Fabrication and Characterization of Lercanidipine Hydrochloride Solid Dispersions by Fusion Technique

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Abstract: The authors aimed to design solid dispersions with Lercanidipine Hydrochloride (LCD) with PVP K-30, Poloxamer-188, and HPMC K4M as carriers. Various mixtures of LCD and Polymers (PVP K-30, Poloxamer-188, and HPMC K4M) were made in 1:1, 1:3, 1:5 and 1:7 ratios, and the solid dispersion was prepared by melting tactic, later compressed into tablets. Drug excipient compatibility studies were examined by DSC and FTIR studies. LCD was found to compatible with carriers used. The LCD solid dispersion was measured for physicochemical quality both in solid dispersions SD, and tablet states. The LCD solid dispersions found to have excellent flow possessions and compression assets. The yield of prepared solid dispersion was observed to be more than 90%), and the formulation LPOX-3 has showed a good yield of 98.9±1.95%. The tablets which were compressed from solid dispersions were found to have a uniform in size, shape, color, and consistency. The tablets were observed to have a uniform in thickness, and weight and ranged from 300.2±1.64 to 301.7±1.64 mg. The loss on friability was less than 1%, and the hardness was more than 4 Kg/cm2 indicates significant mechanical strength and the LCD content was also found to be uniform (96.8±1.35 to 99.9±2.34). The solubility of LCD was found to be good in 0.1N HCl and diminished with an increase in pH of the buffer. LCD released from the tablets were firstly by eruption followed by zero order. The dissolution was found to be good in solid dispersions with LCD: Poloxamer-188 at the ratio of 1:5. The results obtained were satisfactory. The study concludes that LCD solid dispersions (LPOX-3) with 1:5 ratios of LCD and Poloxamer-188 was found to be a better carrier than PVP K-30, and HPMC K4M in increasing the solubility of LCD from the solid dispersions.

Keywords: Lercanidipine, Poloxamer-188, solid dispersions, solubility, dissolution.

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1. INTRODUCTION
The oral route is preferred as it is safe, effective, patient acceptance of all genders and age groups. The formulation aspect of solubility and dissolution are the main issues for drugs with poor solubility. The researchers do various trials in elevating the solubility of such drugs. Several methodologies adopted to uplift the drug solubility viz., co-solvency, complexation, salt formation, adding surfactants, micronization, and pH alteration etc., amongst solid dispersion (SD) methodology situated on the top priority, for its ease, modest, and resourceful scheme in amassing the solubility. Lercanidipine hydrochloride (LCD) is prescribed for its calcium channel blocking activity, it is a BCS class II drug with t½ of 8h and bioavailability of 10%. LCD is prescribed for hypertension and angina patients. The poor aqueous solubility of LCD, which restricts the onset of action. Various polymers were tried as carriers for solid dispersions like Sorbitol, Mannitol, Citric acid, Succinic acid, Polyvinyl Pyrrolidones, Polyethylene Glycols, cellulose derivative, and Eudragits etc., Literature review revealed that many attempts have been tried for making solid dispersions using the carriers used in the study, but no attempts have been made in combination of these carriers (PVP K-30, Poloxamer-188, and HHPMC K4M). So, the scholars made an effort in appraising the LCD solubility by SD made by melting using Poly Vinyl Pyrrolidone (PVP) K-30, Poloxamer-188, and Hydroxy Propyl Methyl Cellulose (HPMC) K4M.

2. MATERIALS AND METHODS
2.1. Materials
The LCD was gifted from Torrent Pharmaceuticals, Mumbai. PVP K-30, Poloxamer-188, HPMC K4M, Microcrystalline Cellulose, Talc, and Magnesium stearate were procured from SD Fine chemicals India. Double distilled water was used when needed.

