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Design and Evaluation of Timolol Maleate Ocuserts

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Timolol maleate ocuserts were prepared using different polymers such as hydroxypropylmethylcellulose, ethyl cellulose, Eudragit RL100 and Eudragit RS100 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. A zero order release formulation I (drug reservoir with 1.25 % hydroxypropylmethylcellulose and 1.25% ethyl cellulose and 2% hydroxypropylmethylcellulose as rate controlling membrane) was subjected to *in vivo* studies. The expected zero order release for one day was observed in formulation I (drug reservoir with 1.25 % hydroxypropylmethylcellulose and 1.25% ethyl cellulose and 2% hydroxypropylmethylcellulose as rate controlling membrane).

The field of ocular drug delivery is one of the most interesting and challenging endeavors faced 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. Despite these limitations, improvements have been made with the objective of maintaining the drug in the biophase for an extended period[1]. Timolol maleate is a beta adrenoreceptor antagonist, which can be used in the treatment of glaucoma, by reducing intraocular pressure. It is presently available as eye drops but has several drawbacks such as loss of drug from tear flow and nasal drainage and patient non-compliance. In this study, an 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 efficacy[2,3].

MATERIALS AND METHODS

Timolol maleate was obtained from Centaur Pharmaceutical Pvt. Ltd., Mumbai, hdroxypropylmethylcellulose (HPMC 15cps), ethyl cellulose (EC 20cps) were received as gift samples from Bangalore Pharmaceutical and Research Labs (P) Ltd., Bangalore. Acrylic polymer Eudragit RS100 and Eudragit RL100 were received as gift samples from Micro Labs, Hosur.

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Preparation of drug reservoir:

The reservoir film containing 8.75 mg of timolol maleate with different polymers at various concentrations were dissolved in ethanol and casted on mercury surface using a ring of 4 cm diameter having 5 ml capacity. After drying at room temperature for 24 h, circular films of 8 mm diameter (an area of 0.5024 cm^2), each containing 0.35 mg drug was cut. (Table 1)

Preparation of rate controlling membrane:

The rate controlling membrane was casted on mercury surface using hydroxypropylmethylcellulose as polymer and dibutylphthalate (30% w/w of polymer) as plasticiser 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[4].

In vitro release studies:

The *in vitro* release studies were carried out using a bi chambered donor-receiver compartment model 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 ocusert was placed inside the donor compartment. The semi permeable membrane was used to simulate ocular *in vivo* conditions like corneal epithelial barrier. In order to simulate the tear volume, 0.7 ml of pH 7.4 -phosphate buffer was placed and maintained at the same level through out the study in the donor compartment, which contain 25 ml of pH 7.4 -phosphate buffer 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 pH 7.4 -phosphate buffer. The drug content was analyzed at 294 nm against reference standard using pH 7.4-phosphate buffer as blank[5] on a Shimadzu UV/Vis spectrophotometer.

Evaluation of ocuserts:

The prepared ocuserts were evaluated for moisture absorption[6], moisture loss[6], 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. 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 a FTIR spectrophotometer (410) in pre-and post-sterilization conditions.

***In vivo* studies:**

Male rabbits (*Orytolagus cuniculus*), 10-12 weeks old, weighing 2.5-3 kg (K.M. College of Pharmacy) were used in present study. They were kept 3 per cage with husk bedding and fed with standard rodent pellet diet and water as much as required. Light and dark cycle of 12 h was maintained throughout the study. The temperature, relative humidity conditions were 28±2° and 60±15%, respectively[7,8]. The experimental protocols have been approved by the Institutional Animal Ethical Committee (IAEC/01/2003/Pharmaceutics)

A group containing 12 healthy rabbits was treated as control. Similarly another set containing same number of rabbits was used as study group. All of them were kept in hygienic conditions to avoid vulnerability to any diseases including ophthalmic type. The sterilized ocusert of formulation I (1.25 % HPMC, 1.25% EC as drug reservoir and 2% HPMC as rate controlling membrane) was placed in the lower eyelid of rabbits. At specific time intervals, the films were removed carefully and analyzed for the remaining drug content[5].

