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Design and Evaluation of Novel Ophthalmic Delivery System of Acyclovir for Herpes Simplex Infection

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ABSTRACT

Acyclovir, an antiviral is effective against human Herpes Simplex viruses, commercially available as a 3 % w/w eye ointment to be applied 5 times a day in the eye. The poor therapeutic response exhibited by conventional ophthalmic ointments due to rapid precorneal elimination of the drug may be overcome by the use of an ocusert inserted in the cul-de-sac of lower eye lid. Inserts containing Acyclovir were prepared by using solvent casting method. Drug reservoir and rate controlling membrane were prepared using different hydrophilic and hydrophobic polymers respectively with Poly ethylene 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 physic chemical properties, mechanical properties and in-vitro release characteristics. A zero order release formulation VI was subjected to UV irradiation for sterilization. The developed formulation was stable, sterile and non-irritant

Keywords: Acyclovir, ocusert, diffusion, hydroxylpropyl methylcellulose, polyvinyl alcohol.

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INTRODUCTION

Topical application of ophthalmically active drugs is the most prescribed route of administration for treatment of various ocular disorders. It is generally agreed that the intraocular bioavailability of topically applied drug is extremely poor. This is mainly due to drainage of excess fluid by the nasolacrimal duct as well as dilution and elimination of the solution by tear turn over. Ocular bioavailability of drug is an important parameter influencing the efficacy of ophthalmic preparation. The commonly available ophthalmic ointments, although better retained than eye drops, do not efficiently release all types of drugs and they are poorly tolerated by many patients. Several approaches have been reported and numerous novel ophthalmic drug delivery systems were developed to achieve a higher bioavailability of drugs. Among these formulations are in-situ gel polymers, microspheres, nanoparticles, liposome and ocuserts [1, 2]. The advantages of ocuserts are solid devices placed in cul-de-sac of eye, in comparison with liquid formulation. Because of the prolonged retention of the device and a controlled release, the effective drug concentration in the eye can be ensured over an extended time period. Dosing of the drugs is also more accurate and the risk of systemic side effects is decreased. Ocuserts offers several advantages such as increased ocular residence time, drug release at a slow, constant rate, accurate dosing, reduction of systemic absorption, better patient compliance, possibility of targeting internal ocular tissues, increased shelf life with respect to aqueous solutions and absence of preservatives, thus reducing the risk of sensitivity reactions [3, 4]. The desired criteria for ocusert include comfort, lack of expulsion during wear, easy of handling and insertion, no interference with vision and oxygen permeability, stability and easy of manufacture. The objective of this study is to prepare ophthalmic inserts (ocusert) of Acyclovir in sand witch model using hydrophilic and hydrophobic polymers by film casting method. These ocuserts are sterile, soft, thin and flexible disks made of appropriate polymeric materials, fitting in to the lower or upper conjuctival sac [5, 6].

MATERIALS AND METHODS

Acyclovir was provided by Kausikh Therapeuticals Pvt. Ltd., Chennai. The polymers HPMC K4M, Polyvinylalcohol, Eudragit RL100, Eudragit RS100 were purchased from Paras pharmachem., Pune. All other ingredients were of analytical grade.

Formulation of ocular inserts for controlled delivery

The preparation of ocular inserts involved three steps

Preparation of the drug containing reservoir film of hydrophilic polymers

For preparation of the drug containing reservoir film, polymeric solutions were prepared by dissolving hydrophilic polymer (HPMC/PVA), along with Acyclovir and poly ethylene glycol

400, in doubly distilled water. The solutions were poured into a glass ring of 8.9 cm diameter placed in a Teflon coated Petri dish. The solvent was allowed to evaporate by placing it inside an oven maintained at 35 ± 2°C, 30 ± 0.5% RH for 24 h [7, 8, 9].

