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Formulation and Evaluation of Controlled Release Ocular Inserts Containing Moxifloxacin Hydrochloride

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ABSTRACT

The eye presents unique opportunities and challenges for the delivery of pharmaceutical dosage forms. Ocular inserts of Moxifloxacin HCl were prepared with the objective of reducing frequency of administration, controlled release and greater therapeutic effect. Moxifloxacin HCl a broad spectrum fourth generation fluroquinolone used in the treatment of conjunctivitis, keratitis, kerato-conjunctivitis etc. In the present wok reservoir type of ocular inserts formulated by sandwiching poly vinyl alcohol containing Moxifloxacin HCl in between two rate controlling membranes of ethyl cellulose and PVP-K30. The reservoir types of ocular inserts containing Moxifloxacin HCl were formulated by film casting technique using PVA as drug reservoir polymer and EC: PVP-K30 as a rate controlling material**.** *In vitro* drug release revealed that the optimized (FM_6) formulation showed a controlled release. *In vivo* studies showed a release of 97.67% over a period of 5 days with high correlation coefficient of *In vitro-In vivo* release studies. In the present study the ocular inserts of Moxifloxacin HCl (FM_6) provided desired drug release for 5 days and remained stable.

Keywords: Moxifloxacin HCL, Ocular inserts, *In vitro* drug release, Microbiological studies, Draize test, *In vivo* studies.

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INTRODUCTION

The eye is a unique organ from anatomical and physiological point of view owing to its sensitivity and structural aspects [1]. The surface of the eye is rich in nutrients and consequently supports a diverse range of microorganisms which constitutes the normal ocular flora. Bacterial keratitis and conjunctivitis are among most common ocular infections and in more than 80% of cases; the infections are caused by *Staphylococcus aureus*, *Streptococcus pneumonia* or *Pseudomonas aeruginosa*[2].

Ophthalmic drug delivery is one of the challenging endeavors facing the pharmaceutical scientists today. The unique anatomy, physiology, and biochemistry of the eye render this organ impervious to foreign substances[3]. Most conventional ocular treatments like eye drops and suspensions call for the topical administration of ophthalmically active drugs to the tissues around the ocular cavity. These dosage forms are easy to install but suffer from the inherent drawback that the majority of the medication they contain is immediately diluted in the tear film as soon as the eye drop solution is instilled into the cul-de-sac and is rapidly drained away from the precorneal cavity by constant tear flow and lacrimo-nasal drainage. Therefore, the targeted tissues absorb a very small fraction of instilled dose. For this reason, concentrated solutions and frequent dosing are required for the instillation to achieve an adequate level of therapeutic effect[3]. Ocular therapy in bacterial infections would be significantly improved if the pre corneal residence time of drugs could be increased[1,5].

Ocular inserts one of the new classes of drug delivery systems, which are gaining worldwide praise, release drugs at a pre-programmed rate for a longer period by increasing the precorneal residence time[6].The goal of this delivery system is to provide a therapeutic amount of drug to the ocular tissues to achieve promptly and then maintain the desired drug concentration by increasing the contact time between the preparation and the conjunctival tissue[7,8].

Fluroquinolone are one of the promising groups of antibiotics currently being used topically to treat conjunctivitis and corneal ulcers[9]. Fluoroquinolones with an 8-methoxy substitution, such as moxifloxacin, have enhanced antimicrobial activities that may limit the selection of resistant mutants in pathogens[8].

In the present research work an attempt was made to formulate the reservoir type ocular inserts of Moxifloxacin by employing film casting technique. The films were formulated by preparing drug reservoir film and rate controlling membrane and sandwiching both the membranes to achieve controlled release.

MATERIALS AND METHOD

Moxifloxacin HCl was obtained as a gift sample from Micro Labs, Bangalore. Poly vinyl alcohol, Poly vinyl pyrrolidone-K30, Ethyl cellulose, PEG-400, acetone and Dibutyl phthalate were procured as gift samples from Karnataka Antibiotics and Pharmaceuticals Pvt Ltd, Bangalore**.** All the reagents used were of analytical grade.

Preparation of the ocular inserts

The ocular inserts of moxifloxacine hydrochloride are prepared by placing the drug reservoir film of moxifloxacine in rate controlling films.

