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Design and evaluation of polymeric ocular drug delivery system for controlled delivery of moxifloxacin hydrochloride: *in vitro* and *in vivo* evaluation

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Abstract

Moxifloxacin hydrochloride is a fluoroquinolone anti-infective agent useful in the treatment of eye infection such as conjunctivitis, keratitis and keratoconjunctivitis. An attempt has been made in the present research to formulate ocular inserts of moxifloxacin hydrochloride to increase residence time and prolong drug release. The ocular inserts were prepared using gelatin (18% and 20%), a natural biodegradable polymer and glycerin (70 % w/w of dry polymer) as a plasticizer. The cross linking was done by dipping cut inserts (8 mm diameter) in 10% w/v solution of glutaraldehyde in isopropyl alcohol (5 mL) for four different time period of 15, 30, 45 and 60 minutes to retard the release of drug. The inserts were then evaluated for their physicochemical parameters like uniformity of thickness, weight, drug content, swelling index and surface pH. The *in vitro* drug release studies were carried out using a bi-chambered donor receptor compartment model. *In vivo* drug release was carried out using rabbits as animal models. Formulations MHF4 and MHF8, which showed prolonged *in vitro* drug release, were subjected to *in vivo* study. *In vitro* and *in vivo* correlation for formulation MHF8 was found to be strong and productive. The drug was found to be active against selected microorganisms as was proved by microbial efficacy studies. Formulation MHF8 was found promising, as it achieved the target of the present study.

Keywords: moxifloxacin hydrochloride, cross-linking, gelatin, *in vitro* and *in vivo* release, ocular insert

Introduction

The ophthalmic delivery of drugs continues to be challenged by the intrinsic physiology of the eye. The efficient removal mechanism that operate at the site of action (rapid tear turn over, blinking) and the low corneal permeability act cooperatively to suppress the effectiveness of ophthalmic formulations and to limit drug bioavailability to less than 5% (Barbu et al. 2005). Moreover, systemic absorption of the drug and additives drained through nasolacrimal duct may result in undesirable effects. An effective way to achieve slow and prolonged absorption in ophthalmic practice is to incorporate a drug into a polymeric film, which when placed in the cul-de-sac of the eye exhibits a prolonged local release for drug action on tissue in the immediate

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vicinity (Chari et al. 1974).

Moxifloxacin hydrochloride (HCl) is a new 8-methoxy derivate of fluoroquinolones with enhanced activity *in vitro* against gram positive bacteria and maintenance of activity against gram negative bacteria (Ostergaard and Sorensen 1998). It is an anti-infective agent useful in the treatment of eye infection such as bacterial conjunctivitis, keratitis and keratoconjunctivitis. It is presently available as eye drops (0.5%). It is administered at dosing interval of 1 drop in the affected eye 3 times a day for 7 days (Eduardo and Crider 2005). The eye drops types dosage form is convenient to use but most of the drug is diluted by tear and rapidly washed out of the sac by constant tear flow which can be avoided by using insert by which the therapeutic efficacy of ophthalmic drug can be greatly improved (Sultana et al. 2005). Various attempts have been made by researchers in order to prepare ocular insert by solvent casting technique using hydroxypropyl methylcellulose (HPMC), methylcellulose (MC) and polyvinyl alcohol with swellable polymeric excipients (Karatas and Baykara 2001, Sreenivas et al. 2006). In the present study, an attempt has been made to formulate ocular insert of moxifloxacin hydrochloride using gelatin, a natural biodegradable polymer and glycerin as a plasticizer by solvent casting method with aim of increasing the residence time, achieving controlled release, reduction in frequency of administration and greater therapeutic efficacy.

Materials and Methods

Material

Moxifloxacin hydrochloride (HCl) was obtained as gift sample from Torrent pharmaceuticals Pvt. Ltd., Gandhinagar, India. Gelatin and glycerin were purchased from SD Fine chemicals, Mumbai, India. Glutaraldehyde was purchased from Oxford Lab., Mumbai, India. All other reagents and solvent used were of analytical grade.

Preparation of ocular inserts

The ocular inserts were prepared using solvent casting method. The ocular inserts were prepared using different concentration of gelatin (18% and 20%) and glycerin (70%) as shown in Table 1. The required quantity of gelatin and glycerin were weighed and dissolved in 3/4 of water and the mixture was heated at 60°C on a water bath until the entire gelatin was dissolved. The weighed amount of moxifloxacin hydrochloride (2.53%) and the remaining water were added and stirred on magnetic stirrer to get uniform dispersion. After complete mixing the casting solution (5 mL) was poured on anumbra glass petridish (63.59 cm^2, internal diameter) containing mercury as substratum. The petridish was cooled at 10°C by placing on ice, until the films were gelled. The gelled films were taken out from ice and allowed to dry at room temperature for 72 h. The petridish was covered by an inverted funnel with cotton plug to prevent aerial contamination of the films during the drying period. The dried films thus obtained were cut to the required size (8 mm diameter) containing 1 mg of drug by a cork borer (Mundada and Shrikhande 2006).

