Formulation And In Vitro Evaluation of Colon Targeted Matrix Tablets of Mebeverine Hydrochloride Using Natural Polymers

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ABSTRACT

BACKGROUND: The present study focuses on the design and evaluation of colon targeted matrix tablets of Mebeverine hydrochloride using natural gums like guar gum, xanthan gum at different concentrations. This novel approach is expected to be promising drug delivery system for delivering Mebeverine HCl to the colon for its local action and thereby minimizing systemic side effects of the drug. METHOD: The tablets were prepared by wet granulation method and the compressed tablets were evaluated for the hardness, uniformity of weight, friability, drug content and in vitro dissolution studies. RESULTS & DISCUSSION: All the physical characteristics evaluated for the tablets were found to be within the acceptable limits. Drug content was found to be in the range of 97.57±0.12 to 100.01±0.39% reflecting good uniformity within the batches of different tablets. The in vitro release study was performed in 0.1N HCl pH 1.2 for 2 hrs followed by phosphate buffer pH 6.8 up to 24 hrs. The optimized formulation F4 containing 40% of guar gum released less amount of drug in first 2 hrs in pH 1.2 compared to other formulations and showed controlled release over a period of 24 hrs. The drug release followed first order kinetics and the mechanism of drug release was found to be both diffusion and dissolution controlled. CONCLUSION: The result of the studies showed that colon targeted matrix tablet containing 40% of guar gum was most likely to provide targeting of mebeverine HCl for local action in the colon.

KEYWORDS: Colon Targeting, Guar Gum, Matrix Tablets, Mebeverine HCl, Xanthan Gum.

INTRODUCTION:

Irritable bowel syndrome (IBS) is one of the most frequently encountered disorders of the GIT that leads to abdominal pain, cramping, changes in bowel movements and other symptoms. Mebeverine is used to relieve symptoms of irritable bowel syndrome that are the result of spasms in the intestinal muscles. These include colicky abdominal pain and cramps, diarrhoea alternating with constipation. Mebeverine hydrochloride is a musculotropic antispasmodic agent with a direct action on the smooth muscle of the gastrointestinal tract especially colon. Mebeverine hydrochloride directly acts on the gut muscles at the cellular levels to relax them. It is having a short biological half-life of 2.5 hrs, plasma protein binding 75% and rapidly absorbed after oral administration with peak plasma concentration occurring in 1-3hrs[1].

Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn’s disease, carcinomas and infections) whereby high local concentration can be achieved while minimizing systemic side effects. Among the various systems developed for colon specific drug delivery, prodrug and polysaccharides based delivery systems rely upon the enzymatic degradation of the carriers in the colon, there by resulting in the drug release. The enzyme-trigger mechanism in such delivery systems makes them highly site-specific. A number of natural polysaccharides (chondroitin sulphate, guar gum, xanthan gum, locust gum, inulin, dextrins, starch, amylose and pectins) degraded by the human colonic flora have been investigated as colonic drug delivery carriers. Various authors have demonstrated the usefulness of pectin, calcium pectinate, chondroitin sulphate and guar gum as potential colon specific drug delivery systems [2-5]. These polymers remain undigested in the stomach and small intestine and are degraded by the vast anaerobic microflora of the colon.

Guar gum, a polysaccharide derivative with glycoside linkage has been used as matrix former for controlling the release of many drugs. Due to specific parameters of structural viscosity, guar gum can be applied in the technology of tablet production. In different formulations guar gum has been used as a binder and disintegrant. Guar gum is a hydrophilic polymer, which until recently had been limited for use
in gelation, thickening, suspending and as emulsifying agent[6]. Xanthan gum is a polysaccharide produced by a pure-culture aerobic fermentation of a carbohydrate with Xanthomonas campestris. The molecule consists of a backbone identical to that of cellulose, with side chains attached to alternative glucose residues. It is used in oral and topical pharmaceutical formulations as a suspending, thickening and stabilizing agent[7].

