



Current Research in Pharmaceutical Sciences

Available online at www.crpsonline.com



ISSN: 2250 – 2688

CODEN: CRPSBZ (USA)



Received: 21/04/2017

Revised: 03/05/2017

Accepted: 26/05/2017

Published: 08/07/2017

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DOI: 10.24092/CRPS.2017.070204

Website: www.crpsonline.com

Quick Response Code:



Formulation and Evaluation of Ocusert Idoxuridine

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ABSTRACT

Ophthalmic insert is defined as sterile preparation with solid or semisolid consisting and whose size and shape are especially designed for ophthalmic application. They offer several advantages as increase ocular residence, possibility of releasing drug at a slow constant rate, accurate dosing and increased shelf life with respect to aqueous solutions. Ocular route of drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. Therefore many ophthalmic drug delivery systems are available. These are classified as conventional and non-conventional drug delivery systems. The main purpose of preparing ocular insert is to increase ocular bioavailability of drug. Idoxuridine is an antiviral agent used in treatment of Herpes-keratitis. In present research, an attempt has been made to formulate ocular inserts of idoxuridine using various polymers such as hydroxyl propyl methyl cellulose, polyvinyl alcohol and Eudragit in different concentrations by solvent casting method using dibutylphthalate as plasticizer with aim of achieving controlled release, reduction in frequency of administration and greater therapeutic efficacy. Prepared ocuserts were evaluated for Uniformity of thickness, Uniformity of weight, Surface pH, folding endurance, drug content and *In vitro* studies.

Keywords- Formulation, Ocusert, Polymer drug content, Rate controlling membrane, Reservoir

1. INTRODUCTION

The eye presents unique opportunities and challenges when it comes to delivery of pharmaceuticals. Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists. Ocuserts are defined as sterile preparations with a solid or semisolid consistency, whose shape & size are mainly designed for ophthalmic application. All different types of ocuserts 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 shown in figure 1. Ocuserts enhances contact time, long-running duration of action, improves bioavailability, reduces the frequency of administration and therefore achieves good patient compliance.¹ Equivalent ocular drug level eliminates systemic side effects and gives undisturbed sleep due to extended drug activity throughout the night. It is also outlook to administer the drug to inflamed eye due to sustained release of the medicament from ocuserts. Furthermore, ocuserts are beneficial in saving time to the healthcare professionals. The efficacy of any ophthalmic drug depends on the tissues for providing hoped therapeutic response. The zero order kinetics characteristics a controlled release type of delivery system whereby the drug is held in a reservoir and is released into the tear film at constant rate to provide a constant concentration in the corner which provides good improved compliance.² The advantage of ocular inserts, which are solid devices placed in the cul-de-sac of the eye in comparison with liquid formulations are numerous. Because of the prolonged retention of the devices and a controlled release, the effective drug concentration in the eye can be ensured over an extended time period. Dosing of the drug is also more accurate and the risk of systemic side-effects is decreased.³

Herpes simplex virus (HSV) is the most problematic. Viral conjunctivitis and bacterial conjunctivitis may affect one or both eyes. Viral conjunctivitis usually produces a watery or mucous discharge. Bacterial conjunctivitis often produces a Thicker, yellow - green discharge and may be associated with a respiratory infection or with a sore throat Idoxuridine is preferentially taken up by the virus infected cells. Because of selective generation of the active inhibitor in the virus infected cell and Its inhibitory effect on viral DNA synthesis, idoxuridine has low toxicity for host cells. This is an alternate approach to improve the bioavailability is the use of polymeric solutions, which change to a gel as a result of exposure to the physiological temperature, pH or ionic composition of lacrimal fluid.⁴

2. MATERIALS AND METHODS

2.1 Collection of sample

Idoxuridine was received as gift sample from Hetro pharma, Hyderabad; HPMC K4M was purchased from Colorcon Asia Pvt. ILd, Goa; All other chemicals used were analytical grade.

