C	Instantaneous	7.29	99.08 ± 0.148	6.78	Satisfactory/ Yellow-brown
A6 D	Instantaneous	7.28	98.65 ± 0.400	6.91	Satisfactory/ Yellow-brown
A7	Instantaneous	8.20	98.5 ± 0.191	6.10	Translucent/Pale yellow
A7 A	Instantaneous	8.19	98.35 ± 0.130	6.23	Translucent/ Yellow-brown
A7 B	Instantaneous	8.16	98.13 ± 0.170	6.29	Translucent/ Yellow-brown
A7 C	Instantaneous	8.16	97.89 ± 0.555	6.36	Translucent/ Yellow-brown
A7 D	Instantaneous	8.15	97.48 ± 0.549	6.57	Translucent/ Yellow-brown

*values are expressed as mean ± SD; A, B- after 30 days stored at 30 ± 2°C, 65 ± 5% RH and 40 ± 2°C, 75 ± 5% RH respectively; C, D- after 60 days stored at 30 ± 2°C, 65 ± 5% RH and 40 ± 2°C, 75 ± 5% RH respectively

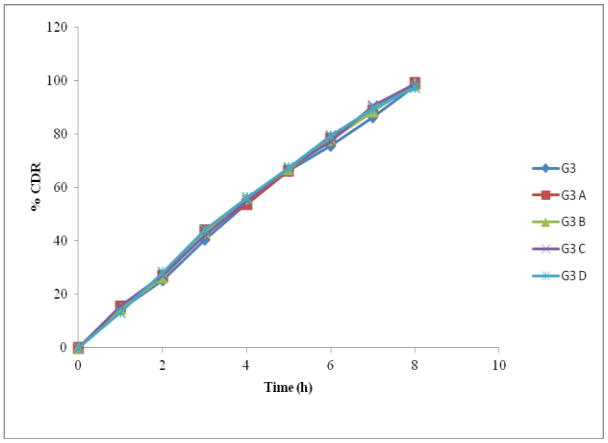

Figure 4: Drug release profile for G3 formulations during stability studies

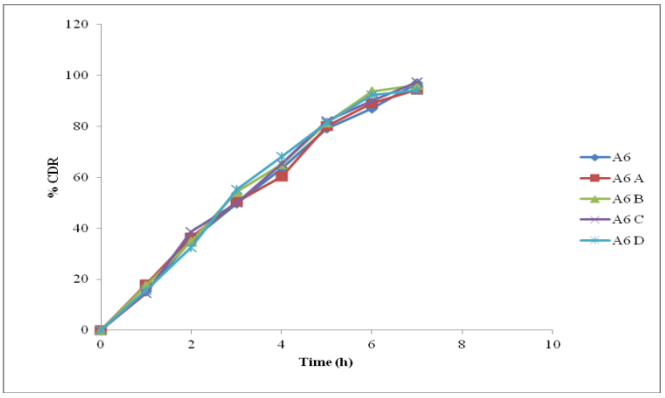

Figure 5: Drug release profile for A6 formulations during stability studies

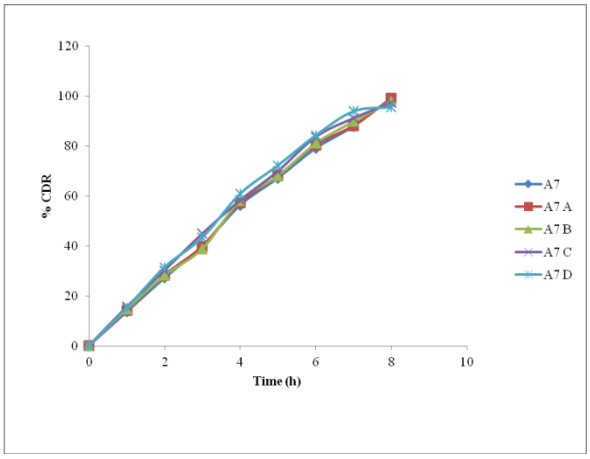

Figure 6: Drug release profile for A7 formulations during stability studies

Antimicrobial studies

G3 formulation and ciprofloxacin marketed eye drops showed measurable difference in area of zone of inhibition (figure 7 and table 6). The higher zone of inhibition values obtained for the formulation in comparison to the standard could be due to the slow and prolonged diffusion of the drug from the polymeric solution due to its higher viscosity. This indicated that ciprofloxacin retained its antimicrobial activity after formulation into a gel.

