Development of Matrix Type Transdermal Patches of Lacidipine: Evaluation of Physicochemical, \textit{in vitro}, \textit{ex vivo} and Mechanical Properties

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Abstract

Transdermal patches were developed for a low oral bioavailable drug, lacidipine (LCDP) employing ethyl cellulose/Eudragit RL100 and polyvinyl pyrrolidone (PVP) as polymeric matrices. The effect of binary mixtures of polymers on physicochemical properties such as thickness, moisture absorption and moisture content; \textit{in vitro} release, \textit{ex vivo} permeation and mechanical properties was evaluated. Ex vivo permeation studies across rat abdominal skin were conducted using Franz diffusion cells. Binary mixture of polymer, ethyl cellulose-PVP and Eudragit RL100-PVP at 2.5:7.5 (LE4) and 5:5 (LP3) showed maximum amount of drug release and \textit{ex vivo} permeation (LE4, 2282.3 µg; LP3, 2765.7 µg). Different kinetic models used to interpret the release kinetics and mechanism indicated that release from all formulations followed zero order release kinetics with fickian diffusion pattern. The flux of LE4 and LP3 formulations showed a flux of 17 and 21.1 µg cm\(^{-2}\) h\(^{-1}\), which could meet the target flux. The tensile strength of LE4 and LP3 were found to be 0.6 and 1.1 Kg mm\(^{-2}\). Matrix type transdermal patches having suitable mechanical properties for LCDP were developed and evaluated.

Keywords: Lacidipine, Transdermal, Drug release, Skin permeation, Matrix patches, Mechanical properties

Introduction

The transdermal route of administration is recognized as one of the potential route for the local and systemic delivery of drugs. This route offers many advantages over the oral dosage form, such as improving patient compliance in long-term therapy, bypassing first-pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing inter- and intra-patient variability, and making it possible to interrupt or terminate treatment when necessary (1). However, the highly organized structure of stratum corneum forms an effective barrier to the permeation of drugs, which must be modified if poorly penetrating drugs are to be administered. The use of chemical penetration enhancers would significantly increase the number of drug molecules suitable for transdermal delivery (2).

LCDP is a calcium channel blocker used in the treatment of hypertension and atherosclerosis cardiovascular disorders. It also possess antioxidant effect and is one of the most vascular selective drugs of the dihydropyridines (3, 4). LCDP undergoes extensive first-pass hepatic metabolism and has a mean absolute bioavailability of about 10 % (4–52 %). LCDP is completely metabolized in the liver by cytochrome P450 3A4 to pharmacologically inactive metabolites (4). The low oral bioavailability restricts its use, therefore
alternative mode of delivery system is desirable, to deliver the drug at effective concentrations to treat hypertension. LCDP was selected as a model drug because; its oral dose is low (2-8 mg), low molecular mass 455.5 g mol\(^{-1}\) and low oral bioavailability.

The system designs for transdermal patches include matrix, microreservoir, reservoir, adhesive and membrane moderated matrix hybrid. Matrix type transdermal patches remain the most popular as they are easy to manufacture (5). Microemulsion based reservoir system was developed with the enhancement of bioavailability from our laboratory (6). The developed system suffers from poor mechanical properties. Transdermal system with suitable mechanical properties would be desired to withstand during wear and tear. Therefore a matrix type system for prolonged release of LCDP having suitable mechanical properties to withstand wear and tear is developed.

The present paper describes the development of matrix type patches for LCDP. The developed patches were also evaluated for physicochemical, \textit{in vitro}, \textit{ex vivo} and mechanical properties.

\textbf{Materials and Methods}

\textbf{Materials:} Lacidipine, Eudragit RL100, ethyl cellulose and poly vinyl pyrrolidone 30 K were obtained as gift samples from Dr Reddy’s Laboratories, Hyderabad, India. All other chemicals and solvents used were of analytical reagent grade.