Thus the present investigation aimed at using natural polysaccharides for the colonic delivery of mebeverine hydrochloride in the form of matrix tablets.

MATERIALS AND METHODS

Materials:

Mebeverine HCl sample was obtained from RA Chem Pharma Ltd, Hyderabad. Guar gum and Xanthan gum were procured from Yarrow chem products, Mumbai. Lactose was procured from Molychem, Mumbai. All other reagents used were of analytical grade.

Characterization of drug and excipients

Fourier transform infrared spectroscopy (FTIR)

It was used to study the interactions between the drug and the polymer. The drug and the polymer must be compatible to produce a stable product. Drug and polymer interactions were studied by using FT-IR. IR spectra analysis of pure mebeverine HCl, mebeverine HCl with polymer and all other excipients were carried out. The peaks and the patterns produced by the pure drug were compared with the combination of polymer.

Preparation of matrix tablets:

The composition of different formulations of Mebeverine HCl matrix tablets is shown in Table 1. The ingredients were weighed accurately and mixed thoroughly. Granulation was done with a solvent blend of water and methanol (1:1). The wet mass was passed through sieve no.12 for the preparation of granules. The granules were dried in a conventional hot air oven at 40ºC. The dried granules were subjected to dry screening by passing through mesh no. 22, blended with a mixture of talc and magnesium stearate and compressed into tablets using 6 station rotary tablet punching machine.

<table>
<thead>
<tr>
<th>Ingredients (mg)</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>
<th>F9</th>
<th>F10</th>
<th>F11</th>
<th>F12</th>
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<tr>
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<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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<tr>
<td>Guar gum</td>
<td>25</td>
<td>50</td>
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<td>200</td>
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<td>-</td>
<td>12.5</td>
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<td>100</td>
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<tr>
<td>Xanthan gum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>50</td>
<td>100</td>
<td>200</td>
<td>12.5</td>
<td>25</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Lactose</td>
<td>255</td>
<td>230</td>
<td>180</td>
<td>80</td>
<td>255</td>
<td>230</td>
<td>180</td>
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<td>Magnesium stearate</td>
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<td>Talc</td>
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</tr>
</tbody>
</table>

Table 1 : Composition of matrix tablets of Mebeverine

Evaluation of granules:

The flow properties of the prepared granules were evaluated by determining the bulk density, tapped density, compressibility index (Carr’s index), Hausner’s ratio and angle of repose.

Angle of repose:

Angle of repose (θ) was determined using fixed funnel method[8]. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules.

The granules were allowed to flow through the funnel so that they form a pile. The height and the radius of the pile were measured and the angle of repose was calculated using the equation

\[ \theta = \tan^{-1}\left(\frac{h}{r}\right) \]

Where \( h \) and \( r \) are the height and radius of the pile.

Bulk density and tapped density:

Accurately weighed granules (M) were transferred to a graduated cylinder to measure the apparent volume or bulk volume (\( V_b \)). The measuring cylinder was tapped for a fixed number of times and tapped volume (\( V_t \)) occupied in the cylinder was measured. The bulk density and tapped density were calculated by the following formula:

\[ \text{Bulk density (} \rho_b \text{)} = \frac{\text{Weight of granules (g)}}{\text{Bulk volume (ml) (} V_b \text{)}} \]

\[ \text{Tapped density (} \rho_t \text{)} = \frac{\text{Weight of granules (g)}}{\text{tapped volume (ml) (} V_t \text{)}} \]

Where \( M = \text{mass of the powder, } V_b = \text{bulk volume of the powder and } V_t = \text{tapped volume of the powder.} \)

Carr’s index and Hausner’s ratio:

Carr’s index[9] and hausner ratio[10] are calculated by using following formula

Carr’s index = \( \left[\left(\text{Tapped density} - \text{Bulk density}\right)/\text{Tapped density}\right]\) * 100

Hausner’s ratio = \( \rho_t / \rho_b \)

Where \( \rho_t = \text{Bulk density and } \rho_b = \text{Tapped density} \)

Evaluation of tablets:

Tablets were tested for hardness[11], thickness, friability[11], weight variation[11], content uniformity and in vitro drug release.
Tablet thickness:
The thickness of the tablet was measured by using vernier calipers.

