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Original article

FORMULATION AND EVALUATION OF CONTROLLED DELIVERY OF ACECLOFENAC THROUGH OCULAR INSERT

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Abstract

Eye drops and eye ointments are conventional ocular dosage forms. They have certain disadvantages like repeated administration, poor availability, massive and unpredictable doses, and drainage of medication by tear fluid. To overcome these problems ocular inserts may be used and they provide several advantages as they increase ocular residence, possibility of releasing drug at a slow constant rate, accurate dosing and increased shelf life with respect to aqueous solutions. Aceclofenac is an excellent non steroidal anti-inflammatory drug. An attempt has been made ocular inserts were prepared by using hydroxy propyl methyl cellulose (HPMC) and ethylcellulose (EC) alone and in combination. Weight variation, thickness, drug content, pH, % moisture absorption, folding endurance, ocular irritation and stability of medicated inserts were evaluated. In vitro transcorneal permeation study was carried out by using a goat cornea. According to the results, 98.24% of drug was released from the formulation containing 3% HPMC and for 3% ethylcellulose 70.25% of drug was released for a period of 24 h. Release followed zero order kinetics. Medicated inserts were subjected to UV irradiation and in-vivo ocular irritation studies were carried out. No significant change was observed in the drug content and physical features during storage at 25°C and 40°C for 9 months. From this study it was concluded that ocular inserts prepared with 3% HPMC and 3% EC in combination showed sustained release and were found to be stable. Formulation of aceclofenac ocular insert achieved the proposed objective by increasing contact time, controlled drug release and decreased frequency of administration.

Key words: *Aceclofenac, HPMC, EC, Ocular inserts.*

Aseklofenak'ın Formülasyonu ve Kontrollü Salımının Oküler İnsert ile Değerlendirilmesi

Göz damlaları ve merhemleri konvansiyonel oküler dozaj şekilleridir. Bu dozaj şekilleri tekrarlı uygulama, düşük yararlanım, yüksek ve tahmin edilemeyen dozlar ve ilacın gözyaşı ile drenajı gibi bazı sakıncalara sahiptir. Bu problemleri aşmak için oküler insertler kullanılabilir ve bu insertler oküler kalış süresini artırma, ilacı yavaş, sabit hızda salma olasılığı, doğru dozlama ve sulu çözeltilere göre artmış raf ömrü gibi avantajlar sağlarlar. Aseklofenak mükemmel bir non steroidal anti-inflamatuvar ilaçtır. Çalışmada hidroksipropil metil selüloz (HPMC) ve etil selüloz (EC) tek başına veya kombine halde kullanılarak oküler insertler hazırlanmıştır. İnsertlerin ağırlık değişkenliği, kalınlık, ilaç içeriği, pH, % nem absorpsiyonu, katlanma dayanıklılığı, oküler iritasyon ve stabilitesi değerlendirilmiştir. İn vitro transkorneal permeasyon çalışması keçi korneası kullanılarak gerçekleştirilmiştir. Sonuçlara göre, %3 HPMC ve %3 EC içeren formülasyonlardan ilacın %98.24'ü 24 saat sonunda salınmıştır. Salım sıfırıncı derece kinetiğini takip etmiştir. İlaçlı insertler UV radyasyona tabi tuulmuşlardır ve in vivo oküler iritasyon çalışmaları yapılmıştır. Formülasyonların 25°C ve 40°C'de saklanması sonucu ilaç içeriği ve fiziksel özelliklerinde herhangi bir değişiklik meydana gelmemiştir. Bu çalışmadan %3 HPMC ve %3 EC kombinasyonu içeren oküler insertlerin uzatılmış salım gösterdiği ve stabil olduğu sonucu çıkarılabilir. Aseklofenak oküler insert formülasyonu, ulaşılmak istenen artmış temas süresi, kontrollü ilaç salımı ve azaltılmış uygulama sıklığı amaçlarına ulaşmıştır.

Anahtar kelimeler: *Aseklofenak, HPMC, EC, Oküler insert.*

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INTRODUCTION

The field of Ocular drug delivery is one of the interesting and challenging endeavors facing the pharmaceutical scientist. The cornea is a transparent tissue in the eye that is responsible for the refraction of incoming light and is a multilayered tissue made up of three major cell layers: the epithelium, the stroma, and the endothelium (1). The most frequently used dosage forms i.e. ophthalmic solutions, suspensions and ointment dosage forms are clearly no longer sufficient to combat some present virulent diseases (2-4). That is ophthalmic solutions and suspensions are compromised in their effectiveness by several limitations, leading poor ocular bioavailability. Many people suffer from a wide variety of ocular diseases, many of which lead to visual impairment and ocular blindness. Certain ocular diseases are quite rare, whereas others, such as cataracts, age-related macular degeneration (AMD), and conjunctivitis, are very common, especially in the aging population. A rapid development of new technologies in ocular drug delivery and new drug candidates, including biologics, to treat these challenging diseases in the anterior and posterior segments of the eye have recently emerged. For increase of new drug candidates and novel delivery techniques for treatment of ocular diseases has recently accelerated. Controlled drug delivery to the eye is restricted due to these limitation imposed by the efficient protective mechanism. Ocular inserts have been developed in which the drug is delivered based on diffusional mechanisms. It delivers the drug at constant rate minimizing side effects by avoiding excessive absorption (5, 6). Aceclofenac is an excellent non steroidal anti-inflammatory, analgesic and antipyretic drug. Aceclofenac possesses better analgesic, antipyretic and anti-inflammatory efficacy than diclofenac and other NSAIDs which are frequently used in clinical therapy of arthritis and inflammation. Due to the lipophilic nature of the drug it will be better absorbed by skin and ophthalmic tissue and will show better action in conditions like conjunctivitis and post cataract inflammation conditions. Eye solutions 0.1% w/v of aceclofenac is available to treat ocular inflammatory conditions. Less ocular availability of topically applied eye drop is a matter of concern for longer time. To overcome the less bioavailability, usually eye drops with higher concentration are formulated or controlled release formulations have been formulated for many drugs. Aceclofenac is sparingly soluble in water hence high concentration formulations are not suitable. Controlled release of drug from ocular insert is an approach to increase drug availability. Amino acid derivative of certain drug (e.g acyclovir) have been reported to have enhance aqueous solubility along with improve ocular availability. In view of poor ocular bioavailability of aceclofenac we have envisage and made controlled release ocusert which can increase the corneal contact time and subsequent bioavailability. In the present study, an attempt has been made to formulate ocular insert of aceclofenac using suitable polymers like hydroxypropylmethylcellulose (HPMC) and ethyl cellulose (EC). 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