2.2. Scheming of Solid dispersions
The numerous plans of LCD, SD were exemplified in table 1.

<table>
<thead>
<tr>
<th>Drug: Carrier</th>
<th>Drug: Carrier ratio</th>
<th>Formulation code</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCD: PVP K30</td>
<td>1:1</td>
<td>LPVP-1</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>LPVP-2</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>LPVP-3</td>
</tr>
<tr>
<td></td>
<td>1:7</td>
<td>LPVP-4</td>
</tr>
<tr>
<td>LCD: Poloxamer 188</td>
<td>1:1</td>
<td>LPOX-1</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>LPOX-2</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>LPOX-3</td>
</tr>
<tr>
<td></td>
<td>1:7</td>
<td>LPOX-4</td>
</tr>
<tr>
<td>LCD: HPMC K4M</td>
<td>1:1</td>
<td>LHPM-1</td>
</tr>
<tr>
<td></td>
<td>1:3</td>
<td>LHPM-2</td>
</tr>
<tr>
<td></td>
<td>1:5</td>
<td>LHPM-3</td>
</tr>
<tr>
<td></td>
<td>1:7</td>
<td>LHPM-4</td>
</tr>
</tbody>
</table>

The polymers were melted based on geometric melting from higher to lower i.e., HPMC-K4M, PVP K-30, then Poloxamer-188 in a ceramic dish. LCD was spread in the molded mass with constant amalgamation. The blend was congealed at room temperature. The SD were stored in a desiccator (ABG Initiatives, Hyderabad, Telangana) for a day, slightly furrowed in a mortar (Aruna Scientific, Hyderabad, Telangana). The formed SD were passed through # 30 mesh (ASTM E 11, Hyderabad, Telangana) to get uniform sized subdivisions.

2.3. Fabricating of solid dispersion tablets
The SD corresponding to 20 mg of LCD were prepared after combination with components (as per table 2) compressed in the 8 station tablet compression machine (Karnavati, India).

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid dispersions equivalent to 20 mg of LCD</td>
<td>150</td>
</tr>
<tr>
<td>Lactose</td>
<td>75</td>
</tr>
<tr>
<td>Starch</td>
<td>15</td>
</tr>
<tr>
<td>Micro Crystalline Cellulose</td>
<td>50</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
<tr>
<td>Weight of the tablets</td>
<td>300</td>
</tr>
</tbody>
</table>
2.4. Evaluations

2.4.1. Melting point
The crystalline chemicals and drugs are available as pure form and have sharp melting points\(^1\). The preliminary evaluation is the determination of the LCD melting point using the melting point apparatus (MT-934, Mumbai). The melting temperature of the LCD was recorded three times.

2.4.2. Solubility studies
LCD pure drug was examined for solubility in 0.1N HCl, water, pH 4.5 Acetate buffer, pH 6.8 and pH 7.4 Phosphate buffers\(^1\).

2.4.3. Drug-excipients compatibility studies
The DSC and FTIR studies were made to check the compatibility amongst the LCD and the carriers used in making SD.

2.4.3.1. Differential Scanning Calorimetry (DSC)
A 1:1 ratio of LCD, and ~20mg of Polymer (PVP K30/Poloxamer 188/HPMC K4M), were placed in DSC crucible and heated from till 500°C in DSC apparatus (DSC-50, Shimadzu, Japan).

2.4.3.2. Fourier-transform infrared (FTIR) spectroscopic study
The dealings among constituents of the SD were established using scanning in FTIR spectroscopy. The FTIR spectra of the LCD, with combination with, were renowned by the FTIR spectrometer (Bruker) by scanning at 4000-400 cm\(^{-1}\).

2.5. Evaluations of LCD Solid Dispersions
The gained SD were scrutinized for the cited strictures.

2.5.1. Flow properties
The SD were assessed for flow restraints viz., angle of repose, densities, Carr's Index, and Hausner's ratio\(^12,13\).

2.5.2. Yield
The weight of dried SD to the total weight of ingredients used in making SD can be assessed by the formula given\(^14\).

2.6. Depiction of tablets made with SD
The SD were compressed into tablets and were measured for the following properties.

2.6.1. Uniformity in size and shape.
The SD tablets were inspected under a dissection microscope (DM-100, Mumbai) for their size and shape\(^15\).

2.6.2. Thickness
The tablets were held between Vernier Caliper's (Qumos Enterprises, India) jaws and breadth was assessed 3 times\(^16\).

2.6.3. Uniformity in weight
20 tablets from each batch of tablets were distinctly weighed with an electronic digital balance (Citizen, CY-104, Mumbai, India) and the average was assessed. The nonconformity was matched with IP limits (±5% for 300 mg tablets)\(^17\).

2.6.4. Hardness
The tablets were pushed between the two extremes of Pfizer tablet hardness tester. The energy to break the tablets was performed 3 times\(^18\).