The cross linking was done by dipping cut inserts (8 mm diameter) in 10% w/v solution of glutaraldehyde in isopropyl alcohol (5 mL) for four different time period of 15, 30, 45 and 60 min to retard the release of drug. In order to remove excess unreacted glutraldehyde from the surface of inserts, the films were transferred to an aqueous sodium metabisulphide solution (2%) and then immediately removed and placed in absolute alcohol bath (Mundada and Shrikhande 2008, Ali et al. 2009) The formulations so prepared were designated as MHF1, MHF2, MHF3, MHF4, MHF5, MHF6, MHF7 and MHF8. The cross linked inserts were kept in desiccators until use.

Table 1: Composition of Moxifloxacin ocular inserts

Formulation code	Hardening time (min)	Drug (w/v)	Gelatin concentration (w/v)	Glycerin concentration (w/w)
MHF1	15	2.53%	18%	70%
MHF2	30	2.53%	18%	70%
MHF3	45	2.53%	18%	70%
MHF4	60	2.53%	18%	70%
MHF5	15	2.53%	20%	70%
MHF6	30	2.53%	20%	70%
MHF7	45	2.53%	20%	70%
MHF8	60	2.53%	20%	70%

Characterization of prepared ocular inserts

Uniformity of thickness

The thickness of the insert was determined using a Vernier caliper (Mitutoy, Japan) at five separate points of each insert. For each formulation, five randomly selected inserts were tested for their thickness (Murthy 1997).

Uniformity of weight

From each batch, five inserts were taken out and weighed individually using digital balance (Asco, India). The mean weight of the insert was noted (Vijayendra et al. 2006, Gupta et al. 2007).

Drug content

Five films were taken from each batch and dissolved or crushed in 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 up to the mark with buffer. One mL of the above sample was withdrawn and the absorbance was measured by UV-VIS spectrophotometer (Systronics-2202, India) at 287.6 nm after suitable dilutions (Trindade et al. 2006).

Water Absorption Characteristics (Swelling index)

Five ocular inserts were weighed and placed separately in beakers containing 4 mL of distilled water. At regular interval (every 5 min), the inserts were removed and the excess water on their surface was removed using a filter paper and then again weighed. The procedure was continued till there was no further increase in the weight (Harishkumar et al. 2004) The swelling index was then calculated by following formula (Jain et al. 2004):

$$\alpha = \frac{Ws - Wo}{Ws}$$

Where α = Swelling index, W_O = Initial weight of ocular inserts and Ws = Weight of inserts after swelling.

Surface pH

The inserts were allowed to swell in closed petridish at room temperature for 30 minutes in 0.1 mL of bidistilled water. The swollen device was removed and placed under digital pH meter (Elico, India) to determine the surface pH (Harishkumar et al. 2004).

Drug – excipients compatibility study

Fourier transport infrared spectroscopy (FTIR)

The FTIR absorption spectra of the pure drug, placebo formulations and drug loaded ocular inserts were recorded in the range of 400 – 4000 cm^{-1} by KBr disc method (2 mg sample in 200 mg KBr) using FTIR spectrophotometer (Perkin-Elmer, Spectrum GX, Chicago IL, USA).

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) scans of pure drug, placebo formulations and drug loaded ocular inserts were performed using DSC-PYRIS-1 (Perkin-Elmer, USA). The analysis was performed with a heating range of 50-480°C and a rate of 10°C min^{1}.

In vitro diffusion study

The *in vitro* diffusion of drug from the different ocular insert was studied using the classical standard cylindrical tube fabricated in the laboratory (bi-chambered donor receptor compartment model). A simple modification of glass tube of 15 mm internal diameter and 100 mm height (Semalty et al. 2008, Patel et al. 2009). The diffusion cell membrane (prehydrated cellophane) was tied to one end of open cylinder, which acted as a donor compartment. An ocular insert was placed inside this compartment. The diffusion cell membrane acted as corneal epithelium. The entire surface of the membrane was in contact with the receptor compartment comprising of 25 mL of isotonic phosphate buffer (pH 7.4) in a 100 mL beaker (Mishra and Gilhotra 2008, Mundada and Shirbhande 2008). The content of receptor compartment was stirred continuously using a magnetic stirrer and temperature was maintained at 37±0.5°C. At specific intervals of time, 1 mL aliquot of solution was withdrawn from the receptor compartment and replaced with fresh buffer solution. The aliquot was analyzed for the drug content using UV-VIS spectrophotometer at 287.6 nm after appropriate dilutions against reference using isotonic phosphate buffer pH 7.4 as blank.

Release kinetics

In order to understand the mechanism and kinetics of drug release, the results of the *in vitro* drug release study were fitted with various kinetic equations such as zero order (% release *vs* t), first order (log% unrelease *vs* t) , Higuchi matrix (% release *vs* square root of time). In order to define a model which will represent a better fit for the formulation, drug release data further analysed by Peppas equation, $Mt/M\infty=kt^{n}$, where Mt is the amount of drug released at time t and M∞ is the amount released at time ∞, the Mt/M∞ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent, a measure of the primary mechanism of drug release. r^2 values were calculated for the linear curves obtained by regression analysis of the above plots (Costa and Sousa Lobo 2008, Sreenivas et al. 2006).

