Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 4 Issue 10 October 2020

Research Article

Preparation and Evaluation of Ocuserts for Increasing the Bioavailability of an Antifungal Drugs

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Received: September 02, 2020

Published: September 28, 2020

Abstract

The main aim of the present study is to formulate an effective ocular insert of Clotrimazole (an antifungal drug), which can produce a better ocular therapy against ocular fungal infections by increased bioavailability through increased drug-eye contact time and controlling the trans-corneal permeation of drug. We intend to optimize the formulation to show constant release of drug for maintenance of dose over a prolonged period of time. For the purpose we prepared ocular insert formulations of Clotrimazole. Various formulations were prepared by use of different polymers, HPMC, EC and combination of both in different proportions 2%, 3% and 4%. The prepared formulations were evaluated for various physical and analytical parameter related to appearance, durability, uniformity of drug contents, *in-vitro* and *in-vivo* release of drug and for stability. Ocuserts of Clotrimazole were prepared by solvent casting method followed by preparing the drug reservoir film and rate controlling membrane separately. Evaluation of ocular inserts for weight and thickness variation were carried out and analyzed by ANOVA. The % drug release from the selected formulation containing HPMC, were found to be 91.78 ± 2.436 at the end of 360 minutes. From current study we can conclude that by using different polymer in rate controlling membrane of an ocusert, release rate of drug from ocusert can be controlled or altered.

Keywords: Ocusert; Clotrimazole; HPMC; EC; ANOVA

Introduction

Ocusert system was firstly developed in 1975 by 'Alza Corporation, in the United State of America. It is a flat, flexible, solid and semisolid device which consists of drug reservoir and rate controlling membrane by using various polymers [1,2]. The prime objective of development of the ocuserts is continuous controlled delivery of ophthalmically active drug to the eye. The ocusert is inserted in the upper or lower cul-de-sac of the eye, which releases the drug at a predetermined rate constant. Thus, improved patient compliance by reduced dose frequency, better therapeutic outcomes by reduced over/under dosing, lesser local side effects/toxicity and increased bioavailability by increased drug eye contact time is observed [3,4]. Generally, all types of ocusert consist of three components namely, "a central drug reservoir" in which the drug is incorporated in a polymer; "rate controlling membrane", which ensures the controlled release of medicament from the drug reservoir; and "an outer annular ring", meant for easy handling and proper insertion [5,6] (Figure 1).

Advantages of ocusert

Ocusert enjoys following advantages over conventional ophthalmic dosage forms:

- Increased ocular contact time and thus improved drug bioavailability [7].

- Increased ocular permeation with respect to standard formulation and thus providing prolong drug activity and hence increased ocular bioavailability of drug [8].
- Administration of an accurate dose in the eye gives better therapy [9].
- Better patient compliance by reduction of the number of administered dose [10].
- Better efficacy by providing a constant drug release [10].
- Increased possibility of internal ocular tissue targeting through non-corneal, (conjunctival and sclera) penetration routes [10].

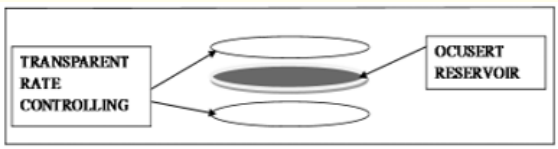

Figure 1: Schematic diagram of ocular insert.

Materials and Methods

Preformulation studies

A study on various physico-chemical properties of procured drug was done along with chemical authentication by physical appearance, melting point determination and FTIR spectra.

Physical appearance

The physical appearance of the drug sample was noted same as that of the official reports [11,12].

Melting point determination

Melting point of the drug sample was determined by using capillary tube method using melting point apparatus (Macro Scientific Works) by filling the drug sample in 3 separate capillaries. The samples were heated slowly and observed continuously for most accurate results. The melting range was recorded which begins when the sample first start to melt and ends when the sample is completely melted [13].