2.6.5. Friability
Surface abrasion may emerge while tablet handling can be assessed by a Roche Friabilator. Initially weighed tablets (10 tablets), were allowed to fall from a height of 6 inches for 100 resolutions, the tablets were de-dusted and weighed again. The loss in weight was assessed by the formula given\(^19\).

2.6.6. Calibration curve
100 mg of LCD dissolved in pH 1.2, HCl solution (0.1M). Dilutions viz., 2, 4, 6, 8 and 10 µg/ mL were prepared and scanned spectrophotometrically at 239 nm then the absorbance verses concentrations produces the calibration curve of LCD\(^20\).

2.6.7. Uniformity of drug content
10 tablets were pulverized. A blend equivalent to 20 mg LCD was dissolved in methanol, diluted and the absorbance was measured at \(\lambda_{\text{max}}\) of 239 nm\(^21\).

2.6.8. In-vitro drug release studies
The USP paddle apparatus containing 0.1N HCl (900mL), stirred at 50 rpm and retained at 37±0.5°C. The media was withdrawn at regular intervals for 1h, filtered using Whatman filter paper and diluted to 10 mL with 0.1N HCl, and analyzed at \(\lambda_{\text{max}}\) of 239 nm by UV/visible spectrophotometer\(^22\). The release data was further kinetically
assessed by zero-order, first-order\textsuperscript{23}, and Hixson Crowell’s models \textsuperscript{24}.

2.7. Scanning Electron Microscopy

The surface topography of SD was confirmed by scanning the surface of SD by scanning electron microscopy\textsuperscript{25} (Perkin Elmer, USA). An accelerating voltage of 20KV was used and the images obtained at the magnification of \( \times500 \).

3. RESULTS AND DISCUSSION

LCD melts at 197.5±1.29°C, designates the purity of the LCD (as it melts in between 196-198°C). The LCD presented good solubility in 0.1N HCl (0.313±0.01µg/mL) relatively in Water, Acetate buffer (pH4.5), Phosphate buffer (pH6.8) and Phosphate buffer (pH7.4). The solubility data for pure LCD was illustrated in figure 1.

![Fig 1. The solubility of pure LCD in various solvents](image1)

The DSC thermograms of LCD with PVP K30, Poloxamer 188/HPMC K4M carriers were moved to the lesser temperatures representing certain associating of LCD with carriers adopted (figure 2).

![Fig 2. DSC thermograms of LCD (A) Pure drug (B) with PVP K30 (C) with Poloxamer 188 (D) with HPMC K4M](image2)

The FTIR study revealed that the distinctive peaks and stretches of LCD pure drugs were also found in LCD – carriers designate no negative discordancy of LCD with carriers used. The FTIR spectra of LCD pure and carriers were shown in figure 3.

![Fig 3. FTIR spectra of LCD A) Pure drug B) with PVP K30 C) with Poloxamer 188 D) with HPMC K4M](image3)
When the LCD-SD assessed for the angle of repose was found to be 25 to 30° i.e., 24.95±0.01 to 29.65±0.02°, which authorizes excellent flow possessions. On the other hand, the compressibility Index was less than 10 (2.935 to 7.978) and Hausner ratio less than 1.09 (1.030 to 1.086), demonstrating good compression assets while tableting. The flow properties of LCD-SD were briefed in table 3.

