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DESIGN, AND EVALUATION OF OCULAR INSERTS FOR CONTROLLED DRUG DELIVERY OF KETOROLAC TROMETHAMINE

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ABSTRACT

Conventional ophthalmic dosage forms are easy to instill but needs to be applied very frequently and suffer from poor bioavailability and therapeutic response due to pre-corneal and, lacrimo-nasal drainage constraints. One of the novel classes of drug delivery systems, ocular inserts, are gaining worldwide popularity, release drugs at a pre-programmed rate for extended period by increasing the precorneal residence time. Ketorolac tromethamine is a potent non-narcotic analgesic with moderate anti-inflammatory activity. It is conventionally used in the short term management of seasonal allergic conjunctivitis, postoperative ocular pain and inflammation. The present study was undertaken mainly to develop a suitable ocular insert matrix system with the aim of increasing the contact time, achieving controlled release, reducing the frequency of administration, improving patient compliance. Different proportions of gelatin, hydroxyl propyl methyl cellulose, and ethyl cellulose (EC) were used along with the plasticizers and prepared by by film casting technique. Prepared inserts were subjected to different physicochemical evaluation tests. Formulation F18 is identified as the optimized one on the basis of in-vitro drug release data and other physic-mechanical characteristics. Release of drug from the optimized formula was found to be of first order model and non-fickian nature. Fourier transform infrared spectroscopic (FTIR) studies have indicated no interaction between the drug and polymers. Ocular irritation tests conducted in rabbit indicated no signs of toxicity.

KEY WORDS: Ocular inserts, Postoperative ocular pain, Ketorolac tromethamine, Gelatin and Hydroxyl propyl methyl cellulose.

INTRODUCTION

Drugs are commonly delivered to the eye through the application of four basic modes of administration. These are systemic, topical, intravitreal, and periocular [1] The pharmacological approach of management of ocular inflammation and pain involves administration of analgesics and anti-inflammatory agents. Corticosteroids used to be the mainstay of topical therapy for this purpose [2] but their effect was outweighed by serious adverse effects like elevation of intraocular pressure, progression of cataracts, increased risk of infection and worsening of stromal melting [3]. As a class, non- steroidal anti-inflammatory drugs (NSAIDs) have proven to be a safe and effective alternative to corticosteroids in the topical management of ocular inflammations and associated pain[4]. Conventional ophthalmic preparation shows the poor bioavailability and therapeutic response due to pre-corneal and lacremo-nasel constraints. The availability of drug from an instilled drug solution is reported to be less than 1% of administered dose [5]. Novel ophthalmic products can offer more therapeutic benefits than simple solutions/suspensions. Ocular inserts (OIs) are sterile new drug delivery systems which releases the drug at predetermined rate [6] . these novel products increase the contact time and ensure a sustained release of drug to meet the therapeutic needs of topical or systemic treatment [7] Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency [8] Ketorolac tromethamine (KTM) is a potent, non-narcotic, non-steroidal analgesic with moderate anti-inflammatory activity and is used in the management of seasonal allergic conjunctivitis, postoperative ocular pain and inflammation [9]. Instillation of KTM (0.5%, w/v) aqueous solution was associated with ocular irritation, mainly burning and stinging. To reduce the incidence of this adverse affect, use of lower concentration of KTM (0.4%, w/v) has been advocated [10]. Present study is mainly undertaken to prepare an ocular film for the release the drug for extended period of time.

MATERIALS AND METHODS

Materials

Ketorolac tromethamine was obtained as a gift sample from Hetero Drugs (P) Ltd., Hyderabad. The polymers Gelatin, HPMC and EC and were purchased from S. D. Fine

Chemicals (P) Ltd., Boisar. All other chemicals and solvents used were of analytical reagent grade.