Preparation of the drug reservoir

The drug reservoir films were prepared using aqueous solution of polyvinyl alcohol by film casting technique. Weighed quantity of polyvinyl alcohol and PEG-400 were solubilized in 10 ml distilled water with continuous stirring. The weighed amount of Moxifloxacin (54 mg equivalent weight) was added to the above solution under stirring condition. The solution was sonicated for 30-40 min. After proper mixing the casting solution(4 ml) was poured in clean glass petridish (diameter 4.5 cm, 12 ml capacity) and was placed in hot air oven at 30 ^{0}C for a period of 24 hrs. The dried films thus obtained were cut by cork borer into elliptical shape of definite size (13.8 mm diameter) containing 54 mg of the drug. The ocular inserts were packed in polythene self-sealed containers and then stored in desiccator under ambient condition[11].

Preparation of the rate controlling films

The rate controlling films were prepared using EC with or without PVP-K30.EC films were prepared in a ratio of 6% and 4%. Four different films of EC: PVP K30 was modelled with a ratio of 8:1, 4:1, 2:1 and 1:1.Weighed quantities of the polymers were solubilized in acetone (10 ml) with continuous mixing along with the addition of plasticizer DBP for a period of 40 min. The matrix solution such prepared was poured onto a clean glass petri plate. The rate of solvent evaporation was controlled by inverting a glass funnel over the petri plate and was kept for 24 hrs. After overnight the dried films were cut using cork borer and used to seal both the sides of the drug reservoir to control the release from the periphery[12].

Sealing of the films

The two rate controlling membranes containing the reservoir film between them were placed over a beaker saturated with ethanol/acetone vapours (60:40) for 1-2 minutes. The procedure resulted in sealing the two rate controlling membranes containing the medicated reservoir film between them. The ocular inserts were stored in an air tight container[11]Final formulations of

controlled release ocular inserts are tabulated in **Table I**.

The optimized ocular inserts were sterilized separately under UV radiation for 15 min at a height of 0.305 m from a fixed UV lamp in a cabinet under aseptic conditions and were finally packed in pre-sterilized amber colored glass vials[17].

Table I: Final formulation of Moxifloxacin HCl ocular inserts

Formula	Moxifloxacine Hcl (mg) (equivalent weight)	Drug reservoir film (10 m l of distilled water)in ml		Rate controlling films (in 10ml acetone)		
		Poly vinyl alcohol	PEG-400	Ethyl Cellulose	Poly vinyl Pyrrolodine	Dibutyl Phthalate
FM_1	54	500	0.21	400	-	0.1
FM_2	54	700	0.21	400	-	0.1
FM_3	54	500	0.21	600	-	0.1
FM_4	54	700	0.21	600	-	0.1
FM_5	54	500	0.21	800	100	0.1
FM_6	54	500	0.21	400	100	0.1
FM_7	54	500	0.21	200	100	0.1
FM_8	54	500	0.21	100	100	

EVALUATIONS OF THE OCULAR INSERTS

Physico chemical evaluation

Uniformity of thickness

The thickness of the insert was determined using a calibrated VernierCaliper (Mitotoyo, Japan) at five separate points of each insert and reported with standard deviation. For each formulation, three randomly selected inserts were tested for their thickness[13].

Uniformity of weight

From each batch, three inserts were taken out and weighed individually using digital balance(Sartorius). The mean weight of the insert was noted[13].

Drug Content

The ocuserts from each formulation containing an equivalent of 54 mg of Moxifloxacin HCl was dissolved or extracted with 10 ml of isotonic phosphate buffer (pH 7.4) in a beaker and were filtered into 25 ml volumetric flask and the volume was made upto the mark with buffer. One ml of the solution was withdrawn and the absorbance was measured by UV-Visible spectrophotometer (Shimadzu UV 1601) at 288nm after suitable dilutions[13].

%Percentage Moisture absorption

This was done to check the physical stability or integrity of the films at humid condition and the study was conducted in triplicate and reported with S.D. The films were weighed and placed in a

desiccator containing 100 ml of saturated solution of aluminium chloride and 80% humidity was maintained. After three days the films were taken out and reweighed[13].The % moisture absorption was calculated with standard deviation.

