DESIGN AND DEVELOPMENT OF PH AND TIME DEPENDENT RELEASE MODULATED MEBEVERINE COLON TARGETED SYSTEM

K. Ranjeeth Reddy¹*, M. Rajendar² and G. Kiran

¹Department of Pharmaceutics, Vaageswari College of Pharmacy.
²Department of Pharmaceutics, St. John College of Pharmacy.

ABSTRACT

The aim of present study was to develop pH & time dependent colon targeted system of Mebeverine for effective application in the treatment of irritable bowel syndrome. In this study colon targeted systems are achieved by two different approaches. First approach was application of Hydroxy propyl methyl cellulose K4M (HPMC K4M) on core tablets by compression coating technique. These were further coated with Eudragit L100 at a coating level of 5 %w/w weight gain. Application of this high viscosity grade prolong the lag time greater than 8h, and were further optimized by using independent variables like concentration of HPMC & hydrophilic material in the outer coat. An increase in concentration of hydrophilic material decrease in the lag time of drug release was observed. The F1, F2 with 20%, 30% HPMC in the outer coat shows a lag time of 4.5h and 5 h respectively. In the second approach the core tablets with different concentration of superdisintegrant (to determine the effect of superdisintegrant on drug release from coated tablets) were coated with ethyl cellulose at different coating level and further coated with Eudragit L100 at a coating level of 10% w/w in order to optimize the drug release after a lag time 5h. The F5c, F7c containing without and with 5 % superdisintegrant&coated with ethyl cellulose at a coating level of 7.5% shows a lag time of between 5-5.5h, 5h and completely release the drug in 6.8 pH buffer in next 2h respectively.

KEYWORDS: colon specific delivery, antispasmodic, superdisintegrant.
INTRODUCTION
Colon drug delivery gained most of researcher’s interest in the last few decades for effective
delivery of drugs for local treatment of colonic diseases like irritable bowel syndrome,
inflammatory bowel disease, colorectal cancer, amoebiasis etc.[1] Colonic drug delivery
 gained importance not only for local treatment of diseases but also for effective delivery of
proteins and peptide drugs.[2] Colonic drug delivery systems also have advantages in the
treatment of diseases like asthma, rheumatoid arthritis where a delay in absorption is
required; this can be provided by colon delivery systems which releases drug after a lag
time.[3-4]

The previous literature report shows that many researchers mainly focused on pro-drug
based, pH dependent, time dependent, microflora activated system in the development of
colon targeted system. Natural polysaccharides were commonly used as carrier in colon drug
delivery system. These polysaccharides were specifically degraded by colonic bacterial
enzymes like β-D-glucosidase, β-D-galactosidase etc.[5-6] Polysaccharide based matrix tablets,
compression coated tablets were prepared for colonic drug delivery using different natural
polysaccharides.[7-10] These polysaccharides were hydrophilic in nature as a result a
premature drug release was observed so that it is difficult to control the release from these
materials. In commercial point of view pH dependent systems were widely used. The pH
dependent system had the limitation like lack in site specificity which leads to premature drug
release and high gastrointestinal pH variability among individuals.[11]

The time dependent systems were designed based on the principle of transit time of
gastrointestinal tract. The small intestinal transit time is relatively constant for 3±1h.[12], a
large variation in gastric empty was observed. The location of drug release was based on this
transit time. The variation in the gastric emptying time leads to release of drug in the small
intestine or par down in the colon.[13-14] As alone pH and time dependent systems were not
suitable for effective colon drug delivery, a combination of pH & time dependent systems
were employed in this study for effective delivery of mebeverine to colon in the prophylaxis
of irritable bowel syndrome.[15,20] The outer enteric coat provides gastric protection in
stomach. The inner layer composed of a time delayed layer which provide a lag time for drug
release.[21]

Irritable bowel syndrome is one of the most commonly encountered gastrointestinal disorders
causing constipation, cramps, abdominal pain. Mebeverine hydrochloride is non selective
antispasmodic drug that directly acting gastrointestinal muscles relieving irritable bowel syndrome symptoms.[16]

The purpose of this study was to develop pH & time dependent system for mebeverine hydrochloride. Mebeverine was well absorbed throughout the gastrointestinal tract and has high first pass metabolism. For effective treatment the drug absorption in the upper part of GIT should be eliminate. The colon targeted system eliminates the drug absorption in the upper part of GIT which deliver high amount of drug to colon for greater antispasmodic activity.

