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FORMULATION AND EVALUATION OF OCULAR INSERTS FOR THE TREATMENT OF GLAUCOMA

Sujith S Nair*, Anjali Rajan MP and Sreena K

Crescent College of Pharmaceutical Sciences, Kannur, Kerala, India 670358.

ABSTRACT

Glaucoma is a condition that damage optic nerve and gets worse over time. It increases the pressure inside your eye. Glaucoma tends to be inherited and may not show up until later in life. The increased intraocular pressure, can damage the optic nerve. Without treatment, glaucoma can cause total permanent blindness within a few years. The problem arises with conventional dosage forms can be overcome by formulating ocular inserts. In this study atenolol is used as model drug. Atenolol is a beta blocker, and it exhibits physico-chemical properties similar to timolol maleate. In this study the influence of various polymers like hydroxypropyl methylcellulose and polyvinyl alcohol in different concentrations on drug release kinetics was studied. The data were subjected to pharmaco-kinetic analysis and various physical characteristics of films were evaluated. *In vitro* release revealed that formulation HPMC4 followed perfect zero order kinetics release. It was also observed that the release of drug increases with concentration of polymer up to an optimum concentration. From the present work, it was concluded that this ocular insert can be an innovative and promising approach for the delivery of atenolol with improved bioavailability, enhanced drug release with better patient compliance and as an effective therapy for the treatment of glaucoma.

Keywords: Glaucoma, Atenolol, Beta blocker, Ocular insert, Hydroxypropyl methylcellulose, Polyvinyl alcohol.

INTRODUCTION

Glaucoma is a condition that damage optic nerve and gets worse over time. It increases the pressure inside your eye. Glaucoma tends to be inherited and may not show up until later in life. The increased intraocular pressure can damage the optic nerve. Without treatment, glaucoma can cause total permanent blindness within a few years. It's the result of high fluid pressure inside your eye. This happens when the liquid in the front part of the eye doesn't circulate the way it should [1].

Normally, the fluid, called aqueous humor, flows out of your eye through a mesh-like channel. If this channel gets blocked, the liquid builds up. That's what causes glaucoma. The reason for the blockage is unknown, but doctors do know it can be inherited, meaning it's passed from parents to children. Less common causes include a blunt or chemical injury to your eye, severe eye infection blocked blood vessels inside the eye and inflammatory conditions. It's rare, but sometimes eye surgery to correct another condition can bring it on. It usually affects both eyes but it may be worse in one than the other. There are two main kinds [1]. Open-angle glaucoma**.** It's the most common type. Your doctor may also call it wide-angle glaucoma. The drain structure in your eye -- it's called the trabecular meshwork -- looks normal, but fluid doesn't flow out like it should. Angle-closure glaucoma, it can also be called as acute or chronic angle-closure or narrow-angle glaucoma. Eye doesn't drain right because the angle between the iris and cornea is too narrow. This can cause a sudden build up of pressure in eye. It's also linked to farsightedness and cataracts, a clouding of the lens inside your eye.

Topical beta blockers are often used as a front line drug for the treatment of glaucoma. These drugs block β_2 receptors present on ciliary epithelium there by reduces aqueous humour formation without affecting pupil size, tone of ciliary muscle, or outflow facility. This effect is probably because, down regulation of adenylcyclase due to

Corresponding Author:-**Sujith S Nair** Email: tosujithsnair@gmail.com

$\beta_2$receptor blockade and a secondary effect due to reduction in ocular blood flow[2].

Pharmaceutical technologists are advanced in developing drug delivery systems with very precise control over drug release for a prolonged period of time, dominating the need for a frequent dosing and minimizing side effects thereby increasing patient compliance and comfort. In conventional mode of therapy, many drugs do not reach the target site in the body in sufficient concentration because of prematurely inactivated and excreted. This problem can be overcome by administering the drugs directly into the intended site of action with lesser dose [2].