\textbf{Preparation of patches:} Matrix type transdermal patches containing LCDP were prepared by film casting technique using different ratios of ethyl cellulose/Eudragit RL 100 and poly vinyl pyrrolidone (Table 1). Weighed quantity of polymers was dissolved in 20 mL of solvent mixture consisting of 1:1 ratio of dichloromethane and methanol. Weighed quantity of LCDP was dissolved in 5 mL of solvent system. The polymeric solution is kept for swelling for 6 hr. Then drug solution, d-limonene as permeation enhancer and dibutyl phthalate as plasticizer are added to the polymeric solution and vortexed for 5 min then transferred into Anumbra petri plate. Drying of these patches is carried out at room temperature for overnight and then in vacuum oven at room temperature for 8 to 12 hrs. The prepared patches were removed, cut to size each having 3.56 cm\(^2\) and stored in desiccator.

\textbf{Weight and thickness variation test:} Each formulated film was prepared in triplicate and ten circular films having an area of 3.56 cm\(^2\) were cut from each plate. Their weight was measured using digital balance (Shimadzu, Japan). The thickness of films was measured using digital screw gauge (Digimatic micrometer, Mitutoyo, Japan).

\textbf{Estimation of LCDP in polymeric films:} The formulated polymeric films were assayed for drug content. Three patches from each formulation series were taken, cut into small pieces and was allowed to dissolve in a 100 mL of 0.5% of w/v Tween 80 solution. The solution was diluted suitably filtered through membrane filter (0.45 µ) and LCDP content was measured using HPLC (7).

\textbf{In vitro release studies:} Drug release from the transdermal patch was studied using dissolution apparatus (Disso 2000, Labindia, India) equipped with an auto sampler and fraction collector for collection and replenishment of samples and dissolution medium respectively. Water impermeable back up membrane was placed on one side of the patch and further was adhered to USP-V (Paddle over disc). It was placed in dissolution vessel containing 500 mL of 0.5% w/v Tween 80 solution as in vitro release medium. The study was conducted at 50 rpm as stirring.
speed and temperature of 32°C. Samples were collected at preset time intervals and analyzed using UV-Vis spectrophotometer (Elico, India) at 282 nm.

**Release kinetics and mechanisms of drug release:** Different kinetic models, zero order, first order (8), Higuchi and Korsmeyer expressions (8, 9) were applied to interpret the drug release kinetics to know the mechanism of drug release from these matrix systems with the help of equations 1-4.

\[
M_t = M_0 + K_0t
\]
\[
\ln M_t = \ln M_0 + K_1t
\]
\[
M_t = K_H t^{1/2}
\]
\[
\frac{M_t}{M_\infty} = K_k t^n
\]

- \(M_t\) cumulative amount of drug release at time \(t\);
- \(M_0\) is the initial amount of drug;
- \(K_0, K_1, K_H, K_k\) are rate constants for zero order, first order, Higuchi and Korsmeyer model respectively;
- \(M_t/M_\infty\) is the fraction of drug release at time \(t\);
- \(n\), release exponent indicative of the operating release mechanism.

The correlation coefficient values (\(r^2\)) presented in table 2.

**Moisture absorption studies:** The films were weighed accurately and placed in a desiccator containing 100 mL of saturated solution of aluminium chloride (79.5 % RH). After 3 days, the films were taken out and weighed, the percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight (10).

**Moisture content:** The patches were weighed and kept in a desiccator containing calcium chloride at 40°C for 24 hr. The final weight was noted when there was no further change in the weight of patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to initial weight (11).

**Measurement of mechanical properties:** Mechanical properties, elongation at break (E.B) and tensile strength (T.S) of the films were evaluated using a microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK), equipped with 25 kg load cell. Film strip (60x10

