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ORIGINAL RESEARCH ARTICLE

Design and Evaluation of Ocular Inserts For Controlled Drug Delivery of Acyclovir

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ABSTRACT

Acyclovir is an antiviral agent used in treatment of Herpes-keratitis. In present research, an attempt has been made to formulate ocular inserts of acyclovir using various polymers such as hydroxypropylmethylcellulose, polyvinylalcohol 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 and drug content etc. Ocuserts are also subjected to *in vitro* diffusion studies. Formulation ACY-11 and ACY-17 showed zero order release was sterilized by gamma irradiation and subjected to *in vivo* studies, ocular toxicity test and stability studies.

Keywords: Ocusert, antiviral, polymer, sterilization

INTRODUCTION

Drugs administered in traditional topical ophthalmic formulation such as aqueous eye drops have poor bioavailability due to rapid pre corneal elimination. To reach therapeutic levels frequent instillation of the drug are required, leading to a low patient compliance. 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 [1]. 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.

The bioavailability of traditional ocular drug delivery systems such as eye drops is very poor because eye is protected by a series of complex defense mechanisms that make it difficult to achieve an effective drug concentration within the target area of the eye. Many approaches have been developed to solve the problem in recent decades, of which colloidal drug delivery system has been paid much attention [2,3,4]. Ophthalmic inserts offer many advantages over conventional dosage forms, like increased ocular residence, possibility of releasing drugs at a slow and constant rate, accurate dosing, and exclusion of preservatives, increased shelf life and reduced systemic absorption.

In the present study, an attempt has been made to formulate ocular insert of gatifloxacin sesquehydrate using hydrophilic polymers like hydroxypropyl methylcellulose (HPMC), methylcellulose(MC) and PEG 400 as plasticizer, while rate-controlling membrane was prepared using hydrophobic ethyl cellulose (EC) and dibutyl phthalate as plasticizer by solvent casting method with aim of increasing the residence time, achieving controlled release, reduction in frequency of administration and greater therapeutic efficacy.

MATERIAL AND METHODS

Acyclovir was procured as gift sample from Ipca Laboratories, Mumbai. All other ingredients were purchased from Himedia Pvt. Ltd., India.

Preparation of drug reservoir

For making ocular inserts solvent casting method was adopted. The eighteen batches (ACY1-ACY18) of acyclovir ocular inserts were prepared by mixing different proportion of drug and polymers. Polymer is dissolved in suitable solvent

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i.e. ethanol or water and plasticizer was added into the solution under stirring condition. The drug was then added to the above solution and stirred four 24 hours. After this casting solution was poured in clean petridish and covered with an inverted funnel to allow slow evaporation at room temperature for 72 hours [5,6]. The dried films thus obtained were cut into circular pieces of definite size. These were then stored in an air tight container.

Preparation of rate controlling membrane

Rate controlling membranes were prepared by dissolving ethyl cellulose in acetone and employing dibutylphthalate as plasticizer in concentration of 30% w/w of the weight of dry polymer. After drying the film at room temperature, circular rings of 10 mm diameter, each containing 5 mg of acyclovir were cut and used to seal both the sides of drug reservoir to control the release from peripheral area [5,6].

Characterization of prepared ocular inserts

Uniformity of thickness

Thickness was determined by using digital vernier calipers at five separate points if each insert.

Uniformity of weight

For each batch three inserts were taken and weighed individually using digital balance.

% Moisture absorption

The test was carried out for checking physical integrity of film under limited condition. The films were weighed and placed in dessicator containing solution of aluminium chloride and 84% humidity was maintained. After 7days moisture absorption was calculated using the formulae [7].

$$\% \text{ Moisture absorption} = \frac{(\text{Final weight} - \text{Initial weight})}{\text{Initial weight}} \times 100$$

% Moisture loss

This parameter is for determining physical integrity of film under dry condition .The films were weighed and placed in dessicator containing anhydrous calcium chloride. After 7 days moisture loss was calculated from the formulae [8,9,10].

$$\% \text{ Moisture loss} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

Surface pH

Insert films were allowed to swell for 30 minutes in 1ml of double distilled water. These swollen films were then removed and placed under digital pH meter to determine surface pH.

