Formulation and evaluation of ophthalmic insert drug delivery system of forskolin

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Forskolin, a diterpene obtained from natural roots of Coleus forskohlii (wild) Briq. (family: Lamiaceae), reduces intraocular pressure (IOP) by 23-28%, which is a desirable feature for an antiglaucoma therapy. Polyvinyl alcohol-14000 based ophthalmic inserts of pure forskolin (PVA-OIF) were prepared as matrix drug delivery with the aim of achieving once a day administration. Ophthalmic inserts were prepared using polymer PVA in various concentrations. The ophthalmic inserts were evaluated for evaluation parameters and in vitro drug release. One-way ANOVA tested in vitro release characteristics statistically. The in vitro release data was treated according to diffusion model proposed by Higuchi and Peppas in order to access the mechanism of drug release. The batch formulated with PVA-14000 (1.5%), showed sustained drug release behavior over a period of 6 hrs.

Key words: Forskolin, glaucoma, intraocular pressure, ophthalmic inserts

INTRODUCTION

"VISION 2020, THE RIGHT TO SIGHT", was the global initiative launched in the year 1999. It is estimated that, worldwide approximately 180 million people are visually impaired; of these between 40 and 45 million are blind. Even more compelling, it is estimated that the number of blind and visually impaired double by 2020, unless concerted action is undertaken to stem this toll. Glaucoma is the third leading cause of blindness worldwide and is responsible for about 52 million cases of blindness¹¹ (12.5% based on the number of legally blind persons in the population at a given time). It is an ocular disease caused by a progressive form of optic nerve damage associated with raised (> 21 mm of Hg) intraocular pressure.¹²,¹³

Forskolin as a drug of choice is a diterpene obtained from natural roots of Coleus forskohlii (family: Lamiaceae). It has intra oculohypotensive effect and hence it is useful in the treatment of glaucoma. Advantages of forskolin in the treatment of glaucoma as an antiglaucoma agent has been reported for reduction in IOP by 23-28% (instilled as 1% solution).⁹,¹⁰ It does not induce miosis - parasympathomimetics induce miosis,¹⁰ which is not a desired effect in the treatment of glaucoma, increases intraocular blood flow - a desirable feature for antiglaucoma agent.¹¹ The effect of forskolin can be increased and possibly potentiated by the use of sympathomimetics, unilateral reduction of IOP. Advantage when only one eye is to be treated. Less contraindication when compared to systemically active drugs. Polymeric inserts increase the precorneal residence time for water insoluble drug.

In past several years, forskolin a diterpene derivative which directly activates the catalytic subunit of adenylate cyclase has attracted attention as a potent antiglaucoma medicament. Several investigators have studied the effects of forskolin in the eye when applied topically; in 1983 Caprioli and Sears first reported that forskolin suspension lowers the IOP in rabbit, monkey, and human eyes by reducing the net aqueous inflow,¹³ which was confirmed by several reports.¹⁴-²⁰ On the other hand, Brubaker argued against forskolin's IOP lowering effect in human eyes. As forskolin has a low solubility in water, a part of this discrepancy in the IOP lowering effect might be explained by its poor ocular penetration. According to Brubaker,²⁰ the significant decrease in IOP after topical application of 1%forskolin, Burstein¹³ documented this could be attributed to the fact that the performed tonography just before the application of the drug which could have increased corneal permeability and enhance the penetration of forskolin. The knowledge of herbal pharmacokinetics of topically applied drugs is essential for understanding.

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its therapeutic effects.[21] Two studies were performed to investigate the effects of forskolin (Hoechst Research) on IOP, in first study two 1% formulations of eye drops were compared with placebo in 10 healthy volunteers, in a subsequent study only one formulation of 1% forskolin was compared with placebo by Meyer.[27]

So, the extensive research is needed as per formulation aspects of ocular drug delivery concern of forskolin, which should be safer to eye. Ocular bioavailability of drugs from eye drops is poor due to precorneal loss factors including tear dynamics non-productive absorption transient residence time in cul-de-sac and the relative impermeability of the cornea epithelial membrane. Only a small fraction of topically applied dose reaches the inner eye, with the actual amount dependent on the physicochemical properties of the drug and its vehicle. Glaucoma treatment needs the drug residence for longer duration in eye to control IOP, so that the pressure exerted on optic nerve will be less. As a result, optic nerve damage will be prevented. To overcome the limitations of using eye drops, the Ophthalmic Insert Drug Delivery System[22-29] (OIDDS) will be superior to deliver the fraction of drug for longer duration with increased corneal residence time and bioavailability of drug. In this experiment, we have focused on formulation of ophthalmic inserts of forskolin designed to deliver forskolin in a sustained manner for more than 6 hrs.