Weight variation:
Twenty (20) tablets from each batch were selected at a random and weighed individually. The average weight was calculated and individual tablet weights were compared with the average weight.

Tablet hardness:
Tablet hardness was measured using a Monsanto hardness tester. Three tablets from each formulation were tested randomly and average reading was noted.

Friability:
Twenty (20) tablets were selected from each batch and weighed. Each group of tablets were rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as percent weight loss from the original tablets.

Estimation of drug content:
Ten tablets from each formulation were powdered. The powder equivalent to 100 mg of Mebeverine HCl was weighed and dissolved in pH 6.8 phosphate buffer. Suitable dilutions were prepared and the solution was analyzed spectrophotometrically at 236nm using UV Visible Spectrophotometer.

Swelling behavior of Matrix Tablets:
The extent of swelling was measured in terms of percent weight gain by the tablet. The swelling behavior of all the formulations was studied. One tablet from each formulation was kept in petri dish containing pH 6.8 phosphate buffer. At the end of 1hr tablet was withdrawn, blotted with tissue paper and weighed. The process is continued for 12 h. Percent weight gain by the tablet was calculated using formula

\[ S.I = \frac{(M_t - M_0)}{M_0} \times 100 \]

Where, S.I = swelling index, \( M_t \) = weight of tablet at time ‘t’ and \( M_0 \) = weight of tablet at time t =0

In vitro drug release studies:
Dissolution studies of all batches were performed employing USP type II Dissolution Testing Apparatus (LABINDIA DS 8000). The dissolution test was performed using 900 ml of 0.1 N HCL (for 2hrs) followed by phosphate buffer pH 6.8 upto 24 hrs at 37°C ±0.5°C and 50 rpm. A 5ml aliquot of the sample was withdrawn periodically at suitable time intervals and volume replaced with an equivalent amount of the dissolution medium. The samples were analyzed spectrophotometrically at 236nm using UV-Visible Spectrophotometer.

RESULTS AND DISCUSSION
In the present study, Mebeverine HCl matrix tablets were prepared using natural polymers Guar gum and Xanthan gum in different concentrations (5%, 10%, 20%, 40%) by wet granulation method.

FT-IR Studies
The IR spectrum of pure drug and physical mixture of drug and polymers were studied. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. Drug-excipient interactions were not observed. This indicates that the drug was compatible with the formulation components. The spectra for pure drug, drug and polymers is shown in fig 1, 2 and 3.

![Infra red spectrum of Mebeverine HCl](image)
Fig 2: Infra red Spectrum of physical mixture of Mebeverine HCl and Guar gum

Fig 3: Infra red spectrum of physical mixture of Mebeverine HCl and other excipients
Evaluation of granules:
The granules of all the formulations were evaluated for angle of re-
pose, bulk density, tapped density, compressibility index and hausner’s
ing. The angle of repose was found to be in the range of $21.43 \pm 0.32$
to $27.82 \pm 2.14$. It indicates that granules have a good flow property.
The bulk density and tapped density were found to be in the range of
$0.31 \pm 0.01$ to $0.40 \pm 0.02$ gm/cc and $0.34 \pm 0.02$ to $0.44 \pm 0.02$ gm/cc
respectively. The compressibility index and hausner’s ratio were found
to be $6.23 \pm 2.08$ to $13.02 \pm 2.53$ and $1.07 \pm 0.02$ to $1.15 \pm 0.03$. All the
results of pre compression parameters were within the prescribed
limits indicating good flow properties of the granules and the data
was shown in Table 2.

