Formulation and Evaluation of Floating Tablet of Gliclazide using HPMC and Xanthan Gum

Vilas S Jadhav*, Pankaj Chandratreya
Swami Vivekananda University, Sagar MP, Indeus Life Sciences Pvt Ltd, Mumbai, Maharashtra, India

Abstract: The objective of this study is to develop floating drug delivery system; specially floating tablet of Gliclazide. Gliclazide is a selective second generation sulphonylurea used in treatment of hyperglycemia and it absorbs rapidly and completely. However its absorption is erratic in diabetic patient due to its impaired gastric motility or gastric emptying. To overcome these drawbacks, the present investigation was to develop a gastro retentive floating tablets of gliclazide. Certain formulations containing retardant materials such as hydroxypropyl methyl cellulose K100LVCR (HPMC) and Xanthan gum, sodium bicarbonate was used as a gas generating agent to reduce floating lag time and other release promoters. The tablets were evaluated for physical characteristics like hardness, weight variation, and friability. In vitro release of drug was performed using 7.4 pH phosphate buffer and dissolution was done for 12hrs. All the physical characters were acceptable and within limits.

Key words – Gliclazide, HPMC, Xanthan gum, Disintegration time; drug release.

Introduction

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms. During the last decade, many studies have been performed concerning the sustain release dosage forms of drug, which have aimed at the prolongation of gastric emptying time (GET).

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus; small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

Gliclazide is an effective oral antidiabetic agent that belongs to the sulfonylureas drug class and is widely prescribed in the management of Non insulin dependent (Type II) diabetes mellitus. It is poorly soluble in aqueous fluids and is majorly absorbed from stomach. Gastro retentive controlled release drug delivery system are needed for gliclazide to enhance its oral bioavailability and also for better control of blood glucose levels to prevent hypoglycaemia to enhance clinical efficiency and patient compliance. Floating tablets of gliclazide were designed in the present study to enhance its bioavailability and to achieve controlled release over 24 h for once a day administration. Floating tablets of gliclazide were designed HPMC K 100 LVCR as matrix formers, sodium bicarbonate as gas generating agent and xanthan gum as floating enhancer. Tablets prepared were evaluated for floating and drug release characteristics.
Materials and method

Materials

Gliclazide was obtained from Bal Pharma, Avicel PH 102 and Xanthan gum was obtained from Signet Chemical Corporation, Mumbai. Aerosil 200 was obtained from Evonik Mumbai and Sodium bicarbonate was procured from Junbunzlor.

Methods

Gliclazide modified release floating tablets were prepared by wet granulation method. Compositions of various formulations are shown in Table 1. The matrix floating tablet of gliclazide were prepared using HPMC K 100 LVCR as release modifying agent and xanthan gum as floating enhancer agent.

Gliclazide and Avicel were sifted through 40 mesh and loaded 3L RMG. Materials were mixed for 10 minutes at 600RPM. Weighed 150 g purified water in glass beaker. Weighed quantity of purified water was added in dry mixed materials at 300RPM of impeller in 3 minutes followed by kneading for 2 more minutes at 500RPM of impeller and 2800 RPM of chopper. Granulated material passed through 8# mesh. Passed materials were dried at 55°C till % LOD was NMT 1%. Wet granulation of all trials were done using fixed quantity of Avicel in the formulation, refer table one was showing formulation composition for all trials.

Table 1 Optimization of Betacyclodextrin quantity.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliclazide</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>425</td>
<td>450</td>
<td>475</td>
<td>500</td>
<td>550</td>
<td>600</td>
</tr>
</tbody>
</table>

A granule prepared by wet granulation was milled through 2.0mm multimill screen at medium speed. HPMC K 100LVCR, Xanthan gum, Sodium bicarbonate and aerosil pharma 200 were sifted through 40 mesh manually. Further milled granules and sifted material were blended in 5L blender for 15 minutes at 10 RPM. For lubrication, magnesium stearate sifted through 40 mesh and lubricated with blended materials for 3 minutes at 15 RPM.

Table 2 Blending:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliclazide and Avicel granules</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>HPMC K 100LVCR</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>Xanthan gum</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>Aerosil Pharma 200</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>210</td>
<td>230</td>
<td>250</td>
<td>270</td>
<td>290</td>
<td>310</td>
</tr>
</tbody>
</table>

Evaluation of pre compression parameters

Bulk and Tapped density

Before final compression of tablets, powdered mixture was subjected to pre compression parameters such as bulk density, tapped density, angle of repose, powder compressibility and Hausner ratio. All the experiments were done in triplicates and expressed as mean± SD.

Bulk Density

Bulk density was determined by measuring the volume of the predetermined or preweighed mass of the powder blend according to the protocol described.