Aceclofenac, (Lupin Pune Research Park) Hydroxypropyl methylcellulose (HPMC 15 cps), Ethyl cellulose (EC 15 cps) were obtained from SD Fine chemicals, Mumbai, India. Dibutyl phthalate purchased from nice chemicals, Cochin. All other reagents and solvent used were of analytical grade.

Preparation of standard plot (UV method) in phosphate buffer (pH 7.4)

Weighed quantity of aceclofenac (10 mg) was dissolved in methanol and the volume made up to 100 ml with methanol to give a concentration of 100 µg/ml. From this stock solution different volumes were transferred into 10 ml volumetric flasks and volume were made 10 ml

with phosphate buffer, pH 7.4 to get different concentrations ranging from 2 to 14 µg/ml concentrations. The absorbance was measured at 275 nm against a blank using UV spectrophotometer. The experiment was repeated in triplicate and the average of three readings was taken to plot the standard curve.

Formulation

Preparation of drug reservoir

The aceclofenac ocular inserts were prepared by solvent casting method (7, 8).The twelve batches (F1 to F12) of formulation were prepared using drug and polymers such as (Table 3). The polymer was dissolved in ethanol (10 ml) to this solution under stirring condition. The weighed amount of aceclofenac (200 mg, passed through sieve# 400) was added to above solution and stirred for 12 h to get uniform dispersion. After proper mixing the casting solution (5 ml) was poured in clean glass petridish (area 50.59 cm^2) and covered with an inverted funnel to allow slow and uniform evaporation at room temperature for 48 h. The dried films thus obtained were cut by cork borer into circular pieces of definite size (8 mm diameter) containing 2.008 mg of drug (3, 4, 5). The ocular inserts were then stored in an airtight container (desiccators) under ambient condition.

Preparation of rate controlling membrane

The rate controlling membrane was prepared using different concentration of polymer (2%, 3%, 4% and 5%) and employing dibutyl phthalate as a plasticizer (Table 3). Dibutyl phthalate was used in the concentration of 30% w/w based on the weight of dry polymer. Films were prepared by solvent casting method using acetone as a casting solvent. After drying at room temperature circular rings of 10 mm diameter were cut using cork borer and the drug reservoir was sandwiched in between the two rate controlling membrane and sealing was done by applying chloroform on the edges of rate controlling membrane (9).

Characterization of prepared aceclofenac ocular inserts

Uniformity of weight

From each batch (n=3), inserts were taken out and weighed individually using digital balance (Asco, India). The mean weight of the insert was noted (9-12).

Uniformity of thickness

The thickness of the insert was determined using a Vernier caliper (Mitotoyo, Japan) at five separate points of each insert. For each formulation (n=3) inserts were taken. (10)

Drug content

Ocular inserts were taken from each batch and dissolved or crushed in 10 ml of isotonic phosphate buffer pH 7.4 in a beaker and were filtered into 25 ml volumetric flask and the volume was made up to the mark with buffer. One ml of the above solution was withdrawn and the absorbance was measured by UV-VIS spectrophotometer (Systronics -2202, India) at 275 nm after suitable dilutions (11-12).

% Moisture absorption

The percentage moisture absorption test was carried out to check physical stability or integrity of the film at humid condition. The films were weighed and placed in desiccators containing saturated solution of aluminum chloride and 84% humidity was maintained (12). After three days, the films were taken out and weighed (13). The % moisture absorption was calculated using the formulae.

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

Surface pH

The aceclofenac inserts were allowed to swell in closed petridish at room temperature for 30 minutes in 0.1 ml of by distilled water. The swollen device was removed and placed under digital pH meter (Elico, India) to determine the surface pH (14-16).

Folding endurance

Folding endurance was determined by repeatedly fold the film at the same place till breaking or first sign of breaking. The number of time the film could be folded at the same place without breaking gives the folding endurance value.

Fourier Transform Infrared Spectroscopy

The spectrum was recorded in the region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug and drug- excipient mixture, 1:1 ratio) in KBr (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained. Spectra were recorded.

Differential Scanning Calorimentry

Thermal properties of the pure drug and the physical mixture of drug and excipients were analyzed by Shimadzu DSC-60, Shimadzu Limited Japan. The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350^{0}C at a heating rate of 10C/ min, using nitrogen as blanket gas.

In-vitro transcorneal permeation studies

Whole eye ball of goat was transported from local butcher shop to the laboratory in cold (4°C) normal saline within 1 hour of slaughtering the animal. The cornea was carefully excised along with 2 to 4 mm of surrounding scleral tissue and was washed with cold normal saline till the washing was free from proteins. As in (Figure 1), Isolated cornea was mounted by sandwiching surrounding scleral tissue between clamped donor and receptor compartments of an all glass modified Franz diffusion cell in such way that its epithelial surface faced the donor compartment. The receptor compartment was filled with 15 ml of freshly prepared buffer solution. One square cm of ocular film was placed on the cornea and opening of the donor compartment was sealed with a glass cover slip, while the receptor fluid was maintained 35°C with constant stirring, using Teflon coated magnetic stir bead. Three ml sample was withdrawn from receptor compartment at various time intervals up to 24 hours and was analyzed spectrophotometrically at 275nm. Each sample withdrawn was replaced with equal volume of buffer (17,18).

