IJPSR (2013), Vol. 4, Issue 1 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 07 September, 2012; received in revised form, 15 October, 2012; accepted, 22 December, 2012

FORMULATION AND EVALUATION OF PROGRAMMED RELEASE OCULAR INSERTS OF MIZOLASTINE

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Keywords:

Antihistamine, Conjuctivitis, Franz-diffusion, Mizolastine, Ocular inserts

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QUICK RESPONSE CODE

IJPSR: ICV- 5.07

Website: www.ijpsr.com

ABSTRACT

The main objective of this study was to prepare controlled release matrix type ocular inserts of mizolastine for the treatment of seasonal allergic conjunctivitis. The films were prepared by solvent casting technique using Eudragit RL100 and RS100 in different ratios with dibutylphthalate as the plasticizer. The films were evaluated for the physicochemical parameters. *In-vitro* studies were carried out using Franz-diffusion cell (bi-chamber compartment model) and *ex-vivo* studies of the optimized formulation were carried out using goat's cornea. *In vivo* studies were performed using rabbit as the animal model. Formulations F4 and F6, which showed controlled and prolonged *in vitro* drug release, were subjected to *in vivo* study. *In vitro* and *in vivo* correlation was found to be good, revealing the efficacy of the formulations. Formulation F6 was found to be promising, as it achieved the objective of the present study.

INTRODUCTION: The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The human eye is a challenging subject for the topical administration of drugs. Solutions, in spite of their limitations (quick elimination from the precorneal area, resulting in poor bioavailability), are still given top priority by the formulators since they are relatively simple to prepare, filter and sterilize.

Eye drops do not remain in contact with the eye for a long time and must be administered at relatively frequent intervals. Suspensions have the advantage of longer contact time in the eye, but also the disadvantage of an irritation potential, due to the particle size of the suspended drugs. Irritation may produce excessive tearing and consequently rapid drainage of the instilled dose. Ointments have the advantages of longer contact time and better storage stability, but also the disadvantage of producing a film over the eye, thereby blurring the vision [1].

The specific aim of designing an ocular therapeutic system is to achieve, optimal concentration of drug at the active site for an appropriate duration [2]. Ocular inserts are novel drug delivery systems, which release the drug at a pre-programmed rate for the controlled period of time by increasing the pre-corneal residence time. Ophthalmic inserts are sterile, soft, thin and flexible disk made of appropriate polymeric materials, fitting into the lower or upper conjunctival sac. Mizolastine, a benzimidazole derivative, is a new, non-sedating antihistamine with additional anti-inflammatory properties, providing relief in seasonal and perennial allergic rhinitis. It is a peripherally acting, selective H1-receptor antagonist [3].

In the present research, an attempt was made to formulate Mizolastine ophthalmic inserts by solvent casting method using Eudragit as polymers. Mizolastine ophthalmic inserts are capable of releasing drug continuously at controlled rate for 5 days.

MATERIALS AND METHODS:

Materials: Mizolastine was received as a gift sample from Dr. Reddy's, Hyderabad. Eudragits were procured from Evonik, Mumbai and Dibutyl phthalate from S.D. Fine Chemicals Ltd., India. All the solvents used were of analytical grade.

Preparation of Ocular Inserts: The mizolastine ocular inserts were prepared by solvent casting technique on Teflon coated petriplates [4]. Formulations were prepared with 2-Hydroxypropyl-β-Cyclodextrin (2-HP-β-CDs), Eudragit RL 100 and Eudragit RS 100 in different concentrations as shown in **Table 1**. Acetone: Methanol form an azeotropic mixture and was found to be most suitable for making satisfactory films. The 2-HP-β-CDs and Eudragits were dissolved in a mixture of acetone and methanol. Mizolastine was then dissolved in the polymer solution and finally dibutylphthalate was incorporated as the plasticizer [5]. The solutions were poured into Teflon coated petri-dish of diameter 7.5cm and solvent was allowed to equilibrate at room temperature for 24 hours. Elliptical shaped ocular inserts of area 0.65 cm^2 were cut out of the film with the help of stainless steel die. The ocular inserts were stored in an airtight container under ambient conditions.