Ocular drug delivery is one of the most challenging tasks faced by Pharmaceutical researchers. Major barriers in ocular medication are the ability to maintain a therapeutic level of the drug at the site of action for a prolonged duration. The introduction of new sensitive diagnostic techniques and therapeutic agents necessitates the development of a successful and advanced ocular drug delivery system [3]. The main objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue, to ensure a sustained release suited for topical or systemic treatment. The advantages of ocular inserts over the traditional ophthalmic preparation can be summarized as it increase ocular residence time hence, prolonged drug activity and higher bioavailability with respect to standard vehicles. All of the benefits specified above cannot be present in a single, ideal device. Each type of insert is a compromise between the desirable properties inherent to solid dosage forms and negative constraints possessed by the structure and components of the insert, fabrication costs, and physical / physiological constraints of the application site.

MATERIALS AND METHODS

The polymers used were proven that having analytical grade. The equipments and apparatus provided were with high standard and validated.

Pre-formulation studies

Pre-formulation testing was an investigation of physical and chemical properties of drug alone and also determination of the quality and purity of excipients used. It is the first step in the rational development of dosage form. Preformulation studies employed include determination of melting point, solubility and organoleptic properties. While designing a formulation of ocular insert it is necessary to give importance on drug-polymer interaction within the system. So it is important to find out whether there is any interaction between Atenolol and polymers used in the formulation. The study was performed using Fourier Transform Infra-red Spectroscopy.

Formulation of ocular insert

Ocular inserts were prepared by solvent casting method [4]. Specified amount of polymer of different concentration was weighed and dissolved in specified amount of water and kept overnight to get a uniform dispersion of the solution in a beaker. Required quantity of drug, Poly ethylene glycol, were dissolved in small amount of purified water in another beaker and then added to the polymeric dispersion. In a separate beaker plasticizers were dissolved in required quantity of ethanol and this ethanolic solution was then added to the drug polymer mixture and stirred using a mechanical stirrer for 1 hour at a speed of 1100 to 1200 rpm for 40-120 minutes to get a uniform dispersion. The obtained uniform mixture was then casted on each Petri plates. It was then dried at room temperature for 24 hours. The obtained films were then wrapped in butter paper which was covered by aluminium foil and was stored in a desiccator.

Evaluation of prepared ocular insert

Ocular inserts were evaluated for parameters like appearance, pH, tensile strength, weight variation, folding endurance, drug content uniformity and *in vitro* drug release.

Visual inspection of formulation

The prepared formulations were evaluated visually for its clarity, transparency and stickiness. The selected formulations were taken for further evaluations [2].

Weight variation test

Inserts from each batch were randomly selected and weighed individually on electronic balance, mean weight of inserts of each formulation was recorded [5].

Folding endurance

The film was folded at centre, between the fingers and the thumb and then opened. This was termed as one folding. The process was repeated till the film showed breakage or cracks in the centre. The total folding operations were named as folding endurance value [6].

Tensile strength

Tensile strength of the film was determined using an apparatus fabricated. The tensile strength can be calculated using the formula,

$$\text{Tensile strength} = \frac{(\boldsymbol{Break\ Force})}{\boldsymbol{a \times b}} \frac{(\mathbf{1}+\triangle \boldsymbol{L})}{\boldsymbol{L}}$$

Where a is the thickness of the film, b is the width of the film , ΔL is the length of elongation, L is the length of the film [7].

Drug content uniformity

Ocular insert was dissolved individually in methanol in a 100ml volumetric flask. Then required volume of solution was taken out and further dilutions were made with STF pH7.4. Similarly, a blank was carried

out using a drug free insert. Then absorbance was taken at 275 nm by UV spectroscopy [8].

***In vitro* drug diffusion study**

The drug release was studied using the classical biochemical donor- receptor compartment model comprising a cylindrical tube and a glass beaker fabricated in the laboratory. A dialysis membrane was tied at one end and it acted as donor compartment. The insert was placed inside this compartment. The entire surface was in contact with receptor compartment containing 25ml of STF. At specific time intervals samples were withdrawn from the receptor compartment and replaced with fresh STF. The samples were analysed using UV spectrophotometer at 275 nm [9].

Stability studies

The stability studies of the optimized films were carried out at a temperature of 40± 2ºC/ 75 % RH,Room temperature: 30± 2^0C; 60 ± 5 %. RH, and refrigerated temperature; 4ºC for 3 months in stability chamber. The film was wrapped in a butter paper followed by aluminium foil and sealed in air tight plastic pouch. The films were evaluated for physical parameters, *in vitro* drug release, pH, and drug content for initial, 30 days and 90 days after storage [10].

