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Release kinetics of betaxolol from a hydrophobic matrix system of PMMA cast with incorporating different proportions of PEO

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ABSTRACT: Because of numerous pre-corneal restrictions, conventional medication has poor bioavailability and a poor therapeutic response. As a result, innovative regulated and sustained ocular drug administration is needed to become the norm in the current pharmaceutical era. The objective of this study was to examine the betaxolol hydrochloride drug release kinetics from a hydrophobic matrix system of PMMA cast containing varying amounts of polyethylene oxide (PEO) and assess if this could enhance the drug's ocular bioavailability and duration of action. Matrix type ocular inserts were prepared by the film casting technique and characterized in vitro by drug release studies using a flow through apparatus that simulated the eye conditions. All the formulations were subjected to physicochemical evaluation. Rabbit model with steroid induced glaucoma was used to establish in vivo efficacy of inserts. Polymer composition and concentration significantly affected the drug release based on change in diffusional path length and formation of gelaneous pores by polymer erosion. Formulations released the drug by non-fickian diffusion including anomalous transport ($0.5<n<1$) and super case II trans- port ($n>1$). It was also observed that increasing the proportion of PEO in to PMMA does not affect the blend miscibility. According to IVIVC, there is no significant difference ($P<0.001$) between the drug release from inserts in vitro and in vivo. When compared to ocular drops (10 h), optimized insert F8 (for 24 h) demonstrated superior in vivo IOP reducing activity. For the treatment of glaucoma, this ocular insert presents a potential once-daily sustained release formulation.

Keywords: Once-a-day ocuserts, Betaxolol hydrochloride, ocular delivery, polymer composite, sustained release, release kinetics.

I. INTRODUCTION

Drugs can be continuously delivered to the eye, which has significant advantages over traditional therapies that require administering drug suspensions or solutions like eye drops. Because eye drops quickly leave the body through the precorneal route, they frequently have low bioavailability and therapeutic response. They are also linked to issues with patient compliance. [1, 2]. After instillation of an eyedrop, typically less than 5% of an applied dose reaches the intraocular tissues. This is due to tightness of the cornea1 barrier and rapid loss of the instilled solution from the precorneal area [3-5].

Extending the duration of contact on the ocular surface and raising corneal permeability are the two primary methods for optimizing ocular medication delivery. The majority of formulation attempts seek to maximize absorption by extending the duration of the drug's residence time in the conjunctival sac.[6,7]. Many colloidal drug carriers like nanoparticles, liposomes, niosomes have been investigated as an alternative approach to deliver the drug at right dosage to right target organ, to prevent degradation, metabolism and cellular efflux in the course of drug delivery [8-10]. A basic concept in ophthalmic research and development is that the therapeutic efficacy of an ophthalmic drug can be greatly improved by prolonging its contact with the corneal surface. Ophthalmic inserts offer many advantages over conventional dosages forms, like increased ocular residence, possibility of releasing drug at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf life. Design, construction and technology of ocular insert in a controlled and sustained ocular delivery device are gaining rapid improvement to overcome these constraints [11,12]. Betaxolol is selective beta-1-adrenegic receptor blocker and

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used in the treatment of ocular hypertension and chronic open angle glaucoma. There are only a few ocular inserts available on the market, made of EVA as a rate controlling membrane [13,14]. Likewise, poly (methyl methacrylate) (PMMA) is also an excellent film-forming polymer but the films of PMMA alone are brittle [15]. It offers more resistance to the diffusion of drug molecules, and is less explored as a polymer for ocular delivery of drugs. The current literatures indicate that no inserts are made of hydrophobic monolithic systems using betaxolol. Therefore, the purpose of this work is to examine the drug release kinetics of betaxolol from a PMMA cast hydrophobic matrix system using various amounts of polyethylene oxide (PEO). When hydrophilic polymer is added to PMMA, the films grow stronger and less brittle, and it is possible that the diffusion will improve.

II. MATERIALS AND METHODS

Betaxolol HCL was obtained as a complimentary gift sample from Indoco Remedies Pvt. Ltd., Mumbai, India. PMMA (molecular weight 120,000) was purchased from Loba Chemie, Mumbai, India. PEO powder (molecular weight 1000,000) was purchased from Alfa Aesar Inc., USA. Other reagents and chemicals used in the research were of analytical grade.

Preparation of Ocular Inserts

Using a 3^2-full factorial design, the matrix films were created via the film casting method from PEO and PMMA. (Table **1** and **2**). Briefly, weighed quantities of the drug and polymers were solubilized in chloroform with continuous mixing using magnetic stirrer at 25 rpm. The solutions were then sonicated for 30 seconds to remove the air. Polymeric drug solutions were poured on to Teflon coated petridish. The matrix films were dried constantly under the ambient conditions. In all the films DBP (30% w/w) was incorporated as a plasticizer [16- 18]. Inserts were sterilized under UV for 1hr [19] and inserts were packed individually in sterilized aluminum foils which were further stored in amber colored glass bottles at room temperature.

Physicochemical Evaluation of Ocular Inserts

The physical characteristics, surface pH, thickness, weight fluctuation, folding endurance, tensile strength, moisture content, water transfer rate, water uptake, and drug content homogeneity of the prepared inserts were assessed.

