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RESEARCH ARTICLE

Formulation Development and Evaluation of Opthalmic ocusert containing Aciclovir

S. Shanmugam[1] , S.Valarmathi[2*], S. Satheesh Kumar[2] , P. Shanmugasundaram[2], M. Senthilkumar[3]

[1]Adhiparasakthi College of Pharmacy, Melmaruvathur, Tamilnadu.
[2]School of Pharmacy, Vels University, Chennai, Tamilnadu.
[3]Annai Velankanni College of Pharmacy, Chennai, Tamilnadu.
*Corresponding Author E-mail: **sahanashree2012@gmail.com**

ABSTRACT:

The aim of formulating aciclovir occusert was to prolong the drug residence time after ocular administration to achieve the controlled release of drug. Aciclovir is a antiviral agent and its use in the treatment of viral infections like herpes simplex infections. Ocular inserts were prepared by solvent casting method. Drug reservoir and rate controlling membrane were prepared using different hydrophilic and hydrophobic polymers respectively with polyethylene glycol 400 as the plasticizer.DSC and IR spectral studies were performed to confirm the interaction of drug and polymers in formulation. The ocusert were evaluated for their physical and chemical and in vitro – release characteristics. The developed formulation was stable sterile and non irritant. The final formulation F2 was subjected to UV irritation for sterilization. In the present work it was concluded that the F2 formulation shows 99.16% controlled release upto 8 hrs when compared to other formulations.

KEYWORDS: Aciclovir, Ocusert, Hydroxy propyl cellulose, FTIR.

INTRODUCTION:

Ocuserts are sterile preparations which are to be placed into cul-de-sac or conjunctiva sac. The major aim of ocuserts is to maintain a therapeutic level at the site of action for prolonged period of time. The therapeutic efficacy of an ocular drug can be greatly improved by prolonging its contact with the corneal surface. Aciclovir is an antiviral agent effective against herpes simplex virus type 1 and 2.ocuserts gives several advantages like increased ocular residence time, drug release at a slow constant rate, accurate dosing, reduction of systemic absorption, better patient compliance, targeting internal ocular tissues. Occusert offers more bioavailability than other formulation. The ocular inserts are otherwise called as cul de sac inserts.Ocular inserts are prepared like sand witch model.

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MATERIALS AND METHODS:

Aciclovir was received as a gift sample from Kausikh therapeutics Pvt Ltd., Chennai. The polymers Hydroxy propyl cellulose, Polyethylene glycol 400, Eudragit RS 100, Ethyl cellulose were purchased from Nice Pharmaceuticals, Kerala. All other ingredients were of analytical grade.

HYGROSCOPIC STUDIES

2mg of aciclovir was taken in a petridish and exposed to room temperature and 2mg of aciclovir was taken in an another petridish and exposed to 40 ˚C after a week samples are weighed. In both the temperature the samples was weight not gained so there was no moisture absorption.

PREPARATION OF OCCUSERTS

Polymeric solutions were prepared by dissolving hydrophilic polymer HPC/PVA along with aciclovir and polyethylene glycol 400 in doubly distilled water.

The solutions were poured into a glass ring of 8.9 cm diameter placed in a Teflon coated petridish. The solvent was allowed to evaporate by placing it inside an oven maintained at 35 ˚C for 24 hrs.

PREPARATION OF RATE CONTROLLING FILMS

To prepare the rate controlling films hydrophobic polymer (ethylcellulose, eudragit RL 100) along with plasticizer Dibutyl phthalate was dissolved in ethanol/acetone (80:20). The solutions were poured into a glass ring 8.9 cm diameter petriplate. The solvent was allowed to evaporate at 25˚C for 24 hrs. Placing rate controlling film around, the drug reservoir and sealing them to obtain ocular inserts. The two rate controlling membranes containing the reservoir film between them were placed over a beaker saturated with ethanol/acetone vapors 60:40 for two minutes.

INTERACTION STUDIES

Interaction studies were conducted by comparing pure drug with polymers by FTIR Spectrophotometry.

EVALUATION OF OCUSERTS

The ocuserts were evaluated for thickness, folding endurance, drug content, surface pH, percentage moisture absorption, and percentage moisture loss and in-vitro diffusion studies.

THICKNESS OF OCUSERT

Using vernier caliper, the thickness was calculated at five different points on the film. The mean thickness and standard deviation (SD) were calculated.