MATERIALS AND METHODS

Materials

Forskolin and its marker compound were obtained from Sami Labs Ltd., Bangalore, India. Polyvinyl alcohol-14000 (PVA), Polyethylene glycol-400 (PEG-400), and methanol were obtained from S.D. Fine Chem., Chennai. The glass moulds for preparation of ophthalmic inserts were fabricated locally.

Formulation of ophthalmic inserts of forskolin (OIF-PVA)

Matrix type ophthalmic inserts of forskolin were prepared by moulding technique. A glass mould of dimensions 10 cm length, 5 cm width and 1.5 cm height with a total surface area by moulding technique. A glass mould of dimensions 10 cm

Evaluation of ophthalmic inserts

Formulations of Ophthalmic Inserts containing Forskolin (OIF) respectively were subjected to different evaluations including the Ophthalmic Inserts without Drug (OID)/Dummy Inserts for evaluation studies. Determination of average weight and weight variation[30] by electronic weight balance, determination of film thickness by optical microscopy technique[31] in which eye piece micrometer was employed. For the determination of drug content,[32] the formulated insert was transferred into a graduated glass stoppered flask which contained 25 ml of methanol, maintained at 37°C. It was closed and shaken vigorously for about 12 hrs period in a metabolic shaker. The solution was filtered and the drug present in the filtrate was determined by UV spectrophotometer at suitable wavelength. Similarly, a blank solution was prepared using a dummy insert. The procedure was repeated three times and the average drug content was calculated. In order to determine the mucoadhesive strength of formulated ophthalmic inserts, a study was conducted using a modified physical balance[33] in which the force required to detach the membrane from the insert was noted. The mucous membrane from the intestine of goat (freshly acquired) was used as model mucus membrane for the testing of mucoadhesion of the prepared inserts. Goat intestinal membrane, excised and washed was tied tightly with the mucosal side upwards, over the protrusion in the stainless steel block.

In vitro release study

To determine the drug release from the formulated ophthalmic inserts, a study was conducted using a fabricated dissolution cell. The cell consisted of a semi-circle reservoir, with 1 mm thickness and 25 mm internal diameter. The test film was placed in the reservoir and dissolution fluid was delivered from the left corner of the reservoir through a hypodermic needle, attached to a flow regulator at 20 drops/min flow rate. The outlet from the cell was collected through the groove made on the top right of the cell. The whole cell was thermostated at constant temperature water (37°C) using a peristaltic pump. A formulated insert was placed on the concave surface and the artificial tear fluid, maintained at 37°C was dropped at a flow rate of 20 drops/min at the middle of the film. The drained out liquid was collected via the groove into collection tubes at 0.25, 0.5, 0.75, 1, 2, 4, 6, 9, 12 hrs intervals. The amount of drug release from the film at different time intervals was determined by UV-visible spectrophotometrically at suitable wavelength.

Study of release kinetics of OIF

To study the, effect of different concentration and nature of polymers in mechanism of drug release, the obtained in vitro release data was statistically analysed using One-Way
Analysis of Variance (ANOVA) by GraphPad InStat Software. For theoretical analysis, the release data was fitted into the Higuchi[34] and Peppas[35] diffusion models to find the mechanism of release.