Sterilization and interaction study

The selected ocular inserts were serialized by γ-radiation before eye irritancy and *in vivo* study. Ocular insets were packaged in aluminum foil. The package was exposed to a total dose of 2.5 mega rads (Charoo et al. 2003). After sterilization, the ocular inserts were also evaluated for sterility test according Indian Pharmacopoeia. Interaction studies were carried out to investigate any interaction between drug and polymers, as well as to study the effect of gamma radiation on drug after sterilization. Interaction studies were carried by UV scanning, infrared studies and assay of ocular inserts (Khan et al. 2008).

Eye irritancy test

The selected ocular inserts (MHF4 and MHF8) were subjected to the irritancy test (OECD guideline, test guideline 405, 2002). The OECD guideline for eye irritancy test is currently the most valuable and reliable method for evaluating hazard or safety of a substance introduced into or around the eye. Eye irritancy potential of a substance was determined on the basis of its ability to cause injury to the cornea, iris, and conjunctiva when a substance is applied to the eye (Draize et al. 1944). Testing was carried out on adult albino rabbits weighing about 2.5 to 3.5 kg of either sex. All rabbits were maintained under 12 h light and dark cycles and were fed with green vegetables throughout the course of study. Food and water was

allowed ad libitum. A twelve rabbits were used for testing the eye irritation potential of the ocular inserts. Ocular inserts were placed into the cul-de-sac of the rabbit while other eye served as a control (Mundada and Shrikhande 2006 and 2008).

In vivo drug release study

Selected ocular inserts (MHF4 and MHF8) sterilized using γ-radiations were used for *in vivo* drug release studies. Two groups containing six healthy rabbits (Sankar et al. 2006) were used to study the drug release *in vivo* from formulations which showed the satisfactory *in vitro* drug release. Each rabbit was kept in good hygienic condition in order to avoid vulnerability to any disease including ophthalmic type. Selected ocular inserts were placed in the cul-de-sac of each rabbit while the other eye served as a control. At periodic intervals (1, 2, 4, 6, 8 and 10 h) the inserts were taken out carefully from the cul-de-sac of each rabbit and analyzed for the remaining drug content. The drug remaining was subtracted from the initial drug content of the insert, which gave the amount of drug released in the rabbit eye. (Mundada and Shrikhande 2006 and 2008).

Microbiological studies

The selected ocular insert were evaluated for microbiological study. The microbiological studies were carried out to ascertain the biological activity of the selected formulation against test microorganism. Nutrient agar seeded with the test organism (*E. coli* and *S. aureus*) was allowed to solidify in the petri dish. An ocular inserts were removed from the pack and carefully placed over the agar layer at a suitable distance (Charoo et al. 2003). The plates were then incubated at 37±0.5°C for 24 h. After incubation the zone of inhibition was measured around the ocular insert.

Stability study

Stability studies were carried out on ocular inserts MHF4 and MHF8, according to ICH guidelines (Brian et al. 2000). A sufficient number of ocular inserts (packed in aluminum foil) were stored in humidity chamber, with relative humidity of 75% and at temperature of 40±0.5°C. The samples were tested for drug content after 0, 30, 60, 90 and 180 days respectively (Khan et al. 2008). The degradation rate constant was determined from the plot of the percentage drug remained vs. time in days (Charoo et al. 2003).

$$\text{Slope} = \frac{-K}{2.303}$$

Where, K is the degradation rate constant.

Results and Discussion

Uniformity of thickness

The thickness of ocular inserts (MHF1 to MHF8) were found to be in range of 0.148 ± 0.0026 mm to 0.175 ± 0.0055 mm as shown in Table 2. The low standard deviation of the measured thickness of all the eight formulations ensured uniformity in thickness.

Uniformity of weight

The weight ocular inserts were found to be in the range of 11.92±0.3004 to 12.95±0.1261 mg (Table 2). The uniformity of the weights of the films indicates good distribution of the drug, polymer and plasticizer.

Table 2: Physicochemical characteristics of various batches of ocular inserts

Formulation code	Weight* (mg)	Thickness* (mm)	Drug content* (mg)	Drug content (%)	Swelling index*	Surface pH*
MHF1	12.15 ± 0.1039	0.166 ± 0.0039	0.986 ± 0.0045	98.60	1.321 ± 0.0232	6.17 ± 0.0683
MHF2	12.37 ± 0.1945	0.162 ± 0.0055	0.984 ± 0.0064	98.40	1.288 ± 0.0345	6.64 ± 0.0965
MHF3	11.92 ± 0.3004	0.155 ± 0.0049	0.978 ± 0.0035	97.80	1.150 ± 0.0319	5.97 ± 0.1369
MHF4	12.71 ± 0.2815	0.148 ± 0.0026	0.988 ± 0.0024	98.80	0.896 ± 0.0269	6.95 ± 0.0577
MHF5	12.55 ± 0.1955	0.175 ± 0.0055	0.966 ± 0.0030	96.60	1.381 ± 0.0488	6.67 ± 0.0981
MHF6	12.64 ± 0.2273	0.171 ± 0.0060	0.982 ± 0.0035	98.20	1.265 ± 0.0302	6.55 ± 0.0539
MHF7	12.61 ± 0.1410	0.165 ± 0.0038	0.978 ± 0.0065	97.80	1.198 ± 0.0159	6.58 ± 0.0820
MHF8	12.95 ± 0.1261	0.162 ± 0.0033	0.984 ± 0.0051	98.40	1.009 ± 0.0367	7.11 ± 0.0596

*Values as Mean ± SD (n = 5)

Drug content

For the various formulations (MHF1 to MHF8), drug content was found to vary between 0.966 ± 0.0030 to 0.988 ± 0.0024 mg (Table 2). The estimation of drug content was found to be almost same with their low standard deviation values.

