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RESEARCH ARTICLE

DESIGN AND EVALUATION OF pH TRIGGERED *IN SITU* OPHTHALMIC GEL OF MOXIFLOXACIN HYDROCHLORIDE AND KETOROLAC TROMETHAMINE COMBINATION

[1,*]Shashank Nayak N. and [2]Srinivasa U.

[1]Ph. D Research Scholar Pacific Academy of Higher Education and Research University Udaipur, Rajasthan, INDIA and Asst Professor, Department of Pharmaceutics, Bapuji Pharmacy College Davanagere
[2]HOD Department of Pharmacognosy, Srinivasa College of Pharmacy, Mangalore, Karnataka India

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ABSTRACT

Eye drops are the most conventional ophthalmic drug delivery system available in the market with various patient compliance problems. In this current work pH triggered in situ ophthalmic gel of Moxifloxacin hydrochloride and Ketorolac tromethamine combination are prepared by using carbopol 934 as gelling agent and carboxy methyl tamarind kernel powder and Hydroxy propyl methyl cellulose K15M as viscosity enhancing agent and rate controlling polymer, Benzalkonium chloride was used as preservative in the above formulation. The formulations were sterilized by autoclaving at 121^0 C at 15 PSI at 20 min. The formulations were evaluated for various parameters like visual appearance, clarity, pH, gelling capacity, drug content and *in vitro* diffusion studies, antimicrobial study, stability study. The drug release pattern was analysed by derivative spectroscopy using derivative spectroscopy. The release pattern of the best formulation indicated that both the drug showed zero order release pattern for a period of 12 hours thus increasing the contact time of drug with ocular tissues and reducing the nasolacrimal drainage. The drug-drug and drug excipient compatibility study was done by FTIR. From this current work it can be concluded that *In situ* ophthalmic gel is an alternative to convention drug delivery system.

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INTRODUCTION

Eye is unique and vital organ. It is considered as window of the soul. We can enjoy and view the whole world only with this organ. There are various eye ailments which targets this organ and can cause loss the eye sight. Therefore various ophthalmic dosage forms are available. They are classified as conventional and newer drug delivery systems. Eye drops are common ophthalmic dosage form which is available till date and this causes poor therapeutic response and bioavailability, because of eleviated tear fluid turnover produces immediate precorneal elimination of instilled drug. A large amount of eye drop instilled produces poor patient non-compliance. Addition of excess drug in the formulation is an approach to overcome bioavailability problem, is highly dangerous if the drug gets drained from the eye and is absorbed into systemic circulation from the nasolacrimal duct. Various ophthalmic devices and delivery systems like inserts, ointments, suspensions and aqueous gels have been produced for enhancing the residence time of added dose and to increase the ophthalmic bioavailability.

Corresponding author: **Shashank Nayak,**
Ph. D Research scholar Pacific Academy of Higher Education and Research University Udaipur, Rajasthan, INDIA and Asst Professor, Department of Pharmaceutics, Bapuji Pharmacy College Davanagere.

These ocular drug delivery systems however have not been used majorly due to various drawbacks like blurred vision from ointments and low patient compliance from inserts. Various *in situ* gelling system have been prepared to increase the precorneal residence time of a drug and improve ophthalmic bioavailability. These systems consist of polymers which exhibit solution to gel phase transformation due to change in specific physico chemical parameter like pH, temperature and ion activation in the cul de sac in this case. Depending on the method used to produce sol-to-gel phase transition on the eye surface the following three types of systems are recognized. They are classified as pH triggered system, temperature dependant system and ion activated system. Using these three methods above *in situ* gelling ophthalmic delivery system is developed (Azmat *et al*., 2015). In this current work pH triggered in situ gel of Moxifloxacin HCl and Ketorolac Tromethamine combination using carbopol 934 as gelling agent and carboxy methylated tamarind kernel powder and Hydroxy propyl methyl cellulose as rate controlling polymer.