Drug content

Five ocular inserts were taken and dissolved in 10ml of double distilled water and filtered. Some dilutions were made from the solution and absorbances were measured by UV-visible spectrophotometer (shimadu-1601) at 253nm.

***In vitro* diffusion study**

In vitro diffusion of the drug from different ocular inserts was studied using K-C diffusion cell. In the donor compartment of the cell ocular insert was placed and in receptor compartment isotonic buffer (pH 7.4) is placed. Egg membrane (semi permeable membrane) was placed between both the compartments. The surface of the membrane was in contact with media in receptor compartment. The media in receptor compartment is stirred continuously using a magnetic stirrer and temperature was maintained 37±0.5ºC. At definite time intervals, 1ml of aliquot of solution was withdrawn from receptor compartment and replaced with fresh buffer solution. The aliquots were analyzed spectrophotometrically at 253 nm [8,9,10].

Sterilization

Sterilization of ocular inserts was done by gamma radiation method before *in vivo* examination.

***In vivo* Drug release study**

Eye irritancy test was carried out with selected ocuserts before performing the *in vivo* release study. Then sterilized ocular inserts were used for *in vivo* drug release studies. Three groups each containing six rabbits was used to study the drug release *in vivo* formulations which showed the desired *in vitro* drug release. Selected ocular films were placed in the ocular sac of each rabbit while the other eye served as the control. At definite intervals (2, 4, 6, 8, 12, 24 hours) ocular films were taken out carefully from the cul-de-sac of each rabbit and analyzed for the drug content.

RESULTS AND DISCUSSION

Uniformity of thickness:

The thickness of ocusert was ranging from 0.309±0.0021mm to 0.412±0.0052mm. The formulations were not so thick to cause irritation in the eye.

Uniformity of weight:

The weight of the ocusert was found to be in the range of 14.5±0.05 to 18.7±0.03 mg. The uniformity of the weight of the films shows the good distribution of the excipients.

Drug content:

Drug content for various formulations was found to be 4.8±0.01 to 5.4±0.03 mg. Ocular inserts show good distribution of acyclovir.

Percentage moisture loss:

Results of this study revealed that formulation ACY17 (6.17±0.04) showed high moisture loss may be due to less hindrance offered by ethylcellulose (4%). Formulation ACY6 (3.11±0.01) showed less moisture loss might be due to presence of more hydrophilic polymer HPMC and high concentration of ethylcellulose (EC 6%). The formulations with low concentration of ethylcellulose (EC 4%) had more tendencies to lose moisture as compared to those containing high concentration of ethylcellulose.

Surface pH:

The surface pH of prepared inserts was found to be in range of 6.09 ± 0.026 to 7.41 ± 0.017**.** This indicated that the prepared inserts would be compatible with tear fluid and would not alter the pH of the tear fluid in the eye.

***In vitro* diffusion study:**

In-vitro drug release study for different formulations showed that these films were capable of extending the drug release upto 24 hr. The formulations which showed better physicochemical parameters with desired drug release were selected. The release of the drug from the selected formulations ACY 4 and ACY 17 were found to be 73.3 % and 86.04% at the end of 24 hours (**Fig 1**). The selected formulations were then evaluated for further studies such as eye irritation test, *in vivo* study and stability study.

Sterility study:

The inserts were sterilized using gamma radiation before carrying out the eye irritancy and *in vivo* drug release study. No microbial or fungal growth was seen in any of the formulations, which indicate that the films were sterilized completely.

Eye irritancy test

Results of this test showed that all inserts prepared using drug reservoir and ethylcellulose as rate controlling membrane were nontoxic and nonirritating to the eye, as total score was zero. Inserts were not expelled out of the cavity of eye of rabbits, suggests that the inserts dimension were appropriate for use.

***In vivo* drug release study**

Formulations ACY 4 and ACY 17 were chosen for further study. *In vivo* studies were performed using rabbits. The *in vivo* drug release study from formulation ACY 17 was found to be in accordance with that of the *in vitro* drug release study. There was no drag out of circular inserts at the time of experiment which suggests that the dimension was suitable as ocular inserts (**Fig 2**).

Stability study

Accelarated stability studies at elevated temperature and humidity showed no significant change in drug content after 180 days. Storage temperature of ocuserts showed in excess of 40°C. The overall degradation is less than 5%, a proposed shelf life of 2 years may be assigned to formulations.