Swelling index

The swelling index values were found to be in range of 0.896±0.0269 to 1.381± 0.0488 (Table 2). The result showed that there was no much variation in the water absorption properties of formulations.

Surface pH

The surface pH of prepared inserts (MHF1 to MHF8) was found be in range of 5.97±0.1369 to 7.11±0.0596 (Table 2). This indicates that the prepared inserts would not alter the pH of the tear fluid in the eye.

Drug – excipients compatibility study

Fourier transport infrared spectroscopy (FTIR)

The pure drug, placebo formulations and selected ocular inserts were subjected to the FTIR analysis. The FTIR spectra (Figure 1A) shows one peak at 3528 nm indicating the –NH

stretching and two peaks at 1708 nm and 1623 nm for the –C=O stretching of –COO and -COOH group respectively. The peaks at 1516 nm, 994 nm, and 803 nm are the major peaks for drug. All the above peaks were also found in drug loaded ophthalmic insert (Figure 1C) that confirms the presence of drug in the polymer without any interaction.

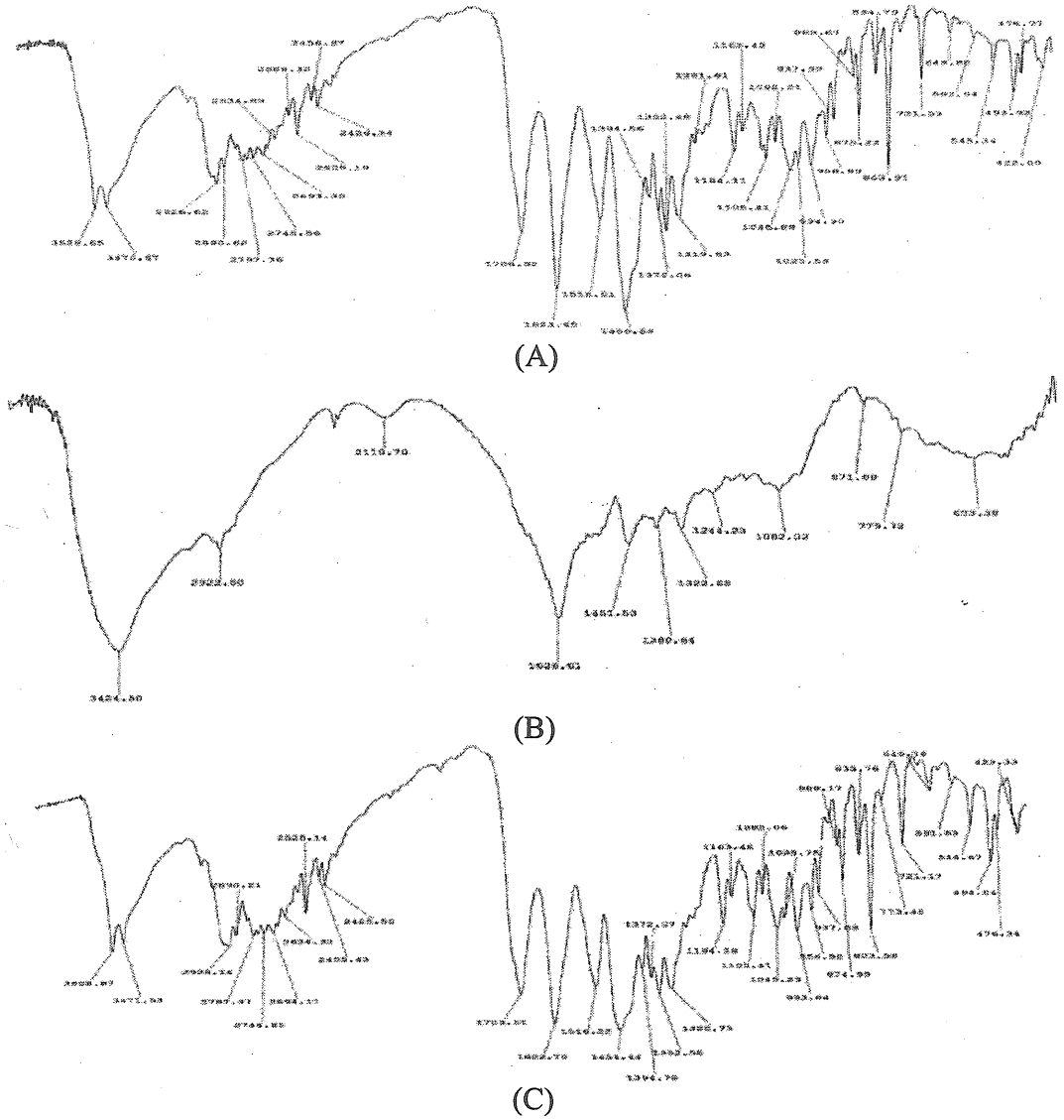

Figure 1. FTIR spectra of (A) pure Moxifloxacin HCl, (B) Placebo formulation (without drug), (C) Drug loaded ocular insert

Differential Scanning Calorimetry (DSC)

The results of DSC study are shown in Fig. 2. DSC thermo grams showed endothermic peak of moxifloxacin hydrochloride (pure drug) at 243.288°C, which corresponded to its melting point. Thermograms of drug loaded ocular inserts showed peak at 235.604°C and placebo formulations (without drug) showed at 82.713°C. There was a slight decrease in the melting point of drug

when prepared in the form of ocular inserts. The results of the thermograms obtained from DSC revealed no interaction between the polymer and the drug in the ocular inserts.