MATERIALS AND METHODS

Moxifloxacin hydrochloride and Ketorolac tromethamine was given as gift sample from micro labs Bangalore.

Carboxy methyl tamarind kernel powder was purchased from tamarind magic Hyderabad, Carbopol 934 and HPMC K15 M was of analytical grade

First order derivative spectroscopy of Moxifloxacin HCL and Ketorolac Tromethamine (Shashank *et al*., 2016)

The obtained zero order peak was converted into first order derivative spectra to get the ZCP of both the drugs, which is further used for simultaneous estimation of drugs in the in situ formulations.

Preparation of pH triggered *in situ* gelling system (Talat, 2013)

Required quantity of both the drugs was dissolved in 70 ml of distilled water, Carbopol 934 and Carboxyl methyl tamarind kernel powder and was weighed and sprinkled over the surface of the solution and kept for 24 hours. For the other set instead of carboxy methyl TKP HPMC K15M was added, Stirring was continued at 20 RPM followed by addition of benzalkonium chloride and the volume was made upto 100 ml with distilled water. The formulae of the preparation is given in Table 1.The preparation was then capped and autoclaved at 121 degree C at 20 min at 15 PSI.

RESULT AND DISCUSSION

First order spectra of Moxifloxacin HCL and Ketorolac tromethamine in Simulated tear fluid

The absorption maxima of Moxifloxacin HCl was found out at 288 nm and for ketorolac tromethamine was found out at 322 nm. The zero order derivative spectra of Moxifloxacin HCL which had absorption maxima of 288 nm was deravatized in software and was converted to first order spectra. The ZCP was found at 286 nm. The zero order spectra of Ketorolac tromethamine which had absorption maxima of 322 nm was deravatized in software to first order spectra. The ZCP was found at 328nm

Visual appearance, Clarity, pH, Drug content (Makwana *et al*., 2016; Kavitha, 2011; Gupta *et al*., 2014; Rasala *et al*., 2011; Shaikh *et al*., 2015)

The preparations were pale yellow and translucent in nature. The pH was in the range of 4.40 to 4.46. The drug content was in the range of 98.99 to 99.76 % for both the drugs.

***In vitro* gellation study**

The Gelling strength of various formulations having different proportions of carbopol and carboxy methyl tamarind kernel powder and HPMC K15M were evaluated by placing a drop of polymeric solution in vials containing 1 ml of freshly prepared simulated tear fluid, at 37 ^{0} C. The gel formed and time taken for gellation was assessed visually. The formulation F8 showed gellation for a period of 12 hours. The composition of artificial tear fluid used was NaCl 0.670 g, sodium bicarbonate 0.200 g, calcium chloride -2 H2O 0.008 g, purified water q.s. 100.0 g. For easy evaluation 20 ml of preparation were mixed with 20 ml of STF and maintained at 37^0 C.

Rheological studies

All eight formulations were in the range of 50 cps before gellation at non physiological condition and upto 10,000 cps after gellation at physiological condition which was analysed by using brook fields viscometer by using T bar spindle and spindle no 0. The formulations indicated pseudo plastic flow, indicating that as shear rate increases viscosity decreases Figure-1, 2,3, 4.

***In Vitro* drug release studies**

The drug release studies was performed by use of moulded using Franz diffusion cell, the cell was kept on magnetic stirrer and temperature was set to 37 ± 0.5^0 C. The release studies of Moxifloxacin HCL and Ketorolac tromethamine in mentioned in Figure 5,6,7,8.