WEIGHT VARIATION

Using digital weighing balance, the weight variation was determined. The inserts were subject to weight variation by individual weighing of 5 randomly selected inserts and mean was calculated.

FOLDING ENDURANCE

Folding the inserts repeatedly at the same place in the center till it breaks between the thumb and finger. Folding endurance value is the number of times the film folded at the same place without breaking gives folding endurance value.

SWELLING INDEX

Three films were weighed and placed separately in beakers containing 4ml water.

At regular time intervals (5mins) the films are removed and the excess water on their surface was removed using a filter paper and then weighed again, continued un till there is no increase in weight.

$\%SW = (W_T - W_O) \times 100$

%SW = Percentage swelling index

W_T = Weight of swollen insert after time T

W_O = Weight of insert at 0 time

SURFACE pH

Inserts were allowed to swell in a closed petridish at room temp for 30 mins in 0.1 ml distilled water .The swollen inserts are placed in a beaker containing distilled water. A combined glass electrode was brought in contact with the ocusert and pH was measured.

DRUG CONTENT

Assay the individual inserts for drug content. Three inserts from each batch were powdered individually and dissolved in 100 ml of water by stirring in a magnetic stirrer for 2 hours. The absorbance of each solution was measured on UV visible spectrophotometer at 254 nm.

PERCENTAGE MOISTURE ABSORPTION

To check the physical stability of the occusert at high humid condition. The occuserts were pre weighed accurately kept in a desiccators containing 100ml of saturated solution of aluminum chloride. After 3 days the films are taken out and weighed again. The percentage moisture absorption was calculated.

% MA =
{Final weight – Initial weight/ initial weight} x 100

PERCENTAGE MOISTURE LOSS

To check the integrity of occusert at dry condition. The occuserts are weighed and kept in a desiccators containing anhydrous calcium chloride for 3 days. After 3 days the films are taken out and weighed.

% ML =Initial weight –Final weight/Final weight x100

INVITRO-DIFFUSION STUDIES

Studied using standard open ended cylindrical glass tube. The pre hydrated cellophane was tied to one end of cylindrical tube which act as a donor compartment. An opthalmic insert was placed inside the donar compartment. The receptor compartment containing 25 ml of simulated tear fluid in 100 ml beaker. The content of the receptor compartment was stirred using magnetic stirrer at 37ºC.±0.5 ºC. At specific time interval 1ml of simulated fluid from receptor compartment was withdrawn and replaced with fresh simulated tear fluid. The withdrawn samples are diluted and analyzed using UV at 254 nm.

RESULTS AND DISCUSSION:

Thickness specifications may be set on an individual product basis. There were no marked variations in the thickness of occuserts within each formulation indicating uniform behavior of film throughout the

sealing process. The thickness of the ocuserts of all formulations was tabulated. FTIR peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates drug is compatible with the formulation components.

From each batch randomly five ocuserts were selected and weighed. It ranges from 5.3 to 6.0 mg. The weight variations of ocuserts of all formulations were tabulated. 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 10ml) displayed little opaqueness and good folding endurance.
To investigate irritation in eye, surface pH was determined. Tear fluid having pH 7.4.Generally for ophthalmic formulation must in the range between 4.5 and 11.5.To prevent corneal damage, ophthalmic formulation should have pH range of 6.5 to 8.5.Surface pH of ocuserts from batch were measured and tabled.
Percentage moisture absorptions were observed from 4% to 9%.Percentage moisture loss were observed from 6% to 9%.Though 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 tabulated.

Formulated a soluble drug insert of aciclovir for its novel drug delivery containing natural hydrophilic polymer Hydroxypropyl cellulose and hydrophobic polymer Ethyl cellulose using solvent casting method. Increases contact time, achieving controlled release, decrease in frequency of administration, increased patient compliance and greater therapeutic efficacy. The formulation F2 containing aciclovir and 4 mg hydroxy propyl celulose sandwiched between ethylcellulose as polymer satisfied required pharmaceutical characteristics of ocular inserts was found to be promising. From the invitro diffusion study it was concluded that F2 formulation shows more release 99.16% with controlled characteristics of 8 hrs when compared to other formulations.

