DESIGN AND DEVELOPMENT OF LOSARTAN POTASSIUM LOADED TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT
Losartan potassium is used in hypertension as beta blockers. This type of high blood pressure medicine makes the heartbeat slow down. But main drawback of conventional losartan potassium formulation is that it undergoes hepatic first pass metabolism. Thus the plasma $t_{1/2}$ is 1.5-2 h thereby decreasing its bioavailability up to 32%. Hence an alternative delivery system for improving the half life and bioavailability is needed. One of the methods most often utilized in such condition is transdermal drug delivery system. Transdermal patches of Losartan Potassium with hydrophilic and hydrophobic polymers containing the drug reservoir were prepared by solvent evaporation method. In this experiment, the membranes of HPMC and eudragit RS 100 were used to achieve controlled release of the drug. The prepared patches showed good promising results for all the evaluated parameters like weight thickness, folding endurances, tensile strength, moisture absorption, % elongation and drug content. In-vitro & Ex-vivo permeation studies were done and drug release patterns were found to be satisfactory.

Key words: Transdermal patches, bioavailability, Ex-vivo study, Rate controlling membranes, solvent evaporation method.

INTRODUCTION
Hypertension or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Blood pressure is summarized by two measurements, systolic and diastolic. Which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). Normal blood pressure at rest is within the range of 100-140mmHg systolic (top reading) and 60-90mmHg diastolic (bottom reading). High blood pressure is said to be present if it is persistently at or above 140/90 mmHg.

The losartan potassium is beta-blockers. This type of high blood pressure medicine makes the heartbeat slow down. Beta-blockers also keep your heart from pumping so hard. This makes blood go through your vessels with less force. The pressure inside your blood vessels goes down.
The main drawback of conventional losartan potassium formulation is that it undergoes hepatic first pass metabolism. Thus the plasma t1/2 is 1.5-2 h thereby decreasing its bioavailability up to 32%. Hence an alternative delivery system for improving the half life and bioavailability is needed. [1, 2]

One of the methods most often utilized in such condition is transdermal drug delivery – meaning Trans dermal drug delivery systems are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin, at a controlled rate to the systemic circulation. [3,4,5] When the transdermal drug flux is controlled by the device itself instead of the skin, delivery of the drug is more reproducible, leading to smaller inter and intrasubject variations because the drug release from the device can be controlled accurately than the permeability of the skin. [6,7,8]

The aim in the development of new transdermal drug delivery devices is to obtain a controlled, predictable, and reproducible release of the losartan potassium into the blood stream of the patient which will improve the biological half life and bioavailability of losartan potassium. [1, 2]

MATERIALS AND METHODOLOGY

Material
The drug Losartan potassium was gifted from West – coast pharmaceutical. Hydroxy propyl methyl cellulose (HPMC) was purchased from Chinasun Group Co LTD. Eudrgit RS 100 was purchased from Evonic industries. Polyethylene glycol 400 (PEG 400) and Span 80 was purchased from S.D. Fine Chem. Ltd, Mumbai. Ethanol was purchased from Sulab laboratories, Vadodara.

Methodology
Preformulation studies
Estimation of Losartan potassium in methanol and phosphate buffer pH 7.4.
Accurately weighed 10 mg of losartan potassium was transferred to a 100 ml volumetric flask, dissolved with required quantity of solvent (methanol or phosphate buffer pH 7.4) and make up to mark with respected solvent. From this solution suitable dilution was made to prepare stock solution of 100μg/ml. Aliquots of working solution of losartan potassium were transferred in to a series of 10 ml volumetric flask and made volume up to the mark with solvent (methanol or phosphate buffer pH 7.4). The absorbance of the
resulting solution was measured at 254 nm using UV - Vis double beam spectrophotometer (Shimadzu 1800 UV/Vis double beam, Japan). [9]

**Solubility determination** [10,11,12]

Excess amount of the drug was dissolved in 5 ml of each solvent (Distilled water, methanol & PEG 400) separately in a volumetric flask to get a saturated solution. The solution was shaken for 24 hrs to assist the attainment of equilibrium with the undisclosed drug particles. After shaking for 24 hrs all solution were centrifuged to collect supernatant liquid. Then measured quantity of solution was withdrawn and successively diluted with respective solvents and analysed spectrophotometrically at $\lambda_{\text{max}}$ 254 nm.

