How to Cite:

**Effect of hydrophilic polymer and binder on drug release of metformin HCl sustained release tablet**

*Sudarshan B. Kakad*
Research Scholar, Bhagwant University, Sikar road, Ajmer-305004, Rajasthan, India
*Corresponding author email: sudarshankakad1990@gmail.com*

*Dr. Punit R. Rachh*
Bhagwant University, Sikar road Ajmer-305004, Rajasthan, India

**Abstract**---To develop an oral sustained release Metformin HCl tablet by wet granulation technique, using different grades of hydroxyl propyl methylcellulose (HPMC) in different concentration and by varying binder concentrations. Metformin HCl was received as gift sample while all other excipients of analytical grade were procured from the market. Formulation optimization was done by three ways to select optimum formula for preparing sustained release matrix tablet. Trail batches were prepared by altering the hydrophilic polymers as well as binder concentration and all the batches are evaluated for pre-compression and post-compression parameters. In first step, concentration of HPMC K4M is optimized by preparing three trial batches while in second step and third step concentration of HPMC K15M and HPMC K100M is optimized by next three-three batches respectively. Amount of HPMC is optimized to 240mg. The drug release of all the optimized HPMC batches were evaluated for in-vitro drug release study in pH 6.8 phosphate buffer solution in comparison with marketed formulation. Drug identification was performed by melting point determination, FTIR, UV and solubility determination. After pre-compression and post-compression evaluation we get the appropriate result in B3, B6 and B9 batches. In-vitro drug release of this three batches was studied and compare with the marketed formulation. Formulation Batch B9 was very similar in drug release as compared to reference sustained release tablet of Metformin HCl. Hence batch B9 is optimized formulation. HPMC K100M was found to be effective hydrophilic polymer to develop sustained release Metformin HCl matrix tablet. With increase in concentration of hydrophilic polymer it sustained the drug release and PVP K30 binder gives appropriate hardness to tablet.
Keywords---sustained release tablet, hydrophilic, HPMC, PVP K30.

Introduction

The oral route of drug administration is the most effective and widely used method of drug delivery because of its high patient compliance, cost-effectiveness, flexibility in the design of dosage form and ease of production.\textsuperscript{1,2} However, this delivery approach has some physiological limitations including: a limited gastrointestinal transit time, an unpredictable level of gastric emptying which varies from person to person, and the presence of an absorption window for several drugs in the upper part of the gastrointestinal tract. Such difficulties prompted researchers to develop a delivery system called the gastro-retentive drug delivery system (GRDDS) which allows the medicament to stay in the stomach for a prolonged and predictable period of time.\textsuperscript{3,4} Sustained-release (SR) oral delivery systems are designed to achieve therapeutically effective concentrations of drug in systemic circulation over an extended period of time. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance.\textsuperscript{5,6}

Diabetes is a chronic disease, which occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Diabetes is a growing challenge in India with estimated 8.7% diabetic population in the age group of 20 and 70 years. Effective clinical maintenance of the type-II diabetic condition needs chronic treatment with oral hypoglycemic agents. The better control over the condition need better systemic availability of drug, maintenance of plasma concentration of drug and adherence of patient to standard treatment with better compliance.\textsuperscript{7}

Metformin HCl, the only available biguanide, remains the first-line drug therapy for patients with Type-II diabetes mellitus, acting by decreasing the hepatic glucose output and peripheral insulin resistance. It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50–60% with a relatively short plasma half-life of 6.2 hrs.\textsuperscript{8,9} The most commonly used method of controlling the drug release includes the drugs in a matrix system. Because of their flexibility hydrophilic polymer matrix system are widely used in oral controlled drug delivery to obtain desirable drug release profile, cost effectiveness, and regulatory acceptance. The overall objective of this study was to develop matrix SR tablets of Metformin HCl using hydrophilic polymers which will control drug release.

Materials and Methods

Metformin HCl was received as gift sample while all other chemicals of analytical grade were procured from the market.