### Table 1. Composition of LCDP transdermal patches

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Ingredient (mg)</th>
<th>LCDP</th>
<th>EC20</th>
<th>ERL100</th>
<th>PVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE1 (10:0)</td>
<td></td>
<td>90</td>
<td>-</td>
<td>2500</td>
<td>-</td>
</tr>
<tr>
<td>LE2 (7.5:2.5)</td>
<td></td>
<td>90</td>
<td>-</td>
<td>1875</td>
<td>625</td>
</tr>
<tr>
<td>LE3 (5.0:5.0)</td>
<td></td>
<td>90</td>
<td>-</td>
<td>1250</td>
<td>1250</td>
</tr>
<tr>
<td>LE4 (2.5:7.5)</td>
<td></td>
<td>90</td>
<td>-</td>
<td>625</td>
<td>1875</td>
</tr>
<tr>
<td>LP1 (10:0)</td>
<td></td>
<td>90</td>
<td>2500</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LP2 (7.5:2.5)</td>
<td></td>
<td>90</td>
<td>1875</td>
<td>-</td>
<td>625</td>
</tr>
<tr>
<td>LP3 (5.0:5.0)</td>
<td></td>
<td>90</td>
<td>1250</td>
<td>-</td>
<td>1250</td>
</tr>
<tr>
<td>LP4 (2.5:7.5)</td>
<td></td>
<td>90</td>
<td>625</td>
<td>-</td>
<td>1875</td>
</tr>
</tbody>
</table>

LCDP, Lacidipine; EC20, Ethyl cellulose 20, ERL 100, Eudrgait RL 100; PVP, Polyvinyl pyrrolidone
Solvent system used is 25 mL of 50:50 of dichloromethane and methanol
Plasticizer 20 % w/v of dibutylphthalate
d-limonene 8 % w/v was incorporated

Development of matrix type transdermal patches of lacidipine
Table 2. Physicochemical, *in vitro* release, *ex vivo* permeation parameters and mechanical properties of LCDP transdermal patches

<table>
<thead>
<tr>
<th>Formula</th>
<th>Weight (mg)</th>
<th>Thickness (µm)</th>
<th>Assay (%)</th>
<th>$Q_{24}^R$ (µg)</th>
<th>$Q_{24}^P$ (µg)</th>
<th>Flux ($µg$ cm$^{-2}$ h$^{-1}$)</th>
<th>$K \times 10^{-3}$ (cm$^2$)</th>
<th>Lag time (h)</th>
<th>T.S (kg mm$^{-2}$)</th>
<th>E.B (% mm$^{-2}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE1</td>
<td>152.3 ± 5.2</td>
<td>201.3 ± 12.5</td>
<td>98.6 ± 6.1</td>
<td>3012.4 ± 95.8</td>
<td>1608.3 ± 107.4</td>
<td>15.9</td>
<td>1.99</td>
<td>4.53</td>
<td>2.8 ± 0.33</td>
<td>15.4 ± 1.41</td>
</tr>
<tr>
<td>LE2</td>
<td>155.6 ± 3.5</td>
<td>205.6 ± 10.4</td>
<td>97.1 ± 5.2</td>
<td>3981.7 ± 271.2</td>
<td>1984.8 ± 214.2</td>
<td>17.7</td>
<td>2.21</td>
<td>3.58</td>
<td>1.8 ± 0.21</td>
<td>28.6 ± 2.80</td>
</tr>
<tr>
<td>LE3</td>
<td>157.1 ± 2.8</td>
<td>207.2 ± 8.7</td>
<td>97.6 ± 3.2</td>
<td>5312.7 ± 206.6</td>
<td>2110.2 ± 203.6</td>
<td>17.2</td>
<td>2.15</td>
<td>2.81</td>
<td>1.1 ± 0.18</td>
<td>67.1 ± 7.17</td>
</tr>
<tr>
<td>LE4</td>
<td>160.4 ± 6.1</td>
<td>210.4 ± 11.4</td>
<td>100.1 ± 1.9</td>
<td>6892.1 ± 214.2</td>
<td>2282.3 ± 173.4</td>
<td>17.0</td>
<td>2.12</td>
<td>2.13</td>
<td>0.6 ± 0.03</td>
<td>86.2 ± 10.14</td>
</tr>
<tr>
<td>LP1</td>
<td>150.2 ± 3.8</td>
<td>185.6 ± 14.3</td>
<td>98.3 ± 4.6</td>
<td>3210.2 ± 216.0</td>
<td>1376.3 ± 124.3</td>
<td>10.5</td>
<td>1.31</td>
<td>5.83</td>
<td>0.3 ± 0.01</td>
<td>18.2 ± 2.71</td>
</tr>
<tr>
<td>LP2</td>
<td>151.5 ± 4.6</td>
<td>186.9 ± 13.6</td>
<td>97.8 ± 4.1</td>
<td>6331.3 ± 271.2</td>
<td>2050.8 ± 113.1</td>
<td>16.7</td>
<td>2.09</td>
<td>5.83</td>
<td>0.5 ± 0.11</td>
<td>30.1 ± 3.04</td>
</tr>
<tr>
<td>LP3</td>
<td>153.2 ± 5.9</td>
<td>190.3 ± 15.1</td>
<td>101.5 ± 3.4</td>
<td>8014.6 ± 201.4</td>
<td>2765.7 ± 148.7</td>
<td>21.1</td>
<td>2.63</td>
<td>4.25</td>
<td>1.1 ± 0.23</td>
<td>72.8 ± 6.85</td>
</tr>
<tr>
<td>LP4</td>
<td>156.3 ± 3.4</td>
<td>193.2 ± 10.2</td>
<td>100.1 ± 1.4</td>
<td>7891.2 ± 214.2</td>
<td>2609.9 ± 211.4</td>
<td>16.9</td>
<td>2.11</td>
<td>4.11</td>
<td>1.4 ± 0.17</td>
<td>95.6 ± 8.26</td>
</tr>
</tbody>
</table>