**Drug excipients compatibility study**

To investigate any possible interaction between the drug and the utilized polymer, IR spectrums of pure losartan potassium, Eudragit RS 100, HPMC and their physical mixture were carried by using FTIR, the range selected was from 400cm$^{-1}$ to 4000 cm$^{-1}$ [13,14,15]

**Formulation of drug loaded transdermal films**

The transdermal film containing losartan potassium was prepared by using selected ratio of HPMC and Eudragit RS 100. The polymers in selected ratios were dissolved in 10 ml the methanol solvent. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. PEG400 in 30% w/w of polymer was used as plasticizer. Then the solution was poured on the Petri dish having mercury and dried at the room temperature. Controlled solvent evaporation was achieved by placing an inverted funnel over the petridish. These were left undisturbed at room temperature for one day. The films could be retrieved intact by slowly lifting from the mercury substrate and kept in the dessicator until used. [16,17,18,19]

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**Table 1: Composition of transdermal films**

[www.pharmasm.com](http://www.pharmasm.com)  Impact factor – 0.3317/ICV – 4.01
### Evaluation parameters for prepared patches \(^{[20,21,22,23]}\)

#### Physical appearance

All the transdermal films were visually inspected for colour, clarity, flexibility and smoothness.

#### Thickness uniformity

Discs of 1 cm\(^2\) patch were subjected to measurement of thickness, using micrometer screw gauge.

#### Folding endurance

This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.

#### Tensile strength and % Elongation

The tensile strength of the transdermal films was measured using tensile strength instrument (locally fabricated instrument). A small film strip (30 x 10 mm) was used. One end of the strip was fixed between adhesive tapes to give support to the film when placed in the film holder. Another end of the film was fixed between the adhesive tapes.
with a small pin sandwiched between them to keep the strip straight while stretching. A small hole was made in the adhesive tape near the pin in which a hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached to the other end to hold the weights. A small pointer was attached to the thread, which travels over scale on the base plate. To determine the tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken. The weight required to break the film was noted as break force.

The tensile strength was calculated by the formula,

\[
\text{Tensile Strength} = \frac{\text{weight required to break film}}{a \times b \times (1+2L/2)}
\]

Where, 
\(a\) = thickness of film
\(b\) = width of film
\(L\) = length of film

The percent elongation was determined by noting the length just before the break point and substituting the formula

\[
\% \text{ Elongation} = \frac{\text{Final length} - \text{Initial length}}{\text{Initial length}} \times 100
\]

**Water vapor transmission rate**

Glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly and dried in an oven. About 1gm anhydrous calcium chloride was placed in the cells and the respective polymer films were fixed over the brim. The cells were accurately weighed and kept in a closed desiccators containing 200ml saturated solution of potassium chloride to maintain a humidity of 84%. The cells were taken out and weighed after 24, 48 and 72 hrs of storage.

The amount of water vapour transmitted was found using the formula.

\[
\text{Water vapour transmission rate} = \frac{\text{Final Weight} - \text{Initial Weight}}{\text{Time}} \times \text{Area}
\]

Water vapour transmission rate is usually expressed as the number of grams of moisture gained/h/cm².

**Drug content uniformity**
1 cm² area of the film was cut and dissolved in sufficient quantity of methanol. The volume was made up to 10 ml. 1 ml was then withdrawn from this solution and diluted to 10 ml. The absorbance was then measured at 254 nm.

**In vitro & EX-vivo drug permeation studies**

A vertical assembled diffusion cell having downstream volume of 50 ml was used. For in vitro drug release study, the cellophane membrane was mounted on the diffusion cell and receiver compartment was filled with 50 ml phosphate buffer of pH 7.4 and the temperature was maintained at 37°C± 0.5°C. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm. The formulated film was placed over the cellophane membrane. 5 ml of sample was withdrawn every hour and replaced with 5 ml fresh buffer to maintain sink condition and their concentration was measured In UV- Spectrophotometer at 254 nm.

