Design and Characterization of Ofloxacin and Dexamethasone Ocular Inserts Using Combination of Hydrophobic and Hydrophilic Polymers

E. Sravanthi Reddy¹, Himansu Bhusan Samal¹, S. A. Sreenivas²

¹Department of Pharmaceutics, Guru Nanak Institutions Technical Campus - School of Pharmacy, Hyderabad, Telangana, India, ²Department of Pharmaceutics, Sree Dattha Institute of Pharmacy, Hyderabad, Telangana, India

Abstract

Aim: The objective of this work was to develop ocular inserts of ofloxacin and dexamethasone and to evaluate their potential for controlled ocular delivery. Materials and Methods: Ofloxacin and dexamethasone were obtained as a gift sample from Indu Drugs, Pvt. Ltd., hydroxy propyl methyl cellulose (HPMC) (P₅₅ and E₁₃) from Pellets Pharma Ltd., HPMC K₄M from NSF Pharma Pvt. Ltd., Eudragit (RL-100 and L-100) from Biogen Exports Pvt. Ltd., polyethylene glycol and ethanol were purchased from S.D. Fine Chemicals, Mumbai, India. Ocular Inserts were prepared by solvent casting technique using polymer Eudragit (RL-100 and L-100) and HPMC (K₄M, P₅₅ and E₁₃) at different concentration and combination. Results and Discussion: 10 formulations (F1-F10) were developed and all the formulations were subjected to evaluation for thickness, weight variation, folding endurance, pH, % moisture absorption, drug content, and in vitro release study. Infrared spectral analysis showed that there is no interaction of drug with polymer which indicates the intactness of drug in the formulation. On the basis of in vitro drug release studies, formulation F6 was found to be better than the other formulations and selected as an optimized formulation, which was further subjected to stability study. No significant change was observed in the drug content and physical features during storage at 25°C/60% RH and 40°C/75% RH for 9 months. Conclusion: In this study, an attempt was made to develop ocuserts of ofloxacin and dexamethasone combination with improved bioavailability, avoidance of repeated administration and dose reduction. From the experimental finding, it can be concluded that HPMC is a hydrophilic polymer good film forming and is a promising agent for ocular delivery. Eudragit was a satisfactory polymeric ingredient to fabricate the rate controlling membrane of the ocusert system. Incorporation of polyethylene glycol enhances the flexibility of film, achieving therapeutic levels of the drug in the formulation and also permeability of the drug through cornea. The kinetic treatment of in vitro dissolution data indicated that the optimized ocusert followed Peppas kinetics with zero-order drug release. The drug remained intact and stable in the ocuserts on storage.

Key words: Dexamethasone, ocular inserts, ofloxacin, solvent casting technique

INTRODUCTION

Delivery of medication to the human eye is an integral part of medical treatment. Conventional ocular dosage forms, i.e., eye drops and eye ointments have certain disadvantages such as poor availability, repeated administration, massive and unpredictable doses and drainage of drug by tear fluid. Ocular inserts offer many advantages over conventional dosage forms such as increased possibility of releasing drugs at a slow and constant rate, ocular residence time, accurate dosing, exclusion of preservatives, and increased shelf-life.¹-³ Moreover, the use of ocular inserts reduces systemic absorption, which or else freely occurs with eye drops. It also will ensure better patient compliance due to lower frequency of administration
and lower incidence of side effects.\textsuperscript{[4,6]} Important criteria for ocular inserts are as follows: (a) elution kinetics of the effective drug from the insert should be of zero or nearly zero-order for a long time, (b) insert should be harmless when retained in the eye for a long time, and (c) the insert must stay easily in the eye and not give any disagreeable feeling to the patients.\textsuperscript{[5]}

