Research in Pharmacy 1(2) : 13-16, 2011 ISSN : 2231-539X
www.researchinpharmacy.com

Regular Article

Design and evaluation of timolol maleate ocuserts

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A remarkable attempt was made to prepare timolol maleate ocuserts, which is significant beta adreno receptor antagonist, by the aid of different of different ratio of composition of polymers such as EC, HPMC and Eudragit RS 100. Twelve batches of suitable ophthalmic films formulated by the method of solvent casting technique. Out of which the best formulation was found out the zero order release was observed in batch and was considered as the least drug releasing one. The formulated ocuserts were flexible, uniform and was meant for physic-chemical evaluator parameters, *in vitro* drug release profile and *in vivo* evaluation made on male rabbit.

Key words: Timolol maleate, Intra ocular pressure, Dibutyl phthalate.

Timolol maleate ocuserts were prepared using different polymers such as EC, HPMC and Eudragit RS 100 at various concentrations. The *in vitro* release of the drug from the formulations was studied using commercial semi permeable membrane. The physicochemical parameters of ocuserts were evaluated. Zero order release for one day was observed in formulation I. (Drug reservoir with 1.25% HPMC and 1.25% EC and 2% HPMC as rate controlling membrane) The field of ocular drug delivery is one of the most interesting and challenging endeavors facing by the pharmaceutical scientist for past 10-20 years. As an isolated organ eye is very difficult to study from a drug delivery point of view (Jain 1997). Despite of these limitations, improvements have been made with objective of maintaining the drug in the bio phase for an extended period.

Timolol maleate is a beta adreno receptor antagonist, which can be used in glaucoma, by reducing intraocular pressure. It is presently available as eye drops but has several drawbacks such as loss of drug from tear flow, lachrymal and nasal drainage and patient non-compliance. In this study and attempt was made to prepare ocular inserts with the target of increasing the contact time, reducing the frequency of administration, improving patient compliance and obtaining greater therapeutic efficiency.

Materials and Methods

Timolol maleate was obtained from Centaur pharmaceuticals Pvt. Ltd. The polymers used were hydroxy propyl methylcellulose (HPMC 15 cps), ethyl Eudragit RS 100 were procured from Micro Labs, Hosur.

Preparation of drug reservoir

The reservoir films containing 8.75mg of timolol maleate with different polymers at various concentrations were casted on mercury surface using a ring of 4cm diameter having 5mL capacity, after drying at room temperature for 24 h, circular films of 8mm diameter (an area of 0.5024 cm^2), each containing 0.35mg drug are cut.

Preparation of rate controlling membrane

The rate controlling membrane was casted on mercury surface using hydroxyl propyl methylcellulose as polymer and Dibutyl phthalate (30% W/W of polymer) as plasticizer and circular membranes of 10 mm diameter were cut using special mould. Both sides of the drug reservoir were sealed to control the release from periphery.

In vitro release studies

The *in vitro* release studies were carried out using bi chambered donor-receiver compartment model (Manvi 1997) designed using commercial semi permeable membrane of transparent and regenerated cellulose type (Sigma dialysis membrane). It was tied at one end of the open-end cylinder, which acted as the donor compartment. The ocuserts was placed inside the donor compartment. The semi permeable membrane was used to stimulate ocular *in vivo* conditions like corneal epithelial barrier. In order to stimulate the tear volume, 0.7mL of phosphate buffer was placed and maintained at the same level throughout the study in the donor compartment, which contain 25 mbf distilled water and stirred continuously using a magnetic stirrer. Samples of 1 mL were withdrawn from the receptor compartment at periodic intervals and replaced with equal volume of phosphate buffer. The drug content was analyzed at 294 nm^3 against reference standard using phosphate as blank on a shimadzu UV visible spectrophotometer.

Evaluation of ocuserts

The prepared ocuserts were evaluated for moisture absorption, moisture loss, thickness, weight variation and drug content. Formulation I (drug reservoir with 1.25% HPMC and 1.25% EC and 2% HPMC as rate controlling membrane) was sterilized by using ethylene oxide (Koteshwar 1992). The test for sterility of formulation I was carried out according to the method prescribed in Indian Pharmacopoeia. Physical stability and drug integrity of formulation I were studied using Fourier Transform infrared spectrophotometer-410 in pre- and post-sterilization conditions.

In vivo studies

Male rabbits (*Orytolagus cuniculus*), 10-12 weeks old weighing 2.5 to 3 kg were selected. They kept three per cage with husk bedding and were fed with standard rodent pellet diet and water. Light and dark cycle of 12 h was maintained throughout the study. The temperature, relative humidity conditions were 28±2 and 60±15% respectively.

A set of healthy rabbits (6 males) were selected and were checked for absence of any diseases including ophthalmic type. Sterilized ocuserts of formulation I (drug reservoir with 1.25% HPMC and 1.25% EC and 2% HPMC as rate controlling membrane) was used for present study content (Sane 1992).

Results and Discussion

In the present study, efforts were made to prepare ocular inserts of Timolol Maleate using different polymers such as HPMC, EC, Eudragit RS 100 and Eudragit RL 100 **Table 1**. The drug delivery system was designed as a matrix and the release was controlled by using polymeric rate controlling membrane.

The physicochemical evaluation (Elhance 1984) of data of (**Table 2, 3**) indicates

that percentage of moisture absorption is more in formulation IV (drug reservoir with 2.5% HPMC and 2.5% C and 2% HPMC as rate controlling membrane). This may be due to the hydrophobic ethyl cellulose membrane and comparatively low concentration of polymers. Though percentage of moisture absorption and the percentage of moisture loss are high, there is no change in the integrity at high humid and dry conditions.