Experiment for Ex vivo diffusion study was carried out in same manner just by replacing cellophane membrane with rat skin as diffusion medium.[9,24]

**Stability study of optimized formulation** [25,26]

Stability study of optimized batch was carried out as per ICH guidelines at 25±2°C, 60±5% RH and 40±2°C,75±5% RH atmospheric conditions in humidity chamber. Stability was also checked at refrigerator condition (2-8°C). After 30 days samples were withdrawn and evaluated for physicochemical properties and in vitro diffusion study.

**RESULTS AND DISCUSSION**

**Preformulation Study**

**Estimation of Losartan potassium in methanol and phosphate buffer pH 7.4.**

Estimation of Losartan potassium was carried out in both the solvent system and found linearity of 0.999 and 0.996 in methanol and phosphate buffer pH 7.4 respectively.

**Solubility determination of Losartan potassium**

Solubility is important consideration during transdermal dosage form development so initial study was carried out to check solubility in various solvent systems. Results indicate that solubility was good in methanol. Results are shown in Table 2: Solubility data in various solvent
### Drug excipient compatibility study

FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. Figure 1, 2, 3 & 4 show the IR spectra of Losartan Potassium, Eudragit RS 100, HPMC and blend of them respectively. The IR spectrum of Losartan Potassium showed that it had major peaks at 3291 cm⁻¹ corresponding to N-H stretching and at 1620 cm⁻¹ corresponding to C=O stretching. In addition, there were several peaks in the frequency range of 845 cm⁻¹ to 528 cm⁻¹ due to C-H aromatic ring ending. From figure 4 clearly seen that there is no interaction between drug and selected polymer.

#### Table 1: Solubility of Losartan Potassium in different solvents

<table>
<thead>
<tr>
<th>SR. NO</th>
<th>SOLVENT</th>
<th>SOLUBILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>0.82± 0.09 mg/L</td>
</tr>
<tr>
<td>2</td>
<td>PEG 400</td>
<td>1.72 ± 0.64 mg/ml</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>20.05 ± 2.28 mg/ml</td>
</tr>
</tbody>
</table>

Figure 1: I.R Spectra of pure drug Losartan Potassium
Figure 2: I.R Spectra Of Eudragit RS 100

Figure 3: I.R Spectra of HPMC

Figure 4: I.R Spectra of DRUG + HPMC + Eudragit RS 100
Formulation of drug loaded transdermal film
Losartan potassium loaded transdermal film was successfully prepared as shown in Table 1.

Evaluation of transdermal films

Physical appearance:
All patches were found transparent, flexible, and smooth.

Thickness:
The thickness of the films varied from 0.52±0.01 to 0.56±0.01mm. The values obtained for all the formulations are given in the Table 3.

Folding Endurance:
The folding endurance was found to be in the range of 108 to 218. Maximum folding endurance was found in 1F2 batch (218±2). The values for all formulations are given in the Table 3. This data revealed that the patches had good mechanical strength along with flexibility.

Tensile strength:
The tensile strength was found to be in the range of 10.90 to 17.11 kg/cm². The formulation 1F2 showed the best tensile strength. The values for all patches are tabulated in Table 3.

% Elongation:
The % elongation was found to be in the range of 22 to 56 %. The formulation 1F5 showed minimum % elongation among all the other films. The results obtained for all the formulations are tabulated in the Table 3.

Water vapour transmission (WVT)
The water vapour transmission was found to be in the range of 0.016 to 0.028 gm/cm²/hr. Formulation 1F1 & 1F3 show highest transmission and formulation 1F2 show lowest transmission. The results obtained for all the formulations are tabulated in the Table 3.

Drug content
All batches showed satisfactory drug content. Higher drug content was found as 95.31±2.72% and 95.16±0.80 % in 1F2 and 2F2 respectively with lower deviation.
All the drug loaded films were found to be quite uniform in thickness, with good folding endurance and tensile strength, and slight change in water vapour transmission was observed.