TABLE 1: FORMULATION COMPOSITIONS OF OCUSERT OF MIZOLASTINE

INGREDIENTS	F1	F2	F3	F4	F5	F6
Eudragit RL100(mg)	-	100	100	50	100	-
Eudragit RS100(mg)	400	300	400	500	300	450
Dibutylphthalate(ml)	0.16	0.16	0.16	0.16	0.16	0.16
Acetone (ml)	13	13	13	13	13	13
Methanol (ml)	7	7	7	7	7	7
2-HP-β-CDs(mg)	-	-	-	-	120	120
Drug (mg)	67.9	67.9	67.9	67.9	67.9	67.9

Interaction Studies: Interaction studies were conducted on the optimized formulations by comparing them with the pure drug and the placebo films. Drug-polymer compatibility was confirmed by ultraviolet, infrared and thin layer chromatography analysis.

PHYSIOCHEMICAL EVALUATION OF OCULAR INSERTS

1. **Thickness Determination:** Thickness of the insert was measured at different points using digital micrometer screw gauge (Mitutoyo, Japan) and mean film thickness was noted [6].

2. **Weight Uniformity:** Ocular inserts were taken from different areas of the film and weighed individually. The mean weight of insert was noted. [7].

3. **Folding Endurance:** The folding endurance is expressed as the number of folds (number of times the insert is folded at the same place, either to break the specimen or to develop visible cracks) [8]. The insert was folded in the centre, between the fingers and the thumb and then opened. This was termed as one folding. The total folding operations was named as folding endurance value.

4. **Water Vapour Transmission:** Glass vials of equal diameter were used as the transmission cells. 1g of anhydrous calcium chloride was placed in the cells and respective polymer film was fixed over brim. The cells were accurately weighted and kept in closed desiccators containing saturated solution of potassium chloride. The cells were taken out and re- weighed after storage. The amount of water vapour transmitted was calculated using following formula [9];

Water Vapour Transmission Rate

$$= \frac{\text{Final weight - Initial weight}}{\text{Time} \times \text{Area}}$$

5. **Drug Content:** The ocular inserts from different areas of the film were taken. Drug content was estimated by triturating the ocular insert in 50ml of methanol with the help of a mortar and pestle. The solution was filtered through whatman no.42 filter paper and drug content determined by UV-Visible spectrophotometer and HPLC method [5].

6. **HPLC Analysis:** The HPLC method for quantification of Mizolastine in ocular films was established. The chromatographic parameters used are [10]:

Column: C18 Column (250mm x 4.6mm x 5µm)

Mobile phase: 0.05 mol/L potassium dihydrogen phosphate, Acetonitrile & Methanol (45:10:45)

UV Detection: 216 nm

Flow rate: 0.8 ml per min

7. ***In vitro* Drug Diffusion Studies:** *In vitro* drug release studies were carried out using a Franz diffusion cell. Ocular inserts were placed in the donor compartment over the dialysis membrane. [11] 0.7 ml of isotonic phosphate buffer of pH 7.4 was placed in the donor chamber, which acted as the tear fluid. 20ml of isotonic phosphate buffer was taken as the receptor medium and the apparatus was maintained at 37± 2°C being continuously stirred using a magnetic stirrer. The samples were withdrawn at regular intervals and analyzed at 287nm.

8. ***Ex-vivo* Corneal Permeation Studies:** Goat cornea was mounted onto a Franz-diffusion cell in such a way that corneum side continuously remained in an intimate contact with ocusert in the donor compartment [12]. The receptor compartment was filled with isotonic phosphate buffer pH 7.4 at 37± 2ºC. The receptor medium was stirred magnetically. Aliquots of 3ml samples were withdrawn at regular time intervals and analyzed for drug content at 287nm.