Inserts were allowed to swell in 0.1 milliliter of distilled water for 30 minutes at room temperature in a closed petridish in order to measure the surface pH. [20]. PH paper was kept on surface and after one minute the color developed was compared with the standard colour scale. Thickness was evaluated using a micro meter of sensitivity of 0.001mm (mitutoyo, Japan); the average of ten readings was taken [21]. From each batch ten inserts were weighed individually using digital balance (Shimadzu, Japan) and mean weight was recorded [22]. Folding endurance was determined by repeatedly folding a small strip of ocular film at the same place till it broke. Drug content was estimated by triturating ocular inserts in 20 ml of phosphate buffer pH 7.4 with the help of mortar and pestle. The solution was filtered and one ml solution was withdrawn, diluted and measured by UV-Visible Spectrophotometer at 274 nm [23].

An apparatus built in the lab was used to measure the tensile strength. A sharp blade was used to cut a short strip of ocular film measuring 5 cm by 1 cm. One end of the film was fixed by placing in the film holder. Another end of the film was fixed with the help of forceps having triangular ends to keep the strip straight while stretching and a hook was inserted. A thread was tied to the hook, passed over the pulley and a small pan attached to the other end to hold weights. A small pointer was attached to the thread that travels over the graph paper affixed on the base plate.

Table 1.Independent Factors for Formulation of Betaxolol Ocular Inserts.

Independent Variable	Factor A Drug to Polymer Ratio (Drug : Total Polymer)			Factor B Polymer to Polymer Ratio (PMMA : PEO)		
	Low	Medium	High	Low	Medium	High
Coded Levels	-1	0	1	-1	0	1
Actual Levels	1:2	1:4	1:6	9:1	8:2	7:3

International Journal of Pharmaceutical Research and Applications
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Table 2.3[2] Full Factorial Design of Betaxolol Ocular Inserts.

Formulation	Factor A Drug to Polymer Ratio		Factor B Polymer to Polymer Ratio (PMMA:PEO)	
	Coded	Actual	Coded	Actual
F1	-1	1:2	-1	9:1
F2	-1	1:2	0	8:2
F3	-1	1:2	1	7:3
F4	0	1:4	-1	9:1
F5	0	1:4	0	8:2
F6	0	1:4	1	7:3
F7	1	1:6	-1	9:1
F8	1	1:6	0	8:2
F9	1	1:6	1	7:3

By using a pulley system, the film was pulled in order to measure its elongation and tensile strength. Up until the film broke, weights were added to the pan at a rate of 5 grams per minute to strengthen the pulling power. Elongation was determined simultaneously by noting the distance traveled by the pointer on the graph paper before the film was broken. The weight necessary to break the film was noted as break force.

Surface Morphology

The polymer blend's surface properties were investigated using scanning electron microscopy[24]. Films were mounted on an aluminum stub using double-sided adhesive carbon tape and coated with gold palladium using JEOL JFC 1600 auto fine coater for 90 seconds. Samples were examined using scanning electron microscope JSM-6380 LV (Jeol Ltd., Tokyo, Japan) at 20 kv accelerating voltage.

Hydrophilicity

The measurement of contact angle was performed at R.T. by optical tensiometry using contact-angle meter (Theta optical tensiometer, Biolin scientific AB, Sweden) equipped with T200 60 fps digital camera[25]. Drops of STF (pH 7.4) were prepared with a precision syringe (1 ml, Hamilton 1001TPLT) and were dropped onto the surface of the poly-mer. The static contact angle was measured at contact time t= 10 s.

Drug-Excipients Compatibility Study

Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectra of the pure drug and physical mixture (betaxolol, PEO and PMMA) were taken as KBr pellets in the range of 4000–650 cm^{-1} (FT/IR-4100 type A spectrophotometer, Jasco, Japan). The infrared analysis of optimized insert was carried out in the same range by ATR-IR spectroscopy (Perkin Elmer Model 1600 FT-IR spectrophotometer with ATR mode Perkin Elmer, USA).

Physical State of Drug

Differential Scanning Calorimetry (DSC)

DSC 1/700 was used to perform differential scanning calorimetry (DSC) scans of pure drug and drug-loaded ocular implant (Mettler Toledo, Germany). The analysis was performed with a heating range of -20 ^{0}C to 250 °C and at a rate of 10°C per minute in nitrogen atmoshere. The sample weight was approximately 6 mg.

X-Ray Diffraction

X-Ray diffraction (XRD) patterns of pure betaxolol and ocular film were recorded using a powder X-Ray diffractometer (XRD-D8 Advance, Bruker, Germany) over the inter-val10-90° $2\theta^{-1}$. The experimental condition were: generator tension (voltage) of 38 kV, generator current of 34 mA, scan step time of 30.6 sec^{-1} and scan step size of 0.049° $2\theta^{-1}$.

International Journal of Pharmaceutical Research and Applications
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In Vitro Drug Permeation Study

Since there was no formal protocol for doing in vitro research on ocular inserts, we created an open flow through assembly using a normal cylindrical tube with a 15 mm diameter to mimic the conditions of the ocular cavity. Dialysis membrane (Dialysis membrane 110, mw cut-off 12000-14000, Hi Media, India), immersed in water for one hour to remove the preservatives followed by rinsing in phosphate buffered saline (PBS) solution, acted as corneal epithelium, was tied to one end of open cylinder which acted as donor compartment. An ocular insert was placed inside this compartment with 0.7 ml of simulated tear fluid (STF pH 7.4). Then, the glass tube was suspended in the dissolution flask of a USP dissolution apparatus such that entire surface of the membrane was in contact with the receptor compartment containing 100 ml of STF. The con- tent of the receptor compartment was stirred continuously at 25 rpm. Samples of 1 ml were withdrawn from the receptor compartment at periodic intervals and replaced by equal volume of fresh solution. The samples were analyzed spectrophotometrically using STF as blank [26, 27]. From the drug permeation data, diffusion rate, steady state flux and permeability coefficient were derived. The results of diffusion study were also fitted to zero-order (%release Vs time), higuchi (%release Vs sq. root of time) and Korsmeyer and Peppas (log % release Vs log time) equation .

