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RESEARCH ARTICLE

Formulation and Evaluation of Controlled Release of Ocular Inserts

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ABSTRACT

Moxifloxacin hydrochloride (Moxifloxacin HCl) is a fluoroquinolone antibiotic widely used in ocular infections. Traditional eye drops are limited by rapid drainage and low bioavailability. This study aimed to formulate stable ocular inserts that provide sustained drug release, enhance antimicrobial efficacy, ensure ocular safety, and establish a strong in vitro–in vivo correlation for predictable therapeutic performance. The λ_{max} of Moxifloxacin HCl in distilled water and simulated tear fluid was 288.5 nm. Drug-polymer compatibility was established through Fourier Transform Infrared spectroscopy. The ocular inserts were prepared using polyvinyl alcohol as the reservoir and ethyl cellulose as the rate-controlling membrane. Physicochemical characteristics, in vitro release of drug in Franz diffusion cell, antimicrobial activity in agar diffusion test, in vivo efficacy in rabbit model, and irritation potential using the Draize test were evaluated. The release kinetics and stability of the drug were studied. Formulation FM6 exhibited uniform thickness of 0.298 ± 0.02 mm with pH 7.27 and drug content of 0.991 ± 0.06 mg. The in vitro release exhibited 99.1% drug delivery within five days with Higuchi kinetics ($R^2 = 0.991$). FM6 exhibits severe antimicrobial activity and sterility. Sustained release and lack of ocular irritation have been established by in vivo studies. Accelerated stability tests did not show any degradation for 3 months. The current study successfully developed and optimised a new sustained-release ocular insert for Moxifloxacin HCl with extended antimicrobial activity and enhanced patient compliance.

Keywords: Moxifloxacin HCl; Ocular Insert; Sustained Release; In Vitro; In Vivo

INTRODUCTION

Ocular drug delivery is hindered by protective barriers, tear turnover, and drainage, lowering bioavailability to below 5% using conventional eye drops[1]. Increased dosing decreased compliance and efficacy. Ocular inserts, sterile devices inserted into the conjunctival sac, deliver drugs with sustained release, increasing residence time and bioavailability[2,3]. Moxifloxacin HCl, a fourth-generation fluoroquinolone, is extensively used in bacterial conjunctivitis and post-surgical infections because of its broad-spectrum activity[4,5]. Controlled-release moxifloxacin decreases the frequency of dosing and systemic exposure, while ensuring effective levels of the drug[6]. Biocompatible polymers, such as HPMC, ethyl cellulose, and PVA, have been studied extensively for use in ocular drug delivery systems[7]. The purpose of this study was to develop and assess controlled-release ocular inserts of moxifloxacin hydrochloride using different polymers to achieve extended drug release, better ocular bioavailability, and increased patient compliance.

MATERIALS AND METHODS

Analytical Determination

λ_{max} Determination and Calibration in Distilled Water: A working graph of Moxifloxacin HCl in distilled water is plotted. First, 10 mg of Moxifloxacin HCl was dissolved in 100 ml of distilled water to prepare a 100 μg/ml solution. Then, 10 ml was diluted to 100 ml to obtain a concentration of 10 μg/ml. Further dilutions were performed to achieve concentrations of 2, 4, 6, 8, and 10 μg/ml. λ_{max} was determined by scanning the 10 μg/ml solution in a Shimadzu double-beam UV spectrophotometer between 200 and 400 nm. Absorbance was measured accordingly.

λ_{max} Determination and Calibration in Simulated tear fluid (STF): In the STF, 10 mg of Moxifloxacin HCl was dissolved in 100 ml of medium. Ten millilitres of this solution

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were pipetted and further diluted to prepare 2–10 μg/ml solutions. The UV scan was performed between 200 and 400 nm using a 10 μg/ml solution. Absorbance was measured in triplicate. STF was prepared with NaCl (0.670 g), sodium bicarbonate (0.200 g), and calcium chloride (0.008 g) in 100 ml of purified water[8].

Melting Point Determination: Melting point of Moxifloxacin HCl was determined by the open capillary method using an Analab digital melting point apparatus.

