Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 10, 2014

Original Article

FORMULATION AND *IN-VITRO* EVALUATION OF MOXIFLOXACIN OCULAR INSERTS

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Received: 28 Jun 2014 Revised and Accepted: 05 Aug 2014

ABSTRACT

Objectives: Most ocular diseases are treated with topical applications of eye drops. After instillation of an eye drop, typically less than 5 % of the applied drug penetrates the cornea and reaches intraocular tissues, while a major fraction of the instilled dose is absorbed and enters the systemic circulation. The objective of present work is to improve ocular bioavailability and corneal contact time of a Moxifloxacin for better permeation through cornea.

Methods: Five formulations were prepared by film casting method. Polyvinyl pyrrolidene, methyl cellulose and hydroxyl propyl methyl cellulose were used as polymers. PEG 400 was used as plasticizer.

Results: The release from the ocular inserts may be considered to follow zero order as evidenced from the regression coefficient (r2) value which is higher for MF4 (.9991). The release from formulation code MF1 was found to be 80 % upto 24 hrs. The release from formulations MF2 and MF3 was 91.7 % and 92.10 % respectively within 24 hrs. The release from formulation 4 was 95.23% within 24 hrs. The release from MF5 was upto 60.73% within 24 hrs. The ocular inserts of formulation MF5 were hard and brittle.

Conclusion: The formulation MF4 has the potential to formulate moxifloxacin ocular inserts. However in-vivo studies in animals and antimicrobial studies are required before this could be evaluated as an alternative to moxifloxacin eye drops.

Keywords: Ocular inserts, Moxifloxacin, Ophthalmic, STF, Release, In-vitro.

INTRODUCTION

Most ocular diseases are treated with topical applications of eye drops. After instillation of an eye drop, typically less than 5 % of the applied drug penetrates the cornea and reaches intraocular tissues, while a major fraction of the instilled dose is absorbed and enters the systemic circulation. Various systems have been designed during the past two decades to minimize ocular absorption of ophthalmic drugs. There are two main strategies for improvements: increasing the corneal permeability and prolonging the contact time on the ocular surface. The goal of ophthalmic drug delivery systems has traditionally been to maximize ocular absorption rather than to minimize systemic absorption. Systemic absorption of ocularly applied drugs is often nearly complete. This has caused systemic side effects varying from mild to life-threatening events [1].

The normal volume of tear fluid in the cul-de-sac of the human eye is about 7 to 8 µL. An eye that does not blink can accommodate a maximum of about 30 µL of fluid, but when blinked can retain only about 10µL. Excessive liquids, both normally produced and externally delivered, rapidly drain from the eye. A single drop of an ophthalmic solution or suspension measures about 50 µL, so much of an administered drop may be lost. Because of the dynamics of the lachrymal system, the retention time of an ophthalmic solution on the eye surface is short and the amount of the drug absorbed is usually only a small fraction of the quantity administered. Decreased frequency of dosing, increased ocular retention time, and greater bioavailability are achieved by formulations that extend corneal contact time, such as Ocular inserts, gel systems, liposome, polymeric drug carriers and ophthalmic suspensions, pre soaked contact lenses and ointments[2].

Drugs are commonly applied to the eye for a localized action on the surface or in the interior of the eye. A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the precorneal loss factors which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac and relative impermeability of the corneal epithelial membrane [3]. The ocular bioavailability of drugs can be assessed by measuring concentration of drugs in tears, cornea, conjunctiva, aqueous or vitreous humor. The concentration of drugs in these tissues should be maintained for sufficient time to achieve effective concentration of the drug. A number of approaches have recently been explored to develop biocompatible and comfortable vehicle for controlled ophthalmic drug delivery. To achieve increased ocular bioavailability, researchers have explored a variety of vehicles including ocular inserts, suspension of nanoparticles, nanocapsules, liposome, collagen shields and therapeutic contact lenses etc. [4].

Moxifloxacin is a fourth generation fluoro-quinolone with high potency against both gram-positive and gram-negative bacterial pathogens. As compared to other fluoro-quinolone moxifloxacin has highest potency against *Staphylococcus aureus* and *Staphylococcus epidermis*. Fluoroquinolones became the gold standard for treating ocular infections [5]. The aim of present study was to develop a sustained release ophthalmic drug delivery system with increased residence time in eye. The delivery of pilocarpine was commercialized by Alza Corporation in 1975. The ocular insert was designed to provide weekly dose of pilocarpine [6]. An erodible insert is available for treatment of dry eye. It is molded into rod shape from hydroxypropyl cellulose polymer. When inserted into lower cul-de-sac, the polymer absorbs tear fluid and forms a gel-like mass that gradually erodes and thickens the tear film for several hours.