In Vivo Release Study

Approval for the use of animals in the study was obtained from Institutional Animal Ethics Committee (1338/c/CPCSEA). On the day of experiments, the sterilized ocular inserts were inserted into one eye of seven rabbits at the same time and contralateral eye served as control. After 1, 2, 4, 6, 10, 22 and 24 hrs, the inserts were carefully re-moved and analyzed for remaining drug content by UV spec- trophotometer.

Ocular Safety Study

Based on the Draize Eye Test, the ocular safety of the given delivery mechanism was investigated. The safety of the created ocular inserts in rabbit eyes was demonstrated by the observations based on the scoring approach [28].

In Vivo Antiglaucoma Activity

The optimized ocular insert of betaxolol was investigated in vivo in normotensive albino rabbits of both sexes to determine its ability to reduce intraocular pressure. The animals were housed under well controlled conditions of temperature, humidity and 12/12– h, light-dark cycle, with free access to food and water. No ocular abnormalities were found on external and slit-lamp examination prior to beginning of the study.

Glaucoma was induced using topical steroid (dexamethasone) by the method prescribed elsewhere. The basal intraocular pressure was measured by schiotz tonometer. The drug formulation was placed in cul-de-sac of rabbits. Total 12 rabbits were divided in to three groups each containing 4 rabbits. First group was treated with marketed preparation of betaxolol HCL eye drop equivalent to 0.50 mg. In second group placebo film and in third group medicated film (F8) of betaxolol HCL was inserted in to lower cul de sac of rabbits. The intraocular pressure (IOP) changes were recorded up to 26 h at specified time intervals. The ocular hypotensive ac- tivity is expressed as the average difference in IOP according to the equation $\Delta IOP = IOP_{'0'\ time} - IOP't'time$.

Stability Study

Stability studies were carried out according to ICH guidelines [33]. Ocular inserts (F8) were stored in amber colored glass bottles at 3 different temperatures 4^{o}C, Room temperature (R.T.) and 40±0.5 ^{o}C for a period of 6 months. The samples were withdrawn after 30, 60, 120 and 180 days and analyzed for physical appearance, drug content and folding endurance.

III. RESULTS AND DISCUSSION

Physico-Chemical Evaluation

In the present investigation solvent evaporation technique is adopted & it was found to be giving thin uniform films. The films were transparent with smooth surface indicating good miscibility of both the polymers. The physicochemical evaluation data presented in Table **3** indicates that the thickness of the matrix films varies from 0.118±0.06 mm to 0.25±0.054 mm. All the formulations exhibited thickness with low standard deviation values ensuring the uniformity of the films prepared by film casting method. Formulations were not thick enough to

International Journal of Pharmaceutical Research and Applications
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produce any irritation while placing and being in cul-de-sac as inferred from ocular irritancy test.

The results showed that weights of formulations ranged from 4.09±0.069 mg to 9.09±0.04 mg. The drug content of all the formulations was found to be within the range of 0.495±0.002 mg to 0.51±0.007 mg for matrix films. The minimum intrabatch variations revealed the suitability of the process used to prepare the ocular inserts.

The folding endurance for all formulations was good. The maximum folding endurance of formulation F3 was 99.3±2.51 foldings and formulation F7 showed minimum folding endurance of 61.3±2.08 foldings. This showed that as the concentration of polymer increased in the formulation, folding endurance was decreased. It was also observed that as the proportion of PEO in PMMA increases, flexibility of films increases as indicated by increasing folding endurance values. High tensile strength values indicate good physical strength of the films. As polymer ratio increases, tensile strength decreases. The surface pH of the prepared inserts varied between 6.5 to 7.5, indicating that the inserts did not have an irritation potential as the pH is within the accepted ocular range [29].

Surface Morphology (SEM)

SEM study (Fig. **1**) revealed that surface of the ocular films are smooth indicating the complete miscibility of PEO with PMMA. This finding is similar to that of J.baldrian who suggested that when the concentration of PEO is less than or equal to 20wt. %, the polymers are completely miscible and the blend is amorphous. This result is also sup- ported by DSC and XRD studies (Figs. **2** & **3**).

Hydrophilicity

Static STF Contact angles (θs) of films were below 50 (data not shown) indicating increasing hydrophilicity of the surface as the concentration of PEO increased in the matrix. As θ_s is only related to the outermost 10Å of each samples, the surface composition of blend is greatly correlated with θ_s. This result also reveals that PEO was uniformly dis- tributed throughout the bulk of PMMA and concentration of PEO at surface increases with bulk concentration, making the insert hydrophilic enough to be wetted by tear fluid and adhere to corneal surface for longer duration.

Table 3.Physicochemical Evaluation Data of Different Batches of Ocular Films.

