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 for 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] Brimonidine Tartrate is a highly selective α2-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 F1, F2, F3, F4, F5, F6, F7, F8 and F9 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 cm² containing 3.6 mg of Brimonidine Tartrate was used for all studies.
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 determination of drugs in ophthalmic inserts and was used in the present work.

In vitro Release studies

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.

Table 1: Composition of formulations

<table>
<thead>
<tr>
<th>Batch code</th>
<th>PV A-4L (mg)</th>
<th>EC: PVP K30 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>250</td>
<td>40:60</td>
</tr>
<tr>
<td>F2</td>
<td>250</td>
<td>50:50</td>
</tr>
<tr>
<td>F3</td>
<td>250</td>
<td>60:40</td>
</tr>
<tr>
<td>F4</td>
<td>300</td>
<td>40:60</td>
</tr>
<tr>
<td>F5</td>
<td>300</td>
<td>50:50</td>
</tr>
<tr>
<td>F6</td>
<td>300</td>
<td>60:40</td>
</tr>
<tr>
<td>F7</td>
<td>350</td>
<td>40:60</td>
</tr>
<tr>
<td>F8</td>
<td>350</td>
<td>50:50</td>
</tr>
<tr>
<td>F9</td>
<td>350</td>
<td>60:40</td>
</tr>
</tbody>
</table>

Drug reservoir contains 90 mg Brimonidine Tartrate. * Based on Polymer 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 vivo release study

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 a UV spectrophotometer 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 compatibility 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 stretching at 3473.91 cm⁻¹.
with a shoulder at 3437.26, -CN stretching at 1300.07, 2362.88 and 2341.66 two band for the carboxlate ion,1718.63 is the peak for -C=O stretching. 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).

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

Authors are thankful to Sun Pharmaceutical Industries Ltd., Silvassa, Gujarat, India, for providing gift samples of Brimonidine Tartrate, to Colorcon Asia Pvt. Ltd., Goa, for providing Ethyl Cellulose and PVP-K30 and to C.D.H.(P) Ltd., New Delhi for providing PVA-L.

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

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

*Each reading is an average of three determinations

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

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

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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

REFERENCES