Percentage Moisture Loss

This was carried out to check the integrity of the films in dry condition. The films were weighed and kept in desiccator containing anhydrous calcium chloride. After three days the films were taken out and weighed. The S.D was calculated. [13]

Folding endurance

Three films prepared from each formulation were determined for folding endurance in triplicate. Folding endurance was determined by repeatedly folding a small strip of the film at the same place till it broke. A mean of three readings were recorded[13].

Surface pH

The inserts were allowed to swell in closed petridish at room temperature for 30 min in 0.1 ml of double distilled water and placed under digital pH meter (Digisun) to determine the surface pH.

***In vitro* release studies**

In vitro release studies were carried out using bi-chambered donor receiver compartment model (Franz diffusion cell). The diffusion cell membrane (sigma dialysis membrane) was tied to one end of the open cylinder, which acted as donor compartment. The ocular insert was placed on a dialysis membrane, which was in contact with receptor medium comprising of 40ml of STF(pH=7.4).The content of the receptor compartment was stirred continuously using a magnetic stirrer and temperature was maintained at $37^0 \pm 0.5^0$C.The receptor medium was stirred continuously at 20rpm to simulate blinking action of eyelids. At specific time interval, 1ml aliquot of the solution was withdrawn and replaced with fresh STF and required dilutions were made. The aliquot was analysed for drug content was analyzed using UV Spectrophotometer at 288.5 nm against reference standard using simulated tear fluid as blank[14,15].

In order to understand the mechanism and kinetics of drug release, the results of *in vitro* drug release study were fitted with various kinetic equations like zero order (%drug release vs time), first order (log% unreleased vs time), Higuchi matrix (%release vs square root of time). Based on the 'R' value, the best-fit model was selected[16].

Characterization of ocular inserts

Drug-excipient interaction studies

Infrared spectroscopy was used to carry out the drug excipient interaction studies. IR absorption

spectra of pure drug, placebo films and the drug containing ocular films were taken in the range of 40-400 cm $^{-1}$ by potassium bromide disc method using IR Spectrophotometer (Shimadzu 8300).

Differential scanning Calorimetry (DSC)

DSC was performed using Mettler TA 4000 systems. DSC of the drug, physical mixture of the polymers and the drug and the optimized film were taken. 3-5 mg of the samples were placed in a sealed aluminum pan and heated at a rate of 10^0 C/ min in 50-300^{0}C range using an empty sealed pan as reference.

Microbiological studies

Sterility testing

Direct inoculation method as described in Indian Pharmacopoeia was used for testing sterility of ocular inserts. Five ocular inserts of the optimized formulation (FM_6) were used for the test. A sterilized ocular insert was placed aseptically in a culture tube containing 10ml of sterile soya bean-casein digest media and fluid thioglycolate medium and the mouth of the test tube was closed tightly with cotton plug. It was incubated at 25±2^{0}C and 30 to 35^0 C for seven days respectively. The tubes were examined visually for sign of any microbial growth during the incubation period[17,9].

In-vitro antimicrobial efficacy

Antimicrobial efficiency studies were carried out to ascertain the biological activity of ocuserts against microorganisms. This was determined in the agar diffusion medium employing "Cup plate technique". A layer of nutrient agar seeded with the microorganism was allowed to solidify in the petriplate. Cups were made on the solidified agar layer with the help of sterile borer of 4mm diameter. Sterile solution of marketed Moxifloxacin HCl eye drops was used as a standard. The standard solution and the developed formulations (ocular film) were taken into separate cups bored into sterile SCDM Agar previously seeded with organisms (*Staphylococcus aureus and Pseudomonas aeruginosa*). After allowing diffusion of solutions for two hours, the plates were incubated for 24 hrs at temperature of 37^{0}C. The zone of inhibition (ZOI) was compared with that of the standard. Each sample was tested in triplicate[18].

Stability studies

Short term accelerated stability study was carried out for the period of 3 months for the formulations. The samples were stored at different storage conditions in amber colored glass bottles at room temperature and refrigerator (2- 8^0 C). Samples were withdrawn for each month till three months and analysed for visual appearance, pH and drug content[19,21].

