DESIGN AND EVALUATION OF CONTROLLED-RELEASE OCULAR INSERTS OF BRIMONIDINE-TARTRATE AND TIMOLOL MALEATE

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ABSTRACT

Objective: The current work was attempted to formulate and evaluate a controlled-release matrix-type ocular inserts containing a combination of brimonidine tartrate and timolol maleate, with a view to sustain the drug release in the cul-de-sac of the eye.

Methods: Initially, the infrared studies were done to determine the drug–polymer interactions. Sodium alginate-loaded ocuserts were prepared by solvent casting technique. Varying the concentrations of polymer—sodium alginate, plasticizer—glycerine, and cross-linking agent—calcium chloride by keeping the drug concentration constant, made a total of nine formulations. These formulations were evaluated for its appearance, drug content, weight uniformity, thickness uniformity, percentage moisture loss, percentage moisture absorption, and in vitro release profile of the ocuserts. Finally, accelerated stability studies and the release kinetics were performed on the optimised formulation.

Results: It was perceived that polymer, plasticizer, and calcium chloride had a significant influence on the drug release. The data obtained from the formulations showed that formulation—F9 was the optimised formulation, which exhibited better drug release. The release data of the optimised formulation tested on the kinetic models revealed that it exhibited first-order release kinetics.

Conclusion: It can be concluded that a natural bioadhesive hydrophilic polymer such as sodium alginate can be used as a film former to load water soluble and hydrophilic drugs like brimonidine tartrate and timolol maleate. Among all formulations, F9 with 400 mg sodium alginate, 2% calcium chloride and 60 mg glycerin were found to be the most suitable insert in terms of appearance, ease of handling, thickness, in vitro drug release and stability.

Keywords: Ocular inserts, Sodium alginate, Glaucoma, in-vitro study, Timolol tartrate, Brimonidine maleate

INTRODUCTION

The conventional medications such as eye ointments and drops administered into the eye have various constraints such as poor bioavailability, reduced therapeutic efficiency due to the precorneal elimination of the drug, and frequent dosing of the medications may also lead to reduced patient compliance. All these limitations can be overcome by the continuous delivery of the medications into the eye, which could be accomplished by formulating an ocular insert [1, 2].

Ocular insert, a type of ocular drug delivery systems, is the interesting and challenging tasks facing by the pharmaceutical researchers till today [3, 4]. Ocular inserts are the sterile ocular films made of a polymeric vehicle comprising drug placed into the cul-de-sac of the eye [5]. It has numerous advantages such as accurate dosing, increased shelf-life, increased residence time, the possibility of slow, constant and pre-programmed drug release, reduced systemic absorption, and ensured patient compliance [6, 7].

Glaucoma, an eye disorder, is characterised by elevated intraocular pressure (IOP), damaged optic nerve, and the ganglion cells. If left untreated, it might lead to progressive and irreversible loss of eyesight. Brimonidine tartrate (BT) and timolol tartrate (TM) are the most widely used medications that lower the IOP [8, 9]. These are the non-selective beta-adrenergic blocker and the selective alpha 2-adrenergic receptor, respectively. These drugs act by lowering the IOP in the eye by impeding the production of aqueous humour [10, 11].

In the current work, an attempt has been made to design and evaluate ocular insert of BT and TM using sodium alginate as a polymer, glycerine as a plasticiser by solvent casting technique, with an objective of achieving controlled release, increasing residence time, decreased dosing frequency, and enhanced therapeutic efficiency.

MATERIALS AND METHODS

Chemicals

The chemicals BT and TM were procured from Micro labs, Bengaluru. The excipients sodium alginate, calcium chloride, and glycerine were procured from SD Fine Chemicals, Mumbai. All the other chemicals used in work were procured from the local market and used without any further purification.

Drug-excipient compatibility studies

Fourier transform infrared (FTIR) spectroscopic studies were conducted using FTIR spectrophotometer Jasco, 460 plus, Japan to determine any interaction between the drug and the excipients. A small amount of the drug was taken and mixed uniformly with potassium bromide (KBr) of the spectrophotometric grade. The prepared mixture was taken in a palate and exposed to the Infrared (IR) beam and spectra were recorded in the range of 400–4000 cm⁻¹ by using FTIR spectrophotometer. The IR spectra of the pure drug with excipient and without excipient were taken separately to point out any drug-excipient interactions.

Formulation of ocular films

Matrix films of sodium alginate containing a combination of BT and TM were prepared by solvent casting technique. The formulation of ocular inserts involves two steps:

Step-1: Preparation of precast Petri plates

A solution of (2% w/v) calcium chloride was prepared and transferred to the Petri plates measuring 2.38 cm in diameter and allowed to evaporate completely. These plates were used to cast the films of sodium alginate.
Step-2: Preparation of the drug loaded film of Sodium alginate
An accurately weighed 7.5 mg of BT and 7.5 mg of TM were dissolved in 10 ml of distilled water. Then, an accurately weighed sodium alginate was dissolved in the aqueous solution of the drug. The resultant solution obtained was cast in a Petri plate. Nine formulations containing different amount of polymer—sodium alginate, glycerine, and concentration of calcium chloride were obtained as per table 1. The different concentrations of glycerine were chosen based on the dry weight polymer. The preparation was left undisturbed for 48 h at room temperature for drying. After drying, they were cut into 9-mm circular films each containing 1 mg of the drug [1-3].