Figure 1. Goat cornea

Stability study

All regulatory bodies accept only real time data for any drug or pharmaceutical for purpose of assessing the shelf life. Only accelerated stability studies might serve as a tool for

formulation screening and stability issues related to shipping or storage at room temperature. The accelerated stability studies were carried out in accordance with the ICH guidelines (19). A sufficient number of ocular inserts (packed in aluminum foil) were stored in humidity chamber, with relative humidity of 75 % and at temperature of 40 ± 0.5°C and long term testing 25°C±2°C, 60%RH. The samples were tested for drug content after 0, 3, 6 and 9 months respectively. The results (Table-6) showed that there was no change in physical appearance of ocular insert. The drug content showed no marked change after nine months and formulation F2 passed the stability test. These results concluded that ocular insert F2 was chemically, physically and microbiologically stable at room temperature for 9 months. However, further studies at different temperatures and humidity conditions are needed to establish their shelf life.

UV irradiation and In vivo ocular irritation test

Approval for the use of animals in the study was obtained from the Banasthali University. Animal Ethics Committee (Banasthali University, Rajasthan, India, Ref.No.BU/BT/184/11-12). New Zealand rabbits of either sex weighing 2.8 to 4.1 kg were used to measure the in vivo ocular irritation test in the eye. Free leg and eye movement was allowed. There were 6 animals in the experimental group and 3 animals in the control group. Both eyes of the control group animals received normal saline. The ocular insert were sterilized by using UV radiation before in vivo study. The ocular insert and other materials were exposed to UV radiation for 1 hour. After sterilization, ocular insert were transferred into polyethylene bag with the help of forceps inside the sterilization chamber itself. The ocular safeties of the ocular inserts were done by the Draize test (Must be "times new roman"). The observations based on scoring approach established the safety of the developed ocular inserts in rabbit eye. The ocular inserts were inserted in both eyes of all animals in the experimental group. Three ocular inserts were removed after each 24 hours from eye of animals of the experimental group. This was repeated for 5 days, namely at each 24-h time point. The amount of drug remaining in each ocular insert was determined as per the assay method of drug in ocular inserts given in interaction studies. Cumulative percent drug released (CDR) in vivo was calculated. (20-22)

Table 1. Draize irritancy test for ocular safety

Ocular tissue	Scoring scale	Calculations	Total
Cornea: Opacity (O)	0,1,2,3,4	O×A×5	80
Area involved (A)	0,1,2,3,4		
Iris: Values for congestion and hemorrhage (I)	0, 1, 2	I×5	10
Conjunctiva : Redness (R)	0, 1, 2, 3		
Chemosis (C)	0, 1, 2 , 3, 4	(R+C+D)×2	20
Discharge (D)	0, 1, 2, 3		
		Total Maximum	110

Note: Score of 0 is normal, 3 and 4 is severe in case of O, R, C and D., Score of 0 is none, 1,2,3,4 is the extent of cornea covered for A. Score of 0 is normal and 2 is severe in case of I.

Table 2. Safety evaluation chart

Score	Rating
0.0– 0.5	Non irritating
0.5 – 2.5	Practically non irritating
2.5 – 15	Minimally irritating
15.0 – 25.0	Mildly irritating
25.0 – 50.0	Moderately irritating
50.0 – 80.0	Severely irritating
80.0 – 110.0	Extremely irritating

RESULT AND DISCUSSION

Preparation of standard plot (UV method) in phosphate buffer (pH 7.4)

The absorbance was measured at 275 nm against a blank using UV spectrophotometer. The experiment was repeated in triplicate and the average of three readings was taken to plot the standard curve. The figure 1 showed the standard plot of phosphate buffer saline pH 7.4.

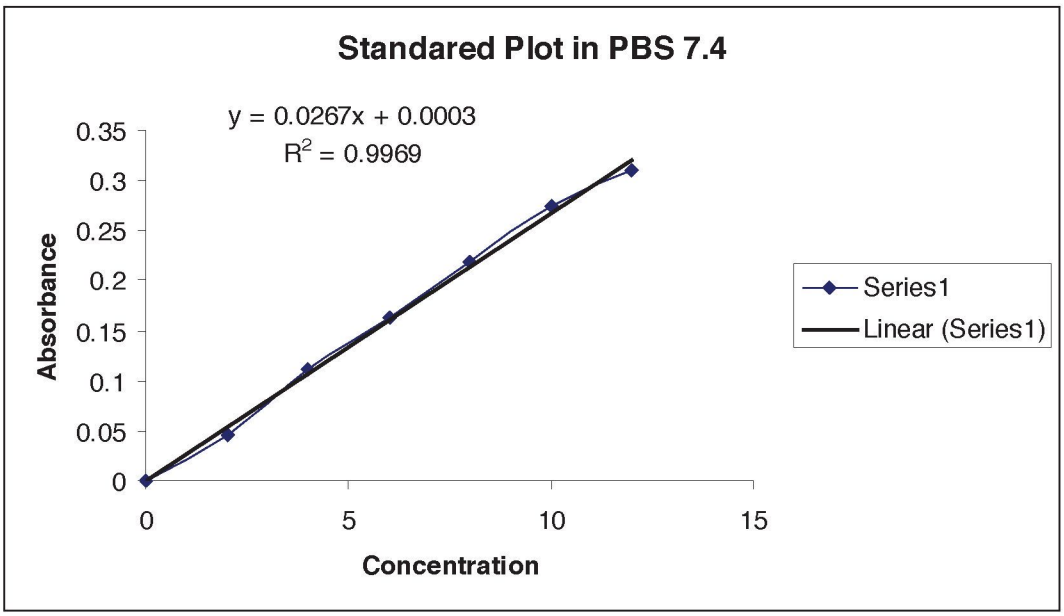

Figure 2. Standard Plot of Aceclofenac in phosphate buffer pH 7.4

Uniformity of weight

The weights of the aceclofenac ocular inserts were found to be in the range of 51 ± 0.3 mg to 76 ± 0.7 mg (Table 4). The uniformity of the weights of the films indicates good distribution of the drug, in polymer and plasticizer

Uniformity of thickness

The thickness of the aceclofenac ocular insert varied between 0.33±0.017 mm to 0.55±0.045 mm. (Table 4) The formulations did not produce any irritation when placed in the cul de sac since they were not thick enough to produce irritation.