Formulation	Weight of Films (mg)*	Thickness (mm)#	Tensile Strength# Kg/cm^2	% Elongation at Break#	Folding Endurance#
F1	4.09± 0.069	0.118± 0.06	0.75 ± 0.03	3.26± 0.21	69±2
F2	4.2± 0.046	0.13± 0.0063	0.68 ± 0.01	8.13± 0.23	90.3±2.08
F3	4.11± 0.052	0.148± 0.0075	0.57 ± 0.01	12.63± 0.4	99.3±2.51
F4	6.43± 0.094	0.19 ± 0.05	0.84 ± 0.02	2.95± 0.32	65.3±3.51
F5	6.49± 0.082	0.20± 0.007	0.72 ± 0.01	7.18± 0.43	81±2.61
F6	6.44± 0.044	0.21± 0.0054	0.65 ± 0.01	12.17± 0.21	94.6±2.08
F7	8.89± 0.057	0.24± 0.003	1.84 ± 0.05	2.28± 0.32	61.3±2.08
F8	9.09± 0.04	0.248± 0.004	0.92 ± 0.02	7.89± 0.46	73.3±2.52
F9	8.91± 0.052	0.25± 0.054	0.80 ± 0.02	11.93± 0.54	89.6±3.78

All readings are in the form of Mean±SD, # Average of 3 runs, *Average of 10 determinations.

International Journal of Pharmaceutical Research and Applications
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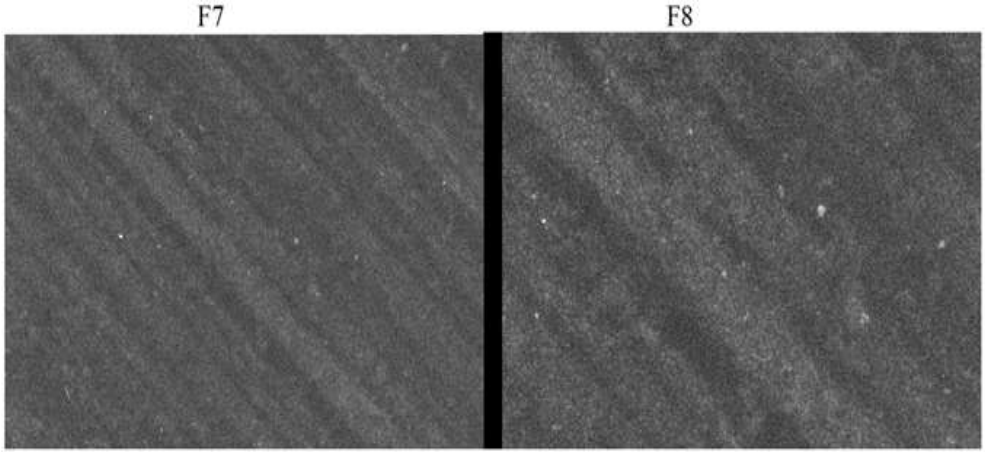

Fig. (1). Scanning electron microscopy (SEM) images of inserts F7 and F8. Experimental condition: magnification= ×1000, Acc. V 20 kV, signal SEI, ___ 10 µm.

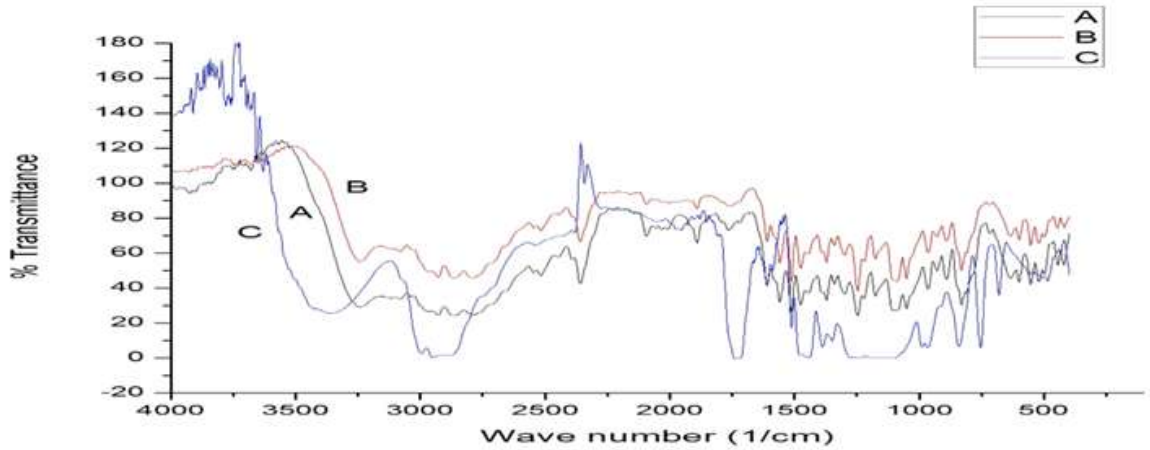

Fig. (2). IR Spectra of (A) Betaxolol HCL (B) Mixture of PMMA/ PEO/BX (C) Ocular Insert F8.