MATERIAL AND METHODS

Moxifloxacin hydrochloride was obtained as a gift sample from Ranbaxy Laboratories Ltd. (Gurgaon, India). Poly ethylene glycol-400, polyvinyl pyrrolidene, methyl cellulose and hydroxyl propyl methyl cellulose were bought from Rankem and CDH. Millipore filter and millipore water were from Millipore. All the chemicals used were of analytical grade.

Formulation of ocular inserts

Five formulations were prepared by film casting method. Polyvinyl pyrrolidene, methyl cellulose and hydroxyl propyl methyl cellulose were used as polymers. PEG 400 was used as plasticizer. Polymers

were dissolved in methanol and then plasticizer and moxifloxacin were added to the solution. The mixture was poured into rectangular shaped plastic molds covered by aluminium foil. The pored mixture was evaporated by placing in a desicator overnight[7]. A thin film of polymer containing drug was obtained and cut into small discs. Each disc was having size 3 mm. The discs were used as ocular inserts containing 0.5 % moxifloxacin.

Swelling studies of ocular inserts

Swelling studies were carried out by placing previously weighted and dried ocular inserts into 3 ml of simulated tear fluid (STF) of pH 7.4 (sodium chloride 0.670 gm, sodium bicarbonate 0.200 gm, calcium chloride dihydrate 0.008 gm, purified water q. s.100 ml).

$$S.I. = \frac{Ws - Wd}{Ws} \times 100$$

Where S. I. = Swelling Index, Ws= Weight of Swollen Ocular Insert

Wd= Weight of Ocular Insert

Uniformity of thickness

The thickness of 10 inserts from each batch was measured at three different randomly selected spots of each insert with screw gauze.

Uniformity of weight

The weight of 10 inserts from each batch was determined and their mean was taken.

Uniformity of content

For uniformity of content, 10 inserts from each batch were weighted individually and dissolved into 50 ml of STF. The solution was filtered. An aliquot of the filtrate was diluted and analyzed for moxifloxacin content at 290 nm in a UV spectrometer (Hitachi).

***In-vitro* drug release studies**

In-vitro drug release studies were performed on ocular inserts through Millipore filter (0.45 µ). The release was carried out in triplicate. A modified Franz diffusion cell consisting of 10 ml glass receptor which also contained an outlet assembly along with a glass donor cell having the side tube for drainage was used for the release studies.

The chamber was surrounded by a water jacket through which water at 37 ^{0}C was circulated from the thermosetting water bath. A Teflon coated magnetic bead was placed at the bottom of the receptor cell to ensure homogeneity of the receptor solution. Simulated tear fluid (STF) was filled in the receptor chamber. Millipore filter was dipped in STF and placed on the receptor chamber of the diffusion cell. The Ocular Insert was placed on the Millipore filter. The donor cell was placed over the contact lens and Millipore filter. The area of the receptor compartment's opening was 0.50 cm^2 and the area of the contact lens was 0.95 cm^2. The area available for diffusion was 0.50 cm^2. The entire cell was clamped over a magnetic stirrer. The donor compartment represents the conjunctival sac whereas the receptor compartment represents the anterior segment of the eye. The samples for *In-vitro* release and drainage were analyzed after suitable dilutions at 290 nm in a UV spectrometer (Hitachi)[4].

RESULT AND DISCUSSION

Moxifloxacin is a fourth-generation synthetic fluoroquinolone antibacterial agent developed by Bayer AG (initially called BAY 12-8039). It is marketed worldwide (as the hydrochloride) under the brand names Avelox, Avalox, and Avelon for oral treatment. In most countries, the drug is also available in parenteral form for intravenous infusion. Moxifloxacin is also sold in an ophthalmic solution (eye drops) under the brand names Vigamox, and Moxeza for the treatment of conjunctivitis (pink eye)[8,9,1]. As compared to other fluoro-quinolone moxifloxacin has highest potency against *Staphylococcus aureus* and *Staphylococcus epidermis*. Moxifloxacin has been developed as 0.5% solution for topical, ocular use as moxifloxacin ophthalmic solution 0.5%. But eye drops exhibit pulse delivery resulting in transient overdose, followed by short period of effective therapeutic concentration then a long period of underdose. Thus, the feasible way to improve ocular bioavailability is to increase the corneal contact time of a drug. This can be achieved by ocular inserts. The in vitro diffusion apparatus used in this study was able to simulate the in vivo conditions and was useful for the drug release studies. One ml of the sample was withdrawn from the receptor at different time intervals up to 24 hrs. The sample withdrawn was replaced with 1 ml of STF. The thickness and weight variation of the prepared ocular inserts was within 3%.

