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A comparative in vitro drug release prospective with two different polymers for the development of floating single unit dosage form of imatinib mesylate for chronic myelogenous leukemia

Kombath R Vinod¹, Vasa Santosh¹, Subhadora Sandhya², Banji J Otilia³, Banji David³, Anugu Padmasri¹

¹. Department of Pharmaceutics, Nalanda College of Pharmacy, Nalgonda, AndhraPradesh, India; ². Department of Pharmacognosy, Nalanda College of Pharmacy, Nalgonda, AndhraPradesh, India; ³. Department of Pharmacology, Nalanda College of Pharmacy, Nalgonda, AndhraPradesh, India.

Correspondence/Correspondencia: Kombath R Vinod
HOD, Department of Pharmaceutics, Nalanda College of Pharmacy, Nalgonda, AndhraPradesh- 508001, India.
Telf: #91 9010055004
Fax: #91 8682 24547
Email: vinodkrpharm@gmail.com

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Aim: The purpose of this investigation was to prepare a gastroretentive drug delivery system of Imatinib mesylate.

Materials and Method: Floating tablets of imatinib mesylate were prepared employing HPMC K4M and HPMC K15M by effervescent technique; these grades of HPMC were evaluated for their gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and dissolution studies.

Results: The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good in vitro buoyancy. The tablet swelled radially and axially during in vitro buoyancy studies. It was observed that the tablet remained buoyant for >12 hours. The tablets with HPMC K4M were found to float for longer duration as compared with formulations containing HPMC K15M. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed. From the radiographic pictures obtained at different time intervals, it has been proved that that the tablet was floating during the observed time intervals up to 6h against all peristaltic movements.

Conclusion: Gastric retention of Imatinib mesylate unit dosage form was achieved by floatation. HPMC K4 gave better release up to 98.4% in 12 hrs. All the gastroretentive floating tablets showed good floatation during the period of drug release, and the drug release was found to follow non-fickian diffusion type.

KEY WORDS: Imatinib mesylate, gastroretention, floating tablets, in vitro buoyancy.
INTRODUCTION

Imatinib mesylate is a protein-tyrosine kinase inhibitor; inhibits the abnormally functioning Bcr-Abl tyrosine kinase, which is produced by the Philadelphia chromosome abnormality found in chronic myeloid leukemia (CML). This drug inhibits cell proliferation and induces apoptosis (programmed cell death) in the Bcr-Abl cell lines and in the leukemic cells generated by CML, inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation. More recently, the imatinib has been approved for the treatment of mesenchymal cell neoplasms of the intestinal tract. It has now been discovered that Imatinib mesylate can be used as a treatment for patients suffering from hepatic fibrosis based on its ability to down regulate stellate cell activation in culture and in vivo. The usual oral recommended dose of Imatinib for humans is between 50 and about 1600 mg/day, in two or four doses. The formulations provide rapid dissolution of the active ingredient that in turn results in its rapid increase in blood plasma levels above the therapeutic steady state levels, immediately after administration followed by a decrease in blood plasma levels up to subtherapeutic plasma levels after about twelve hours following oral administration, thus requiring additional dosing with the drug in accelerated or blast crisis phase of CML.

As Imatinib mesylate is very slightly soluble to insoluble in neutral/alkaline region of intestine where its absorption is maximum, it is not absorbed to the same extent once it passes the upper small intestine, especially with the conventional dosage forms. Imatinib must be continuously released in the stomach before it reaches the absorption window thus ensuring optimal bioavailability.4-7. Ironically, there is no reported work on Imatinib as gastroretentive dosage form. Hence, there is a call for developing a new formulation and its process for imatinib that maintains optimum therapeutic steady state plasma concentrations to avoid inter-patient variability and side effects by maintaining dosage form for 12 hours in the gastric region by designing controlled release gastroretentive drug delivery system, and therefore, research efforts have been focused on development of gastric retention platforms.