### Table 3: Different parameters of transdermal films

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness (mm)</th>
<th>Folding</th>
<th>Tensile strength (kg/cm²)</th>
<th>WVT (Gm/cm²/hr)</th>
<th>% elongation</th>
<th>% drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>1F₁</td>
<td>0.53±0.04</td>
<td>148±4</td>
<td>12.12±0.85</td>
<td>0.026 ± 0.01</td>
<td>42±1.04</td>
<td>85.54±1.40</td>
</tr>
<tr>
<td>1F₂</td>
<td>0.52±0.11</td>
<td>218±2</td>
<td>17.09±0.44</td>
<td>0.016 ± 0.03</td>
<td>56±0.85</td>
<td>95.31±2.72</td>
</tr>
<tr>
<td>1F₃</td>
<td>0.54±0.06</td>
<td>178±7</td>
<td>13.89±0.72</td>
<td>0.028 ±0.01</td>
<td>39±1.15</td>
<td>81.95±0.77</td>
</tr>
<tr>
<td>1F₄</td>
<td>0.53±0.02</td>
<td>187±8</td>
<td>14.46±0.35</td>
<td>0.018 ±0.02</td>
<td>50±1.34</td>
<td>86.04±1.42</td>
</tr>
<tr>
<td>1F₅</td>
<td>0.56±0.01</td>
<td>108±2</td>
<td>11.90±1.10</td>
<td>0.019 ±0.01</td>
<td>22±0.89</td>
<td>87.75±2.71</td>
</tr>
<tr>
<td>2F₁</td>
<td>0.52±0.01</td>
<td>126±4</td>
<td>14.79±0.75</td>
<td>0.021 ±0.01</td>
<td>30±1.36</td>
<td>92.38±0.79</td>
</tr>
<tr>
<td>2F₂</td>
<td>0.56±0.06</td>
<td>209±7</td>
<td>15.11±0.29</td>
<td>0.017 ±0.01</td>
<td>34±0.87</td>
<td>95.16±0.80</td>
</tr>
<tr>
<td>2F₃</td>
<td>0.53±0.02</td>
<td>158±3</td>
<td>13.48±0.06</td>
<td>0.019±0.01</td>
<td>50±0.96</td>
<td>94.66±0.83</td>
</tr>
<tr>
<td>2F₄</td>
<td>0.53±0.05</td>
<td>162±1.52</td>
<td>14.27±0.03</td>
<td>0.021±0.01</td>
<td>43±0.76</td>
<td>87.69±1.72</td>
</tr>
<tr>
<td>2F₅</td>
<td>0.52±0.02</td>
<td>117±4</td>
<td>10.90±0.03</td>
<td>0.024±0.01</td>
<td>49±0.36</td>
<td>90.92±0.60</td>
</tr>
</tbody>
</table>

Values are expressed in mean ± SD, n = 3

### In vitro drug release

Prepared batches of drug loaded transdermal films were evaluated for in vitro diffusion study in phosphate buffer pH 7.4. From the results of in vitro diffusion it was found that drug diffusion was 81.93±0.20% for batch 1F₂ after 24 hours. So it gave good results in terms of cumulative diffusion amongst other batch of transdermal films formulations.

### Table 4: In vitro release data

<table>
<thead>
<tr>
<th>Time(hr)</th>
<th>% cumulative drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.26±1.41 11.37±1.84</td>
</tr>
<tr>
<td>2</td>
<td>16.32±1.67 15.03±0.47</td>
</tr>
<tr>
<td>3</td>
<td>22.32±2.24 18.12±2.56</td>
</tr>
<tr>
<td>4</td>
<td>26.98±2.84 23.45±1.35</td>
</tr>
<tr>
<td>5</td>
<td>33.39±3.53 36.62±3.83</td>
</tr>
<tr>
<td>6</td>
<td>37.39±1.45 39.34±3.28</td>
</tr>
<tr>
<td>24</td>
<td>81.93±3.28 79.62±2.46</td>
</tr>
</tbody>
</table>

Values are expressed in mean ± SD, n = 3
Values are plotted as mean ± SD, n = 3

Figure 5: In vitro drug release plot

**EX-vivo skin permeation studies**

1F₂ batch of drug loaded transdermal films was evaluated for EX-vivo diffusion study in phosphate buffer pH 7.4. From the results of EX-vivo diffusion it was found drug diffusion was 70.63±0.62% for batch 1F₂ after 24 hours which correlate with in vitro diffusion study.