$Q_{24}^R$, cumulative amount of LCDP released in 24 h; $Q_{24}^P$, cumulative amount of LCDP permeated in 24 h; K, permeation coefficient.
mm) free from air bubbles or physical imperfections, was held between two clamps positioned at a distance of 3 cm. A cardboard was attached on the surface of the clamp to prevent the film from being cut by the grooves of the clamp. During measurement, the top clamp at a rate of 2 mm s\(^{-1}\) pulled the strips to a distance till the film broke. The force and elongation were measured when the films were broken. Results from film samples, which were broken at end were not included in observations. The mechanical properties are calculated using equation 5 and 6.

\[
T.S.(\text{Kg mm}^{-2}) = \frac{\text{[Force at break (Kg)]}}{\text{Initial cross sectional area of the patch (mm}^{2})}\]

(5)

\[
E.B (%\text{mm}^{-2}) = \frac{\text{[Increase in length (mm)]}}{\text{Original length x 100}} \times \frac{\text{Cross sectional area (mm}^{2})}{\text{}}\]

(6)

**Preparation of rat abdominal skin:** The animal study was conducted in accordance with the approval of the animal ethical committee, Kakatiya University, India. Wistar rats weighing 150–200 g were sacrificed using anaesthetic ether. The hair of test animals was carefully trimmed with electrical clippers and the full thickness skin was removed from the abdominal region. The epidermis was prepared surgically by heat separation technique (12), which involved soaking the entire abdominal skin in water at 60\(^{\circ}\)C for 45 s, followed by careful removal of the epidermis. The epidermis was washed with water and used for **ex vivo** permeability studies.

**Ex vivo permeation studies:** Franz diffusion cell with a surface area of 3.56 cm\(^2\) was used for **ex vivo** permeation studies. The rat skin was mounted between donor and receptor compartments of the diffusion cell with stratum corneum facing the donor compartment. The transdermal patch was placed over the skin and a dialysis membrane (Hi-Media, Mumbai, India) was placed over the patch so as to secure the patch tightly from getting dislodged from the skin (the transdermal patch was sandwiched between the skin and dialysis membrane). The receiver compartment of the diffusion cell was filled with 12 mL of phosphate buffer pH 7.4 containing 40 % v/v polyethylene glycol (PEG) 400 and the setup was placed over a magnetic stirrer with temperature maintained at 37\(^{\circ}\)C. PEG 400 was incorporated to maintain sink conditions and the contents of receptor compartment were agitated at 400 rpm and was placed over a multi-magnetic stirrer (Cintex, Mumbai, India). The study was conducted at 37\(^{\circ}\)C and samples of 1 mL were collected at preset time points and replenished with PBS (pH 7.4) containing 40 % v/v PEG 400. The cumulative amount of LCDP permeated was determined using HPLC (7) and concentration was corrected for sampling effects according to the equation 7 (13).

\[
C_{n} \text{n} = C_{n} \text{i} \times \frac{V_{T}}{V_{T} - V_{S}} \times \frac{C_{n-1}}{C_{n-1}}\]

(7)

where \(C_{n} \text{n}\) is the corrected concentration of the \text{n}\textsuperscript{th} sample, \(C_{n} \text{i}\) is the measured concentration of LCDP in the \text{n}\textsuperscript{th} sample, \(C_{n-1} \text{i}\) is the corrected concentration in the (n-1)\textsuperscript{th} sample. \(C_{n-1}\) is the measured concentration of LCDP in the (n-1)\textsuperscript{th} sample, \(V_{T}\) is the total volume of the receiver fluid and \(V_{S}\) is the volume of the sample drawn.

