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Research Article

Preparation and Evaluation of Ocular Inserts containing Brimonidine Tartrate

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ABSTRACT
Ophthalmic inserts of Brimonidine Tartrate (BT) were prepared in polyvinyl alcohol-L (PVA-L) matrix. The influence of rate controlling membranes made of ethyl cellulose (EC) in combination of polyvinyl pyrrolidone-K30 (PVP-K30) in different proportions on drug release kinetics was studied. The data were subjected to regression analysis. The physical characteristics of the films were evaluated. All the films prepared found to be uniform in thickness and in weight. In vitro results revealed that all the formulations followed super case II kinetics release (n > 1). The study confirmed the Brimonidine Tartrate can be delivered through films made of PVA-L matrix cast with EC with a combination of PVP-K30. It was also observed that increasing the proportion of PVP-K30 into EC increased the rate of release of Brimonidine Tartrate. Optimizes formulation F2 were evaluated for *in vivo* release characteristics using rabbits as animal models. The optimized formulation F2 was stable at accelerated storage condition 40°C / 75 % RH and nonirritant.

Keywords: Brimonidine Tartrate, ophthalmic inserts PVA-L, EC, PVP-K30, *in vitro* release.

INTRODUCTION

The eye as a portal for drug delivery is generally used foe local therapy against systemic therapy in order to avoid the risk of eye damage from high blood concentration of drug, which is not intended. The anatomy, physiology and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. Most ocular treatments like eye drops and suspensions call for the topical administration of ophthalmically active drugs to the tissues around the ocular cavity. These dosage forms are easy to instill but suffer from the inherent drawback that the majority of the medication they contain is immediately diluted in the tear film as soon as the eye drop solution is instilled into the cul-de-sac and is rapidly drained away from the pre-corneal cavity by constant tear flow and lacrimo-nasal drainage. Therefore, the target tissue absorbs a very small fraction of the instilled dose. For this reason, concentrated solutions and frequent dosing are required for the instillation to achieve an adequate level of therapeutic effect. [1] One of the new classes of drug delivery systems, ophthalmic inserts, which offer many advantages over conventional dosage forms, like increased ocular residence, possibility of releasing drugs at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf life. [2-4]

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Brimonidine Tartrate is a highly selective α_2-adrenoceptor agonist which reduces intra-ocular pressure (IOP) by reducing aqueous humour production and increasing aqueous humour outflow via the uveoscleral pathway. [5]

The aim of the present investigation is to study the drug release kinetics of Brimonidine Tartrate from a monolithic reservoir system of PVA-L cast with rate controlling membranes made of EC and PVP-K30.

MATERIALS AND METHODS

Materials

Brimonidine Tartrate was obtained as gift sample from Sun Pharmaceutical Industries Ltd., Silvassa, Gujarat. PVA-L was obtained as gift sample from C.D.H. (Pvt.) Ltd., New Delhi and Ethyl Cellulose and PVP-K30 from Colorcon Asia Pvt. Ltd., Goa.

Preparation of ophthalmic inserts

Ophthalmic inserts containing Brimonidine Tartrate were prepared by solvent casting technique-employing mercury as substrate. In the present study, total nine formulations were formulated. They are designated as F_1, F_2, F_3, F_4, F_5, F_6, F_7, F_8 and F_9 respectively. The detailed compositions of the inserts are given in Table 1.

Preparation of drug reservoir

The monolithic drug reservoir patches were prepared from aqueous solutions of PVA-L with inclusion of Brimonidine Tartrate and PEG-400 (plasticizer).The films were cast by mercury substrate method. [6] A glass ring was placed in a pool of mercury, and then the matrix solution containing the drug was loaded onto this ring. It was allow drying uniformly at 40°C for 24 hours. An area of 0.5024 cm^2 containing 3.6 mg of Brimonidine Tartrate was used for all studies.