Methods

Preparation of ocular films [11]

a) Preparation of gelatin films:-The required quantity of gelatin and glycerin were weighed and dissolved in water and the mixture was heated at 60^0C on a water bath until the entire gelatin was dissolved. The weighed amount of KTM (passed through sieve # 400) was added and stirred for 6 hours at 40^0C on magnetic stirrer to get uniform dispersion. After complete mixing, the casting solution (15ml) was poured in clean petridish. The petridish was cooled to 10^0C by placing on ice until the films were gelled. The gelled films were taken out from ice and allowed to dry at room temperature for 24 hours. The dried films thus obtained were cut into required size (8mm diameter) by cork borer and stored for further use.

b) Preparation of HPMC films

The required quantity of HPMC was weighed and dissolved in distilled water by gentle stirring on magnetic stirrer. Glycerin was added as plasticizer to the above solution under stirring conditions. KTM, previously passed through sieve # 400, was added and stirred for 6hrs to get clear solution. After complete mixing, 15 ml of casting solution was poured in clean anumbra Petri dish of area 63.64sq.cm. Then the Petri dish was allowed to dry at room temperature for 24hrs. The dried films thus obtained were cut into size of (8mm diameter) by cork borer, wrapped in aluminum file and stored till used.

c) Preparation of Ethyl cellulose films

Required quantity of ethyl cellulose was dissolved in alcohol containing diethylphalate as plasticizer. KTM is added to this solution and stirred for about 2 hours. The drug polymer solution containing the plasticizer is allowed to stand overnight and then placed under vacuum to remove air bubbles. 15 ml of polymeric drug solution was then poured into pre-lubricated glass mould and allowed to get dried at 50˚C for 6 hours in hot air oven. After drying, the films were removed and cut into circular disc of 8 mm diameter and stored for further use.

Evaluation of ocular films

Physical characterization: The ocuserts were evaluated for their physical characteristics such as shape, color, texture, and appearance.

The ocular films were evaluated for thickness [12], weight variation, drug content uniformity [13] and swelling index [14] Thickness was measured using a dial caliper (Mitutoyo, Japan) at different points and the mean values were calculated. Ocular film weights and weight variation tests were determined by using electronic balance.

Folding endurance

Folding endurance was determined by taking a small strip of the prepared films and cut evenly and separately folded at the same place till it breaks. The number of times the ocusert could be folded at the same place without breaking gives the folding endurance [15].

To check the uniformity of the drug in the cast film, films were cut at different places and each film was placed in 10 ml of water to extract KTM, the resulting solution was filtered and further dilution was made with water and the absorbance at 322 nm was measured Spectrophotometrically. The concentration of the drug was determined from the standard curve. Same procedure was adopted for other formulations of cast films in triplicates and mean drug content and standard deviation were calculated.

To check the swelling index three films were weighed and placed separately in beakers containing 4 ml of distilled water. After a period of 5 minutes, the films were removed and the excess water on their surface was removed using a filter paper and then again weighed till there was no increase in the weight. The swelling index was then calculated by dividing the increase in weight by the original weight and was expressed as percentage.

Ocular irritation

The potential for ocular irritation and/or damaging effects of the ocusert under test were evaluated by observing them for any redness, inflammation, or increased tear production. Formulation was tested on five rabbits by placing the inserts in the cul-de-sac of the left eye. Both eyes of the rabbits under test were examined for any signs of irritation before treatment and were observed up to 12 hours.

***In vitro* diffusion studies**

Semi permeable membrane obtained from Sigma Chemicals Co. having a molecular weight cut off 12,000 Daltons was used for this study. This membrane was tied to one end of the open cylinder, which acts as donor compartment. The ocular film was placed inside the compartment. The semi permeable membrane acts as corneal epithelium. Then the open

cylinder was kept over a beaker containing 50 ml of phosphate buffer pH 7.4 which acts as receptor compartment. This was continuously stirred (50 rpm) using a magnetic stirrer. The temperature was maintained at 37 ± 1^0C. 1ml of the sample solution was withdrawn at hourly intervals from the receptor compartment and the same quantity was replaced with phosphate buffer pH 7.4. The cumulative percentage of drug released was determined using UV-VIS Spectrophotometer at 314 nm (Elico SL 159). The experiment was carried out in triplicate and average values were reported.

