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FORMULATION AND EVALUATION OF IN SITU GEL OF MOXIFLOXACIN HCL AND KETOROLAC TROMETHAMINE

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ABSTRACT

The present study was aimed at the formulation and evaluation of an ophthalmic in situ gel containing Moxifloxacin hydrochloride and Ketorolac tromethamine for prolonged ocular residence time and sustained drug release. Conventional ophthalmic formulations suffer from poor bioavailability due to rapid precorneal elimination and frequent tear turnover, resulting in reduced therapeutic efficacy and frequent dosing. In situ gel systems were therefore developed to overcome these limitations and enhance ocular drug retention. The formulations were prepared using Carbopol® 940/934 in combination with HPMC E4M by the dispersion method. A total of ten formulations (F1–F10) were developed and evaluated for appearance, pH, drug content, viscosity, gelling capacity, and in vitro drug release. All formulations were found to be clear, transparent, and free from particulate matter with pH values ranging from 6.9 to 7.2, indicating suitability for ophthalmic administration. Drug content was found within acceptable limits, ranging from 95.0% to 99.2%. Viscosity studies revealed that the formulations exhibited suitable rheological behavior for ocular application, with viscosity increasing as polymer concentration increased. Gelling capacity studies demonstrated rapid sol-to-gel transition and prolonged gel integrity, confirming effective in situ gel formation. *In vitro* drug release studies showed sustained release of both drugs over a period of 8 hours. Among all formulations, F7 exhibited the most desirable characteristics with controlled drug release reaching 98.85% at the end of 8 hours. The study concluded that the developed in situ gel system could effectively prolong ocular retention, sustain drug release, improve therapeutic efficacy, and enhance patient compliance in the treatment of ocular infections and inflammation.

Keywords: Moxifloxacin hydrochloride, Ketorolac tromethamine, In situ gel, Ophthalmic drug delivery, Carbopol®, HPMC E4M, Sustained drug release, Ocular bioavailability, Gelling capacity, Drug release kinetics.

INTRODUCTION

Ocular drug delivery is one of the most challenging areas in pharmaceutical research due to the unique anatomy and physiology of the eye. Conventional ophthalmic dosage forms such as eye drops and ointments often exhibit poor bioavailability because of rapid precorneal elimination, nasolacrimal drainage, tear turnover, and limited corneal permeability (Patel *et al.*, 2010; Novack and Robin, 2024). As a result, only a small fraction of the administered drug reaches the intraocular tissues, leading to reduced therapeutic efficacy and the need for frequent

administration. Frequent dosing may further decrease patient compliance, especially in chronic ocular conditions (Novack and Robin, 2024). To overcome these limitations, in situ gel drug delivery systems have gained considerable attention in ophthalmic therapy. In situ gels are polymeric formulations that exist as a liquid before administration and undergo gelation upon exposure to physiological conditions such as pH change, temperature, or ionic interactions in the eye (Vigani *et al.,* 2020).

These systems combine the advantages of both eye drops and gels by providing ease of administration along with prolonged precorneal residence time. The formation of gel after instillation enhances ocular contact time, improves drug retention, reduces drug loss through drainage, and provides sustained drug release (Kolawole and Cook, 2023).

Moxifloxacin hydrochloride is a broad-spectrum fourth-generation fluoroquinolone antibiotic widely used in the treatment of bacterial eye infections such as conjunctivitis, keratitis, and corneal ulcers. It acts by inhibiting bacterial DNA gyrase and topoisomerase IV enzymes, thereby preventing bacterial replication. Although moxifloxacin is highly effective against a broad range of ocular pathogens, conventional eye drop formulations require repeated administration due to rapid elimination from the ocular surface (Miller, 2008).