Bulk Density (Db) = (M) / (Vo)                    \[1, 2\]

Where,
M = Mass or weight of the powder blend
Vo = Apparent volume of the powder blend into the cylinder
Tapped Density

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder was mechanically tapped and volume readings were taken until little further volume change was observed. The mechanical tapping was achieved by raising the cylinder and allowing it to drop under its own weight from a specified distance.

\[
\text{Tapped density (Dt)} = \frac{M}{V_f} \quad \text{[3]}
\]

Where,
- \(M\) = Mass or weight of the powder blend
- \(V_f\) = Final volume of the powder blend into the cylinder.

Carr’s Index or Compressibility Index (I)

This was calculated by the formula and expressed as percentage (%)

\[
I = \frac{Dt - Db}{Dt} \times 100\% \quad \text{[4]}
\]

Where
- \(Db\) = Bulk density,
- \(Dt\) = Tapped density.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula-

\[
\text{Hausner Ratio} = \frac{Dt}{Db} \quad \text{[5]}
\]

Where,
- \(Db\) = Bulk density,
- \(Dt\) = Tapped density.

Angle of Repose

The determination of angle of repose of powder blend was carried out by employing fixed funnel method.

\[
\text{Angle of Repose} = \tan^{-1}\left(\frac{H}{R}\right) \quad \text{[6]}
\]

Where,
- \(H\) = height of the pile,
- \(R\) = radius of the pile.

Evaluation of post compression

These tests are as following:-

- Appearance
- Thickness
- Hardness
- Weight variation
- Friability
- Dissolution
- Drug content
- Stability studies

Appearance

The general appearance of tablet is its visual identity and all over elegance, shape, color, surface textures. These all parameters are essential for consumer acceptance. Tablets have smooth, clean surface, round concave shaped, white color tablet with pleasant taste.

Thickness:

The thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets selected were used for determination of thickness that expressed in Mean± SD and unit is mm.
Weight variation:

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated [6,7].

Friability test:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Roche friabilator is rotated at 25rpm for 4 minutes for 100 rounds. The tablets were dedusted and weighed again. The percentage weight loss was calculated using the formula [6,7].

\[
\% f = \frac{W0 - W1}{W0} \times 100
\]

Here, \(\% f\) = Percentage friability

\(W0\) = Initial weight (Before test)

\(W1\) = Final weight (After test)

Drug content:

10 tablets were powdered and 100mg drug equivalent powder dissolved in suitable media 0.1N HCl. Volume of the solution made up to 100ml by that media. Solution was filtered and diluted 100times and analyzed spectrophotometrically and further calculation carried out to determine drug content in one tablet [6,7].

In vitro dissolution studies

The drug release study was performed using USP I basket apparatus at 37\(\pm1\)\(^{\circ}\)C and 100 rpm using 900 ml of is phosphate buffer (pH 7.4) Sample of 5 ml were withdrawn at predetermined time interval and filter through 0.45 micron membrane filter, diluted suitable and analyzed at 225nm. Percentage drug dissolved at different time intervals was calculated using BeersLambert’s law equation. [7,8].

Stability Study:

The stability of samples was monitored upto 3-month at ambient temperature and relative humidity(30\(^{\circ}\)C/65% RH). Periodically samples were removed and characterized for disintegration time, hardness, drug-content and dispersion time.

Results and Discussion

Flow Properties of Granules:

Angle of Repose of Granules: All batches were evaluated for flow property. The results of all the batches were shown in table 3.

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Angle of Repose((^{\circ}))</th>
<th>Carr’s Index (%)</th>
<th>Hausner’s Ratio(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>28.56</td>
<td>14.2</td>
<td>1.16</td>
</tr>
<tr>
<td>F2</td>
<td>29.25</td>
<td>15.6</td>
<td>1.18</td>
</tr>
<tr>
<td>F3</td>
<td>28.10</td>
<td>12.8</td>
<td>1.17</td>
</tr>
<tr>
<td>F4</td>
<td>27.90</td>
<td>12.6</td>
<td>1.18</td>
</tr>
<tr>
<td>F5</td>
<td>29.36</td>
<td>16.6</td>
<td>1.24</td>
</tr>
<tr>
<td>F6</td>
<td>28.56</td>
<td>17.1</td>
<td>1.25</td>
</tr>
</tbody>
</table>

From the results of flow properties of the all batches, it is concluded that all batches had good flow property.
Post compression parameters

The powder blend was compressed using 4 station compression machine. Tablets prepared by using mentioned formula have found to be good without any chipping, capping and sticking. Various physical parameters like thickness, hardness, weight variation, friability, hardness, dissolution were measured to evaluate tablets. All the formulations have therefore thought to show the acceptable physical parameters of tablets.

