Formulation and evaluation of controlled release ocular inserts of betaxolol hydrochloride

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Abstract—Betaxolol Hydrochloride is a cardio selective β1 adrenergic receptor blocking agent used in the treatment of chronic open angle glaucoma and ocular hypertension. In the present study, an attempt was made to formulate Betaxolol HCl ocular inserts. In matrix type the formulations for Betaxolol containing 10%, 12%, and 14% w/v of Gelatin, 1%, 1.5%, 2%, 2.5% and 3% w/v for Chitosan were prepared by solvent casting method and plasticizer were used in different concentration for smoothing texture of the ocular inserts. The prepared batches of ocular inserts were evaluated for weight variation thickness, drug content uniformity, swelling index. An increase in average weight and thickness is due to increase in polymer concentration. IR spectral studies were performed to confirm the interaction of drug with excipients. All formulations were tested for in vitro drug release (Simulated tear fluid) by vial method. The formulations GH₃ and C₅ show a maximum cumulative percentage drug release of 98.76% and 97.72% at the end of 12th hrs, respectively. The drug release in all formulations decreases as the polymer concentration increases. The dissolution data of formulation were subjected to first order, Higuchi’s, and peppas equations. Drug release from the ocuserts by diffusion controlled mechanism. No significant change in the drug content and physical features was observed during storage at 25°C/60% RH and 40°C/75% RH for the selected formulation for three months.

Keywords—Betaxolol Hydrochloride, Chitosan, Gelatin, Ocular inserts.

I. INTRODUCTION

Betaxolol, Hydrochloride a cardio selective β1 adrenergic receptor blocking agent used in the treatment of chronic open angle glaucoma and ocular hypertension. Continuous delivery of drugs to the eye offers major advantages over conventional therapies that involve administration of drug solutions or suspensions as eye drops. Eye drop administration often results in poor bioavailability and therapeutic response due to rapid precorneal elimination of the drug and is also associated with patient compliance problems. The frequent periodic instillation of eye drops becomes necessary to maintain a continuous level of medication. This gives the eye a massive and unpredictable dose of medication. These factors necessitate the formulation of a controlled release ocular drug delivery system which maintains a steady state drug release. 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, and increased shelf life. The use of hydrophilic polymer does not ensure the prolonged time of residence of medicament in the eye. The water insoluble polymers have the drawback of causing corneal abrasion, irritation, etc. The present study is an attempt to formulate ocular inserts of Betaxolol Hydrochloride using biodegradable polymers like Gelatin and Chitosan.

II. MATERIALS METHODS

Materials

Betaxolol Hydrochloride was obtained as a gift sample from FDC Pharmaceuticals (P) Ltd., Mumbai. Chitosan was obtained as a gift sample from Central Institute of Fisheries Technology, India. Gelatin was purchased from S.D.Fine Chemicals (P) Ltd., Boisar. All other chemicals and solvents used were of analytical reagent grade.

Methods

Preparation of Ocular Inserts

Method used for the preparation of ocular inserts is solvent casting technique. Table 1 shows composition of ocular inserts. The required quantity of Polymers and glycerin were weighed and dissolved in purified water for gelatin and in acetic acid (1% v/v) for chitosan, the mixture was heated at 60°C on a water bath until the entire polymer was dissolved. The weighed amount of Betaxolol Hydrochloride (passed through sieve
# 400) was added and stirred for 6 h at 40°C on magnetic stirrer to get uniform dispersion. After complete mixing the casting solution 15 ml for gelatin and 50 ml for chitosan was poured in clean petridish (Anumbra®, area of 63.64 cm²approximately). The petridish was cooled at 10°C by placing on ice until the inserts were gelled. The gelled inserts were taken out from ice and allowed to dry at room temperature for 24 h. The dried inserts thus obtained were cut into required size (8mm diameter) by cork borer and wrapped individually in aluminum foil and stored till used for evaluation.

Cross linking of the gelatin ocular inserts.

The prepared inserts of gelatin were hardened by using 5 ml of 10%- w/v solution of glutaraldehyde in isopropyl alcohol for a time period of 30min, the inserts were transferred to an aqueous sodium metabisulfite solution (2%-w/v) and then immediately removed and placed in absolute alcohol bath to remove the excess of glutaraldehyde from the inserts. If the excess of glutaraldehyde was not removed from the surface, it may cause irritation to the eye.

Evaluation of ocular inserts6,7

The ocular inserts were evaluated for thickness, weight variation, swelling index and drug content uniformity. The thickness was measured using a dial caliper (Mitutoyo, Japan) at different points and the mean values were calculated. Ocular inserts weights were determined by using electronic balance.

To check the uniformity of the drug in the film, three inserts were taken from each batch and individually dissolved or crushed in 5 ml of simulated tear fluid and the resultant solution was filtered. An aliquot of the filtrate was suitably diluted and analyzed spectrophotometrically (Shimadzu -UV1700) for Betaxolol HCl content at 233 nm. The concentration of the drug was determined from the standard curve. Same procedure was adopted for other formulations in triplicate and mean drug content and standard deviations were calculated.

Swelling index9

Three inserts were weighed and placed separately in beakers containing 4ml of distilled water. After a period of 5 minutes, the inserts 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.

