Formulation Characterization and Evaluation of Matrix type Transdermal Patches of Carvedilol

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Abstract: The present study was carried out to formulate, characterize and evaluate a matrix-type transdermal formulation containing Carvedilol with different ratios of polymer (Eudragit RL100, HPMC and Ethyl Cellulose) combinations plasticized with dibutylphthalate by the solvent evaporation technique. The interference of the polymers were ruled out by infrared spectroscopy. In-vitro release study was performed using Franz diffusion cell with cellophane membrane as barrier. The prepared patches were tested for their physicochemical characteristics such as thickness, drug content uniformity, Percentage moisture uptake and folding endurance. In-vitro release studies of Carvedilol-loaded patches in phosphate buffer saline of pH 7.4 exhibited drug release in the range of 52% to 81% in 24h for the formulations F1-F6. The in-vitro drug permeability studies of optimized formulation F1 was found to be 48.67 µg/cm²/hr. Data of in vitro release from patches were fit in to different equations and kinetic models to explain release kinetics. The release of Carvedilol from the optimized formulation F1 follows zero order kinetics and the mechanism of drug release was concluded as diffusion controlled. The developed transdermal patches increase the efficacy of Carvedilol for the therapy of hypertension.

Keywords: Carvedilol; Transdermal; Eudragit RL 100, HPMC E15, EC; In-vitro permeation.

1. INTRODUCTION

Transdermal drug delivery systems (TDDS) are adhesive drug containing devices of defined surface area that delivers predetermined amount of drug to the intact skin at a preprogrammed rate1. The transdermal delivery has gained importance in recent years2. The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa, and improved patient compliance3.

2. PLAN OF WORK

A) Preparation of transdermal patches.
B) Physico-chemical evaluation


2.1 Preparation of Transdermal patches

Transdermal patches containing Carvedilol were prepared by solvent evaporation method using varying ratios of different grades of polymers. The polymers Eudragit RL100, HPMC E15 and Ethyl cellulose (total weight = 1000 mg) were weighed in requisite ratios and dissolved in 15 ml of methanol to form a 15% w/v solution. To the above solution 110mg of Carvedilol was then added and stirred by using a magnetic stirrer until drug dissolves. Then 20% of plasticizer, DBP was added to the above solution. The solution was poured in a glass petri dish of 65cm² area and dried at room temperature for 24 hours. The organic solvent evaporates to leave stable patches.

Table No.1: Formulation design of Carvedilol transdermal patches

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug (mg)</th>
<th>HPMC E15 (mg)</th>
<th>EC (mg)</th>
<th>Eudragit RL100 (mg)</th>
<th>Dibutylphthalate (%)</th>
<th>Methanol (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>110</td>
<td>1000</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>F2</td>
<td>110</td>
<td>-</td>
<td>1000</td>
<td>-</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>F3</td>
<td>110</td>
<td>-</td>
<td>-</td>
<td>1000</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>F4</td>
<td>110</td>
<td>800</td>
<td>-</td>
<td>200</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>F5</td>
<td>110</td>
<td>600</td>
<td>400</td>
<td>-</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>F6</td>
<td>110</td>
<td>400</td>
<td>200</td>
<td>-</td>
<td>20</td>
<td>15</td>
</tr>
</tbody>
</table>

2.2 Evaluation of transdermal formulation

Physical appearance
All the transdermal systems were visually inspected for colour, clarity, flexibility and smoothness.

Folding Endurance
Folding endurance of the film was determined manually by folding a small strip of the film (4x3 cms) at the same place till it breaks. The maximum number of folding operation done at the same place of the film without breaking, gives the...
value of folding endurance, where the cracking point of the films were considered as the end point.

**Thickness of the films**

The thickness of the patches was measured at three different places by using a Digital Screw Gauge micrometer (Mitutoyo, Japan) and mean thickness was calculated.

**Weight uniformity**

The dried patches were weighed on electronic balance (Sartorius UK). The average of 3 observations was calculated.

**Drug content**

Transdermal systems of specified area (5.088 cm²) was cut into small pieces and taken into 50 ml volumetric flask, 25ml of phosphate buffer saline pH 7.4 was added and gently heated to 450°C for 15 min and kept for 24 hrs with occasional shaking. Then the volume was made up to 50ml again with phosphate buffer saline pH 7.4 and further dilutions were made from this solution. Similarly, a blank was carried out using a drug free patch. The solutions were filtered and absorbances were read at 242 nm by UV spectrophotometer.

**Percentage moisture uptake**

The weighed films were kept in a desiccator at room temperature for 24 hours. They were then taken out and exposed to 84% relative humidity using a saturated solution of potassium chloride in a desiccator until a constant weight was achieved. Then the films were weighed and percentage moisture uptake was calculated by using the following formula:

\[
\text{Percentage moisture uptake} = \frac{\text{Final wt.} - \text{Initial wt.}}{\text{Initial wt.}} \times 100
\]

**Percentage moisture content**

The prepared films were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 hours. The films were weighed repeatedly until they showed a constant weight. The percentage moisture content was calculated using the following formula:

\[
\text{Percentage moisture content} = \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Final wt.}} \times 100
\]

**In-vitro Permeation Study**

In vitro permeation studies were carried out from each formulation by using modified Franz diffusion cell. The surface area of the release membrane was 3.14 cm². The volume of a receptor medium was 50 ml and composed of phosphate buffer saline (pH 7.4) and stirred by a magnetic bead at 150 rpm. Temperature of the receptor fluid was maintained at 37±0.5°C.