Table 1: Composition of formulations

Batch code	PVA-L (mg)	EC: PVP K30 (mg)
F1	250	40:60
F2	250	50:50
F3	250	60:40
F4	300	40:60
F5	300	50:50
F6	300	60:40
F7	350	40:60
F8	350	50:50
F9	350	60:40

Drug reservoir contains 90 mg Brimonidine Tartrate.
**** Based on Polymer weight***

Preparation of rate controlling membranes

The rate controlling membranes were prepared from EC: PVP-K30 in different proportions. Weighed quantities of the polymers ratio were solubilized in ethanol with continuous stirring. The matrix solution such prepared was pipette and poured onto a glass ring placed in a mercury pool. The rate of evaporation was controlled by inverting the cut funnel over the petridish. In all the films Dibutyl phthalate (DBP) 30% w/w was incorporated as a plasticizer.

Evaluation of ophthalmic inserts

The above films were evaluated for the thickness of each film using optical microscopic technique. The average of three readings was taken. The mean thickness and standard deviation were calculated. Weight variation test was done by weighing three inserts individually using a digital balance. The average weight of the insert was taken as the original weight In vitro diffusion studies were performed in a fabricated flow through assembly using artificial tear fluid pH 7.4 as media. The uniformity of drug content of the ophthalmic insert was determined, based on the dry weight of drugs and polymers used by means of a UV spectrophotometric method. Formulation were dissolved separately in 10 ml ATF pH 7.4 and stirred for 30 minutes on a magnetic stirrer at 100 rpm. The resulting solutions were quantitatively transferred to volumetric flasks, and diluted suitably with pH 7.4 ATF. The resulting solutions were filtered and analyzed for Brimonidine Tartrate content at 270 nm.

***In vitro* Release studies [7]**

To simulate the actual physiological conditions prevailing in eye, an in vitro open flow through assembly was designed for in vitro determination of drugs in ophthalmic inserts and was used in the present work.

Description of open flow through assembly

A 2 ml glass tube open at both ends was used as an in vitro diffusion cell. Two fluted glass adapters were fused at both open ends so that one formed the other fluted end was used to withdraw samples. The inlet of this tube was connected to a reservoir containing artificial tear fluid pH 7.4. The head of the reservoir was kept constant. Flexible PVC tubing was connected from this reservoir to the cell, in which 2 ml of ATF was maintained constant. The rate of flow of ATF was controlled with a valve.

Procedure

ATF pH 7.4 was put into the reservoir. A small volume of fluid was allowed to drain away, so as to remove any entrapped air bubbles in the cell. An ophthalmic insert was stuck onto a thin small, circular Teflon disc, so that only one surface was exposed to the diffusion fluid. This disc was steadily inserted into the cell containing 2 ml of fluid. The temperature of the fluid was kept at 35 ± 1ºC constantly. At regular intervals the diffusion fluid was taken to analyze for drug content using a UV spectrophotometer at 270 nm.

The in vitro data were analyzed by a zero order kinetics equation as well as Korsemeyer equation [8] to understand the release profile and release mechanism. When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration. The rate of release of the drug can be described mathematically as follows:

$$\text{Rate of release} = (dCs/t) = k$$

Where, Cs = concentration of the drug present in the matrix,

k = rate constant, t = time

Since Cs is a constant, and x = amount of drug released described as

$$dx / dt = k \text{ integration of the equation yields}$$

$$x = k\,t + \text{constant}$$

A plot of x versus t results in a straight line with the slope = k. The value of k indicates the amount of the drug released per unit of time and the intercept of the line at time zero is equal to the constant in the equation. The curves plotted may have different slopes, and hence it becomes difficult to exactly pinpoint which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, in vitro data were also analyzed using Korsemeyer's equation.

Korsemeyer et al. used a simple empirical equation to describe general solute release behavior from controlled release polymer matrices:

$$m_t/m_\alpha = k * t^n$$

Where, m_t/m_α = fraction of drug released,

k = kinetic constant,

t = release time

n = the diffusional exponent for drug release.

The slope of the linear curve gives the 'n' value. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism. When n = 1, the release rate is independent of time (zero order) (case II transport); n = 0.5 for Fickian diffusion; and when 0.5 < n < 1, diffusion and non-Fickian transport are implicated. Lastly, when n >1.0 super case II transport is apparent. 'n' is the slope value of log m_t/m_α versus log time curve.

