FORMULATION AND EVALUATION OF DORSOLAMIDE HCL OCULAR INSERT

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ABSTRACT

Matrix type of ocular insert was prepared using hydrophilic polymer PVP K 30 in different concentration by solvent casting method. The compatibility study of drug and polymer was performed by FTIR and DSC study and results revealed that drug and polymer are compatible to each other. Physicochemical evaluations like weight variation, thickness, content uniformity, moisture absorption, moisture loss test were performed. In vitro release study was carried out for all formulations and overall results revealed that as concentration of polymer increases there was slow release of Dorsolamide HCl occurred from the formulation.

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**Introduction**

Conventional ocular preparation like eye drop, solutions or suspensions often result in poor bioavailability and therapeutic response due to rapid pre corneal elimination of the drug resulting in poor patient compliances because patient need to take several time in a day in order to achieve therapeutic concentration.\(^{(1,2)}\) Ophthalmic inserts offer many advantage over conventional dosage form like increase ocular residence, possibility of releasing drug at a slow and constant rate\(^{(3)}\) Dorsolamide HCl is a topically active carbonic anhydrase inhibitor developed to circumvent the side effects of Acetasolamide in treatment of open angle glaucoma.\(^{(4)}\) Its ocular formulation has been marketed in USA since 1995.\(^{(4)}\) Dorsolamide HCl is given in divided dose several time in a day in the form of eye drop. As per standard literature eye drop contains the preservative having potential to cause adverse effect to ocular tissue.\(^{(5)}\) In this study an attempt was made to prepare preservative free ocular insert with the basic objective of increase pre corneal residence time, reducing the frequency of administrations and thus enhance the patient compliance and therapeutic efficacy.

**Materials and Methods**

Dorsolamide HCl and PVP K 30 were received as a gift sample from INTAS Pharma, Ahmedabad. Dialysis membrane was procured from Himedia, Mumbai. Other chemicals and solvents used in the study were of analytical grade.

**Formulation Method**

The inserts were prepared by solvent casting method. Polymer and drug were passed through 400 ≠ sieve.

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Dorsolamide HCl (mg)</th>
<th>PVP K 30 (% w/v)</th>
<th>Plasticizer PEG-400 (% w/w)</th>
<th>Casting Solvent Distilled water (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>1</td>
<td>1</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>R2</td>
<td>1</td>
<td>2</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>R3</td>
<td>1</td>
<td>3</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>R4</td>
<td>1</td>
<td>4</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>R5</td>
<td>1</td>
<td>5</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>R6</td>
<td>1</td>
<td>6</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>

Weighed quantity of polymer PVP K 30 was dissolved in 10 ml distilled water under continuous stirring as per the quantity mentioned in Table 1. Dorsolamide HCl equivalent to 1.0 mg per ocular insert was added to the polymeric solution. The medicated polymer solution was sonicated for fifteen
minutes to remove air bubbles. Then plasticizer PEG-400 30% of dry weight of polymer was added under continuous stirring. Then resultant solution was stirred on teflon coated petri plate (Diameter 5 cm and area 19.625 cm²) and covered with inverted funnel to allow slow and uniform evaporation of solvent at 40⁰C for 24 h. The dried film thus obtained was cut by 6 mm cork borer to get ocular insert. Insert was sterilized under UV for 1 min and individual insert was packed in sterilized aluminum foil which was further stored in desiccator at room temperature.⁶,⁷

**Compatibility study**

FTIR and DSC study are helpful to confirm identity of drug and to detect the interaction of drug with polymers. The drug polymer compatibility test was carried out using Fourier Transformer Infra Red Spectrophotometer (FTIR). A base line correction was made by dried Potassium bromide. Infrared spectra of drug and polymers alone and combination with drug and polymers were recorded by FTIR Affinity 21 CE, Schimadzu. The DSC study were carried out by using Perkin-Elmer series 7 DSC scanning from 40 ⁰C to 300 ⁰C at 10 ⁰C per minute.⁸

**Uniformity of thickness**

The thickness of the insert was determined using Micrometer gauze (Mitotoyo, Japan) at ten different points of each insert.⁹

**Uniformity of weight**

From each batch, ten inserts were taken out and weighed individually using digital balance. The mean weight of the insert was recorded.¹⁰

overnight to get uniform distribution. After proper mixing the casting solution was poured

**Drug content**

Ocular insert was dissolved in required quantity of methanol. The resultant mixture was transferred to 50 ml and dilution was carried out with simulated tear fluid. Volumetric flask was allows to shake for 1 h. Similarly blank was prepared using drug free insert. Drug content was determined by UV Spectroscophotometer at 252 nm.⁶,⁷

**% Moisture absorption**

The percentage moisture absorption test was carried out to check physical stability or integrity of the film at humid condition. The films were weighed and placed in desiccator containing saturated solution of sodium chloride and 84% humidity was maintained. After three days, the films were taken out and reweighed. The % moisture absorption was calculated using the formula.⁹,¹¹