### Table 3. flow character Specifications of LCD-SD

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of repose (°)</th>
<th>Bulk Density</th>
<th>Tapped Density</th>
<th>Carr’s Index</th>
<th>Hausner Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPVP-1</td>
<td>27.84±0.01</td>
<td>0.529</td>
<td>0.545</td>
<td>2.935</td>
<td>1.030</td>
</tr>
<tr>
<td>LPVP-2</td>
<td>26.25±0.02</td>
<td>0.569</td>
<td>0.598</td>
<td>4.849</td>
<td>1.050</td>
</tr>
<tr>
<td>LPVP-3</td>
<td>25.84±0.03</td>
<td>0.658</td>
<td>0.678</td>
<td>2.949</td>
<td>1.031</td>
</tr>
<tr>
<td>LPVP-4</td>
<td>24.95±0.01</td>
<td>0.628</td>
<td>0.648</td>
<td>3.086</td>
<td>1.031</td>
</tr>
<tr>
<td>LPOX-1</td>
<td>26.65±0.02</td>
<td>0.458</td>
<td>0.487</td>
<td>5.954</td>
<td>1.063</td>
</tr>
<tr>
<td>LPOX-2</td>
<td>25.29±0.06</td>
<td>0.518</td>
<td>0.537</td>
<td>3.538</td>
<td>1.036</td>
</tr>
<tr>
<td>LPOX-3</td>
<td>26.21±0.08</td>
<td>0.635</td>
<td>0.665</td>
<td>4.511</td>
<td>1.047</td>
</tr>
<tr>
<td>LPOX-4</td>
<td>29.23±0.05</td>
<td>0.648</td>
<td>0.698</td>
<td>7.163</td>
<td>1.072</td>
</tr>
</tbody>
</table>

Values in mean ±SD; trials made (n=3)

The yield of LCD-SD was observed to be good (>90%), and LPOX-3 has a good yield of 98.9±1.95%. The LCD-SD tablets were seeming to have a uniform in size, shape, pale white-colored, odorless with a smooth surface. The tablets were found to have a uniform in thickness, ranged from 4.50±0.01 to 4.52±0.04 mm, and weight and ranged from 300.2±1.64 to 301.7±1.64 mg. The loss on friability was between 0.15±0.02 to 0.84±0.02%, which is < 1%, and the hardness was ranged from 5.8±0.05 to 8.7±0.02 (>4 Kg/cm²) representing that the tablets bearing significant mechanical strength and the LCD content was also found to be uniform (96.8±1.35 to 99.9±2.34). All these values were explained in table 4.

### Table 4. Physical Characteristics for tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Uniformity of Weight (mg)</th>
<th>Hardness (cm²)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Yield (%)</th>
<th>Assay (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPVP-1</td>
<td>300.2±3.29</td>
<td>7.9±0.06</td>
<td>4.51±0.02</td>
<td>0.84±0.02</td>
<td>97.1±1.20</td>
<td>96.8±1.35</td>
</tr>
<tr>
<td>LPVP-2</td>
<td>301.0±1.27</td>
<td>8.4±0.05</td>
<td>4.50±0.03</td>
<td>0.68±0.02</td>
<td>98.0±3.28</td>
<td>97.9±1.95</td>
</tr>
<tr>
<td>LPVP-3</td>
<td>301.2±2.38</td>
<td>6.1±0.03</td>
<td>4.51±0.06</td>
<td>0.48±0.01</td>
<td>98.3±1.54</td>
<td>98.8±2.35</td>
</tr>
<tr>
<td>LPVP-4</td>
<td>301.3±1.39</td>
<td>8.7±0.02</td>
<td>4.52±0.04</td>
<td>0.32±0.02</td>
<td>97.6±2.35</td>
<td>97.9±4.25</td>
</tr>
<tr>
<td>LPOX-1</td>
<td>301.1±3.25</td>
<td>6.5±0.01</td>
<td>4.51±0.02</td>
<td>0.49±0.02</td>
<td>96.8±3.16</td>
<td>96.9±1.25</td>
</tr>
<tr>
<td>LPOX-2</td>
<td>300.2±1.64</td>
<td>7.2±0.03</td>
<td>4.50±0.01</td>
<td>0.15±0.02</td>
<td>95.2±1.37</td>
<td>98.4±3.02</td>
</tr>
<tr>
<td>LPOX-3</td>
<td>301.2±2.35</td>
<td>7.1±0.01</td>
<td>4.50±0.01</td>
<td>0.34±0.02</td>
<td>98.9±1.95</td>
<td>97.7±2.20</td>
</tr>
<tr>
<td>LPOX-4</td>
<td>301.5±1.68</td>
<td>6.8±0.02</td>
<td>4.50±0.02</td>
<td>0.35±0.03</td>
<td>98.5±3.16</td>
<td>98.4±1.62</td>
</tr>
<tr>
<td>LHPM-1</td>
<td>301.6±2.36</td>
<td>6.3±0.01</td>
<td>4.51±0.01</td>
<td>0.62±0.02</td>
<td>96.5±1.25</td>
<td>98.5±2.31</td>
</tr>
<tr>
<td>LHPM-2</td>
<td>300.3±1.28</td>
<td>7.2±0.05</td>
<td>4.50±0.06</td>
<td>0.18±0.01</td>
<td>96.3±1.39</td>
<td>97.2±1.24</td>
</tr>
<tr>
<td>LHPM-3</td>
<td>301.7±1.64</td>
<td>5.8±0.05</td>
<td>4.52±0.03</td>
<td>0.44±0.02</td>
<td>98.2±3.26</td>
<td>99.7±3.25</td>
</tr>
<tr>
<td>LHPM-4</td>
<td>301.6±1.39</td>
<td>7.4±0.02</td>
<td>4.51±0.04</td>
<td>0.39±0.01</td>
<td>96.4±2.48</td>
<td>99.9±2.34</td>
</tr>
</tbody>
</table>