Table 1 Stability studies on the formulation I

Day	Drug Content (mg)		
	4°	37°	60°
0	0.354	0.354	0.354
5	0.352	0.352	0.350
12	0.349	0.347	0.345
21	0.345	0.342	0.338

Each value represents an average of two readings. *The formulation become rigid and brittle which was originally smooth and flexible.

Table 2 Composition of various polymers and plasticizers in different formulations

Formulation code	Drug reservoir		Rate controlling membrane	Plasticizer
	EC	HPMC	HPMC	Dibutyl phthalate
F-I	1.25	2	2	30 % W/W
F-II	2.5	1.25	2	30 % W/W
F-III	1.25	2.5	2	30 % W/W
F-IV	2.5	2.5	2	30 % W/W
	EUDRL 100	**HPMC**		
F-V	1.25	1.25	2	30 % W/W
F-VI	1.25	2.5	2	30 % W/W
F-VII	2.5	1.25	2	30 % W/W
F-VIII	2.5	2.5	2	30 % W/W
	EUDRL100	**EUDRS100**		
F-IX	1.25	1.25	2	30 % W/W
F-X	2.5	1.25	2	30 % W/W
F-XI	1.25	2.5	2	30 % W/W
F-XII	2.5	2.5	2	30 % W/W

Table 3 Physicochemical evaluation of ocuserts of Timolol Maleate

Formulation code	PMA ± SD	PML ± SD	Thickness in mm ± SD	Weight uniformity in mg ± SD	Folding Endurance ± SD	Drug content in mg ± SD
F-I	5.02 ± 0.38	22.24 ±0.24	0.232 ± 0.007	20.48 ±0.74	76 ± 1.74	0.354 ± 0.148
F-II	5.28 ± 0.26	24.82 ±0.42	0.247 ± 0.007	21.74 ±0.65	77 ± 1.16	0.358 ± 0.094
F-III	5.89 ± 0.09	22.94 ±0.04	0.258 ± 0.008	22.08 ±0.24	79 ± 2.08	0.346 ± 0.125
F-IV	6.58 ± 0.19	20.71 ±0.33	0.296 ± 0.011	24.80 ±0.77	82 ± 1.84	0.362 ± 0.115
F-V	5.08 ± 0.36	22.54 ±0.28	0.302 ± 0.000	22.28 ±0.65	80 ± 1.24	0.346 ± 0.280
F-VI	5.22 ± 0.24	21.43± 0.11	0.312 ± 0.012	23.84± 0.82	82 ± 1.16	0.312 ± 0.012
F-VII	5.16 ± 0.42	18.21 ±0.01	0.318 ± 0.000	24.26 ±0.28	83 ± 2.08	0.361 ± 0.156
F-VIII	5.78 ± 0.36	15.38 ±0.12	0.324 ± 0.008	25.20 ±0.16	85 ± 1.34	0.352 ± 0.550
F-IX	4.86 ± 0.11	16.18 ±0.31	0.316 ± 0.009	23.80 ±0.46	84 ± 1.15	0.360 ± 0.112
F-X	4.38 ± 0.89	15.76 ±0.85	0.328 ± 0.013	24.46 ±0.25	86 ± 2.16	0.362 ± 0.216
F-XI	3.76 ± 0.38	13.48 ±0.52	0.334 ± 0.092	24.89 ±0.84	85 ± 1.94	0.355 ± 0.128
F-XII	3.62 ± 0.06	11.14 ±0.89	0.344 ± 0.008	25.80 ±0.76	88 ± 2.18	0.348 ± 0.174

Thickness of the ocuserts varies between (0.232 to 0.344). The formulations are not very thicker and coinciding with ocuserts of Pile20 marketed in US by Alza corporation and do not produce any irritation while placing and being in cul-de-sac. The minimum standard deviation values reveled the fact that process used in the study is capable of giving films of uniform magnitude.

In vitro dissolution study of formulation I (drug reservoir with 1.25% HPMC and 1.25% EC and 2% HPMC as rate controlling membrane) was found to release in a zero order pattern for the extended period of 24 h. It also fulfilled many requirements of novel "Once a day" delivery system. Hence, it was considered as the formulation of choice for in vivo studies.

In vivo release studies have shown that the formulation I (drug reservoir with 1.25% HPMC and 1.25% EC and 2% HPMC as rate controlling membrane) is capable of releasing the drug for 24h almost in the same pattern, which was found in *in vitro* studies. The delivery system was found to release 88.93% of loaded drug at the end of 24 h. The regression analysis6 was carried to establish correlation between *in vitro* and *in vivo* release data. The correlation value of ± 0.9876 indicated correctness of the *in vitro* method followed and adaptability of the delivery system to the biological system where it can release the drug in concentration independent manner. Formulation I (drug reservoir with 1.25% HPMC and 1.25% EC and 2% HPMC as rate controlling membrane) passed the test for sterility.

Accelerated stability study was carried out for formulation I (drug reservoir with 1.25% HPMC and 1.25% EC and 2% HPMC as rate controlling membrane) by exposing the ocular inserts at 4^{o} C, 37^{o}C and 60^{o} C. Drug integrity at accelerated storage condition was checked by IR spectral analysis.

Conclusion

Formulation I (drug reservoir with 1.25% HPMC and 1.25% EC and 2% HPMC as rate controlling membrane) has achieved the targets of present study such as increased residence time, prolonged zero order release, reduction in the frequency of administration and thus may improve patient compliance.

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