Ketorolac tromethamine is a potent non-steroidal anti-inflammatory drug (NSAID) commonly used in ophthalmic preparations for the management of ocular pain, inflammation, postoperative irritation, and allergic conjunctivitis. It works by inhibiting cyclooxygenase enzymes and reducing prostaglandin synthesis. However, similar to other ophthalmic solutions, conventional ketorolac eye drops suffer from poor ocular retention and limited bioavailability (Sinha *et al.,* 2009). Combination therapy using Moxifloxacin HCl and Ketorolac tromethamine offers the advantage of simultaneously managing ocular infection and inflammation (Kuriakose *et al.,* 2022).

Development of an in situ gel containing both drugs may therefore provide prolonged therapeutic action, improved ocular bioavailability, reduced dosing frequency, and enhanced patient compliance. The incorporation of suitable polymers such as Carbopol, Hydroxypropyl methylcellulose (HPMC), sodium alginate, or gellan gum can facilitate controlled drug release and effective gel formation upon ocular administration.

The present study was therefore aimed at the formulation and evaluation of an in situ gel containing Moxifloxacin HCl and Ketorolac tromethamine for ocular delivery. The developed formulations were intended to improve precorneal residence time and provide sustained release of both drugs. The prepared in situ gels would be evaluated for various physicochemical parameters including appearance, pH, viscosity, gelling capacity, drug content, in vitro drug release, sterility, and stability in order to determine their suitability as an effective ophthalmic drug delivery system.

MATERIALS AND METHODS

Material

Moxifloxacin hydrochloride and Ketorolac tromethamine were used as the active pharmaceutical ingredients for the preparation of ophthalmic in situ gel formulations. Carbopol® 940 and Carbopol® 934 were

used as pH-sensitive gelling polymers, while HPMC E4M was utilized as a viscosity-enhancing and sustained release polymer. Sodium chloride was added for isotonicity adjustment, and methyl paraben along with propyl paraben were used as preservatives. Distilled water was used as the vehicle for preparation of the formulations. All chemicals and reagents used in the study were of analytical grade.

Methods

Preparation of in situ gel formulations

The composition of in situ gel formulations containing Moxifloxacin HCl and Ketorolac Tromethamine is presented in Table 1. These formulations were prepared using varying concentrations of Carbopol® 940/Carbopol® 934 in combination with HPMC E4M by the dispersion method. Briefly, 75 mL of distilled water was preheated to 70 °C, into which methylparaben and propylparaben were dissolved, followed by the addition of sodium chloride (NaCl), HPMC, and Carbopol®. The mixture was kept at room temperature overnight to ensure complete hydration of the polymers. Separately, sulfacetamide sodium was dissolved in 25 mL of distilled water and then incorporated into the polymeric solution with continuous stirring until a uniform solution was obtained. The final formulations were transferred into sterile amber-colored bottles and sterilized by autoclaving at 121°C for 15 minutes. The prepared gels were stored at 4 °C until further use (Indu *et al.*, 2000).

Evaluation of In Situ Gel Formulations

Appearance and clarity, pH, and drug content

The appearance and clarity of the formulations were assessed visually against both black and white backgrounds to detect the presence of any particulate matter. The pH of each formulation was measured using a digital pH meter (METTLER Toledo, S220 Seven Compact™ pH/Ion) to ensure ocular compatibility and minimize irritation upon administration (Patil *et al.,* 2015).

For drug content determination, 1 mL of formulation was dissolved in 100 mL of simulated tear fluid (STF, pH 7.4) and further diluted with the same medium. The absorbance was measured at 257 nm using a UV–Visible spectrophotometer (Wu *et al.,* 2007). STF (pH 7.4) was prepared using 0.670 g NaCl, 0.200 g $NaHCO_3$, and 0.008 g $CaCl_2 \cdot 2H_2O$, dissolved in distilled water to a final volume of 100 mL. All measurements were carried out in triplicate.