Table 1: Formulation table

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Preparation of Drug Reservoir								
Acyclovir*	10	10	10	10	10	10	10	10
HPMC K4M*	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 Membrane								
Eudragit RS100*	4	2	4	2	-	-	-	-
Eudragit RL100*	-	-	-	-	4	2	4	2
PEG 400**	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

Preparation of rate controlling films

To prepare the rate controlling films, hydrophobic polymer (Eudragit RS100/ Eudragit RL100), along with plasticizer, dibutyl phthalate were dissolved in ethanol/acetone (80:20) mixture. The solutions were poured into a glass ring of 8.9 cm diameter placed in a Teflon coated Petri plate. The solvent was allowed to equilibrate at 25 ± 0.5° C, 45 ± 0.5 % RH for 24 h [10, 11, 12].

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

Circular shaped ocular inserts were cut out of medicated reservoir film with the help of a cork borer (special device).These ocular inserts were placed on a rate-controlling membrane and another rate controlling membrane was kept over it. The two rate controlling membranes containing the reservoir film between them were placed over a beaker saturated with ethanol/acetone vapors (60:40) for 1–2 minutes. The final ocular inserts consisted of three films; reservoir films containing the drug were sandwiched in between the rate controlling membrane to control the release. Each ocular insert contained 1mg of the drug. The ocular inserts were stored in an airtight container under ambient conditions [13, 14].

Interaction studies

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

Evaluation

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

Thickness

Insert thickness was measured by a Vernier caliper at five different points on the film. The mean thickness and standard deviation (SD) were calculated [15].

Weight variation

Weight was calculated by digital balance. The inserts were subjected to weight variation by individual weighing of 5 randomly selected inserts and mean was calculated [16].

Folding Endurance

Folding Endurance of the film was determined by repeatedly folding the inserts at the same place till it breaks. 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 [17].

Swelling studies

Three films were weighed and placed separately in beakers containing 4 ml of distilled water. At regular intervals of time (every 5 min), the films were removed and the excess water on their surface was removed using a filter paper and then again weighed. The procedure was continued till there was no increase in the weight. The percentage swelling index was then calculated using this formula [18]

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

Where,

%SW = percentage swelling index;

W_T = weight of swollen insert after time T;

W_O = original weight of insert at zero time;

Surface pH

Surface pH of ocuserts was determined in order to investigate the possibility of any side effects in an eye. Attempt was made to keep the surface close to the tear fluid pH. Inserts were allowed to swell in a closed Petri dish at room temperature for 30 minutes in 0.1 ml of double distilled water. The swollen inserts were removed and placed in distilled water in a beaker. A combined glass electrode was brought in to contact with the ocusert and pH was measured [19].

Drug content

Uniformity of drug content was determined by assaying the individual inserts. Three inserts from each batch were powdered individually and each was dissolved in 100 ml of purified water by stirring on a magnetic stirrer for 2 hours. The absorbance of each of these solutions was then measured on UV-visible spectrophotometer at 254 nm.

Percentage moisture absorption

Percentage moisture absorption test was carried out to check the physical stability of the ocusert at high humid condition. The ocuserts were pre weighed accurately and kept in desiccators containing 100 ml of saturated solution of aluminum chloride. After 72 hours (3 days), the films were taken out, weighed and percentage moisture absorption was calculated by using formula [20]

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

Where, %MA = percentage moisture absorption

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 [20]

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

Where, %ML = percentage moisture loss

In-vitro diffusion studies

The in-vitro drug release studies were carried out using diffusion cell. 0.7 ml of isotonic phosphate buffer of pH 7.4 was placed in the donor chamber, which acted as tear fluid. Ocusert was placed in the donor compartment over a dialysis membrane. 25 ml of isotonic phosphate buffer was taken as the receptor medium and the apparatus was maintained at 37° ± 2° C and was continuously stirred using magnetic stirrer. The samples were withdrawn at regular intervals and analyzed at 254 nm [21].