Drug content

For the various formulations (F1 to F12) of aceclofenac ocular insert drug content was found to vary between 1.68 ± 0.061 to 2.19 ± 0.025 mg (Table 4). The drug content was found to be almost same with their low standard deviation values.

% Moisture absorption

The % moisture absorption study revealed that formulation F8 (8.69 ± 0.16) showed high moisture loss may be due to less hindrance offered by ethyl cellulose (5%). Formulation F2 (5.5 ± 0.24) showed less moisture loss might due to presence of more hydrophilic polymer (HPMC). The results are shown in the Table 4.

Surface pH

The surface pH of prepared inserts was found in range of 6.24 ± 0.024 to 7.63 ± 0.056 (Table 4). This indicates that the prepared inserts would not alter the pH of the tear fluid in the eye.

Folding endurance

Folding endurance of aceclofenac ocular insert was measured of breaking strength and endurance. This is the number of time the film may be folded at one place until it breaks or sign of breakage. The various formulations (F1 to F12) of aceclofenac ocular insert folding endurance were found to be 49.21±1.67 to 65.45±2.54. This result shows enough strength of ocular insert to withstand handling shock.

Fourier Transform Infrared Spectroscopy

The FTIR spectra of pure drug aceclofenac, placebo formulations (without drug) and drug loaded ocular inserts were recorded. The results are shown in the Figure 3 to 6 .C=O stretching of COOH and CH bending of CH3 group respectively confirms the presence of drug in the polymer without any interaction and the peaks at 1857.95 nm, 2553.01 nm, 3027.69 and 963.53 nm show as major peaks for drug. All the above peaks are also present in drug loaded ocular inserts.