Drug-Excipient Compatibility Study: Fourier Transform Infrared (FTIR) spectroscopy was employed to study the drug-excipient interactions. IR spectra were scanned in the region 400–4000 cm^{-1} employing 0.1 mm thickness KBr pellets. Spectra of the pure drug and blends with excipients were compared to ensure absence of interaction[9,10].

Development of Ocular Inserts

Dose Calculation: Moxifloxacin HCl eye drops at 0.5% w/v concentration release 0.25 mg per drop, with a standard treatment regimen of three drops daily for five days, equating to 3.75 mg. Considering the drainage of tears (approximately 75% loss of drug), the therapeutically active dose was only 0.938 mg. Hence, ocular inserts were constructed to release 1.1 mg of Moxifloxacin HCl each for five days, considering minimal loss of drug during delivery.

Drug Quantity for Petri Dish: For an ocular insert surface area of 0.65 cm^2, and the internal area of the petri dish being around 15.896 cm^2, around 27 mg of drug was needed per petri dish. Therefore, 54 mg of Moxifloxacin HCl was utilised for the 10 mL casting solution.

Preliminary Investigations of Ocular Films

Various polymers and plasticisers have been evaluated for ocular inserts based on their folding endurance, flexibility, and texture. Chitosan was tacky, PVP K-30 brittle, and alginate blends unstable. PVA with PEG-400 was chosen as the reservoir film and EC with PVP-K30 and DBP as the rate-controlling membranes. The films were cast, dried overnight at 40°C, and assessed for their suitability.

Preparation of Controlled Release Ocular Inserts

Drug Reservoir Preparation: Films of the reservoir were prepared by casting PVA and PEG-400 in distilled water. A dose of 54 mg Moxifloxacin HCl was mixed with 10 ml of this solution. Sonication for 30–40 min was followed by casting 4 ml into glass petri dishes of 4.5 cm diameter and drying at 30°C for 24 h. Dried films were elliptically cut into inserts and stored in desiccators[9].

Rate-Controlling Membrane Preparation: Ethyl cellulose (EC), either alone or with PVP-K30, was employed to cast membranes in proportions of 6%, 4%, and EC:PVP ratios of 8:1, 4:1, 2:1, and 1:1. The polymers were dissolved in acetone with DBP, stirred for 40 min, and cast on petri dishes. Solvent evaporation was regulated using an inverted funnel. Films were dried overnight, cut, and stored[11].

Sealing of Films: Reservoir films were placed between the two rate-controlling membranes. These assemblies were kept in a beaker containing acetone:ethanol vapours (60:40) for 1–2 min to properly seal them. The inserts were kept in air-tight containers[9].

Evaluation of Ocular Inserts - Physicochemical Evaluation

Uniformity of Thickness: Insert thickness was determined using a digital Vernier caliper at five points. Three inserts per batch were evaluated[10].

Uniformity of Weight: Three inserts from each batch were individually weighed by a digital balance and mean weight was reported[10].

Drug Content: Individual inserts were dissolved in 10 ml phosphate buffer (pH 7.4), filtered into a 25 ml flask, and diluted. The absorbance was read at 288 nm[10].

% Moisture Absorption and Loss: Films were stored in desiccators in humid (aluminum chloride) or dry (calcium chloride) conditions for three days, weighed initially and finally, and % change determined[10].

Folding Endurance: Each strip of film was folded over and over at the same location until it ruptured. The fold number was counted[10].

Surface pH: Swollen inserts were measured using a digital pH meter after 30 min in distilled water.

In vitro Release Studies

Release studies were conducted using a Franz diffusion cell and a dialysis membrane. Inserts were incubated with 40 ml STF at pH 7.4 and maintained at 37±0.5°C. The mixture was then stirred at 20 rpm. Aliquots were removed at intervals, supplemented with fresh STF, and analyzed spectrophotometrically at 288.5 nm[11,12].

Release Kinetics: Data were analysed by fitting to the zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. Best-fit model was identified from regression coefficients (R^2 values)[13].

Sterilization: Optimized inserts were sterilized under UV radiation for 15 minutes at 0.305 m height under aseptic conditions and packaged in pre-sterilized amber vials[14].

Microbiological Studies

Sterility Testing: Sterility was determined by using the direct inoculation method following Indian Pharmacopoeia guidelines, utilizing five inserts from FM6 formulation[15].