***In vivo* release study [9]**

For the purpose, six male albino rabbits each weighing 2-2.5 kg were selected. They were fed on standard diet. In which one serves as a control by placing blank insert in cul-de-sac of both eyes. The ophthalmic inserts were placed in the cul-de-sac of both eyes of five rabbits. At regular time intervals, the remaining ocular inserts were removed carefully and analyzed for the drug content using an UV spectrophotometric method at 270 nm. The drug content obtained was subtracted from the initial drug content in the ophthalmic insert which gave the amount of drug released in rabbit's eye.

Stability Studies

The optimized formulation was packed in aluminum foil. It was then stored at 40°C / 75 % RH according to ICH [10]. Samples were withdrawn after three month and evaluated for change in drug release pattern.

Drug Excipients compatibility studies

The drug-excipients compatibilities studies were confirmed by infrared spectrophotometer using KBr disc method. The IR spectra obtained was elucidated for important groups. The identification peaks were found i.e. -NH streching at 3473.91

Table 2: Weight variation, Thickness, Drug content and regression values of zero order and korsemeyer models

Batch Code	Weight variation* (mg)	Thickness* (mm)	Drug Content*	Zero Order		Korsemeyer	
				k	r	n	r
F1	17.92 ± 0.24	0.317 ± 0.0452	99.5 ± 0.34	7.17	0.9998	1.99	0.9999
F2	17.48 ± 0.43	0.358 ± 0.0063	98.7 ± 0.25	4.16	0.9999	2.00	0.9999
F3	17.84 ± 0.16	0.403 ± 0.0247	97.8 ± 0.15	3.39	0.9999	2.00	0.9999
F4	19.63 ± 0.52	0.310 ± 0.0027	99.2 ± 0.36	6.74	0.9999	1.99	0.9999
F5	19.25 ± 0.21	0.362 ± 0.0218	98.4 ± 0.22	4.00	0.9992	2.01	0.9996
F6	19.73 ± 0.36	0.394 ± 0.0145	99.8 ± 0.42	3.18	0.9999	2.03	0.9996
F7	21.71 ± 0.45	0.322 ± 0.0037	98.5 ± 0.18	6.24	0.9999	2.00	0.9999
F8	21.87 ± 0.08	0.357 ± 0.0196	97.6 ± 0.10	3.92	0.9986	2.10	0.9990
F9	22.06 ± 0.18	0.400 ± 0.0061	99.6 ± 0.54	3.05	0.9997	2.09	0.9991

***Each reading is an average of three determinations**

with a shoulder at 3437.26, -CN streching at 1300.07, 2362.88 and 2341.66 two band for the carboxlate ion,1718.63 is the peak for -C=O streching. The IR spectrum is depicted in Fig. 4.

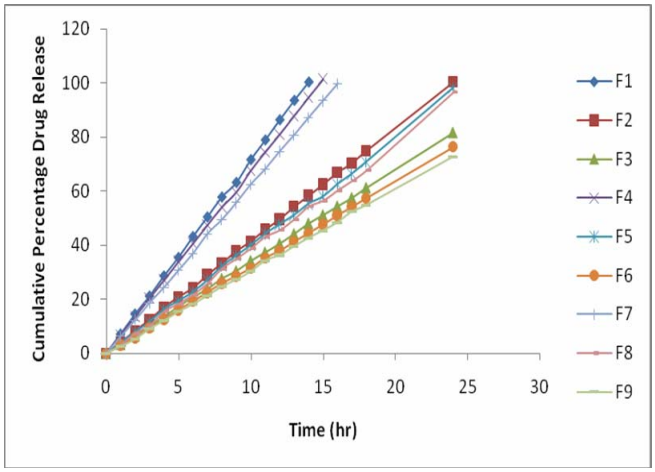

Fig. 1: Comparative drug release profile of inserts

RESULTS AND DISCUSSION

The prepared inserts were translucent, colorless and smooth in texture, uniform in appearance and show no visible crack or imperfection. The inserts had a thickness varying from 0.310 ± 0.0027 to 0.403 ± 0.0247 mm and weight varying from 17.48 ± 0.43 to 22.06 ± 0.18 mg. The drug content was consistent in all batches and varied from 97.6 ± 0.10 % to 99.8 ± 0.42 % (Table 2).

