Formulation and evaluation of sustain release matrix tablets of carvidolol phosphate

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ABSTRACT
The purpose of the present study was to formulate and evaluate once daily sustained release matrix tablets of carvidolol phosphate. Carvedilol Phosphate is a nonselective beta blocker indicated in the treatment of mild to severe congestive heart failure. Various formulations of sustained release tablets of Carvidolol phosphate were developed using various polymers Guar gum, SCMC, HPMC100M in different concentrations by direct compression method. Observations of all formulations for physical characterization had shown that all of them comply with the specifications of official pharmacopoeias and a standards reference. Results of in-vitro release profile indicated that formulation (F9) was the most promising formulation as the extent of drug release from this formulation was high (100.75%) as compared to other formulations. From the above results and discussion it is concluded that formulation of sustain release tablets of carvidolol phosphate containing Guar gum (33.33%) formulation F9 can be taken as an ideal for optimized formulation of sustain release tablets for 24 hours release as it fulfills all the requirements for sustained release tablets.

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Materials and methods
Carvedilol phosphate procured by Symed labs ltd, Hyderabad, Guar gum and Sodium Carboxy methyl cellulose, Lactose purchased by Qualines, New Delhi, HPMC K100 M CR gift sample by Cadila Pharm, Ahmedabad

Table-1 Composition F1-F5 matrix tablets formulations containing SCMC

<table>
<thead>
<tr>
<th>Ingredients(Mg)</th>
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<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
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<tbody>
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<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
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<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>Lactose</td>
<td>234</td>
<td>214</td>
<td>194</td>
<td>174</td>
<td>154</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<td>300</td>
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</table>

Formulation matrix tablets of carvildol phosphate

Preparation of carvedilol phosphate matrix tablets
All the matrix tablets, each containing 20 mg of carvedilol phosphate were prepared by direct compression method. Accurately weighted amounts of drug, polymer, and diluents were mixed geometrically in a mortar. This mixture was passed through no.80 sieve and thoroughly mixed in a polyethylene bag for 15 minutes. The powder blend was then blended was then lubricated with magnesium stearate and talc for 2 minutes and compressed into tablets on a rotator machines using 9 mm round, flat-faced punches. In the formulations prepared, the retardants included were hydrophilic polymers, HPMC K100M, Guar gum, sodium carboxy methyl cellulose. Lactose was used as diluents, magnesium stearate and talc were used as lubricant.
Composition of different formulations were given in the following tables:

**Table-2 Composition F1-F5 matrix tablets formulations containing Guar gum**

<table>
<thead>
<tr>
<th>Ingredients (Mg)</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
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<td>20</td>
<td>20</td>
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<tr>
<td>Guar gum</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
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<td>Lactose</td>
<td>234</td>
<td>214</td>
<td>194</td>
<td>174</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Total</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
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</tbody>
</table>

**Table-3. Composition F1-F5 matrix tablets formulations containing HPMCK100M**

<table>
<thead>
<tr>
<th>Ingredients (Mg)</th>
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<th>F12</th>
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</thead>
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<td>20</td>
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<td>HPMC K 100M</td>
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<td>80</td>
<td>100</td>
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<td>Lactose</td>
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<td>194</td>
<td>174</td>
</tr>
<tr>
<td>Magnesium stearate</td>
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<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
</tbody>
</table>

Characterization of polymer and granules of formulations

- **Bulk density**

  The bulk density was determined by gently pouring the powders into a 100 mL volumetric cylinder to a total volume of 90 mL. After weighing the above volume of powder, the bulk density was determined using equation as presented below.

  \[
  \text{Density} = \frac{\text{Weight (gm)}}{\text{Volume (mL)}}
  \]

- **Tapped Density**

  It was determined by placing a graduated cylinder, containing a known mass of drug or polymer coated granules, on mechanical tapping apparatus, which was operated for a fixed number of taps until the powder bed volume has reached a minimum. Using the weight of a powder or coated granules in a cylinder and this volume, the tapped density was computed.

- **Compressibility and Hausner Ratio:**

  From the above results, the compressibility of the powder was calculated as the following ratios:

  \[
  \text{Compressibility (\%)} = \{1 - \text{bulk density/tap density}\} \times 100
  \]

  The Hausner ratio is defined as the ratio between tap and bulk density of powders.