RESULTS AND DISCUSSIONS

The study embodies, the effect of certain formulation/process variables on the physicochemical and in vitro performance was studied. Ophthalmic inserts OIF-HPMC were formulated after investigating the purity of the drug. It was noticed that increase in different polymer concentrations, 1, 1.5, and 2% batches of PVA-OIF were found the suitable. Two plasticizers were taken, namely, PEG-400 and glycerin. It was observed that the films formed by PEG-400 were softer and more acceptable as compared to glycerin. Glycerin gave slightly brittle films. Hence, PEG-400 was selected as ideal plasticizer. From the results, it was found that, PVA-14000 (1.5%) and 10% PEG-400 as plasticizer formed films with ideal physical properties and mucoadhesive strength. Moist heat sterilization of the polymeric solution, followed by surface λ-irradiation at 25 kGy-irradiation dose, for more than 2 min is suitable to achieve sterility of the ophthalmic inserts. According to the evaluation parameters, which are shown in result form in Table 1, the thicknesses of formulated inserts were increased on increasing the polymer concentration. The thickness of films corresponding to 1, 1.5, 2, 2.5, and 3% w/v polyvinyl alcohol were 71 ± 0.0030, 71 ± 0.0037, 73.3 ± 0.0050, 74.1 ± 0.04, and 75.8 ± 0.0030, respectively. It is due to the proportional increase in the solid content of polymer solution present in unit surface area. The average weights of the film were also found to increase from 0.812 to 0.955 g again due to the proportional increase in the solid content. The values of 1, 1.5, 2, 2.5, and 3% w/v polyvinyl alcohol solution were 0.812± 0.08, 0.880± 0.16, 0.925± 0.04, 0.947± 0.03, and 0.955± 0.02 g/cm², respectively. No significant difference in drug content was noted when increase in polymer concentration. The values for 1, 1.5, 2, 2.5, and 3% w/v polymer concentration were 9.10± 0.32, 9.16± 0.21, 9.20± 0.32, 9.26± 0.21, and 9.35± 0.21 mg/cm², respectively. Increase in polymer concentration, increased the mucoadhesive strength of formulated films. The values of mucoadhesion for 1, 1.5, 2, 2.5, and 3% w/v polymer batches were 20.12± 0.68, 22.60± 0.12, 25.35± 0.49, 26.80± 0.09, and 28.05± 0.35 g, respectively. It is due to large hydration networks and the resulting chain interpretation, with high polymer concentration.

Calibration curve for forskolin was developed in methanol using UV spectrophotometer and the λ_max was found to be 292 nm, the slope (K) and intercept (B) values were 17.964, and -0.1782, respectively. The in vitro drug release was found to be in the range of 83–90% during a period of 6 hrs. PVA-OIF (1.5%) was found to sustain the drug release. The results are shown in Figure 1.

Tukey-Kramer Multiple comparison test and Bartlett’s test (as per ANOVA) the differences among Standard Deviations were extremely significant. The Higuchi model showed the zero order mode of release (correlation coefficient, r = 0.992), of the formulated (PVA-OIF) insert. The least sum of residuals shown by ideal batches to Peppas (log time-log drug release) equation and slope values above 0.227 affirmed that the release pattern was of diffusion without swelling.

CONCLUSION

A batch prepared with 1.5% OIF (PVA) and 10% plasticizer was found to give the most acceptable ophthalmic inserts, whereas the same batch of 1% will give a cost effective approach for formulations, as the release is moreover same. This Ophthalmic Insert Drug Delivery System (OIDDS) of the forskolin may be an effective drug delivery with increased corneal residence time and with sustained therapeutic action in an in-vivo model for treatment of a glaucomatous eye with a reduction in intraocular pressure for prolonged time, which is a need of ideal antiglaucoma agent.

Table 1: Effect of polymer concentration on the physicochemical properties of ophthalmic inserts/films

<table>
<thead>
<tr>
<th>S. no.</th>
<th>Evaluation parameter</th>
<th>PVA polymer concentration % w/v</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>1</td>
<td>Thickness µm</td>
<td>71 ± 0.030</td>
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<tr>
<td>2</td>
<td>Average weight and weight variation (g/cm²)</td>
<td>0.812 ± 0.38</td>
</tr>
<tr>
<td>3</td>
<td>Mucoadhesive strength</td>
<td>20.12 ± 0.68</td>
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<tr>
<td>4</td>
<td>Drug content (mg/cm²)</td>
<td>9.10 ± 0.32</td>
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</tbody>
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Average of three separate determinations ± SEM
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