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

**% Moisture loss**

The percentage moisture loss was carried out to check the integrity of the film at dry condition. The films were weighted and kept in desiccator containing anhydrous calcium chloride. After three days, the films were taken out and reweighed. The percentage moisture loss was calculated using the formula.¹²

\[
\% \text{ Moisture loss} = \left( \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \right) \times 100
\]
Surface pH
The inserts were allowed to swell in closed Petri plate at room temperature for 30 minutes in 0.1 ml of bidistilled water. The swollen insert was removed and placed under digital pH meter to determine the surface pH.6

In Vitro Release Study
Semi permeable dialysis membrane number 60 procured from Himedia which has molecular weight cut off 12000 to 14000 with 2.4 nm pore size was used in the study. This dialysis membrane act as corneal epithelium. A simple cylindrical glass tube of 15mm internal diameter and 100 mm height was used. The dialysis membrane was tied to one end of open cylinder, which acted as a donor compartment. An ophthalmic insert was placed inside this compartment. The entire surface of the membrane was in contact with the receptor compartment comprising 25 ml of simulated tear fluid (pH 7.4) in a 100 ml beaker. The content of receptor compartment was stirred continuously using a magnetic stirrer and temperature was maintained at 37°C ± 0.5°C. At specific intervals 1 ml aliquot of solution was withdrawn from the receptor compartment and replaced with fresh simulated tear fluid. The aliquot was analyzed for the drug content using UV-Vis spectrophotometer (Model 1800, Schimadzu, Japan) at 252 nm after appropriate dilutions against reference using simulated tear fluid.12,13

Results and Discussion
Compatibility Study
It was observed from the FTIR spectra (Figure 1) of Dorsolamide HCl, PVP K 30 and mixture of these two confirms that important peaks NH stretching mode of SO₂NH₂ at 3372 nm, C-H stretching mode of thoophene at 3040 nm, NH₂⁺ stretching mode at 2300 nm, C=C stretching mode at 1589 nm, SO₂ asymmetric stretching mode of sulphonamide at 1345nm, SO₂ asymmetric stretching mode of sulphone at 1306 nm, SO₂ symmetric stretching mode of sulphonamide at 1159 nm, SO₂ symmetric stretching mode of sulphone at 1132 nm. are present in FTIR spectra of Dorsolamide HCl and mixture of Dorsolamide HCl and PVP K 30.

![Figure 1: FTIR Spectra of A) Dorsolamide HCl B) PVP K 30 C) Physical mixture of Dorsolamide HCl and PVP K 30](image-url)
It proved that drug and polymer are compatible to each other; there was no interaction between drug and excipients. It was observed from DSC Spectra (Figure 2) that melting endotherm of Dorsolamide HCl was 264.00 °C and in physical mixture it remains unaltered. Melting endotherm obtained from DSC spectra are in close agreement with theoretically melting point of Dorsolamide HCl. This data confirm that there was no interaction between drug and polymers.

**Uniformity of Weight**

The weights of all inserts were found to be in the range of 3.53 to 7.30 mg (Table 2) with least standard deviation indicates uniform distribution of drug, polymer and plasticizer.

### Table 2: Physico chemical evaluation of Dorsolamide HCl ocular insert. Mean ± SD (**n=10,**n=3)

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Weight ** (mg)</th>
<th>Thickness** (mm)</th>
<th>Drug Content* (%)</th>
<th>Surface pH*</th>
<th>Folding Endurance*</th>
<th>Moisture Absorption* (%)</th>
<th>Moisture Loss* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>3.53 ±0.516</td>
<td>0.047 ±0.001</td>
<td>99.3 ±0.305</td>
<td>7.4</td>
<td>190</td>
<td>±2.301</td>
<td>±0.570</td>
</tr>
<tr>
<td>R2</td>
<td>4.01 ±0.527</td>
<td>0.063 ±0.002</td>
<td>98.50 ±0.210</td>
<td>7.2</td>
<td>201</td>
<td>±3.255</td>
<td>±0.890</td>
</tr>
<tr>
<td>R3</td>
<td>4.61 ±0.516</td>
<td>0.078 ±0.001</td>
<td>99.93 ±0.204</td>
<td>7.2</td>
<td>230</td>
<td>±2.110</td>
<td>±0.554</td>
</tr>
<tr>
<td>R4</td>
<td>5.51 ±0.316</td>
<td>0.090 ±0.005</td>
<td>99.96 ±0.110</td>
<td>7.4</td>
<td>246</td>
<td>±3.145</td>
<td>±0.620</td>
</tr>
<tr>
<td>R5</td>
<td>6.23 ±0.483</td>
<td>0.105 ±0.004</td>
<td>99.57 ±0.256</td>
<td>7.4</td>
<td>225</td>
<td>±2.560</td>
<td>±0.450</td>
</tr>
<tr>
<td>R6</td>
<td>7.30 ±0.527</td>
<td>0.125 ±0.006</td>
<td>99.32 ±0.132</td>
<td>7.4</td>
<td>202</td>
<td>±3.270</td>
<td>±0.580</td>
</tr>
</tbody>
</table>
Uniformity of thickness
The thickness of the prepared insert varies from 0.047 to 0.125 mm (Table 2). All the formulations showed uniform thickness and low standard deviation confirms uniformity of prepared inserts. Results from thickness parameters revealed that the formulations were not that much thick to produce any irritation while placing inside the cul-de-sac.

