INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES

(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com

Research Article

DESIGN AND EVALUATION OF MOXIFLOXACIN POLY VINYL ALCOHOL OCCULAR FILMS

***SARITHA A[1] AND ANURADHA M S[1]**

[1]Department of Pharmaceutical Technology, Krupanidhi College of Pharmacy, VarthurHobli, Bengaluru, Karnataka-560035.

*Corresponding Author

Abstract

Ocular films of Moxifloxacin HCl were prepared with the objective of reducing frequency of administration, obtaining controlled release and greater therapeutic effect in treatment of eye infections. Moxifloxacin HCl a broad spectrum fourth generation fluroquinolone agent used in the treatment of eye infection such as conjunctivitis, keratitis, kerato-conjunctivitis etc. In the present wok an attempt was made to formulate ocular films by using poly vinyl alcohol containing Moxifloxacin HCl The ocular films containing Moxifloxacin HCl were formulated by film casting technique using PVA as polymer.The formulations were subjected to physicochemical evaluations. *In vitro* drug release revealed that the optimized formulation showed a good controlled release pattern with a drug release the end of 120 hrs (5 days). Higuchi plot revealed that release follows diffusion by zero order release kinetics. 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.

Introduction

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[1,2].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[3].

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.[4,5].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 instill 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 dose6. For this reason, concentrated solutions and frequent dosing are required for the instillation to achieve an adequate level of therapeutic effect[4]. Ocular therapy in bacterial infections would be significantly improved if the pre corneal residence time of drugs could be increased[7,8].

Conjunctivitis is an inflammation of the conjunctiva due to infectious or noninfectious causes may be allergic, chemical, or mechanical[8].Fluroquinolone are one of the promising groups of antibiotics currently being used topically to treat conjunctivitis and corneal ulcers[9]. Fluroquinolone (ciprofloxacin, gatifloxacin, levofloxacin,

Moxifloxacin, and ofloxacin) inhibit DNA gyrase (topoisomerase II) and topoisomerase IV. Fluoroquinolones with an 8-methoxy substitution, such as moxifloxacin, have enhanced antimicrobial activities that may limit the selection of resistant mutants in pathogens[9].

In the present research work an attempt was made to formulate ocular films of Moxifloxacin by employing film casting technique to achieve controlled release.

Materials and Methods

Moxifloxacin HCl was obtained as a gift sample from Micro Labs, Bangalore. Poly vinyl alcohol, Poly vinyl pyrrolidone-K30, 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 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].

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 MoxifloxacinHCl 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 (pre-hydrated cellophane) 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.

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.

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).

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 ± 2^0C 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

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 MoxifloxacinHCl 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 37^0C. The zone of inhibition (ZOI) was compared with that of the standard. Each sample was tested in triplicate.

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].

Results and Discussion

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 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

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

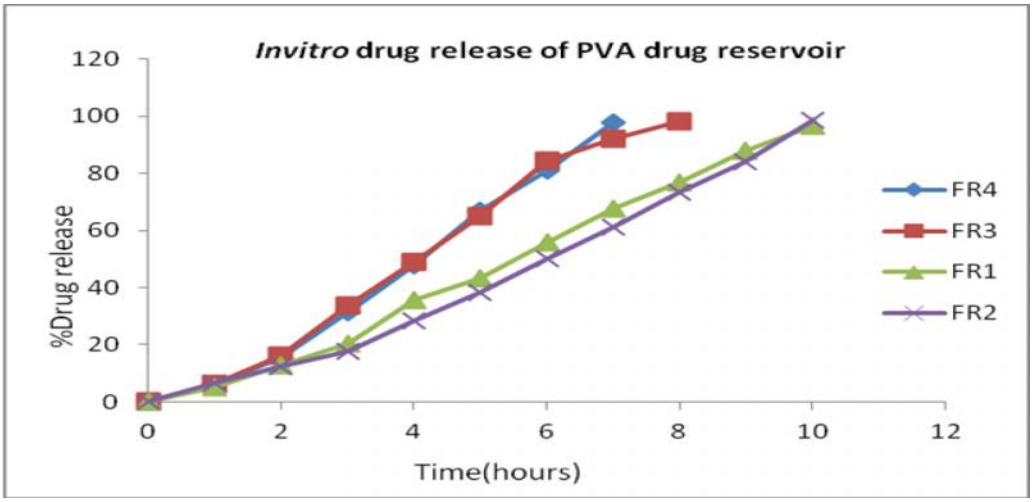
Surface pH

The surface pH of all the prepared ocuserts were found to be in the range of 6.5 to 7.27. 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.