The interaction of Brimonidine Tartrate with polymer was studied using FTIR spectroscopy. It was found that drug had no interaction with polymer as revealed from figure 4.In order to understand the drug release mechanism, the release data was tested assuming common kinetic model [11] (Table 2). It indicates that the release of drug from the patches might have followed super case II kinetics. Drug release pattern from inserts is shown in figure 1.The formulation F2 showed the potential of sustaining the drug release for 24 hrs and hence formulation F2 was selected as optimized formulation. *In vivo* release studies have shown that the formulation F2 is capable of replacing the drug for 24 hrs almost in same pattern, which was found in *in vitro* studies. It was found to release 96.18 % % of loaded drug at 24 hrs. To establish the correlation between in vitro in vivo release data, regression analysis was carried out. The correlation value of 0.999 indicated correctness of the in vitro method followed and adaptability of the delivery system to the biological system where it can release the drug in concentration independent manner Fig. 2. Formulation F2 passed the test for sterility. There was no sign of any irritation, redness, swelling or haziness in the rabbit's eyes used for the study indicating that insert is free from ocular toxicity and safe for ocular use. Stability study performed show no significant changes in drug release from the film which suggest that the film was stable (Fig. 3).

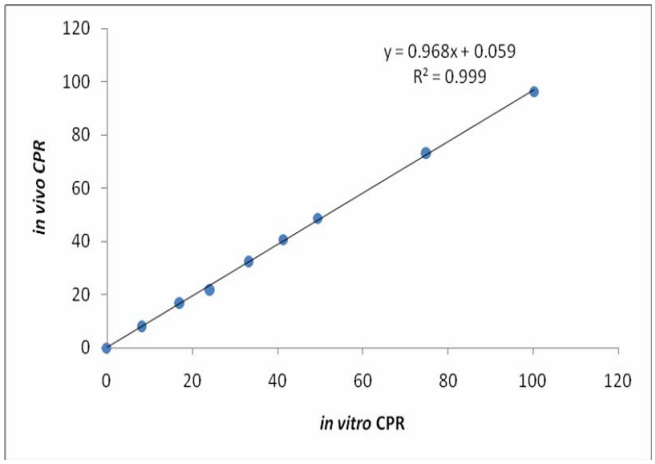

Fig. 2: *In vitro-In vivo* correlation of F2

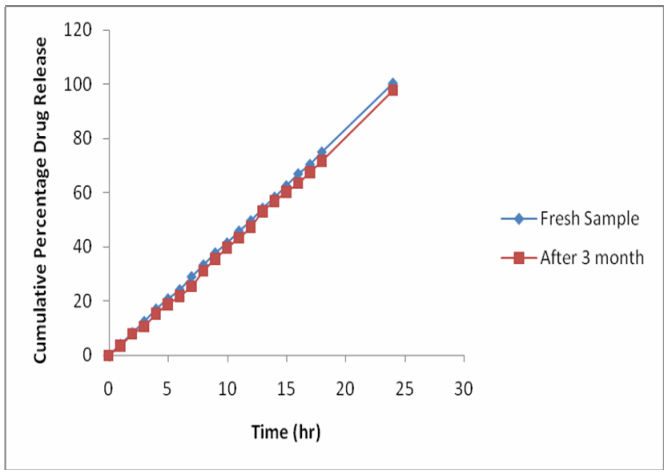

Fig. 3: Drug release profiles of batch F2 evaluated for stability study

CONCLUSION

Developed insert achieved the targets of present study, such as increase residence time, prolonged zero order release, reduction in frequency of administration, and thus improve patient compliance.