Viscosity

The viscosity of formulations was determined using a DV-III ULTRA Programmable Rheometer (Model LV) fitted with spindle SC4-18, immersed in the formulation sample. The spindle speed was maintained at 20 rpm and the temperature at 25°C (Mandal *et al.*, 2012). Viscosity was calculated using Bingham's model, with all measurements performed in triplicate to ensure reproducibility and to confirm that the formulations possessed adequate viscosity to prevent rapid precorneal elimination.

Gelling capacity

The gelling capacity of the formulations was evaluated by adding 1 mL of formulation into a test tube containing 5 mL of STF (pH 7.4) maintained at 37°C (Deulker *et al.,* 2013). The sol–gel transition time and the duration for which the gel remained intact were visually recorded. To enhance visualization, congo red dye was incorporated into the formulation. Gel strength was graded as:

- (–) no gelation
- (+) poor gelation
- (++) good gelation
- (+++) excellent gelation.

***In vitro* drug release studies**

In vitro release studies were conducted using the dialysis membrane diffusion method (Mohanambal *et al.,* 2010; Nayak *et al.,* 2012). The membrane, pre-soaked overnight in STF, was tied at one end to form a bag, into which 1 mL of formulation and 0.5 mL of STF were placed to simulate gel formation. The other end was sealed, and the bag was immersed in 100 mL of STF (pH 7.4) maintained at 37 °C in a shaker water bath at 50 rpm. Aliquots of 2 mL were withdrawn at predetermined time intervals (0.5, 1, 2, 3, 4, 6, and 8 h), and replaced with equal volumes of fresh STF to maintain sink conditions. Samples were analyzed using a UV–Visible spectrophotometer.

Antimicrobial efficacy studies

Antimicrobial activity of the optimized formulation was assessed using the well diffusion method (El-Laithy *et al.,* 2011). Wells were bored into sterile Mueller–Hinton agar plates previously seeded with *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*. The test formulations were placed into the wells, and plates were incubated at 37°C for 24 h. Antimicrobial efficacy was determined by measuring the zones of inhibition (in mm).

RESULTS AND DISCUSSION

The present study was undertaken to formulate and evaluate an in situ gel containing Moxifloxacin Hydrochloride and Ketorolac Tromethamine using Carbopol® 940/934 in combination with HPMC E4M for enhanced ocular retention and sustained drug release. The developed formulations were evaluated for physicochemical characteristics, viscosity, gelling capacity, *in vitro* drug release, and release kinetics to determine their suitability as ophthalmic in situ gel systems.

All prepared formulations (F1–F10) were found to be clear and free from visible particulate matter, indicating uniform dispersion of polymers and drugs within the formulations. Clarity is an essential requirement for ophthalmic preparations to avoid irritation and ensure patient acceptability. The pH of all formulations ranged between 6.9 and 7.2, which is close to the physiological pH of tears and therefore suitable for ocular administration without causing significant irritation or discomfort. Drug content values ranged from 95.0% to 99.2%, indicating uniform distribution of both drugs throughout the formulations and minimal drug loss during preparation.

Viscosity is an important parameter affecting ocular residence time and drug release behavior. The viscosity of the formulations increased with increasing concentrations of Carbopol® and HPMC E4M. Formulations containing higher polymer concentrations, particularly F5, F6, F9, and F10, showed higher viscosity values due to increased polymer chain entanglement and hydration. Increased viscosity contributes to prolonged precorneal residence time and sustained release of drugs; however, excessively high viscosity may affect ease of instillation. The optimized formulation F7 exhibited suitable viscosity, providing a balance between ease of administration and prolonged ocular retention.

The gelling capacity study demonstrated that all formulations underwent sol-to-gel transition upon contact with simulated tear

fluid. Formulations containing higher concentrations of polymers showed shorter gelation times and prolonged gel intactness. The gel strength increased progressively with increasing polymer concentration due to stronger polymeric network formation. Formulations F4, F5, F6, F9, and F10 exhibited excellent gel strength (+++), indicating effective in situ gel formation and sustained integrity. Optimized formulation F7 showed satisfactory gelation properties with appropriate gel strength and prolonged gel retention.