***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 2: *In vitro* drug release of the drug reservoir

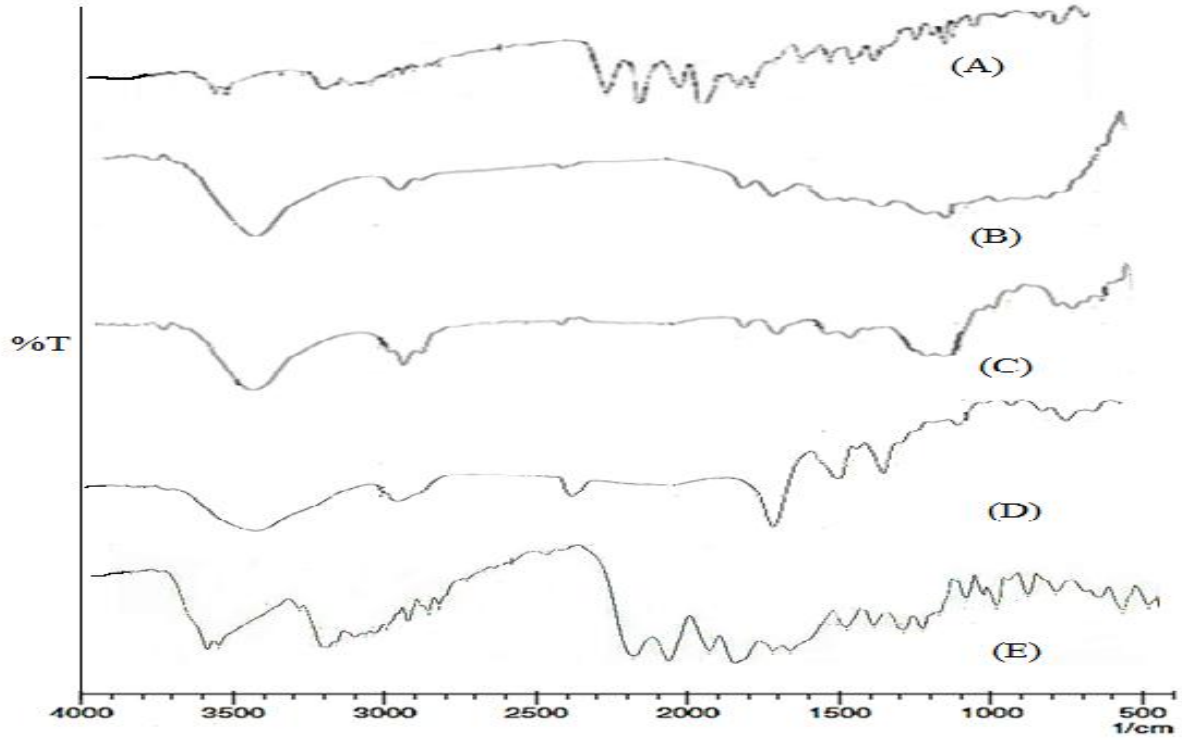


The zero order plot was found to be fairly linear for the formulation as indicated by their coefficient of determination values. The coefficients of determination,'R2' was found to be 0.9910.. For planar geometry the value of n=0.5 indicates a Fickian diffusion mechanism, for 0.5<n<1.0, indicates non-fickian transport and n=1 implies case-II transport. Slope value (n=>0.5) suggests that followed non-fickian transport. 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$^{-1,}$ 992cm^{-1}and 803cm^{-1} represent major peaks of the drug. All the above peaks were observed in the fina l 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 **Figure1.**

Figure 1: 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.

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 any forms 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 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.

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 research work was to “Formulate and evaluate of ocular inserts of Moxifloxacin HCl” for controlled release. Moxifloxacin HCl is a broad spectrum antibacterial agent used in the treatment of ocular infections. the rationale for the controlled release ocular inserts were met and the stability study conducted proved the ocuserts to be stable. Finally it could be concluded from all the studies conducted that the formulation was a viable alternative to the 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 resulting in better patient compliance.

References

1. Bourlais CL, Acar L, Zia H, Sado PA, Needhan S, Leverge R. Ophthalmic drug delivery systems – Recent Advances. Progress in Retinal and Eye Research 1998;17(1):33-58.
2. Daniel M, Mills R, Moret N. Microbial Keratitis: What's the preferredinitial therapy? Br J Ophthalmol 2003; 87:1167-74.
3. Macha S, Hughes PM and Mitra AK. Overview of ocular drug delivery. In: MitraAK,editor. Ophthalmic Drug Delivery Systems.2nded, Revised and Expanded. New York: Marcel Dekker, Inc; 2003.p.1-2.
4. Chien YW. Ocular drug delivery and delivery systems. In: Novel drug delivery systems. 2nded. New York: Marcel Dekker;1992.p.269.
5. Hui HW, Robinson JR. Ocular drug delivery systems. New York: Marcel Dekker; 1993.p.261-75.
6.Soppinath KS, Aminabhavi TM, Dave AM, Kumar SG, Rudzinski WE. Stimulus responsive"smart" hydrogels as novel drug delivery systems. Drug DevInd Pharm 2002;28:957-74.
7. Bawa R. Ophthalmic drug delivery systems. New York Marcel Dekker, Inc; 1993. Vol 58.p.224-48.
8. Chang MH, Fung HB. Besifloxacin: A topical fluoroquinolone for the treatment of bacterial conjunctivitis. Clinical Therapeutics 2010;32(3):454-71.
9. Tanwar YS, Patel D, Sisadia SS. In-vitro and in-vivo Evaluation of Ocular Inserts of Ofloxacin. DARU 2007;15(3):139-145.
10. Rajasekaran A, Karthika K, Padmapreetha J, Abirami J, Sivakumar V. Design and Evaluation of polymeric Controlled Release Natamycin Ocular Inserts. Katmandu University. Journal of Science, Engineering and Technology 2010;6(1):108-115.
11. Sultana Y, Aquil M, Ali A, Ocular Insert of for Controlled Delivery of Pefloxacinmisylate: Preparation and Evaluation. ActaPharma (Italian) 2005;55:305-314.
12. Rao V, Shyale S. Preparation and evaluation of ocular inserts containing norfloxacin. Turk J Med Sci 2004;34:239-46.
13. Patel UL, Chotai NP, Nagda CD. Design and Evaluation of Ocular Drug Delivery System for Controlled Delivery of Gatifloxacinsesquihydrate: In-vitro and in-vivo evaluation. Pharm DevTechnol 2012;17(1):15-22.
14. Patel D, Patel MM, Patel NM, Patel M. Prparation and Evaluation of Ocular Inserts containing Brimonidinetartarate. Int J Pharm and Clinical Res 2009;1(1):19-22.