Preformulation studies

Drug Identification and Characterization\textsuperscript{10, 11}
• Melting Point Determination
• Fourier Transform Infra-Red (FTIR) analysis
• UV Spectrophotometric Analysis
• Solubility determination

**Preparation of Granules and Optimization of formulation**

**Preparation of Granules for Compression:**

Sustained release Metformin HCl matrix tablet were prepared by wet granulation technique. Different formula was designed using varying hydrophilic polymers and its concentration as well as its binder concentration. Weigh accurately Metformin HCl, HPMCK100M and Avicel as per composition and passed through sieve and mixed homogeneously. Prepare the wet mass of this mixture by blending solution. Wet mass passed through a sieve to get a uniform size granules and dried at 60°C. The obtained granules mixed with magnesium stearate, Aerosil. After evaluation of pre-compression parameters, compression was done on 8 stations single rotary press machine. Formulations were evaluated for post compression parameters.

**Table 1**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity / Tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B1</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>500</td>
</tr>
<tr>
<td>HPMC K4 M</td>
<td>160</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K100 M</td>
<td>-</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>145</td>
</tr>
<tr>
<td>PVP K30</td>
<td>15</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>10</td>
</tr>
<tr>
<td>Aerosil</td>
<td>5</td>
</tr>
<tr>
<td>Avicel</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>850</td>
</tr>
</tbody>
</table>

**Evaluation of Pre-compression Parameters:**

**Bulk density:** Bulk Density was determined using following formula

\[
BulkDensity = \frac{M}{V_b}
\]

Where, \(M\) = mass of powder taken (g) and \(V_b\) = bulk Volume (cm3)

**Tapped density:** Tapped density was calculated using following formula

\[
TappedDensity = \frac{M}{V_t}
\]
Where, \( M \) = mass of powder taken (g) and \( V_t \) = tapped volume (cm\(^3\))

**Carr’s Index or Compressibility index:** It was calculated from bulk density and
tapped density as per following formula

\[
Carr's\ Index = \frac{Tapped\ Density - \text{bulk}\ density}{Tapped\ Density} \times 100
\]

**Hausner Ratio:** Ratio of tapped density to bulk density is also a measure of flow
properties and is termed as Hausner ratio.

\[
Hausner\ ratio = \frac{Tapped\ Density}{Bulk\ Density}
\]

**Angle of repose:** Angle of repose is determined by funnel method using following
formula.

\[
\tan \theta = \frac{h}{r}
\]

\( h \) = height of the pile and \( r \) = radius of powder cone

**Evaluation of Post compression Parameters:** \(^{15,\ 16}\)

- **Weight variation:** Twenty tablets were weighed individually and average
  weight was determined. The individual tablet weight was compared with
  average tablet weight. For sustained release tablet, tablet weight is 900.00
  mg and the maximum percent difference allowed is 5.0% i.e. \( \pm 45.00 \) mg.

- **Friability Test:** Friability for the sustained release tablets was determined
  by 100 revolutions at 25 rpm. Friability of the tablets should be less than
  1%.

- **Hardness:** Tablet was selected at random from individual formulations and
  hardness was measured using digital hardness tester.

- **Dissolution Test:** The tablets were evaluated for *in vitro* drug release was
  carried out using USP dissolution apparatus.

The following conditions were applied.

- **USP Dissolution apparatus:** Type II (Paddle)
- **Media:** pH 6.8 buffer
- **Volume of dissolution medium:** 900 ml
- **Speed of paddle rotation:** 75 RPM
- **Temperature:** 37\( \pm \) 0.5\(^\circ\)C
- **Sampling point:** 1, 2, 4, 6, 8, 10 and 12 hours

The dissolution profiles of test batches were compared with marketed product. Comparison between marketed product and test batches was done using two
statistical factors called difference factor (f1) & similarity factor (f2). The difference
factor (f1) calculate the percentage difference between two profiles i.e. standard
dissolution profile & test sample dissolution profile at each sampling points and
corresponds to a relative error measure between the two profiles. f1 value should
lie between 0 and 15. Ideally it should be as closer as possible to 0.
The similarity factor ($f_2$) was defined by CDER and FDA as the logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and the reference products. It was calculated from the mean dissolution data according to the following equation.

$$F_2 = 50 \times \log \left[1 - \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{0.5} \times 100$$

- $n$ - No. of time points
- $R_t$ - The reference profile at the time point $t$
- $T_t$ - The test profile at the same point.

