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Research Article

MOXIFLOXACIN LOADED CONTACT LENS FOR OCULAR DELIVERY-AN *IN VITRO* STUDY

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ABSTRACT

The contact lens usage has greatly increased not only in India but all over the World in recent years. There are many companies like Johnson & Johnson , Baush & Lomb, Biomedics, Freshlook, Ciba Vision etc. which are marketing contact lenses in India. The purpose of this investigation was to evaluate p-HEMA contact lens of Johnson & Johnson (Acuvue) for the *invitro* drug release and drainage through Millipore filter and transcorneal permeation of moxifloxacin through excised goat cornea. Moxifloxacin hydrochloride (0.5% w/v) solution of different pH (5.0, 5.5, 5.9, 6.5 and 7.2) was prepared in isotonic phosphate buffer (0.0667 M). The uptake of moxifloxacin hydrochloride (0.5% w/v) by polyhydroxyethylmethacrylate (p-HEMA) contact lens at pH 5.0, 5.5, 5.9, 6.5 or 7.2 and time intervals of 1, 2, 6, 12 or 24 hrs was determined at room temperature.

Keywords: Contact lens, Moxifloxacin, P-HEMA, pH, Release, Transcorneal permeation.

INTRODUCTION

Eyes are very important for the human body and we must protect them. Eyes are the windows of soul. Without eyes, the five basic senses would not be complete. Tears are nature's lotion for the eyes. The eyes see better for being washed by them.

Pharmaceutical preparations are applied topically to the eye to treat surface or intraocular conditions, including bacterial, fungal and viral infections of the eye or eyelids; allergic or infectious conjunctivitis or inflammations; and dry eye due to inadequate production of fluids bathing the eye.

The normal volume of the 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. For example, following administration of pilocarpine ophthalmic solution, the solution is flushed from the pre corneal area within 1 to 2 minutes, resulting in the ocular absorption of less than 1 % of the administered dose. This necessitates repeated administration of the solution. Decreased frequency of dosing, increased ocular retention time, and greater bioavailability are achieved by formulations that extend corneal contact time, such as gel systems, liposome, polymeric drug carriers and ophthalmic suspensions, pre soaked contact lenses and ointments. [1]

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. [2] 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. [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 suspension of nanoparticles, nanocapsules, liposome, collagen shields and therapeutic contact lenses etc. Among these, soft contact lenses have been widely studied owing to their high degree of comfort, biocompatibility and significant increase in drug residence time and bioavailability[4,5,6].

MATERIAL AND METHODS

Moxifloxacin hydrochloride was obtained as a gift sample from Ranbaxy Laboratories Ltd. (Gurgaon, India). Daily wear contact lens Acuvue was received from Johnson & Johnson. Calcium chloride, disodium hydrogen phosphate, hydrochloric acid, sodium bicarbonate, sodium dihydrogen phosphate was bought from Rankem, Millipore filter and millipore water was from Millipore, sodium chloride (CDH), used was of analytical grade. Fresh whole eyeballs of goat were obtained from butcher's shop (Ambedkar Nagar, New Delhi, India) within one hour of slaughtering of the animals.

Preparation of Drug Solution

Moxifloxacin hydrochloride (0.5% w/v) solution of different pH (5.0, 5.5, 5.9, 6.5 and 7.2) was prepared in isotonic phosphate buffer (0.0667 M). The required pH of drug solution was adjusted by sodium bicarbonate and hydrochloric acid.

Contact Lens

Daily wear contact lenses 1-Day Acuvue (Johnson & Johnson) were used. The characteristic of contact lens used were as follow:

Commercial Name	:	Acuvue
Polymer	:	Etafilcon A
Storage	:	Buffered saline
Listed water content	:	58 %

Swelling of lens at different pH

The contact lens was removed from packaging and dried at room temperature. The weight of dry lens was taken. The lens was dipped

in 3ml drug solution of pH 5.0, 5.5, 5.9, 6.5 or 7.2 for one h. After 1 h the weight of swollen lens was taken and the Swelling Index (S.I.) was calculated by the following formula:

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

Where S.I. = Swelling Index

Ws= Weight of Swollen Lens

Wd= Weight of Dry Lens

In- vitro drug uptake by lens at different pH and different time intervals

The uptake of moxifloxacin hydrochloride (0.5% w/v) by polyhydroxyethylmethacrylate (p-HEMA) contact lens at pH 5.0, 5.5, 5.9, 6.5 or 7.2 and time intervals of 1, 2, 6, 12 or 24 hrs was determined at room temperature. The lens was removed from the packaging with the help of forceps and dipped into Millipore water for 5 min. and then dipped into the phosphate buffer of respective pH at which the drug uptake was to be carried out. Again the lens was held with the help of forceps and wiped with tissue paper to remove excess fluid. The lens was then dipped in vial containing 3 ml of the drug solution at given pH for 1, 2, 6, 12 or 24 hrs. The drug uptake was determined as the difference between the initial and final concentrations of the drug solution into which the lens was dipped. All the readings were taken in triplicate. The drug concentrations were determined spectrophotometrically using UV spectrophotometer (Hitachi) at 290 nm.

***In-vitro* drug release and drainage studies**

The *in-vitro* drug release and drainage studies were performed on the drug loaded contact lenses, dipped in drug solution of different pH 5 , 5.5 , 5.9 , 6.5 or 7.2 for 1 hour through Millipore filter (0.45 µ). The release and drainage 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 side tube for drainage was used for the release studies. A side arm allowed sampling of the receptor cell. 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.

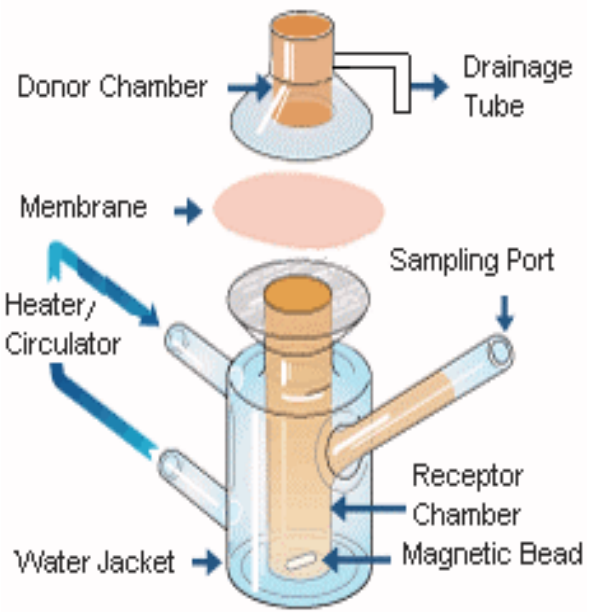

Fig. 1: Franz Diffusion Cell

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) was filled in the receptor chamber. Millipore filter was dipped in STF and placed on the receptor chamber of diffusion cell. The contact lens 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 where as 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).

***In-vitro* transcorneal permeation study**

Freshly excised goat cornea was fixed between clamped donor and receptor compartments of an all-glass modified Franz diffusion cell in such a way that its epithelial surface faced the donor compartment and the endothelial surface faced the receptor compartment. The corneal area available for diffusion was 0.50 cm^2. The receptor compartment was filled with 10 ml freshly prepared bicarbonate ringer solution (pH 7.2), and all air bubbles were expelled from the receptor compartment. The contact lens soaked in drug solution for one hr at pH 5.9, 6.5 or 7.2 was kept on the cornea. The receptor fluid was kept at 37 ^{o}C with constant stirring using a Teflon-coated magnetic stir bead. Permeation and drainage study was continued for 120 minutes. Samples were diluted with bicarbonate ringer solution suitably. All the samples were analyzed for moxifloxacin content by measuring absorbance at 290 nm in UV spectrometer (Hitachi).

The permeation (%) was calculated as follows:

$$\text{Permeation (\%)} = \frac{\text{Amount of drug permeated in Receptor}}{\text{Drug uptake by contact lens}} \times 100$$

At the end of the experiment, each cornea (freed from adhering sclera) was weighed, soaked in 1 ml methanol, dried overnight at 90 ^{o}C, and reweighed. From the difference in weights, corneal hydration was calculated.