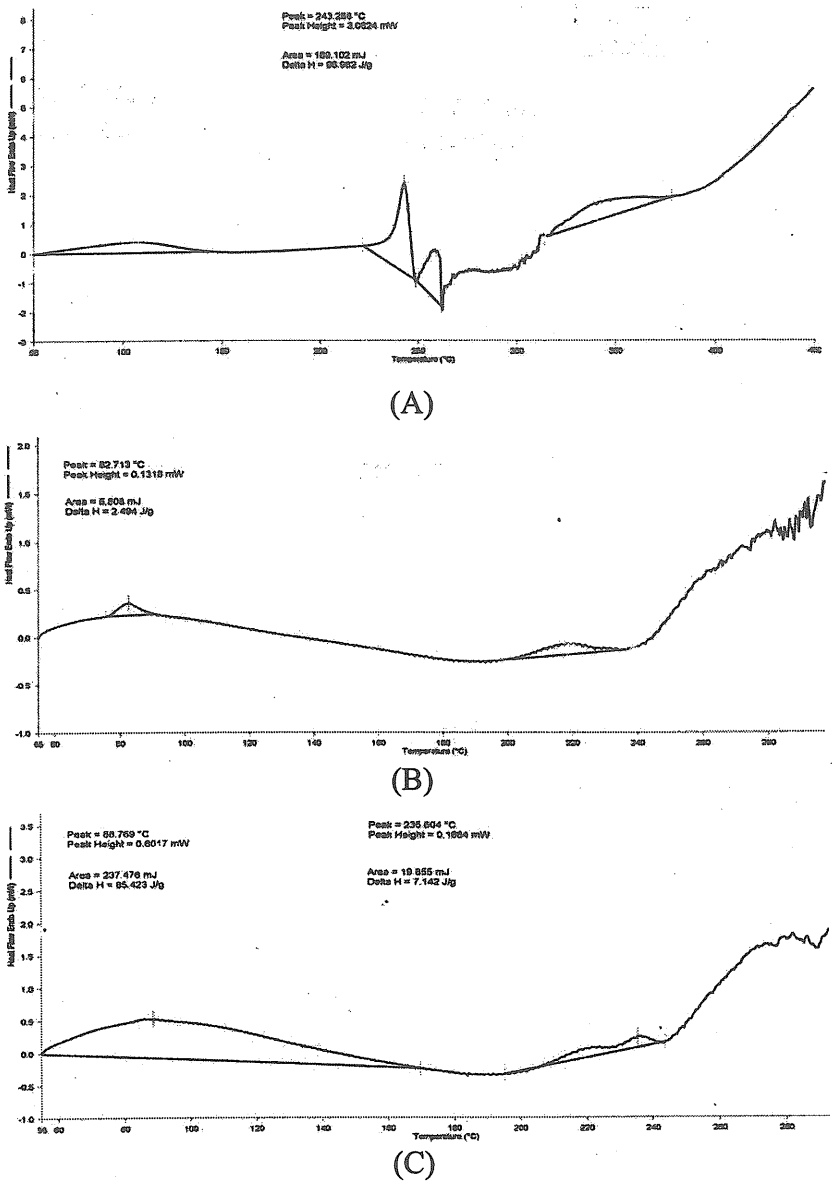

Figure 2. DSC thermograms of (A) pure moxifloxacin HCl, (B) Placebo formulation (without drug), (C) Drug loaded ocular inserts

In vitro diffusion study

In the present study, *in vitro* drug release was carried out in triplicate. At different time intervals, the sample was withdrawn and cumulative percentage drug release was calculated on the basis of mean amount of drug present in the respective films. *In vitro* drug release study for formulations MHF1 to MHF8 revealed that these formulations were capable of extending the drug release up to 8-10 h. Formulation MHF8 showed maximum drug release of about 95.01% at the end of 10 h, whereas MHF4 controlled the release showing maximum 93.22% drug release

at the end of 8 h. The percentage of drug release of all eight formulations is presented in Fig. 3. The formulations (MHF4 and MHF8) that gave good results with the highest percentage were selected for *in vivo* and microbiological studies.