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RESULTS AND DISCUSSION

Thickness

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

Formulation Code	Thickness (mm)**	Weight variation (mg) **	Folding endurance *
F1	0.228±0.009	5.6±0.122	73
F2	0.240±0.012	5.84±0.167	69
F3	0.240±0.012	5.86±0.151	73
F4	0.240±0.012	5.90±0.200	64
F5	0.244±0.014	5.94±0.167	77
F6	0.236±0.008	5.92±0.130	78
F7	0.244±0.014	6.00±0.158	70
F8	0.244±0.014	6.06±0.167	65

All the values are expressed as mean± S.D., ** n=5, *n=3

Thickness specifications may be set on an individual product basis. 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 tabled.

Weight variation

From each batch randomly five ocuserts were selected and weighed. It ranges from 5.6 to 6.0 mg. The weight variations of ocuserts of all formulations were tabled.

Folding endurance

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.

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Swelling index

Table 6: Swelling index of Acyclovir ocusert

S. No.	Formulation	% swelling index ± SD
1	F1	89.08 ± 0.163
2	F2	91.86 ± 0.697
3	F3	83.61 ± 0.614
4	F4	85.46 ± 0.723
5	F5	91.05 ± 0.862
6	F6	92.65 ± 0.801
7	F7	83.51 ± 0.254
8	F8	83.60 ± 0.224

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

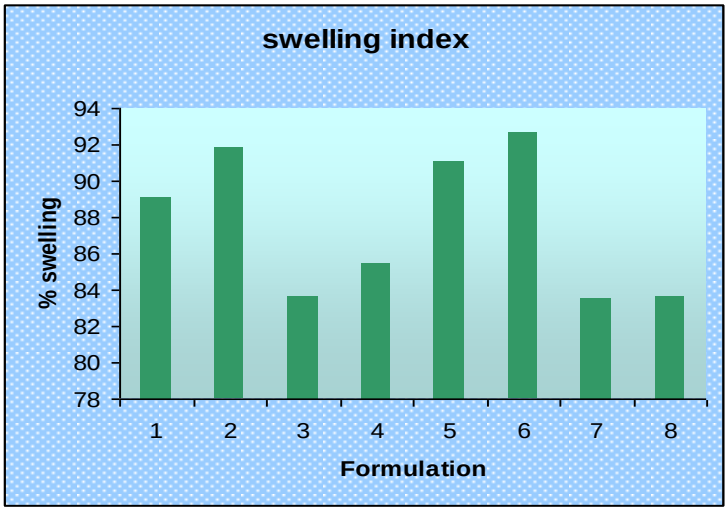

Figure 3: Swelling index of Acyclovir ocusert

Previously weighed ocusert was placed in distilled water and they were taken and weighted for each hour until it become constant. Swelling index was calculated and tabled.

Surface pH

Table 4: Surface pH of Acyclovir ocusert

S. No.	Formulation code	pH
1	F1	7.50
2	F2	7.80
3	F3	7.62
4	F4	7.60
5	F5	7.68
6	F6	7.54
7	F7	7.70
8	F8	7.68

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To investigate irritation in eye, surface pH was determined. Tear fluid having pH 7.4. Generally for ophthalmic formulation must in the pH 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 each batch were measured and tabled.

Drug content

Table 5: Drug content uniformity of Acyclovir ocuserts

S. No.	Formulation code	% drug content ± SD
1	F1	98.32 ± 0.209
2	F2	97.77 ± 0.478
3	F3	98.43 ± 0.065
4	F4	98.35 ± 0.230
5	F5	98.36 ± 0.167
6	F6	99.16 ± 0.258
7	F7	96.68 ± 0.183
8	F8	96.04 ± 1.600

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

Results of the content uniformity test complied with the BP 2005 requirements. These results showed that the method for the preparation of inserts gave reproducible results.