***In vivo* studies of ocular inserts**

Ocular irritation studies-Draize test

The ocular safety of the administered delivery system was conducted based on the Draize test. Albino rabbits were used as test species. One eye (right eye) is designated the test eye and the contralateral eye serves as a matched control and is usually left untreated. The sterilized optimized ocular insert was placed in the conjunctival sac of the eye of the rabbit, normal blinking was allowed, although the eyelids can be held together for several seconds after instillation. The rabbit eye was checked for any signs of irritation and redness at an interval of 1, 24, 48, 72 hours and finally one week after exposure[19,20].

***In vivo* release studies**

Approval for the use of animal was obtained from Institutional Animal Ethics Committee (IAEC). Five rabbits with the body weight in the range of 2-2.5kgs were selected. They were fed on standard diet and all of them were kept in hygienic condition to avoid vulnerability to any diseases. The sterilized ocular inserts were inserted in the cul-de-sac of the right eye of the rabbit and similarly a blank was placed in the left eye to serve as control. At specific time intervals the films were removed carefully from the eye and analysed for the drug content remaining using UV spectrophotometric method at 288 nm. The drug content obtained was subtracted from the initial drug content in the ocuserts, to give the amount of drug released in the rabbit's eye[9,17].

Statistical analysis

Statistical analysis of the release data was carried out by using one way ANOVA for repeated measures followed by DUNNETT multiple comparison tests to determine whether type of rate controlling membrane affected the release of Moxifloxacin from ocular inserts. All the results are reported as means±SD (n=3);$p< 0.05$ was considered to be statistical significance[9].

***In vitro: In vivo* correlation**

It was calculated by taking %*in-vivo* and %*in-vitro* release of Moxifloxacin hydrochloride at different time intervals. The results of *in vivo* drug release were correlated with that of the *in vitro* drug release study the correlation coefficient obtained thus were compared[19].

RESULTS AND DISCUSION

Physicochemical Evaluations

Uniformity of thickness

The thicknesses of the films were evaluated in triplicates and it was found to be in the range of 0.289±0.006mm to 0.341±0.004mm.The results are tabulated in the **Table ii** It was assumed that

the thickness of the ocuserts increased slightly as the concentration of the polymer increased and also because of the increased deposition of the polymers.

Uniformity of weight

The weights of the ocular inserts were taken in triplicates. The formulations FM_1 to FM_8 were weighed and the weights of the inserts were found to be in the range of 19.82±0.24 to 20.29±0.33mg is tabulated in the Table-2. Increase in weight was seen due to the incorporation of polymers and fusing of the rate controlled films with the drug reservoir in comparison to the reservoir films alone FM_1containing less polymer concentration showed the least weight whereas FM_5 containing large concentration of EC showed increased weight.

Drug content

The drug content of all the formulation was found to be in the range of 0.97±0.04mg to 0.991±0.06mg. The results showed in **Table 2** indicates similar values without significant deviations. It was concluded that the method for preparation of ocular inserts gave reproducible results.

%Moisture absorption

The % moisture absorption was calculated for all formulations in triplicate. The moisture absorption ranged between 4.67±0.003 to 12.45±0.21.Results are given in the **Table 2**. The % moisture absorption was found to be more in FM_8 and least in FM_5. It was concluded that there was more absorption in the formulation FM_8 which contained large concentration of hydrophilic polymer PVA and was assumed that less concentration of EC offered minimum hindrance to the transfer of moisture. In contrast FM_5 had shown low moisture absorption which may be due to the high concentration of EC as rate controlling membrane.

%Moisture loss

The values were found to be between 7.2±0.011 to 12.18±0.012. It was observed that when the formulations were kept at dry condition, maximum moisture loss occurred. The results shown in **Table 2**.Formulation FM_4 showed maximum amount of moisture loss and formulation FM_6 showed minimum moisture loss. The increased loss of moisture was due to the lower concentration of EC as it offered less hindrance to moisture loss. The decreased loss might be due to the presence of increased concentration of EC. The formulation containing PVA had more tendencies to lose moisture

Folding endurance

The folding endurance was obtained by manually folding the film repeatedly at a point till it broke. Folding endurance was found to be in the range of 75±4.6 to 92±3.5.Results tabulated in

Table 2. The folding endurance values of the films were found to be optimum and therefore the films exhibited good physical and mechanical properties.