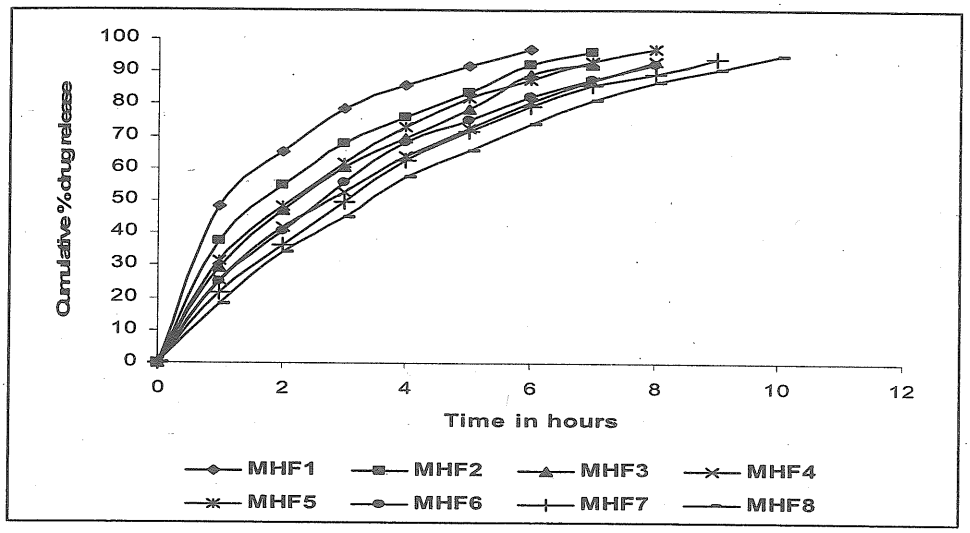

Figure 3. *In vitro* diffusion of moxifloxacin HCl from MHF1 to MHF8 formulations

Release kinetics

The data obtained from *in vitro* studies of all eight formulations were analyzed by various kinetic models to know the order of release. The kinetic models used were zero order, first order, Higuchi and Krosmeyer-Peppas equations (Table 3).

Table 3: Kinetic data of Drug Release from MHF1 to MHF8

Formulation Codes	Zero Order Kinetic		First Order Kinetic			Higuchi's Model		Krosemeyer-Peppas model		
	K_0	r^2	Slope	K_1	r^2	K_h	r^2	K_p	n	r^2
MHF1	14.24	0.8303	- 0.223	- 0.513	0.9914	33.65	0.9861	49.26	0.392	0.9933
MHF2	12.37	0.8900	- 0.187	- 0.431	0.9701	35.69	0.9949	38.58	0.483	0.9962
MHF3	12.48	0.9339	- 0.156	- 0.359	0.9783	38.94	0.9957	30.39	0.592	0.9946
MHF4	10.93	0.9481	- 0.130	- 0.299	0.9853	37.32	0.9992	26.26	0.623	0.9970
MHF5	11.19	0.9062	- 0.175	- 0.403	0.9721	36.52	0.9899	32.66	0.549	0.9914
MHF6	11.00	0.9307	- 0.135	- 0.311	0.9920	37.61	0.9903	26.21	0.637	0.9883
MHF7	10.11	0.9423	- 0.131	- 0.302	0.9839	37.47	0.9919	22.77	0.679	0.9900
MHF8	9.21	0.9513	- 0.123	- 0.283	0.9703	36.37	0.9959	19.72	0.717	0.9883

K: release rate constant; r^2: Coefficient of determination; n: release exponent

The release constants were calculated from the slope of the respective plots. Higher correlation was observed in the Higuchi equation (r^2>0.99) than zero order and first order plot which indicates diffusion controlled mechanism. In the present study, the value for n was found to be in the range of 0.392 to 0.717 (MHF1 to MHF8) indicating that the release mechanisms followed either fickian (case 1) or anomalous (non-fickian) transport as the case may be. The selected formulations MHF4 and MHF8 were having 'n' value 0.623 and 0.717, respectively, indicating that the release mechanism followed anomalous (non-fickian) transport.

Sterilization and interaction study

The selected inserts (MHF4 and MHF8) were sterilized using γ-radiation. Sterilized inserts were tested for sterility as per Indian Pharmacopoeia 1996. No microbial or fungal growth was seen in any of the formulations, which indicated that the inserts were sterilized completely. All γ-irradiated inserts complied sterility test IP. No interaction between drug and polymer due to sterilization by gamma radiation was found when tested by UV absorption studies and FTIR study. The UV absorption spectra for pure drug before and after sterilization showed similar pattern. The similar peaks were observed in the FTIR spectra of sterile drug as that of parent moxifloxacin hydrochloride. This shows that the drug was not changed chemically, revealing the suitability of γ-radiation for the sterilization of ocular inserts.

Eye irritancy test

The results of the eye irritancy test revealed that all inserts prepared using gelatin as reservoir and hardened (cross linked) using glutraldehyde for different time intervals were nontoxic and non-irritating to the eye, as total score was zero. Since inserts were not expelled out of the cul-de-sac of the rabbits, it suggests that the insert's dimensions (8 mm) were appropriate for use.

In vivo drug release study

Formulation MHF4 and MHF8 were chosen for *in vivo* drug release study, as both inserts prolonged the release of moxifloxacin hydrochloride. *In vivo* release studies were performed using rabbits. Ocular inserts were removed carefully at periodic intervals (1, 2, 4, 6, 8, and 10 hrs) and analyzed for residual drug content. The drug remaining was subtracted from the initial drug content of the insert, which gave the amount of drug released in the rabbit eye. The results are shown in Fig. 4. The *in vivo* drug release study from formulations MHF4 and MHF8 were found to be in accordance with that of the *in vitro* drug release study. Hence, we tried to correlate *in vivo* results with the *in vitro* percentage drug release. The correlation values were found to be 0.9976 and 0.9984 for formulations MHF4 and MHF8, respectively. The linearity was found in both formulations but formulation MHF8 exhibited a good correlation and better linearity (Fig. 5).