Percentage moisture absorption and Percentage moisture loss

Figure 2: Percentage moisture absorption and moisture loss of ocuserts

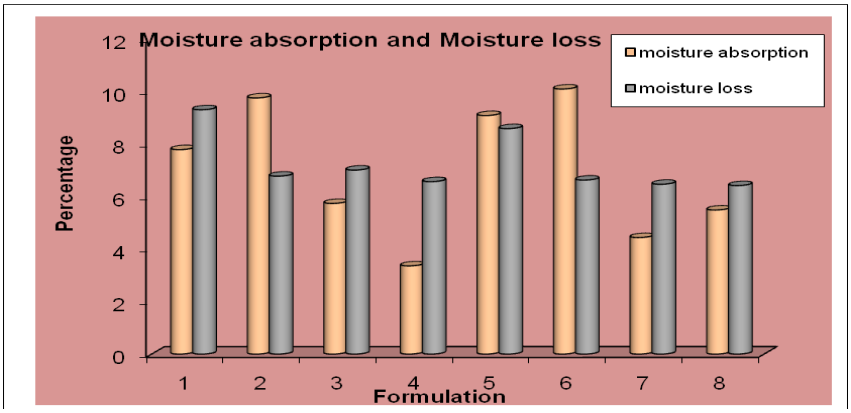

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Table 3: Percentage moisture absorption and percentage moisture loss

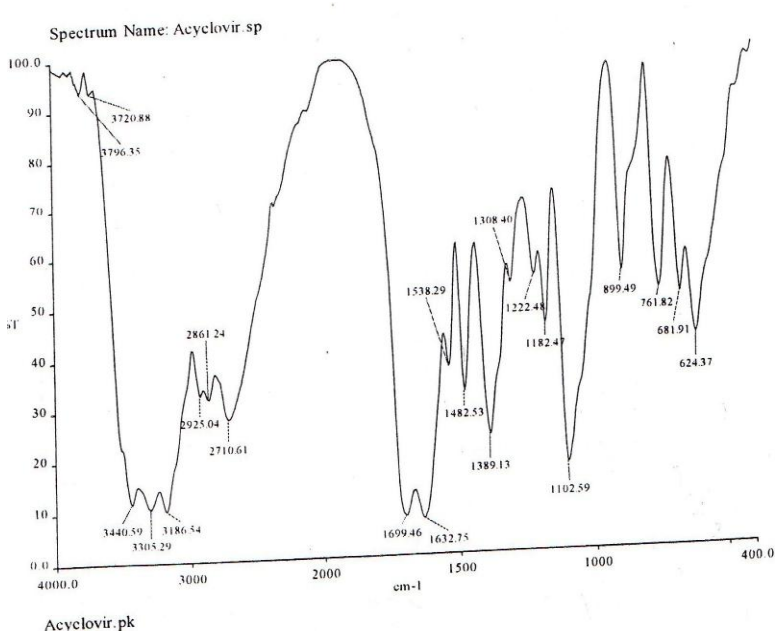
S. No.	Formulation code	% moisture absorption* ± SD	% moisture loss* ± SD
1	F1	7.79 ± 0.919	9.31 ± 0.08
2	F2	9.76 ± 0.810	6.78 ± 0.87
3	F3	5.74 ± 0.810	7.01 ± 0.95
4	F4	3.36 ± 0.020	6.57 ± 0.98
5	F5	9.09 ± 0.880	8.59 ± 0.93
6	F6	10.10 ± 0.075	6.63 ± 0.90
7	F7	4.44 ± 0.780	6.47 ± 0.85
8	F8	5.49 ± 0.820	6.42 ± 0.82

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

Percentage moisture absorptions were observed from 3% to 10%. Percentage moisture losses 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 tabled.