HPMC K4M and ethylcellulose were applied on the core tablets and further coated with enteric coating material Eudragit L100 for preparing pH & time dependent system.[17] The application of outer enteric coating layer (pH dependent) provides acid protection in stomach. The inner HPMC and ethylcellulose layer helps in time dependent release ie. time dependent factor. The superdisintegrant present in the core tablet helps in rapid drug release.

MATERIALS AND METHODS

Materials
Mebeverine hydrochloride was obtained as a gift sample from Synthokem labs, Hyderabad. HPMC K4M, Ethylcellulose was received as a gift sample from Colorcon Asia Pvt Ltd. Eudragit L100 was received as a gift sample from Corel Pharma Pvt Ltd. Other excipients used in tablet formulation and coating process were of standard pharmaceutical grade and all chemical reagents, solvents were of analytical grade.

Methods
Preparation of mebeverine colon targeted tablets using HPMC as the inner layer
Preparation of core tablets: The core tablets for compression coating with HPMC were prepared by direct compression. Each core tablet of 200 mg consisted of 135 mg mebeverine, microcrystalline cellulose as diluents and a mixture of talc and magnesium stearate in 2:1 as shown in table 1. Sodium starch glycolate was incorporated at 5% concentration level to obtain fast disintegration characteristics. Mebeverine and other excipients were thoroughly mixed and passed through sieve 16. The mixture was compressed into tablets using 8-mm round flat punches on rotary tablet press (Cadmach). These tablets were tested for weight variation, hardness, content uniformity, friability.
Table 1: Composition of Mebeverine Hydrochloride Core Tablet

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mebeverine</td>
<td>135</td>
</tr>
<tr>
<td>SSG</td>
<td>10</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>6</td>
</tr>
<tr>
<td>MCC</td>
<td>43</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>200</strong></td>
</tr>
</tbody>
</table>

Preparation of mebeverine compression coated tablets: The core tablets were compression coated with 200 mg of different coat mixture as shown in Table 2. About 50% of coat material was placed in the die cavity (diameter 10 mm). The core tablet was carefully placed in the centre of die cavity, which was filled with remaining coat material. Then it was compressed around the core tablet using 10-mm concave punch. The prepared compression coated tablets were tested for weight variation, hardness, friability etc.

Table 2: Compression Coat Composition of the Different Prepared Formulas

<table>
<thead>
<tr>
<th>FORMULATION</th>
<th>HPMC(%)</th>
<th>SDL(%)</th>
<th>PVP(%)</th>
<th>MCC(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>10</td>
<td>75</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>F2</td>
<td>20</td>
<td>65</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>F3</td>
<td>30</td>
<td>55</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>F4</td>
<td>40</td>
<td>45</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Coating of tablets: The HPMC press coated tablets were coated with Eudragit L100 using R&D coater. A 5% Eudragit solution was prepared in iso propyl alcohol using di-butylphthalate as plasticizer (20% (w/w) based on polymer), and talc was added to the coating solution to prevent the adhering of tablets during coating process. Coating process was continued until a desired level of 10% weight gain was obtained.

Preparation of mebeverine colon targeted tablets using ethylcellulose as the inner layer
Mebeverine core tablets were prepared by using direct compression technique. Mebeverine and other excipients as shown in the table 3 were passed through 60 sieve. This mixture was compressed into tablet by 12-mm concave punches using rotary tablet press (Cadmach). Three different formulations were prepared by varying the concentration of superdisintegrant in the formulation. These prepared tablets were evaluated for weight variation, friability, and content uniformity.
Preparation of mebeverine colon targeted tablets

The prepared mebeverine core tablets were coated with ethylcellulose using R&D coater. A 5% w/v ethylcellulose was prepared in isopropyl alcohol using di-butyl-phthalate as plasticizer (20% (w/w) based on polymer), and talc was added to the coating solution to prevent the adhering of tablets during coating process. Coating process was continued until a desired level of 2.5%, 5%, & 7.5% weight gains were obtained.

Outer enteric coating layer was comprised of Eudragit L100.Eudragit L100 (5% w/v) coating solution was applied on the ethylcellulose coated tablets using pan coating technique by following the process variable as shown in the table 4. Coating was continued until a desired level of 10% w/w weight gain was achieved. At the end of each stage tablets were dried in hot air oven at 40°C for 24 h.