Drug excipient compatability studies

The compatibility of drug with the excipients was studied by Fourier transform infrared (FTIR) spectroscopy. The stability of the drug in the formulation was confirmed by IR spectral analysis. IR spectra of pure drug and formulations were obtained using (Brucker FTIR-) by KBr disc method. The scanning range was 500 to 4000 cm−1, and the resolution was 1 cm−1.

Accelerated Stability Studies

The optimized formulations in its final pack were stored at 30±2^0C/65±5% RH and 40±2^0C/75±5% RH for 3 months in Stability chamber (Thermolab, India). The samples were withdrawn at every 10 day time intervals and analyzed for physical parameters and drug content.

RESULTS AND DISCUSSION

The composition formulae of the ocuserts is depicted in table 1.The prepared inserts were found to be translucent, light yellow to colorless and smooth in texture, uniform in appearance and show no visible crack or imperfection. The physiochemical evaluation data presented in Table 2. The inserts had a thickness varying from 0.19 ± 0.01 to 0.43 ± 0.04 mm and weight varying from 10.81±0.0212 to 22.66±0.0211 mg. The drug content was consistent in all batches and varied from 917.6 ± 0.01 % to 99.41 ± 0.02 %.The folding endurance of inserts ranges from 84 to 97. Swelling index ranged between 1.06± 0.0108 to 2. 86±0.0114, suggesting that there was not much variation in the water absorption capability of formulations.. The formulations did not produce any irritation when placed in the cul de sac, since they were not thick enough to produce irritation (photograph). IR spectra analytical reports indicated that there was no interaction between drug and excipients used.(figures4 to 7).

Table 1.Physico-chemical Evaluation of Ocular Inserts

Formulations	Weight in (mg) ± SD	Thickness in (μm) ± SD	Swelling Index (%)	Folding endurence	% Drug content
F_1	11.1 ± 0.0101	0.19±0.01	1.30 ± 0.0220	84	98.68 ± 0.03
F_2	17.4 ± 0.0121	0.26±0.01	1.85 ± 0.0103	91	95.33 ± 0.07
F_3	12.8 ± 0.0113	0.22 ± 0.07	1.98 ± 0.0111	89	99.00 ± 0.05
F_4	13.2 ± 0.0134	0.27 ± 0.05	2.14 ± 0.0114	84	98.30 ± 0.05
F_5	14.76 ± 0.0212	0.28±0.05	2.18 ± 0.0124	88	99.41 ± 0.02
F_6	18.33 ± 0.0100	0.30 ± 0.03	2.29 ± 0.0231	97	97.74 ± 0.04
F_7	20.66 ± 0.0242	0.31 ± 0.03	2.40 ± 0.0241	93	93.49 ± 0.05
F_8	16.73 ± 0.0112	0.28 ± 0.02	2.83 ± 0.0101	87	98.55 ± 0.03
F_9	16.66 ± 0.0212	0.29 ± 0.01	2.86 ± 0.0114	92	94.48 ± 0.02
F_{10}	10.8 ± 0.0210	0.25 ± 0.07	1.35 ± 0.0112	96	99.38 ± 0.21
F_{11}	11.37± 0.0211	0.30 ± 0.04	1.42 ± 0.0224	84	93.40 ± 0.09
F_{12}	18.53 ± 0.0118	0.29 ±0.02	1.96 ± 0.0218	87	91.76 ± 0.01
F_{13}	14.59 ± 0.0134	0.31 ± 0.04	2.28 ± 0.0113	91	93.66 ± 0.02
F_{14}	12.21± 0.0123	0.34 ±0.05	2.32 ± 0.0213	89	99.79 ±0.01
F_{15}	10.81± 0.0121	0.33 ± 0.06	2.36 ± 0.0311	95	92.87 ± 0.09
F_{16}	16.52± 0.0102	0.30 ± 0.02	1.37 ± 1.0101	92	98 ± 0.02
F_{17}	19.31 ± 0.0211	0.38 ± 0.04	1.29 ± 1.0112	97	98.18 ± 0.01
F_{18}	22.66 ± 0.0211	0.44 ± 0.02	1.22 ± 0.0215	86	91.32 ± 0.03
F_{19}	20.76 ± 0.0202	0.39 ± 0.01	1.19 ± 0.0312	89	94.84 ± 0.07
F_{20}	22.66 ± 0.0021	0.43 ± 0.04	1.16 ± 0.0101	91	96.60 ± 0.07
F_{21}	18.4 ± 0.0031	0.43± 0.02	1.06 ± 0.0108	92	90.26 ± 0.03