Surface pH

The surface pH of all the prepared ocuserts were found to be in the range of 6.5 to 7.27.Results given in **Table 2**. The obtained pH values of the ocular inserts of Moxifloxacin HCl indicated that this can be suitable dosage form for ophthalmic use. This indicated that the inserts would not alter the pH of tear fluid in eye.

Table 2 Physicochemical parameters of ocular inserts

Moxifloxacin Formulations	Thickness	Weight	pH	Drug Content(mg)	Folding endurance	% moisture absorption	% moisture loss
FM_1	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
FM_2	0.315±0.02	20.10±0.26	6.7	0.97±0.04	79±2.9	9.62±0.011	11.49±0.005
FM_3	0.308±0.05	19.97±0.32	6.9	0.97±0.04	75±4.6	7.18±0.248	8.34±0.03
FM_4	0.311±0.07	20.16±0.16	6.9	0.97±0.04	84±5.5	7.41±0.006	12.45±0.21
FM_5	0.341±0.01	20.29±0.33	7.1	0.97±0.04	82±3.5	4.67±0.003	9.1±0.02
FM_6	0.298±0.02	20.11±0.11	7.2	0.97±0.04	90±2.2	5.92±0.005	7.2±0.011
FM_7	0.311±0.03	20.5±0.21	7.2	0.97±0.04	85±3.1	7.91±0.00	10.1±0.003
FM_8	0.289±0.12	19.91±0.15	7.1	0.97±0.04	87±4.2	9.83±0.031	11.18±0.012

***In vitro* drug release**

The *in vitro* release studies of FM_1 to FM_5 formulations were conducted for two days and the formulations does not showed the significant difference in the drug release. But the release observed for films containing EC alone was delayed so, a hydrophilic additive like poly vinyl pyrrolidine was incorporated to decrease the retardant effect of ethyl cellulose.

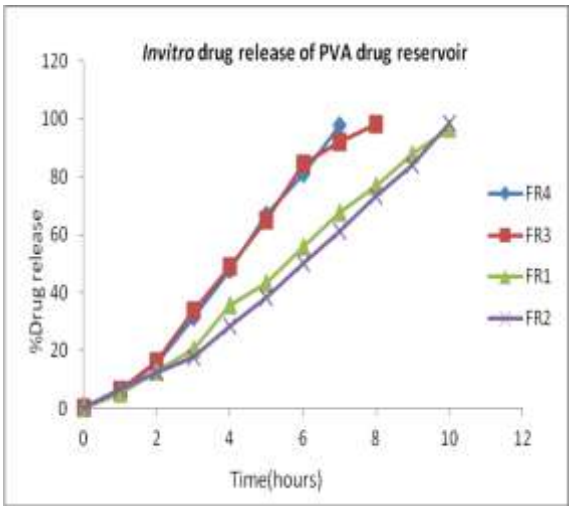

Figure 1: ***In vitro* drug release of the drug reservoir**

The release studies of films containing EC with PVP (FM_6, FM_7, FM_8) were studied up to a period of 120 hrs. The release of drug from FM_6 was found to be 99.1% at the end of 120hrs,

FM_7 the release was found to be 95.71% at 108 hrs and FM_8 the drug release was 98.36% at the end of 108 hrs. FM_6 showed a release of 99.1% at the end of 120 hours (5 days) which may be due to lower permeability of EC and higher permeability of PVP K-30 was considered for further studies.