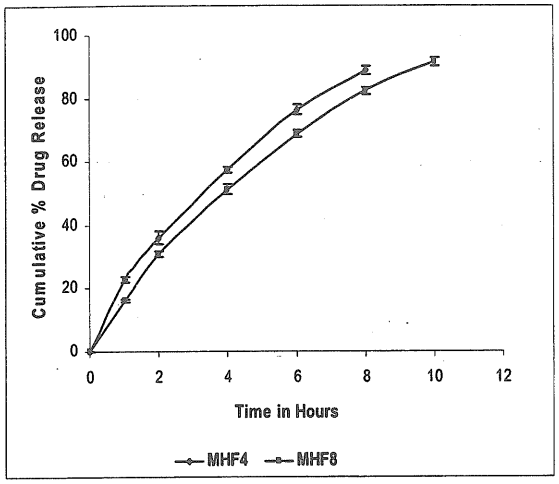

Figure 4. *In vivo* diffusion of moxifloxacin HCl from MHF4 and MHF8 formulations

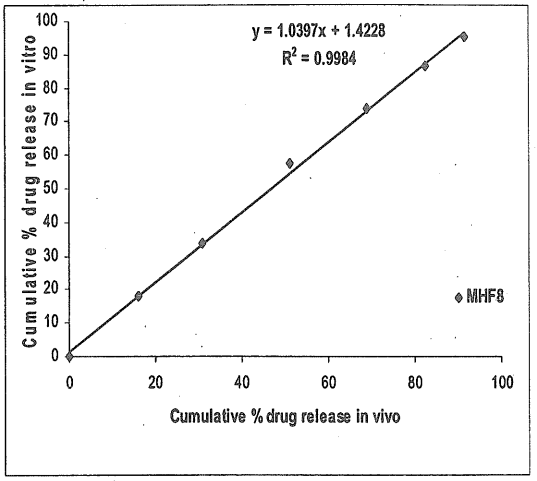

Figure 5. *In vitro* and *In vivo* correlation study of MHF8 formulations

Microbiological studies

The selected ocular inserts (MHF4 and MHF8) showed good antimicrobial activity when tested microbiologically on solidified agar. Clear zones of inhibition were obtained in said formulations against both test organisms namely *S.aureus* and *E.coli* (Table 4).

Table 4: *In vitro* inhibition of the growth of microorganisms by selected ocular insert

Formulation code	Zone of inhibition* (mm) ± SD	
	S. aureus	*E. coli*
MHF4	49.0 ± 3.055	37.2 ± 2.309
MHF8	46.2 ± 2.440	39.0 ± 2.749

*Values as Mean ± SD (n = 3)

Stability study

Accelerated stability studies at elevated temperature and humidity revealed no significant change in drug content after 180 days. Ocular inserts could be stored safely at study temperature. However, storage temperature should not in excess of 40°C. The degradation rate constant for formulations MHF4 and MHF8 were found to be 1.4879×10^{-4} and 1.4081×10^{4} day^{-1}, respectively as shown in Fig. 6. The overall degradation is less than 5%, a tentative shelf-life of 2 years may be assigned to formulation as per ICH guidelines.

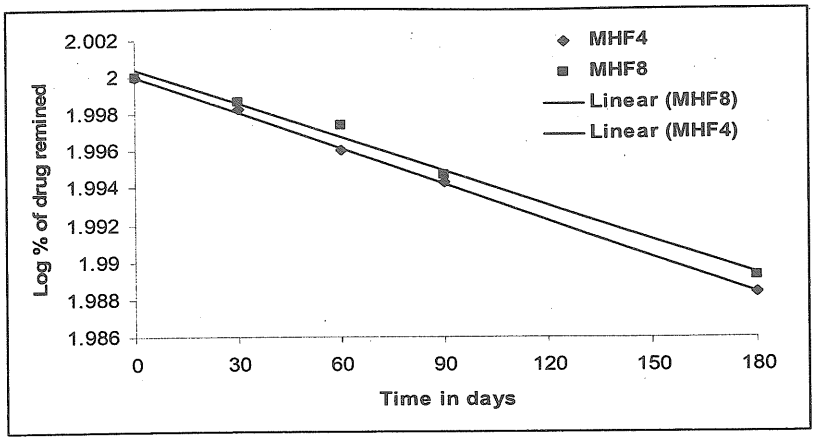

Figure 6. Plot of log % of drug remained vs. time for ocular inserts MHF4 and MHF8

Conclusion

Various batches of moxifloxacin ocular inserts were prepared by solvent casting method and characterized. The formulation (MHF8) containing 20% gelatin hardened for 60 min using 10% glutraldehyde solution satisfied required pharmaceutical characteristics of ocular inserts and was found promising. The formulation per se is bio-degradable and would be able to offer benefits such as i.e., increasing residence time, prolonging drug release, reducing frequency of administration, and there by may help to improve patient compliance. However, their potential to improve ocular bioavailability in humans needs to be investigated further.

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References

Ali, M., Iqbal, M. and Rao, K.S. (2009). Evaluation of progesterone loaded glutraldehyde cross-linked chitosan implants. *Ind. Pharmacist* 79: 95-98.