Table:1 Formulation of aciclovir

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
PREPARATION OF DRUG RESERVOIR								
Aciclovir*	10	10	10	10	10	10	10	10
HPC*	2	4	-	-	2	4	-	-
PVA**	-	-	2	4	-	-	2	4
PEG 400**	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Distilled water	10	10	10	10	10	10	10	10
PREPARATION OF RATE CONTROLLING FILMS								
Ethyl cellulose*	4	2	4	2	-	-	-	-
Eudragit RL 100	-	-	-	-	4	2	4	2
PEG400**	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Acetone	10	10	10	10	10	10	10	10

*Quantity in %**quantity in ml

Table 2: Thickness, weight variation and folding endurance of aciclovir ocusert

S.No	**Formulation code**	**Thickness(mm)***	**Weight variation(mg)***	**Folding Endurance value ***
1	F1	0.218±0.007	5.72±0.127	70
2	F2	0.222±0.013	5.45±0.156	63
3	F3	0.247±0.017	5.36±0.143	78
4	F4	0.235±0.012	6.01±0.129	71
5	F5	0.243±0.015	5.43±0.167	64
6	F6	0.240±0.009	5.72±0.127	76
7	F7	0.236±0.012	5.90±0.187	78
8	F8	0.236±0.010	6.01±0.198	71

All the values are expressed as mean ±S.D, n* = 3

Table 3: Surface pH and Swelling index of aciclovir ocuserts

S.No	**Formulation code**	**Surface pH**	**Swelling index %**
1	F1	7.40	95.21±0.145
2	F2	7.33	85.48±0.654
3	F3	7.93	79.94±0.768
4	F4	7.42	89.01±0.877
5	F5	7.39	82.78±0.234
6	F6	7.21	86.90±0.722
7	F7	7.67	94.59±0.881
8	F8	7.65	94.45±0.765

All the values are expressed as mean ±S.D, n=3

Table 4: Drug content uniformity of aciclovir ocuserts

S.No	Formulation code	%drug content ±SD
1	F1	96.55±0.243
2	F2	98.22±0.321
3	F3	97.32±0.500
4	F4	99.12±0.169
5	F5	97.21±0.157
6	F6	96.68±0.230
7	F7	97.77± 0.012
8	F8	96.44± 0.453

All the values are expressed as mean ±S.D, n=3

Table 5: Percentage moisture absorption and percentage moisture loss

S.No	Formulation code	Moisture loss%± SD	Moisture absorption%±SD
1	F1	6.12 ± 0.990	5.68 ± 0.04
2	F2	7.80 ±0.432	7.55 ±0.43
3	F3	8.09 ±0.030	8.98 ±0.99
4	F4	5.78 ±0.876	4.99 ±0.86
5	F5	9.08± 0.321	6.77 ±0.97
6	F6	5.67± 0.432	7.68 ±0.65
7	F7	8.90 ±0.876	9.07 ±0.54
8	F8	8.09 ±0.954	5.90 ±0.44

All the values are expressed as mean ± S.D, n=3

Table 6: Invitro diffusion study

S.No	Formulation code	Time in hrs	%Drug Release
1	F1	6hrs	98.14
2	F2	8 hrs	99.16
3	F3	5 hrs	95.61
4	F4	6hrs	96.18
5	F5	7hrs	96.74
6	F6	7hrs	96.92
7	F7	5hrs	94.12
8	F8	5 hrs	94.67