Table 2: Precompression parameters of formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density (g/cm³)</th>
<th>Tapped density (g/cm³)</th>
<th>Carr's index</th>
<th>Hausner's ratio</th>
<th>Angle of repose Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.40±0.02</td>
<td>0.44±0.02</td>
<td>9.19±2.06</td>
<td>1.10±0.03</td>
<td>24.37±0.35</td>
</tr>
<tr>
<td>F2</td>
<td>0.31±0.01</td>
<td>0.34±0.02</td>
<td>9.19±3.14</td>
<td>1.10±0.04</td>
<td>25.71±0.75</td>
</tr>
<tr>
<td>F3</td>
<td>0.37±0.01</td>
<td>0.40±0.03</td>
<td>7.46±3.78</td>
<td>1.08±0.04</td>
<td>25.76±0.70</td>
</tr>
<tr>
<td>F4</td>
<td>0.40±0.02</td>
<td>0.42±0.03</td>
<td>6.62±2.43</td>
<td>1.07±0.03</td>
<td>26.92±1.92</td>
</tr>
<tr>
<td>F5</td>
<td>0.33±0.02</td>
<td>0.38±0.02</td>
<td>12.18±1.34</td>
<td>1.14±0.02</td>
<td>25.14±0.50</td>
</tr>
<tr>
<td>F6</td>
<td>0.36±0.01</td>
<td>0.39±0.01</td>
<td>7.23±0.15</td>
<td>1.08±0.02</td>
<td>26.95±1.51</td>
</tr>
<tr>
<td>F7</td>
<td>0.40±0.02</td>
<td>0.42±0.01</td>
<td>6.52±2.04</td>
<td>1.07±0.02</td>
<td>23.52±1.00</td>
</tr>
<tr>
<td>F8</td>
<td>0.36±0.03</td>
<td>0.39±0.01</td>
<td>8.11±4.82</td>
<td>1.09±0.06</td>
<td>27.82±2.14</td>
</tr>
<tr>
<td>F9</td>
<td>0.35±0.03</td>
<td>0.41±0.04</td>
<td>13.02±2.53</td>
<td>1.15±0.03</td>
<td>21.43±0.32</td>
</tr>
<tr>
<td>F10</td>
<td>0.38±0.02</td>
<td>0.40±0.02</td>
<td>6.23±2.08</td>
<td>1.07±0.02</td>
<td>25.33±1.17</td>
</tr>
<tr>
<td>F11</td>
<td>0.34±0.01</td>
<td>0.39±0.03</td>
<td>11.43±4.15</td>
<td>1.13±0.05</td>
<td>27.77±1.22</td>
</tr>
<tr>
<td>F12</td>
<td>0.36±0.03</td>
<td>0.40±0.02</td>
<td>9.39±3.43</td>
<td>1.10±0.04</td>
<td>22.15±1.56</td>
</tr>
</tbody>
</table>

Physico-chemical evaluation of tablets:
The thickness of the tablets ranged from $2.70 \pm 0.10$ to $2.90 \pm 0.10$ mm.
All the batches showed uniform thickness. The hardness of the for-
mulated matrix tablets was found between $4.17 \pm 0.29$ to $5.33 \pm 0.29$ kg/
cm^2. The friability was found to be $0.30 \pm 0.06$ to $0.49 \pm 0.36$, which is
an indication of satisfactory mechanical resistance of tablets. The
drug content estimation showed values in the range of 97.57±0.12 to
100.01±0.39% which reflects good uniformity in the drug content
among different formulations. All the formulations showed values
within the prescribed limits and the data was shown in Table 3.