In vitro antimicrobial activity tests: In vitro antimicrobial activity tests were conducted to evaluate the biological activity of the synthesized ocuserts against certain microorganisms. The test was performed using the agar diffusion method with the cup-plate technique. A layer of nutrient

agar seeded with Staphylococcus aureus (S. aureus) and Pseudomonas aeruginosa (P. aeruginosa) was first poured into sterile Petri plates and left to solidify. A sterile 4 mm borer was used to create wells in agar seeded with microbes. Standard Moxifloxacin drops and test formulations were added, diffused for two hours, and incubated at 37°C for 24 h. Zones of inhibition were measured and compared; tests were done in triplicate to ensure reliability and reproducibility[16].

Drug Release Determination from Ocular Inserts

The best ocular insert was microbiologically tested for controlled drug release over a period of five days. S. aureus and P. aeruginosa were used as test microorganisms in the investigation. Ten millilitres of seeded agar were poured into plates, solidified, and an ocular insert was placed. After 24-hour incubation, the inserts were transferred daily to fresh plates for five days. Zones of inhibition were measured daily to assess drug release using standard calibration curves[9].

Ocular Irritation Studies – Draize Test

Ocular irritation studies were conducted using the Draize test on albino rabbits, with the right eye treated and left eye as the control. A sterilised ocular insert was placed in the conjunctival sac and the eyes were monitored at intervals of up to one week for signs of irritation. Observed changes in the cornea, iris, and conjunctiva at 1, 24, 48, and 72 hours, and then one week post-administration were scored using a standard grading system to evaluate the degree of irritation[12,17].

In vivo Release Studies

The in vivo drug release was studied in five healthy rabbits following IAEC approval. Sterile inserts and blanks were placed in the right and left eyes, respectively. The inserts were removed at intervals and analysed by UV spectrophotometry at 288 nm. The drug release was calculated by subtracting the residual content from the initial drug load. Drug release data were analysed using one-way ANOVA and Dunnett's test to assess the membrane effects. Results are expressed as the mean ± SD (n=3), with significance set at $p < 0.05$[15].

In vitro: In vivo Correlation

The in vitro - in vivo drug release correlation was determined by comparing the in vitro and in vivo percentages of the drug released at corresponding time periods. The release data obtained by in vivo studies were compared against the in vitro data, and a correlation coefficient was determined by plotting the result to find whether the in vitro model is predictive and linear with respect to in vivo environment[18].

Stability Study

Accelerated three-month short-term stability studies were performed for ocular insert formulations. The samples were stored under two conditions in amber-coloured glass vials: room temperature and refrigeration (2–8°C). Samples were withdrawn monthly and examined for visual appearance changes, pH, and drug content. This evaluation was used to determine the physical and chemical stability of the formulations under different storage conditions[18,19].

RESULTS

Analytical Determination

Determination of λmax and Construction of Calibration Curve in Distilled Water: The λmax of Moxifloxacin HCl in distilled water was determined to be 288.5 nm. A calibration curve was plotted using the absorbance values at this wavelength, which increased linearly with concentration, showing compliance with Beer's Law. The absorbance at concentrations from 0 to 10 μg/ml was measured, and the maximum absorbance was found to be 0.918 ± 0.0025 at 10 μg/ml.

Determination of λ_{max} and Construction of Calibration Curve in STF: In STF at pH 7.4, the λ_{max} of Moxifloxacin HCl did not change at 288.5 nm. The standard plot shows a linear correlation between the concentration and absorbance. The highest absorbance recorded was 0.810 ± 0.0025 at 10 μg/ml.

Preliminary Studies

Melting Point: The melting point of moxifloxacin hydrochloride was 242°C, which confirms its purity and thermal stability.

Interaction Studies: Compatibility studies were performed using FTIR spectroscopy. The IR spectra of the pure drug and polymers (PVA, PVP-K30, and EC) and the combined formulation were compared. (Figure 1) Spectral analysis demonstrated the existence of all characteristic peaks of Moxifloxacin HCl in the final formulation, indicating that there was no substantial interaction between the drug and polymers. The -NH group stretching appeared at 3528 cm^{-1}, and the carbonyl group C=O stretch appeared near 1708 cm^{-1}, which is consistent with the pure drug.