Ofloxacin is a synthetic fluoroquinolone agent widely used in ocular gingitis, ocular conjunctivitis, and other ocular disorders for symptomatic relief of pain and inflammation.\textsuperscript{[8]} Ofloxacin is a broad-spectrum antibacterial agent with activities against Gram-negative bacteria (Escherichia coli, Klebsiella pneumoniae, Serratia species, Proteus species, Pseudomonas aerogenosa, and Haemophilus influenzae) and Gram-positive bacteria (Staphylococcus species, Streptococcus enterococci). Ofloxacin is reportedly used for topical applications. The drug undergoes substantial hepatic first-pass metabolism and from the administered dose only about 50\% of reaches systemic circulation. This originates the need of an alternative choice of route of administration for such drugs. The ofloxacin also possesses the ideal characteristics such as short biological half-life, poor bioavailability and smaller dose, etc., to be formulated into an ocular inserts.\textsuperscript{[9]}

Dexamethasone has been one of the most frequently used topical ocular corticosteroids, which plays a long-lasting role in anti-inflammatory, antiallergy and antishock activities.\textsuperscript{[9]} It is a synthetic, poorly soluble, and crystalline corticosteroid. Dexamethasone reduces the intraocular inflammation as well as the breakdown of the blood ocular barrier in proliferative vitreoretinopathy. Although extensive research work has been reported on ocular inserts, it could be evidenced from the literature that ofloxacin and dexamethasone combination is not reported.

In this study, it was aimed to prepare ocular inserts containing combination of ofloxacin and dexamethasone along with Eudragit (RL-100 and L-100) and hydroxy propyl methyl cellulose (HPMC) (K₅₅, Pₛₛ, and Eₜₜ) at different concentration and combination to overcome the disadvantages associated with conventional ophtalmic dosage forms (eye drops and suspensions), to achieve longer duration of action delivering the drug in zero-order kinetics.

### Preparation of ocular inserts

Ocular inserts were prepared by solvent casting technique.\textsuperscript{[10]} Glass molds were used for casting the films. Eudragit (RL-100 and L-100) and HPMC (Pₛₛ, E₁₅, K₄M) combinations were dissolved in ethanol mixture with PEG as a plasticizer in a beaker using magnetic stirrer to get different concentrations of polymeric solutions [Table 1]. Into these solutions, drug dispersion of required quantity was added. After complete mixing, the solution was poured into a clean glass mold placed on a horizontal plane. The solvent present was allowed to evaporate slowly by inverting a glass funnel by plugging it with cotton in the stem at room temperature for 24 h. After complete evaporation of solvent, cast films were obtained. These formulations were sterilized separately by exposing to ultraviolet radiation for 90 min in a cabinet under aseptic conditions and were finally packaged in presterilized aluminum foil. The ocular inserts were placed in a desiccator until use.\textsuperscript{[11]}

### Characterization of ocular inserts

The ocular inserts were evaluated for various evaluation parameters

**Physical appearance**

All the formulated ocular inserts were visually inspected for color and transparency.

**Surface texture**

The surface texture of the film was evaluated by touching the surface of the film.

**Uniformity of thickness**

The thickness of ophtalmic inserts was determined with the help of micrometer screw gauge. The thickness of each film was determined at different places, and the standard deviation was calculated.

**Weight variation**

Six inserts all of same sizes from each formulation were individually weighed on electronic weighing balance and the average weights as well as standard deviation were calculated. All measurements (weight and thickness) were determined after residual solvent has been removed from samples by storing the films in desiccator with anhydrate calcium chloride at an appropriate 0\% RH and 27 ± 2°C for a week before evaluation and testing.\textsuperscript{[12,13]}

**Drug content**

Percentage drug content was determined by assaying the inserts. The ocular insert was placed into a 10 ml volumetric
flask containing simulated tear fluid of pH 7.4 and sonicated for 20 min to extract the drug from the insert. The resultant solution was filtered through a G-2 glass filter. From this, the sample was taken, diluted suitably and analyzed spectrophotometrically by measuring the absorbance at 294 and 236 nm.

