FORMULATION AND EVALUATION OF MODIFIED RELEASE MATRIX TABLET OF A MODEL ANTIBIOTIC

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ABSTRACT - The purpose of the investigation was Formulation and Evaluation of Modified release matrix tablet of Model antibiotic, for which Bioequivalence will be proved with reference product and a better bioavailability, may be expected than reference product. Drug and polymer compatibility was studied by Physical observation and FTIR study. The drug and polymer in the optimized formulation was found to be compatible. Model tablet was prepared by Direct compression method. 750mg of Model drug was taken in a single tablet of 1200mg. The evaluation parameter such as Weight variation, Thickness, Hardness, Friability, Drug content uniformity, In-vitro drug release studies in different dissolution media i.e., 0.1 N HCL, 0.01 N HCL, 4.5 AB, 6.8 PB, stability testing of matrix tablets using ICH accelerated stability conditions were performed. The results were within the limit. From the release profile, F7 was selected to be the best formulation as it showed complete and most comparable release with respect to reference product. The order of release was zero order, mechanism of release was diffusion controlled and exponent of release was Non-fickian type diffusion controlled.

Key words – Modified release, Matrix tablet, Antibiotic, Non-fickian

INTRODUCTION  
The present research work aims to develop a stable Modified Release Hydrophilic Matrix tablet of Model drug X, a second generation antibiotic, for which Bioequivalence will be proved with reference product and a better bioavailability may be expected than reference product. It focuses in development of patent non infringing Hydrophilic Matrix tablet. Since the dawn of modern medicine, researchers have continually searched for new and improved ways to administer medicinal products. Although conventional oral formulations are still the most widely administered dosage forms, they are improved today by many different controlled-release technologies, including delayed-onset and extended/sustained-release formulations. No doubt many new different types of delivery systems entered to the market and created a large impact on patient’s compliance and convenience. Still the Oral ingestion has been the most commonly employed route of drug delivery and a major area of research now a days. Over the years, greater attention has been focused on the development of modified release dosage forms.

Drug Profile  
API Specification Model Drug is a Semi-synthetic, broad-spectrum second-generation cephalosporin antibiotic used to treat certain infections caused by bacteria such as pneumonia lung, skin, throat, and urinary tract infections.

![Chemical structure of Second Generation Cephalosporin](Image)

Table 1 (Formulation table)

<table>
<thead>
<tr>
<th>Ingredients</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>
</tr>
</thead>
<tbody>
<tr>
<td>Model Drug*</td>
<td>787.81</td>
<td>787.81</td>
<td>787.81</td>
<td>787.81</td>
<td>787.81</td>
<td>787.81</td>
<td>787.81</td>
<td>787.81</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>50.19</td>
<td>50.19</td>
<td>50.19</td>
<td>50.19</td>
<td>50.19</td>
<td>50.19</td>
<td>50.19</td>
<td>50.19</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>HPC-M</td>
<td>50</td>
<td>40</td>
<td>35</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>HPMC E5</td>
<td>272</td>
<td>282</td>
<td>287</td>
<td>292</td>
<td>297</td>
<td>302</td>
<td>305</td>
<td>305</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Talc</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Aerosil 200</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total Weight</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
</tr>
</tbody>
</table>

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METHODOLOGY
Drug polymer compatibility study
Physical Observation
FTIR study
Evaluation of precompression parameters
Bulk Density (B.D.) = Mass of Powder M (gms)/ Apparent Volume V₀ (ml)
Tap Density (T.D.) = Mass of Powder M (gms)/ Tapped Volume Vₐ (ml)
Hausner’s Ratio = Tap Density (T.D.) / Bulk Density (B.D.)
Angle of Repose θ= tan⁻¹ (H/R)

Analytical studies
Determination of λ max of drug X
Construction of calibration curve of drug X

Formulation design
Direct compression method, Dry granulation method, Wet granulation method

Evaluation of matrix tablets
Thickness, Weight Variation Test, Drug Content, Hardness, Friability

Data Analysis (Curve Fitting Analysis):
• To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:
  • Cumulative percentage drug released Vs Time (In-Vitro drug release plots)
  • Cumulative percentage drug released Vs Square root of time (Higuchi’s plots)
  • Log cumulative percentage drug remaining Vs Time (First order plots)
  • Log percentage drug released Vs Log time (Peppas plots)

Stability studies
In order to assess the stability of drug product, accelerated stability studies were conducted for the selected batch F₇. The development batch were packed in blister pack and kept for stability at 40°C ±2 °C/75% RH ±5% for 3 months.