**Result and Discussion**

**Drug Identification and Characterization**

- Melting point determination: Melting point of the drugs was found 223-226°C.
- *Fourier Transform Infra-Red (FTIR) analysis: A FT-IR spectrum of pure drug as shown in figure.*

FTIR of Metformin HCl showed characteristic sharp peaks at 3194, 3306, 3395 cm$^{-1}$ due to N-H stretching vibrations, 1064.74 & 1172.76 cm$^{-1}$ corresponding to C-N stretching, 656.88 cm$^{-1}$ due to N-H wagging. The peaks observed in the FTIR spectra of pure drug were found to be matching with reported values for Metformin HCl thus confirming identity and purity of drug.

**UV Spectrophotometric Analysis**

**Calibration Curve**

The calibration curves of Metformin HCl in pH 6.8 Phosphate buffer solution pH 6.8 at 232nm were developed and absorbance values are given in Tables. It was found to obey Beer’s law in prepared concentration range 5-30 µg/ml.
Table 2
Standard calibration curve of Metformin HCl in pH 6.8 phosphate buffer

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Concentration (µg/ml)</th>
<th>Abs ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>0.268 ± 0.015</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>0.511 ± 0.018</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>0.769 ± 0.028</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>1.022 ± 0.013</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>1.277 ± 0.048</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>1.521 ± 0.072</td>
</tr>
</tbody>
</table>

Figure 2. Calibration Curve of Metformin HCl in 6.8 phosphate buffer

Optimization of Formulation

Pre-compression parameter evaluation:

Table 3
Evaluation of pre-compression parameter

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Angle of Repose</th>
<th>Bulk Density(g/ml)</th>
<th>Tapped Density(g/ml)</th>
<th>Carr's Index (%)</th>
<th>Hausner Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27.59</td>
<td>0.8169</td>
<td>0.9541</td>
<td>14.38</td>
<td>1.1679</td>
</tr>
<tr>
<td>2</td>
<td>26.00</td>
<td>0.8064</td>
<td>0.9293</td>
<td>13.22</td>
<td>1.1524</td>
</tr>
<tr>
<td>3</td>
<td>25.51</td>
<td>0.7861</td>
<td>0.8992</td>
<td>12.57</td>
<td>1.1438</td>
</tr>
<tr>
<td>4</td>
<td>27.07</td>
<td>0.8143</td>
<td>0.9433</td>
<td>14.22</td>
<td>1.1657</td>
</tr>
<tr>
<td>5</td>
<td>26.02</td>
<td>0.8064</td>
<td>0.9259</td>
<td>12.49</td>
<td>1.1526</td>
</tr>
<tr>
<td>6</td>
<td>25.01</td>
<td>0.7886</td>
<td>0.8896</td>
<td>11.35</td>
<td>1.1280</td>
</tr>
<tr>
<td>7</td>
<td>27.07</td>
<td>0.8116</td>
<td>0.9328</td>
<td>12.99</td>
<td>1.1493</td>
</tr>
<tr>
<td>8</td>
<td>26.00</td>
<td>0.8012</td>
<td>0.9191</td>
<td>12.82</td>
<td>1.1471</td>
</tr>
</tbody>
</table>
Post-compression parameter evaluation:

Table 4
Evaluation of post compression parameter

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Avg. Tab Wt. (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (Kg/cm²)</th>
<th>Assay (%)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>852 ±1.52</td>
<td>7.00 ±0.01</td>
<td>7.6</td>
<td>99.6</td>
<td>0.56</td>
</tr>
<tr>
<td>2</td>
<td>853 ±1.33</td>
<td>7.10 ±0.02</td>
<td>7.7</td>
<td>101.3</td>
<td>0.48</td>
</tr>
<tr>
<td>3</td>
<td>848 ±1.52</td>
<td>6.90 ±0.01</td>
<td>7.9</td>
<td>100.5</td>
<td>0.42</td>
</tr>
<tr>
<td>4</td>
<td>854 ± 1.15</td>
<td>7.10 ±0.01</td>
<td>7.3</td>
<td>98.8</td>
<td>0.52</td>
</tr>
<tr>
<td>5</td>
<td>851 ± 1.76</td>
<td>7.00 ±0.01</td>
<td>7.4</td>
<td>100.2</td>
<td>0.47</td>
</tr>
<tr>
<td>6</td>
<td>849 ± 1.15</td>
<td>7.00 ±0.01</td>
<td>7.8</td>
<td>102.6</td>
<td>0.43</td>
</tr>
<tr>
<td>7</td>
<td>854 ± 1.45</td>
<td>7.10 ±0.01</td>
<td>7.6</td>
<td>98.9</td>
<td>0.51</td>
</tr>
<tr>
<td>8</td>
<td>851 ± 1.20</td>
<td>7.00 ±0.01</td>
<td>7.8</td>
<td>99.7</td>
<td>0.47</td>
</tr>
<tr>
<td>9</td>
<td>849 ± 0.88</td>
<td>6.90 ±0.01</td>
<td>7.9</td>
<td>100.2</td>
<td>0.39</td>
</tr>
</tbody>
</table>

In-vitro Drug release

Percent Cumulative drug release was evaluated for trial batches prepared by using different types of hydrophilic polymers and concentration as well as varying concentration of binder in comparison with marketed sustained release tablet of Metformin HCl. The Drug release for B3, B6 and B9 batch was slow as compared to remaining trial batches. In-vitro drug release of Metformin HCl in B6 and B9 batch was comparable to release profile of marketed formulation. But, Similarity factor f1 and f2 calculation showed that formulation B9 was very similar in drug release as compared to reference sustained release tablet of Metformin HCl.

Table 5
Dissolution profiles

<table>
<thead>
<tr>
<th>Time in hours</th>
<th>Reference</th>
<th>B7</th>
<th>B8</th>
<th>B9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27.92</td>
<td>32.14</td>
<td>29.28</td>
<td>28.62</td>
</tr>
<tr>
<td>2</td>
<td>44.46</td>
<td>48.9</td>
<td>46.36</td>
<td>45.24</td>
</tr>
<tr>
<td>4</td>
<td>67.64</td>
<td>71.26</td>
<td>69.68</td>
<td>66.76</td>
</tr>
<tr>
<td>6</td>
<td>81.48</td>
<td>89.42</td>
<td>84.72</td>
<td>81.24</td>
</tr>
<tr>
<td>8</td>
<td>91.28</td>
<td>96.38</td>
<td>92.58</td>
<td>90.34</td>
</tr>
<tr>
<td>10</td>
<td>99.12</td>
<td>99.98</td>
<td>99.76</td>
<td>98.96</td>
</tr>
<tr>
<td>F1 similarity factor</td>
<td>4.36</td>
<td>1.74</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>F2 similarity factor</td>
<td>69.62</td>
<td>83.92</td>
<td>96.42</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

The purpose of the present study was to formulate and evaluate sustained release matrix tablet of Metformin HCl containing Hydroxyl propyl Methylcellulose as hydrophilic polymer and PVP K30 binder. Sustained release tablets were prepared by wet granulation technique. In first step, concentration of HPMC K4M is optimized by preparing three trial batches while in second step and third step concentration of HPMC K15M and HPMC K100M is optimized by same way. Amount of HPMC and PVP K30 is optimized. The drug release of all the optimized HPMC batches were evaluated for in-vitro drug release study in pH 6.8 phosphate buffer solution in comparison with marketed formulation. Formulation B9 was selected as optimum formulation for showing sustained drug release 98.96% at 10 hours. Obtained result conclude that, when concentration of HPMC increases it forms good matrix for controlling the release rate of Metformin HCl and HPMC K100M is the best hydrophilic polymer for sustained release matrix tablet.

References

2. Sudarshan B. Kakad, and Dr. Punit R. Rachh, A review on Bi-layer tablet: an emerging trend, European Journal of Pharmaceutical and Medical Research, 2019,6(8), 223-229


