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Design and Evaluation of Ciprofloxacin Hydrochloride (Ocuserts)

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Ciprofloxacin hydrochloride ocuserts were prepared using different polymers in various proportions and combinations. The *in vitro* release of the drug from the formulations was studied using a commercial semipermeable membrane. The physico-chemical parameters of the ocuserts were evaluated. A zero order release formulation VI (Drug reservoir with 2% HPMC and 6% EC as rate controlling membrane) was subjected to *in vivo* studies using rabbits. The results indicated a good correlation between *in vitro* and *in vivo* studies. The expected release for an extended period of 24 hours was observed in formulation VI (Drug reservoir with 2% HPMC and 6% EC as rate controlling membrane).

Ciprofloxacin hydrochloride is a broad spectrum antibacterial agent useful in the treatment of eye infections such as conjunctivitis[1], keratitis and kerato conjunctivitis[1]. It is presently available as eye drops and eye ointments. The conventional dosage forms have certain disadvantages such as loss of drug through tear flow, lacrimal and nasal drainage, lesser absorbtion, increased frequency of administration and patient non-compliance. In the present study an attempt was made to prepare an ocusert[2,3] with the aims of increasing the contact time, achieving controlled release, reducing the frequency of administration, improving patient compliance and obtaining greater therapeutic efficacy[4].

MATERIALS AND METHODS

Ciprofloxacin hydrochloride (I.P.) was kindly provided by Tablets India Limited, Chennai. The polymers used were hydroxy propyl methyl cellulose (15 cps), methyl cellulose (40 cps), ethyl cellulose (20 cps) and polyvinyl pyrrolidone which were purchased from S. D. Fine Chem. Boisar and microcrystalline cellulose (MCC) was procured from Loba Chemie, Mumbai.

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Preparation of Drug Reservoir

The series of reservoir films containing 26.04 mg of ciprofloxacin hydrochloride with varying percentages of polymer were casted on a mercury surface using a ring of 4 cm diameter having 3 ml capacity. After drying at room temperature for 24 hours, circular films of 8 mm diameter (an area of 0.56 cm^2) each containing 1.16 mg of drug were cut (Table 1).

Preparation of rate controlling membrane

A rate controlling membrane was casted on a glass plate using the polymer ethylcellulose by incorporating diethyl pthalate as plasticizer and circular membranes of 10 mm diameter were cut (Table 1). Both sides of the drug reservoir were sealed using the rate controlling membrane to control the release[5].

In vitro release studies

Commercial semipermeable membrane of transparent and regenerated cellulose type (sigma dialysis membrane) was tied to one end of the open cylinder which acted as the donor compartment. An ocusert was placed inside this compartment. The semipermeable membrane acted as

Table -1: Composition of Formulations

Formulation	Rate Controlling Membrane	Drug Reservoir				Plasticiser For Drug Reservoir	Plasticiser For Rate Controlling Membrane
	Ethyl Cellulose	Hydroxy propyl methyl cellulose	Polyvinyl Pyrolidone	Micro crystalline cellulose	Methyl cellulose	Glycerin (per 10ml)	Diethyl Pthalate (per 10ml)
I	6%	4%	-	-	-	0.5ml	0.02 ml
II	5%	4%	-	-	-	0.5 ml	0.015 ml
III	4%	4%	-	-	-	0.5ml	0.01 ml
IV	6%	3%	-	-	-	0.4ml	0.02 ml
V	4%	3%	-	-	-	0.4 ml	0.01 ml
VI	6%	2%	-	-	-	0.3ml	0.02 ml
VII	4%	2%	-	-	-	0.3 ml	0.01 ml
VIII	6%	-	-	-	1%	0.1ml	0.02 ml
IX	4%	-	-	-	1%	0.1 ml	0.01 ml
X	6%	3.6%	0.4%	-	-	0.4ml	0.02 ml
XI	4%	3.6%	0.4%	-	-	0.4 ml	0.01 ml
XII	6%	3.6%	-	0.4%	-	0.4ml	0.02 ml
XIII	4%	3.6%	-	0.4%	-	0.4 ml	0.01 ml
XIV	6%	3.2%	0.4%	0.4%	-	0.5ml	0.02 ml
XV	4%	3.2%	0.4%	0.4%	-	0.5 ml	0.01 ml

corneal epithelium. The tear volume was maintained with the help of 0.7 ml distilled water. The entire surface of the membrane was in contact with the receptor compartment containing 25 ml of distilled water. The content of the receptor compartment was stirred continuously using a magnetic stirrer.