Acknowledgments

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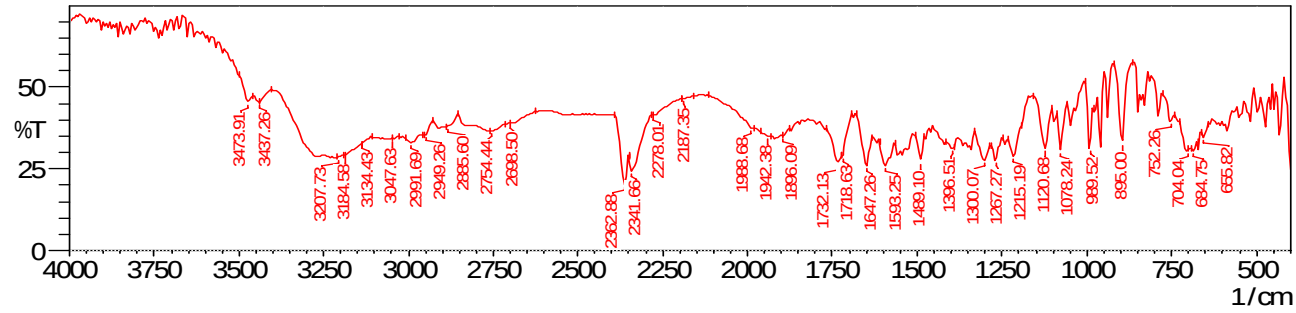
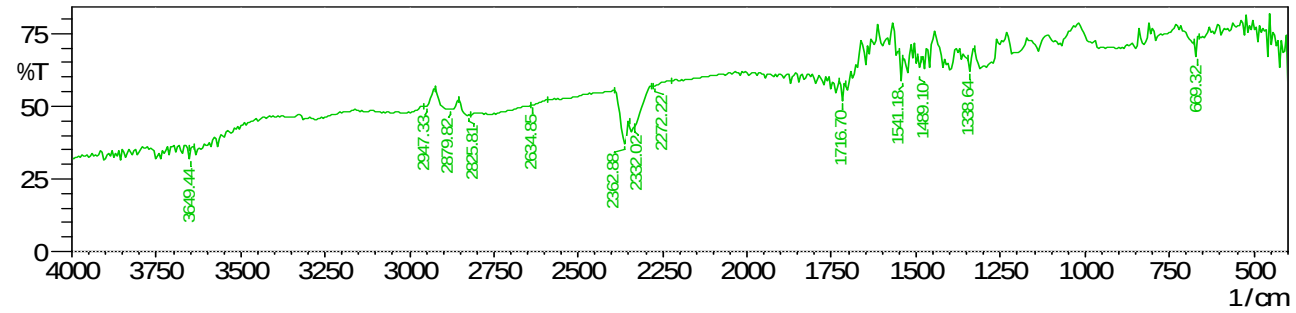
Fig. 4: Interaction study of Brimonidine Tartrate with PVA

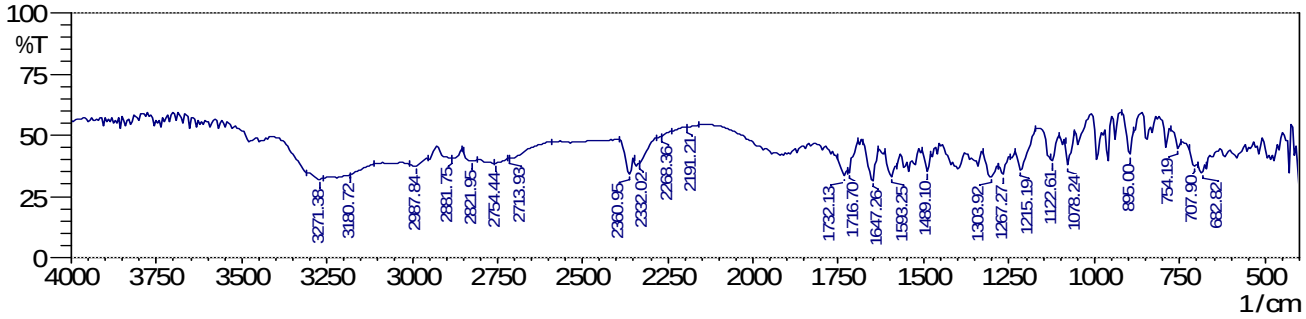
a) FT– IR of Brimonidine Tartrate



b) FT– IR of PVA



c) FT– IR of Brimonidine Tartrate + PVA



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