ABSTRACT

Objective: Felodipine, a BCS class II calcium channel blocker, is used in the management of hypertension and angina pectoris. Due to the poor solubility and low bioavailability of the drug, there is a necessity to design an alternative route to achieve a constant plasma concentration of felodipine for its maximum therapeutic utility and can be achieved by transdermal route.

Methods: In this study, matrix type transdermal patches were prepared using different combinations of hydrophilic polymer, namely, polyvinylpyrrolidone (PVP) and hydrophobic polymer, namely, ethyl cellulose (EC) by solvent evaporation technique and were subjected for characterization.

Results: The Fourier transform infrared studies confirmed the compatibility between drug and polymers. Hydrophilic nature of the polymers greatly influenced physical characteristics and dissolution rate. Equal percentage of PVP and EC yielded patches with good folding endurance. The concentration of plasticizer present in the patches gave them desired folding endurance, and it increased with the presence of hydrophilic polymer. The formulation with highest PVP concentration, F3, exhibited a maximum drug release of 96.23% for 24 hrs. While the formulation with highest EC concentration, F5, exhibited only 74.45% drug release for 24 hrs.

Conclusion: From the data, formulation F2 (PVP/EC, 2:1) can be concluded as best formulation due to its desired physical characteristics, good initial drug release, sustained release behavior, and good in vitro permeation. This formulation can be further studied in a clinical scenario.

Keywords: Calcium channel blocker, Felodipine, Transdermal, Permeation.
the samples was obtained in the range of 4000/cm to 400/cm using a PerkinElmer-FTIR 8201 PC spectrophotometer by the KBr disc method [12].

**Preparation of transdermal patches**

Different ratios (Table 1) of PVP and EC were taken in the open-ended cylindrical glass molds to prepare the matrix type transdermal patches of felodipine. Backing membrane was cast by pouring 4% w/v of PVA solution in the molds previously wrapped with aluminum foil. It was allowed to dry at 60°C in hot air oven for 6 hrs. The two polymers were taken in requisite ratio and dissolved in chloroform. Di-n-butyl phthalate was taken in 30% w/w of polymer composition and used as plasticizer. Drug was added, 20% w/w of polymer composition, to form homogenous dispersion with plasticizer and polymers. Three milliliters of dispersion were cast on previously prepared PVA backing membrane and dried at 40°C for 6 hrs. The prepared patches were kept in desiccators until used [13].

**Thickness**

Thickness of both the backing membrane and patch was measured using digital calipers. The average thickness of the backing membrane and the whole patch were determined [14,15]. The average thickness of the adhesive matrix containing the drug was determined using the following equation:

\[
\text{Thickness of adhesive matrix} = \text{Thickness of whole patch} - \text{Thickness of backing membrane}
\]

**Moisture content**

The prepared patches were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hrs. The individual films were weighed again until it showed a constant weight [16]. The percentage of moisture content was calculated as:

\[
\frac{\text{Initial wt of the film} - \text{Final wt of the film}}{\text{Initial wt of the film}} \times 100 = \% \text{Moisture content}
\]

**Moisture uptake**

The patches were weighed and kept in a desiccator at normal room temperature for 24 hrs. This patch was taken out and exposed to 84% RH (saturated solution of potassium chloride) in a desiccator. After 3 days, the patches were taken out and weighed [17]. The percentage of moisture uptake was calculated as:

\[
\frac{\text{Final wt of the film} - \text{Initial wt of the film}}{\text{Initial wt of the film}} \times 100 = \% \text{Moisture uptake}
\]

**In vitro drug release study**

**Ex vivo permeation**

Franz diffusion cell was used to study the permeation of transdermal patch. Full thickness of rat abdominal epidermis was mounted onto a Franz diffusion cell. Place the patch in such a way that stratum corneum side of rat skin was in contact with transdermal patch in the donor compartment and the dermis side was in constant contact with the receptor solution. The receptor compartment was filled with 20% v/v PEG 400 in normal saline and stirred magnetically. A 1 ml of sample was withdrawn at different time intervals and analyzed for drug content and replaced with an equal volume of 20% v/v PEG 400 in normal saline at each time interval. The cumulative amount of drug permeated was calculated for 12 hrs and plotted against time [19].

**RESULTS AND DISCUSSION**

To determine the drug partition coefficient between skin and in vitro study fluid, octanol and phosphate buffer pH 7.4 were considered to be a standard system. The studies were conducted in triplicate. The mean value of all these experiments was considered as partition coefficient. The log P of felodipine was found to be 4.46. The log P clearly indicates that felodipine possesses optimum lipophilic nature to be formulated into a transdermal delivery system.