9. **Ocular Irritancy Test:** The inserts were sterilized before the draize eye irritancy test [13]**.** It is the most valuable and reliable method for evaluating hazard or safety of a substance introduced into or around the eye. Testing was carried out on adult albino rabbits of either sex weighing about 1 to 2 kg.

10. ***In-vivo* Studies:** The approval for use of animals in the study was obtained from the Institution Animal Ethics Committee IAEC/CCP/12/PR-015. *In vivo* study was carried out using six healthy rabbits of either sex weighing 1 to 2 kg to measure the release of the drug in the eye. The sterilized ocular inserts of formulations were placed in the conjunctival cul-de-sac of the rabbit's eye and at the same time other eye served as the control. Inserts were carefully removed after 6, 24, 48, 72, 96, 120 hrs respectively and analysed for the remaining drug content by HPLC. Cumulative percentage drug released was calculated [14].

11. **Stability Studies:** The stability studies of ocular inserts were conducted according ICH guidelines [15]. The ocular inserts were packed in blister (PVC-Aluminium) and stored at 40±0.5°C / 75±5% RH, 25°/60% RH, 40°C for 3 months. Samples were withdrawn on days 0, 30, 60 and 90 and analyzed for physico chemical properties, assay and drug release.

RESULTS AND DISCUSSION: The present investigation was undertaken with the objective of preparing controlled release ocular inserts of mizolastine using Eudragits and 2-HP-β-CDs as the polymers. The prepared batches were found to be uniform and flexible, proving the efficiency of Dibutyl phthalate as a plasticizer. Physicochemical evaluation studies (**Table 2**) revealed that all the batches were uniform with respect to thickness, weight of individual insert, and drug content, proving the suitability of the solvent casting method for preparing the inserts. The minimum standard deviation values suggested that the method adopted for casting films on the Teflon surface was satisfactory.

TABLE 2: PHYSIOCHEMICAL EVALUATION

Formulation Code	Thickness (mm)*	Weight (mg)*	Folding endurance*	Drug content*(%)	WVT (g/h/cm^2)
F1	0.16 ± 0.011	11.35 ± 0.204	79	96.9 ± 0.321	0.0044±0.0018
F2	0.16 ± 0.005	11.67 ± 0.356	87	97.8 ± 0.716	0.0070±0.0001
F3	0.17 ± 0.009	12.43 ± 0.545	86	98.5 ± 0.459	0.0016±0.0008
F4	0.17 ± 0.005	12.31 ± 0.401	89	99.7 ± 0.830	0.0010±0.0003
F5	0.17 ± 0.006	12.46 ± 0.411	88	97.9 ± 0.545	0.0012±0.0006
F6	0.18 ± 0.023	12.38 ± 0.516	84	99.4 ± 0.810	0.0037±0.0005

*Average of three determinations numbers in parenthesis indicate standard deviation

Interaction studies were carried out to study the drug – polymer interaction if any. The UV and IR spectra of the formulations exhibited absorption peaks similar to that of the pure drug sample. There were no other peaks in the IR spectra of the formulations, revealing the compatibility of the drug with the excipients used in the formulations.

In vitro drug release study for formulations F1 to F6 revealed that these formulations were capable of extending the drug release up to 120 hrs. Formulation F4 released 97.85% drug, whereas F6 controlled the release for five days with a maximum of 99.54%. The Cumulative percentage drug release from the formulations is presented in **Figure 1**. The formulations that released the drug slowly at a constant rate were selected for *in vivo studies.*