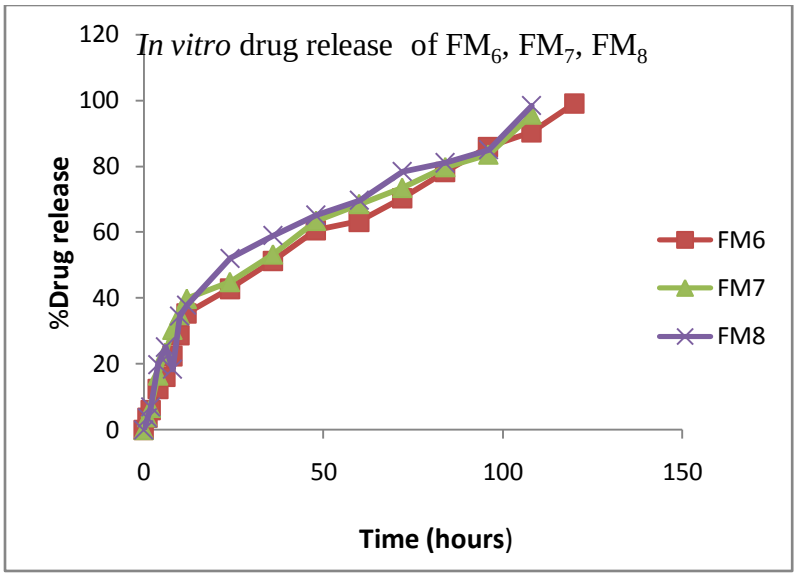

Figure 2*: In vitro* drug release of the selected formulation FM_6, FM_7 and FM_8

The zero order plot was found to be fairly linear for the formulation FM_6 as indicated by their coefficient of determination values. The coefficients of determination,'R2' was found to be 0.9910 for FM_6. For planar geometry the value of n=0.5 indicates a Fickian diffusion mechanism, for 0.5<n<1.0, indicates non-fickian transport and n=1 implies case-II transport. Slope value (n=>0.5) suggests that FM_6 followed non-fickian transport.

The best fit kinetic model for the optimized formulation FM_6 was Higuchi (R^2=0.991) and value of n was 0.609.It was observed that the drug diffused slowly from the ocular inserts. Higuchi matrix equation confirmed the release by diffusion controlled mechanism. Korsemeyer-Peppas 'n' value of prepared ocular inserts was found to be above 0.609 this indicated that the drug release from the optimized ocular insert (FM_6) followed zero order kinetics and the release mechanism being Higuchi.

Characterization of Ocular Inserts

The FTIR of Moxifloxacin Hydrochloride displayed the peak at 3528cm^{-1} indicates –NH stretching, two peaks at 1708cm^{-1} and 1623cm^{-1} for –C=O stretching of –C=O (carbonyl group) and –C=C were seen. The peak at 1298 cm^{-1} indicates the peak of –C-O. The –F (fluoride attachment) was seen in a range of 1400-1000 cm^{-1}. The peaks at 1519cm^{-1}, 992$cm^{-1}$and 803cm^{-1} represent major peaks of the drug. All the above peaks were observed in the final formulation

which indicated no interaction between Moxifloxacin and polymers when compared with infrared spectrum of pure drug as all functional group frequencies were present. Their respective generated scans are shown in Figure 3.