### Table 1: Formulation of various batches of ocular inserts

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT (mg)</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>TM (mg)</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Water (ml)</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Sodium alginate (mg)</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>300</td>
<td>300</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Glycerine (mg)</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Calcium chloride (%)</td>
<td>2.0</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Evaluation of ocular films
All the prepared ocular films were evaluated by following parameters:

**Drug content uniformity**
Drugs-loaded ocular films of diameter 9 mm were placed in 10-mL volumetric flask and equilibrated with 10 ml of sodium phosphate buffer for 24 h. The flasks were shaken intermittently during this period and filtered. From the filtrate, 1 ml of sample was withdrawn, diluted accordingly, and assayed spectrophotometrically at 250 nm for BT and 295 nm for TM.

**Uniformity of thickness**
The thickness of each ocular insert was measured at three different points by using Baker digital caliper. The average of three readings was taken to determine the thickness of the film.

**Uniformity of weight**
From each batch, three ocular films were taken randomly and weighed individually using a digital balance.

**Percentage moisture loss**
The percentage moisture loss was performed to determine the integrity of the ocular film at dry conditions. Three concerts from each batch were chosen randomly, weighed, and kept in the desiccator containing anhydrous calcium chloride. After 3 d, the ocuserts were withdrawn and weighed again. The percentage moisture loss was determined by the formula:

\[
\text{%Moisture Loss} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

**Percentage moisture absorption**
Percentage moisture absorption test was performed to determine the integrity of the ocular insert at moisture conditions. Three inserts were taken randomly and weighed individually. The inserts were placed in the desiccator and exposed to high relative humidity (RH) using a saturated solution of potassium chloride. The percentage moisture absorption was calculated by the formula:

\[
\text{%Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

**In vitro drug release studies**
The in vitro release studies were determined by using the classical standard cylindrical tube of diameter 15 mm. Commercial semi-permeable membrane tied at one end of the open cylinder acts as a donor compartment in which the ocuserts was placed. The semi-permeable membrane that acts similar to the corneal epithelium was in contact with the receptor compartment containing 50 ml of 7.4 pH phosphate buffer. The content in the receptor compartment was stirred continuously by using a magnetic stirrer and the temperature was maintained at 37±0.5 °C.

For each predetermined interval, 1 ml of the aliquot was withdrawn and exchanged with the same volume of freshly prepared buffer solution. The collected aliquots were determined spectrophotometrically at 250 and 295 nm for BT and TM, respectively against pH 7.4 phosphate buffer as a reference standard. The percentage drug release of each formulation for each hour for 24 h was calculated from the slope of the calibration standard curve [4-6].

**Accelerated stability study**
Accelerated stability studies for the optimised F9 formulation of the ophthalmic insert was determined by exposing them to three storage conditions of temperatures (25±2 °C, 37±2 °C, and 42±2 °C) for 3 mo. After the specific period, the ocuserts were detected for any physical changes such as appearance, colour, thickness, texture, flexibility and drug content [12].

The data obtained from the in vitro release make use of various kinetic models to describe the release kinetics. The drug release data obtained from the dissolution test were plotted in various models [13, 14].

**Zero order rate kinetics**
It describes that the release rate of the formulation is independent of the drug concentration. The formulation which follows zero order kinetics is expressed by the Eqn. 1.

\[
c = c_0 - K_0 t \quad \text{(Eqn. 1)}
\]

Where,

\[c = \text{amount of drug dissolved or released}
\]
\[c_0 = \text{initial concentration of the drug in solution}
\]
\[K_0 = \text{zero order rate constant, expressed in units of concentration/time.}
\]

\[t = \text{time in hours.}
\]

**First order rate kinetics**
In first order kinetics, the release rate of the formulation is dependent on the drug concentration. As the concentration of drug increases the release rate also increases linearly. It is expressed in an equation.

\[
\log c = \log c_0 + \frac{K_1 t}{2.303} \quad \text{(Eqn. 2)}
\]

\[c = \text{initial drug concentration}
\]
\[c = \text{drug concentration at time } t
\]
\[K_1 = \text{the first order rate constant}
\]
\[t = \text{time in hours}
\]

**Higuchi square root kinetics**
It is the most famous mathematical equation to define the drug release from the micro particles, which is expressed in the Eqn. 3.

\[
c = K_2 t^{1/2} \quad \text{ (Eqn. 3)}
\]

\[c = \text{drug concentration}
\]
\[K = \text{the first order rate constant}
\]
\[t = \text{time in hours}
\]
RESULTS AND DISCUSSION

The current work is focused to design and evaluation of a controlled-release ocuserts containing a combination of BT and TM to treat glaucoma. Studies had revealed that fixed dose combinations of both the drugs are well tolerated in patients with glaucoma with least side effects [15-17]. Hence, an attempt was done to design ocular inserts that could remain in the cul-de-sac of the eye for a sustained period of time with a vision to maximise the ocular bioavailability.