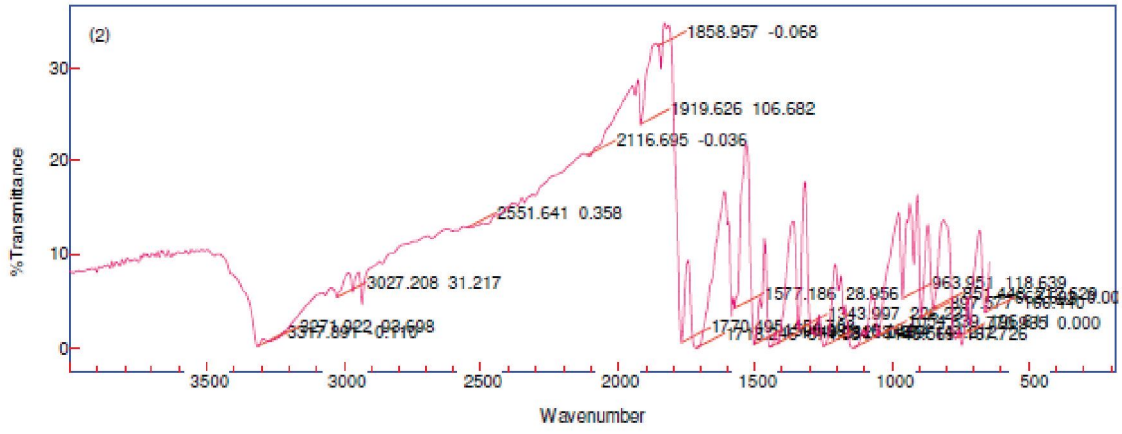

Figure 3. IR spectra of pure Aceclofenac

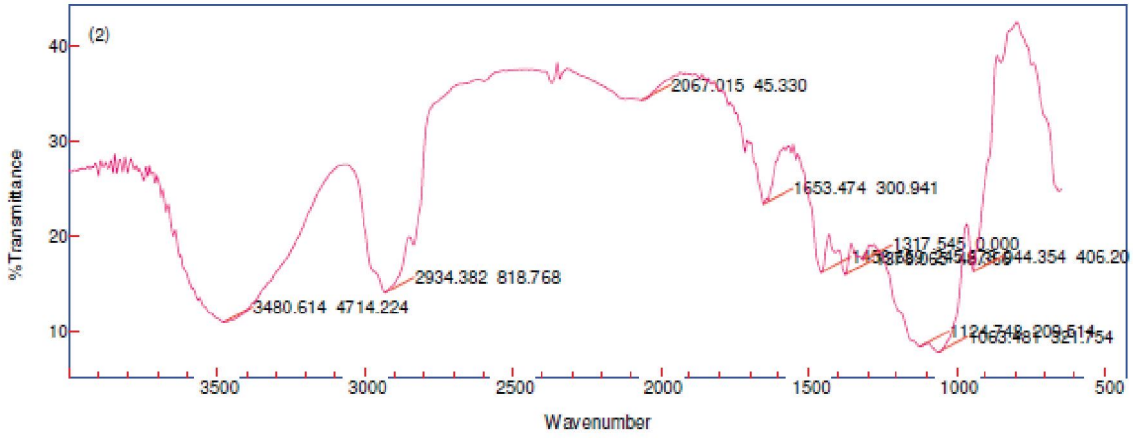

Figure 4. IR spectra of HPMC

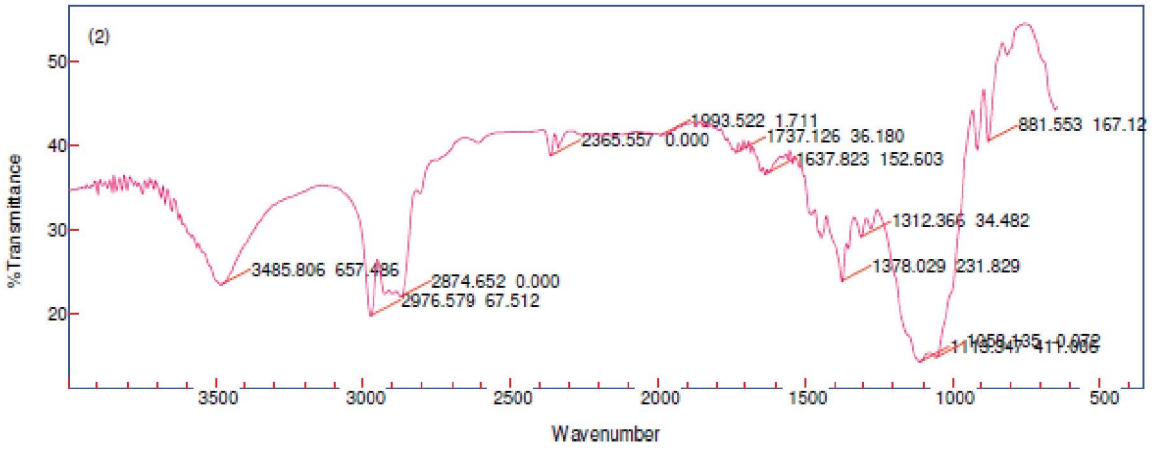

Figure 5. IR spectra of EC

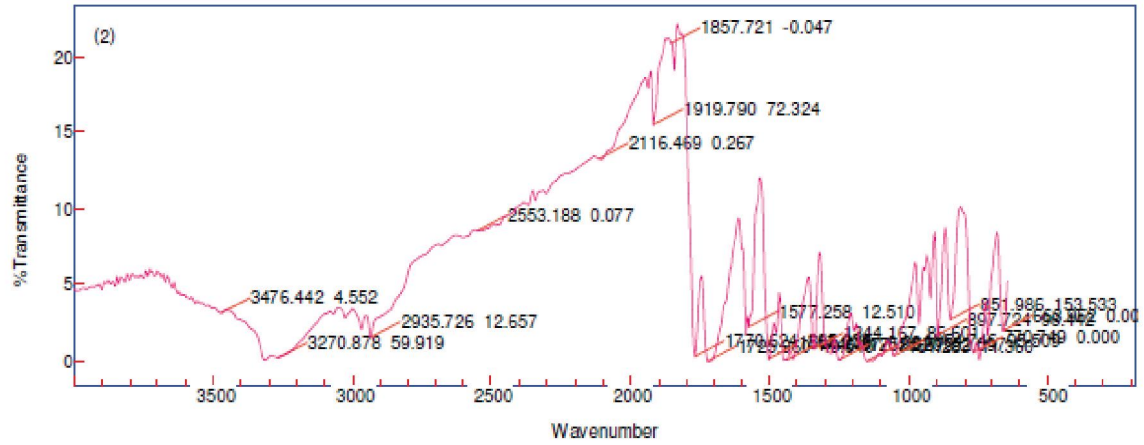

Figure 6. IR spectra of Aceclofenac + HPMC + EC

Differential Scanning Calorimetry

DSC is useful in the investigation of solid-state interactions. The DSC analysis of pure aceclofenac showed a sharp endothermic peak at 157.2°C corresponding to its melting point. The thermograms were generated for pure drug and drug excipient mixtures. The DSC analysis of physical mixture of the drug and excipients revealed negligible change in the melting point of aceclofenac in the presence of other excipients (150.5°C for the mixture of aceclofenac, HPMC and EC). The thermograms are shown in Fig 7 and 8.