RESULT AND DISCUSSION

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*. Moxifloxacin has been developed as 0.5% solution for topical, ocular use as moxifloxacin ophthalmic solution 0.5%. [7] But eye drops exhibit pulse delivery resulting in transient overdose, followed by short period of effective therapeutic concentration then a long period of underdose. We have tried to use Daily wear contact lenses as drug delivery device for moxifloxacin. Lenses soaked in drug solution could be applied to the eye. The said approach could prolong the contact time of the drug with the cornea and thus improve penetration of drug through the cornea. [8]

Thus the feasible way to improve ocular bioavailability is to increase the corneal contact time of a drug. This can be achieved by soaked contact lenses. For this a model is required to study drug release, drainage and transcorneal permeation of drugs from soaked contact lenses. The in vitro diffusion apparatus used in this study was able to simulate the in vivo conditions and was useful for the drug release, drainage and transcorneal permeation studies. An I.V. diffusion set was used to control the flow of STF over contact lens, which resembles the drainage of tears. The flow rate of STF was adjusted to 2 to 3 drops per minute to simulate drainage rate of an adult eye. One ml of the sample was withdrawn from the receptor at 15, 30,45,60,90,120,180,240 and 300 minutes. The sample withdrawn was replaced with 1ml of STF. The drained STF from the donor at the above mentioned time intervals were also collected separately.

The swelling of the lens at different pH is shown in Table 1.

Table 1: Swelling of lens at different pH of moxifloxacin solution (0.5 % w/v).

S. No.	pH	Swelling Index
1	5.0	54.63+0.512
2	5.5	56.78+0.384
3	5.9	55.64+0.465
4	6.5	58.40+0.477
5	7.2	54.51+0.777

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

Swelling was found between 54.63 to 58.4 % being maximum at pH 6.5.

In-vitro drug uptake by lens at different pH and different time interval is shown in Table 2.

Table 2: Drug uptake (mg) by lens at different pH of moxifloxacin solution (.5 % w/v) and different time intervals (hrs)

Time(Hr)	pH 5.0	pH 5.5	pH 5.9	pH 6.5	pH 7.2
1	1.125+.032	1.349+.021	1.199+.012	1.439+.036	0.884+.052
2	1.134+.021	1.321+.028	1.192+.019	1.458+.043	0.882+.057
6	1.113+.021	1.342+.032	1.192+.019	1.422+.048	0.893+.052
12	1.103+.022	1.332+.021	1.203+.012	1.422+.012	0.882+.057
24	1.134+.021	1.321+.028	1.203+.012	1.409+.043	0.882+.057

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

In-vitro uptake of moxifloxacin hydrochloride (0.5% w/v) by p-HEMA contact lens at pH 5.0 , 5.5 , 5.9 , 6.5 or 7.2 for time intervals of 1 , 2 , 6 , 12 or 24 hrs was determined at room temperature and it was found that the drug uptake was approximately constant during the soaking period 1-24hrs and was maximum at pH 6.5. The amount of drug uptake remains constant for soaking time above 10min for poly-hydroxymethacrylate (p-HEMA). [9]

Data reveals rapid release (2-4 hours) at different pH. Similar results have been obtained previously for ciprofloxacin. [8] Rapid kinetics has also been reported for ciprofloxacin cromolyn sodium, idoxuridine, pilocarpine and prednisolone. [10] The drug release data was evaluated for zero order, first order and Higuchi release kinetics and the results are shown in Figure 2, 3 and 4.

All the plots were linear but considering the R^2 value the drug release from the soaked lenses could be better explained as zero order as R^2 value is in the range of 0.99.

Table 3: Cumulative *in-vitro* % drug release from lens soaked at pH 5.0, 5.5, 5.9, 6.5 or 7.2 of moxifloxacin solution (0.5 % w/v).

	Cumulative *In-vitro* Drug Release (%)				
Time (Min.)	**pH5.0**	**pH5.5**	**pH 5.9**	**pH 6.5**	**pH 7.2**
15	1.95 + .0015	5.32 + .0015	3.9 + .0012	1.45 + .0015	2.35 + .0012
30	4.45 + .0017	11.52 + .0009	9.39 + .0015	5.12 + .0015	6.49 + .0015
45	7.61 + .0013	18.62 + .0012	15.62 + .0009	9.89 + .0015	11.42 + .0019
60	11.75 + .0022	28.01 + .0012	23.44 + .0019	15.77 + .0012	19.03 + .0012
90	16.74 + .0009	43.23 + .0012	32.83 + .0018	22.52 + .0012	27.21 + .0012
120	22.35 + .0009	59.34 +.0009	43.14 + .0015	29.75 + .0012	36.28 + .0012
150	29.02 + .0015		54.19 + .0018	37.57 + .0009	45.8 + .001
180	36.68 + .0009		65.66 + .0017	46.15 + .0019	56.1 + .0012
210	45.5 + .0015			56.74 + .0019	66.96 + .0009
240	55.03 + .0015			67.95 + .0015	79.84 + .0019