Characterization of Ocular Inserts

Physicochemical Evaluations: The Ocular inserts were tested for different physicochemical characteristics. The thickness varied from 0.289 ± 0.006 to 0.341 ± 0.004 mm. The weights were between 19.82 ± 0.24 mg and 20.29 ± 0.33 mg. The pH on the surface varied from 6.5 to 7.27, which is within the acceptable ocular pH. Drug content varied from 0.97 ± 0.04 mg to 0.991 ± 0.06 mg. Moisture uptake varied from 4.67 ± 0.003% to 12.45 ± 0.21%, whereas moisture loss varied

Table 1: Physicochemical parameters of ocular inserts

Formulations	Thickness (mm)	Weight (mg)	pH	Drug content (mg)	Folding Endurance	% Moisture absorption	% Moisture Loss
FM1	0.299±0.01	19.82±0.24	6.5	0.97±0.04	82±5.8	9.41± 0.271	12.11± 0.11
FM2	0.315±0.02	20.10±0.26	6.7	0.981±0.03	79±2.9	9.62 ± 0.011	11.49± 0.05
FM3	0.308±0.05	19.97±0.32	6.9	0.984±0.05	75±4.6	7.18± 0.248	8.34± 0.03
FM4	0.311±0.07	20.16±0.16	6.9	0.989±0.04	84±5.5	7.41±0.006	12.45 ± 0.21
FM5	0.341±0.01	20.29±0.33	7.14	0.978±0.02	82±3.5	4.67±0.003	9.1 ± 0.02
FM6	0.298±0.02	20.11±0.11	7.27	0.991±0.06	90±2.2	5.92±0.005	7.2±0.011
FM7	0.311±0.03	20.15±0.21	7.2	0.985±0.03	85±3.1	7.91±0.004	10.11±0.03
FM8	0.289±0.12	19.91±0.15	7.15	0.988±0.05	87±4.2	9.833±0.031	11.18±0.012

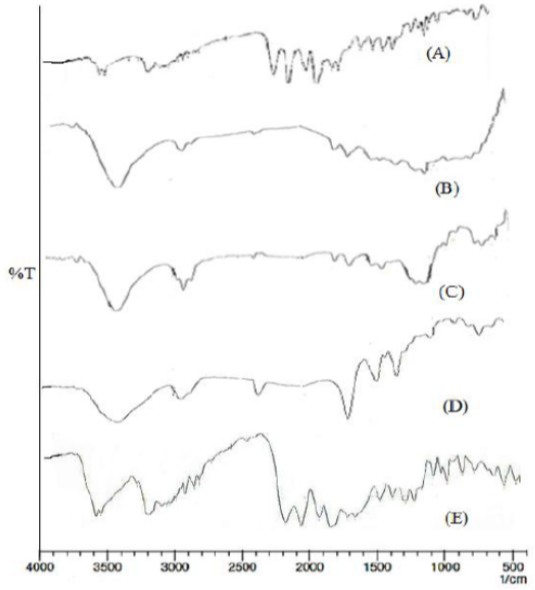

Fig. 1: IR Spectra of (A) Moxifloxacin HCl; (B) PVA; (C) EC; (D) PVP-K30; (E) FM6 optimized formulation