RESULTS

The results of the **physico chemical characteristics** of the selected formulations after preliminary evaluation and visual inspection are given in table no.3.

***In vitro* diffusion study**

The invitro diffusion studies were conducted on formulations using the classical biochemical donor – receptor compartment model comprising a cylindrical tube and a glass beaker fabricated in the laboratory. The drug release profiles of prepared films were tabulated and the release of drug is shown in figure 1 and 2. From the in vitro diffusion studies formulations HPMC4 and PVA 5 were selected and when comparing the two it was found that HPMC4 has more drug content and faster drug release were selected for the further kinetic release and stability studies.

Kinetics / release pattern of the selected formulation

For analyzing the mechanism of drug release kinetics of the film HPMC4, the data obtained were fitted to various kinetic equations of zero order, first order, Higuchi model and Korsmeyer- Peppas model. The regression coefficient was calculated. Graphs of kinetic models were plotted with suitable data and regression coefficients obtained are summarized in table no 4.

Stability studies

The optimized formulation HPMC4 was evaluated for the stability studies and it was found that there is no significant change in appearance, pH, folding endurance, drug content, invitro diffusion and percentage drug release.

Table 1. Formulation of ocular insert with HPMC E15

Ingredients	Formulation code				
	HPMC1	HPMC2	HPMC3	HPMC4	HPMC5
Atenolol	50	50	50	50	50
HPMC E15	100	200	300	400	500
PEG400	1.5	1.5	1.5	1.5	1.5
Ethanol	5	5	5	5	5
Water	q.s	q.s	q.s	q.s	q.s

Table 2. Formulation of ocular insert with PVA

ingredients	Formulation code				
	PVA 1	PVA2	PVA3	PVA4	PVA5
Atenolol	50	50	50	50	50
PVA	100	200	300	400	500
PEG400	1.5	1.5	1.5	1.5	1.5
Ethanol	5	5	5	5	5
water	q.s	q.s	q.s	q.s	q.s

Table 3. Physicochemical characteristics of the selected formulations

Formulations	Average thickness	Average weight	Tensile strength	Surface pH	Folding endurance	Drug content
HPMC3	0.02±0.0057	0.0043±0.0005	1.23±0.03	7.5±0.152	97.66±4.041	97.13±0.02
HPMC4	0.02±0.0115	0.01226±0.001	1.48±0.01	7.6±0.208	204.65±4.61	98.5±0.32
HPMC5	0.04±0.0056	0.00667±0.005	2.57±0.01	7.6±0.152	119.33±3.512	99.2±0.06

PVA3	0.01±0.005	0.0053±0.0015	0.92±0.007	7.6±0.1	88.92±4.041	97.5±0.34
PVA4	0.01±0.0055	0.004±0.0005	1.39±0.004	7.53±0.11	95.72±2.642	98.13±0.2
PVA5	0.03±0.0057	0.0046±0.0015	2.01±0.002	7.57±0.15	227.012±5.50	97.63±0.01

Values expressed as mean ±S.D, n=3

Table 4. Data of regression coefficient of different kinetic models

Formulation Code	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Korsmeyer- Peppas (R^2)
HPMC4	0.673	0.601	0.692	0.844