*Mean ± SD, n =3.

Table 2

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20	F21
	10% w/v			12% w/v			14% w/v			10% w/v		12% w/v		14% w/v		14% w/v		16% w/v		18% w/v	
Drug (mg)	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25	25
Gelatin (gm)	1.5	1.5	2	1.8	2	1.8	2.1	2.1	2	-	-	-	-	-	-	-	-	-	-	-	-
HPMC (gm)	-	-	-	-	-	-	-	-	-	1.5	1.5	1.8	1.8	2.1	2.1	-	-	-	-	-	-
EC (gm)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2.1	2.1	2.4	2.4	2.7	2.7
Glycerin (ml)(40% w/w of polymer)	0.5	-	-	0.6	-	-	0.7	-	-	0.5	-	0.6	-	0.7	-	-	-	-	-	-	-
Glycerin (ml) (50% w/w of polymer)	-	0.6	-	-	7	-	-	0.8	-	-	0.6	-	0.7	-	0.8	-	-	-	-	-	-
Glycerin (ml) (60% w/w of polymer)	-	-	1	-	-	0.9	-	-	1	-	-	-	-			-	-	-	-	-	-
DEP (ml) (40% w/w of polymer)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.8		0.9	-	1	-
DEP (ml) (50% w/w of polymer)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.9	-	1.1	-	1.2
Water (ml)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15	-	-	-	-	-	-
Alcohol (ml)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	15	15	15	15	15	15

COMPOSITION OF FORMULATIONS

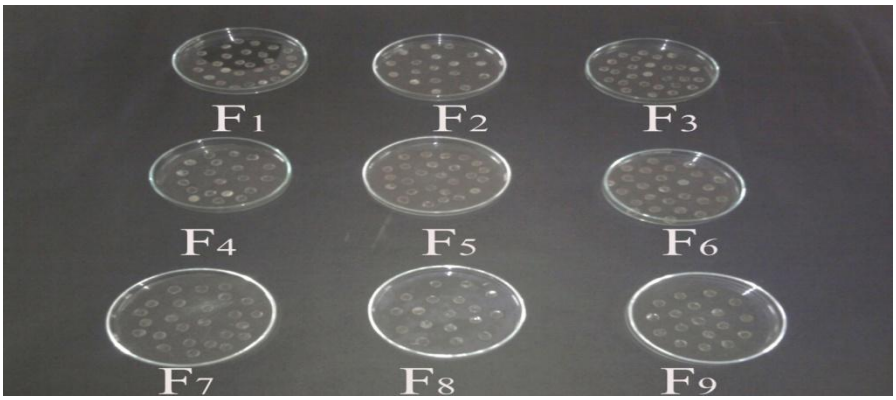
Table.3. Curve fitting data for all table for F1 to F9

