FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF RANOLAZINE

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ABSTRACT
The present study was aimed to develop Ranolazine extended release tablets for the treatment of Angina, specifically reduces calcium overload in the ischemic myocyte through inhibition of the late sodium current (I\text{Na}). Ranolazine extended release tablets enhance patient compliance and reduce adverse effects. A total of 9 formulations were developed using varying proportions of Hydroxy propyl methyl cellulose, carbomer as release retardant polymers by wet granulation technique. FT-IR studies revealed that there was no interaction between drug and polymers used. Before compression the granules were evaluated for precompression parameters such as bulk density, tapped density, cars index, hausners ratio, angle of repose. After compression tablets were evaluated for appearance, weight variation, hardness, thickness, drug content, friability, in vitro release studies and stability studies.

INTRODUCTION
Presently, these conventional dosage forms are primarily, prescribed pharmaceutical products. To achieve and to maintain the concentration of an administered drug within therapeutically effective range, it is often necessary to take drug dose several times a day. This results in fluctuating drug levels in plasma [1-5]. In conventional oral drug delivery systems, there is a very little control over release of the drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses. Such situations often result in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leading to marked side effects [5-9]. Controlled drug delivery systems have been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage forms.

MATERIALS
Microcrystalline cellulose 101 from Accent mirogel industry, Carbopol from MSN Pharma, Meglumine from MSN Pharma, Hydroxy propyl methyl cellulose from Dow Chemical company, Polyvidone from MSN Pharma, Magnesium stearate from EMCO industries, sodium hydroxide pellets from FINE industries, Aerosil from MSN Pharma and all are of pharmacist grade [10].

Wet granulation method
Preparation of Extended Release Tablets:
• All the ingredients were weighed accurately as per the manufacturing formula.
• Ranolazine, microcrystalline cellulose, carbopol 974p and HPMC (Rutocel) were passed through #40 mesh sieve & collected in a polybag.
• Above sifted materials was loaded in a planetary mixer and mixed for 15 min at slow speed.
• About 0.5 gm of sodium hydroxide pellets was added in a 55 ml of purified water and added to the contents of planetary mixer.
• The wet dough mass was was passed through #16 meshes sieve and dried at 50-55°C by using tray drier for 6 to 7hrs, till desired LOD is achieved.
• Oversized granules passed through 2.0 mm multimill at medium speed in forward direction.
• Finally milled granules was passed through #16 meshes sieve and loaded in a double cone blender.
• Magnesium stearate was passed through #40 meshes and it was added to the contents of double cone blender and mixed for 10 min.
• Material was loaded in a hopper and compresses the powder into tablets by using (Cad mach) compression machine with (17.5x8.0) mm standard concave punches. Check for weight variation, hardness (Hardness tester, Pharmatest-PTB-311E), friability (Friabilator (USP), Electro lab- EF-2), thickness to meet the parameters [12-14].

PRECOMPRESSION PARAMETERS
The granules were evaluated for Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio. The angle of repose was determined by fixed funnel method to assess the flow property of granules. Bulk density is the ratio between a given mass of the powder or granules and its bulk volume. Tapped density is the ratio between a given mass of powder or granules and the constant or fixed volume of powder or granules after tapping. Bulk and tapped densities were determined using digital bulk density apparatus. The compressibility index and the Hausner ratio are determined by measuring both the bulk volume and tapped volume of powder (or) granules.

Hausner's Ratio = Tapped density/Bulk density
Carr’s index (%) = [TD-BD] / TD ×100
Where, TD = Tapped density, BD = Bulk density.