Table 1. Composition of *In situ* ophthalmic gel

INGREDIENTS(% W/V)	F1	F2	F3	F4	F5	F6	F7	F8
Moxifloxacin HCL	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ketorolac Tromethamine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol 934	0.3	0.4	0.5	0.6	0.3	0.3	0.3	0.3
Hydroxyl propyl methyl cellulose K15M	0.4	0.5	0.6	0.7	-	-	-	-
Carboxy methyl Tamarind kernel powder	-	-	-	-	0.2	0.25	0.3	0.35
Benzalkonium chloride	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Distilled water QS	100	100	100	100	100	100	100	100

Table 2. Evaluation of appearance, clarity and pH and drug content

Formulations	Appearance	Clarity	pH	Moxi (DC) %	Keto (DC) %
F1	Pale yellow	Translucent	4.40	99.56	99.46
F2	Pale yellow	Translucent	4.40	99.34	99.10
F3	Pale yellow	Translucent	4.44	99.27	99.34
F4	Pale yellow	Translucent	4.46	98.99	99.34
F5	Pale yellow	Translucent	4.45	99.00	99.76
F6	Pale yellow	Translucent	4.41	99.55	99.67
F7	Pale yellow	Translucent	4.40	99.76	99.04
F8	Pale yellow	Translucent	4.43	99.34	99.45

Table 3. Gelling strength of the formulations

Formulation	Gelling strength	Duration of gelling
F1	++	6 hours
F2	++	7 hours
F3	+++	9 hours
F4	++++	12 hours
F5	++	7 hours
F6	+++	8 hours
F7	++++	10 hours
F8	++++	12 hours