RESULT AND DISCUSSION

In the present study, efforts have been made to prepare ocular inserts of timolol maleate using different poly-

TABLE 1: COMPOSITION OF VARIOUS POLYMERS AND PLASTICISER IN DIFFERENT FORMULATIONS

Formulation code	Drug Reservoir (%)				Rate Controlling Membrane (%)	Plasticiser (%w/w)
	HPMC	EC	EUD RL100	EUD RS100	HPMC	Dibutylphthalate
F I	1.25	1.25	-	-	2	30
F II	1.25	2.50	-	-	2	30
F III	2.50	1.25	-	-	2	30
F IV	2.50	2.50	-	-	2	30
F V	1.25	-	1.25	-	2	30
F VI	2.50	-	1.25	-	2	30
F VII	1.25	-	2.50	-	2	30
F VIII	2.50	-	2.50	-	2	30
F IX	-	-	1.25	1.25	2	30
F X	-	-	2.50	1.25	2	30
F XI	-	-	1.25	2.50	2	30
F XII	-	-	2.50	2.50	2	30

TABLE 2: PHYSICOCHEMICAL EVALUATION OF FORMULATIONS

Formulation code	% moisture absorption*	% moisture loss*	Thickness* (mm)	Weight uniformity*(mg)	Folding endurance*	Drug content* (mg)
F I	5.02 (0.38)	26.2 (0.24)	0.232 (0.007)	20.5 (0.74)	76 (1.74)	0.354 (0.048)
F II	5.28 (0.26)	24.8 (0.42)	0.247 (0.007)	21.7 (0.65)	77 (1.16)	0.358 (0.094)
F III	5.89 (0.09)	22.9 (0.04)	0.258 (0.008)	22.1 (0.24)	79 (2.08)	0.346 (0.125)
F IV	6.58 (0.19)	20.7 (0.33)	0.296 (0.011)	20.8 (0.77)	82 (1.84)	0.341 (0.086)
F V	5.08 (0.36)	22.5 (0.28)	0.302 (0.001)	22.3 (0.65)	80 (1.24)	0.362 (0.115)
F VI	5.22 (0.24)	21.4 (0.11)	0.312 (0.012)	23.8 (0.82)	82 (1.16)	0.346 (0.280)
F VII	5.16 (0.42)	18.2 (0.01)	0.318 (0.001)	24.3 (0.28)	83 (2.08)	0.361 (0.156)
F VIII	5.78 (0.36)	15.4 (0.12)	0.324 (0.008)	25.2 (0.16)	85 (1.34)	0.352 (0.550)
F IX	4.86 (0.11)	16.2 (0.31)	0.316 (0.009)	23.8 (0.46)	84 (1.15)	0.360 (0.112)
F X	4.38 (0.89)	15.8 (0.85)	0.328 (0.013)	24.5 (0.25)	86 (2.16)	0.362 (0.216)
F XI	3.76 (0.38)	13.5 (0.52)	0.334 (0.092)	24.9 (0.84)	85 (1.94)	0.355 (0.128)
F XII	3.62 (0.06)	11.1 (0.89)	0.344 (0.008)	25.8 (0.76)	88 (2.18)	0.348 (0.174)

*Average of three determinations. Numbers in parenthesis indicate standard deviation.

mers such as HPMC, EC[9], Eudragit RS100, and Eudragit RL100 (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 data of Table 2 indicates that the percentage of moisture is more in formulation IV (2.5% HPMC, 2.5% EC as drug reservoir and 2% HPMC as rate controlling membrane). This may be due to the hydrophilic nature of HPMC. The percentage of moisture loss is more in formulation I (1.25 % HPMC, 1.25% EC as drug reservoir and 2% HPMC as rate controlling membrane). This may be due to the presence of 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. Thickness of the ocuserts varies between 0.232 and 0.344 mm (Table 2). The formulations are not very thicker and coinciding with ocuserts of Pilo-20 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 revealed the fact that process used in the study is capable of giving films of uniform magnitude. This fact on the reliability of the process is further confirmed by drug content analysis data.