The thickness of all the formulated ocular inserts was in comparison with that of marketed product—Pilo-20 inserts that could remain in the cul-de-sac of the eye for a sustained period of time with a vision to maximise the ocular bioavailability. Of all formulations tested, the optimised F9 was found stable at completion of 24 h.

Ocular inserts of formulations F1–F3 having low polymer concentration resulted in the poor drug release; F4–F6 with medium concentration resulted in moderate release, whereas F7–F9 with higher concentration resulted in the better drug release on completion of 24 h.

Table 2: Comparison of characteristic infrared peaks BT and TM with and without Excipients

<table>
<thead>
<tr>
<th>Characteristic peaks (wave number cm⁻¹)</th>
<th>Corresponding functional groups</th>
<th>Characteristic absorption range</th>
</tr>
</thead>
<tbody>
<tr>
<td>3409</td>
<td>-C=O (stretching)</td>
<td>1670–1820</td>
</tr>
<tr>
<td>3272</td>
<td>C–N–O (aliphatic)</td>
<td>3000–3100</td>
</tr>
<tr>
<td>3040</td>
<td>C=O (stretching)</td>
<td>1600–1900</td>
</tr>
<tr>
<td>2917</td>
<td>C=O (stretching)</td>
<td>1670–1820</td>
</tr>
<tr>
<td>1707</td>
<td>C=O (stretching)</td>
<td>1670–1820</td>
</tr>
<tr>
<td>1500</td>
<td>C=O (stretching)</td>
<td>1670–1820</td>
</tr>
</tbody>
</table>

*Sodium alginate

Table 3: Drug content of different ocular inserts

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug content (mg/cm²)</th>
<th>Timolol maleate (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.48±0.003</td>
<td>0.49±0.004</td>
</tr>
<tr>
<td>F2</td>
<td>0.49±0.005</td>
<td>0.49±0.004</td>
</tr>
<tr>
<td>F3</td>
<td>0.49±0.003</td>
<td>0.49±0.004</td>
</tr>
<tr>
<td>F4</td>
<td>0.48±0.006</td>
<td>0.47±0.007</td>
</tr>
<tr>
<td>F5</td>
<td>0.48±0.008</td>
<td>0.47±0.008</td>
</tr>
<tr>
<td>F6</td>
<td>0.48±0.006</td>
<td>0.47±0.008</td>
</tr>
<tr>
<td>F7</td>
<td>0.47±0.004</td>
<td>0.47±0.002</td>
</tr>
<tr>
<td>F8</td>
<td>0.47±0.003</td>
<td>0.47±0.001</td>
</tr>
<tr>
<td>F9</td>
<td>0.49±0.002</td>
<td>0.50±0.006</td>
</tr>
</tbody>
</table>

Values were expressed as mean±Standard Deviation (SD) of sample replicate, n=3

Table 4: Data showing physical characteristics of BT and TM of ocular inserts prepared

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Thickness (mm) of different ocular inserts</th>
<th>Weight (gm) of different ocular inserts</th>
<th>Percentage moisture absorption of different ocular inserts</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.212±0.003</td>
<td>0.17±0.0000</td>
<td>8.66±0.026</td>
</tr>
<tr>
<td>F2</td>
<td>0.200±0.004</td>
<td>0.20±0.0005</td>
<td>7.36±0.070</td>
</tr>
<tr>
<td>F3</td>
<td>0.219±0.003</td>
<td>0.18±0.0026</td>
<td>6.92±0.026</td>
</tr>
<tr>
<td>F4</td>
<td>0.208±0.011</td>
<td>0.21±0.0026</td>
<td>4.04±0.026</td>
</tr>
<tr>
<td>F5</td>
<td>0.217±0.005</td>
<td>0.21±0.0026</td>
<td>8.81±0.036</td>
</tr>
<tr>
<td>F6</td>
<td>0.227±0.003</td>
<td>0.22±0.0020</td>
<td>3.25±0.036</td>
</tr>
<tr>
<td>F7</td>
<td>0.247±0.001</td>
<td>0.33±0.0026</td>
<td>3.04±0.056</td>
</tr>
<tr>
<td>F8</td>
<td>0.251±0.003</td>
<td>0.35±0.0020</td>
<td>3.22±0.036</td>
</tr>
<tr>
<td>F9</td>
<td>0.251±0.003</td>
<td>0.33±0.0026</td>
<td>4.27±0.070</td>
</tr>
</tbody>
</table>

Values were expressed as mean±Standard Deviation (SD) of sample replicate, n=3
The bioavailability of topically applied drug as eye drop is extremely poor and can be enhanced by ocular inserts formulated with natural bioadhesive polymers. In the present study ocular inserts of brimonidine tartrate and timolol maleate prepared from natural bioadhesive polymer, sodium alginate exhibited good control in the release of the drug for a period of 24 h. Further studies need to be carried out to check the feasibility of the inserts as an alternative choice for the treatment of glaucoma.

**CONFLICT OF INTERESTS**
Declared none

**REFERENCES**


**CONCLUSION**

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