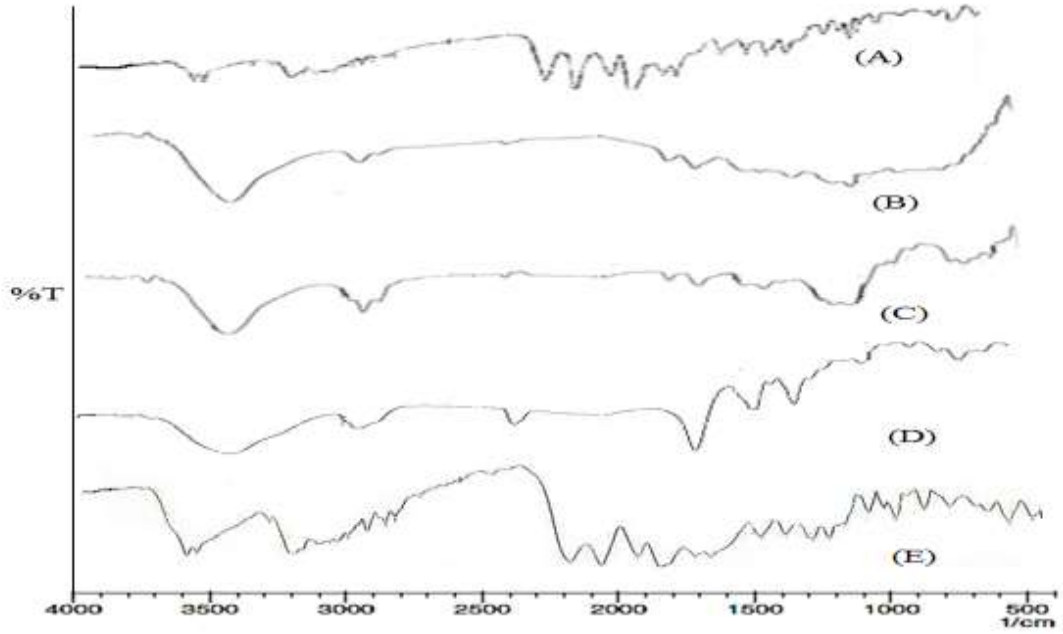

Figure 3: **IR spectra of Moxifloxacin Hydrochloride Ocular Inserts**

KEY-(A) Moxifloxacin HCl (B) Polyvinyl alcohol (C) Ethyl Cellulose (D) Poly Vinyl Pyrrolidone-K30 (E) FM_6 Optimized formulation.

Differential scanning calorimetry (DSC)

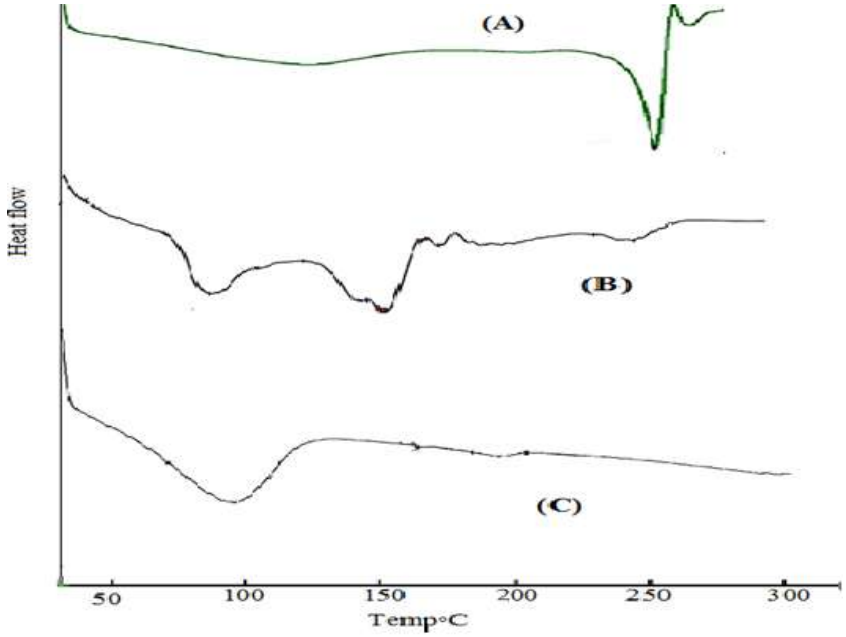

Figure 4: **DSC thermogram of Moxifloxacin Hydrochloride Ocular Inserts**

KEY- (A) pure Moxifloxacin HCl (B) Physical mixture containing the drug and polymers (C) Optimized film FM_6

The thermal analysis of the pure drug Moxifloxacin hydrochloride showed a sharp peak at 250.9^0 indicating the melting point of the drug. The physical mixture of the formulation showed a broad peak at 248.9^0 C indicating the melting of Moxifloxacin HCl and the peaks at 88.69^0 C,143^0 C,174^0 C indicating the melting of PVP-K30, EC and PVA respectively as shown in Figure 4.The DSC of the optimized FM_6 showed a broad peak in the range of 174^0C to 193^0C which is indicative of melting peak of poly vinyl alcohol and it did not show the significant peak of Moxifloxacin and carrier which indicated the complete dissolution of the drug in the polymer in the ocular film formation and a glass transition temperature was observed at 149.94^0 C which was assumed that the transition of the film from the solid form to elastic form has occurred which indicated the flexible characters of the film.