FT-IR spectrum of Clotrimazole drug

FT-IR spectra of pure drug (Clotrimazole), polymer Sodium Carboxy Methyl Cellulose (NaCMC), and combination of Clotrimazole and Sodium Carboxy Methyl Cellulose were carried out to check compatibility of drug with excipient. Solid powder samples were oven dried at around 300^{0}C, finely crushed, mixed with potassium bromide (1:10 ratio by weight) and pressed at 15000 psig to make disc.The pellets were then scanned using FT-IR Spectrophotometer (Shimadzu IR Affinity 1, Tokyo, Japan). The wavelength ranged from 500 to 4500 cm^{-1} with a resolution of 4 cm^{-1}. The FT-IR spectra of mixture were compared with the FT-IR Spectra of pure drug and pure polymer for important peaks [14].

Preparation of Standard Curve of Clotrimazole drug in methanol

Standard stock solution of Clotrimazole having concentration 116 µg/ml was prepared by dissolving Clotrimazole in methanol. From this stock solution different concentration of 11.6, 23.2, 34.8, 46.4, 58.0, 69.6, 81.2, 92.8, 104.4, and 116.0 µg/ml were prepared by diluting with methanol. The absorbances of these solutions were measured at λ_{max} (260.8 nm). A calibration curve of Concentration v/s Absorbance was plotted in Microsoft excel.

Preparation of ocuserts

Ocuserts of Clotrimazole were prepared by solvent casting method followed by preparing the drug reservoir film and rate controlling membrane separately.

For preparing ocusert reservoir film drug Clotrimazole and 2% polymer NaCMC was dissolved in a solution of water and ethanol in 1:1 ratio. Then plasticizer PEG-400 (30% w/w of dry polymer) was added and stirred up to 3 hrs, casted on petri dish, dried in hot air oven at 40°C temperature up to 24 hrs and then ocusert reservoirs film was cut by 8 mm size cork borer to produce discs of ocusert reservoirs.

Formulation code	Ocusert reservoir			
	Clotrimazole (mg)	Na CMC %W/V	PEG-400 %W/W	Water+ Ethanol (1:1) ml
F(NaCMC)2	50 mg	2%	30%	15

Table 1: Composition of ocusert reservoir.

For preparing rate controlling membrane 2%, 3%, and 4% of different polymers HPMC, EC, and combination of both in 1:1 ratio was dissolved in ethanol. Then plasticizer di-n- dibutyl phthalate (30% w/w of dry polymers) was added and stirred up to 6 hrs at 35°C temp., after stirring its solution casted on petri dish, dried in hot air oven at 40°C up to 24 hrs and then rate controlling membrane film was cut by 10 mm size cork borer to produce discs of rate controlling membrane of ocuserts.

Formulation code	Rate controlling membrane			
	HPMC %W/V	EC %W/V	DBP %W/W of polymer	Ethanol ml
F1	2%	-	30%	15
F2	3%	-	30%	15
F3	4%	-	30%	15
F4	-	2%	30%	15
F5	-	3%	30%	15
F6	-	4%	30%	15
F7	1	1	30%	15
F8	1.5	1.5	30%	15
F9	2	2	30%	15

Table 2: Composition of rate controlling membrane.

Sealing of ocusert reservoir disc was done by sandwiching each reservoir disc between two rate controlling discs membranes by applying ethanol or chloroform [16].

Evaluation of ocuserts

Prepared ocuserts were evaluated for following parameters:

- **Weight variation:** The weight variation test of ocuserts was carried out by individually weighing randomly selected 20 ocuserts on high precise weighing balance (least count 0.1 mg) and average weight variation of 20 ocuserts were calculated and ANOVA was applied for statistical evaluation [17].
- **Thickness:** The thickness of ocuserts was measured by digital vernier calipers, (having least count 0.01 mm) at different points of ocuserts and average thickness of 20 ocuserts was calculated and variations in thickness were analyzed statistically by ANOVA [18].
- **Folding endurance:** Folding endurance of the ocuserts was determined by repeatedly folding the ocuserts at the same place till it breaks and thus average folding endurance of ocuserts was calculated [19].
- **Surface pH:** Surface pH of the ocuserts was determined by allowing them to swell in a petri dish at room temperature for 30 min in 10 mL of distilled water. The swollen devices were removed and placed on sensing electrode of pH meter and the average surface pH of ocuserts was calculated [20].