- **Evaluation of physical properties of matrix tablets:**

  The prepared matrix tablets Carvedilol phosphate were evaluated for the following Parameters were shown in table.

- **Weight variation:**

  Twenty (20) tablets from each batch were individually weighed in milligram (mg) on digital balance. The average weight and standard deviation were calculated and the results were expresses as compliance or non-compliance of set limits.

- **Tablet thickness:**

  The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Digimatic digital outside micrometer (Mitutoyo, Japan). The average thickness and standard deviation were reported.

- **Tablet hardness:**

  Tablets hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm² and the average hardness, and standard deviation was reported.

- **Friability:**

  Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilitor. The tablets were then dedusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

**Determination of drug content of matrix tablets:**

The drug content of the matrix tablets was determined according to in house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 85% to 115% of the stated amount.

**Procedure:**

Ten tablets with pre determined weight from each batch were taken and crushed in a mortar and weight equivalent to one average tablet was taken, transferred to a 250 ml volumetric flask 50 ml of methanol was used to solubilize the Ciprofloxacin and 0.1N HCl was added. The flask was shaken over the cyclomixer. It was taken out and the solution was filtered using membrane filter. Then filtrate was sufficiently diluted with 0.1 N HCl and by spiking the sample the peak area was recorded at 276 nm. The drug content of the standard and the control containing drug powder and with out Drug respectively were determined. The drug content was determined by the formula. The absorbance of control was deducted from test and standard. Drug content was determined by using UV-visible spectroscopy. Result are shown in table.

\[
\text{% Drug content of the batch = } \frac{\text{Amount in test}}{\text{Amount in standard}} \times 100
\]

**Results**

Comparative percentage drug release of marketed formulation and optimized formulation F9

The % drug release profile of marketed formulation and F9 formulation in shown in graph. Marketed formulation (Cardivas) showed 95% of drug release up to 12 hrs only. The prepared F9 formulation showed sustained release (100.75%) up to 24 hrs. comparing the both formulations the prepared matrix tablets showed good sustained action than the marketed formulation.
Table 1: Physical property of compressed matrix tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose</th>
<th>Bulk Density mean SE, N=3</th>
<th>Tapped Density</th>
<th>Carrs Index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>20.33±0.042</td>
<td>0.614±0.005</td>
<td>0.751</td>
<td>10.74</td>
</tr>
<tr>
<td>F2</td>
<td>23.96±0.01</td>
<td>0.608±0.003</td>
<td>0.764</td>
<td>13.38</td>
</tr>
<tr>
<td>F3</td>
<td>18.21±0.02</td>
<td>0.576±0.004</td>
<td>0.722</td>
<td>12.28</td>
</tr>
<tr>
<td>F4</td>
<td>18.10±0.03</td>
<td>0.641±0.001</td>
<td>0.688</td>
<td>10.11</td>
</tr>
<tr>
<td>F5</td>
<td>19.51±0.057</td>
<td>0.624±0.12</td>
<td>0.776</td>
<td>12.82</td>
</tr>
<tr>
<td>F6</td>
<td>21.11±0.026</td>
<td>0.620±0.11</td>
<td>0.697</td>
<td>13.39</td>
</tr>
<tr>
<td>F7</td>
<td>20.64±0.023</td>
<td>0.621±0.11</td>
<td>0.729</td>
<td>12.17</td>
</tr>
<tr>
<td>F8</td>
<td>24.14±0.042</td>
<td>0.618±0.05</td>
<td>0.727</td>
<td>11.38</td>
</tr>
<tr>
<td>F9</td>
<td>18.19±0.06</td>
<td>0.622±0.07</td>
<td>0.706</td>
<td>12.60</td>
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<tr>
<td>F10</td>
<td>21.18±0.02</td>
<td>0.581±0.031</td>
<td>0.672</td>
<td>11.90</td>
</tr>
<tr>
<td>F11</td>
<td>24.18±0.41</td>
<td>0.575±0.012</td>
<td>0.766</td>
<td>10.07</td>
</tr>
<tr>
<td>F12</td>
<td>24.13±0.051</td>
<td>0.624±0.07</td>
<td>0.699</td>
<td>12.52</td>
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</table>