The steady state flux was calculated from the slope of steady state portion of the line in the plot of drug amount permeated Vs time. Permeability coefficient (Kp) was calculated by dividing the flux with dose. The lag time was calculated from the intercept on the time axis in the plot of cumulative amount permeated Vs time. The target flux was calculated using equation 8.

\[
\text{Target flux} = \frac{(C_{s} \text{ss} \times CL_{t} \times BW)}{A}\]

(8)

where \(C_{s} \text{ss}\) is the LCDP concentration at therapeutic level (8.6 µg L\(^{-1}\)) and CL\(_{t}\) the total body clearance, 83.9 mL h\(^{-1}\) (calculated from volume of distribution, 2300 mL kg\(^{-1}\)and half life 19 h) (14), BW the standard human body weight of 60 kg, A represents the surface area of the diffusion cell.
(i.e. 3.56 cm²). The calculated target flux value for LCDP was 12.16 µg cm⁻² h⁻¹.

**FTIR studies:** LCDP, ethyl cellulose, Eudragit RL100, PVP, polymer mixture and physical mixture of polymers and LCDP were placed in clear glass containers and exposed to 40°C/75 % RH for 4 weeks. After 4 weeks, the samples were subjected to FTIR studies by making pellets with KBr.

**Stability studies:** The stability study for optimized formulations (LE4 and LP3) was conducted according to the International Conference on Harmonisation (ICH) guidelines (15). Sufficient samples of the formulations were wrapped in aluminium foil and stored in a petri dish at a temperature of 40 ± 2°C/75 ± 5 % R.H (Skylab Instruments & Engineering Pvt Ltd, Thane, India) for 6 months. Samples were withdrawn at intervals of 1, 2, 3, and 6 months and analyzed for drug content using the HPLC (7).

**Statistical analysis:** Statistical comparisons were made using Student’s t-test using Sigmastat software (Jandel Corp., CA, USA). Results were considered significant at 95 % confidence interval (p < 0.05) and results were expressed as mean ± SD.

**Results and Discussion**

**Formulation of transdermal patches of LCDP:** Polymer films were formulated with varying concentrations of ethyl cellulose or ERL 100 and PVP. The experiment was initiated by taking 2 gm of polymer and 90 mg of drug. As the polymer concentration increased the films could accommodate more amount of LCDP. Precipitation of the drug was noticed with 2 g of polymer and when the polymer was increased, the precipitation was decreased. No precipitation was observed with 2.5 g and above of the polymer. Therefore the amount of polymer selected was 2.5 gm and in order to improve drug release PVP at different ratios was incorporated. The physical appearance of the films was transparent suggesting that the drug was completely solubilized in the polymeric matrix. Based on preliminary experiments, d-limonene at a concentration of 8 % v/w (showed maximum permeation of LCDP across rat skin) was incorporated as penetration enhancer.

The results of weight variation test for various transdermal films are shown in Table 2. Results of weight variation test indicated uniformity in weight of the patches, as evidenced by RSD values, which were less than 6.

Thickness of films varied from 201.3 (LE1) to 210.4 µm (LE4); 185.6 (LP1) to 193.2 µm (LP4) in respective series. The results (Table 2) suggest that the change in polymer composition did not produce any significant effect (p>0.05) on the thickness. The thickness was found to be uniform as it was evidenced from RSD values, which were less than 6.

The results of content uniformity are shown in table 1 and indicate good uniformity in drug content. The drug content was from 97.1 to 101.5 % in formulation LE2 and LP3 respectively.