In-vitro drug release

Figure 1 : IR spectral studies



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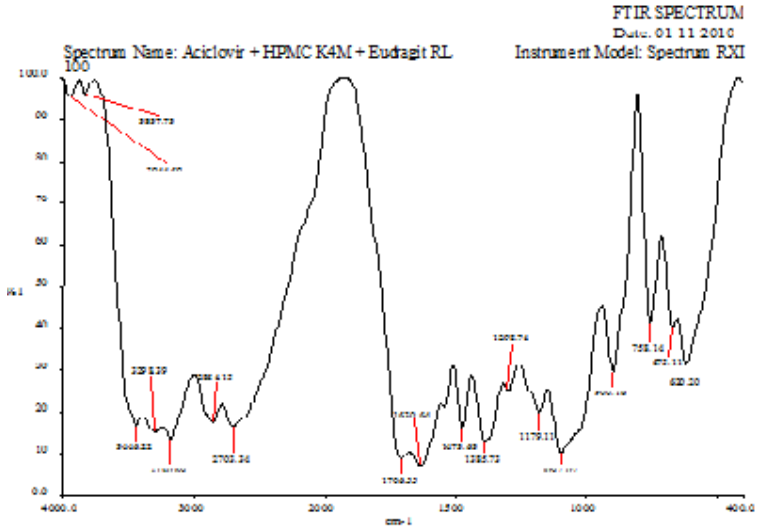

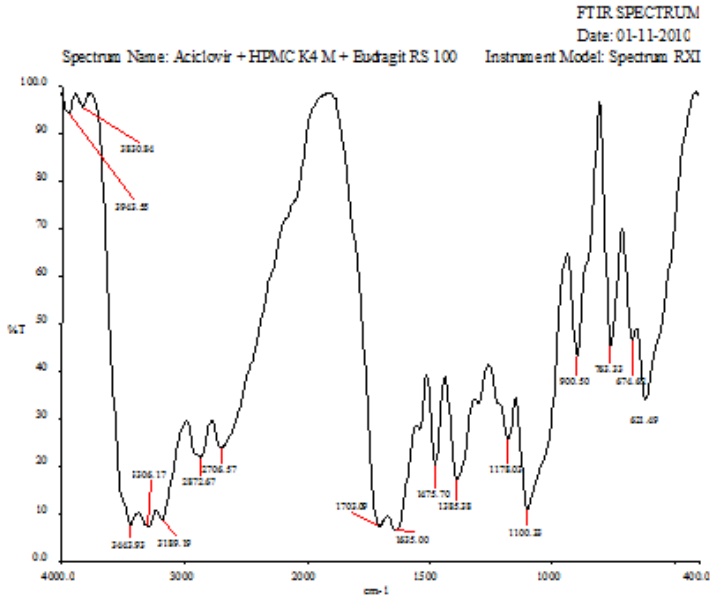

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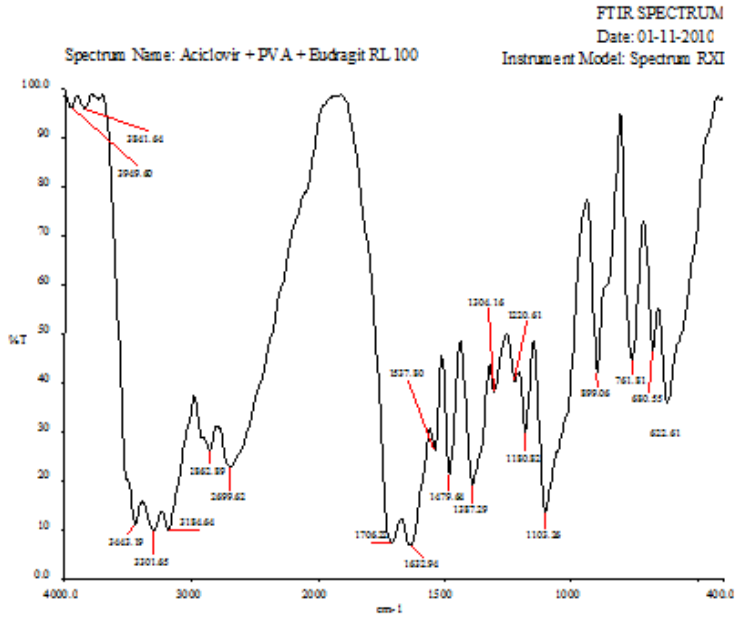