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

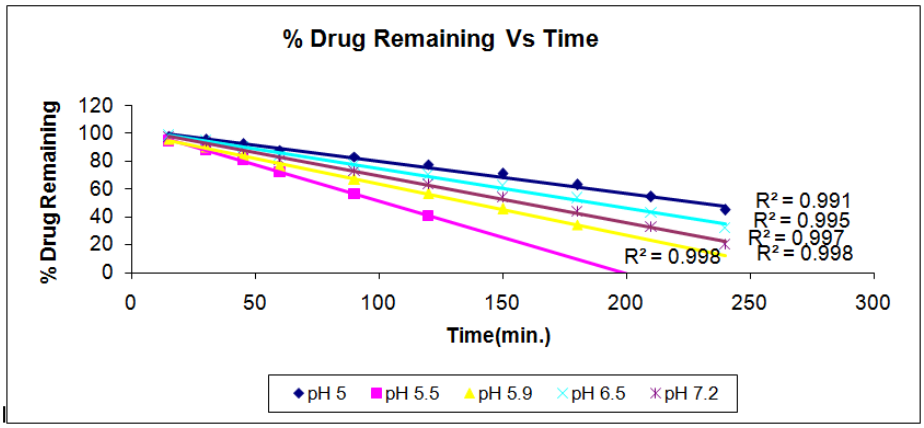

Fig. 2: Percent drug remaining in lens soaked at pH 5.0, 5.5, 5.9, 6.5 or 7.2 Vs Time

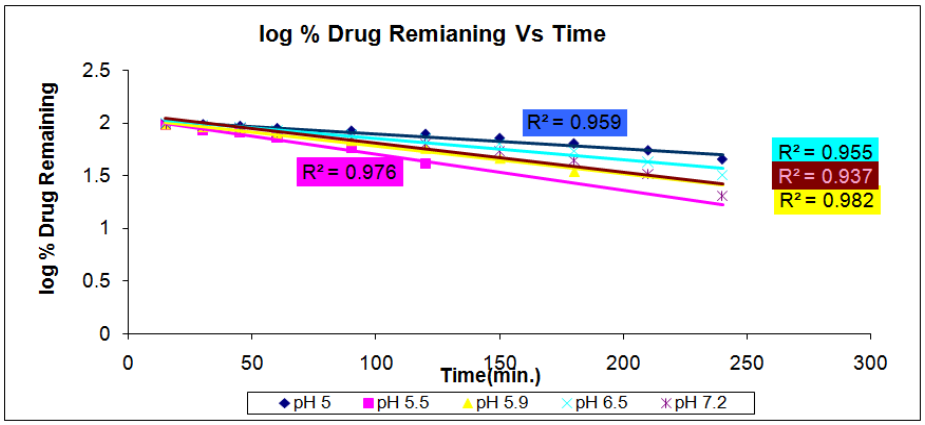

Fig. 3: Log percent drug remaining in lens soaked at pH 5.0, 5.5, 5.9, 6.5 or 7.2 Vs Time

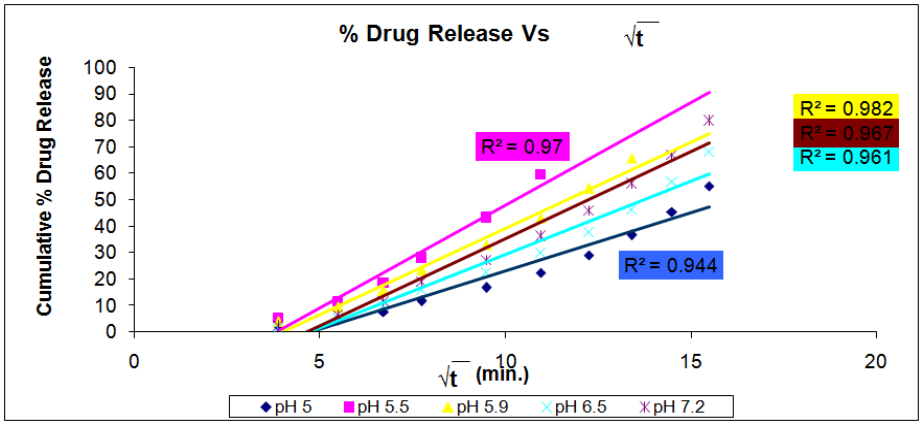

Fig. 4: Cumulative percent drug release from lens soaked at pH 5.0, 5.5, 5.9, 6.5 or7.2 Vs Square root of Time (SQRT)

Table 4: Cumulative *in-vitro* % drug drainage from lens soaked at pH 5.0, 5.5, 5.9, 6.5 or 7.2 of moxifloxacin solution (.5 % w/v).