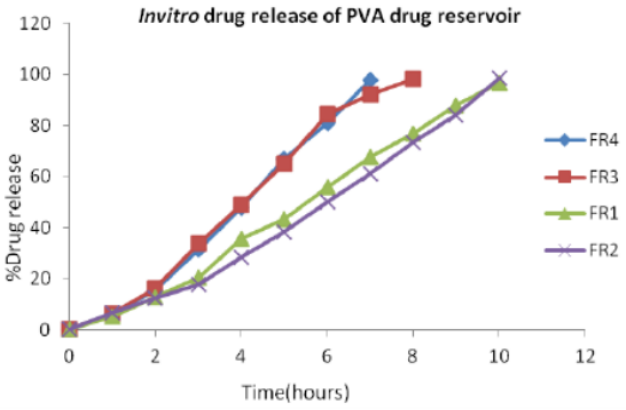

Fig. 2: In vitro drug release profiles of the drug reservoir

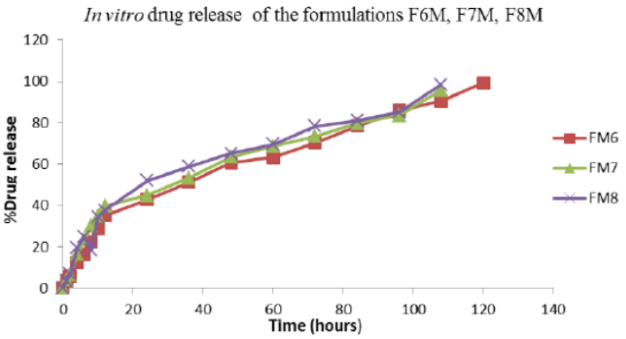

Fig. 3: In vitro drug release of the selected formulation FM6, FM7 and FM8 Kinetic Analysis

from 7.2 ± 0.011% to 12.18 ± 0.012%. (Table 1) Folding endurance was between 75 ± 4.6 and 92 ± 3.5°, showing good flexibility of the inserts.

In vitro Drug Release

Release studies were initially performed on drug reservoirs (FR1–FR4) without rate-controlling membranes. FR1 was the highest at 98.36% at 10 h, which was closely followed by FR3 at 98.1% at 8 h (Figure 2). Based on their performance, FR1 and FR2 were chosen for the formulation.

Formulations FM1–FM5 were conducted for 48 h, and the highest release was found in FM5 (59.1%). FM6 to FM8 were screened for 5 days (120 hours), and FM6 indicated the highest drug release of 99.1% and was thus the optimized formulation (Figure 3).

Kinetic modelling was used for FM6, FM7, and FM8. For each formulation, the Higuchi model provided the best fit (R^2 values: 0.991 for FM6, 0.9703 for FM7, and 0.9831 for FM8), suggesting diffusion-controlled release. The "n" values from the Korsmeyer-Peppas model (between 0.60 and 0.61) supported non-Fickian (anomalous) transport behaviour (Table 2).

Microbiological Studies

Sterility Studies: Sterility tests performed on FM6, FM7, and FM8 using Fluid Thioglycollate Medium as well as Soybean Casein Digest Medium validated that all three products were

Table 2: Kinetic assessment of the formulations FM6, FM7 and FM8

Formulation	Zero order	First order	Higuchi	Krosmeyer Peppas	n Value	Best fit model
FM6	0.9425	0.8138	0.9910	0.9653	0.6093	Higuchi
FM7	0.8828	0.8652	0.9703	0.9267	0.6022	Higuchi
FM8	0.8965	0.8318	0.9831	0.9286	0.6137	Higuchi

sterile throughout a period of 7 days' incubation period, with no microbial growth recorded.

In vitro Antimicrobial Efficacy

The antimicrobial activity of FM6, FM7, and FM8 formulations against microbial strains S. aureus and P. aeruginosa was expressed as the zone of inhibition in millimeters (mm). Each formulation has with control (C) or a test (T). Against S. aureus, the control formulations yielded inhibition zones of 22.41 ± 0.41 mm (FM6), 21.92 ± 0.89 mm (FM7), and 22.33 ± 0.58 mm (FM8), whereas the respective test formulations yielded slightly larger zones of 23.40 ± 0.35 mm, 23.36 ± 0.44 mm, and 23.95 ± 1.50 mm, respectively. This reflected an improvement in the antibacterial activity of the test formulations. A similar trend was observed for P. aeruginosa, albeit with smaller inhibition zones. Control groups were 16.54 ± 0.29 mm (FM6), 16.02 ± 0.81 mm (FM7), and 16.04 ± 0.03 mm (FM8), while the test formulas indicated better zones of 17.23 ± 0.12 mm, 17.01 ± 0.15 mm, and 16.65 ± 0.12 mm, respectively. These results indicate that all test formulas contain higher antimicrobial activity than their controls and have higher activity against S. aureus than P. aeruginosa. (Figure 4).