Content Uniformity
The drug content of all the formulation was found to be in the range of 98.50 to 99.93 %. (Table 3) It was observed that there was minimum intra batch variation and uniform distribution of drug which in turn confirm the suitability of the process used in formulation of ocular insert.

Surface pH
The surface pH of the prepared inserts varied between 7.2 to 7.4 (Table 2) which is comparable with the pH of tear fluid i.e. 7.4. This indicates that the formulations will not produce any irritation while it is placed inside the cul de sac.

In vitro Release Study
It was observed that almost 100 % drug released from all formulations occurred at the end of 180 to 300 minutes (Figure 3). Fast release of drug from formulation R₁ occurred may be due to low

Folding Endurance
The folding endurance of all the formulations was found to be good. The results from folding endurance test revealed that the folding endurance increases with increase in polymer concentration up to 4% then after the value of folding endurance decreases with increase in concentration of polymer. All the batches exhibited good folding endurance value which withstands external stress (Table 2).

Moisture absorption Test
Moisture absorption of prepared formulations was found to be in the range of 3.8 to 8.35% (Table 2). The data revealed that as concentration of polymer increases tendency to absorb moisture increases. This happened because of hydrophilic nature of PVP K 30. It was also observed that there was no change in physical appearance and integrity of the formulations.

Moisture loss Test
Moisture loss of prepared formulation was found to be in the range of 2.01 to 5.81% (Table 2). The data revealed that as concentration of polymer increases tendency to moisture loss increases. concentration and hydrophilic nature of polymer. The overall result revealed that as the concentration of polymer increases there was slow release of drug from formulation occurred.
Table 3: In vitro release study of Dorsolamide HCl ocular insert.

<table>
<thead>
<tr>
<th>Time (mins)</th>
<th>R_1^*</th>
<th>R_2^*</th>
<th>R_3^*</th>
<th>R_4^*</th>
<th>R_5^*</th>
<th>R_6^*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>24.3±1.2</td>
<td>22.1±2.13</td>
<td>20.15±2.03</td>
<td>19.14±0.61</td>
<td>18.13±1.05</td>
<td>16.05±2.1</td>
</tr>
<tr>
<td>60</td>
<td>42.6±0.59</td>
<td>35.25±2.06</td>
<td>35.02±2.16</td>
<td>33.16±1.18</td>
<td>30.56±2.01</td>
<td>27.14±1.58</td>
</tr>
<tr>
<td>90</td>
<td>53.45±1.1</td>
<td>49.14±1.85</td>
<td>46.89±1.19</td>
<td>42.1±1.45</td>
<td>37.84±2.11</td>
<td>33.69±1.59</td>
</tr>
<tr>
<td>120</td>
<td>58.74±1.61</td>
<td>55.48±1.36</td>
<td>53.28±1.89</td>
<td>48.06±2.06</td>
<td>45.03±1.36</td>
<td>42.03±1.48</td>
</tr>
<tr>
<td>150</td>
<td>80.23±1.59</td>
<td>76.89±0.85</td>
<td>65.2±2.01</td>
<td>56.53±2.19</td>
<td>53.43±0.59</td>
<td>47.05±2.08</td>
</tr>
<tr>
<td>180</td>
<td>99.25±0.50</td>
<td>88.14±0.56</td>
<td>74.13±1.19</td>
<td>69.15±1.06</td>
<td>64.01±0.89</td>
<td>55.61±0.69</td>
</tr>
<tr>
<td>210</td>
<td>99.12±1.15</td>
<td>85.19±1.26</td>
<td>76.26±0.89</td>
<td>73.96±0.67</td>
<td>66.68±0.87</td>
<td></td>
</tr>
<tr>
<td>240</td>
<td>100.01±0.85</td>
<td>88.41±0.75</td>
<td>84.56±1.11</td>
<td>76.09±1.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>270</td>
<td>100.03±0.54</td>
<td>99.59±0.89</td>
<td>88.06±0.54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>100.05±0.68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean±SD (*n=3)

Figure 3: In vitro Cumulative drug release of Dorsolamide HCl ocular inserts.

**Conclusion**

The formulation of oclusert containing Dorsolamide HCl seems to be promising and further addition of rate controlling membrane may provide controlled release pattern and same fact can be considered for further research. Further in vivo study must be carried out to check the efficacy of the preparations.

**Acknowledgement**

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References