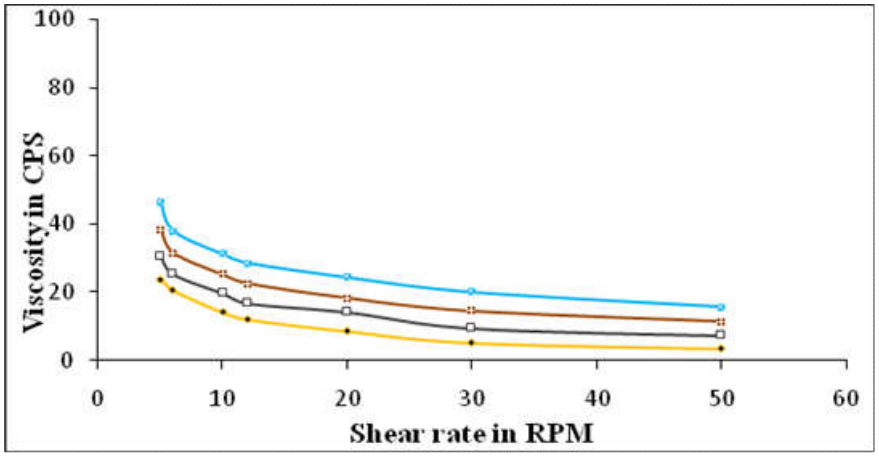

Figure 1. Viscosity of formulation (F1 to F4) at pH4.4

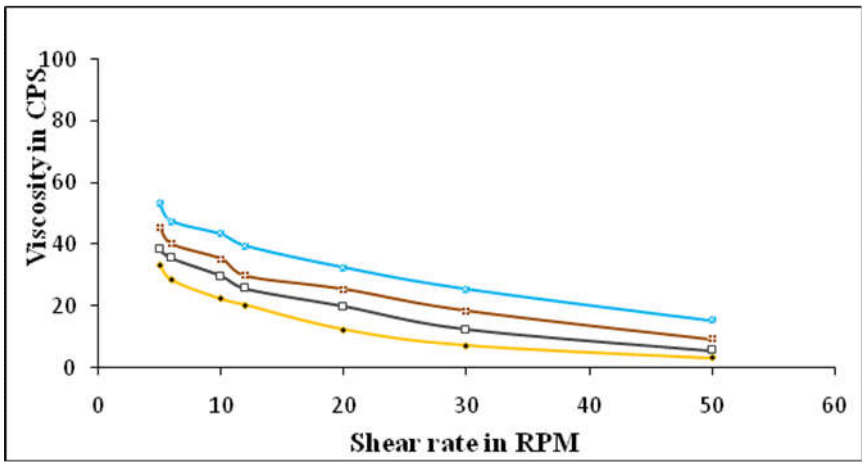

Figure 2. Viscosity of formulation (F5 to F8) at pH4.4

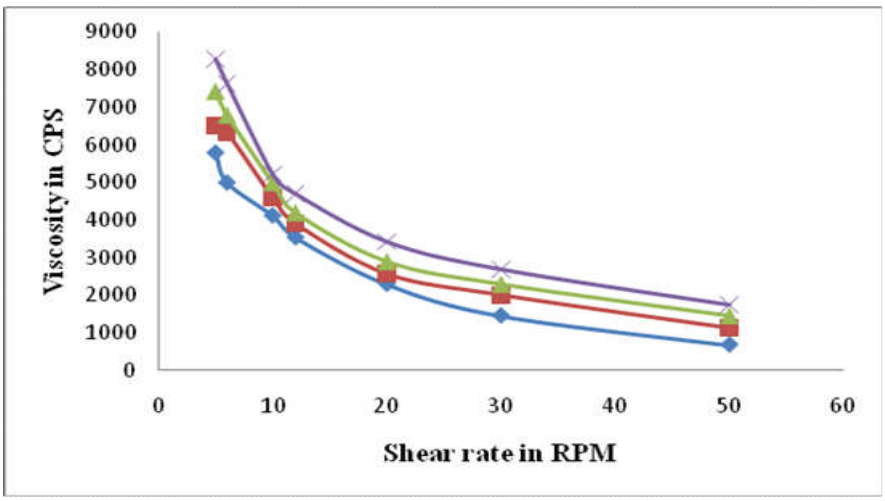

Figure 3. Viscosity of formulation (F1 to F4) at pH 7.4