2.2 Preparation of drug reservoir

For preparation of the drug containing reservoir film, polymeric solutions were prepared by dissolving hydrophilic polymer (HPMC/PVA), along with idoxuridine and poly ethylene glycol 400, in twice as distilled water. The solutions were poured into a glass ring of (8.9mm) 0.9 cm diameter placed in a Teflon coated Petri dish. The solvent was allowed to evaporate by placing it inside an oven maintained at $35 \pm 2^\circ\text{C}$, $30 \pm 0.5\%$ RH for 24h.

2.3 Preparation of rate controlling membrane

Hydrophobic polymer (Eudragit RS 100/ Eudragit RL 100), along with plasticizer, dibutyl phthalate were dissolved in ethanol/acetone (80:20) mixture, to prepare the rate controlling films. The solutions were poured into a glass ring of (8.9 mm) 0.9 cm diameter placed in a Teflon coated Petri plate. The solvent was allowed to equilibrate at $25 \pm 05^\circ\text{C}$, $45 \pm 0.5\%$ RH for 24h.

2.4 Placing rate controlling films around the drug reservoir and sealing them to obtain ocular insert

With the help of a cork borer (special device), circular shaped ocular inserts were cut out of medicated reservoir film. These ocular inserts were placed on a rate-controlling membrane containing the reservoir film between them was placed over a beaker saturated with ethanol/acetone vapors (60:40) for 1-2 minutes. The ultimate ocular inserts consisted of three films;

reservoir films containing the drug were sandwiched in between the rate controlling membrane to control the release. The ocular inserts were stored in an airtight container under ambient conditions.⁵

2.5 Evaluation Methods

2.5.1 Uniformity of Thickness

By a Vernier caliper, insert thickness was measured at five or six different points on the film. The mean thickness of ocusert and standard deviation (SD) were calculated.

2.5.2 Uniformity of Weight

Five films were taken from each batch and by using electronic balance their individual weights were determined.

2.5.3 Folding Endurance

By repeatedly folding the inserts at the same place till it breaks, folding endurance of the film was determined. The ocuserts was folded in the center, between finger and thumb and then opened. This was one folding. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance.⁶

2.5.4 Swelling Index

Three films were weighed and placed separately in beakers containing 4ml of simulated tear fluid. After a period of 5 minutes, the films were removed and the excess water on their surface was removed carefully using a filter paper and then again weighed till there was no increase in the weight and then the swelling index was calculated using the following formula:

$$\% \text{ SW} = [(WT - WO) / WO] \times 100$$

Where, %SW = percentage swelling index; WT = weight of swollen insert after time T; WO = original weight of insert at zero time;

2.5.5 Uniformity of Drug Content

By assaying the individual inserts, the uniformity of drug content was determined. Three films were taken from each batch and individually dissolved or crushed in 5 ml of simulated tear fluid in a beaker and filter it into the beaker 0.5 ml of the filtered solution was taken in 20ml beaker and diluted to 15 ml with

simulated tear fluid. The absorbance of each of these solutions was then measured on UV-visible spectrophotometer at 254 nm.⁷

2.5.6 Percentage Moisture Absorption

To check the physical stability of the ocusert at high humid condition, percentage moisture absorption test was carried out. This test is also necessary. The ocuserts were pre weighed accurately and kept in desiccators containing 100 ml of saturated solution of aluminium chloride. Films were taken out, after 72 hours (3 days) weighed and percentage moisture absorption was calculated by using formula.

$$\% \text{ MA} = [(\text{final weight} - \text{initial weight}) / \text{initial weight}] \times 100$$

Where, %MA = percentage moisture absorption

2.5.7 Percentage Moisture Loss

This test was carried out to check the integrity of ocusert at dry condition. The ocuserts were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 72 hours (3 days), the films were taken out, weighed and percentage moisture loss was calculated by using formula.

$$\% \text{ ML} = [(\text{initial weight} - \text{final weight}) / \text{final weight}] \times 100$$