The samples (2ml) were withdrawn at regular intervals (1, 2, 3, 4, 5, 6, 7, 8, 24 hours), filtered and analyzed for drug content from receiver compartment and replaced by same volumes of freshly prepared phosphate buffer saline (pH 7.4). The samples were analyzed by spectrophotometrically at 242nm.

### 3. RESULTS AND DISCUSSION

Table: 2. Data showing physical parameters of Carvedilol transdermal patches

<table>
<thead>
<tr>
<th>S. No</th>
<th>Formula</th>
<th>Folding endurance</th>
<th>Thickness (mm)</th>
<th>Weight variation (gm)</th>
<th>% Moisture uptake</th>
<th>% Moisture content</th>
<th>Tensile strength (kg/mm²)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>217±3.1</td>
<td>0.110±0.029</td>
<td>1.003</td>
<td>1.05</td>
<td>14.28</td>
<td>0.575±0.01</td>
<td>96.77±0.05</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>170±15.2</td>
<td>0.103±0.023</td>
<td>1.012</td>
<td>0.75</td>
<td>5.45</td>
<td>0.385±0.01</td>
<td>91.45±0.05</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>170±7.50</td>
<td>0.083±0.011</td>
<td>1.063</td>
<td>0.88</td>
<td>3.44</td>
<td>0.424±0.01</td>
<td>89.48±0.06</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>178±6.39</td>
<td>0.100±0.017</td>
<td>1.037</td>
<td>1.71</td>
<td>5.55</td>
<td>0.474±0.00</td>
<td>92.27±0.4</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>179±8.08</td>
<td>0.097±0.028</td>
<td>1.092</td>
<td>1.36</td>
<td>11.11</td>
<td>0.324±0.01</td>
<td>90.72±1.2</td>
</tr>
<tr>
<td>6</td>
<td>F6</td>
<td>120±4.72</td>
<td>0.092±0.015</td>
<td>1.097</td>
<td>1.23</td>
<td>7.01</td>
<td>0.384±0.01</td>
<td>96.34±1.0</td>
</tr>
</tbody>
</table>

\(S.D_{\text{in}}=3\).

**In-vitro diffusion studies of Carvedilol Transdermal patches**

The in-vitro release of Carvedilol across cellophane membrane from formulation F1, F2, F3, F4, F5, F6, were 81%, 52%, 68.3%, 74.9%, 79.53% and 72.9%, respectively. The flux for the formulations was 48.67, 30.27, 42.34, 46.10, 48.71, 44.93 μg/cm²/h and diffusion coefficient was 7.7×10⁻³, 4.8×10⁻³, 6.7×10⁻³, 7.3×10⁻³, 7.7×10⁻³, 7.1×10⁻³.

It was revealed from the above result that with increasing in the concentration of HPMC the Carvedilol released also increased. It might be attributed due to the hydrophilic nature of HPMC. In the formulation of F1, containing HPMC the Carvedilol released also increased. It might be attributed due to the hydrophilic nature of HPMC. In the formulation of F1, containing HPMC the Carvedilol released also increased. It might be attributed due to the hydrophilic nature of HPMC.
Permeation data analysis
The permeability parameters of different formulations are given in the following table.

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Formulation</th>
<th>Jss± SD (µg/cm²/hr)</th>
<th>Kp± SD *10⁻² (cm/hr)</th>
<th>Enhancemnt Ratio (Er)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>48.67 ± 0.77</td>
<td>0.77 ± 0.01</td>
<td>1.183609</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>30.27 ± 0.48</td>
<td>0.48 ± 0.01</td>
<td>0.736138</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>42.34 ± 0.67</td>
<td>0.67 ± 0.01</td>
<td>1.029669</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>46.10 ± 0.73</td>
<td>0.73 ± 0.01</td>
<td>1.121109</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>48.71 ± 0.77</td>
<td>0.77 ± 0.01</td>
<td>1.184582</td>
</tr>
<tr>
<td>6</td>
<td>F6</td>
<td>44.93 ± 0.71</td>
<td>0.71 ± 0.01</td>
<td>1.092656</td>
</tr>
</tbody>
</table>

Drug release kinetics
The release of Carvedilol from the optimized formulation F1 follows zero order kinetics and the mechanism of drug release was concluded as diffusion controlled.

4. CONCLUSION
On the basis of the in vitro characterization it was concluded that Carvedilol could be administered transdermally through matrix type TDDS developed in our laboratory. Transdermal patches consisting of the rate-controlling polymers Eudragit RL100, HPMCE15, EC demonstrated sustained and controlled release of the drug during in vitro permeation.

REFERENCES