In vitro drug release studies revealed that the formulations exhibited sustained release behavior over a period of 8 hours. Formulations containing lower polymer concentrations released the drugs more rapidly, whereas higher polymer concentrations retarded drug diffusion and prolonged release. The initial burst release observed in some formulations may be due to the release of drug present near the surface of the gel matrix. Formulation F7 demonstrated a controlled and sustained drug release profile with 98.85% cumulative drug release at 8 hours, indicating its suitability as an optimized formulation. The sustained release effect may be attributed to the gel-forming and swelling properties of Carbopol® and HPMC, which create a diffusion barrier for drug release. Release kinetic analysis of optimized formulation F7 demonstrated higher regression coefficient values for Higuchi (R^2 = 0.9841) and Korsmeyer–Peppas models (R^2 = 0.9869), suggesting that drug release predominantly followed diffusion-controlled release from the polymeric matrix. The lower regression coefficient observed in the first-order model indicated that release was not concentration dependent. The findings suggest that the drug release mechanism involved diffusion along with polymer relaxation and swelling behavior.

The study demonstrated that Carbopol® and HPMC-based in situ gel formulations can effectively prolong ocular residence time and provide sustained release of Moxifloxacin HCl and Ketorolac Tromethamine. Among all formulations, F7 exhibited the most desirable physicochemical properties, suitable viscosity, satisfactory gelling capacity, and controlled drug release profile. The developed in situ gel system therefore represents a promising ophthalmic drug delivery approach for the effective management of ocular infections and inflammation with improved patient compliance and reduced dosing frequency.

Table 1: Composition of Moxifloxacin HCl and Ketorolac tromethamine *In situ* gel formulations

Ingredients (% w/v)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Moxifloxacin HCl	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ketorolac Tromethamine	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Carbopol® 940	0.3	0.5	0.8	0.8	0.8	0.8	–	–	–	–
Carbopol® 934	–	–	–	–	–	–	0.6	0.8	0.8	0.8
HPMC E4M	0.6	0.6	0.6	1.0	1.5	2.0	1.0	1.0	1.5	2.0
Sodium chloride	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Propyl paraben	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Water (q.s. to)	100	100	100	100	100	100	100	100	100	100

Table 2: Results of Moxifloxacin HCl and Ketorolac Tromethamine In Situ Gel Formulations

Formulation Code	Appearance & Clarity	pH (Mean ± SD)	Drug Content (% ± SD)
F1	Clear, no particulate matter	6.9 ± 0.02	98.5 ± 0.8
F2	Clear, transparent	7.0 ± 0.03	96.1 ± 0.6
F3	Clear	7.0 ± 0.01	98.9 ± 0.7
F4	Clear	7.1 ± 0.02	97.3 ± 0.5
F5	Clear	7.1 ± 0.02	95.0 ± 0.4
F6	Clear	7.2 ± 0.03	98.8 ± 0.6
F7	Clear	7.0 ± 0.02	99.2 ± 0.5
F8	Clear	7.1 ± 0.01	97.7 ± 0.7
F9	Clear	7.1 ± 0.03	95.0 ± 0.4
F10	Clear	7.2 ± 0.02	96.9 ± 0.6

Table 3: Viscosity of In-Situ Gel Formulations (F1–F10)

Formulation Code	Viscosity (cP) at 25 °C (Mean ± SD, n=3)
F1	1520 ± 18
F2	1685 ± 22
F3	1920 ± 25
F4	2105 ± 27
F5	2380 ± 30
F6	2615 ± 35
F7	1750 ± 20
F8	1980 ± 28
F9	2255 ± 32
F10	2490 ± 30

Table 4: Gelling Capacity of In-Situ Gel Formulations (F1–F10)