Samples of 1 ml were withdrawn from the receptor compartment at periodic intervals and automatically replaced by equal volume of distilled water. The drug content was analysed at 278 nm against reference standard using distilled water as blank 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 (table 2). The intactness of the formulation was confirmed by IR studies on a Perkin-Elmer (577) Grating Infrared spectrophotometer using KBr disc[7] and by UV studies on a Perkin-Elmer (402) UV/Vis spectrophotometer using distilled water as solvent[8]. Formulation VI (drug reservoir with 2% HPMC and 6% EC as rate controlling membrane) showing zero order and maximum release was irradiated by UV radiation. The test for sterility was carried out as per Indian Pharmacopoeia.

Table - 2: Physico-Chemical Evaluation of formulations

Formulation	Percent Moisture Absorbtion* ±SD	Percent Moisture Loss* ±SD	Thickness** ±SD (mm)	Weight** ±SD (mg)	Drug content* ±SD (mg)
I	6.89 ± 0.70	12.97 ± 0.59	0.354 ± 0.10	25.92 ± 0.81	0.976 ± 0.012
II	6.19 ± 0.95	7.63 ± 0.60	0.346 ±0.48	24.42 ± 0.67	0.963 ± 0.024
III	10.21 ± 0.9	17.63 ± 0.77	0.336 ±1.01	24.38 ± 0.77	1.011 ± 0.019
IV	5.50 ± 0.04	12.95 ± 0.52	0.318 ±1.46	24.20 ± 0.65	1.041 ± 0.034
V	8.26 ± 0.64	13.62 ±0.66	0.312 ±1.32	23.80 ± 0.69	0.970 ± 0.018
VI	4.67 ± 0.44	8.82 ± 0.69	0.296 ±1.85	22.08 ± 0.94	0.997 ± 0.015
VII	6.30 ± 0.50	8.12 ± 0.55	0.284 ±1.74	21.74 ± 0.65	1.032 ± 0.030
VIII	3.84 ± 0.08	6.78 ± 0.39	0.247 ± 0.76	19.24 ± 0.72	0.972 ± 0.010
IX	6.64 ± 0.30	8.75 ± 0.53	0.232 ±0.78	18.84 ± 0.38	0.992 ± 0.019
X	7.44 ± 0.09	10.68 ± 0.65	0.348 ±1.32	25.2 ± 0.16	1.021 ± 0.006
XI	7.77 ± 0.48	13.11 ± 0.42	0.332 ± 0.73	20.48 ± 0.74	0.998 ± 0.148
XII	5.98 ± 0.48	10.55 ± 0.37	0.342 ± 0.81	26.1 ± 0.28	0.996 ± 0.018
XIII	6.56 ± 0.60	9.65 ± 0.90	0.344 ± 0.94	25.8 ± 0.36	1.012 ± 0.008
XIV	7.86 ± 0.52	7.91 ± 0.25	0.374 ± 1.01	26.4 ± 0.60	1.009 ± 0.018
XV	7.91 ± 0.45	9.30 ± 0.87	0.368 ± 1.21	25.76 ± 0.96	0.985 ± 0.012

*Average of five determination

**Average of three determination

In vivo study

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

A set containing 12 healthy rabbits were treated as control. Similarly another set containing same number of rabbits were utilized for the present study. All of them were kept free from diseases including opthalmic type. Each side of ocuserts were exposed to U.V. light for 10 minutes at 25 cm height from the fixed U.V. lamp. The UV irradiated ocusert of formulation VI (drug reservoir with 2% HPMC and 6% EC as rate controlling membrane) was placed in the lower eyelids of rabbits. At specific intervals of time, the films were removed carefully and analyzed for the remaining drug content[5].

RESULTS AND DISCUSSION

Efforts were made to prepare the ocuserts of ciprofloxacin hydrochloride using polymers such as HPLC, PVP, MCC, MC and EC[11] (Table 1). The physico chemical evaluation data presented in Table-2 indicates that the percent moisture absorption was more in formulation III due to HPMC (which is hydrophilic in nature) and 4% EC rate controlling membrane which was very thin when compared to 5% and 6% EC. Though the percent moisture

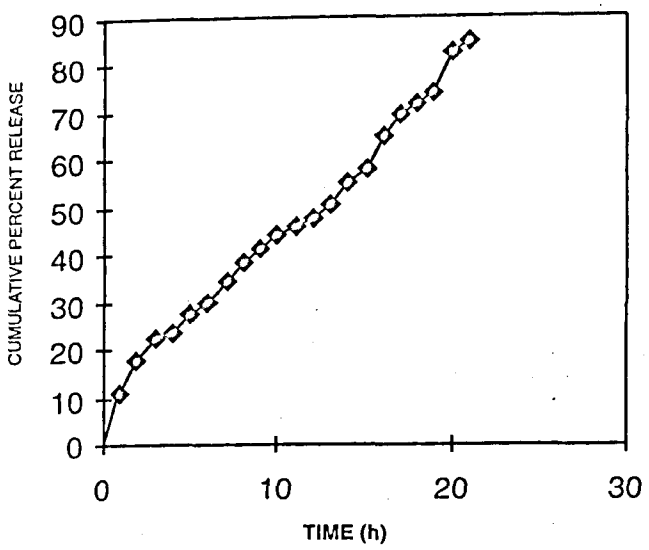

Fig.1 : *In vitro* release of ciprofloxacin hydrochloride from formulation VI (Drug reservoir with 2% HPMC and 6% EC as rate controlling membrane).