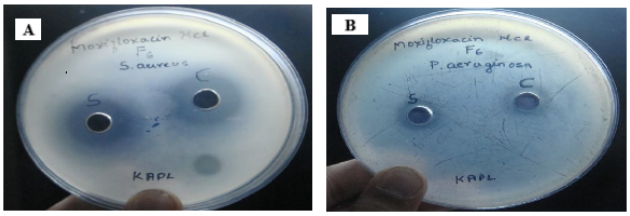

Fig. 4: (A) ZOI of Formulation FM6 and marketed product (Moxicip 0.5% w/v) seeded withS. aureus: T-FM6 Optimized inserts; C-Moxicip eye drops 0.5% w/v; (B) ZOI of Formulation FM6 and marketed product (Moxicip 0.5% w/v) seeded with P. aeruginosa

Microbiological Determination of Drug Release from Ocular Insert

Optimized formulation FM6 was assessed for drug release for five days by both in vitro and microbiological tests. The percentage of drug released increased progressively with time. On day one, the in vitro drug release was 42.85%, whereas S. aureus and P. aeruginosa released 37.52% and 25.43% of the drug, respectively. On day five, the drug release was 99.1% in vitro, whereas those of S. aureus and P. aeruginosa were 99.5% and 95.2%, respectively. These findings demonstrate sustained and consistent drug release from the ocular insert.

Ocular Irritation Studies – Draize Test

The optimized formulation FM6 was also subjected to ocular irritation testing using the Draize test. No irritation, damage, or abnormal clinical response was noted in the cornea, iris, or conjunctiva. The total irritation score was zero, which is a good indication of ocular compatibility. Pre-instillation and five-day post-application photographs revealed a lack of irritation.

In-Vivo Release Studies

For in vivo testing, FM6 was inserted inside the cul-de-sac region of a rabbit eye, and drug release for five days was observed. On the first day, 39.5% of the drug was released. Every day, an increase in the percentage of drug release was recorded, reaching 97.67% by the fifth day. These results confirmed that the formulation ensured prolonged release of the drug in a biotic environment.

In vivo: in vitro study correlation

An in vivo-in vitro correlation between the drug release data of the in vivo and in vitro experiments of the formulation FM6 was found. The in vivo-in vitro correlation was strong, with an R^2 value of 0.9975. The drug percentages released in vivo were found to be in close agreement with the in vitro results on each day of the study, validating the predictive nature of in vitro testing for in vivo performance.

Stability Studies

Three-month stability studies were performed at room temperature under refrigeration. At room temperature, no alterations in the visual appearance of the formulation were observed. Slight pH (from 7.17 to 6.81) and a decrease in drug content (from 98.72% to 97.12%) were observed. Similarly, under refrigerated conditions (4°C), no visual alterations occurred, with only slight pH (from 7.15 to 6.92) and drug content (from 98.15% to 97.11%). These results further confirm that FM6 was stable and active during the test.

DISCUSSION

The present study was able to formulate and assess controlled-release ocular inserts of Moxifloxacin HCl to enhance drug bioavailability as well as patient compliance in bacterial infections of the eye. Preformulation and compatibility studies confirmed the spectral characteristics and stability of the drug with excipients. The inserts, which were prepared by film casting with PVA and PEG-400 for the reservoir and EC with PVP-K30 as the rate-controlling membrane, showed consistent physicochemical characteristics, such as uniform thickness, weight, folding endurance, and close-to-neutral surface pH. The drug content was uniform, and microbial contamination was not detected, which ensured sterility of the inserts. In vitro release studies showed sustained drug release over 120 h with the best-fitting optimised formulation (FM6) obeying zero-order and Higuchi kinetics, signifying a diffusion-controlled release mechanism. Antimicrobial studies revealed substantial inhibition zones comparable to commercially available eye drops, indicating the therapeutic potential of the formulation. Rabbits' in vivo experiments confirmed the sustained drug release of five days, with a cumulative release value of 97.67%, and Draize tests did not observe any manifestations of ocular irritation, assuring the safety of ophthalmic use.

The findings of the present study are supported by previous studies conducted by Pawar et al., who also reported controlled drug release and greater antimicrobial efficiency using HPMC and Eudragit as ocular insertion polymers of moxifloxacin[20]. Similarly, Nayak et al. and Mandal et al. observed prolonged drug release through the use of in situ gels, although the release durations were relatively shorter than those in the present study[21,22]. Gupta and Singhvi highlighted the need for pH-sensitive systems to achieve sustained ocular delivery, affirming the utility of controlled-release systems to extend the ocular residence time[23]. Patel et al. demonstrated the efficiency of polymer inserts in delivering extended drug release of gatifloxacin, supporting the present formulation strategy employing hydrophilic and hydrophobic polymers to modulate release[10]. In contrast, Yellanki et al., used both natural and synthetic polymers in gelling systems but with less release control rates compared to the present insert-based system[24].