Barbu, E., Sarvaiya, I., Green, K.L., Nevel, T.G. and Tsibouk, J. (2005). Vinylpyrrolidone-co- (meth) acrylic acid insert for ocular drug delivery: synthesis and evaluation. *J. Biomed. Mater. Res.* 74: 343-349.

Brian, R., Matthews, G. and Michael, W. (2000). Stability storage and testing of ophthalmic products for global registration. *Drug Dev. Ind. Pharm.* 26: 1227 – 1237.

Chari, S.S., Makoid, M.C., Erikson, S.P. and Robinson, J.R. (1974). Drop size and initial dosing frequency problems of topically applied ophthalmic drugs. *J. Pharm. Sci.* 64: 333-338.

Charoo, N.A., Kohli, K., Ali, A. and Anwer, A. (2003). Ophthalmic delivery of ciprofloxacin hydrochloride from different polymer formulations: *in vitro* and *in vivo* studies. *Drug Dev. Ind. Pharm.* 29: 215-221.

Costa, P. and Sousa Lobo, J.M. (2001). Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci.* 13:123-133.

Draize, J.H., Woodward, G. and Calvery, H.O. (1944). Methods for the study of irritation and toxicity of substance applied topically to the skin and mucous membrane. *J. Pharmacol. Exp. Ther.* 82: 377-390.

Eduardo, A. and Crider, J. (2005). Ophthalmic infections and their anti-infective challenges. *Surv. Ophthalmol.* 50 (supp l): S1- S6.

Gupta, A., Sharma, S.K. and Ahuja, M. (2007). *In vitro* and *in vivo* evaluation of gellan based ocular inserts of phenylephrine. *Acta Pharm. Sci.* 49: 55-63.

Harishkumar, S.L., Balasubramaniaum, J. and Kumar, M.T. (2004). *In vitro* characterization of physically reinforced ocular inserts of Indomethacin. *Acta Pharm. Turc.* 46: 17-24.

Jain, S.K., Chourasia, M.K., Jain, A.K. and Jain, R.K. (2004). Microspheres bearing salbutamol for nasal delivery. *Drug Del.* 11: 113-122.

Karatas, A. and Baykara, T. (2001). Studies on Indomethacin insert prepared by water soluble polymers: The relation between dissolution rate and swelling behavior. *Farmaco* 56: 197-202.

Khan, S., Ali, A., Singhavi, D. and Pramod, Y. (2008). Controlled ocular delivery of acyclovir trough rate controlling ocular insert of eudragit: A technical note. *AAPS PharmSciTech.* 9: 169-172.

Mishra, D.N. and Gilhotra, R.M. (2008). Development studies on gel-forming erodible ocular polymeric films of Gatifloxacin sesquehydrate. *Acta Pharm. Sci.* 50: 145-152.

Mundada, A.S. and Shrikhande, B.K. (2006). Design and evaluation of soluble ophthalmic insert for controlled release of ciprofloxacin hydrochloride. *Drug. Dev. Ind. Pharm.* 32: 443-448.

Mundada, A. and Shrikhande, B.K. (2008). Formulation and evaluation of ciprofloxacin hydrochloride soluble ocular insert. *Curr. Eye Res.* 33: 469-475.

Murthy, S.N. (1997). Biodegradable polymers matrix based ocuserts of diclofenac sodium. *Indian Drugs* 34: 336-338.

OECD guideline (2002). Acute eye irritation/corrosion, test guideline 405.

Ostergaard, C., Sorensen, J.D., Knudsen, J.D. and Frimodt-Moller, N. (1998). Evaluation of moxifloxacin, a new 8-methoxyquinolone, for treatment of meningitis caused by a penicillin-resistant pneumococcus in rabbits. *Antimicrob. agents Chemother.* 42: 1706-1712.

Patel, U., Chaudhary, K.A., Chotai, N.P. and Chirag, N. (2008). Formulation and evaluation of indomethacin ophthalmic inserts. *Indian J. Pharm. Educ. Res.* 42: 348-352.

Sankar, V., Chandrasekaran, A.K., Durga, S., Geetha, G. and Ravichandran, V.A. (2006). Design and evaluation of diclofenac sodium ophthalmic inserts. *Acta Pharm. Sci.* 48: 5-10.

Semalty, M., Semalty, A. and Kumar, G. (2008). Formulation and characterization of mucoadhesive buccal film of glipizide. *Indian J. Pharm. Sci.* 70: 61-65.

Sreenivas, S.A., Hiremanth, S.P. and Godbole, A.M. (2006). Ofloxacin ocular inserts: Design, formulation and evaluation. *IJPT* 5: 159-162.

Sultana, Y., Aquil, M. and Ali, A. (2005). Ocular insert for controlled delivery of pefloxacin mesylate: preparation and evaluation. *Acta Pharm.* 55: 305-314.

Trindade, M.A.G., Cunha, P.A.C. and Araujo, T.A. (2006). Interaction study of moxifloxacin with Cu(II) ion using square-wave voltammetry and its application in the determination in tablets. *Ecl. Quim.* 31: 31-38.

Vijayendra, S.M., Nanjawade, B.K. and Manvi, F.V. (2006). Development of sustained ocular drug delivery system for betaxolol. *Indian J. Pharm. Educ. Res.* 40: 165-168.

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