In the present investigation, floating tablets of Imatinib mesylate were prepared by effervescent approach using HPMC K4M and HPMC K15M. The aim of the work was to evaluate the effect of gel-forming polymer HPMC on floating properties and release characteristics of the prepared tablets.

MATERIALS AND METHODS

Materials

Imatinib mesylate was received as a generous gift sample from Dyssymetric Labs Pvt. Ltd, Hyderabad, India. HPMC K4M and HPMC K15M were received as gift samples from Dyssymetric Labs Pvt. Ltd, Hyderabad, India. Magnesium stearate, hydrochloric acid, Microcrystalline cellulose and sodium bicarbonate were purchased from SD Fine-Chem Ltd, Ahmedabad, India. Purified talc was purchased from E. Merck (India) Ltd., Mumbai. All other ingredients were of laboratory grade.

Formulation of imatinib mesylate tablets

The Compositions of different formulation trials with different polymers were presented in the Table 1. Accurately weighed quantities of polymer, avicel were taken in a mortar and mixed geometrically. To this mixture required quantity of Imatinib mesylate was added and mixed slightly with pestle. This mixture was passed through 40# and later collected in a plastic bag and blended for 5 min. To this required amount of sodium bi carbonate and were added and again mixed for 5 min. Later required quantity of magnesium stearate, and talc were added and the final blend was again passed through 40#. Thus obtained blend was mixed thoroughly for 10 min and compressed into tablets with a same force using single punch tablet machine (Cadmach Machinery Ltd., Ahmedabad, India). The tablets were round and flat with an average diameter of 12.0 ± 0.1 mm and a thickness of 3.2 ± 0.2 mm.

FTIR study

Drug interaction studies were undertaken by Perkin-Elmer FTIR study to know the presence of any interaction of the drug with excipients used for preparing the tablets. For this the samples containing pure drug alone, formulation containing HPMC K4M, formulation containing HPMC K15M were analyzed in the spectral range 400 to 4000 Cm⁻¹ using KBr pellet technique.

Flow properties of powder blend

The flow properties of powder blend (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio. 7.

\[
\text{Angle of repose } \Theta = \tan^{-1} \left( \frac{h}{r} \right)
\]

Where h is height of the pile and r is the radius of its base of pile. Hausner ratio (HR) and Carr index (IC) were calculated according to the two equations given below:

\[
\text{HR} = \frac{\rho_t}{\rho_b} \quad \text{IC} = \frac{(\rho_t - \rho_b)}{\rho_t}
\]

Where \(\rho_t\)- tapped density and \(\rho_b\)- bulk density.
Characterization and evaluation of floating tablets

The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester), friability using 10 tablets (Roche type friabilator), drug content, in vitro buoyancy and in vitro dissolution studies. The results were expressed as mean ± S.D. (n = 5). The in vitro buoyancy and floating lag time was determined by following procedure, the tablets were placed in a 100 ml beaker containing pH 3 dissolution media. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time for which the dosage form constantly remained on the surface of medium was taken as the total floating time.

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45μ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 236nm using 0.1 N hydrochloric acid as blank.

The release rate of Imatinib mesylate from floating tablets were determined using USP Dissolution Testing Apparatus 2 (paddle method; ELECTROLAB TDT-08L, Mumbai). The dissolution test was performed using 900ml of pH 3 dissolution media, at 37 ± 0.5°C and 50 rpm. Aliquots of 1 mL were withdrawn from the dissolution apparatus hourly and the samples were replaced with same volume of fresh dissolution medium. The samples were filtered through a 0.45μ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 236 nm using a UV/V is spectrophotometer (ELICO SL 159, Mumbai Indian Equipment Corporation, Mumbai). Cumulative percentage drug release was calculated and the same was plotted against time. Statistical analysis was carried out by using “GraphPad Instat” software. All the experimental data were expressed as mean ± SD.

Kinetic assessment

To study the nature and release pattern of the drug, model fitting curves were used.

