RESEARCH PAPER

Accepted 2 June 2000
Revised 8 May 2000
Received 7 January 2000
Indian J. Pharm. Sci., 2000, 62 (5) 334-338

# Design and Evaluation of Ketorolac Tromethamine Ocuserts

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**Ketorolac tromethamine ocuserts were prepared using different polymers such as HPMC, PVP, MC and EC at various concentrations. The *in vitro* release of the drug from the formulations was studied using commercial semi permeable membrane. The physico chemical parameters of ocuserts were evaluated. A zero order release formulation 3 (Drug reservoir with 3% HPMC and 4% EC as rate controlling membrane) was subjected to *in vivo* studies. The expected zero order release for one day was observed in formulation 3 (Drug reservoir with 4% HPMC and 3% EC as rate controlling membrane).**

Ketorolac tromethamine is a non-steroidal antiinflammatory drug useful in relieving ocular itching caused by seasonal allergic conjunctivitis[1]. It is presently available as eye drops, which need to be administered six times a day. Moreover, the conventional eye drops dosage form has several draw backs such as loss of drug from tearflow, lachrymal and nasal drainage, increased frequency of administration and patient non-compliance. In the present study an attempt was made to prepare ocular inserts[2,3] with the target of increasing the contact time, reducing the frequency of administration, improving patient compliance and obtaining greater therapeutic efficacy[4].

## MATERIALS AND METHODS

Ketorolac tromethamine was obtained from Sun Pharmaceuticals. The polymers such as hydroxypropylmethylcellulose (15 cps), methylcellulose (40 cps), polyvinylpyrrolidone (K-30) and ethylcellulose (20 cps) were procured from S.D. Fine Chem., Boisar.

### Preparation of Drug Reservoir:

The reservoir films containing 22.45 mg of ketorolac tromethamine with different polymers at various concentrations were casted on mercury surface using a ring of 4 cm diameter having 3 ml capacity. After drying at room temperature for 24 h, circular films of 8 mm diameter (an area of 0.56 $cm^2$) each containing 1 mg of drug were cut Table 1.

### Preparation of rate controlling membrane:

The rate controlling membrane was casted on a glass plate using ethylcellulose as polymer and dibutylphthalate (30% w.w of polymer) as plasticiser and circular membranes of 10mm diameter were cut using a special mould. Both sides of the drug reservoir were sealed to control the release from periphery[5].

### *In vitro* release studies:

The *in vitro* release studies were carried out using bichambered donor-receiver compartment model designed using commercial semipermeable membrane of transparent and regenerated cellulose type (Sigma dialysis membrane). It was tied at one end of the open cylinder, which acted as the donor compartment. The ocusert was placed inside the donor compartment. The semipermeable membrane was used to simulate ocular *in vivo* conditions like corneal epithelial barrier. In order to simulate the tear volume, 0.7 ml of distilled water was placed and maintained at the same level throughout the study in the donor compartment. The entire surface of the membrane is in contact with reservoir compartment, which contain 25 ml of distilled water and stirred continuously using a

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

| Formulation code | Rate Controlling Membrane | Drug Reservoir (%) | | | Plasticizer (per 10 ml) | |
|---|---|---|---|---|---|---|
| | | | | | Drug Reservoir | Rate controlling membrane |
| | EC(%) | HPMC | MC | PVP | Glycerin | Dibutyl pthalate |
| F1 | 4 | 4 | — | — | 0.5 | 0.015 |
| F2 | 3 | 4 | — | — | 0.5 | 0.01 |
| F3 | 4 | 3 | — | — | 0.4 | 0.015 |
| F4 | 3 | 3 | — | — | 0.4 | 0.01 |
| F5 | 4 | 2 | — | — | 0.3 | 0.015 |
| F6 | 3 | 2 | — | — | 0.3 | 0.01 |
| F7 | 4 | — | 1 | — | 0.2 | 0.015 |
| F8 | 3 | — | 1 | — | 0.2 | 0.01 |
| F9 | 4 | — | 0.75 | 0.25 | 0.2 | 0.015 |
| F10 | 3 | — | 0.75 | 0.25 | 0.2 | 0.01 |
| F11 | 4 | — | 0.5 | 0.5 | 0.2 | 0.015 |
| F12 | 3 | — | 0.5 | 0.5 | 0.2 | 0.01 |

magnetic stirrer. Samples of 1 ml were withdrawn from the receptor compartment at periodic intervals and replaced with equal volume of distilled water. The drug content was analyzed at 313 nm[6] against reference standard using distilled water as blank on a Shimadzu UV/ Visible spectrophotometer.