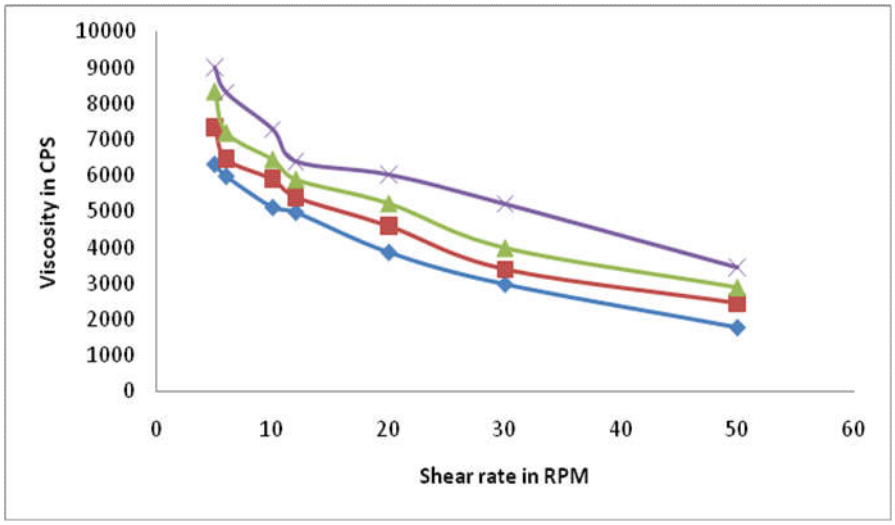

Figure 4. Viscosity of formulation (F5 to F8) at pH 7.4

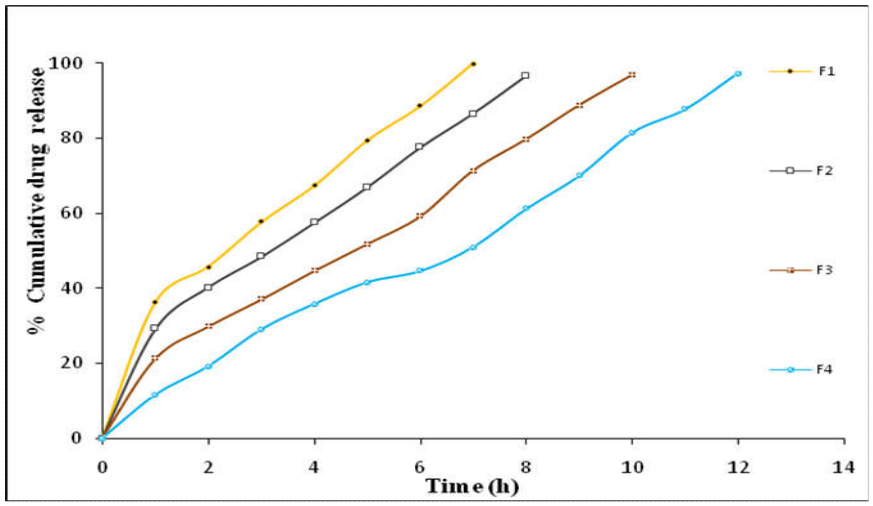

Figure 5. Release study of Moxifloxacin HCL (F1 to F4)

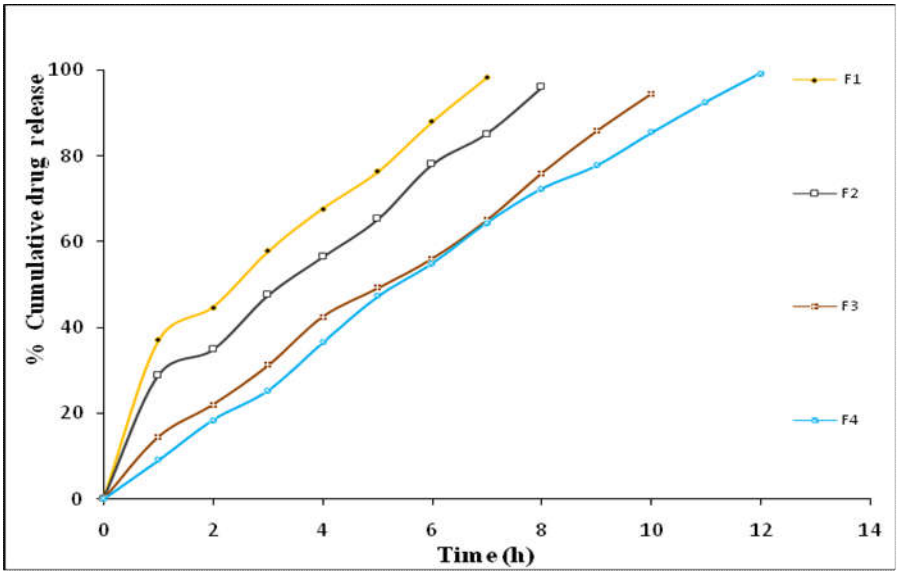

Figure 6. Release study of Ketorolac tromethamine (F1 to F4)