Table 3: Composition of different core tablets

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mebeverine</td>
<td>135</td>
<td>135</td>
<td>135</td>
</tr>
<tr>
<td>SSG</td>
<td>-</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Avicel</td>
<td>245</td>
<td>235</td>
<td>225</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Aerosil</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mg.Stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 4: Composition of coating solutions

<table>
<thead>
<tr>
<th>Spray solution</th>
<th>Eudragit L100-55</th>
<th>Ethylcellulose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymer weight (gm)</td>
<td>10</td>
<td>4.5</td>
</tr>
<tr>
<td>Talc (gm)(50% of polymer)</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>Dibutyl Phthalate (gm)</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>(10% of polymer wt)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG 400 (gm)</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>Isopropyl alcohol (%)</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>Acetone (%)</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Solid content (%)</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 5: coating parameters for different polymer systems

<table>
<thead>
<tr>
<th>Process Parameters</th>
<th>Eudragit L100-55</th>
<th>Ethylcellulose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet bed temperature(°c)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Inlet air temperature(°c)</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td>Atomising air pressure (psi)</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Pan speed (rpm)</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Dispersion solid content (%)</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Spray rate gm/min</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>
Determination of drug content in the tablet formulation

Twenty tablets of each prepared formula were weighed and transformed into powder form. A quantity of the powdered tablet which is equivalent to 0.135 g of mebeverine HCl was mixed with 100 mL of 0.1 M HCl and heated for 10 Min in a water bath 40°C with occasional shaking. The Resultant mixture was cooled and a sufficient amount of 0.1 M HCl was added to produce 250 mL solution which was then filtered. A sufficient amount of 0.1 M HCl was added to 10 mL of the filtrate in order to produce 100 mL; 15 mL of the resulting solution was then diluted to 100 mL with the same solvent. The absorbance of this solution was measured at a maximum wave length (λ max) of 263 nm. The content of mebeverine HCl was calculated by taking the maximum value at 263 as the value of A (1%, 1 cm).

In-vitro dissolution studies

In-vitro dissolution studies were preformed for mebeverine colon targeted system by using a change in pH method. Dissolution studies were carried out using USP dissolution apparatus II (paddle method, Electrolab) at 50 rpm, 37°C±0.5°C using 900 ml dissolution medium. The prepared tablets were tested for drug release initially using 700 ml of 0.1 N HCl (pH 1.2) for 2h (average gastric emptying time) later 200 ml of 0.2 M tribasic sodium phosphate solution was added and pH was adjusted to 7.4 and 6.8 by using 2M NaOH or 2M HCl for 3h and until the end. Aliquot samples were collected at predetermined intervals, filtered through Whatman filter paper and analysed using double beam UV-visible spectrophotometer (Schimadzu) at 263 nm. The cumulative percentage release for mebeverine was calculating using beer’s-lamberts curve generated in respective medium. The drug release studies were performed in triplicate, the mean cumulative percentage of drug calculated (±SD) was plotted against time.

Stability studies

The optimized formulation of release modulated mebeverine colon targeted system was stored at accelerated stability conditions 40°C±2°C/ 75%±5% RH for 6 months. After a specified time period tablets were observed for change in physical appearance, colour, and drug content.[18, 19]

RESULTS AND DISCUSSION

The core tablets used in the preparation of HPMC press coated tablets were prepared by direct compression coating technique. The incorporation of sodium starch glycolate in the core tablet aids in fast disintegration. The weight variations for all formulations before and
after coating were within the acceptable limit less than 5% and friability was less than 1%. The mean hardness for all the formulations was between 5.5-6.5 kg. The drug content value for core tablets of HPMC press coated is 94%-101%. The drug content of core tablets coated with ethyl cellulose was found to be 96%-104%.

**In vitro dissolution tests**

**In vitro drug release studies of colon targeted system with HPMC as the inner layer.**

The purpose of compressing HPMC around the core tablet was to delay the drug release in the small intestine for 3-4 hours after outer enteric coat dissolved. In order to reach the tablet to ileo-cecal junction or proximal colon the concentration of HPMC K4M in the compression coat need to be optimized because being high viscosity grade the amount of polymer had a significant effect on drug release. A concentration of 90%, 80% HPMC in the outer coat shows a lag time greater than 8 h in the pH 7.4 buffer medium. The tablet with lag time greater than 8h reach the distal part of colon where drug absorption is very low. To fulfil our purpose of delaying drug release to 3-4 h a hydrophilic material should be incorporated in the coat material, spray dried lactose was selected to meet our criteria.