Figure 7: Antimicrobial studies showing zone of inhibition where 1- marketed preparation; 2- G3 formulation

Table 6: Antimicrobial study of G3 formulation

Formulation	Zone of inhibition* (mm)
Marketed eye drop	31.5 ± 1.1
G3 formulation	34.4 ± 0.1

*values are expressed as mean ± SD

Drug release kinetics

The drug release mechanism from the best formulation (G3) was further investigated. The zero order plots showed a regression value of 0.995 indicating the zero order release characteristics of the formulation (table 7). In order to find out the mechanism of drug release, the *in vitro* drug release data was graphically treated according to Higuchi's equation. Correlation value of Higuchi's plot revealed that the mechanism of drug release is by diffusion. The *in vitro* kinetic data was subjected to Peppa's model, and all the values revealed the fact that the drug release followed a super case II transport diffusion.

Table 7: Release kinetics of formulation G3

Formulation Code	R^2			N
	Zero order	First order	Higuchi model	Peppa's model
G3	0.995	0.8011	0.9895	0.9387

Ocular irritancy studies of the best formulation

In all three sections for 1 h, 24 h, 48 h, 72 h and 1 week observations, the scores given to the rabbits were less than the maximum total scores. So, results showed that there was no markable irritation to the sensitive ocular tissues by the formulation and hence the formulation was safe to use in ocular treatment (table 8a and 8b).

Table 8a: Ocular irritancy study- Rabbit cornea and iris observation

Observations	After 1h			After 24h			After 48h			After 72h			After 1 week		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
1 Cornea															
A Opacity – Degree of density (area which is most dense taken for reading)															
Scattered or diffuse area – details of iris clearly visible	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Easily discernible translucent areas, details of iris slightly obscured															
Opalescent areas, no details of iris visible, size of pupil barely discernible															
B Opaque, iris invisible Area of cornea involved															
One quarter (or less) but not zero	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

	Greater than one quarter – less than one-half															
	Greater than one-half less than three quarters															
	Greater than three quarters up to whole area															
	Score equals A x B x 5. Total maximum = 80															
	Total Score	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
2	**Iris**															
	A Values															
	Folds above normal, congestion, swelling, circumcorneal injection (any one or all of these or combination of any thereof), iris still reacting to light (sluggish reaction is positive)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	No reaction to light hemorrhage; gross destruction (any one or all of these)															
	Score Equals A x 5 Total possible maximum = 10															
	Total Score	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**

Table 8b: Ocular irritancy study- Rabbit conjunctiva observation

Observations	**After 1h**			**After 24h**			**After 48h**			**After 72h**			**After 1 week**		
	A	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**	**A**	**B**	**C**
Conjunctiva															
A Redness (refers to palpebral conjunctiva only)															
Vessels definitely injected above normal	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
More diffuse, deeper crimson red, individual vessels not easily discernible															
Diffuse beefy red															
B Chemosis															
Any swelling above normal (includes nictitating membrane)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Obvious swelling with partial eversion of the lids															
Swelling with lids about half closed															
Swelling with lids about half closed to completely closed															
C Discharge															
Any amount different from normal (does not include small amount observed in inner canthus of normal animals)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Discharge with moistening of the lids and hairs just adjacent to the lids															
Discharge with moistening of the lids and considerable area around the eye															
Score (A + B + C) x 2 Total maximum = 20															
Total Score	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**	**6**

Comparison of best developed formulation with marketed formulation

Results indicated that Gelrite formulation (G3) sustained the release upto 8 h as compared to marketed formulation which showed release in around 3 h (figure 8). Hence the developed formulation can be a viable alternative to conventional eye drops.

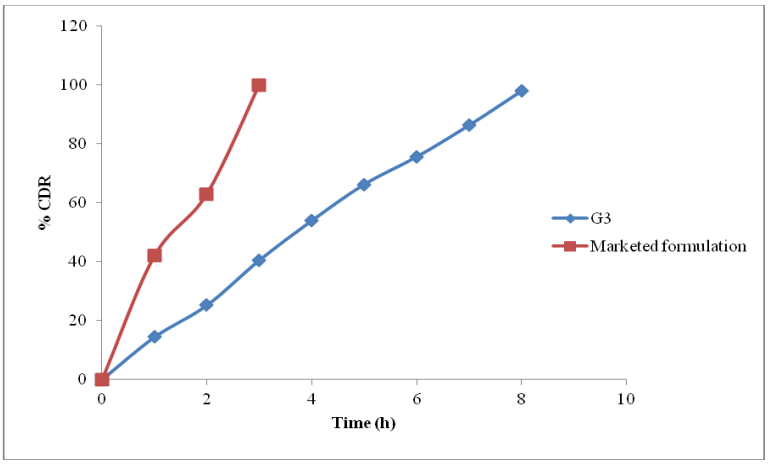

Figure 8: Comparison of *in vitro* drug release of G3 formulation with marketed ciprofloxacin HCl eye drops.