**Evaluation of Ocuserts:**

The prepared ocuserts were evaluated for moisture absorption[7], moisture loss[7], thickness, weight variation and drug content. Formulation 3 (drug reservoir with 3% HPMC and 4% EC as rate controlling membrane) was sterilized by using ethylene oxide. The test for sterility of formulation 3 was carried out according to the method prescribed in Indian Pharmacopoeia. Physical stability and drug integrity of formulation 3 were studied using a Perkin-Elmer (577) grating infrared spectrophotometer in pre-and post-sterilization conditions.

***In vivo* Studies:**

Male rabbits (*Orytolagus cuniculus*), 10-12 weeks old, weighing 1-2 kg were used in present study. They were kept 3 per cage with husk bedding and fed with suitable diet and water as much as required. A dark and light cycle of 12 h was maintained. The temperature and relative humidity conditions were 28±2° and 60±15% respectively[8,9].

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 in order to avoid the vulnerability to any diseases including ophthalmic type. The ethylene oxide sterilized ocusert of formulation 3 (3% HPMC as drug reservoir and 4% EC 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[6].

## RESULTS AND DISCUSSION

In the present study, efforts have been made to prepare ocular inserts of ketorolac tromethamine using different polymers such as HPMC, MC, PVP and EC[10] Table 1. The drug delivery system was designed as a matrix and the release was controlled by using polymeric rate controlling membrane.

TABLE 2 : PHYSICO CHEMICAL EVALUATION OF FORMULATIONS

| Formulation code | Per cent moisture absorption* | Per cent moisture loss* | Thickness* (mm) | Weight* (mg) | Drug content* (mg) |
|---|---|---|---|---|---|
| F1 | 7.03 (0.53) | 10.10 (0.26) | 0.336 (0.27) | 20.07 (0.92) | 0.996 (0.08) |
| F2 | 8.95 (0.43) | 13.10 (0.61) | 0.267 (0.17) | 18.67 (1.58) | 1.001 (0.06) |
| F3 | 6.06 (0.81) | 11.20 (0.95) | 0.293 (0.09) | 19.07 (0.53) | 0.986 (0.05) |
| F4 | 8.85 (0.40) | 12.10 (0.73) | 0.270 (0.06) | 19.92 (0.53) | 1.020 (0.03) |
| F5 | 5.59 (0.62) | 8.52 (0.45) | 0.302 (0.21) | 18.83 (0.37) | 1.023 (0.06) |
| F6 | 6.48 (0.58) | 10.15 (0.62) | 0.293 (0.22) | 20.66 (0.81) | 1.046 (0.06) |
| F7 | 5.78 (0.77) | 6.64 (0.72) | 0.241 (0.11) | 20.18 (1.88) | 0.993 (0.05) |
| F8 | 6.93 (0.61) | 7.57 (0.47) | 0.252 (0.02) | 19.64 (0.11) | 1.03 (0.09) |
| F9 | 6.30 (0.91) | 6.45 (0.31) | 0.261 (0.59) | 18.23 (0.46) | 1.018 (0.17) |
| F10 | 8.68 (0.46) | 7.57 (0.47) | 0.23 (0.75) | 19.02 (0.22) | 1.025 (0.15) |
| F11 | 6.15 (0.55) | 6.51 (0.15) | 0.27 (0.36) | 20.10 (0.41) | 1.027 (0.06) |
| F12 | 8.12 (0.93) | 7.12 (0.21) | 0.25 (0.37) | 18.60 (0.82) | 0.998 (0.08) |

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

The physico chemical evaluation study revealed that formulation 5 (2% HPMC as matrix and 4% EC as rate controlling membrane) had minimum moisture absorption. This may be due to the presence of hydrophobic ethyl cellulose membrane, which has hindered the moisture absorption Table 2. Moisture loss studies have revealed that the formulation 2 (Drug reservoir 4% HPMC and 3% EC as rate controlling membrane) had maximum moisture loss. This may be due to the high concentration of HPMC, which has capability to absorb atmospheric moisture. Moreover the rate controlling membrane of 3% EC offers less resistance for moisture transfer. This peculiar property of the delivery system might have been the cause for maximum moisture loss of the system. The formulation 9 (Drug reservoir with 0.75% MC and 0.25% PVP and 4% EC as rate controlling membrane) has shown minimum moisture loss. This may be attributed to the presence of hydrophilic matrix at lower concentration than that of other batches and presence of hydrophobic ethyl cellulose outer covering at higher concentration. This combination might have given synergestic effect in order to impede the rate of moisture loss.