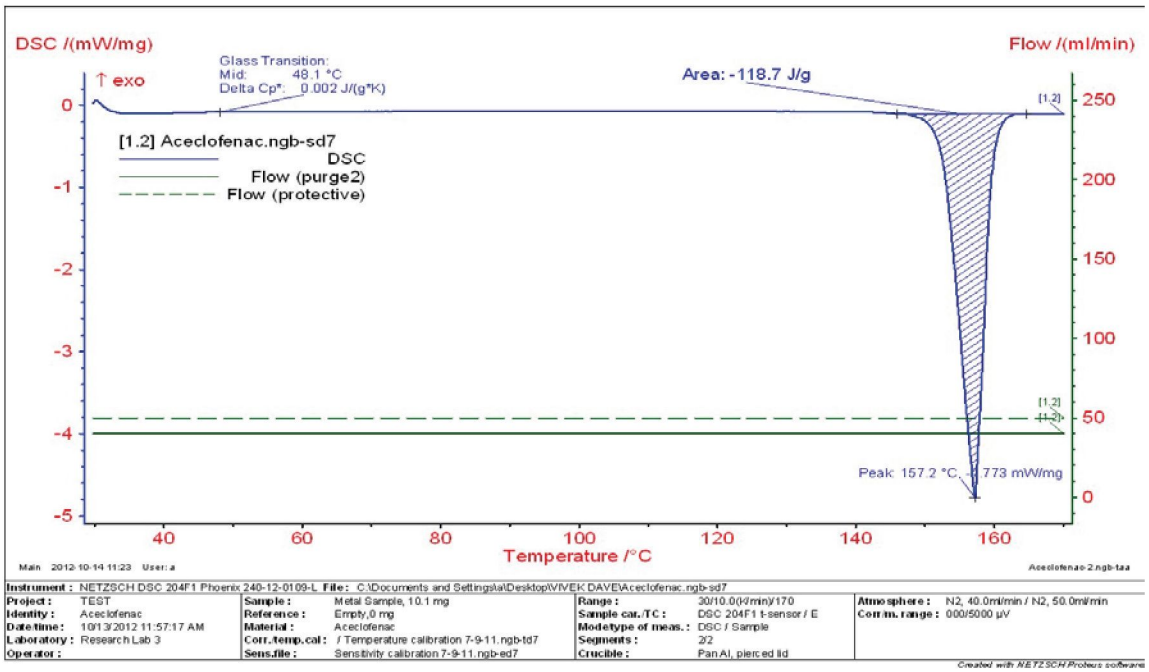

Figure 7. DSC spectra of Aceclofenac

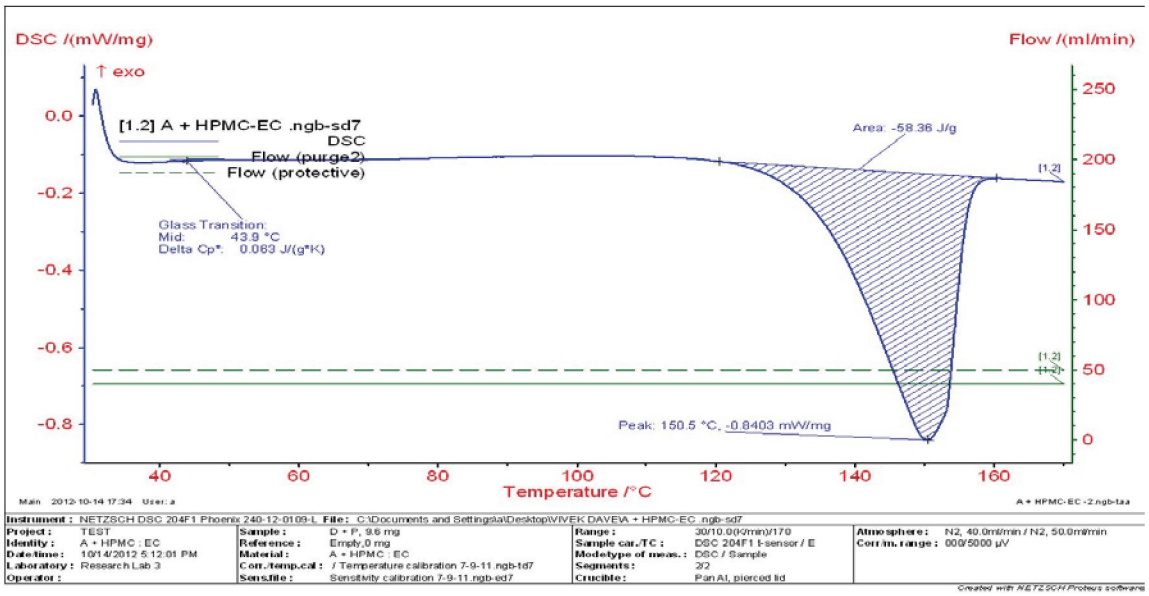

Figure 8. DSC spectra of formulaton Aceclofenac + HPMC + EC

Table 3. Optimization of the formulation ocular insert

Formulation code	Drug reservoir (Drug) mg + Polymer (%w/v solution)	Rate controlling membrane			
		HPMC	Ethylcellulose	Combination (HPMC/EC) 1:1	Dibutyl phthalate(% w/w of polymer)
F1	200 mg+3%	2%	-	-	30%w/w
F2	200 mg+3%	3%	-	-	30%w/w
F3	200 mg+3%	4%	-	-	30%w/w
F4	200 mg+3%	5%		-	30%w/w
F5	200 mg+3%	-	2%	-	30%w/w
F6	200 mg+3%	-	3%	-	30%w/w
F7	200 mg+3%	-	4%	-	30%w/w
F8	200 mg+3%	-	5%	-	30%w/w
F9	200 mg+3%	-	-	2%	30%w/w
F10	200 mg+3%	-	-	3%	30%w/w
F11	200 mg+3%	-	-	4%	30%w/w
F12	200 mg+3%	-	-	5%	30%w/w

Table 4. Evaluation of Aceclofenac ocular insert of different batches

Formulation code	Weight (mg)	Thickness (mm)	Drug content (mg)	Surface pH	% moisture absorption	Folding endurance
F1	55±0.3	0.33±0.017	1.95±0.041	6.9±0.018	6.2±0.12	50.25±1.54
F2	57±0.4	0.45±0.020	1.99±0.049	7.3±0.021	5.5±0.24	49.21±1.67
F3	61±0.4	0.51±0.037	2.19±0.025	7.18±0.055	7.3±0.12	54.2±1.64
F4	74±0.5	0.53±0.052	1.88±0.056	7.26±0.041	8.55±0.26	58.85±2.64
F5	51±0.3	0.52±0.023	1.86±0.058	6.68±0.025	6.1±0.10	50.24±1.55
F6	59±0.4	0.46±0.025	1.68±0.061	7.15±0.065	5.8±0.24	49.28±1.65
F7	75±0.5	0.53±0.025	2.12±0.054	7.23±0.054	7.9±0.12	56.34±1.64
F8	53±0.6	0.54±0.035	1.85±0.096	6.99±0.089	8.69±0.16	65.45±2.54
F9	54±0.5	0.55±0.045	1.96±0.054	6.24±0.024	6.7±0.84	51.56±1.5
F10	60±0.4	0.45±0.056	1.72±0.098	7.63±0.056	5.7±0.65	50.52±1.65
F11	72±0.6	0.52±0.059	1.99±0.045	7.19±0.068	7.7±0.54	60.12±1.54
F12	76±0.7	0.51±0.061	1.96±0.064	7.28±0.054	8.2±0.45	53.45±2.54

Value as means ± SD (n=3)