CONCLUSION

Ciprofloxacin hydrochloride, a broad spectrum antibiotic used in ocular therapy was formulated as *in situ* gel-forming preparations. Various trial batches were prepared using two different gelling agents, viz. Gelrite and sodium alginate in combination with HPMC E50LV. The formulation was liquid in nature under normal conditions and converted to the gel form upon physiologic conditions (presence of ions in tear fluid). Formulation with Gelrite 0.6 % w/v showed optimum clarity and stability when compared to the sodium alginate batch. This formulation showed a sustained release upto 8 h with good antimicrobial efficacy. Hence the developed formulation may be a viable alternative to conventional eye drop due to its ability to sustain the drug release through prolonged precorneal residence time.

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REFERENCES

1. Eaga CM, Kandukuri JM, Allenki V, Rao M. In-situgels- a novel approach for ocular drug delivery. Der Pharmacia Lettre 2009;1(1):21-33.
2. Peppas N, Langer R. New challenges in Biomaterials. Science 1994;263:1715-20.

3. Sindhu A, Sharon F, Bharath S, Basavaraj BV, Deveswaran, Madhavan V. Sustained ophthalmic delivery of ofloxacin from an ion activated in situ gelling system. Pak J Pharm Sci 2009;22(2):175-9.
4. Zhidong L, Jaiwei L, Shufang N, Hui L, Pingtian D, Weisan P. Study of a Pharmalginate- HPMC based in situ gelling ophthalmic delivery system for gatifloxacin. Int J Pharm. 2006; 315:7-12.
5. Jones MR, Massersmith PB. In-situ forming biomaterials. Oral Maxillofacial Surg Clin N Am 2002;14:29-38.
6. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev. 2001;53:321-39.
7. Muller WH, Deardoff DJ. Ophthalmic vehicles: the effect of methylcellulose on the penetration of homatropine hydrobromide through the cornea. J Am Pharm Assoc Am Pharm Assoc (Baltim). 1956;45(5):334–41.
8. Ozturk F, Kurt E, Inan UU, Kortunay S, Ilker SS, Basci NE, *et al.* The effects of prolonged acute use and inflammation on the ocular penetration of topical ciprofloxacin. Int J Pharm 2000;204(1-2);97-100.
9. Louie TJ. Ciprofloxacin: an oral quinolone for the treatment of infections with gram-negative pathogens. Can Med Assoc J 1994;150(5):669-76.
10. Wilhelmus KR, Hyndiuk RA, Caldwell DR, Abshire RL, Folkens AT, Godio LB. 0.3% Ciprofloxacin ophthalmic ointment in the treatment of bacterial keratitis. Arch Ophthalmol 1993;111(9):1210-18.
11. Sterility testing. United States Pharmacopeia (USP 32-NF 27). Rockville, MD: The United States Pharmacopeial Convention INC; 2009. p. 80.
12. Antimicrobial effectiveness testing. United States Pharmacopeia (USP 32-NF 27). Rockville, MD: The United States Pharmacopeial Convention INC; 2009. p. 67.
13. Varshosaz J, Tabbakhian M, Salmani Z. Designing of a thermosensitive chitosan/poloxamer *in Situ* gel for ocular delivery of Ciprofloxacin. The Open Drug Delivery Journal 2008;2:61-70.
14. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J Pharm Sci 1963;52:1145-49.
15. Korsmeyer RW, Gurny R, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm, 1983;15(1):25-35.

16. Derelanko MJ, Hollinger MA, editors. Handbook of Toxicology. 2nd ed. CRC Press LLC; 2002.
17. Draize J, Woodward G, Calvery O. Methods for the study of irritation and toxicity of substance applied topically to the skin and mucous membrane. J Pharm Col Exp Ther 1994;82:377–90.