Theoretical drug contents of each ocusert

For calculating average drug contents in each formulation, first of all theoretical amount of drug in each ocusert reservoir was calculated by measuring the area of casted film, amount of drug loaded in it and then calculating average area of an ocusert applying following formula.

Theoretical amount of drug =

$$\frac{\text{Drug loaded in casted film} \times \text{Area of ocusert in each ocusert reservoir}}{\text{Area of casted film}}$$

Calculations have been given in appendix 1.

Average drug content

Accurately weighed three ocuserts were dissolved in phosphate buffer solution of 7.4 pH and the solution was stirred up to 15 minutes. After stirring drug solution was filtered through Whatman filter paper No. 40 and drug content were estimated by measuring absorbance on U.V spectrophotometer and average drug content of ocuserts was calculated from developed U.V spectrophotometric method of drug estimation. The whole procedure was done in triplicate and average was reported [21].

Moisture content

The prepared ocuserts were accurately weighed individually and kept in a desiccator containing calcium chloride at room temperature. After a specific time interval 3, 6, 12, 24 and 48 hrs ocuserts were weighed again until they showed a constant weight and average % moisture content of ocuserts was calculated [22].

$$\% \text{ moisture content} = \frac{\text{Initial weight} - \text{Final weight} \times 100}{\text{Initial weight}}$$

Moisture uptake

The prepared ocuserts were accurately weighed individually and kept in a desiccator containing a 100 mL saturated potassium chloride solution at room temperature and relative humidity 82.65% ± 0.25%. After a specific time interval 3, 6, 12, 24, and 48 hrs they were taken out and weighed again and exposed at room temperature and relative humidity 82.65% ± 0.25% using a saturated solution of potassium chloride in a desiccator until a constant weight was obtained and then average % moisture uptake was calculated [23].

$$\% \text{ moisture uptake} = \frac{\text{Final weight} - \text{Initial weight} \times 100}{\text{Initial weight}}$$

In vitro drug release studies

In-vitro release of drug in phosphate buffer 7.4 pH (Ophthalmic simulated media) from prepared ocuserts was carried out using self assembled modified diffusion cell (Figure 5). We fabricated diffusion cell assembly by using a standard test tube open on both ends and the diameter of 15 mm. We tied corneal membrane of goat eye at the one end of open glass tube which acted as a donor compartment. The ocuserts was placed inside the donor compartment of the diffusion cell with 0.2 ml of phosphate buffer 7.4 pH ophthalmic saline media (OSM). Then the glass tube was suspended in the beaker such that entire surface of the membrane was in contact with the receptor compartment containing 20 ml of phosphate buffer 7.4 pH (OSM) and after that the whole assembly was placed on magnetic stirrer with constant agitation speed (50 rpm) at 37°C temperature. The receptor fluid was removed for drug analysis by replacing fresh receptor fluid. The concentration of drug was determined by developed U.V spectrophotometric method of drug analysis [23,24].

Results and Discussion

Pre-formulation studies

The drug Clotrimazole was identified and characterized by the tests for identification as per official monographs [22,24].

The physical appearance of the procured drug sample was found to be same as that of the official reports. Results are shown in table 1.

The average melting point of procured sample of Clotrimazole was found to be 143.83°C which is within the range (141 - 145°C) given in official monograph. Results have been shown in table 2.

The FTIR Spectrum of procured drug Clotrimazole and that of ocusert reservoir containing the (CLTZ) drug and polymer (NaCMC) both were taken and have been shown in figure 2 to 4 respectively.