The spectrum of pure drug shows absorption band at 3389/cm due to the stretching N-H group of dihydropyridine moiety. The band between 2946/cm and 3070/cm was due to stretching aromatic and aliphatic C-H bond. The absorption band at 1694/cm can be attributed to carbonyl group present on the side chain of dihydropyridine moiety. The band at 1495/cm indicate C=C bond. The bands present at 1204/cm indicate C-O stretching. The spectrum of the mixture showed that they were in good agreement with the spectra of felodipine. Thus, from the spectra in Fig. 1, it was understood that there was no significant interaction between felodipine and polymers used in the preparation of transdermal patches.

PVP and EC combination was also preferred in preparation of transdermal patches for sustaining the release of diclofenac [20]. The transdermal patches for felodipine were analyzed for various physical characterizations such as moisture content, moisture uptake, thickness, and folding endurance. The summary of the characterization parameters was given in Table 2. The moisture content and moisture uptake studies on patches revealed that an increase in the concentration of PVP resulted in high moisture content and high moisture uptake ability (Fig. 2).

On the other hand, the formulations exhibited, increasing the EC proportion resulted in patches with low moisture uptake ability. This was no significant interaction between felodipine and polymers used in the preparation of transdermal patches.

**Statistical analysis**

All data were represented as the mean ± standard deviation. The graphs and error bars were depicted using GraphPad Prism 5 software (GraphPad Software, Inc., San Diego, CA).

**Table 1: Formulation of transdermal patches**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Ratio of PVP:EC</th>
<th>Total weight of PVP and EC (mg)</th>
<th>Chloroform (ml)</th>
<th>Di-n-butyl phthalate (ml)</th>
<th>Felodipine (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1:1</td>
<td>250</td>
<td>10</td>
<td>30% w/w of polymers</td>
<td>20% w/w of polymers</td>
</tr>
<tr>
<td>F2</td>
<td>2:1</td>
<td>250</td>
<td>10</td>
<td>30% w/w of polymers</td>
<td>20% w/w of polymers</td>
</tr>
<tr>
<td>F3</td>
<td>5:1</td>
<td>250</td>
<td>10</td>
<td>30% w/w of polymers</td>
<td>20% w/w of polymers</td>
</tr>
<tr>
<td>F4</td>
<td>1:2</td>
<td>250</td>
<td>10</td>
<td>30% w/w of polymers</td>
<td>20% w/w of polymers</td>
</tr>
<tr>
<td>F5</td>
<td>1:5</td>
<td>250</td>
<td>10</td>
<td>30% w/w of polymers</td>
<td>20% w/w of polymers</td>
</tr>
</tbody>
</table>

PVP: Polyvinylpyrrolidone, EC: Ethyl cellulose
nature of EC. At the same time, the patches with more PVP percentage also seen to be thicker than that of patches with more EC percentage. Low moisture content in the formulations maintains the stability and protects the film from being completely dried. It also protects the patches from being susceptible to microbial contamination and also yields thin patches [21]. The patches with high moisture content were observed to be bulky and thicker. Thickness of the patch is an important criteria which gives more patient compliance [22]. Weight variation was observed to be negligible and helped to maintain the uniformity of dose. By increasing the percentage of PVP, a higher folding endurance was observed and it decreased with increasing the percentage of hydrophobic polymer (EC). Equal percentage of PVP and EC yielded patches with good folding endurance. The concentration of plasticizer present in the patches gave them desired folding endurance, and it increased with the presence of hydrophilic polymer.

In vitro drug release is an important tool to predict the in vivo behavior of drug [23]. Table 3 shows the release profiles of patches carried out for 24 hrs. In the formulation F3, which had highest percentage of PVP, a maximum drug release of 96.23% was seen at the end of 24 hrs. In the formulations, F2 and F3, an initial burst release was observed. PVP reduced the crystalline nature of felodipine and resulted in increased drug release. The rate of release was decreased with decreasing proportion of PVP and increasing proportion of EC. The formulation F5 which contains maximum EC concentration exhibited lowest drug release of 74.45%, and their dissolution profile is depicted in Fig. 3. This clearly indicates the sustained release behavior of EC due to its hydrophobic nature. The patches containing equal amounts of PVP and EC exhibited a good drug release of 80.24% which can be helpful in maintain a stable plasma concentration.