**Surface pH**

The surface pH of the inserts was determined by placing two drops of double distilled water over it, allowing it to swell. After this, the swollen devices were placed on the pH paper to determine the surface pH. After 1 min, the color that developed was compared with the standard color scale.

**Folding endurance**

The folding endurance is expressed as the number of folds or number of times the insert is folded at the same place, either to break the specimen or to develop visible cracks. This test is important to check the ability of sample to withstand folding and this test also gives an indication of brittleness. The film was folded in center, between fingers and the thumb and then opened. This was termed as one folding. The process was repeated till the insert produced a break or cracks in center of insert. The total folding operations found were named as folding endurance value.

**Percentage moisture absorption**

The ocuserts were preweighed accurately and kept in a desiccator that contains anhydrous calcium chloride. After a period of 3 days, the films were taken out and reweighed.

\[
\text{Percentage moisture absorption} = \left( \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \right) \times 100
\]

**Percentage swelling index**

Swelling of the polymer depends on the concentration of the polymer, ionic strength, and the presence of water. Water uptake was determined gravimetrically. The inserts were placed on a filter paper, which was presoaked overnight in an agar gel plate (2% m/v agar in simulated tear fluid, pH 7.4) and weighed (presoaked filter paper + insert). The inserts were incubated at 32°C (the eye surface temperature). Inserts with filter paper were removed at predetermined time periods and the surface water was removed with the help of a filter paper and reweighed using an analytical balance.

The % of swelling was calculated using the following formula:

\[
\text{% Swelling} = \left( \frac{W_f - W_0}{W_0} \right) \times 100
\]

Where, \(W_f\) is the weight of the swollen insert after time \(t\) and \(W_0\) is the initial weight of the insert.

**In vitro transcorneal permeation study**

**Corneal preparation**

The whole eye ball of the sheep was obtained from a butcher’s shop within ½ h of slaughtering of the animal and was transported to the laboratory in cold (4°C) normal saline.
(0.9% w/v NaCl) immediately. The cornea was carefully excised along with 2-4 mm of the surrounding scleral tissues and was washed with cold normal saline till it was free from proteins.

**Permeation experiment**

Fresh cornea was mounted by sandwiching the surrounding scleral tissue between the clamped donor and the receptor cells of the modified version of a Franz diffusion cell in such a way that its epithelial surface (apical) faced the donor compartment and the endothelial surface faced the receptor compartment. The cell was placed on a magnetic stirrer in a holding position. The receptor compartment was filled with 11 ml of freshly prepared simulated tear fluid (pH 7.4) and stirred using Teflon coated magnetic stir bar. The ocular insert was placed to the epithelial side of the cornea in the donor cell and stirring of the receptor fluid (jacketed with water at 32 ± 1°C) was started. At appropriate intervals, 1 ml samples were withdrawn from the receptor compartment and the withdrawn sample volume was replaced with an equal volume of fresh simulated tear fluid to ensure sink conditions. The aliquots were analyzed spectrophotometrically at 294 and 236 nm. Each formulation was continued for about 24 h and was performed in triplicate.

**Ocular irritation test**

The potential ocular irritation and/or damaging effects of the ocusert under test were evaluated by observing them for any redness, inflammation (or) increased tear production. Formulation was tested on rabbits by placing the inserts in the cul-de-sac of the left eye. Both eyes of the rabbits under test were examined for any signs of irritation before treatment and were observed up to 12 h.

**Accelerated stability studies**

Optimized formulation was subjected to short-term stability testing. Ocusert wrapped in aluminum foil and kept in a humidity chamber maintained at 40 ± 2°C/75% ± 5% RH 1 month as per ICH guidelines. Changes in the appearance, surface pH, folding endurance, and drug content of the stored films were investigated during the period and after 1 month.