All batches were formulated to have thickness as minimum as possible in order to minimize irritation to the eyes. All the batches were found to have thickness in the range of 0.23 to 0.336 mm Table 2. The minimum standard deviation values revealed the fact that the 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 3 (3% HPMC as matrix and 4% EC as rate controlling membrane) was

TABLE 3 : STABILITY STUDIES ON THE FORMULATION F3

| Day | Drug content (µg) | | |
|---|---|---|---|
| | 4° | 37° | 60° |
| 0 | 1007.8 | 1007.5 | 1007.5 |
| 5 | 994.5 | 984.5 | 965.5 |
| 13 | 987.3 | 968.5 | 921.5* |
| 22 | 972.5 | 954.5 | 878.3* |
| 30 | 964.5 | 933.1 | 827.4* |

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

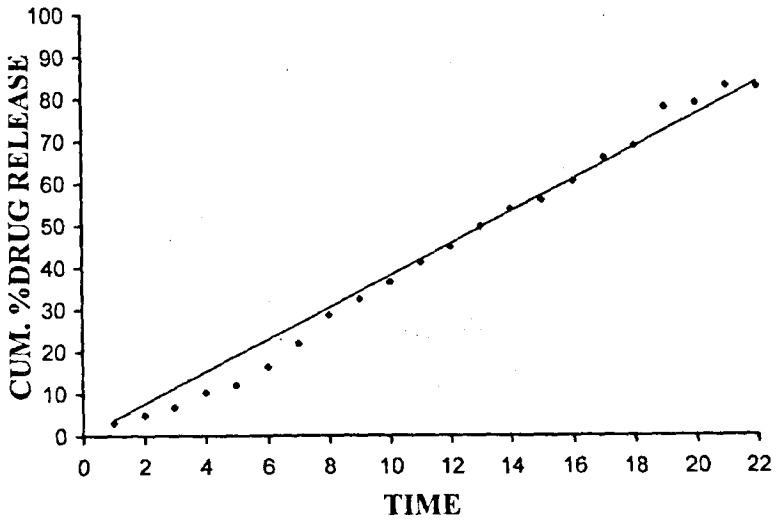


**Fig. 1 : *In vitro* release of ketorolac tromethamine from F3.**

**Formulation 3 consisting of 3% HPMC drug reservoir and 4% EC as rate controlling membrane was subjected to *in vitro* release studies in a bichambered donor-receiver compartment model. Drug release was measured spectrophotometrically at 313 nm.**

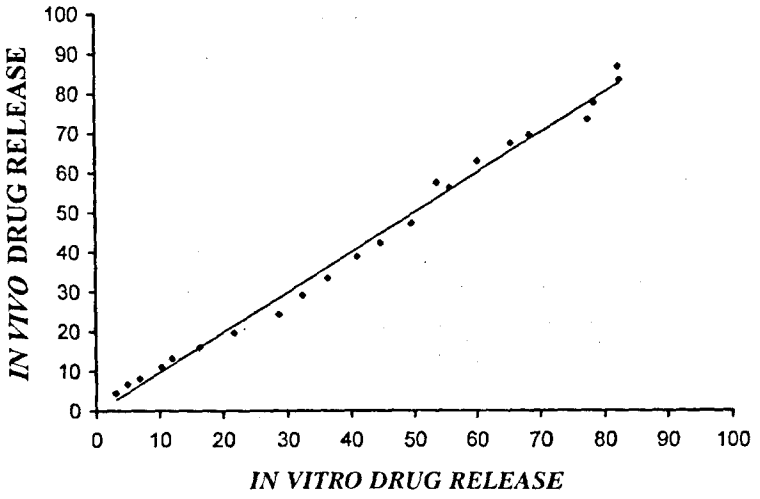


**Fig. 2 : *In vitro-in vivo* correlation for the release of ketorolac tromethamine from F3**

**Formulation 3 consisting of 3% HPMC drug reservoir and 4% EC as rate controlling membrane was subjected to *in vitro* studies using bichambered donor-receiver compartment model and *in vivo* studies using rabbits. The correlation coefficient was found to be 0.9958.**

found to release in zero order pattern for the extended period of 22 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 3 (3% HPMC as matrix and 4% EC as rate controlling membrane) is capable of releasing the drug for 22 h almost in the same pattern which was found in *in vitro* studies. The delivery system was found to release 93.2% of loaded drug at the end of 22 h. To establish the corre-

lation between *in vitro-in vivo* release data, the regression analysis[11] was carried out. The correlation value of 0.9958 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 3 (drug reservoir with 3% HPMC and 4% EC as rate controlling membrane) passed the test for sterility.

Accelerated stability study was carried out for formulation 3 (Drug reservoir with 3% HPMC and 4% EC as rate controlling membrane) by exposing the ocular inserts at 4°, 37° and 60° for one month. The data revealed that the formulation 3 at 4° and 37° unlike at 60°. Drug integrity at accelerated storage condition was checked by IR spectral analysis.

In conclusion, formulation 3 (3% HPMC as drug reservoir and 4% EC 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 the patient compliance.

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