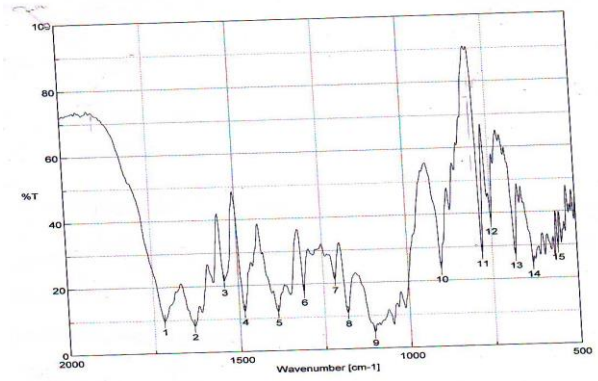

Fig.1: FTIR of Aciclovir with ethyl cellulose

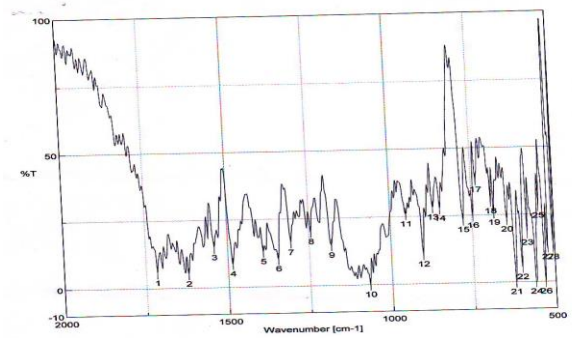

Fig.2: FTIR of Acyclovir with PEG 400

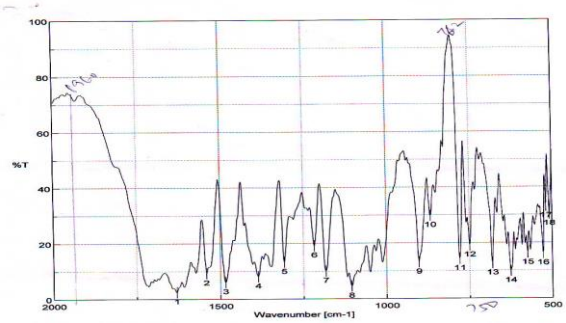

Fig.3: FTIR of Aciclovir

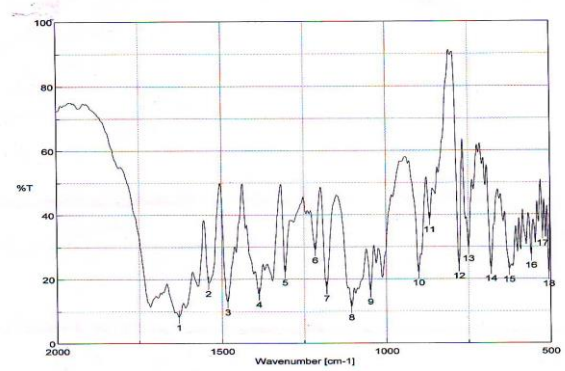

Fig.4: FTIR of Aciclovir with PVA

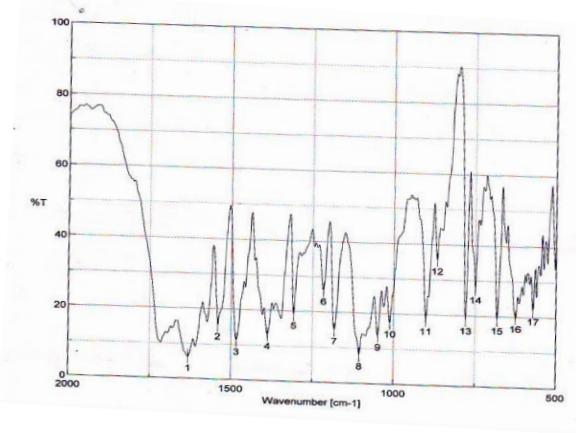

Fig.5: FTIR of Acyclovir with HPC

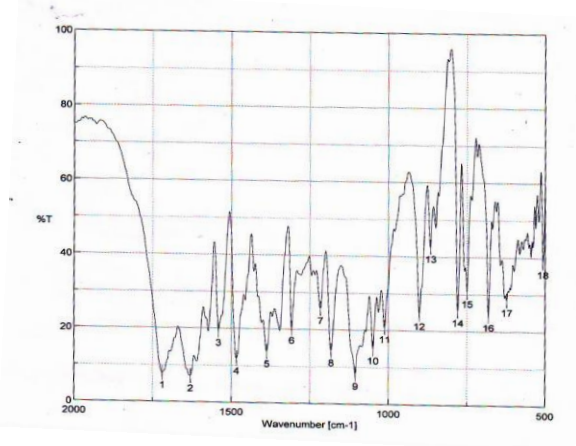

Fig.6: FTIR of Aciclovir with Eudragit RL 100

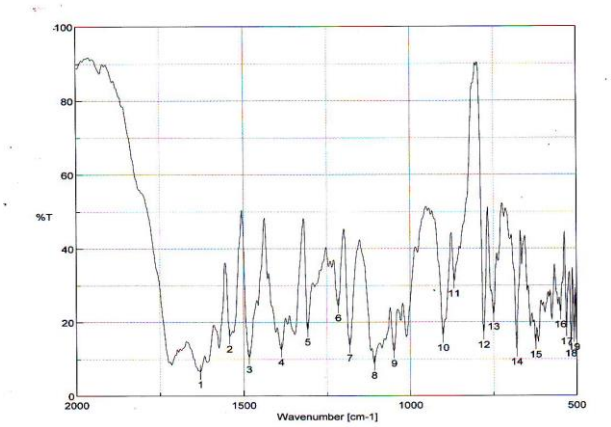

Fig.7: FTIR of Aciclovir with Dibutylpthalate

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