### RESULTS AND DISCUSSION

**Accelerated stability studies**

Accelerated stability studies of the optimized formulation (F6) at elevated temperature and humidity showed no significant change in drug content and physical appearance after 1 month [Table 5].

**Ocular irritation test**

Results of this test showed that all inserts prepared using hydrophobic and hydrophilic polymers were non-irritating to the eye of rabbit, after testing about 6 h and 12 h. Inserts were not expelled out of the cavity of eye of rabbits, suggests the inserts dimension were appropriate for use [Table 7].

**Thickness**

Thicknesses of the ocuserts were found to be directly related to the concentration of the polymers. Thickness of the ocuserts varied between 0.232 ± 0.75 and 0.366 ± 0.27 mm [Table 2]. The result showed that thickness was uniform and ocuserts were not thick enough to produce any irritation while placing and being in cul-de-sac.

**Weight variation**

The weight of formulations was determined by digital electronic balance. The result showed that weights of formulations were ranging from 7.83 ± 0.037 to 16.92 ± 0.013 mg [Table 2]. This indicates that there was no significant weight variation in all formulations.

### Table 2: Physicochemical characteristics of formulation F1-F10

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Appearance</th>
<th>Surface texture</th>
<th>Thickness (mm)</th>
<th>Weight variation</th>
<th>% Moisture loss</th>
<th>% Moisture absorption</th>
<th>% Swelling index</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.366 (0.27)</td>
<td>8.16 (0.016)</td>
<td>10.10 (0.26)</td>
<td>1.890</td>
<td>87.51</td>
</tr>
<tr>
<td>F2</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.267 (0.17)</td>
<td>9.14 (0.027)</td>
<td>13.12 (0.59)</td>
<td>2.317</td>
<td>87.12</td>
</tr>
<tr>
<td>F3</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.293 (0.09)</td>
<td>8.00 (0.018)</td>
<td>11.22 (0.93)</td>
<td>2.094</td>
<td>91.67</td>
</tr>
<tr>
<td>F4</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.270 (0.06)</td>
<td>8.24 (0.010)</td>
<td>12.10 (0.75)</td>
<td>2.196</td>
<td>92.32</td>
</tr>
<tr>
<td>F5</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.302 (0.21)</td>
<td>8.21 (0.028)</td>
<td>8.61 (0.42)</td>
<td>1.534</td>
<td>85.93</td>
</tr>
<tr>
<td>F6</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.293 (0.22)</td>
<td>7.83 (0.037)</td>
<td>10.13 (0.03)</td>
<td>1.734</td>
<td>86.81</td>
</tr>
<tr>
<td>F7</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.241 (0.11)</td>
<td>9.10 (0.017)</td>
<td>6.68 (0.71)</td>
<td>1.740</td>
<td>85.23</td>
</tr>
<tr>
<td>F8</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.252 (0.02)</td>
<td>8.67 (0.001)</td>
<td>7.57 (0.41)</td>
<td>1.645</td>
<td>85.11</td>
</tr>
<tr>
<td>F9</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.261 (0.59)</td>
<td>16.92 (0.013)</td>
<td>6.45 (0.33)</td>
<td>1.324</td>
<td>84.95</td>
</tr>
<tr>
<td>F10</td>
<td>Transparent</td>
<td>Smooth</td>
<td>0.232 (0.75)</td>
<td>14.78 (0.012)</td>
<td>6.55 (0.15)</td>
<td>1.102</td>
<td>83.61</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD (n=3).
Moisture loss

Among the formulations tested F2 and F9 show maximum and minimum moisture loss, i.e. 13.12 ± 0.59 and 6.45 ± 0.33, respectively [Table 2]. The minimum moisture loss shown by the formulation F9 was mainly due to the polymer as rate controlling membrane, which retain the moisture within the matrix.