Values in mean ±SD; trials made (n=3)

The solubility of LCD was found to be good in 0.1N HCl and diminished with an increase in pH of the buffer. Among them, LPOX-4 signified good solubility in 0.1 N HCl. The entire description of solubility was embodied in figure 4.
LCD followed Beer’s Lambert’s law at 2 to 10 µg/mL. The regression ($R^2$ value was detected to be 0.9992 with a slope of 0.0749x+0.0157. The LCD was determined by plotting the calibration curve of the LCD. LCD released from the tablets were firstly by eruption < 10 min and the end of 1h the LCD was released in zero order. The dissolution of prepared tablets was found good in SD with LCD: Poloxamer-188 at the ratio of 1:5 (figure 5), which followed zero order. The kinetic study revealed that the LCD-SD followed first-order release kinetics and illustrated in figures 6 and 7.

**Fig 4. Solubility details of Lercanidipine solid dispersions prepared with A) PVP K30 B) Poloxamer-188 C) HPMC K4M**

**Fig 5. In vitro dissolution profile of LCD with A) PVP K30 B) Poloxamer-188 C) HPMC K4M**
The SEM analysis revealed that SD with PVP K30 and Poloxamer-188 produce an amorphous SD. In the case of Poloxamer-188, which acts as a crystal inhibitor, this may be the reason for the enhancement of dissolution. The SEM analysis images were represented in figure 8.

LCD was found to show elevated solubility in 0.1M HCl compared to its pure LCD. The angle of repose of LCD-SD represented excellent flow properties, additionally, the compressibility Index and Hausner ratio proved the good
compression assets of prepared SD. The yield of LCD-SD was found enhanced (up to 98.9±1.95%) compared to other approaches using PVP K-30. The LCD-SD tablets were found to have uniformity in physicochemical constraints including the loss on friability was below 1% with >4 Kg/cm² hardness, and uniformity in LCD drug content. This rapid dissolution needed to assist in enhancing the release of LCD from the SD. The prepared SD showed good LCD release within 10 min, which might be due to the solubility enhancing stuff of Poloxamer-188 when combined with LCD. The release rate was significantly increased when the LCD: Poloxamer-188 ratio was at 1:5. Similar observations were also reported by Shamsuddin et al. The LCD release from all the SD followed first-order kinetics, as the plot observed in between log percentage drug remaining versus time was found to be linear with a coefficient of correlation (R² = 0.9964). The correlation coefficient (r) values of the first-order release model are found to be 0.9912-0.9964, which is in good in elevation of in vitro dissolution of Lercanidipine and it followed first-order release kinetics. The SEM analysis revealed that SD with PVP K30 and Poloxamer-188 produce an amorphous SD, this may be the reason for the enhancement of dissolution.

4. CONCLUSION

The study discovered that the solid dispersions prepared by Poloxamer-188 were good carriers for elevating the solubility of Lercanidipine by making solid dispersions. The LPOX-4 formulation with LCD: Poloxamer-188 made by the melting methodology were good in elevation of in vitro dissolution of Lercanidipine and it followed first-order release kinetics.

5. AUTHORS CONTRIBUTION STATEMENT

Nazemmoon Reddy conceived the presented idea, developed the theory and performed the computations. Swarnalatha Dugasani, and Devanna Nayakanti verified and corrected the manuscript. All authors discussed the results and contributed to the final manuscript.

6. CONFLICTS OF INTEREST

Conflicts of interest declared none.

7. REFERENCES