Table 4: Post Compression parameters

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Weight variation</th>
<th>Thickness</th>
<th>Hardness</th>
<th>Friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>210±0.74</td>
<td>3.10±0.09</td>
<td>80±0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>F2</td>
<td>230±0.33</td>
<td>3.20±0.11</td>
<td>88±0.15</td>
<td>0.241</td>
</tr>
<tr>
<td>F3</td>
<td>250±0.28</td>
<td>3.35±0.21</td>
<td>85±0.42</td>
<td>0.199</td>
</tr>
<tr>
<td>F4</td>
<td>270±0.30</td>
<td>3.50±0.19</td>
<td>90±0.60</td>
<td>0.185</td>
</tr>
<tr>
<td>F5</td>
<td>290±0.85</td>
<td>3.60±0.15</td>
<td>90±0.56</td>
<td>0.248</td>
</tr>
<tr>
<td>F6</td>
<td>310±1.18</td>
<td>3.80±0.18</td>
<td>95±0.29</td>
<td>0.126</td>
</tr>
</tbody>
</table>

Table 5: Post Compression Evaluation

<table>
<thead>
<tr>
<th>Batch No.</th>
<th>Floating lag time</th>
<th>Floating time (hours)</th>
<th>% drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>18</td>
<td>12</td>
<td>99.5</td>
</tr>
<tr>
<td>F2</td>
<td>19</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>F3</td>
<td>16</td>
<td>12</td>
<td>99.9</td>
</tr>
<tr>
<td>F4</td>
<td>14</td>
<td>12</td>
<td>99.8</td>
</tr>
<tr>
<td>F5</td>
<td>20</td>
<td>&gt;15</td>
<td>100.2</td>
</tr>
<tr>
<td>F6</td>
<td>19</td>
<td>&gt;15</td>
<td>99.8</td>
</tr>
</tbody>
</table>

In-vitro drug release:

Dissolution parameter: Medium: pH 7.4 Phosphate buffer
Volume: 900 ml
Apparatus: USP Type I
Speed: 50 rpm
Time Point: 1,2,4,8 and 12 hours.
Temperature: 37°C
Identification: At 225.1 nm in UV-Visible spectrophotometer

Table 6: In-vitro drug release profile of batches F1 to F6

<table>
<thead>
<tr>
<th>Time in min</th>
<th>Cumulative % drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch no</td>
<td>F1</td>
</tr>
<tr>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
</tr>
</tbody>
</table>
Discussion

The present study was aimed at not only to improve the release of drug, gliclazide, in the acidic pH, but also to release the drug in controlled fashion. Also, to make the formulation remain in the stomach for a longer period of time, gastro retentive dosage form was designed, to make the therapy more effective as the drug is known for incomplete absorption in diabetic patients as explained before. The polymers used in the formulation are well-established polymers for the said dosage form. The roles of polymers are to control the release as well as to make the formulation buoyant. The tablets were prepared by direct compression method after mixing the ingredients with the help of mortar and pestle. The granules of different formulations were evaluated for angle of repose, compressibility index, and drug content. The results of angle of repose indicate reasonably good flow property of granules. The compressibility index values in the range of 12.7 to 17.1 (<25), further support flow property of granules. The drug content of all the formulations was found to be more or less uniform. Tablets of all the formulations were subjected to many in-process parameters evaluation such as physical appearance, thickness, content uniformity, weight variation, hardness, and friability tests. Also, the tablets were circular in shape with no visible cracks with smooth appearance. Weight variation test revealed that the tablets were within the range of pharmacopoeial limit. Good uniformity in drug content was found among different formulations of the tablets, and the percentage drug content was more than 98%. All the formulations showed reasonably good hardness value. Further, to strengthen these values, friability test values are also considered. The weight loss of less than 1% in friability test is considered as acceptable value for conventional tablet. This indicates that the tablets can withstand the mechanical shocks reasonably well during handling. Formulations were prepared by different concentrations of HPMC K100LVCR and xanthan gum polymers. All the polymers were chosen as they are well-established in the similar studies and have good swelling properties. The rate of swelling of polymer depends upon the amount of water taken up by polymer. Sodium bicarbonate is added in the formulation which upon contact with carbon dioxide and expels from the dosage form creating pores through which water can penetrate into the dosage form and increase wetting. Formulations F5 has been selected as the best formulation among all the other formulations. Formulation F5 provides better invitro release. The data obtained from invitro release studies were fitted to various mathematical models like Higuchi, Peppas model, first order, the best fit model in all the cases. The release was found to be non–fickian as the n value for m3 and g3 was found to be 0.52, 0.51. The formulation was found to follow first order.

Stability study:

Three months stability study at ambient temperature and relative humidity (30 °C / 65% RH) of formulation F5 revealed that the formulation was stable and there were no significant changes observed for hardness, drug content and disintegration time. Hence, the results of stability studies reveal that the developed formulation has good stability.

References


*****