Where, % ML = percentage moisture loss

2.5.8 In vitro Diffusion Studies

The *in vitro* diffusion of drug from the different ophthalmic insert was studied using the customary standard cylindrical tube fabricated in the laboratory. A simple modification of open ended glass tube was used. The diffusion cell membrane (pre hydrated cellophane) was tied to end of open cylinder, which acted as a donor compartment. An ophthalmic insert was placed inside this compartment. The diffusion cell membrane acted as corneal epithelium. The entire surface of the membrane was in contact with the receptor compartment containing 25 ml of simulated tear fluid in 100 ml beaker. The content of receptor compartment was stirred continuously using a magnetic stirrer and temperature was maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. At specific time interval, 1ml of the sample solution was withdrawn from the receptor compartment and replaced with fresh simulated tear fluid solution. The aliquot was analyzed for the drug content using UV-VIS Spectrophotometer at 254 nm after appropriate dilutions against reference using simulated tear fluid as blank.⁸

3. RESULTS AND DISCUSSION

The prepared ocuserts were uniform in appearance with smooth texture and no visible cracks or imperfection.

The weights of all the films were found to be in the range of 5.86 to 6.06 mg. The uniformity of weight of the film indicates good distribution of the drug, polymer and plasticizer. The weight variations of ocuserts of all formulations were noted in table.

While the mean thickness ranged between 0.15 ± 0.011 to 0.19 ± 0.019 mm. On an individual product basis, thickness specifications may be set. There were no marked variations in the thickness of ocuserts within each formulation indicating uniform behavior of film throughout the sealing process. The thickness of the ocuserts of all formulations was noted in table.

Folding endurance of a film was a measure of breaking strength and endurance. This is the number of times the film may be folded at one place until it breaks or sign of breakage appears. Data was in the range of 84 to 95 times. The folding endurance results shows enough strength of ocuserts to withstand handling shocks. Sometimes ocuserts comprises of hydrophilic polymers and likely to gain moisture from environment. Hence, it becomes imperative to measure moisture uptake extent for such formulation. Moisture uptake value for prepared formulations was from 10.10 to 7.79% of total ocusert weight after exposing this to predetermined environment having 75% RH.

Use of less amount of plasticizer was observed to cause brittleness in the medicated discs, but use of greater amount of plasticizer (1ml plasticizer per 10 ml) displayed little opaqueness and good folding endurance. For all formulations manually, the folding endurance was measured.

The drug content was found from 95.63 to 96.04 %. The drug content of ocuserts of all formulations were noted in table. The Percentage moisture absorptions were observed from 10.10 to 7.79%. Percentage moisture losses were observed from 6.63% to 9.31%. The percentage moisture absorption and percentage moisture loss were high, there was no change in integrity at high humid and dry conditions which was observed by physical appearance. The values were calculated and tabled. Mean drug content for the prepared formulas after being extracted in STF ranged from 95.43 ± 0.065 % to 99.16 ± 0.258 % . These results revealed that none of the prepared formulas deviated from 100% drug content by more than 5%. This indicates that the used method of preparation resulted in reproducible uniform distribution of both drugs within the polymeric matrix of the film. Results of measuring surface pH revealed that all ocusert formulas lay in the

Table 1: Preparation of drug reservoir

Ingredients	F1	F2	F3	F4	F5	F6
Iodoxuridine	10	10	10	10	10	10
HPMCK4M	-	-	3	6	-	-
PVA	3	6	-	-	3	6
PEG400	0.8	0.8	0.8	0.8	0.8	0.8
Distilled water	10	10	10	10	10	10

Table 2: Preparation of rate controlling membrane

Ingredient	F1	F2	F3	F4	F5	F6
Eudragit RS100*	6	3	2	-	-	-
EudragitRL100*	-	3	6	3	6	3
PEG400**	0.8	0.8	0.8	0.8	0.8	0.8
Acetone**	10	10	10	10	10	10