Table .3.Curve fitting data

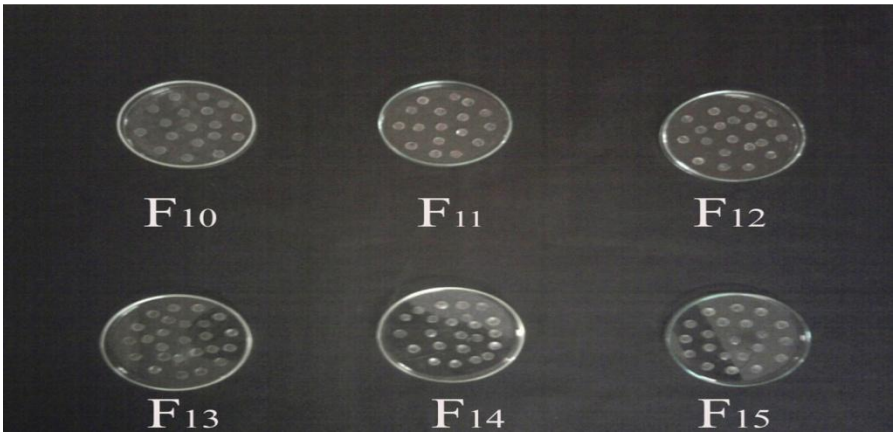
Formulations	Zero order Equation		First order Equation		Higuchi's Equation		Peppas Equation	
	Slope	Regression coefficient (R^2)	Slope	Regression coefficient (R^2)	Slope	Regression coefficient (R^2)	Slope	Regression coefficient (R^2)
F_1	0.7151	0.8126	-0.0114	0.9668	8.6982	0.975	1.0004	0.9658
F_2	0.7161	0.7914	-0.0124	0.9603	8.785	0.966	1.0045	0.9629
F_3	0.7272	0.7599	-0.0163	0.9575	9.0635	0.9573	1.0147	0.9602
F_4	0.7167	0.8466	-0.0107	0.9692	8.5877	0.9857	0.9941	0.9704
F5	0.7215	0.8217	-0.0116	0.9743	8.7566	0.9814	1.0014	0.9678
F_6	0.7251	0.78	-0.0134	0.9761	8.969	0.9677	1.0108	0.9631
F_7	0.6871	0.8326	-0.0087	0.9756	8.284	0.9813	0.9874	0.9687
F_8	0.4732	0.7542	-0.0092	0.989	7.4199	0.9534	0.9225	0.9486
F_9	0.4696	0.716	-0.0117	0.9918	7.4828	0.9345	0.9272	0.9421

The drug dara is shown in figures from 1 to 3. From the dissolution studies it is concluded that as the concentration of gelatin , HPMC and ethyl cellulose increases, drug release from the formulations decreases. The formulation with gelatin as polymer showed complete release of drug in 2 to 3 hrs. The formulation with HPMC as polymer showed complete release of drug in 3 to 4 hrs. As the concentration of EC increases, drug release from the formulation decreases. As the concentration of glycerin in formulation is increased drug release was increased, which could be attributed to its high rate and extent of swelling. This finding was also supported by results of swelling studies where the highest swelling index was exhibited by the formulation containing highest concentration of glycerin, indicating that increase in water soluble plasticizer (glycerin) content results in faster swelling and release from ocular inserts. The release data were also subjected to model fitting analysis to know the mechanism of drug release from the formulations by treating the data according tozero order first order Higuchi's and Peppas eqauations. The linearity and slope indicates that the release of drug from the films have followed *First order* model and non fickian nature. The *Hguchi* plots reveled that the release of drug to be by diffusion controlled mechanism (.Data shown in table 3) From the above discussions it can be concluded that formulation containing EC 14, 16 and 18 % w/v i.e, F16, F18 and F20 have achieved the objectives of increased contact time, prolonged release and decreased frequency of administration and thus may improve the patient compliance.Based on results obtained, the formulation showing the best drug release