Table 3: Physical parameters of matrix tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight variation (mg) Mean ± SD</th>
<th>Hardness (kg/cm²) Mean ± SD</th>
<th>Friability (%) Mean ± SD</th>
<th>Drug content (%) Mean ± SD</th>
<th>Thickness (mm) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>499.45±2.24</td>
<td>4.17±0.29</td>
<td>0.31±0.07</td>
<td>97.57±0.12</td>
<td>2.90±0.10</td>
</tr>
<tr>
<td>F2</td>
<td>499.8±1.4</td>
<td>4.33±0.58</td>
<td>0.36±0.09</td>
<td>98.50±0.15</td>
<td>2.77±0.21</td>
</tr>
<tr>
<td>F3</td>
<td>500.1±1.59</td>
<td>4.67±0.76</td>
<td>0.35±0.11</td>
<td>99.45±0.15</td>
<td>2.77±0.25</td>
</tr>
<tr>
<td>F4</td>
<td>498.8±1.63</td>
<td>5.00±0.5</td>
<td>0.32±0.06</td>
<td>99.35±0.15</td>
<td>2.70±0.20</td>
</tr>
<tr>
<td>F5</td>
<td>500.95±2.42</td>
<td>4.33±0.58</td>
<td>0.49±0.36</td>
<td>98.33±0.13</td>
<td>2.90±0.10</td>
</tr>
<tr>
<td>F6</td>
<td>498.3±2.49</td>
<td>4.67±0.76</td>
<td>0.34±0.05</td>
<td>100.01±0.39</td>
<td>2.90±0.17</td>
</tr>
<tr>
<td>F7</td>
<td>498.05±2.54</td>
<td>4.83±0.29</td>
<td>0.32±0.03</td>
<td>99.09±0.62</td>
<td>2.90±0.10</td>
</tr>
<tr>
<td>F8</td>
<td>497.65±2.5</td>
<td>5.33±0.29</td>
<td>0.30±0.06</td>
<td>98.05±0.43</td>
<td>2.90±0.20</td>
</tr>
<tr>
<td>F9</td>
<td>498.7±2.03</td>
<td>4.17±0.29</td>
<td>0.35±0.11</td>
<td>97.69±0.27</td>
<td>2.80±0.36</td>
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<tr>
<td>F10</td>
<td>500.1±1.79</td>
<td>4.67±0.76</td>
<td>0.31±0.07</td>
<td>98.41±0.22</td>
<td>2.87±0.23</td>
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<td>F11</td>
<td>500.1±2.2</td>
<td>4.83±0.29</td>
<td>0.49±0.36</td>
<td>99.16±0.06</td>
<td>2.70±0.10</td>
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<tr>
<td>F12</td>
<td>499.1±2.61</td>
<td>5.17±0.29</td>
<td>0.36±0.09</td>
<td>99.87±0.23</td>
<td>2.77±0.25</td>
</tr>
</tbody>
</table>

Swelling studies:
Swelling index of all the formulations was shown in Fig 4. As time
increases the swelling index was increased, because weight gained by
tablet was increased proportionally. The direct relationship was ob-
served between swelling index and gum concentration, as gum con-
centration increases, swelling index was increased. The formulations
containing 5% and 10% of polymer lost their integrity within 8hrs
where as formulations containing 20% and 40% polymers showed
increase in swelling index during period of 12 hrs without losing their
integrity. Comparison between Guar gum and Xanthan gum, it has
been observed that swelling index of Guar gum was significantly more
compared to Xanthan gum. Formulation F4 containing 40% Guar gum
has shown greater swelling index among all the formulations.