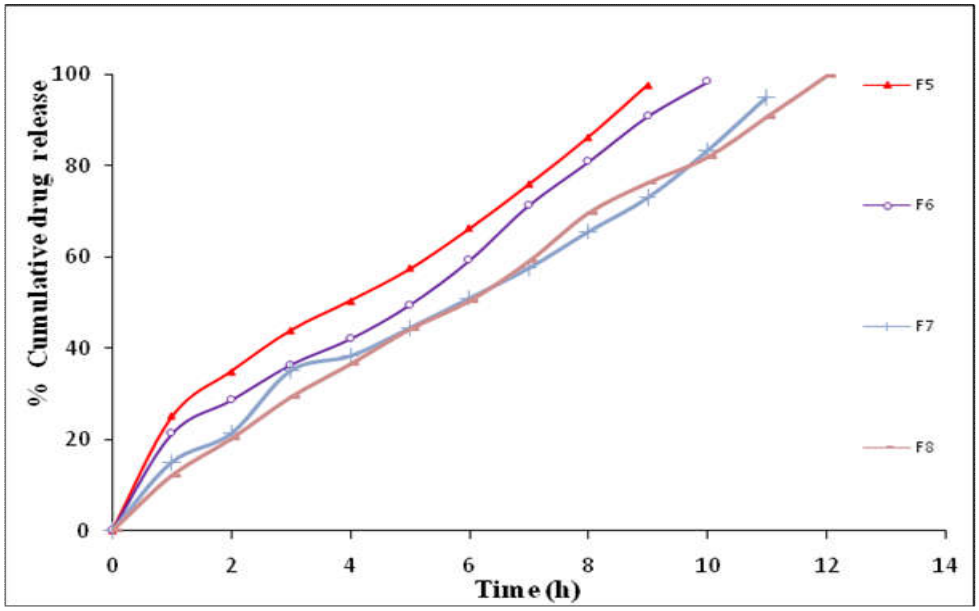

Figure 7. Release study of Moxifloxacin HCL (F5 to F8)

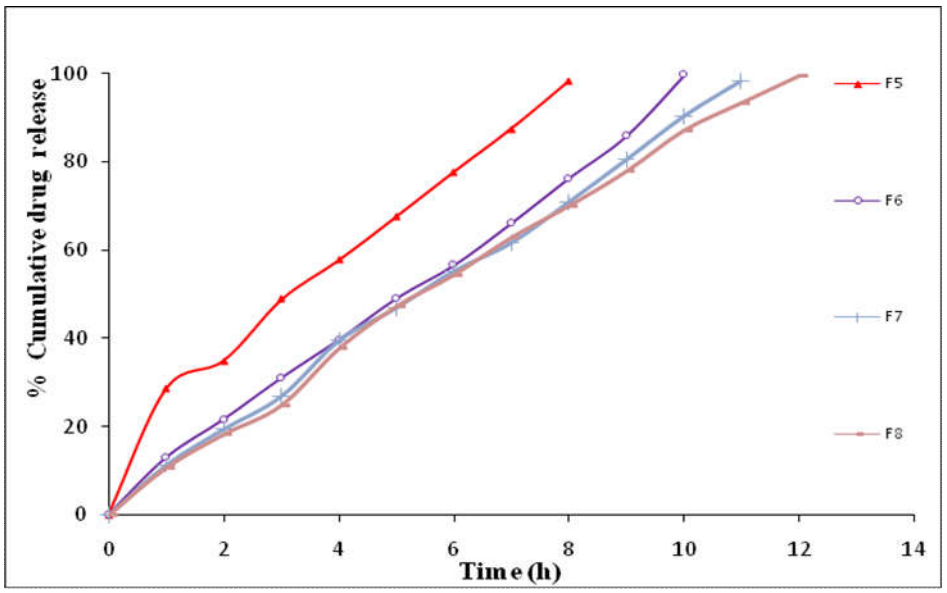

Figure 8. Release study of Ketorolac tromethamine (F5 to F8)

Table 4. Regression co-efficient analysis and best model fit analysis-Formulation F 1 to F 8 –Moxifloxacin HCL

Formulation code	Zero order	Peppas	Higuchi	First order	n Value	Best fit model
F1	0.9476	0.9789	0.9893	0.6693	0.5256	Zero order Higuchi
F2	0.9660	0.9848	0.9812	0.8513	0.5757	Zero order Peppas
F3	0.9876	0.9783	0.9521	0.8222	0.6691	Zero order Peppas
F4	0.9913	0.9899	0.9186	0.7745	0.8418	Zero order Peppas
F5	0.9748	0.9798	0.9655	0.7709	0.6050	Zero order Peppas
F6	0.9881	0.9654	0.9370	0.7618	0.6859	Zero order Peppas
F7	0.9876	0.9852	0.9376	0.8045	0.7559	Zero order Peppas
F8	0.9976	0.9979	0.9389	0.6043	0.8572	Zero order Peppas

The best formulae F8 showed controlled release for a period of 12 hours and showed peppas model of kinetics.