Drug-Excipients Compatibility Study

Interpretation of IR spectrum of Betaxolol (Fig. **2A**) shows characteristic peaks at 3237 cm^{-1} (Hydroxyl group O-H stretching), 2928 cm^{-1} (Methyl C-H stretching), 2858 cm^{-1} (Methylene C-H stretching), 1612 cm^{-1} (Aromatic ring C=C-C stretching), 1557 cm^{-1} and 1513 cm^{-1} (Secon- dary amine N-H bending), 1474 cm^{-1} (Methylene C-H bending), 1376 cm^{-1} (Methyl C-H sym. bending), 1246 cm^{-1} (alkyl aryl ether c-o-c stretching), 1179 cm^{-1} (aromatic in plane C-H bending), 1087 cm^{-1} (aliphatic ether c-o-c stretch- ing) and 1050 (Amine C-N stretching). FTIR spectra of mixture (Fig. **2B**) and insert F8 (Fig. **2C**), in comparison to IR spectra of pure drug, show no substantial shifting of the position of the functional groups, indicating no major interaction between drug and polymers. However, broadening and reduced intensity of peaks in IR spectra of inserts indicates encapsulation of betaxolol in polymeric matrix. Although shifting and broadening of drug peak at 3237 cm^{-1}in the IR spectra of Insert F8 indicate that hydrogen bonding has occurred between the lone electron pairs of the oxygen atom of polymers and the hydrogen atom of the hydroxyl group ofthe drug.

Physical State of Drug

DSC

From the overlay of the DSC thermograms, it has been observed that Betaxolol is crystalline in nature (Fig. **3**). Thermogram exhibited a sharp melting endotherm at an onset temperature of 112.82 ^{0} C, a peak temperature of 119.76 ^{0} C and a heat of fusion of 6.97 J/g. While the thermogram of film shows crystallization of betaxolol from glass at 67.18 ^{0} C followed by fusion at 116.89 ^{0} C. The thermal behavior of film suggested that the drug is present in the film

International Journal of Pharmaceutical Research and Applications
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as semicrystalline form as the fusion peak in the film is very weak compared to the pure drug.

XRD

XRD spectrum of Betaxolol (Fig. **4**) revealed that the drug is crystalline in nature. XRD pattern of film showed that characteristic peaks of betaxolol were reduced in number and intensity indicating that the drug crystallinity was decreased in the inserts.

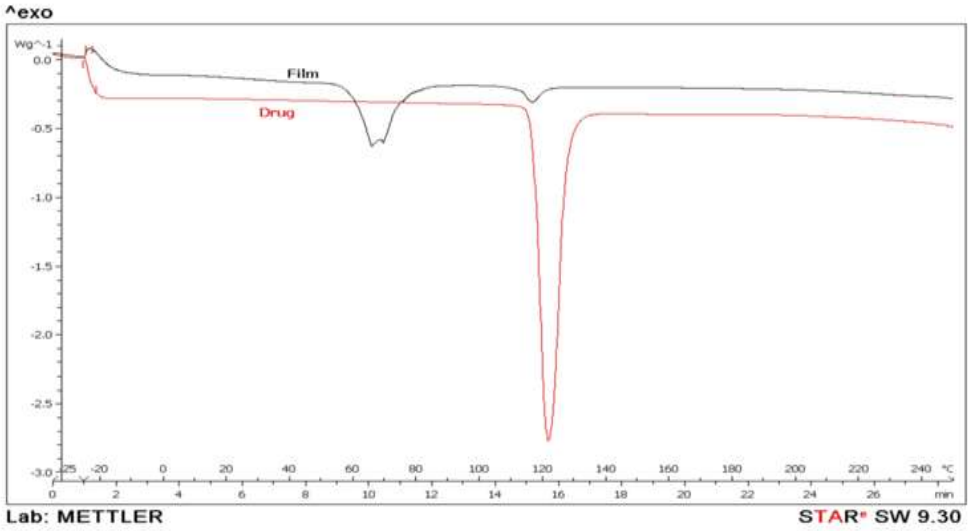

Fig. (3). DSC spectra of pure drug and ocular film.

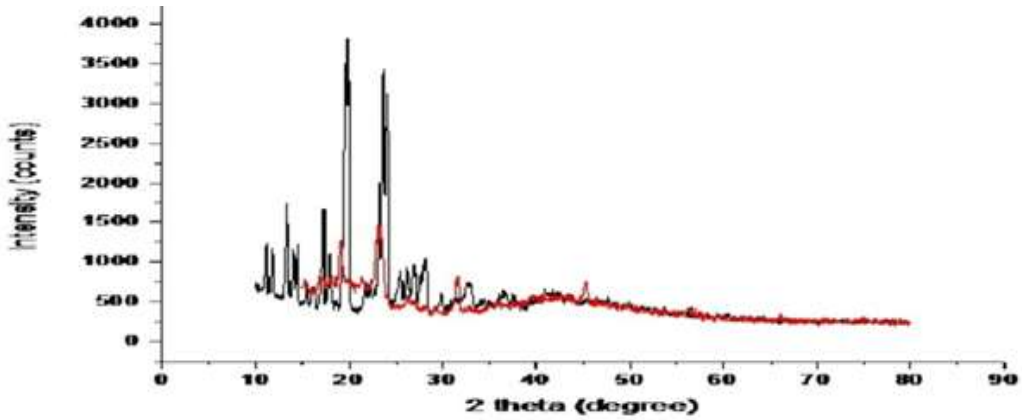

Fig. (4). XRD patterns of Betaxolol (black line) and Insert F8(red line).

In Vitro Diffusion Study

In vitro results revealed that drug release from inserts was influenced by both the factors namely polymer concentration and polymer composition.

Effect of Polymer Concentration

In vitro permeation profile shows that concentration of polymer in the film plays a very important role on drug permeation. ANOVA study shows that factor A (drug to polymer ratio) has significant effect on maximum drug permeated i.e. (Fig. **5**) shows that as concentration of polymer increases there was decrease in drug permeation.

Result of flux (Table **4**) also favors that drug release was inversely proportional to polymer concentration. Among all batches, maximum flux was found in case of F3 i.e. 0.01730 mg/cm^{2}hr.