In vitro dissolution study of formulation I (1.25 % HPMC, 1.25% EC as drug reservoir and 2% HPMC as rate controlling membrane) was found to release in a zero order pattern for the extended period of 24 h (fig. 1). 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 (1.25 % HPMC, 1.25% EC as drug reservoir and 2% HPMC as rate controlling membrane) is capable of releasing the drug for 24 h almost in the same pattern, which was found in *in vitro* studies. The delivery system was found to release 88.9% of loaded drug at the end of 24 h. The regression analysis[10] was carried to establish correlation be-

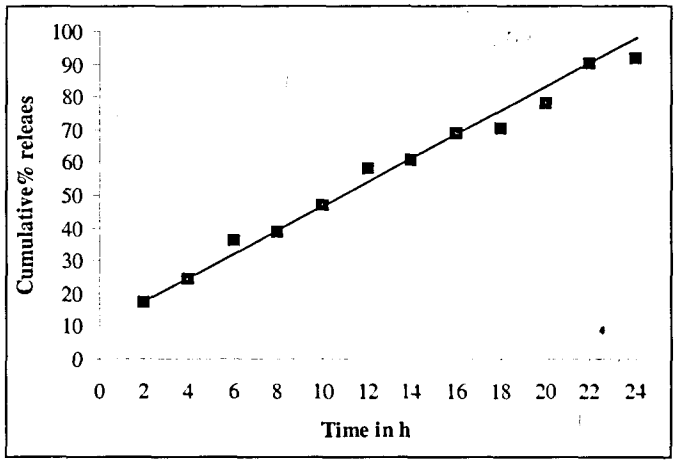

Fig 1: *In vitro* release of timolol maleate from F I

Formulation I consisting 2% HPMC as rate controlling membrane and 1.25% HPMC and 1.25% EC drug reservoir was subjected to *in vitro* release studies in a bi chambered donor-receiver compartment model. Drug release was measured spectrophotometrically at 294 nm.

tween *in vitro-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 (fig. 2). Formulation I passed the test for sterility.

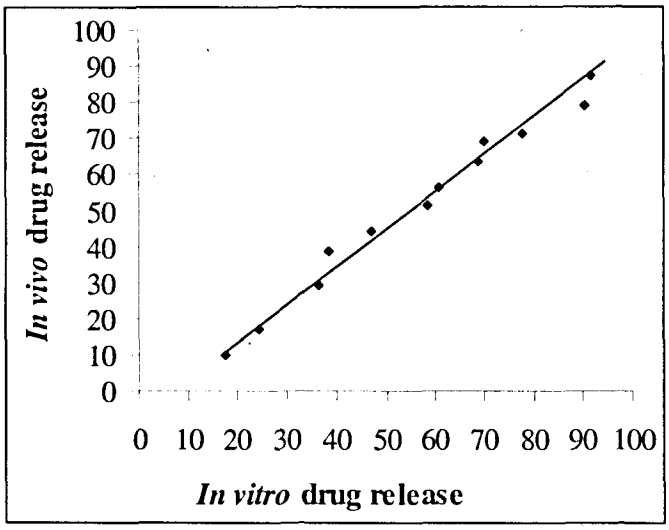

Fig 2: *In vitro-In vivo* correlation for the release of timolol maleate from F I.

Formulation I consisting 2% HPMC as rate controlling membrane and 1.25% HPMC and 1.25% EC drug reservoir was subjected to *in vitro* studies using bi chambered donor-receiver compartment model and *in vivo* studies using rabbits. The correlation coefficient was found to be 0.9876.

Accelerated stability study was carried out for formulation I by exposing the ocuserts at 4°, 37° and 60° for one month. The data reveled that the formulation I at 4° and 37° was smooth and flexible but at 60° it became rigid and brittle (Table 3). The period of expiry of the formulation I was determined using Free and Blythe theory[11]. It shows that 90% potency with 70 days stored at 25°. IR spectral analysis shows that principle peak of the drugs are found. Several peaks in finger print region are identical which shows there is no interaction with polymer. These observations indicate the intactness of the drug in formulation.

TABLE 3: 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 became rigid and brittle which was originally smooth and flexible.

In conclusion, formulation I 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 the patient compliance.

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