Sterility studies

The formulations were taken for sterility testing by direct inoculation technique and no sort of growth of any forms of microorganisms were observed in the formulations in both FTM and SCDM. Table 3

Antimicrobial activity

The Zone of Inhibition was better with E coli(38 ±0.43mm with formulation and 42±0.55 mm with marketed preparations)

Table 5. Regression co-efficient analysis and best model fit analysis- Formulation F 1 to F 8 –Ketorolac tromethamine

Formulation code	Zero order	Peppas	Higuchi	First order	n Value	Best fit model
F1	0.9424	0.9724	0,9891	0.8199	0.5108	Zero order Higuchi
F2	0.9722	0.9706	0.9736	0.8644	0.5997	Zero order Higuchi
F3	0.9965	0.9928	0.9340	0.8569	0.8297	Zero order Peppas
F4	0.9948	0.9971	0.9399	0.7547	0.9732	Zero order Peppas
F5	0.9746	0.9739	0.9734	0.7852	0.6135	Zero order Peppas
F6	0.9969	0.9952	0.9198	0.5614	0.8779	Zero order Peppas
F7	0.9983	0.9968	0.9285	0.7624	0.9170	Zero order Peppas
F8	0.9964	0.9951	0.9374	0.6998	0.9319	Zero order Peppas

Table 6. Sterility testing data

Formulation Code	Days of incubation													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
F1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F2	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F3	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F4	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F5	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F6	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F7	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F8	-	-	-	-	-	-	-	-	-	-	-	-	-	-

"-"demonstrates no growth of microorganisms

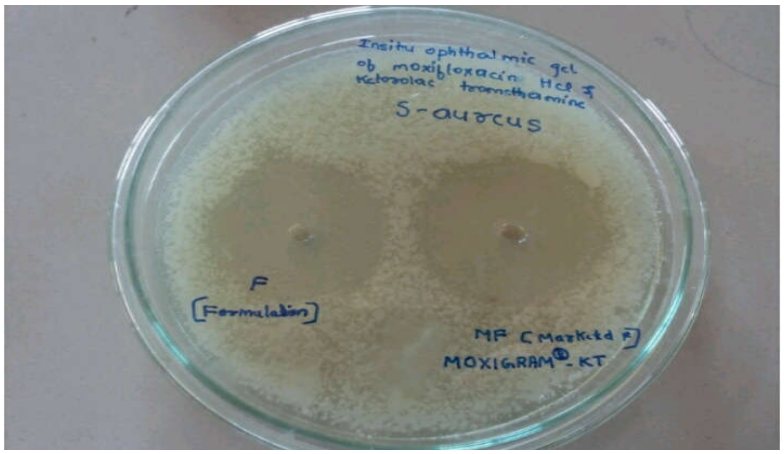

Figure 9. ZOI of Moxifloxacin HCL with S aureus

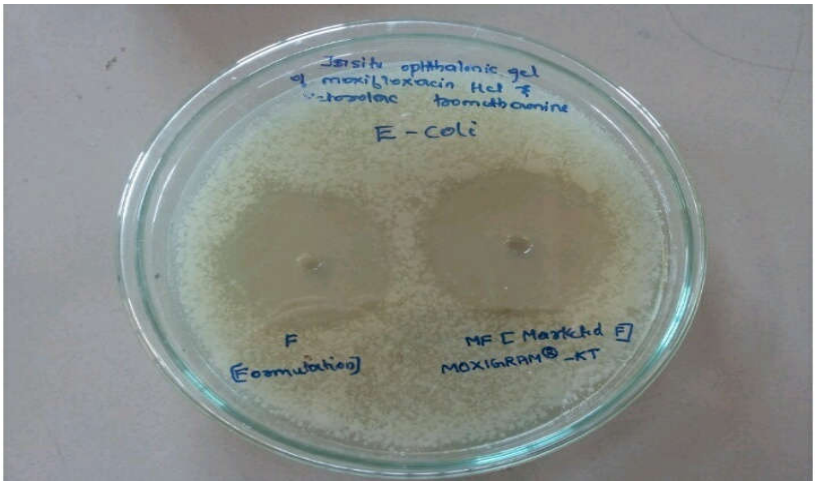

Figure 10. ZOI of Moxifloxacin HCL with E coli

when compared to S aureus (41± 0.78mm with formulations and 44±0.98 mm with marketed preparation) Fig-.The present study results indicate that Moxifloxacin hydrochloride and ketorolac tromethamine combination in situ gel form retained its antimicrobial efficacy.