Diffusion of molecule through polymer matrix was rate limiting step for permeation of molecule. The process of drug release in most controlled release devices is governed by diffusion, and the polymer matrix has a strong influence on the diffusivity as the motion of a

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small molecule is restricted by the three-dimensional network of polymer chains. It has been reported that diffusion rate of molecule is inversely proportional to diffusion path [30]. Thickness of inserts increases with increasing the amount of polymer. This lead to an increase in diffusion path of molecules and so less release was observed in case of formulation containing high concentration of polymer. Descending order of cumulative drug permeated was found in following order:

Eye drops>F3> F6 > F2 > F5 > F1 > F9 > F4 > F8 > F7

Effect of Polymer Composition

In vitro permeation study shows that change in polymer blend will alter the drug permeation profile. ANOVA study shows that factor B (HPMC to EC ratio) has significant effect on drug permeation profile.

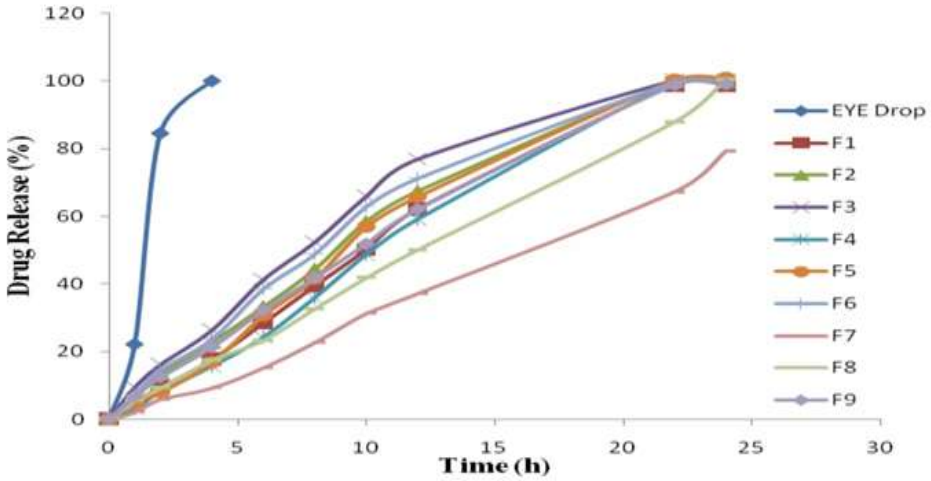

Fig. (5). In vitro drug release profile of ocusert.

Table 4.Permeation Parameters of Betaxolol Through Membrane.

Formulation	Diffusion Rate D_R	Flux J_S	Permeability Coefficient K_P
	mg/h	mg/cm^2h	cm/h
F1	0.0247	0.013958	2.79×10^{-2}
F2	0.0273	0.015459	3.09×10^{-2}
F3	0.0306	0.017299	3.46×10^{-2}
F4	0.0236	0.013364	2.67×10^{-2}
F5	0.0252	0.014275	2.86×10^{-2}
F6	0.0286	0.016195	3.24×10^{-2}
F7	0.0170	0.009609	1.92×10^{-2}
F8	0.0221	0.012514	2.50×10^{-2}
F9	0.0256	0.014499	2.90×10^{-2}

Average diffusion rate of formulation F1 to F3 was found 0.0247, 0.0273 & 0.0306 mg/h respectively. This shows that diffusion rate was increased with increase in PEO concentration. Similar observations were also found in case of batches F4 to F6 and F7 to F9. Result of flux also indicates that drug release was directly proportional to PEO concentration.

Results showed that increasing concentration of PMMA will retard the drug

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release and so drug permeation. Release rates were increased when the concentration of PEO increased in the formulations. This is because as the proportion of this polymer in the matrix increased, there was an increase in the amount of water uptake and hydration of the polymeric matrix and thus more drugs was released. The polyether chains of PEO can form strong hydrogen bonds with water, therefore, when inserts are brought into contact with an aqueous medium, the polymer tends to hydrate, forming a superficial gel which eventually erodes as the polymer dissolves. This is due to the fact that dissolution of aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to decrease in the mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate.

The kinetic treatment of diffusion data is shown in Table **5**. It can be concluded that Korsemeyer and Peppas model fit the best for all the formulations as correlation coefficient value for all the inserts were more than 0.98. This is followed by Higuchi and zero order equation. Inserts F4, F5 and F7 released drug according to super case II transport mechanism while drug release from rest formulations followed anomalous transport. Drug release from such matrices may be controlled by polymer swelling or erosion, or drug diffusion in the hydrated gel, or by these processes altogether.

In Vivo Studies

The ocular insert showed 99.87% of drug release in vivo at the end of 24 hours which was comparable to in vitro drug release (Fig. **6**). Thus there was good in vitro – in vivo correlation for the ocular insert F8 indicating the effectiveness of the formulation to be used in vivo. Difference factor of 0.0004 and similarity factor of 80.29 for the in vitro-in vivo release data of formulation F8 indicates no significant difference between in vitro release and in vivo performance of the inserts.

Table 5.Kinetic Treatment of Release Study Data of Ocular Inserts.