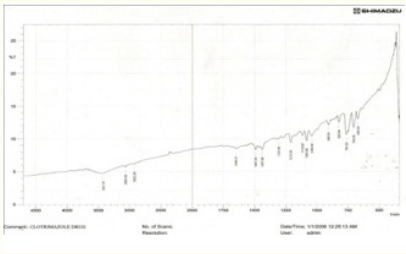

Figure 2: FTIR spectra of procured drug: Clotrimazole.

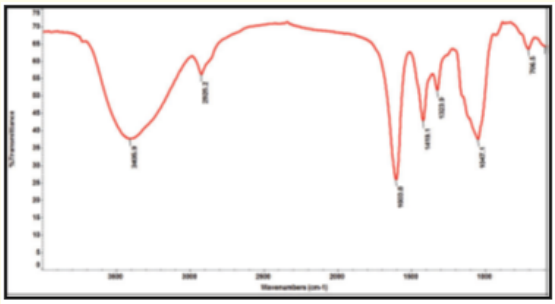

Figure 3: FTIR spectra of NaCMC polymer.

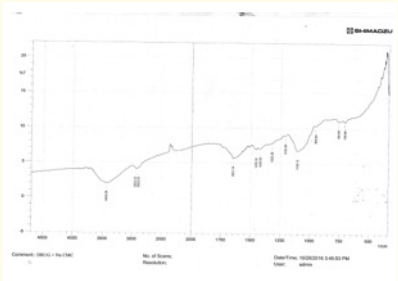

Figure 4: FTIR spectra of ocusert reservoir (CLTZ and NaCMC).

Standard curve of clotrimazole drug in methanol

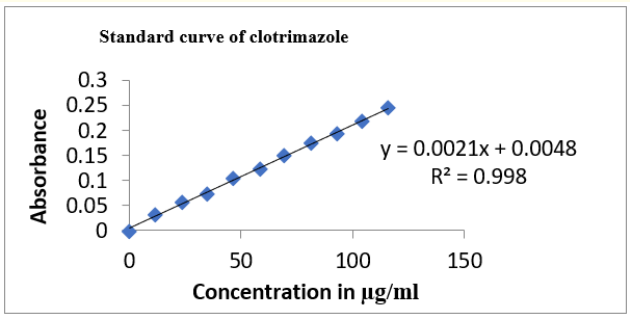

Figure 5

Ocuserts formulations

The details of composition of ocuserts prepared by method described in methodology and codes assigned to them are given in table. Photograph of different formulations (ocuserts) are shown in figure.

Physicochemical evaluation

In the present study solvent casting technique was adopted and it was found to be given a thin uniform ocular insert films. All pre-

pared ocular insert film had good appearance with smooth surface. Ocusert films prepared were semi-transparent. Surface texture was smooth and uniform. Evaluation of ocular inserts for weight and thickness variation were carried out and analyzed by ANOVA.

Formulation Code	Rate controlling membrane				Ocusert reservoir			
	Polymer		Plasticizer	Solvent	Drug	Polymer	Plasticizer	Solvent
	HPMC % W/V	EC % W/V	DBP % W/W of polymer	Ethanol ml	Clotrimazole (mg)	Na CMC % W/V	PEG-400 % W/W	Water+Ethanol (1:1) ml
F1	2	-	30	15	50	2	30	15
F2	3	-	30	15	50	2	30	15
F3	4	-	30	15	50	2	30	15
F4	-	2	30	15	50	2	30	15
F5	-	3	30	15	50	2	30	15
F6	-	4	30	15	50	2	30	15
F7	1	1	30	15	50	2	30	15
F8	1.5	1.5	30	15	50	2	30	15
F9	2	2	30	15	50	2	30	15

Table 3: Composition of prepared ocuserts.