**Table 5: EX-vivo skin permeation studies of batch 1F₂**

<table>
<thead>
<tr>
<th>Time(hr)</th>
<th>% cumulative drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.32±0.41</td>
</tr>
<tr>
<td>2</td>
<td>5.13±2.56</td>
</tr>
<tr>
<td>3</td>
<td>8.22±1.24</td>
</tr>
<tr>
<td>4</td>
<td>12.45±1.46</td>
</tr>
<tr>
<td>5</td>
<td>15.64±2.64</td>
</tr>
<tr>
<td>6</td>
<td>21.36±3.19</td>
</tr>
<tr>
<td>24</td>
<td>74.63±3.62</td>
</tr>
</tbody>
</table>

Values are expressed in mean ± SD, n = 3
Stability Study

Optimized batch was studied for their stability in three different conditions. Transdermal film of Losartan potassium was evaluated for different parameters and in vitro drug release study initially and after one month period. Results were shown in table 6 and 7. Results indicate that, at room temperature release profile was satisfactory but that release profile was very slightly changed in presence of higher temperature and humidity condition that provided by accelerated stability condition. But release profile was not that much altered that create doubt on stability of our final optimized transdermal film of Losartan potassium.

Table 6: Different parameters of optimized batch after 30 days storage in different environment condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>Thickness (mm)</th>
<th>Folding endurance</th>
<th>Tensile strength (kg/cm²)</th>
<th>WVT (Gm/cm²/hr)</th>
<th>% elongation</th>
<th>% Drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.52±0.04</td>
<td>212±2</td>
<td>17.18±0.4</td>
<td>0.016±0.03</td>
<td>55±1.05</td>
<td>95.74±0.87</td>
</tr>
<tr>
<td>Accelerated</td>
<td>0.53±0.04</td>
<td>220±9</td>
<td>18.12±0.7</td>
<td>0.017±0.06</td>
<td>56±0.57</td>
<td>94.55±0.64</td>
</tr>
<tr>
<td>Freezing</td>
<td>0.53±0.04</td>
<td>211±4</td>
<td>16.14±0.4</td>
<td>0.016±0.04</td>
<td>56±1.49</td>
<td>94.34±1.91</td>
</tr>
</tbody>
</table>

Values are expressed in mean ± SD, n = 3

Figure 6: Ex – vivo drug release plot
Table 7: In vitro release data of optimized batch after 30 days storage in different environment condition

<table>
<thead>
<tr>
<th>Time(hr)</th>
<th>% cumulative drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>1</td>
<td>2.01±0.22</td>
</tr>
<tr>
<td>2</td>
<td>3.89±0.65</td>
</tr>
<tr>
<td>3</td>
<td>4.49±0.54</td>
</tr>
<tr>
<td>4</td>
<td>8.98±0.38</td>
</tr>
<tr>
<td>5</td>
<td>12.07±0.85</td>
</tr>
<tr>
<td>6</td>
<td>17.24±0.34</td>
</tr>
<tr>
<td>24</td>
<td>82.47±0.47</td>
</tr>
</tbody>
</table>

Values are expressed in mean ± SD, n = 3
A = Accelerated condition (40ºC &75% RH)
B= Normal condition (40ºC &75% RH)
C= Freezing condition (2-8 ºC)

Figure 7: Ex – vivo drug release plot after stability period
CONCLUSION
The main drawback of conventional Losartan potassium formulation is that it undergoes hepatic first pass metabolism and also has very low bioavailability up to 32%. Hence an alternative delivery system for improving the half life and bioavailability is needed. In the present work an attempt was made to prepare and evaluate Losartan potassium transdermal films using different ratios of polymers such as HPMC and Eudragit RS100. All prepared batches had shown good promising results for all the evaluated parameters. Based on the In vitro & Ex-vivo drug release and drug content result, formulation 1F2 was concluded as an optimized formulation, which shows higher percentage of drug release and also meets other specification like thickness, folding endurance, tensile strength, WVT, % elongation, % drug content. So at last by preparing Losartan potassium transdermal films it can be assumed that transdermal delivery system may improves the biological half life and bioavailability of losartan potassium but it can be only confirmed by doing some further studies.

REFERENCES


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