Formulation	Zero Order	Higuchi	Korsmeyer – Peppas	
	R^2	R^2	R^2	N
F1	0.9869	0.9789	0.995	0.9573
F2	0.9714	0.9869	0.9944	0.8522
F3	0.933	0.9836	0.9867	0.7785
F4	0.9904	0.9721	0.9937	1.095
F5	0.9752	0.9826	0.9871	1.024
F6	0.9517	0.9891	0.9881	0.8423
F7	0.9951	0.9445	0.9935	1.107
F8	0.9986	0.9552	0.9963	0.9215
F9	0.9859	0.9847	0.9979	0.8661

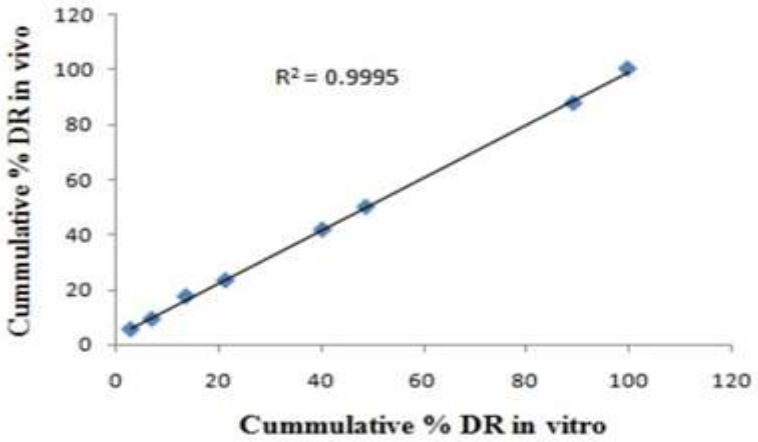

Fig. (6). In vitro – in vivo correlation for formulation F8.

International Journal of Pharmaceutical Research and Applications
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The ocular safety score of the formulation F8 was found to be 3 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 inserts. Thus, it can be concluded that inserts were safe for ocular administration.

In vivo IOP lowering study results (Fig. **7**) revealed that in comparison to eye drops, formulation F8 showed better control of IOP up to 24h ($P< 0.001$).

A single instillation of one drop of 0.5% betaxolol eye drops controlled IOP well to the base level up to the period of 8 h and then after IOP was increased, while same dose of betaxolol from insert F8 controlled IOP up to 24 h. Peak effect was observed at 4 h and 6 h in case of eye drops and F8 respectively. The interesting finding of the study was that IOP was also lowered effectively in control eyes of eye drop treated group, which was not the case for inserts treated group. This can be an indirect measure of systemic absorp tion of the drug following eye drops treatment, indicating that ocusert provides better control over systemic side effects.

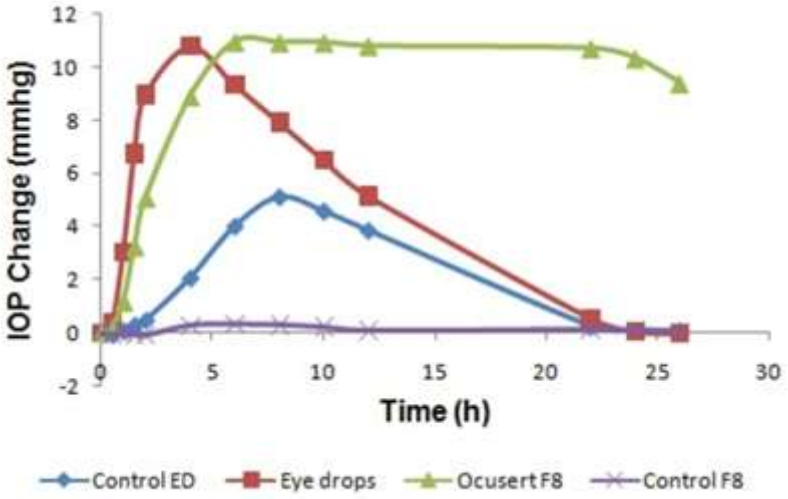

Fig. (7). IOP lowering study.

Stability Study

Stability study of the ocular insert F8 was performed at R.T., 4°C and 40°C for the period of 6 months. The results showed that there was no change in physical appearance of ocular inserts. The drug content showed no marked change after six months and folding endurance were good indicating no change in flexibility of the films. These results concluded that ocular insert F8 was chemically and physically stable at RT for 6 months. However, further studies at different temperatures and humidity conditions are needed to establish their shelf life.

IV. CONCLUSION

The ocular inserts prepared and evaluated in the current study are transparent and uniform in physicochemical properties. Due to addition of hydrophilic polymer, the surface of inserts was hydrophilic enough to be easily wetted by tear film. The blend of PEO in PMMA matrix was found to be homogenous and blend was amorphous in nature. No phase separation was observed in polymer composite as revealed from SEM, DSC and XRD studies. Thus the present work showed that incorporation of hydrophilic polymer into hydrophobic matrix system can be successfully done in order to model ocular inserts providing promising controlled release delivery system. Blending of PEO into PMMA matrix was uniform and it was observed that increasing the proportion of PEO in to PMMA increases the rate of release of betaxolol. The control of IOP, systemic absorption and hence possible side effects using inserts was found to be better than conventional eye drops. Thus, on the basis of In vivo antiglaucoma activity, ocular safety test and stability studies, it can be concluded that this betaxolol ocular insert can be a promising once-

a-day controlled release formulation after due considerations of human in vivo studies.