Cumulative *In-vitro* Drug Drainage (%)					
Time (Min.)	**pH 5.0**	**pH 5.5**	**pH 5.9**	**pH 6.5**	**pH 7.2**
15	3.82 + .0009	1.62 + .0015	2.41 + .0006	1.24 +.0015	1.79 + .0015
30	7.03 + .0019	5.9 + .0022	6.82 + .0018	2.69 +.0015	3.91 + .0012
45	8.99 + .0015	10.64 + .0015	9.97 + .0019	4.49 +.0012	5.37 + .00009
60	10.24 + .0015	12.71 + .0015	12.55 + .0012	5.32 + .0009	6.83 + .0006
90	13.89 + .0017	17.29 + .0019	16.45 + .0019	11.21 + .0018	9.96 + .0015
120	16.29 + .0017	18.47 + .0015	19.45 + .0015	14.46 + .0135	12.65 + .0012
150	17.98 + .0009		22.11 + .0015	16.4 + .002	14.1 + .0015
180	18.87 + .0006		23.44 + .0015	17.85 + .0015	15.11 +.001
210	19.59 + .0006			19.03 + .0015	16.01 + .0007
240	19.94 + .0013			19.76 + .0012	16.46 + .0009

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

In vitro permeation study was evaluated through freshly excised goat cornea and the results are shown in Table 5.

Table 5: Effect of pH of moxifloxacin solution (.5 % w/v) loaded contact lenses on permeation of drug through excised goat cornea.

pH	**Drug content (mg) in contact lens soaked in in drug solution for 1 hr.**	**Amount permeated (mg) (120 minutes)**	**Transcorneal permeation (%) (120 minutes)**	**Amount drained (mg) (120 minutes)**	**Percent drained (120 minutes)**	**Corneal hydration (%)**
5.9	1.165+0.002	0.129+0.001	11.07+.04	0.257+0.002	22.06+.032	79.93+0.12
6.5	1.328+0.001	0.190+0.002	14.30+.02	0.296+0.002	22.28+.043	79.3+0.152
7.2	0.871+0.001	0.205+0.001	23.53+.04	0.283+0.001	32.49+.032	79.0+0.152

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

Maximum quantity permeated was obtained by contact lens soaked in drug solution of pH 7.2. Moxifloxacin is an amphoteric molecule having pKa1 of 6.25 and pKa2 of 9.29. At pH above or below the pI (Isoelectric point, pH 7.77) the molecule will be charged while at pI it will be devoid of charge hence will have maximum lipid solubility. Thus higher permeation of moxifloxacin at pH 7.2 could be explained due to higher lipid solubility of the drug, as the pH is in the vicinity of pI. [11,12] Corneal hydration shows that there has been no corneal damage as the hydration remained below 80 %.[13]

CONCLUSION

It was found that the drug uptake by p-HEMA lens was approximately constant during the soaking period 1-24hrs. The maximum average drug uptake was observed at pH 6.5. It can be concluded from the present study that the uptake of moxifloxacin was pH dependent maximum at pH 6.5. The average drug release at different pH was observed between 2 - 4 hrs. The drug release data was evaluated for zero order, first order and Higuchi release kinetics. Release from the soaked lenses could be better explained as zero order as R^2 value was found maximum for zero order release. The data for *in vitro* transcorneal permeation study suggests maximum permeation for contact lens soaked in drug solution was at pH 7.2. Corneal hydration remained below 80%.

Moxifloxacin is having half life of 12 hrs so soft contact lens can be used as drug delivery system for moxifloxacin. For the drugs having shorter half life or if the drug release is required for longer duration of time then other techniques like molecular imprinting, drug eluting contact lenses, copolymerization of contact lenses etc. may be used.

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