The formulated ocular insert FM6 in the present study was a good and safe delivery system for the extended release of moxifloxacin, which might minimise the frequency of dosing and maximise patient compliance relative to traditional eye drops or shorter-acting in situ gels.

CONCLUSION

The optimised ocular insert formulation, FM6, demonstrated excellent analytical, physicochemical, and microbiological characteristics. This indicated prolonged drug release in vitro and in vivo, with a high in vitro–in vivo correlation. FM6 had good antimicrobial action and good tolerance in Draize tests and proved to be stable for three months. Collectively, these findings confirm that FM6 is a strong and stable ocular drug delivery system for Moxifloxacin HCl.

REFERENCES

1. Mishra G, Gaudana R, Tamboli V, Mitra A. Recent Advances in Ocular Drug Delivery. *Targeted Delivery of Small and Macromolecular Drugs*. 2010;p. 421–453. Available from: https://www.researchgate.net/publication/300340102_Recent_Advances_in_Ocular_Drug_Delivery.
2. Saettone MF, Salminen L. Ocular inserts for topical delivery. *Advanced Drug Delivery Reviews*. 1995;16(1):95–106. Available from: https://dx.doi.org/10.1016/0169-409x(95)00014-x.
3. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. *Advanced Drug Delivery Reviews*. 2005;57(11):1595–1639. Available from: https://doi.org/10.1016/j.addr.2005.07.005.
4. Miller D. Review of moxifloxacin hydrochloride ophthalmic solution in the treatment of bacterial eye infections. *Clinical Ophthalmology*. 2008;2(1):77–91. Available from: https://pubmed.ncbi.nlm.nih.gov/19668391/.
5. O'brien TP. Evidence-based Review of Moxifloxacin. *International Ophthalmology Clinics*. 2006;46(4):61–72. Available from: https://pubmed.ncbi.nlm.nih.gov/17060792/.
6. Urtti A. Challenges and obstacles of ocular pharmacokinetics and drug delivery. *Advanced Drug Delivery Reviews*. 2006;58(11):1131–1135. Available from: https://dx.doi.org/10.1016/j.addr.2006.07.027.
7. Sahane N, Banarjee S, Gaikwad D, Jadhav S, Thorat R. Ocular inserts: a review. *International Journal of Current Research and Review*. 2010;2(1):3–16. Available from: https://ijcrr.com/uploads/2279_pdf.pdf.
8. Rozier A, Mazuel C, Grove J, Plazonnet B. Gelrite®: A novel, ion-activated, in-situ gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol. *International Journal of Pharmaceutics*. 1989;57(2):163–168. Available from: https://dx.doi.org/10.1016/0378-5173(89)90305-0.
9. Sultana Y, Aqil M, Ali A. Ocular inserts for controlled delivery of pefloxacin mesylate: Preparation and evaluation. *Acta pharmaceutica*. 2005;55(3):305–314. Available from: https://pubmed.ncbi.nlm.nih.gov/16375841/.
10. Patel UL, Chotai NP, Nagda CD. Design and evaluation of ocular drug delivery system for controlled delivery of gatifloxacin sesquehydrate: In vitro and in vivo evaluation. *Pharmaceutical Development and Technology*. 2012;17(1):15–22. Available from: https://pubmed.ncbi.nlm.nih.gov/20649410/.
11. Rao MV, Shyale S. Preparation and Evaluation of Ocular Inserts Containing Norfloxacin. *Turkish Journal of Medical Sciences*. 2004;34(4):239–246. Available from: https://journals.tubitak.gov.tr/medical/vol34/iss4/4/.
12. Patel D, Patel M, Patel N, Patel M. Preparation and evaluation of ocular insert containing brimonidine tratrate. *International Journal of Pharmacy and Clinical Research*. 2009;1(1):19–22. Available from: https://impactfactor.org/PDF/IJPCR/1/IJPCR,Vol1,Issue1,Article5.pdf.
13. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles. *European Journal of Pharmaceutical Sciences*. 2001;13(2):123–133. Available from: https://dx.doi.org/10.1016/s0928-0987(01)00095-1.
14. Sankar V, Chandrasekaran A, Durga S, Geetha G, Ravichandran V, Vijayakumar A, et al. Design and evaluation of diclofenac sodium ophthalmic inserts. *Acta Pharmaceutica Sciencia*. 2006;48:5–10. Available from: https://actapharmsci.com/uploads/pdf/pdf_88.pdf#:~:text=Diclofenac%20sodium%20ophthalmic%20inserts%20were,of%20medicated%20inserts%20were%20evaluated.
15. Tanwar Y, Patel D, Sisodia S. In vitro and in vivo evaluation of ocular inserts of ofloxacin. *DARU Journal of Pharmaceutical Sciences*. 2007;15(03):139–145. Available from: https://www.researchgate.net/publication/279559819_In_vitro_and_