Zero order model, \( M_t = M_0 + k_0 t \). Graph was plotted \( M_t/100 Vs t \)
First order model, \( M_t = M_0 e^{-kt} \). Graph was plotted \( \log M_t Vs t \)
Higuchi model, \( M_t = M_0 t^{\frac{1}{2}} \). Graph was plotted \( \log M_t Vs t^{\frac{1}{2}} \)
Korsmeyer- Peppas model, \( M_t/M_0 = k'_t^n \). Graph was plotted \( \log M_t/100 Vs \log T \)

Where \( M_t \) is the amount of drug released in time t, \( M_0 \) is the initial amount of the drug, \( k_0 \) is the zero order release constant, \( k_0 \) is the first order release constant, \( k' \) is the Higuchi rate constant, \( k' \) is the Korsmeyer- Peppas release constant and \( n \) is the release exponent that characterizes the mechanism of drug release.

Radiographic studies

Institutional animal ethical committee certificate (NCOP/IAEC/approved/11/2010) was obtained prior to the commencement of pharmacological studies. After overnight fasting, six healthy rabbits were taken and fed lightly. The tablets were given orally and allowed to take adequate amount of water ad libitum. Water was given ad libitum. Radiographs were obtained at different time intervals like before the administration of tablet, 30min, 3rd h, 6th h and after 24th h.

RESULTS

The FTIR spectral graphs of pure drug (fig 1a) and formulations with two different grades of HPMC (K4M and K15M) are shown in figure 1A and 1B respectively. The powder blend prepared for compression of floating tablets was evaluated for their flow properties (Table 2). Angle of repose was in the range of 27.6° to 29.3° with powder blend containing HPMC K4M and 26.7° to 28.7° with HPMC K15M. Bulk density ranged between 0.56 to 0.58 gm/cm³ with powder blend containing HPMC K4M and 0.593 to 0.624 gm/cm³ with HPMC K15M. Tapped density

### Table 1. Composition of Floating Tablets of Imatinib mesylate

<table>
<thead>
<tr>
<th>Ingredients (mg per tablet)</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>Imatinib mesylate</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Avicel</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
<td>50</td>
<td>40</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>
ranged between 0.634 to 0.680 gm/cm\(^3\) with powder blend containing HPMC K4M and 0.667 to 0.692 gm/cm\(^3\) with HPMC K15M. Carr index and Hausner ratio were found to be in the range of 0.10 - 0.14 and 1.12 - 1.17 respectively for powder blend of different formulations.

**Evaluation of floating tablets**

The results of the physical characterization of the tablets of both the formulation are summarized in Table 3. The weight of the tablet varied between 223 mg to 232 mg for different formulations with low standard deviation values. The hardness for different formulations was found to be between 6.10 to 6.15 kg/cm\(^2\). The friability was below 0.5% for all the formulations. The drug content varied between 97.23 to 99.54 mg in different formulations. All the tablets were prepared by effervescent approach.

All the batches of tablets were found to exhibit short floating lag times in the range 64 to 122 s, for F1 and F3 respectively. The tablets with low-viscosity grade HPMC K4M exhibited short floating lag time and floated for longer duration as compared with formulations containing high viscosity grade HPMC K15M. This indicated that the molecular weight distribution or viscosity of the gel-forming polymer HPMC influenced the in vitro buoyancy.

The drug release from floating tablets was found to be 85.3 to 99.6% for F1 to F4 with HPMC K4M. The drug release from formulations containing high-viscosity grade HPMC K15M (F5 to F8) varied between 78.2 to 99.3%. The prepared formulations sustained the drug release for a period of > 12 hours. Comparing the two different grades of HPMC (K4M and K15M), it was found that F2 & F6 showed better release characteristics with excellent in vitro buoyancy.