Table 2: Physical properties of compressed matrix tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness (kg/cm2)</th>
<th>Thickness (mm)</th>
<th>Weight variation (mg)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6.10±0.25</td>
<td>3.2±0.12</td>
<td>2.30</td>
<td>0.39±0.07</td>
<td>97.89±3.29</td>
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<tr>
<td>F2</td>
<td>5.87±0.40</td>
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<tr>
<td>F3</td>
<td>5.08±0.27</td>
<td>3.1±0.03</td>
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<tr>
<td>F4</td>
<td>6.15±0.41</td>
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<tr>
<td>F5</td>
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<td>99.15±4.11</td>
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<tr>
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<td>0.45±0.05</td>
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<tr>
<td>F7</td>
<td>6.12±0.43</td>
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<td>100.11±2.98</td>
</tr>
<tr>
<td>F8</td>
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<td>2.01</td>
<td>0.38±0.01</td>
<td>99.14±2.78</td>
</tr>
<tr>
<td>F9</td>
<td>6.16±0.40</td>
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<td>2.05</td>
<td>0.46±0.02</td>
<td>98.14±3.18</td>
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<tr>
<td>F10</td>
<td>5.57±0.10</td>
<td>2.9±0.05</td>
<td>1.98</td>
<td>0.41±0.05</td>
<td>96.45±3.66</td>
</tr>
<tr>
<td>F11</td>
<td>6.09±0.21</td>
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<td>1.56</td>
<td>0.46±0.03</td>
<td>103.16±2.89</td>
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<tr>
<td>F12</td>
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<td>1.82</td>
<td>0.43±0.04</td>
<td>95.98±2.99</td>
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</tbody>
</table>

Table 3: In-vitro drug release of Carvedilol phosphate

<table>
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<tr>
<th>Time (Hr)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
<th>F11</th>
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</thead>
<tbody>
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<td>0.5</td>
<td>29.96</td>
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<td>48.10</td>
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<td>39.57</td>
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<td>81.44</td>
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<td>57.40</td>
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<td>92.85</td>
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<td>98.07</td>
<td>98.07</td>
<td>98.07</td>
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</table>
Conclusion

The present study demonstrated that hydrophilic polymers cellulose esters (HPMC K100M, SCMC) and natural polymers (guar gum) could be successfully employed for formulating sustained release matrix tablets of Carvedilol phosphate. Among the hydrophilic matrix formers, the rate of drug release was in the following orders: Guar gum > HPMC K100M > SCMC. The release rate was almost similar for guar gum, SCMC and HPMC K100m up to 24 hrs. Among all formulation showed the maximum release up to 24 hrs and it is selected as the best formulation.

References


| Table 4. % drug release Comparative percentage drug release of marketed formulation and optimized formulation F9 |
|---|---|---|---|---|
| Time(hrs) | Marketed tablets | F9 |
| 0.5 | 9.75 | 22.08 |
| 1 | 15.56 | 27.06 |
| 2 | 25.06 | 30.35 |
| 4 | 39.59 | 36.32 |
| 6 | 51.06 | 43.44 |
| 8 | 56.73 | 51.08 |
| 10 | 85.49 | 54.91 |
| 12 | 95.97 | 74.34 |
| 18 | 86.51 |  |
| 24 | | 100.53 |

| Table 5. Kinetic study of Carvedilol phosphate |
|---|---|---|---|---|
| Formulation Code | Zero order | First order | Higuchi | Peppas |
| | r² | n | r² | n |
| F1 | 0.924 | 0.907 | 0.958 | 0.911 | 0.418 |
| F2 | 0.644 | 0.565 | 0.745 | 0.593 | 0.152 |
| F3 | 0.866 | 0.789 | 0.874 | 0.746 | 0.265 |
| F4 | 0.869 | 0.840 | 0.887 | 0.801 | 0.278 |
| F5 | 0.965 | 0.868 | 0.911 | 0.899 | 0.537 |
| F6 | 0.688 | 0.645 | 0.799 | 0.711 | 0.197 |
| F7 | 0.781 | 0.685 | 0.847 | 0.773 | 0.234 |
| F8 | 0.862 | 0.892 | 0.935 | 0.920 | 0.324 |
| F9 | 0.934 | 0.932 | 0.968 | 0.933 | 0.389 |
| F10 | 0.745 | 0.856 | 0.871 | 0.846 | 0.198 |
| F11 | 0.973 | 0.838 | 0.926 | 0.913 | 0.462 |
| F12 | 0.969 | 0.819 | 0.811 | 0.946 | 0.717 |