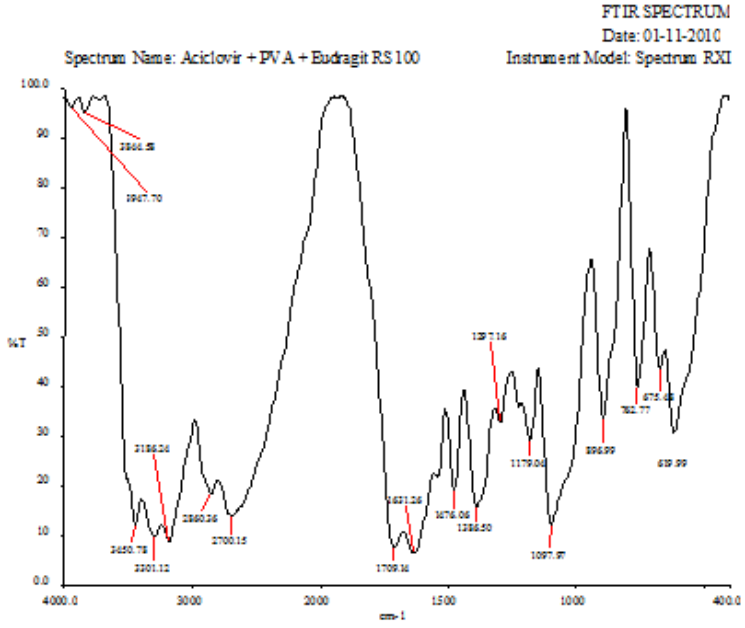

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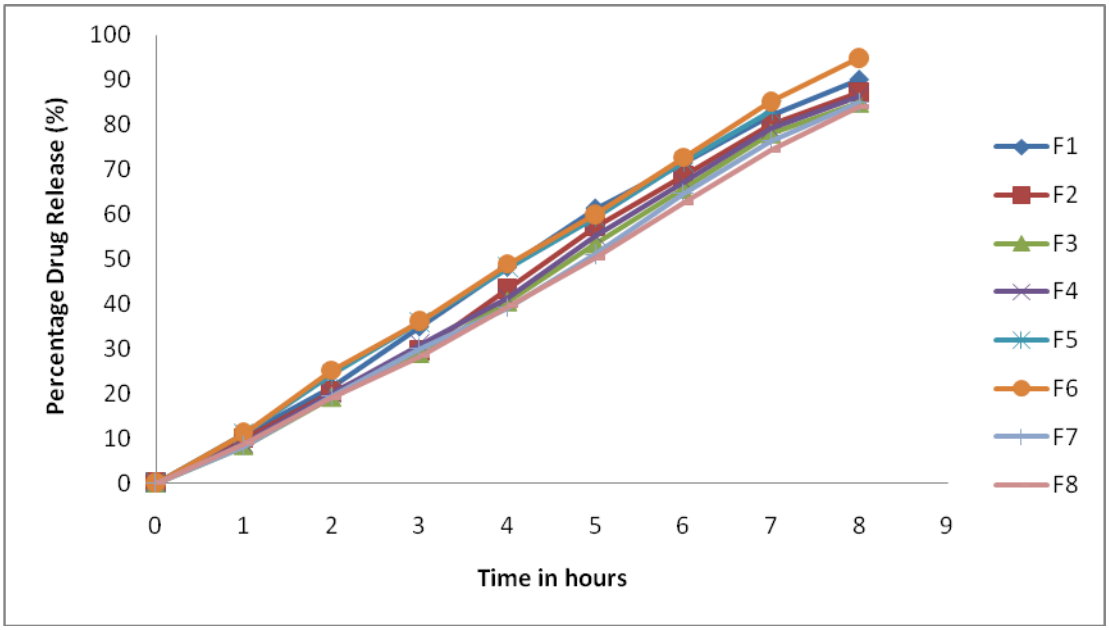

Figure 4: *In-vitro* drug release of Acyclovir ocusert

In-vitro drug release revealed that 94% of drug released from the formulation F6 containing 4% HPMC and 2% Eudragit RL100 in combination through an semi permeable dialysis membrane over an extended period of 8 hours as depicted in figure

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