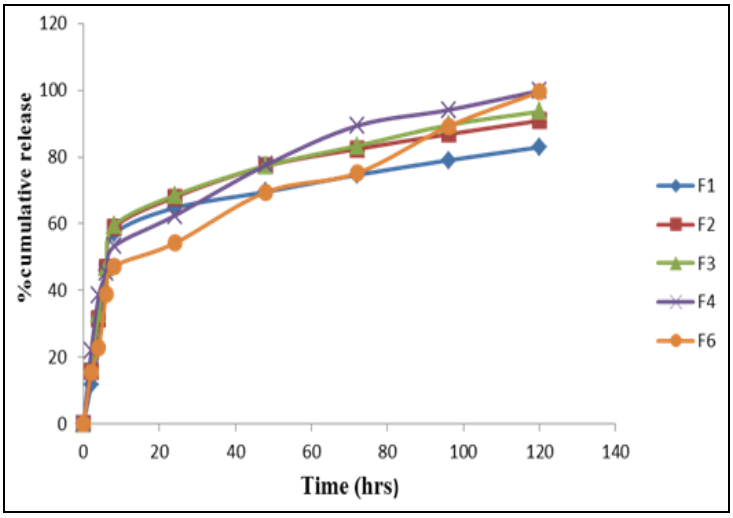

FIG. 1: COMPARATIVE RELEASE PROFILE OF MIZOLASTINE FROM OCULAR INSERTS (F1 TO F6)

TABLE 3: CORRELATION COEFFICIENT (R) VALUES

Formulation Code	Zero order	First order	Higuchi	Korsmeyer-Peppas	Hixson- Crowell
F1	0.633	0.809	0.822	0.673	0.760
F2	0.674	0.852	0.907	0.647	0.838
F3	0.692	0.865	0.938	0.639	0.872
F4	0.779	0.855	0.976	0.627	0.927
F5	0.893	0.971	0.981	0.782	0.959
F6	0.892	0.949	0.958	0.776	0.967

The data obtained from *in vitro* studies of all six formulations was subjected to kinetic treatment to study the order of release. Regression coefficient values obtained for each formulation were compared to get the release kinetics (**Table 3**). R^2 values obtained by Zero order, First order, Korsemeyer-Peppas, Hixson-Crowell and Higuchi kinetic equation revealed that *in vitro* drug release followed square root of time (Higuchi release) kinetics. It was interpreted that the drug release from the inserts was taking place by diffusion mechanism.

The stability studies carried out indicated that the ocular inserts were stable and there was no effect on the drug content and *in vitro* release.

Animal studies were carried out as per the protocol approved by the animal ethical committee under the protocol no. IAEC/CCP/12/PR-015. The results of Ocular irritancy test revealed that inserts prepared using Eudragit were non-toxic and non-irritating to the eye. No signs of redness, watering of the eye and swelling were observed with the optimized formulation.

In vivo release study was conducted using six healthy rabbits of either sex to measure the amount of drug remaining in the sterilized ocular inserts at periodic time intervals. The drug release from the formulation F4 and F6 after 5 days was found to be 80.59 % and 91.66 % respectively. **Fig. 2** shows the cumulative percent drug release from F4 & F6 formulation.

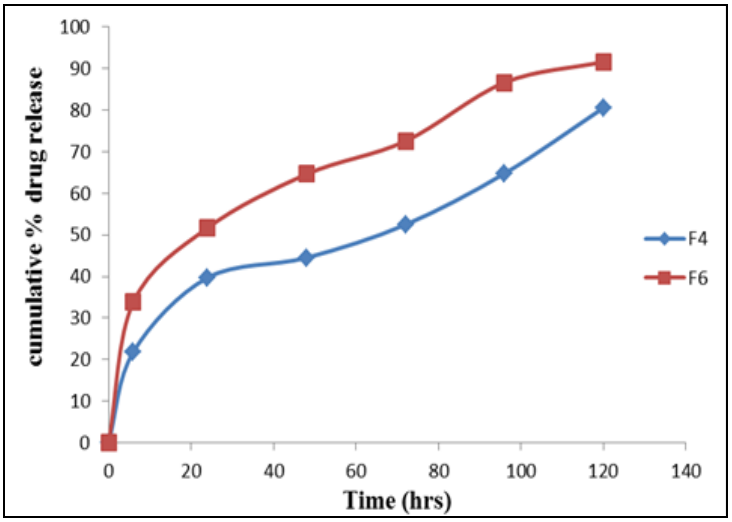

FIG. 2: *IN-VIVO* RELEASE PROFILE OF OPTIMIZED FORMULATION F4 & F6

In-vitro-in-vivo Correlation of formulation F4 and F6 was obtained by plotting Scatter diagram between cumulative percent drug released, *in vivo* and *in vitro* respectively (**Fig. 3 and 4** respectively). The correlation was good with both the formulations and r^2 value for F4 and F6 was 0.921 and 0.977 respectively..