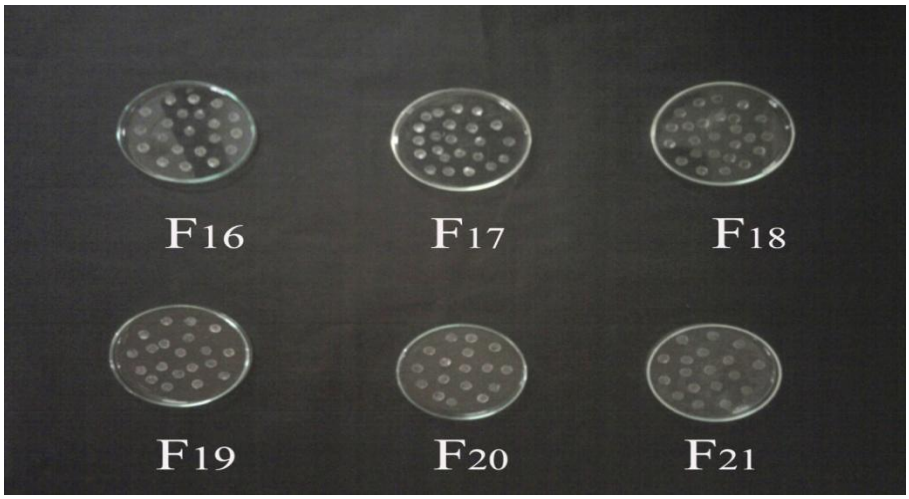
profile and appearance, F18 was selected and subjected to stability studies. From the results of accelerated stability studies it was found that the formulations were stable and the drug content was found to be within limits.



Photograph. 1. Ocular Inserts of KTM using gelatin as polymer.