After dissolving enteric coat drug release from the coat was observed because being water soluble drug mebeverine release from the core tablet by diffusion through gelled HPMC matrix and erosion of gelled HPMC matrix. No formulation shows the drug release in 0.1N HCl after changing the pH of medium to pH 7.4 different release profiles were observed for F1 to F4. F1 with 10% polymer and 75% dextrose shows a lag time of 4.5 h. Premature drug release was observed due to high amount of lactose in coat cause more diffusion of drug through it and 17.5% drug was released after 5h. The F2, F3 containing 20%, 30% polymer in the coat shows lag time nearly 5 & 5.5 h respectively. The increase in the lag time was because of increase in the concentration of polymer in the coat material. Only 10.14%, 6.16% drug release was observed after 5h for F2, F3 respectively. F4 containing 40% polymer shows a further increase in the lag time was observed and drug release was very slow compared to other formulations. The addition of polyvinyl pyrrolidine and micro crystalline cellulose improve the binding capacity of polymer and compression characteristics of the coat.
In vitro drug release studies of colon targeted system using ethyl cellulose as the inner layer

The formulations were containing two layers, inner ethyl cellulose coating and outer enteric coating. All formulations having outer enteric coating at a level of 10% (w/w) weight gain. The formulations were coated with ethyl cellulose at different coating levels like 2.5%, 5%, & 7.5% (w/w) weight gain. The formulations were differing in the amount of sodium starch glycolate in the core tablets. At a coating level of 10% (w/w) weight gain enteric coating was sufficient to impart enteric effect and provide an additional lag time in pH 7.4 buffer. F5 formulation without superdisintegrant act as a control and having different coating levels of ethyl cellulose 2.5%, 5% & 7.5% (F5a, F5b &F5c respectively). F5a with a coating level of 2.5% shows a lag time of 4-4.5h and release 32.12% of drug at the end of 5h. An increase in the ethyl cellulose coating level 5% & 7.5% for F517b, F5c shows an increase in lag time to 5-5.5h. An increase in coating level of ethyl cellulose prolong the lag time in pH 7.4 buffer.

Formulations F6&F7 contain 2.5% and 5% sodium starch glycolate respectively. The presence of SSG in the core tablet aid in the rapid release of drug by rupturing the outer ethyl cellulose membrane. The drug release profiles of F6&F7 shows that there is no big difference in the drug release. Formulation F7 with 5% SSG acts as a test compared to F5. F7 with different ethyl cellulose coating (F7A, F7B &F7C) shows a rapid drug release when compared to F5. F5A with 2.5% w/w coating releases 53.52% of drug in 5h. Upon increasing coating level to 7.5% (w/w) weight gain, a decrease in the drug release in 7.4 pH buffer was observed.
F5C, F7C containing same coating level of ethyl cellulose (7.5% w/w weight gain) shows different release profiles. F5C without super disintegrant, F7C with 5% SSG shows a difference in lag time of drug release, because SSG present in the core tablet aid in faster release compared to F5C which decreases the lag time of F7C. F7A & F7C containing same amount of SSG differ in coating levels of 2.5%, 7.5% (w/w) weight gain respectively. Due to low level of coating and presence of SSG in F7A shows a drug release of 53.52% at the end of 5h and F7C shows only 6.5% drug release in 5h. The difference in drug release was because of high diffusional path length at higher coating level.

**Fig 2: Comparative in-vitro drug release profiles of mebeverine colon targeted tablets ethyl cellulose as inner layer and enteric coated with Eudragit L100 (F5-F7)**

**CONCLUSION**

pH and time dependent system containing a core tablet in the centre and coated with inner HPMC/ ethyl cellulose layer and outer enteric Eudragit L100 layer. This delivery system can be successful for the delivery of mebeverine to colon for effective treatment of irritable bowel syndrome. This delivery system can be prepared using pan coating technique with reasonable processing time. From in vitro dissolution studies we conclude that the optimized batch shows no drug release in acidic condition and release the drug after a lag time. The concentration of HPMC and lactose greatly affect the lag time and drug release. In case of formulations with ethyl cellulose in the inner coat, the coating level of ethyl cellulose and concentration of superdisintegrant in core tablets mainly effect the drug release. It can be concluded that this colon drug delivery systems has good potential for the delivery of drugs to the colon.
REFERENCES