Formulation Code	Weight variation (mg) ± SD*, (P value)	Thickness (mm) ± SD*, (P value)	Folding endurance ± SD#	Surface pH ± SD#	Average drug content in each formulation (% of theoretical amount/ocusert = 0.9308) ± SD#	% Moisture content ± SD×, (P value)	% Moisture uptake ± SD×, (P value)
F1	28.205 ± 1.669 p<0.0001	0.0262 ± 0.016 p<0.0001	78.33 ± 6.02	7.16 ± 0.404	92.42 ± 3.309	3.19 ± 0.056 p<0.0061	2.98 ± 0.111 p<0.0246
F2	37.1 ± 2.018 p<0.0001	0.326 ± 0.02 p<0.0001	72 ± 14.0	7.23 ± 0.351	89.01 ± 1.028	2.55 ± 0.02 p<0.0007	3.17 ± 0.036 p<0.0025
F3	47.165 ± 2.499 p<0.0001	0.364 ± 0.026 p<0.0001	64.33 ± 4.16	7.6 ± 0.5	90.72 ± 2.138	3.19 ± 0.053 p<0.0055	4.34 ± 0.036 p<0.0025
F4	24.45 ± 2.722 p<0.0001	0.224 ± 0.021 p<0.0001	51 ± 2.0	7.2 ± 0.3	87.31 ± 0.946	3.39 ± 0.044 p<0.0037	2.42 ± 0.177 p<0.0616
F5	34.38 ± 2.177 p<0.0001	0.229 ± 0.017 p<0.0001	45.66 ± 2.51	7.46 ± 0.416	83.9 ± 0.882	4.57 ± 0.046 p<0.0041	4.21 ± 0.036 p<0.0025
F6	47.165 ± 2.499 p<0.0001	0.354 ± 0.027 p<0.0001	44.66 ± 4.16	7.5 ± 0.519	87.31 ± 0.823	3.15 ± 0.036 p<0.0025	3.55 ± 0.053 p<0.0055
F7	24.78 ± 2.268 p<0.0001	0.224 ± 0.016 p<0.0001	95 ± 3.60	7.066 ± 0.208	89.01 ± 2.67	3.40 ± 0.026 p<0.0013	3.19 ± 0.07 p<0.0097
F8	33.18 ± 0.891 p<0.0564	0.308 ± 0.014 p<0.0001	74 ± 13.07	7.2 ± 0.360	87.31 ± 2.094	3.69 ± 0.026 p<0.0013	3.08 ± 0.044 p<0.0037
F9	44.395 ± 2.096 p<0.0001	0.38 ± 0.02 p<0.0001	78.66 ± 3.51	7.166 ± 0.35	89.01 ± 1.612	4.60 ± 0.026 p<0.0013	4.30 ± 0.046 p<0.0041

Table 4: Physicochemical evaluation of Clotrimazole ocuserts.

*Average of twenty readings, #Average of three readings, × Average of five readings.