In-vitro transcorneal permeation studies

In the present study, in vitro drug release was carried out in triplicate. At different time intervals, the sample was withdrawn and cumulative percentage drug release was calculated on the basis of mean amount of drug present in the respective ocular insert. Whole eye ball of goat was transported from local butcher shop to the laboratory in cold (4°C) normal saline within 1 hour of slaughtering the animal. The cornea was carefully excised along with 2 to 4 mm of surrounding scleral tissue and was washed with cold normal saline till the washing was free from proteins. Isolated cornea was mounted by sandwiching surrounding scleral tissue between

clamped donor and receptor compartments of an all glass modified Franz diffusion cell in such way that its epithelial surface faced the donor compartment. The receptor compartment was filled with 15 ml of freshly prepared buffer solution. One square cm of ocular film was placed on the cornea and opening of the donor compartment was sealed with a glass cover slip, while the receptor fluid was maintained 35°C with constant stirring, using Teflon coated magnetic stir bead. Three ml sample was withdrawn from receptor compartment at a time interval of 120 min upto 24 hr. and was analyzed spectrophotometrically at 275nm. In vitro drug release study for formulations F1 to F12 revealed that these formulations were capable of extending the drug release up to 24 hr. The percentage drug release of all the formulations is presented in Figure 9 to 11 The formulations which showed better physicochemical parameters with desired drug release were selected. The release of drug containing HPMC from the selected formulations F1, F2, F3, F4 were found to be 91.33%, 98.24% ,89.25% and 82.89%, at the end of 24 hours. The percentage drug release containing EC of formulation F5, F6, F7, F8 were found to be 62.23%, 70.25%, 59.32%, and 53.24%, at the end of 24 hours. Hence the optimized formulation is F2 which shows greater drug release profile. On comparing F2 and F6, F2 was showed better drug release. There is no increase shown when the combination is used 1:1. Formulation F10 were found to be 84.45%. The selected formulations were then evaluated further studies such as eye irritation test and stability study.