Ex vivo permeation studies are a predictive assessment of in vivo performance of drug. The cumulative amount of drug permeated after 12 hrs was calculated and was given in Table 4. A maximum permeation of 76.83% was observed in the formulation F3, which had a maximum proportion of PVP. This result clearly indicates that an increase in hydrophilic polymer (PVP) in the patch increases the skin permeation of the drug. Increase in the concentration of hydrophobic polymer (EC) inhibited the drug permeation. This can be clearly noticed from the formulation containing maximum amount of EC, F5, allowed only 43.35% of drug to permeate after 12 hrs of study. About 60.83% of drug

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**Table 2: Physical characterization of transdermal patches**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Folding endurance*</th>
<th>Thickness* (mm)</th>
<th>Percentage moisture content* (%)</th>
<th>Percentage moisture uptake* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>177±12</td>
<td>0.189±0.25</td>
<td>5.90±0.10</td>
<td>11.28±0.01</td>
</tr>
<tr>
<td>F2</td>
<td>189±31</td>
<td>0.201±0.98</td>
<td>7.36±0.12</td>
<td>12.33±0.12</td>
</tr>
<tr>
<td>F3</td>
<td>223±15</td>
<td>0.240±0.23</td>
<td>8.01±0.05</td>
<td>16.91±0.05</td>
</tr>
<tr>
<td>F4</td>
<td>171±18</td>
<td>0.199±0.73</td>
<td>3.46±0.29</td>
<td>6.35±0.26</td>
</tr>
<tr>
<td>F5</td>
<td>169±09</td>
<td>0.233±0.59</td>
<td>1.28±0.06</td>
<td>4.70±0.21</td>
</tr>
</tbody>
</table>

*Data were presented as mean±standard deviation (n=6)

**Table 3: In vitro dissolution profile of transdermal patches**

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>6.02±1.13</td>
<td>12.21±1.51</td>
<td>15.60±1.09</td>
<td>4.25±1.83</td>
<td>4.28±1.52</td>
</tr>
<tr>
<td>1</td>
<td>12.08±2.26</td>
<td>23.02±1.62</td>
<td>24.21±1.50</td>
<td>11.56±1.12</td>
<td>8.65±1.93</td>
</tr>
<tr>
<td>2</td>
<td>29.23±1.39</td>
<td>37.29±1.43</td>
<td>34.23±1.46</td>
<td>19.24±1.72</td>
<td>13.47±1.27</td>
</tr>
<tr>
<td>4</td>
<td>36.89±1.42</td>
<td>41.35±2.30</td>
<td>53.24±1.77</td>
<td>32.29±2.38</td>
<td>26.02±2.48</td>
</tr>
<tr>
<td>8</td>
<td>50.35±2.16</td>
<td>54.24±1.19</td>
<td>68.03±3.33</td>
<td>48.89±1.55</td>
<td>43.09±1.61</td>
</tr>
<tr>
<td>12</td>
<td>62.64±2.96</td>
<td>76.21±1.25</td>
<td>79.56±2.17</td>
<td>53.32±1.42</td>
<td>48.32±1.17</td>
</tr>
<tr>
<td>24</td>
<td>80.24±1.48</td>
<td>92.37±2.19</td>
<td>96.23±2.28</td>
<td>60.65±1.50</td>
<td>55.45±2.58</td>
</tr>
</tbody>
</table>

Data were presented as mean±standard deviation (n=6)

**Table 4: Ex vivo skin permeation studies**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Percentage cumulative drug permeated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>60.83%±1.77</td>
</tr>
<tr>
<td>F2</td>
<td>67.37%±1.41</td>
</tr>
<tr>
<td>F3</td>
<td>76.83%±2.17</td>
</tr>
<tr>
<td>F4</td>
<td>50.27%±1.94</td>
</tr>
<tr>
<td>F5</td>
<td>43.35%±1.45</td>
</tr>
</tbody>
</table>

Data were presented as mean±standard deviation (n=6)

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**Fig. 1: Fourier transform infrared spectra of felodipine and physical mixtures**

**Fig. 2: Moisture studies on transdermal patches. Data are presented as mean±standard deviation (n=6)**

**Fig. 2: Moisture studies on transdermal patches. Data are presented as mean±standard deviation (n=6)**

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permeation was seen in the formulation F1, which had equal proportion of hydrophilic and hydrophobic polymers.

CONCLUSION

EC and PVP combination can be used to prepare the transdermal patches of felodipine or other calcium channel blockers. The prepared patches are capable of surmounting the low bioavailability factor associated with oral administration of felodipine. From the data, formulation F2 (PVP/EC, 2:1) can be concluded as best formulation due to its desired physical characteristics, sustained release behavior, and good in vitro permeation. This formulation can be further studied in a clinical scenario.

ACKNOWLEDGEMENT

The authors are thankful to the College of Pharmacy, SRM University, Kattankulathur, Chennai, Tamil Nadu, for their valuable help for carrying out this research work.

REFERENCES