**DISCUSSION**

The work was intended to prepare gastroretentive floating tablets using HPMC K4M and HPMC K15M in various proportions. FTIR spectrogram of pure drug Imatinib and two formulations of both grades of HPMC were comparable with respect to the peak intensity, revealed there is no interaction of the drug with the excipients used in the formulations. The flotation buoyancy of the tablets was achieved by effervescent technique using sodium bicarbonate. The magnesium stearate and talc were used as lubricant and glidant, respectively. Flow properties of granules are inevitable parameters in the preparation of tablet formulation. The values of flow properties of all parameters indicated that the prepared powder blend exhibited good flow properties, since the values were within the acceptable standard range.

The variation in weight was within the range of ± 5% complying with pharmacopoeia specifications, indicating uniformity in weight. Hardness and friability tests revealed satisfactory mechanical strength and good mechanical properties.

FTIR done as a part of preformulation studies indicates there is no pharmaceutical interaction.
Table 2. Flow properties of powder blend in the formulation of tablet

<table>
<thead>
<tr>
<th>Code</th>
<th>Angle of repose (°)</th>
<th>Bulk density (gm/cm³)</th>
<th>Tapped density (gm/cm³)</th>
<th>Hausner ratio (Hₚₙ)</th>
<th>Carr index (Iₖ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>28.7°</td>
<td>0.561 ± 0.032</td>
<td>0.652 ± 0.083</td>
<td>1.16</td>
<td>0.13</td>
</tr>
<tr>
<td>F2</td>
<td>29.3°</td>
<td>0.567 ± 0.045</td>
<td>0.634 ± 0.043</td>
<td>1.11</td>
<td>0.11</td>
</tr>
<tr>
<td>F3</td>
<td>27.6°</td>
<td>0.574 ± 0.058</td>
<td>0.674 ± 0.048</td>
<td>1.17</td>
<td>0.14</td>
</tr>
<tr>
<td>F4</td>
<td>28.1°</td>
<td>0.582 ± 0.026</td>
<td>0.652 ± 0.083</td>
<td>1.12</td>
<td>0.10</td>
</tr>
<tr>
<td>F5</td>
<td>28.4°</td>
<td>0.593 ± 0.053</td>
<td>0.667 ± 0.063</td>
<td>1.12</td>
<td>0.11</td>
</tr>
<tr>
<td>F6</td>
<td>27.9°</td>
<td>0.607 ± 0.057</td>
<td>0.679 ± 0.057</td>
<td>1.11</td>
<td>0.10</td>
</tr>
<tr>
<td>F7</td>
<td>26.7°</td>
<td>0.601 ± 0.048</td>
<td>0.682 ± 0.049</td>
<td>1.13</td>
<td>0.12</td>
</tr>
<tr>
<td>F8</td>
<td>28.7°</td>
<td>0.593 ± 0.043</td>
<td>0.692 ± 0.075</td>
<td>1.16</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Results are represented as mean ± SD; n=3.

Table 3. Physical evaluation parameters of imatinib mesylate tablets

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Weight variation (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Drug Content (%)</th>
<th>Drug release kinetic modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>224.60 ± 2.12</td>
<td>6.10 ± 0.24</td>
<td>3.38 ± 0.05</td>
<td>0.1</td>
<td>97.23</td>
<td>Peppas (0.9959)</td>
</tr>
<tr>
<td>F2</td>
<td>228.33 ± 1.45</td>
<td>6.15 ± 0.18</td>
<td>3.37 ± 0.06</td>
<td>0.27</td>
<td>99.12</td>
<td>Peppas (0.9891)</td>
</tr>
<tr>
<td>F3</td>
<td>225.80 ± 1.63</td>
<td>6.25 ± 0.37</td>
<td>3.28 ± 0.03</td>
<td>0.19</td>
<td>98.32</td>
<td>Zero order (0.9815)</td>
</tr>
<tr>
<td>F4</td>
<td>223.09 ± 2.43</td>
<td>6.45 ± 0.26</td>
<td>3.38 ± 0.04</td>
<td>0.22</td>
<td>99.54</td>
<td>Peppas (0.9919)</td>
</tr>
<tr>
<td>F5</td>
<td>226.05 ± 2.51</td>
<td>6.25 ± 0.54</td>
<td>3.33 ± 0.06</td>
<td>0.18</td>
<td>99.43</td>
<td>Peppas (0.9936)</td>
</tr>
<tr>
<td>F6</td>
<td>224.37 ± 3.89</td>
<td>6.18 ± 0.35</td>
<td>3.45 ± 0.06</td>
<td>0.21</td>
<td>98.67</td>
<td>Peppas (0.9966)</td>
</tr>
<tr>
<td>F7</td>
<td>229.09 ± 3.12</td>
<td>6.50 ± 0.48</td>
<td>3.38 ± 0.05</td>
<td>0.16</td>
<td>98.97</td>
<td>Peppas (0.9882)</td>
</tr>
<tr>
<td>F8</td>
<td>232.65 ± 2.20</td>
<td>6.45 ± 0.25</td>
<td>3.35 ± 0.25</td>
<td>0.16</td>
<td>98.28</td>
<td>Peppas (0.9925)</td>
</tr>
</tbody>
</table>