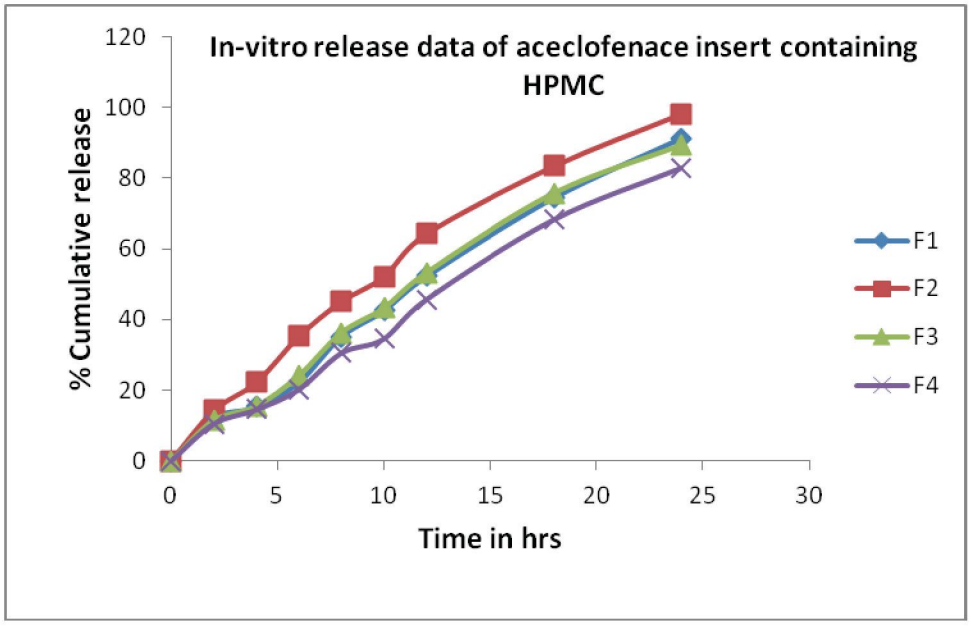

Figure 9. Comparative study of aceclofenac ocular insert containing HPMC

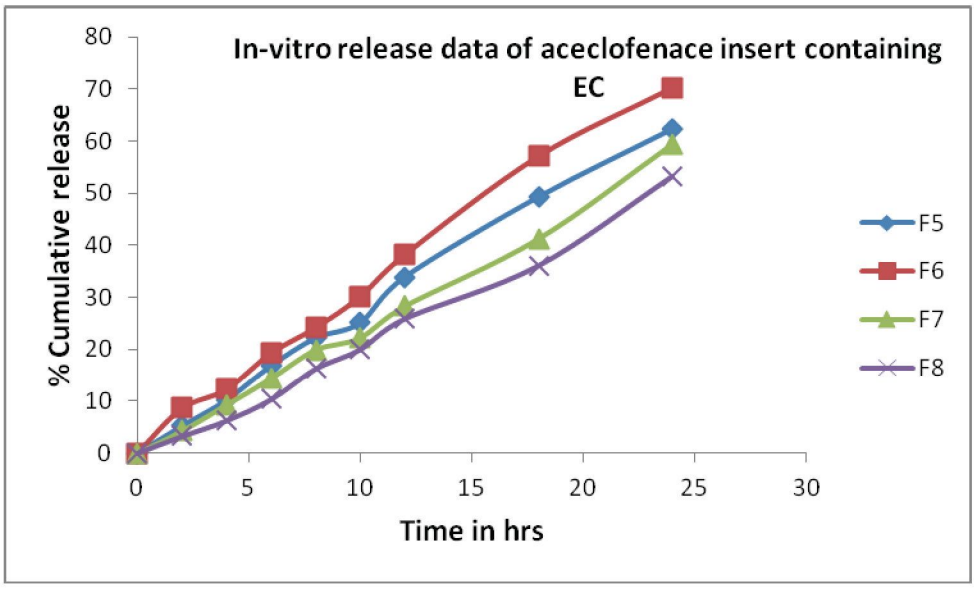

Figure 10. Comparative study of aceclofenac ocular insert containing EC

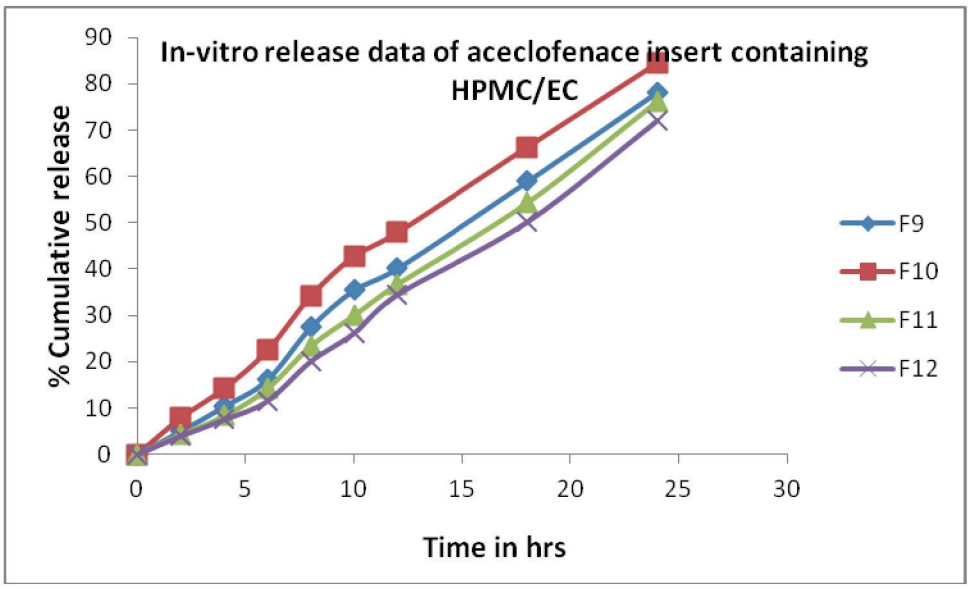

Figure 11. Comparative study of aceclofenac ocular insert containing HPMC/EC

Drug release kinetics

The In vitro drug diffusion data was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations, Higuchi and Korsmeyer models to ascertain the mechanism of drug diffusion. The results of linear regression analysis of data including regression coefficient are summarized in table 5. When the regression coefficient 'r' value of zero order and first order plots were compared, it was observed that the 'r' values of zero order were in the range of 0.96 to 0.99 whereas the 'r' values of first order plots were found to be in the range of 0.58 to 0.97 indicating drug release from all the formulations were found to follow zero order kinetic.

Table 5. Drug release kinetic

Formulation code	Zero order	First order	Higuchi	Krosmeyer peppas	
	RMS Values				n
F1	0.9877	0.5838	0.9789	0.9788	0.76
F2	0.9926	0.6789	0.9933	0.9642	0.57
F3	0.9854	0.6865	0.9796	0.9847	0.74
F4	0.9889	0.6954	0.9888	0.9911	0.75
F5	0.9958	0.9769	0.9654	0.9657	0.58
F6	0.9874	0.9625	0.9631	0.9698	0.54
F7	0.9889	0.9625	0.9592	0.9609	0.57
F8	0.9665	0.9741	0.9569	0.9799	0.71
F9	0.9865	0.9724	0.9689	0.9632	0.56
F10	0.9877	0.9714	0.9651	0.9617	0.58
F11	0.9789	0.9784	096468	0.9723	0.77
F12	0.9788	0.9648	0.9782	0.9821	0.86

Stability study

Stability data indicates the formulations were stable and no major degradation was found (Table 6) and a shelf life of 9 month was assigned to the ocular insert (F-2).

Table 6. Stability study of aceclofenac ocular insert.

Formulation code/ Months	25°C±2°C ± 60 %RH					40°C±2°C ± 75 %RH				
	Physical appearance	% Drug content				Physical appearance	% Drug content			
		0	3	6	9		0	3	6	9
F2	+++	98± 0.8	96± 2.3	95± 0.9	94± 6.7	+++	98± 0.8	96± 2.6	94± 5.9	93± 4.5

Ocular irritation test

Formulation F 2 was used in this test the formulation was found to non irritating with no ocular damage or abnormal clinical signal to cornea, iris and conjunctiva as show in the table 7. Hence formulation was suitable for eye installation . The ocular safety score of the formulation F2 was found to be controlled at the end of 24 hours and therefore, considered as minimally irritating. This irritation might be due to the organic solvent used in the preparation of the rate controlling membrane. Thus, it can be concluded that they were safe for ocular administration.

Table 7. Ocular irritation study as per as draize test protocol.

Eye part	Cornea	Iris	Conjunctiva	Total
Score	0	0	0	0

CONCLUSION

In the present study an attempt was made to develop ocular insert of Aceclofenac with improved bioavailability, avoidance of repeated administration and dose reduction. From the experimental result, it can be concluded that Hydroxy Propyl methyl cellulose is a good film forming hydrophilic polymer and is a shows potential agent for ocular drug delivery system. Incorporation of Dibutylphthalate enhances the permeability of Aceclofenac and thus therapeutic levels of the drug could be achieved. Various batches of aceclofenac ocular inserts were prepared using solvent casting method and evaluated The in- vitro, in-vivo results suggest that the lower hydrophilicity of rate-controlling membrane plays an important role in retarding the release of the drug from reservoir ocular inserts. The drug remained intact and stable in the ocular insert in storage, with no apparent chemical interaction between the drug and the excipients. Further work is in progress to establish the therapeutic utility of these systems by pharmacokinetic and pharmacodynamic in human beings this said to be promising formulation would be able to offer benefits such as increase residence time, controlled drug release, reduction in frequency of administration and may help to improve the patient compliance. 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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