REFERENCES

[1]. Jain N.K. "Controlled and novel drug delivery". First Edition 1997, Reprint 2009, CBS publishers and distributors, 11 Darya Ganj, New Delhi-110002 (India) (1997): 82-89.
[2]. Beringer Paul., et al. "Remington the science and practice of pharmacy". 21st edition 2005, third Indian reprint 2009, Wolter kulwer publication (India) Pvt. Ltd., New Delhi (2005):850-862.
[3]. Thamizhvanan K., et al. "Current status and advanced approaches in ocular drug delivery system". IJCP and CR 2.2 (2012): 77-82.
[4]. Cheien YW. "Drugs and the pharmaceutical sciences novel drug delivery systems". Second edition, revised and expanded, volume 50, Informa health care USA inc. 52 Vanderbit avenue New York NY 10017, page no. 269-270.
[5]. Thakur Richa and Swami Gaurav. "Promising implication of ocuserts in ocular disease". JDDT 2.2 (2012): 18-19.
[6]. Gamal El SS., et al. "Formulation and evaluation of Acyclovir ophthalmic inserts". AJPS 3.2 (2008): 58.
[7]. Imam Sarim., et al. "Novel ocular dosage form in the treatment of glaucoma". The Pharma Research 1 (2009): 76-78.
[8]. Gevariya Hitesh B. "Formulation and evaluation of sustained release ocular drug delivery system for an anti-glaucoma drug". Saurashtra University (2013): 1-21.
[9]. Bankar GS and Rhodes CT. "Drug and the pharmaceutical sciences modern pharmaceutics". Second edition, revised and expanded, Volume 40, Marcel Daker, inc., 270 Madison Avenue, New York, New York 10016, page no. 573-574.
[10]. Brahmankar DM and Jaiswal S.B. "Biopharmaceutics and pharmacokinetics a treatise, second edition, reprint 2010, Vallabh prakashan New Delhi-110088. 473.
[11]. Kumar KP Sampath., et al. "Ocular inserts novel controlled drug delivery system". TPIJ 1.12 (2013): 1-14.
[12]. Karthikeyam D. "The concept of ocular inserts as drug delivery systems: An overview". AJP (2008): 194-196.
[13]. Dabhi V., et al. "Ocular inserts as controlled drug delivery systems". IJPRBS 3.5 (2014): 468-480.
[14]. Hashem M F., et al. "Formulation, characterization and clinical evaluation of micro-emulsion containing Clotrimazole for topical delivery". AAPS PharmSciTech 12.3 (2011): 879.
[15]. Bansal S., et al. "Nanaocrystals: current strategies and trends technology". 4 (2012): 6.
[16]. Jain NK. "Introduction to novel drug delivery system". first edition- 2010, Vallabh prakashan, C-5, SMA coop. industerial estate, GT karnal road, Delhi-110033, page no. 115.
[17]. Dinda S.C. "Advances in pharmaceutical technology". Pharmamed press 4-4-316, Giriraj Lane Sultan Bazar, Hyderabad-500095. (2011): 398-401.
[18]. Shankar V., et al. "A text book of novel drug delivery system". 2012, Pharmamed press 4-4-316, Giriraj Lane Sultan Bazar, Hyderabad -500095. Page no. 398-401.
[19]. Parmar B Ramesh and Dr HM Tank. "Design, formulation and evaluation of reservoir type controlled released Moxifloxacin hydrochloride ocular inserts". AJRPS 3.1 (2013): 19-24.
[20]. Singh RK and Khatri OP. "A scanning electron microscope based new method for determining degree of substitution of sodium carboxy methyl cellulose". Journal of Microscopy 246 (2012): 43-52.
[21]. Banu S, Farheen SA. Ocular Drug Delivery System: A Novel Approach. Asian Journal of Research in Pharmaceutical Science. 2019;9(2):97-106.
[22]. Kumari A, Sharma P, Garg V, Garg G. Ocular inserts - Advancement in therapy of eye diseases. J Adv Pharm Technol Res. 2010;1(3):291-6.
[23]. Rajesh A, Poonam D, Sangeeta A. Ocular drug delivery system: ocular insert. International Journal of Universal Pharmacy and Bio Sciences. 2012;1(2):30-8.
[24]. Kumari A, Sharma PK, Garg VK, Garg G. Ocular inserts - Advancement in therapy of eye diseases. J Adv Pharm Technol Res. 2010;1(3):291-6.
[25]. Ghosh S, Barik B. Formulation and in vitro evaluation of once daily sustained

release formulation of aceclofenac. Tropical journal of pharmaceutical research. 2010;9(3):265-73.

[26]. Freire F, Aragão C, de Lima e Moura T, Raffin F. Compatibility study between chlorpropamide and excipients in their physical mixtures. Journal of thermal analysis calorimetry. 2009;97(1):355-7.

[27]. Renu C, Swati B. Drug–excipient compatibility screening—Role of thermoanalytical and spectroscopic techniques. Journal of Pharmaceutical and Biomedical Analysis. 2014;87:82-97.

[28]. Oliveira G, Ferraz H, Matos J. Thermoanalytical study of glibenclamide and excipients. Journal of thermal analysis calorimetry. 2005;79(2):267- 70.

[29]. Ibrahim HK, El-Leithy IS, Makky AA. Mucoadhesive Nanoparticles as Carrier Systems for Prolonged Ocular Delivery of Gatifloxacin/ Prednisolone Bitherapy. Molecular Pharmaceutics. 2010;7(2):576-85.

[30]. Kalyanwat R, Shrivastava B, Pathak K. Preparation and Evaluation of bioadhesive ocular inserts of aceclofenac. International Journal of Pharmaceutical Sciences Review and Research. 2016;41:207-13.