Moisture absorption

Among the formulations tested F10 and F2 shows the minimum and maximum moisture uptake, i.e., 1.102 and 2.317, respectively [Table 2]. The maximum moisture uptake from ocusert may be due to the high concentration of HPMC, which readily absorbs moisture when exposed to atmosphere. Moreover, the minimum moisture uptake was due to more hydrophobic nature of F10.

Swelling index

Swelling index for all the 10 formulations was carried out and maximum and minimum values were found to be 91.67-F3 and 83.61-F10, respectively [Table 2 and Figure 1].

Folding endurance

The folding endurance for all formulations was good. The maximum folding endurance for F10 ophthalmic insert was 261 folding which may be due to the presence of PEG and formulation F1 showed minimum folding endurance folding 97 [Table 3].

In vitro transcorneal permeation study

The cumulative percent of drug released from the ocular inserts as a function of time is shown in Figure 2. The overall

**Table 3: Physicochemical characteristics of formulation F1-F10**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Surface pH</th>
<th>Folding endurance</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.30</td>
<td>97</td>
<td>1.953 (0.013)</td>
</tr>
<tr>
<td>F2</td>
<td>7.32</td>
<td>135</td>
<td>1.969 (0.006)</td>
</tr>
<tr>
<td>F3</td>
<td>7.48</td>
<td>163</td>
<td>1.962 (0.021)</td>
</tr>
<tr>
<td>F4</td>
<td>7.22</td>
<td>170</td>
<td>1.968 (0.023)</td>
</tr>
<tr>
<td>F5</td>
<td>7.12</td>
<td>195</td>
<td>1.943 (0.037)</td>
</tr>
<tr>
<td>F6</td>
<td>7.29</td>
<td>221</td>
<td>1.967 (0.015)</td>
</tr>
<tr>
<td>F7</td>
<td>7.61</td>
<td>213</td>
<td>1.953 (0.023)</td>
</tr>
<tr>
<td>F8</td>
<td>7.39</td>
<td>226</td>
<td>2.196 (0.013)</td>
</tr>
<tr>
<td>F9</td>
<td>7.26</td>
<td>243</td>
<td>1.916 (0.010)</td>
</tr>
<tr>
<td>F10</td>
<td>7.39</td>
<td>261</td>
<td>1.974 (0.027)</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD (n=3). SD: Standard deviation
cumulative percentage drug release for formulation F1-F10 was found to be 97.56, 98.51, 98.37, 98.55, 97.65, 98.67, 96.70, 98.58, 99.15, and 98.81, respectively, at the end of 24 h, as shown in Table 4. Formulation F6 shows highest (98.67%) and formulation F7 shows lowest (96.70%) drug release at the end of 24 h. The data obtained from the in vitro transcorneal permeation studies of all 10 formulations were subjected to kinetic treatment to determine the order of release [Table 6]. In our experiments, in vitro release profiles of all the formulations of ocuserts truly fit zero-order behavior, and they could be best expressed by Peppas plots
for the release of drug. Therefore, to get once a day delivery, ocuserts was fabricated using Eudragit and HPMC K4M in different proportions.

CONCLUSION

In this study, an attempt was made to develop ocuserts of ofloxacin and dexamethasone combination with improved bioavailability, avoidance of repeated administration, and dose reduction. Drugs showed no interaction with excipients in FTIR study. From the experimental finding, it can be concluded that HPMC is a hydrophilic polymer good film forming and is a promising agent for ocular delivery. Eudragit was a satisfactory polymeric ingredient to fabricate the rate controlling membrane of the ocusert system. Incorporation of polyethylene glycol enhances the flexibility of film, achieving therapeutic levels of the drug in the formulation and also permeability of the drug through cornea. The kinetic treatment of in vitro dissolution data indicated that the optimized ocusert followed Peppas kinetics with zero-order drug release. The drug remained intact and stable in the ocuserts on storage. Further future work will be progressed to establish the therapeutic utility of these systems by pharmacokinetic and pharmacodynamic studies in human beings.

REFERENCES


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