Fig 1: *In-vitro* diffusion studies of selected formulations

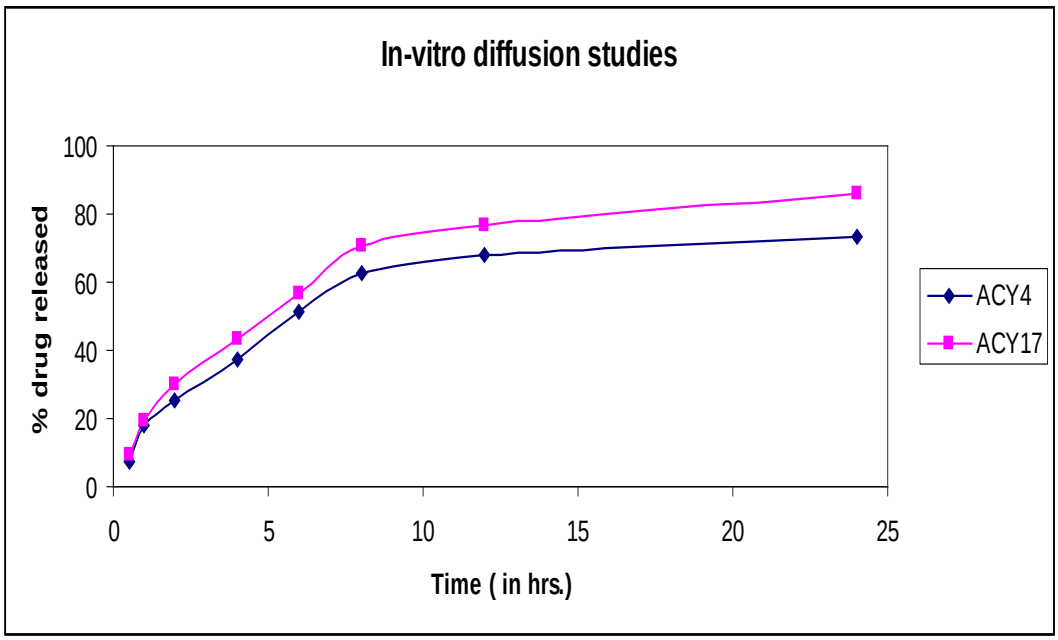

Fig 2: In-vivo studies of formulation ACY17

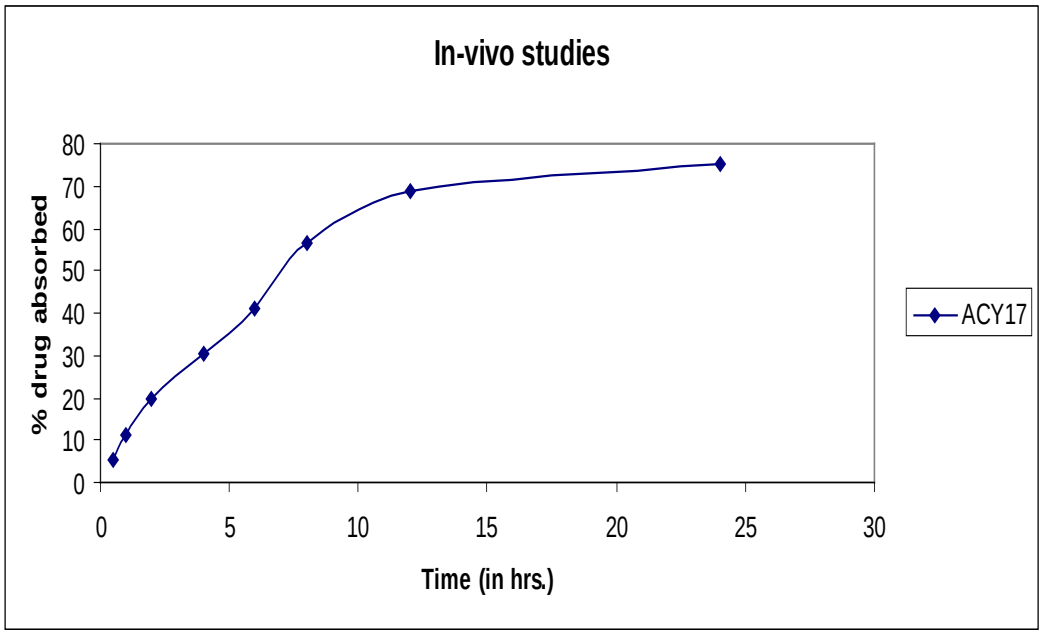

Table 1: Composition of acyclovir ocusert

Formulation code	Drug reservoir						Rate controlling membrane
	Drug	HPMC	PVA	Eudragit L-100	Drug: olymer Ratio	Plasticizer	
ACY1	150	75			1:0.5		4%
ACY2	150	75			1:0.5		6%
ACY3	150	150			1:1		4%
ACY4	150	150			1:1		6%
ACY5	150	175			1:1.5		4%
ACY6	150	175			1:1.5		6%
ACY7	150		150		1:1		4%
ACY8	150		150		1:1		6%
ACY9	150		300		1:2		4%
ACY10	150		300		1:2		6%
ACY11	150		450		1:3		4%
ACY12	150		450		1:3		6%
ACY13	150			150	1:1		4%
ACY14	150			150	1:1		6%
ACY15	150			300	1:2		4%
ACY16	150			300	1:2		6%
ACY17	150			450	1:3		4%
ACY18	150			450	1:3		6%

30 % of the weight of the polymer

Table 2: Physicochemical evaluation of ocular inserts

Formulation code	Weight	Thickness	Drug content	Surface pH	%Moisture absorption
ACY1	30.11±0.001	0.296± 0.0044	5.014±0.0012	6.83 ± 0.046	6.34 ± 0.231
ACY2	33.09±0.007	0.338± 0.0046	5.102±0.0008	6.75 ± 0.058	5.46 ± 0.190
ACY3	34.31±0.002	0.306± 0.0055	5.021±0.0032	6.56 ± 0.017	6.94 ± 0.140
ACY4	35.73±0.011	0.348± 0.0063	5.009±0.0011	6.75 ± 0.026	5.84 ± 0.177
ACY5	36.43±0.007	0.314± 0.0041	5.211±0.0009	6.77 ± 0.017	9.26 ± 0.201
ACY6	39.77±0.009	0.352± 0.0036	5.242±0.0012	7.13 ± 0.026	7.44 ± 0.286