Photograph. 2. Ocular Inserts of KTM using HPMC as polymer



Photograph. .3. Ocular Inserts of KTM using Ethyl cellulose as polymer

Photograph showing ocular insert in rabbit

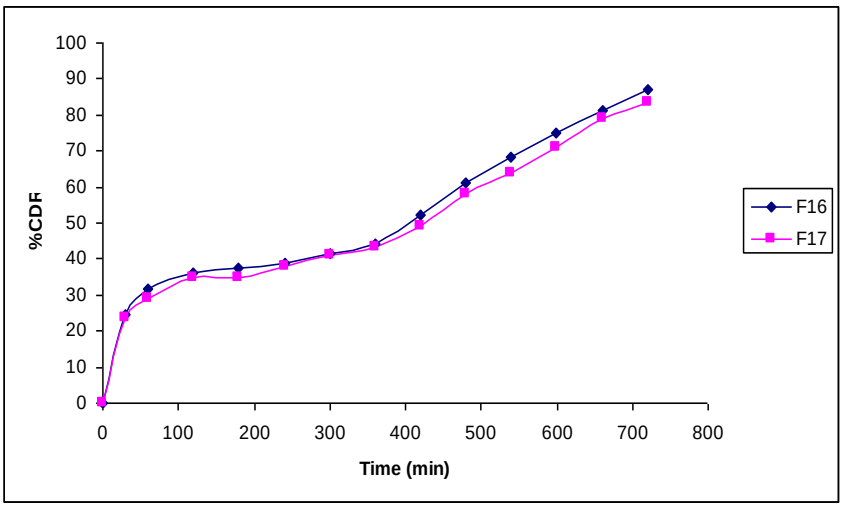


Figure. 1. In- vitro drug release profile of F16 and F17

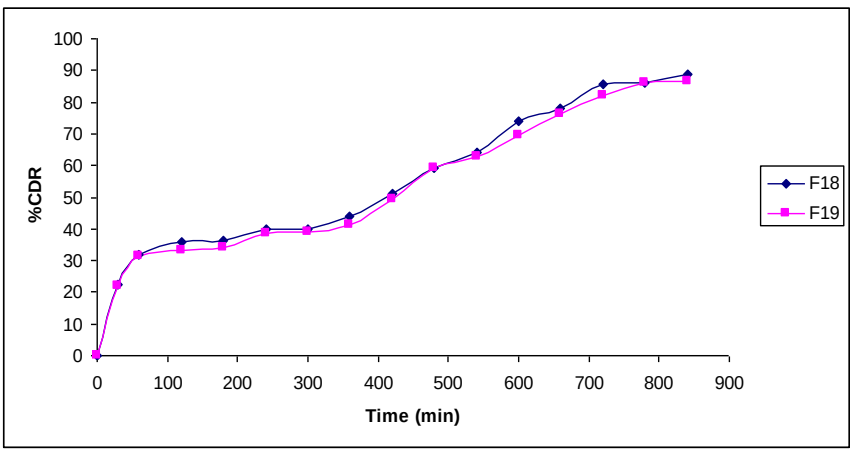


Figure.2. In- vitro drug release profile of F18 and F19

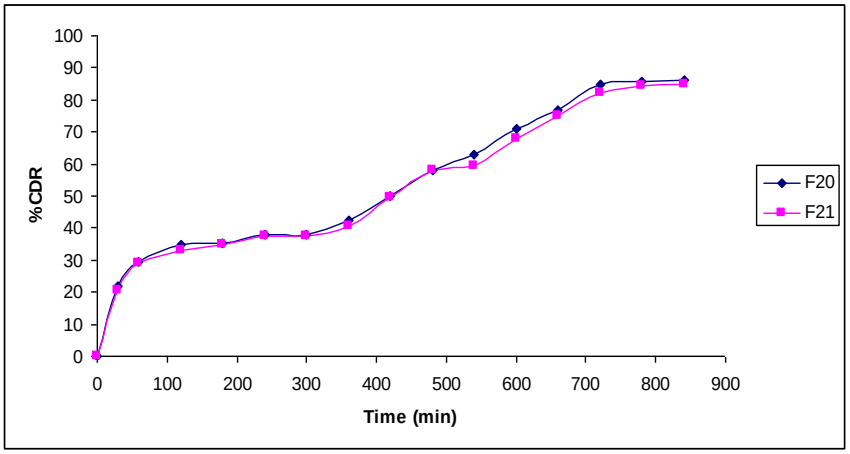


Figure.3. In- vitro drug release profile of F18 and F19

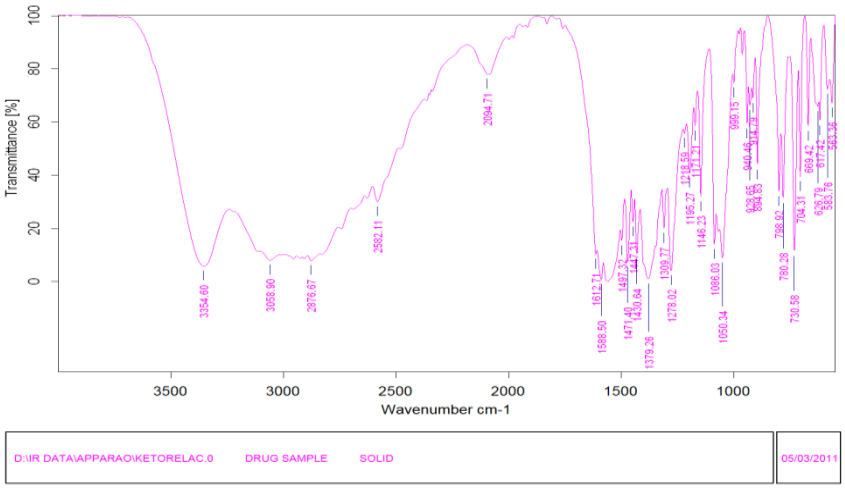


Figure.4. FTIR Spectra of KTM

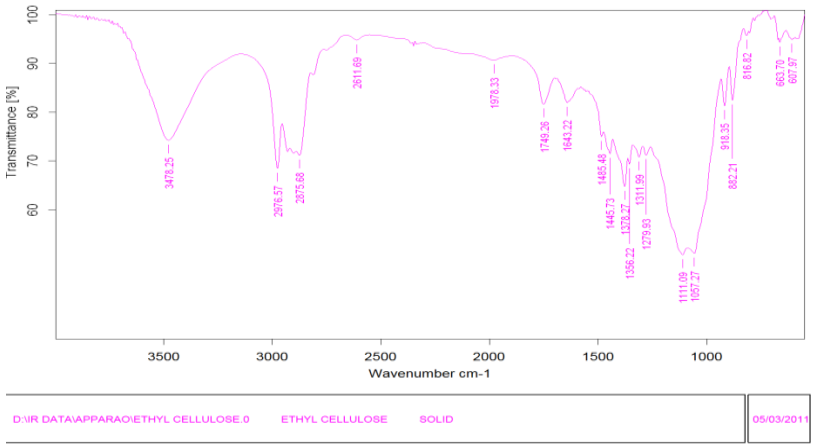


Figure5. FTIR Spectra of ethyl cellulose

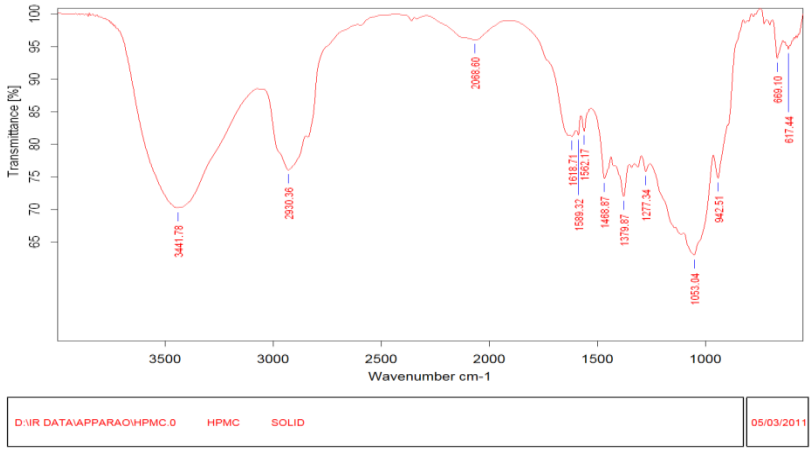
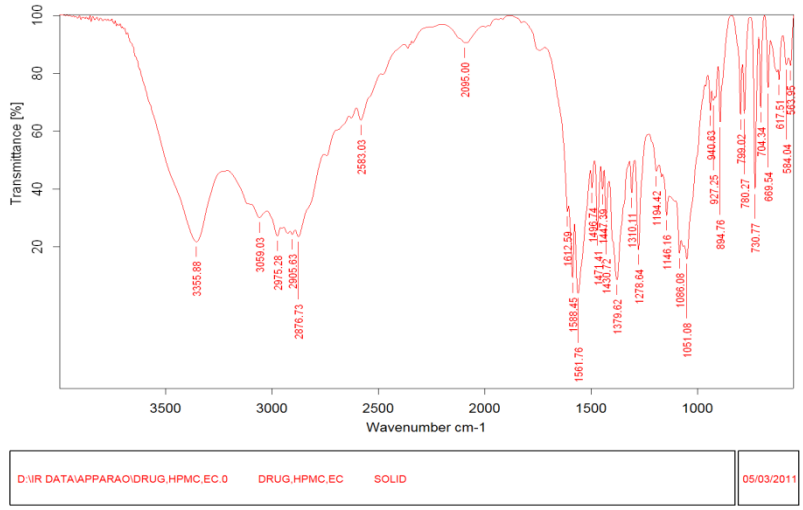


Figure 6. FTIR Spectra of HPMC



sFigure. 7. FTIR Spectra of drug and polymer

CONCLUSION

Experimental findings indicates that HPMC is a good film forming hydrophilic polymer and is a promising agent for ocular delivery. Ethyl cellulose was a satisfactory polymeric ingredient to fabricate the rate controlling membrane of the ocusert system. Incorporation of glycerine enhances the permeability of KTM, and thus therapeutic levels of the drug could be achieved. The kinetic treatment of *in vitro* dissolution data indicated that the ocusert followed non-Fickian diffusion kinetics and there was complete absence of eye irritation and redness of the rabbit eye. From the results obtained, it can be concluded that formulation containing EC 14%w/v(F16), 16% w/v (F18) and 18 % w/v (F20) has achieved the objectives of increased contact time, prolonged release, decreased frequency of administration and thus may improve the patient compliance.

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