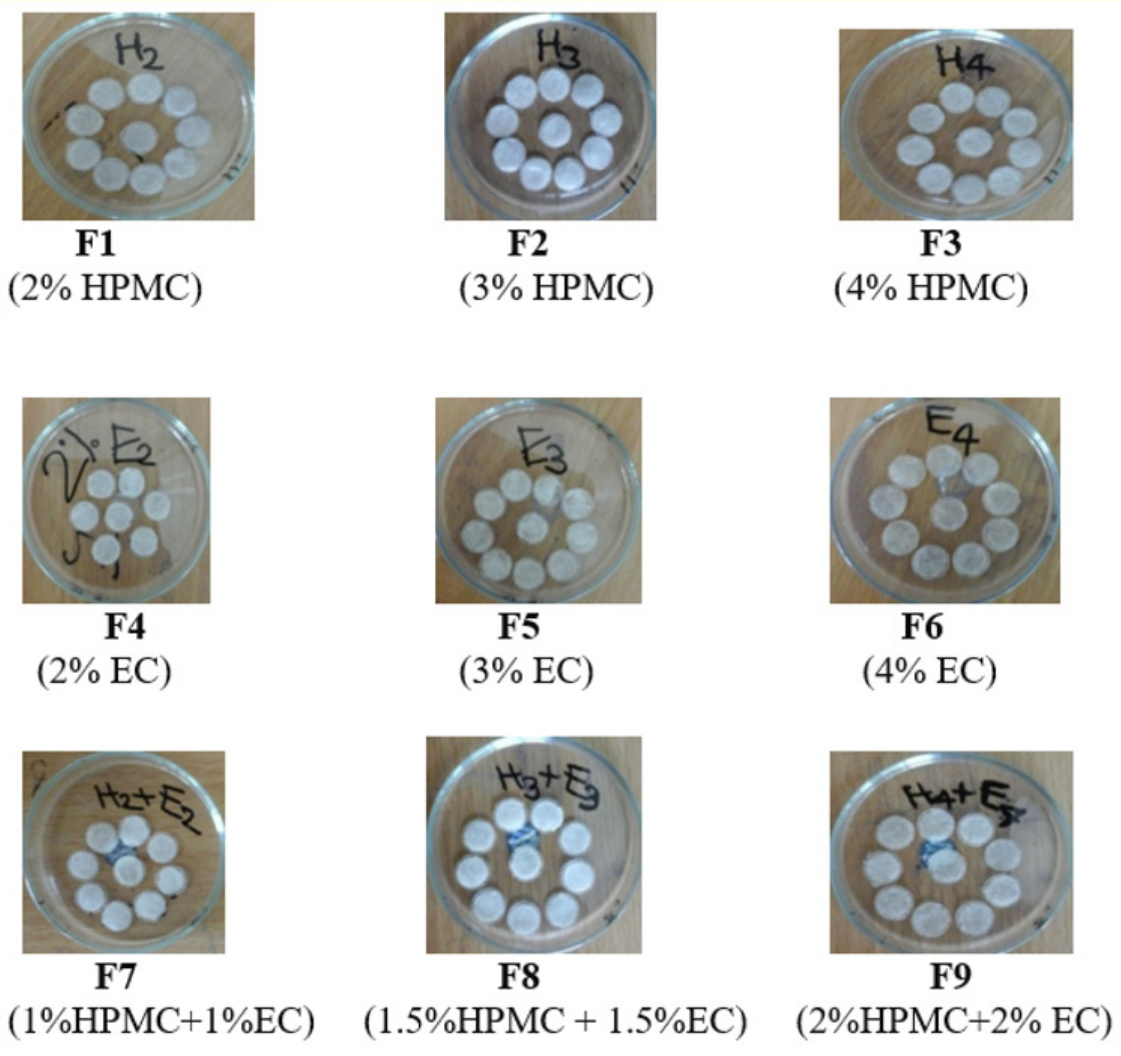

Figure 6: Formulated ocuserts F1 to F9.

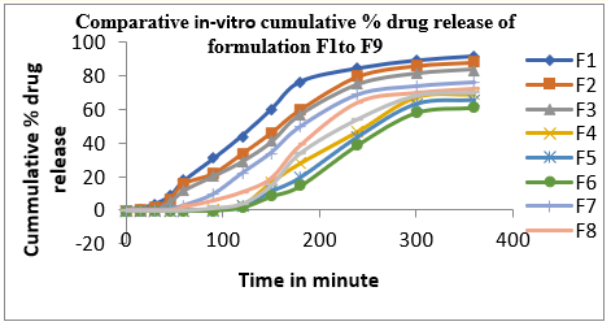

Figure 7: Comparative *in-vitro* cumulative % drug release profile of formulations F1to F9.

Conclusion

From current study we can conclude that by using different polymer in rate controlling membrane of an ocusert release rate of drug from ocusert can be controlled or altered. In present study polymers used in rate controlling membrane of ocusert showed following sequence of release rate (as shown by Figures) HPMC > 1:1 Combination of HPMC and EC > EC.

Furthermore, change in concentration of a polymer in rate controlling membrane alters the release rate of drug from ocusert and it was found that increasing the concentration of a polymer in rate controlling membrane retards the release rate as shown by (Figures) 2% polymer > 3% polymer > 4% polymer.

For achieving an effective required release of drug whether instantaneous or prolonged release, further study on different polymers in different concentration is suggested.

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