in_vivo_evaluation_of_ocular_inserts_of_ofloxacin.
16. Mishra D, Gilhotra RM. Development studies on gel-forming erodible ocular polymeric films of Gatifloxacin sesquehydrate. *ACTA Pharmaceutica Sciencia*. 2008;50(2):145–152. Available from: https://www.actapharmsci.com/uploads/pdf/pdf_315.pdf.
17. Wilhelmus KR. The Draize Eye Test. *Survey of Ophthalmology*. 2001;45(6):493–515. Available from: https://dx.doi.org/10.1016/s0039-6257(01)00211-9.
18. Gevariya HB, Patel JK, Girhepunje K, Pal R. Sustained ophthalmic delivery of levofloxacin from once a day ocuserts. *International Journal of Pharmacy and Pharmaceutical Sciences*. 2009;1(1):24–32. Available from: https://www.researchgate.net/publication/265084460_Sustained_ophthalmic_delivery_of_levofloxacin_from_once_a_day_ocuserts.
19. Upadhyaya N, Patidar A, Agrawal S, Gupta D. Development and evaluation of polymeric sustained release levofloxacin ocuserts. *Research Journal of Pharmaceutical*. 2011;2(3):411–420.
20. Pawar P, Katara R, Majumdar D. Design and evaluation of moxifloxacin hydrochloride ocular inserts. *Acta Pharmaceutica*. 2012;62(1):93–104. Available from: https://dx.doi.org/10.2478/v10007-012-0002-5.
21. Mandal S, Thimmasetty MK, Prabhushankar GL, Geetha MS. Formulation and evaluation of an in situ gel-forming ophthalmic formulation of moxifloxacin hydrochloride. *International Journal of Pharmaceutical Investigation*. 2012;2(2):78–82. Available from: https://dx.doi.org/10.4103/2230-973x.100042.
22. Nayak SN, Sogali SB, Thakur RS. Formulation and evaluation of pH triggered in situ ophthalmic gel of Moxifloxacin hydrochloride. *International Journal of Pharmaceutical and Pharmaceutical Sciences*. 2012;4(2):452–461. Available from: https://www.researchgate.net/profile/Ram-Thakur-4/publication/282197210_Formulation_and_evaluation_of_pH_triggered_in_situ_ophthalmic_gel_of_Moxifloxacin_hydrochloride/links/639971e6e42faa7e75bed7e2/Formulation-and-evaluation-of-pH-triggered-in-situ-ophthalmic-gel-of-Moxifloxacin-hydrochloride.pdf.
23. Gupta S, Singhvi I. Sustained ophthalmic delivery of moxifloxacin hydrochloride from an pH triggered in situ gelling system. *Research Journal of Pharmacy and Technology*. 2012;5(12):1538–1542. Available from: https://rjptonline.org/HTMLPaper.aspx?Journal=Research%20Journal%20of%20Pharmacy%20and%20Technology;PID=2012-5-12-4.
24. Yellanki SK, Anna B, Kishan MR. Preparation and in vivo evaluation of sodium alginate-poly (vinyl alcohol) electrospun nanofibers of forskolin for glaucoma treatment. *Pakistan Journal of Pharmaceutical Sciences*. 2019;32(2):669–674. Available from: https://pubmed.ncbi.nlm.nih.gov/31081781/.