Sterility studies

The formulation FM_6 was found to be sterile when subjected to sterility study by direct inoculation as described in Indian Pharmacopoeia and no growth of anyforms of microorganisms were observed in the formulations in both Fluid thioglycolate medium and Soyabean casein digest medium.

Antimicrobial efficacy

Antimicrobial efficacy studies were carried out by using *Staphylococcus aureus*,*Pseudomonas aeruginosa*as test microorganisms by cup plate technique. Clear zones of inhibition were observed and the diameter of zone of inhibition produced by formulation FM_6 was nearby to those produced by the marketed eye drops. After incubation up to 24 hours, it was found that all formulations were having effective antimicrobial action.

Ocular irritation studies- Draize test

Approval for the use of animal was obtained from Institutional Animal Ethics Committee (IAEC). Results revealed that the inserts prepared using drug reservoir (PVA) and ethyl cellulose as rate controlling membrane were non-toxic and non-irritating to the eye. There was no sign of any irritation, redding, swelling or haziness in the rabbits eyes indicating that the insert was free from ocular toxicity and safe for ocular use.

***In vivo* drug release studies**

Initially the release for the first day was found to be 39.5% shown in Table 3. For 120hrs study (5 days), total observed release was 97.67%. The results obtained from the formulation FM_6

were in accordance with that of the *in vitro* drug release study. The results reported as mean±SD (n=3); $p<0.05$ was considered as statistical significant.

Table 3: In vivo drug release in rabbit

Days	Percentage of drug released
1	39.5±2.76
2	57.52±1.93
3	71.42±3.12
4	83.77±1.09
5	97.67±2.18

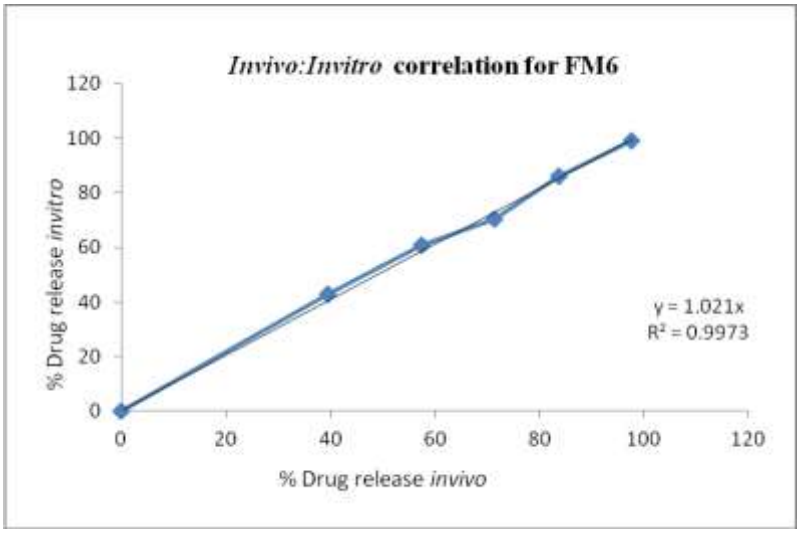

Figure 5: ***In vitro: In vivo* correlation of FM_6**

***In vivo: In vitro* correlation**

The cumulative percentage drug release from *in vivo-in vitro* studies almost gave similar results as obtained from *in vitro* experiments. The correlation value was found to be 0.99 for FM_6. The formulation FM_6 gave a good correlation and better linearity (Figure 5) and the strong correlation revealed the efficacy of the formulation. There was no drag out of the inserts from the eyes of the rabbit which suggests that the particular dimension was suitable as ocular inserts.

Stability studies

Accelerated stability studies at elevated temperature and humidity revealed no significant change in physical appearance, pH and drug content. This study showed that there was no definite change observed in the intactness of the drug and it was found to be stable after accelerated study for 3 months.

CONCLUSION

The rationale of the work to "Formulate and evaluate of ocular inserts of Moxifloxacin HCl" for

controlled release for treating bacterial conjunctivitis can be achieved. Finally it could be concluded that the optimized formulation was a viable alternative to conventional eye drops by virtue of its ability to enhance bioavailability through controlled drug delivery, longer precorneal residence time, ease and reduced frequency of administration with better patient compliance.

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