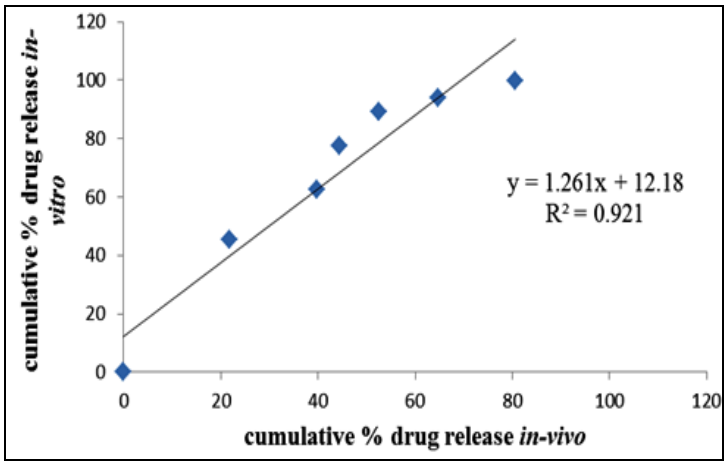

FIG. 3: SCATTER DIAGRAM BETWEEN CUMULATIVE PERCENT DRUG RELEASE *IN VITRO* AND *IN VIVO* OF OPTIMIZED FORMULATION F4

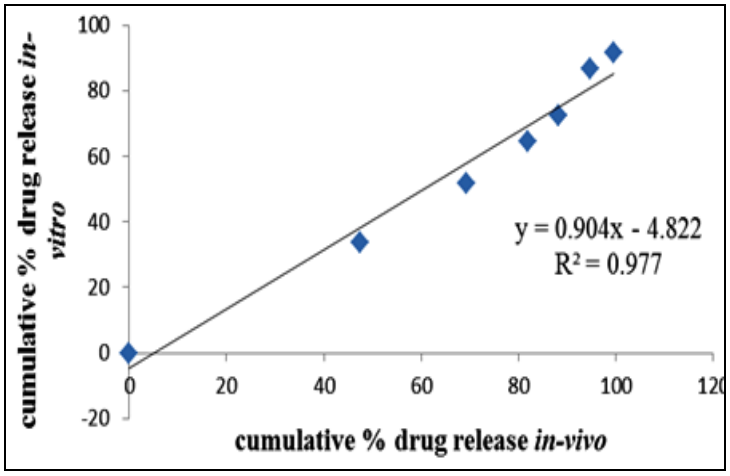

FIG. 4: SCATTER DIAGRAM BETWEEN CUMULATIVE PERCENT DRUG RELEASE *IN VITRO* AND *IN VIVO* OF OPTIMIZED FORMULATION F6

CONCLUSION: Matrix type ocular inserts of mizolastine prepared using Eudragits RL 100 & RS 100 were capable of releasing the drug continuously at controlled rate for 5 days. However, their potential to treat seasonal allergic rhinitis in humans needs to be investigated further.

ACKNOWLEDGEMENTS: The authors are grateful to Dr. Reddy's Laboratories , Hyderabad for providing the gift sample of mizolastine and Department of Pharmacology, Chitkara University for providing assistance in performing animal studies.

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How to cite this article:
Degwy MAAEAAED, Tayel S, El-Nabarawi MA and Randa El Rehem TA: *In vitro* and *in vivo* evaluation of Diclofenac potassium Lyophilized Orally Disintegrating Tablets. *Int J Pharm Sci Res*. 2013; 4(1); 497-501.