Drug Excipients compatibility study by IR.

The stability of the drug in the formulation was confirmed by IR spectral analysis. IR spectra of pure drug and formulations were determined using Shimadzu FTIR-8400S Spectrophotometer by KBr Disc method.

In-vitro Drug Release Studies10

The in vitro drug release from the different ocular inserts was studied using the vial method. Each insert was placed in 10 ml capacity vials containing 5 ml of simulated tear fluid that was previously warmed at 37 ± 1°C. These vials were placed over hot plate (maintained at temperature 37 ± 1°C) that was positioned on an electromagnetic sieve shaker (Electrolab-EMS-8). Shaker was kept at minimum shaking speed to simulate the blinking of eye. Aliquots of 1 ml samples at specific interval of time were withdrawn carefully using pipette and equivalent amount of fresh dissolution fluid was replaced. The aliquots withdrawn were suitably diluted with Simulated tear fluid and was analyzed at 233 nm using Shimadzu-UV1700 Spectrophotometer against blank.

Accelerated Stability Studies

The optimized formulations in its final pack were stored at 25°C /60%RH and 40°C/75%RH for 3 months in Humidity chamber (Thermolab). The samples were withdrawn at every 10 day time intervals and analyzed for physical appearance and drug content.

III. RESULTS AND DISCUSSION

The thickness of the formulations containing gelatin varies from0.281±0.021 to 0.364±0.017mm, for formulation containing gelatin hardened for 30 minutes varies from 0.303±0.014 to 0.385±0.028 and for formulation containing chitosan varies from0.295±0.041 to 0.341±0.029 mm, the results showed that the thickness was uniform. The weight of formulations containing gelatin varies from 16.66±0.01 to 20.70±0.01 mg, for formulations containing gelatin hardened for 30 minutes varies from 16.68±0.01 to 20.83±0.01 mg and for formulations containing chitosan varies from10.59±0.01 to 18.53±0.01 mg, for all formulations, as the polymer concentration increases weight of the inserts increases. The drug content in all formulations were found to contain 91.76±0.01% to 99.79±0.01 % of Betaxolol Hydrochloride, which complies with BP. IR spectra analytical reports shown in Fig 1 indicating that there was no interaction between drug and excipients used.
The swelling index of all formulations varies from 1.71±0.02 to 2.78±0.01% shown in the Fig 2. The results showed that swelling index increased as the concentration of gelatin increases, where as hardening of gelatin formulations for 30 minutes with glutaraldehyde decreased the swelling index which may be due to decreased in water permeability, further the swelling index decreased as the concentration of chitosan increases, which may be attributed to its relatively poor water solubility. Increase in the concentration of glycerin in gelatin, hardened gelatin and chitosan formulations increased the swelling index.

The ocular inserts prepared with gelatin released the drug in 2-3 h. The formulations with gelatin hardened for 30 minutes showed complete release of drug within 8-12 h. The formulation prepared with chitosan showed complete release of drug within 3-12 h. As the concentration of polymer increases, drug release from the formulations 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 content results in faster swelling and release from ocular inserts.

When the formulation containing gelatin was hardened for 30 minutes with glutaraldehyde the drug release decreased.

The release of the drug from the ocular inserts containing gelatin and chitosan has followed first order kinetics and fickian diffusion transport whereas the ocular inserts containing gelatin hardened for 30 minutes followed zero order kinetics and non-Fickian diffusion transport.

Among all the formulations, the best formulations were GH containing gelatin 14% w/v hardened for 30 mins with glutaraldehyde and containing chitosan 3% w/v, since they showed retarded release of drug up to 12 h. The formulations GH and Cs were subjected to stability studies.

From the result of accelerated stability studies it was found that the formulations were stable and the drug content was found to be within limits.

IV. CONCLUSION

From the results it can be concluded that formulations GH containing gelatin 14% w/v hardened for 30 minutes with glutaraldehyde and Cs containing Chitosan 3% w/v has achieved the objectives of increased contact time, prolonged release, and decreased frequency of administration and thus may improve the patient compliance.

V. ACKNOWLEDGEMENTS

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REFERENCES

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Table 1: Composition of Formulations

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Ingredients (% w/v)</th>
<th>Glycerin (% w/w of dry weight of polymer)</th>
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<tr>
<td>G1</td>
<td>0.33</td>
<td>40</td>
<td>GH1</td>
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<td>GH2</td>
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<td>GH6</td>
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</tr>
<tr>
<td>C1</td>
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</tr>
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</tr>
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</table>

G-Gelatin inserts, GH-Gelatin inserts hardened for 30 minutes, C-Chitosan inserts. In all formulations Benzyl alkonium chloride (0.01%w/v) was used as preservative.

*Formulations of gelatin hardened for 30 min with glutaraldehyde.

Figure 1: FTIR Spectra of Betaxolol HCl (A), Betaxolol HCl + Gelatin hardened for 30 Minutes with Glutaraldehyde (B) and Betaxolol HCl + Chitosan (C).
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**Figure 2:** Percentage swelling index of all formulations

**Figure 3:** *In Vitro* drug release profiles of formulations containing gelatin ocular inserts hardened for 30 minutes with glutaraldehyde.

**Figure 4:** *In Vitro* drug release profiles of formulations containing chitosan.