In-vitro drug release study:
The in vitro drug release studies shows that the cumulative percent
drug release for the formulations F1, F2, F3 and F4 was 98.03% after
2hrs, 99.43 % after 11hrs, 98.43% after 20hrs and 79.8% after 24hrs.
Formulations F5, F6, F7, and F8 showed drug release of 101.85% after
10hrs, 101.23% after 14hrs, 99.49% after 20 hrs and 91.04% after 24hrs.
Formulations F9, F10, F11 and F12 showed drug release of 101.65%
after 10hrs, 95.32% after 12hrs, 101.45% after 20hrs and 89.34% after
24hrs.(Fig 5)

Figure 5: cumulative Percent drug released Vs time plots of Mebeverine matrix tablets,(n=3), A: F1,F2,F3,F4,F5 and F6 ; B: F7,F8,F9,F10,F11 and F12
From the in vitro drug release studies it was observed that increasing the amount of gum in the formulation, resulted in slower rate and decreased amount of drug release from the tablet. The formulations containing low concentration of gums failed to control the drug release in first 2hrs in pH 1.2. The formulations F4, F8, F12 containing polymer in the concentration of 40% succeeded in sustaining the drug release upto 24hrs. However formulation F4 containing 40% Guar gum is considered as optimized formulation as it released less amount of drug in first 2 hrs in pH 1.2 compared to other formulations. This shows that Guar gum is capable of protecting the drug from being completely released in the physiological environment of stomach. From the drug release studies of formulations F9, F10, F11, and F12 it was found that there was no synergistic effect observed when Guar gum and Xanthan gum were used in combination in the ratio of (1:1).

To evaluate the kinetics and the mechanism of drug release, the release data was fitted to various mathematical models representing Zero order, First order, Higuchi, Hixon-crowell and Korsmeyer-peppas (Table 4). In all the formulations the r values were found higher in first order models than zero order models indicating release followed first order kinetics (Figure 6). From the regression values of Higuchi and Hixon-Crowell (Figure 7, 8) plots it was observed that the drug release from the matrix tablets may be due to diffusion or dissolution or combination of both the processes. When the release data was analyzed as per Peppas equation, for the formulations F1 and F9, the release exponent n < 0.45 indicating that the release mechanism was fickian diffusion. For the formulations F2, F3, F4, F5, F6, F7, F8, F10, F11 and F12 the release exponent n > 0.45 but < 0.89 indicating that the release mechanism was non-fickian diffusion.

Table 4: Release characteristics of mebeverine matrix tablets

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Correlation Co-efficient (r) value</th>
<th>Korsmeyer - Peppas Release mechanism</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Zero order</td>
<td>First order</td>
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<tr>
<td>F1</td>
<td>0.874</td>
<td>0.992</td>
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<tr>
<td>F2</td>
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<td>F3</td>
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<td>0.956</td>
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<td>F7</td>
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<td>F8</td>
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<td>0.989</td>
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<td>0.976</td>
</tr>
<tr>
<td>F12</td>
<td>0.729</td>
<td>0.941</td>
</tr>
</tbody>
</table>

Figure 6: Log Percent drug undissolved Vs time plots of Mebeverine matrix tablets,(n=3), A: F1,F2,F3,F4,F5 and F6 ; B: F7,F8,F9,F10,F11 and F12

![Graph A](image1.png)

![Graph B](image2.png)
Figure 7. cumulative Percent drug released Vs Square root of time plots of Mebeverine matrix tablets,(n=3), A: F1,F2,F3,F4,F5 and F6 ; B: F7,F8,F9,F10,F11 and F12

Figure 8. Cube root of % drug remaining Vs time plots of Mebeverine matrix tablets,(n=3), A: F1,F2,F3,F4,F5 and F6 ; B: F7,F8,F9,F10,F11 and F12

CONCLUSION:
This study deals with the investigations carried out with the objective of developing formulations for colon targeting of mebeverine HCl using natural polymers Guar gum and Xanthan gum. From the above results and discussion, it was concluded that as we increase the polymer concentration in a matrix tablet there is significant decrease in drug release. Optimized formulation F4 containing 40% Guar gum released less amount of drug in first 2 hrs in pH 1.2 compared to other formulations thereby making it available for local action in colon. Thus, matrix tablets of mebeverine HCl using natural, biodegradable and biocompatible polymers were successfully formulated, evaluated and found to be suitable candidates for colon targeted delivery.

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