Formulation Code	Sol–Gel Transition Time (sec)	Duration of Gel Intactness (h)	Gel Strength Grade
F1	60 ± 5	2.0 ± 0.2	+
F2	48 ± 4	3.1 ± 0.3	++
F3	42 ± 3	4.0 ± 0.2	++
F4	38 ± 2	5.0 ± 0.3	+++
F5	32 ± 2	6.0 ± 0.2	+++
F6	30 ± 2	6.5 ± 0.3	+++
F7	50 ± 3	3.2 ± 0.2	++
F8	40 ± 3	4.5 ± 0.2	++
F9	34 ± 2	5.5 ± 0.3	+++
F10	31 ± 2	6.2 ± 0.2	+++

Table 5: *In Vitro* Drug Release Profile of In-Situ Gel Formulations (F1–F10)

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)	F10 (%)
0.5	18.2 ± 0.5	15.6 ± 0.6	14.8 ± 0.4	12.4 ± 0.5	11.6 ± 0.3	10.8 ± 0.4	15.32±0.5	13.2 ± 0.5	12.0 ± 0.3	11.5 ± 0.4
1	29.5 ± 0.6	26.4 ± 0.5	24.8 ± 0.6	20.6 ± 0.5	19.4 ± 0.4	18.5 ± 0.3	25.65±0.6	22.5 ± 0.6	20.4 ± 0.4	19.8 ± 0.3
2	48.6 ± 0.7	45.8 ± 0.6	43.5 ± 0.5	36.2 ± 0.6	34.8 ± 0.4	33.2 ± 0.5	34.45±0.8	39.8 ± 0.5	37.4 ± 0.5	36.5 ± 0.4
3	62.4 ± 0.8	59.5 ± 0.7	56.2 ± 0.5	48.5 ± 0.7	46.2 ± 0.6	44.5 ± 0.5	55.65±0.9	52.8 ± 0.6	50.6 ± 0.6	49.5 ± 0.5
4	75.8 ± 0.9	71.6 ± 0.8	69.2 ± 0.6	59.2 ± 0.8	57.4 ± 0.5	55.8 ± 0.6	68.85±0.7	63.5 ± 0.7	61.2 ± 0.6	60.5 ± 0.5
6	92.5 ± 1.0	88.6 ± 0.9	86.2 ± 0.8	78.5 ± 0.9	76.2 ± 0.7	74.5 ± 0.6	78.85±0.4	82.8 ± 0.8	80.5 ± 0.7	79.2 ± 0.6
8	99.2 ± 0.5	97.5 ± 0.6	95.6 ± 0.6	89.8 ± 0.5	88.2 ± 0.5	87.4 ± 0.4	98.85±0.3	90.5 ± 0.5	89.2 ± 0.4	88.5 ± 0.4

Table 6: *In vitro* drug release kinetics study of optimized formulation F7

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	15.32	1.185	84.68	1.928
1	1.000	0.000	25.65	1.409	74.35	1.871
2	1.414	0.301	34.45	1.537	65.55	1.817
3	1.732	0.477	55.65	1.745	44.35	1.647
4	2.000	0.602	68.85	1.838	31.15	1.493
6	2.449	0.778	78.85	1.897	21.15	1.325
8	2.828	0.903	98.85	1.995	1.15	0.061

Table 7: Regression analysis data of optimized formulation F7

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
F7	0.9622	0.8329	0.9841	0.9869

CONCLUSION

The present study successfully formulated and evaluated an ophthalmic in situ gel containing Moxifloxacin Hydrochloride and Ketorolac Tromethamine using Carbopol® and HPMC polymers. The prepared formulations exhibited suitable physicochemical properties, satisfactory gelling capacity, and sustained drug release behavior. Among all formulations, F7 showed optimum viscosity, effective gel formation, and prolonged drug release over 8 hours. The developed in situ gel system may therefore serve as a promising ocular drug delivery approach for improving therapeutic efficacy, prolonging ocular residence time, reducing dosing frequency, and enhancing patient compliance in the treatment of ocular infections and inflammation.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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