Fig 1. *In vitro* drug diffusion of Formulation of ocular insert with HPMC E15

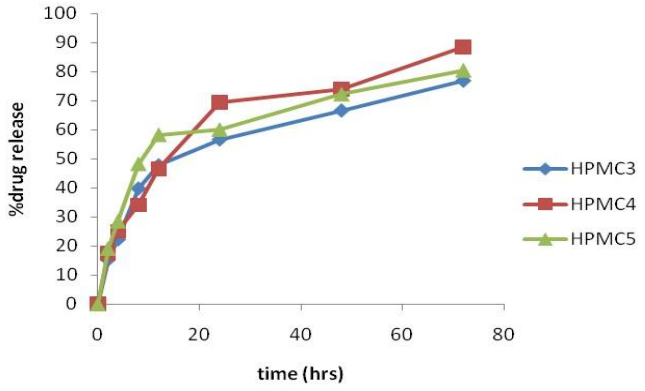
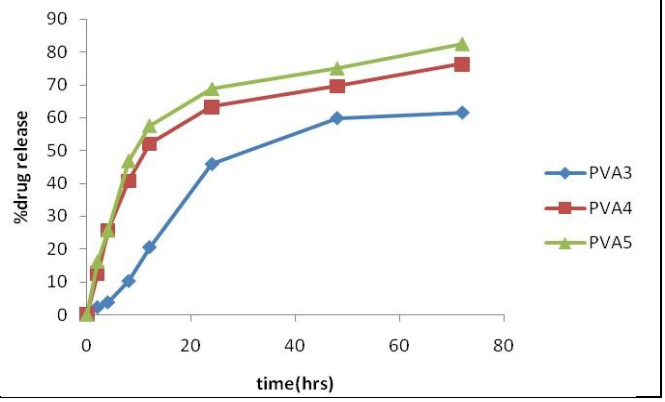


Fig 2. *In vitro* drug diffusion of Formulation of ocular insert with PVA



DISCUSSION

The identification of the drug was done by performing the melting point and FTIR studies. From the result obtained the melting point was found to be 158ºC which complies with the official standards indicating the purity of the sample. From the analysis of the peaks obtained at showed that no major differences were observed in characteristic absorption peak indicating the identity of the drug. The Organoleptic and solubility studies were carried out and the results obtained indicate that both the parameters of the drug comply with Pharmacopoeial standards. The drug was scanned in UV spectrophotometer for determining the absorption maxima (λ_{max}). The λ_{max} was found to be 275 nm. The FTIR spectra of the drug and mixtures of drug and polymer shows that there is no interaction had taken place between the drug and polymer. Hence there is no interaction between the drug and the polymer. The visual inspection of the prepared films was done. From the visual inspection studies it was found that films with low concentration of polymer were brittle in nature and is also having sticky nature. As the concentration of the film forming polymer increases the sticky nature of the film decreased. It was also found that as the concentration of polymer increases above certain limit the toughness of the film was found to increases. Films with moderate concentration of polymer were found to have good, flexible film forming property. The pH of the films was found to be in the range between 7.5± 0.1528 &7.70 ±0.1000. Since the pH of the films was around neutral pH, there will not be any kind of irritation on the mucosal lining of oral cavity. The thickness of the fast dissolving oral thin films was evaluated. The thickness of the films were found to be From the evaluation it was found that as the concentration of polymer increases, the thickness of the film increases. The weight variation test was performed on the selected samples. It was observed that as the concentration of the polymer increases, the weight of the films increases. Tensile strength was found to increase with increase in concentration of the polymer. Estimation of drug content indicated that the drug is uniformly distributed throughout the film for most of the films evidenced by the low values of standard deviation. The *in vitro* diffusion studies were conducted on formulations. For all the polymers used in the formulation, it was observed that films formed by higher concentration of polymer was found to show slow diffusion rate which indicates that increase in level of polymer, results in formation of high viscous gel layer caused by more intimate contact between the particles of the polymer resulting in decreased mobility of the drug particle in swollen matrices, finally leading to decrease in release rate. From the formulation containing HPMC E50, the film HPMC4 was found to release more amount of drug 88.32% drug in 72hrs and from the film containing PVA as polymer PVA 5was found to release more amount of drug that is 82.34% in 72hrs. The films prepared from HPMC4 were found to release more quickly and was found that the optimized formulation HPMC4 follows zero order kinetic model as it had highest R^2 value with Korsmeyer – Peppas mechanism.

CONCLUSION

Ocular insert HPMC4 contains 400mg HPMC E15, 1.5ml PEG 400, was considered as best formulation as it showed suitable satisfactory physicochemical characteristics, with maximum invitro release of 88.32 %. From the present work, it was concluded that this ocular insert can be an innovative and promising approach for the delivery of atenolol with improved bioavailability, enhanced drug release with better patient compliance and as an effective therapy for the treatment of glaucoma. Further studies may be conducted on dose adjustment and on clinical safety in future to prove its complete safety and efficacy.

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CONFLICT OF INTEREST

No interest

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