**In vitro drug release studies:** The release profiles of LCDP from transdermal patches were
shown in Fig 1. Formulations LE4 (6892.1 µg) and LP3 (8014.6 µg) showed maximum amount of release among their series with zero order ($r^2>0.9$) release kinetics as it was evidenced from correlation coefficients. It was apparent from the release profiles of formulations, that the drug release was governed by polymer composition. As the concentration of hydrophilic polymer (PVP) increased in the formulations, the drug release rate increased substantially. There appeared a significant difference (p<0.05) in the final amount of drug release, which might be due to the fact that the amount of water soluble polymer influences the drug release from the patches. For all formulations the first order, zero order and higuchi correlation coefficients were calculated and shown in Table 3. All formulations followed fickian model of release pattern as it was evidenced from release exponent (0.16<$n$>0.39), indicating that the release mechanism was diffusion mediated.

**Moisture absorption and moisture content:**
Moisture absorption and moisture content studies provide information regarding stability of the formulation (5). The moisture absorption in the formulations ranged from 0.03 to 1.71 % and 0.24 to 2.5 % in LE and LP series respectively. The moisture content in the patches ranged from 0.02 to 0.39 % and 0.05 to 0.39 % in LE and LP series respectively (Fig 2). The results revealed that the moisture absorption and moisture content was found to increase with increasing concentration of hydrophilic polymer (PVP). The small moisture content in the formulations helps them to remain stable and from becoming a completely dried and brittle film (16) and low moisture absorption protects material from microbial contamination and bulkiness of the films (17). The rank order of moisture absorption and moisture content respectively were LE1 < LE2 < LE3 < LE4 and LP1 < LP2 < LP3 < LP4; LE1 < LE2 < LE3 < LE4 and LP1 < LP2 < LP3 < LP4.

![Fig 2. Moisture absorption and moisture content of LCDP transdermal patches](image.png)

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Moisture absorption</th>
<th>Moisture content</th>
</tr>
</thead>
<tbody>
<tr>
<td>LP1</td>
<td>0.981</td>
<td>822.7</td>
</tr>
<tr>
<td>LP2</td>
<td>0.975</td>
<td>1052.0</td>
</tr>
<tr>
<td>LP3</td>
<td>0.979</td>
<td>1684.4</td>
</tr>
<tr>
<td>LP4</td>
<td>0.981</td>
<td>1799.3</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Moisture absorption</th>
<th>Moisture content</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE1</td>
<td>0.994</td>
<td>56.6</td>
</tr>
<tr>
<td>LE2</td>
<td>0.964</td>
<td>63.2</td>
</tr>
<tr>
<td>LE3</td>
<td>0.958</td>
<td>61.4</td>
</tr>
<tr>
<td>LE4</td>
<td>0.941</td>
<td>60.7</td>
</tr>
<tr>
<td>LP1</td>
<td>0.940</td>
<td>37.4</td>
</tr>
<tr>
<td>LP2</td>
<td>0.937</td>
<td>59.5</td>
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<td>LP3</td>
<td>0.937</td>
<td>75.2</td>
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<tr>
<td>LP4</td>
<td>0.904</td>
<td>60.3</td>
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**Table 3.** *In vitro* release kinetics of LCDP transdermal patches

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Peppas-Korsemeyer</th>
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<tbody>
<tr>
<td>LE1</td>
<td>0.974</td>
<td>0.633</td>
<td>0.069</td>
<td>0.981</td>
</tr>
<tr>
<td>LE2</td>
<td>0.964</td>
<td>0.604</td>
<td>0.062</td>
<td>0.975</td>
</tr>
<tr>
<td>LE3</td>
<td>0.958</td>
<td>0.581</td>
<td>0.054</td>
<td>0.961</td>
</tr>
<tr>
<td>LE4</td>
<td>0.941</td>
<td>0.559</td>
<td>0.045</td>
<td>0.979</td>
</tr>
<tr>
<td>LP1</td>
<td>0.940</td>
<td>0.536</td>
<td>0.043</td>
<td>0.981</td>
</tr>
<tr>
<td>LP2</td>
<td>0.937</td>
<td>0.575</td>
<td>0.050</td>
<td>0.981</td>
</tr>
<tr>
<td>LP3</td>
<td>0.937</td>
<td>0.565</td>
<td>0.046</td>
<td>0.974</td>
</tr>
<tr>
<td>LP4</td>
<td>0.904</td>
<td>0.537</td>
<td>0.338</td>
<td>0.899</td>
</tr>
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</table>