IR spectral analysis
FT-IR analysis of pure drug, individual polymer and combination of drug and polymers in higher concentration were taken for the study. Samples were compressed with potassium bromide and transformed into disk and scanned between 4000-400 cm in a SHIMADZU FT-IR (IR Affinity spectrophotometer)

POST COMPRESSION PARAMETERS
Thickness, Diameter and Hardness
Thickness and diameter of the tablets were determined using Vernier caliper. Hardness or tablet crushing strength was measured using Monsanto tablet hardness tester

Weight variation test
Twenty tablets were selected at random and average weight was determined. The individual tablets were weighed and compared with average weight not more than two of the individual weights deviate from the average weight of tablets by more than 5%.

Friability test
The friability of tablets was determined by “Roche” friabilator. Ten tablets were taken and weighed. The tablets were subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm for 4 minutes, dropping the tablets from a distance of six inches with each revolution. After operation, the tablets were dedusted and reweighed. The Percentage friability was determined using the formula: Percentage Friability = [(Initial Weight – Final Weight)/ Initial Weight] × 100

Drug content estimation
Ranolazine content in the extended release tablets was estimated by UV Spectrophotometric method based on measurement of absorbance at 233 nm using 0.1 HCl solution.

INVITRO DISSOLUTION STUDIES OF TABLETS [15,16]
Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP XXVII paddle method and 900 ml of 0.1N HCL as the dissolution medium. The medium was allowed to equilibrate to temp of 37°C ± 0.5°C. Tablet was placed in the vessel and the vessel was covered. The apparatus was operated for 24 hrs in 0.1N HCL at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 272 nm using uv-spectrophotometer.

Release Kinetics
The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Peppas-Korcemeyer equation. The results are given in Table 2 and 3.

Zero Order Release Kinetics
It defines a linear relationship between the fraction of drug released versus time.

Q = k_o t
Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.
First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

\[ \ln(1-Q) = -k_1t \]

Where, \( Q \) is the fraction of drug released at time \( t \) and \( k_1 \) is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi’s equation

It defines a linear dependence of the active fraction released per unit of surface (\( Q \)) on the square root of time.

\[ Q = K_2 \sqrt{t} \]

Where, \( K_2 \) is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick’s law, square root time dependant.

Power Law

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Peppas and Korsemeyer equation (Power Law).

\[ \frac{M_t}{M_\alpha} = k.t^n \]

Where, \( M_t \) is the amount of drug released at time \( t \) and \( M_\alpha \) is the amount released at time \( \alpha \), thus the \( \frac{M_t}{M_\alpha} \) is the fraction of drug released at time \( t \), \( k \) is the kinetic constant and \( n \) is the diffusional exponent. To characterize the mechanism for both solvent penetration and drug release \( n \) can be used as abstracted in Table 1. A plot between log of \( \frac{M_t}{M_\alpha} \) against log of time will be linear if the release obeys Peppas and Korsemeyer equation and the slope of this plot represents “\( n \)” value.

RESULTS AND DISCUSSION

Table 1. Diffusion exponent and solute release mechanism for cylindrical shape

<table>
<thead>
<tr>
<th>Diffusion Exponent</th>
<th>Overall solute diffusion mechanism</th>
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<tbody>
<tr>
<td>0.45</td>
<td>Fickian diffusion</td>
</tr>
<tr>
<td>0.45&lt;n&lt;0.89</td>
<td>Anomalous (non-fickian) diffusion</td>
</tr>
<tr>
<td>0.89</td>
<td>Case II transport</td>
</tr>
<tr>
<td>n&gt;0.89</td>
<td>Super Case II transport</td>
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Table 2. Composition of Ranolazine Extended Release Tablets