ACY7	29.31±0.004	0.259± 0.0030	5.203±0.0022	6.50 ± 0.082	5.35 ± 0.121
ACY8	31.12±0.012	0.297± 0.0053	5.211±0.0009	6.67 ± 0.044	4.67 ± 0.191
ACY9	33.13±0.006	0.263± 0.0054	5.301±0.0011	6.25 ± 0.035	5.89 ± 0.226
ACY10	36.45±0.003	0.301± 0.0067	5.311±0.0022	6.40 ± 0.017	4.74 ± 0.137
ACY11	38.24±0.021	0.278± 0.0027	5.244±0.0009	7.41 ± 0.017	7.86 ± 0.166
ACY12	40.81±0.022	0.312± 0.0044	5.272±0.0011	6.09 ± 0.026	6.10 ± 0.231
ACY13	31.09±0.005	0.256±0.0012	5.341±0.0023	7.03 ± 0.093	4.92 ± 0.137

ACY14	32.71±0.009	0.301± 0.0021	5.441±0.0034	6.95± 0.033	4.67 ± 0.131
ACY15	34.65±0.025	0.328± 0.0011	5.314±0.0031	6.82± 0.041	5.46 ± 0.141
ACY16	38.31±0.021	0.358± 0.0013	5.423±0.0021	6.54± 0.043	5.25 ± 0.021
ACY17	39.04±0.041	0.377± 0.0022	5.442±0.0044	7.35± 0.054	5.84 ± 0.177
ACY18	41.74±0.055	0.394± 0.0032	5.421±0.0022	7.00± 0.044	5.11 ± 0.021

CONCLUSION

Various batches of acyclovir ocular inserts were prepared using solvent casting method and evaluated. The said promising formulation would be able to offer benefits such as increase residence time, prolonged drug release, reduction in frequency of administration and there by may help to improve the patient compliance with the limitation that formulation is non-erodible. Further work may be carried out to establish the therapeutic utility of this system by pharmacokinetic and pharmacodynamic studies in human beings.

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