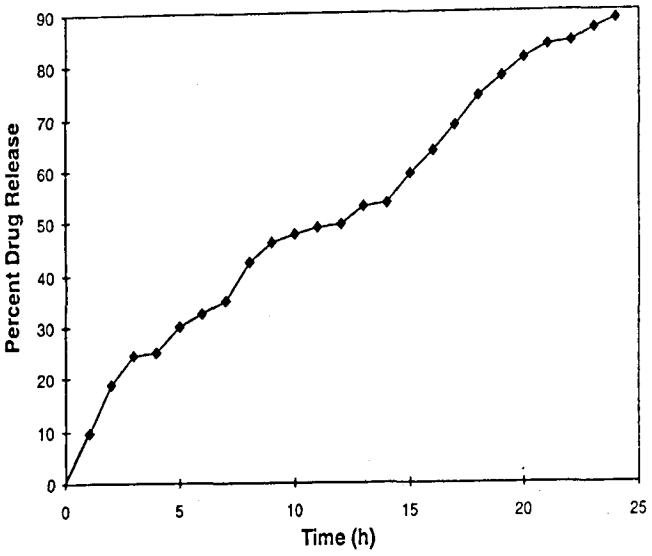

Fig.2 : *In vivo* release of ciprofloxacin hydrochloride in rabbits eye from formulation VI (Drug reservoir with 2% HPMC and 6% EC as rate controlling membrane).

absorption and the percent moisture loss were very high, there was no change in integrity at high humid and dry conditions which was observed by physical appearance.

The thickness of the ocusert varied between 0.232±0.78 mm to 0.374 ±1.01 mm. The formulations did not produce any irritation when placed in the cul de sac since they were not thick enough to produce irritation. The weight of each ocusert ranged from 18.8 ±0.38 to 25.92±0.81 mg (Table 2).

In vitro study showed the required drug release from formulation VI (drug reservoir with 2% HPMC and 6% EC as rate controlling membrane) through an artificial membrane over an extended period of 21 hours (Fig.1). Though some other formulations had shown the zero order release, the amount of drug released was less when compared to formulation VI. *In vivo* release of formulation VI in the lower eyelids of rabbits was 88.5% for 24 hours (Fig. 2). The release pattern followed the zero order kinetics.

In vitro and *in vivo* correlation was carried out for the therapeutic efficacy of the pharmaceutical formulation. The correlation coefficient[12] of formulation VI was found to be 0.9966[12] which confirms the correctness of *in vitro* release method followed (Fig 3). Formulation VI also passed the test for sterility.

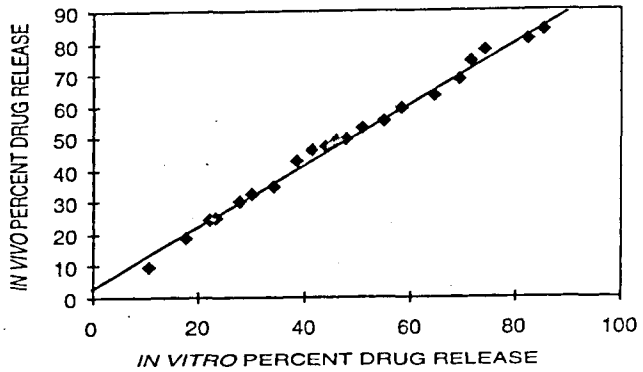

Fig.3 : *In vitro in vivo* correlation for the release of Ciprofloxacin hydrochloride from formulation VI (Drug reservoir with 2% HPMC and 6% EC as rate controlling membrane) showing a coefficient value of 0.9966.

Accelerated stability studies indicated that they had been stable both physically and chemically at 4° and 37°. The physical appearance of the formulation exposed to 60° showed a marked change after 5 days. The shelf life of formulation VI was found to be 61 days when determined by Free and Blythe Theory[13].

In conclusion, these results indicate that formulation VI (drug reservoir with 2% HPMC and 6% EC as rate controlling membrane) of ciprofloxacin hydrochloride has achieved the objectives of increased contact time,

prolonged release, decreased frequency of administration and thus may improve the patient compliance.

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