Development of matrix type transdermal patches of lacidipine
The results of mechanical properties are shown in Table 2 and Fig 3. Formulation LE1 and LP4 exhibited greater values of TS (2.75 kg mm$^{-2}$ and 1.42 kg mm$^{-2}$ for LE1 and LP4 respectively). Formulation LE4 (15.4 mm$^{-2}$) and LP4 (95.6 mm$^{-2}$) showed greater values of elongation at break in their respective series. The results revealed that as the concentration of PVP increased in LE series, the tensile strength was found to decrease and vice versa seen in elongation at break. Both TS and E/B were found to be increased with increasing concentration of PVP in LP series. These observations indicate that formulation LE4 and LP3 patches were found to be strong, not brittle and flexible.

**Ex vivo permeation of LCDP from transdermal patches:**

The results of drug permeation from transdermal patches of LCDP through rat skin are presented in Table 2 and Fig 3. Formulation LE1 and LP4 exhibited greater values of TS (2.75 kg mm$^{-2}$ and 1.42 kg mm$^{-2}$ for LE1 and LP4 respectively). Formulation LE4 (15.4 mm$^{-2}$) and LP4 (95.6 mm$^{-2}$) showed greater values of elongation at break in their respective series. The results revealed that as the concentration of PVP increased in LE series, the tensile strength was found to decrease and vice versa seen in elongation at break. Both TS and E/B were found to be increased with increasing concentration of PVP in LP series. These observations indicate that formulation LE4 and LP3 patches were found to be strong, not brittle and flexible.

Mechanical properties of films: The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, TS and E/B. A soft and weak polymer is characterized by a low TS and E/B; a hard and brittle polymer is defined by a moderate TS and low E/B; a soft and tough polymer is characterized by a moderate TS and high E/B; where as a hard and tough polymer is characterized by a high TS and E/B (18). Hence, it is suggested that a suitable transdermal film should have a relatively high TS and E/B.
Fig 4. Formulations LE4 and LP3 showed maximum drug permeation among their series. The patches LE1, LE2, LE3, LE4, LP2, LP3 and LP4 could meet the target flux (12.16 µg cm⁻² h⁻¹). However, the formulations showed higher lag times except formulation LE4. Therefore the patches LE4 (2282.3 µg) and LP3 (2765.7 µg) were considered to be optimum formulations. In ex vivo permeation studies, the permeation pattern is similar to in vitro release pattern. The results revealed that LCDP was released from the formulation and permeated through rat abdominal skin and hence could possibly permeate through the human skin. The permeation profiles were found follow higuchi kinetics as it was evidenced from correlation coefficients (0.976-0.996).

**FTIR studies:** The FTIR spectral analysis of LCDP alone showed that the principal peaks were observed at wave numbers of 3349.8, 2974.9, 1702, 1675.4, 1496.4 and 1310.8. In the spectra of the physical mixture of LCDP, ERL and PVP were 3349.7, 2979.5, 1702.6, 1675.7, 1498, and 1311.3; 3349.4, 2974.5, 1675.8, 1497.9 and 1311.3 wave numbers were observed for the mixture of LCDP, ethyl cellulose and PVP. However, some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. These results suggest that there is no interaction between the drug and polymers used in the study. The polymers used are in controlled/sustained release matrix type patches because of their compatibility with a number of drugs (19).

**Stability study:** The stability of the optimized formulations (LE4 and LP5) was investigated as per ICH guidelines. On storing the TDDS at a temperature of 40±2 °C/75±5 % RH for 6 months, 1.52 % (LE4) and 1.89 % (LP3) degradation was observed. As the degradation is less than 5 % in the formulation, a shelf life of 2 years could be assigned.

**Conclusions**

Matrix type transdermal therapeutic systems of lacidipine could be prepared with the required flux having suitable mechanical properties. Further work is recommended in support of its efficacy claims by long term pharmacokinetic and pharmacodynamic studies in human beings.

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