Results are represented as mean ± SD; n=3.

resistance of the tablet respectively. Drug content with low coefficient of variation indicated content uniformity in the prepared batches.

Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium ( pH 3 ). The sodium bicarbonate provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets.

The tablet swelled radically and axially during in vitro buoyancy studies. Fig 2: shows the floating nature of the tablets. The liberated gas must have trapped and protected within the gel, formed by hydration of polymer ( HPMC ), thus decreasing the density of the tablet below 1 and tablet became buoyant. From in vitro drug release profile of all the formulations could be better expressed by Korsemeyer-Peppas model as they showed a good linearity with ‘R’ value of 0.988-0.9961. F3 formulation alone was observed to follow zero order kinetics.

Figure 2. In vitro buoyancy test of Imatinib mesylate floating tablets in 0.1 N Hcl after 10 sec ( A ) 64 sec ( B ) 2 min ( C ) 4 hours ( D ) 8 hours ( E ) and 12 hours ( F ).

Floatation studies clearly demonstrates the dosage started submerging and floating in 64 sec and 2 min respectively and kept buoyant up to 12 hrs.
For the convenience of radiological studies and considering the comparatively narrow alimentary track, tablets were incorporated with barium sulphate as a radio-opaque agent and the size of the tablets were reduced. Adequate precautions were taken for the specially designed tablets to get comparative in-vitro buoyancy behavior with that of the original tablets in discussion. By reducing size of the tablet, authors claim that the gastroretentive behavior was achieved not by inability of the swollen tablet to leave the stomach, but rather with its floating properties. X ray was also taken prior to the per oral administration of the tablet to make sure that the observed opaque substance in the stomach of rabbit is due to the administered product but not some foreign matter already existed. From the radiographic pictures obtained at different time intervals, it has been proved that that the tablet was floating during the observed time intervals up to 6h. The position of the tablet was found to have distorted towards right but found to retain at the 8th thoracic vertebral. It can be hypothetically assumed that gel forming property of HPMC might have contributed for this floatation behaviour. The radiographic pictures are shown in Fig.3. It was also observed that tablet was cleared after 24 hours (Fig 3e). The tablet has overcome the peristaltic movements of the GIT and enabled to float for considerable time before emptying the gastric region. But while no in vitro – in vivo correlation was found at any period.

**CONCLUSION**

Gastric retention of Imatinib mesylate unit dosage form was achieved by floatation. HPMC K4 gave better release up to 98.4% in 12 hrs. It has to be concluded that objective of the present research in developing gastroretentive drug delivery system was achieved by formulating floating tablets of Imatinib mesylate. All the gastroretentive floating tablets showed good floatation during the period of drug release, and the drug release was found to follow non-fickian diffusion type. To achieve good gastroretention, floating dosage forms has to be taken along with plenty of water, and low viscous diet.

**ACKNOWLEDGMENTS**

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