<table>
<thead>
<tr>
<th>S.NO</th>
<th>INGREDIENT</th>
<th>F1 mg/tab</th>
<th>F2 mg/tab</th>
<th>F3 mg/tab</th>
<th>F4 mg/tab</th>
<th>F5 mg/tab</th>
<th>F6 mg/tab</th>
<th>F7 mg/tab</th>
<th>F8 mg/tab</th>
<th>F9 mg/tab</th>
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<tbody>
<tr>
<td>1</td>
<td>RANOLAZINE</td>
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<td>500</td>
<td>500</td>
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<td>500</td>
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<td>2</td>
<td>MCC PH101</td>
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<td>115</td>
<td>110</td>
<td>105</td>
<td>100</td>
<td>95</td>
<td>90</td>
<td>85</td>
<td>80</td>
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<td>CARBOPOL 974P</td>
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<td>METHOCEL K4M</td>
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<td>MEGLUMINE</td>
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<td>8</td>
<td>MAGNESIUM STEARATE</td>
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<td>AEROSIL</td>
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<td>5</td>
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<td>NAOH</td>
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<td>2</td>
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</table>

PRECOMPRESSION PARAMETER

Table 3. Micromeric properties

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Bulk density (gm/ml)</th>
<th>Tapped density (gm/ml)</th>
<th>Hausner ratio</th>
<th>Carr’s index (%)</th>
<th>Angle of repose (θ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.32</td>
<td>0.41</td>
<td>1.28</td>
<td>21.95</td>
<td>27.38</td>
</tr>
<tr>
<td>F2</td>
<td>0.30</td>
<td>0.38</td>
<td>1.26</td>
<td>21.052</td>
<td>28.14</td>
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<tr>
<td>F3</td>
<td>0.31</td>
<td>0.38</td>
<td>1.22</td>
<td>18.42</td>
<td>26.85</td>
</tr>
<tr>
<td>F4</td>
<td>0.33</td>
<td>0.37</td>
<td>1.12</td>
<td>10.810</td>
<td>27.12</td>
</tr>
</tbody>
</table>
### Table 4. Post compression studies

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Weight variation n=20</th>
<th>Hardness (kg/cm²) n=3</th>
<th>Friability (%) n=20</th>
<th>Thickness (mm) n=20</th>
<th>Content uniformity n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>694±0.23</td>
<td>11±0.57</td>
<td>0.49±0.1</td>
<td>5.9±0.58</td>
<td>99.28±</td>
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<tr>
<td>F2</td>
<td>690±0.62</td>
<td>10±0.62</td>
<td>0.57±0.42</td>
<td>6±0.82</td>
<td>97.16±</td>
</tr>
<tr>
<td>F3</td>
<td>689±0.18</td>
<td>13±0.46</td>
<td>0.38±0.35</td>
<td>5.7±0.51</td>
<td>98.94±</td>
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<tr>
<td>F4</td>
<td>691±0.42</td>
<td>9±0.34</td>
<td>0.24±0.15</td>
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<td>99.68±</td>
</tr>
<tr>
<td>F5</td>
<td>687±0.26</td>
<td>10±0.54</td>
<td>0.39±0.21</td>
<td>5.4±0.6</td>
<td>99.41±</td>
</tr>
<tr>
<td>F6</td>
<td>693±0.34</td>
<td>9±0.26</td>
<td>0.46±0.55</td>
<td>6.06±0.78</td>
<td>98.19±</td>
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<tr>
<td>F7</td>
<td>692±0.23</td>
<td>11±0.37</td>
<td>0.42±0.11</td>
<td>6±0.98</td>
<td>100.26±</td>
</tr>
<tr>
<td>F8</td>
<td>689±0.37</td>
<td>10±0.48</td>
<td>0.29±0.03</td>
<td>5.9±0.12</td>
<td>99.68±</td>
</tr>
<tr>
<td>F9</td>
<td>691±0.29</td>
<td>9±0.68</td>
<td>0.37±0.015</td>
<td>5.8±0.3</td>
<td>100.12±</td>
</tr>
</tbody>
</table>

Fig 1. Comparison of invitro drug releases of formulation F4, F5, F6

Fig 2. Comparison of invitro drug releases of formulation F4, F5, F6

Fig 3. Comparison of invitro drug releases of formulation F7, F8, F9

Fig 4. First order plot for formulation F8, F9 and marketed product
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