Compatibility study by FTIR

The drug polymer interaction study was done by FTIR, Figure 11 which showed that drugs and polymers are compatible with each other. The functional group of pure drug aloe and in combination with excipients are listed in table no 7 and 8

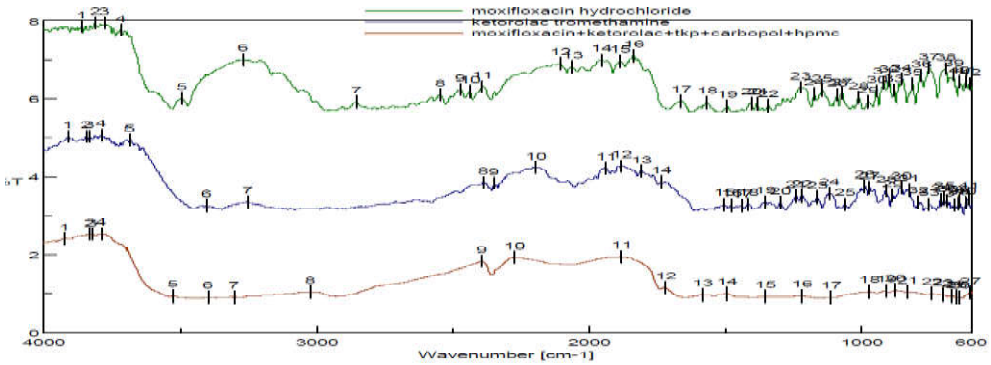

Figure 11. Compatibility study of drug and polymer by FTIR

Table 7. Reported and observed IR frequency of Moxifloxacin HCL and its physical mixture

Functional group	Reported frequency (in cm^{-1})	Observed frequency in pure drug (in cm^{-1})	Observed frequency in mixture with Ketorolac and other polymers (in cm^{-1})
F	1400-1000	1018.35	1022.24
C=O	1725-1680	1710.95	1711.92
N-H	3500-3310	3479.91	3481.98
-OH	3550-3450	3528.78	3526.95

Table 8. Reported and observed IR frequency of ketorolac tromethamine and its physical mixture

Functional group	Reported frequency (in cm^{-1})	Observed frequency In pure drug (in cm^{-1})	Observed frequency in mixture with Moxifloxacin and other polymers (in cm^{-1})
C-C	1600-1450	1509.12	1505.50
O-H	3550-3450	3530.32	3535.91
N-H	3250-3400	3255.25	3249.67
C=O	1720-1680	1680.69	1685.65

Irritation study- Red blood cell lysis test (Vinardell, 2008)

The irritation study was done by analysis of RBC of humans without formulation, and with formulation. The study demonstrated that RBC didnot swell or shrink with formulations indicating it is isotonic. This was done by taking the photographs of slide at 45 X

Accelerated stability study

Stability study was done according to ICH guidelines for 6 months indicated that the formulation F8 retained its various characteristics during the study list. There was slight change in pH and drug content and gelling capacity were not altered during its stability study

Summary and Conclusion

This approach of work showed that formulation F8 having 0.3% w/v of carbopol 934 and 0.35 % of carboxy methyl TKP showed controlled release for a period of 12 hours and kinetic data indicated that it followed Zero order peppas model of kinetics. Hence it can be concluded that *in situ* ophthalmic of moxifloxacin HCL and ketorolac tromethamine combination can be a boon to ophthalmic drug delivery and replacement of conventional eye drop.

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