Table 3: Evaluation parameters of formulation of ocuserts

Form. code	Thickness (mm)	Weight variation (mg)	Folding endurance	% drug content	% swelling index	% Moisture absorption	% Moisture loss
F1	0.15±0.011	5.86±0.151	84	95.43 ± 0.065	83.51 ± 0.254	10.10± 0.075	6.63 ± 0.90
F2	0.16±0.015	5.86±0.151	91	98.35 ± 0.230	85.46 ± 0.723	4.44 ± 0.780	8.59 ± 0.93
F3	0.17±0.016	5.86±0.151	97	98.36 ± 0.167	91.05 ± 0.862	5.49 ± 0.820	7.79 ± 0.919
F4	0.17 ± 0.024	5.92±0.130	88	99.16 ± 0.258	83.61 ± 0.614	5.74 ± 0.810	7.01 ± 0.95
F5	0.18 ± 0.011	6.00±0.158	93	96.68 ± 0.183	89.08 ± 0.163	5.74 ± 0.810	7.01 ± 0.95
F6	0.19 ± 0.019	6.06±0.167	95	96.04 ± 1.600	91.86 ± 0.697	7.79 ± 0.919	9.31 ± 0.08

Table 4: *In vitro* drug release of formulation

Time (hr)	F1	F2	F3	F4	F5	F6
1	9.1	10.6	11.6	12.1	14.1	18.5
2	17.2	21.2	22.6	21.6	24.6	27.9
3	33.1	34.5	35.6	36.1	38.2	43.6
4	44.9	51.5	48.8	49.4	51.6	55.9
5	56.4	59.4	61.1	60.3	63.7	67.5
6	72.2	76.9	75.9	77.5	79.2	83.3
7	80.3	83.6	85.4	86.1	89.5	93.2
8	89.7	91.1	93.1	92.6	94.4	97.3

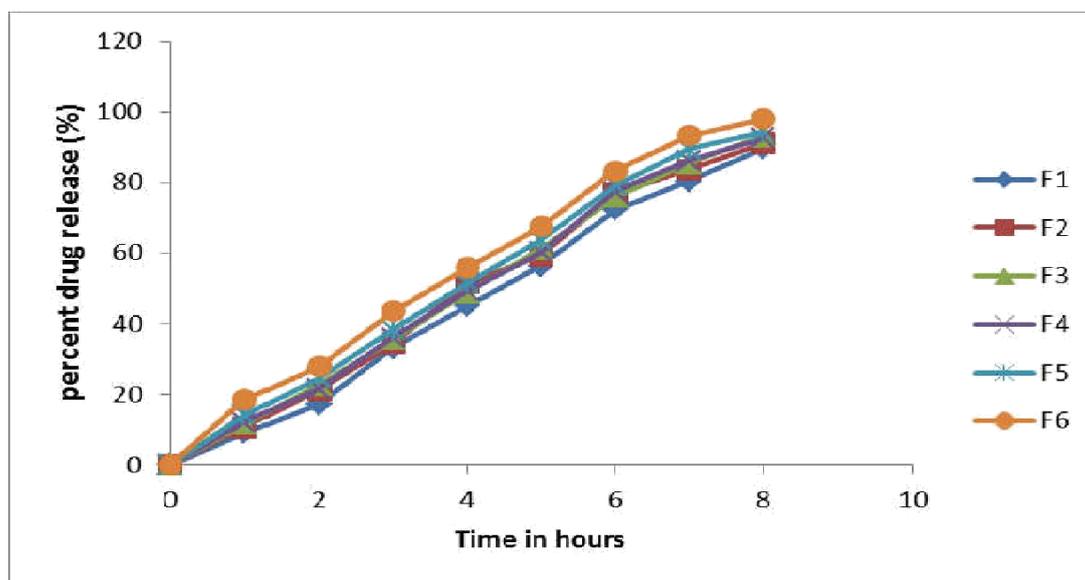


Figure 1: In-vitro drug release of idoxuridine ocusert

physiological range of the eye (5.5-7.5). Therefore, the prepared ocuserts were having the essential requirement to prevent irritation potential as they did not alter the pH of tear fluid.

4. CONCLUSION

Reservoir type ocular inserts comprising reservoir film of hydrophilic polymer (HPMC/PVA), along with idoxuridine and

poly ethylene glycol 400, in doubly distilled water were prepared by film casting technique on Teflon coated Petri dishes and tested for drug content, physical characteristics, interaction between drug and polymers due to sterilization by gamma radiations and *in vitro* drug release. The formulation F6 was found to be satisfactory in terms of required pharmaceutical characteristics of ocular inserts and was found promising drug release characteristics.

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