Table 1: Formulation code and composition of moxifloxacin cast film

Ingredients (mg)	Code				
	MF1	MF2	MF3	MF4	MF5
Moxifloxacin	250	250	250	250	250
Polyvinyl pyrrolidene	400	--	--	400	400
Methyl cellulose	--	400	-	400	400
Hydroxylpropyl methyl cellulose	--	--	400	400	400
Poly ethylene glycol-400	0.3 ml	0.3 ml	0.3 ml	0.3 ml	--

Composition of various ocular insert formulations using the different combination of polymers, with and without plasticizer along with their formulation codes are shown in Table no. 1.

Table 2: Swelling of Ocular inserts

Formulation code	Swelling Index
MF1	61.52+0.413
MF2	66.32+0.712
MF3	66.64+0.475
MF4	68.12+0.786
MF5	59.91+0.124

Value represents Mean + S. E. (n=3)

Table 3: Cumulative *In-vitro* % drug release from moxifloxacin ocular inserts

Formulation code	Cumulative *In-vitro* Drug Release (%)
MF1	80.23 + 0.0006
MF2	90.21 + 0.0023
MF3	90.98 + 0.0012
MF4	95.64 + 0.0009
MF5	75.23 + 0.0023

Value represents Mean + S. E. (n=3)

Table 4: Regression values of zero order, first order and Higuchi model

Formulation code	Zero Order	First Order	Higuchi Model
MF1	.9923	.9901	.9918
MF2	.9910	.9900	.9906
MF3	.9921	.9911	.9916
MF4	.9991	.9961	.9985
MF5	.9911	.9903	.9909

Swelling of formulated ocular inserts in STF was studied and results are shown in table 2. Maximum and Minimun swelling index was obtained for formulation MF4 and MF5 respectively.

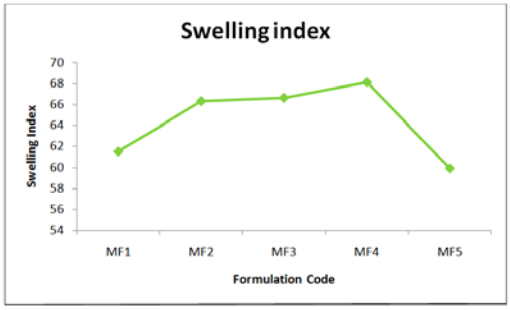

Fig. 1: **Swelling of Ocular inserts**

Drug release studies were carried out in STF using Franz diffusion Cell. Maximum cumulative drug release was obtained for MF4 with the release value 95.64 + 0.0009 and minimum cumulative drug release were obtained for MF5 with the release value 75.23 + 0.0023.

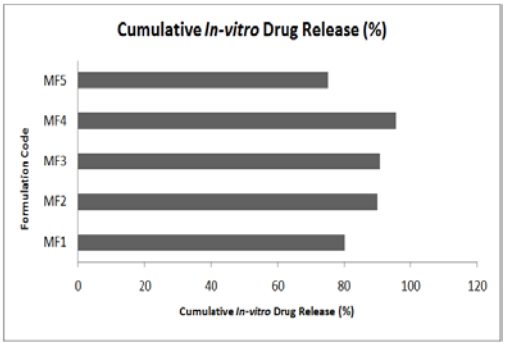

Fig. 2: **Cumulative *in vitro* drug release**

The release from the ocular inserts may be considered to follow zero order as evidenced from the regression coefficient (r^2) value which is higher for MF4 (.9991). Matrix release has been reported for flubipfofen[11] and indomethacin[12] in different study. The reason may be the Millipore filter used as membrane in Franz Diffusion Cell. It was seen that some solution was accumulated in the donor compartment above the Millipore membrane. That could be the reason for different results obtained for the release study as reported previously [11,12]. The release from formulation code MF1 was found to be 80 % upto 24 hrs. The release from formulations MF2 and MF3 was 91.7 % and 92.10 % respectively within 24 hrs. The release from formulation 4 was 95.23% within 24 hrs. The release from MF% was upto 60.73% within 24 hrs. Ocular inserts of formulation MF5 were hard and brittle.

From swelling studies, it is clear that the formulation MF5 has minimum swelling index. Thus it can be concluded that the plasticizer[13] is very important constituent of the formulations prepared. The drug release from the unplasticized inserts, formulation MF5 was lower as compared to all other formulations. The plasticizer enhances the hydrophobicity of the polymer matrix resulting in enhanced swelling and consequent increase in the porosity of the matrix, thus leading to higher drug release.

CONCLUSION

The formulation MF4 has the potential to formulate moxifloxacin ocular inserts. However, *in-vivo* studies in animals and antimicrobial studies are required before this could be evaluated as an alternative to moxifloxacin eye drops.

CONFLICT OF INTERESTS

Declared None

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