<table>
<thead>
<tr>
<th>Storage Condition</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>40°C  ±2 °C/75% RH ±5%</td>
<td>1, 3, 6 Months</td>
</tr>
<tr>
<td>30°C ±2 °C/65% RH ±5%</td>
<td>1, 3, 6 Months</td>
</tr>
<tr>
<td>25°C ±2 °C/60% RH ±5%</td>
<td>1, 3, 6 Months</td>
</tr>
</tbody>
</table>

RESULT AND DISCUSSIONS
Evaluation of pre-compression parameter
Angle of repose tells about the flow ability of the blend. It is one of the important parameter in tablet manufacturing. In the present investigation angle of repose was found to be highest for F₁ and lowest for F₆. F₇ has angle of repose 25.78 which indicates good flow.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Angle of repose (°)</th>
<th>Compressibility Index</th>
<th>Bulk density (%)</th>
<th>Tapped density (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₁</td>
<td>24.30</td>
<td>25.48</td>
<td>0.54</td>
<td>0.72</td>
</tr>
<tr>
<td>F₂</td>
<td>26.77</td>
<td>26.10</td>
<td>0.52</td>
<td>0.71</td>
</tr>
<tr>
<td>F₃</td>
<td>25.28</td>
<td>23.98</td>
<td>0.53</td>
<td>0.73</td>
</tr>
<tr>
<td>F₄</td>
<td>28.31</td>
<td>24.38</td>
<td>0.55</td>
<td>0.73</td>
</tr>
<tr>
<td>F₅</td>
<td>24.51</td>
<td>25.65</td>
<td>0.54</td>
<td>0.72</td>
</tr>
<tr>
<td>F₆</td>
<td>23.89</td>
<td>27.14</td>
<td>0.51</td>
<td>0.70</td>
</tr>
<tr>
<td>F₇</td>
<td>25.78</td>
<td>24.66</td>
<td>0.55</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Physical Observation
Samples were observed for four weeks and any change with reference to the control sample was recorded. No appreciable changes were observed during the study. From this it was predicted that there was no physical interaction between drug, polymers and excipients.

FTIR STUDY
The Fourier transform infrared (FTIR) spectroscopy study of drug X, different polymers and the combination of drug – polymers was carried out with SHIMADZU 8400S FTIR spectrophotometer. The pure drug was dispersed with KBr in the ratio of approximately 1:100. It was then placed in the sample holder, scanned and FTIR spectra were obtained. Similarly the FTIR spectra...
of polymer as well as the drug – polymer combinations were obtained. From the obtained FTIR spectra the drug polymer interaction was studied.
Calibration Curve in 0.1N HCl

\[ y = 0.020x + 0.009 \]
\[ R^2 = 0.999 \]

Calibration Curve in pH 4.5 Acetate buffer

\[ y = 0.019x + 0.005 \]
\[ R^2 = 0.998 \]

Calibration Curve in pH 6.8 Phosphate buffer

\[ y = 0.018x + 0.001 \]
\[ R^2 = 0.998 \]

(Fig 1. Standard Calibration Curve)
Evaluation of Matrix Tablet

(Fig 2. Graphical analysis of Evaluation Parameters)

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Weight variation (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content uniformity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F7</td>
<td>1200</td>
<td>18.5</td>
<td>0.310</td>
<td>99.8</td>
</tr>
<tr>
<td>F9</td>
<td>1202</td>
<td>18.8</td>
<td>0.308</td>
<td>99.6</td>
</tr>
<tr>
<td>F10</td>
<td>1200</td>
<td>19.2</td>
<td>0.302</td>
<td>98.9</td>
</tr>
<tr>
<td>F11</td>
<td>1205</td>
<td>17.8</td>
<td>0.401</td>
<td>98.8</td>
</tr>
<tr>
<td>F12</td>
<td>1204</td>
<td>17.6</td>
<td>0.392</td>
<td>99.4</td>
</tr>
<tr>
<td>F13</td>
<td>1200</td>
<td>18.9</td>
<td>0.314</td>
<td>99.7</td>
</tr>
<tr>
<td>F14</td>
<td>1201</td>
<td>18.6</td>
<td>0.336</td>
<td>99.8</td>
</tr>
</tbody>
</table>

(Table 3. Evaluation of Matrix Tablet)

Drug Release kinetic profile of formulated matrix tablets

Zero Order Release of Model drug X

First Order Release

% Drug Release

Time (min)

120

100

80

60

40

20

0

0 50 100 150 200 250 300

Time (min)

2.5

2

1.5

1

0.5

0

F1  F2  F3  F4  F5  F6  F7  F8
The purpose of the investigation was to develop and evaluate the modified release matrix tablets of model antibiotic to achieve better therapeutic effect. Drug polymer compatibility was studied by FTIR and visual study. The drug and polymer in the optimized formulation was found to be compatible. Modified release Matrix tablets were successfully prepared by direct compression method. The precompression parameters such as compressibility index, bulk and tapped density, angle of repose were calculated. Different tablet evaluations such as drug content, weight uniformity, hardness, thickness, and friability of the prepared matrix tablet were carried out. The results were found satisfactory. Formulation F7 was selected to be the best formulation as it showed complete and most comparable release with respect to reference product. The order of release is found to be zero order and mechanism of release is found to be Non-Fickian diffusion. The selected batch was kept in accelerated stability showed satisfactory physical stability at 40°C and 75% RH respectively. No appreciable changes were found in any of the formulations. In vivo study is the future scope of this investigation.
REFERENCES