Formulation and Evaluation of Compressed Coated Tablets of Mosapride Citrate for Colonic Delivery

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A B S T R A C T

The objective of the present research study is to develop compression coated tablets of Mosapride citrate with a view of minimizing the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of colon by employing Guar gum as a compression coat over the Mosapride citrate core tablets. The standard graph of Mosapride citrate was constructed in 0.1N Hcl and 7.2 pH phosphate buffer. FTIR spectra revealed that there was no interaction between the drug and the excipients. The study indicated that the prepared formulations were good as the physicochemical parameters were found to be within the pharmacopoeial limits. In vitro drug release studies were conducted for 2hrs in 0.1N Hcl and in 7.2 pH phosphate buffer up to 24hrs. All the formulations remained intact for 24hr. As the concentration of polymer is increased the release rate of drug was decreased. All the formulations followed Zero order kinetics, showed good correlation in Higuchi Kinetics clearly indicating that the drug release mechanism was predominantly Diffusion controlled. When the data was fitted to Korsmeyer’s- Peppas equation the slope values suggested that the release of Mosapride citrate from all the formulations followed Non Fickian diffusion. From the study we found that the tablets compression coated with Guar Gum would be potential as a formulation in delivering the drug to the colon as well as for the effective and safe therapy of Inflammatory bowel disease (IBD).

Keywords: Mosapride citrate (MSP), Inflammatory bowel disease (IBD), Guar gum, Compression coated.

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1. Introduction [1-8]
An ideal drug delivery system specifically to the colon avoids the drug release in stomach and small intestine, but begins delivery at the beginning of the large bowel where conditions are most favourable for drug dispersion and absorption.

Targeted drug delivery systems to the colon provide the following therapeutic advantages:

a. Reduces the adverse effects and improves efficacy in case of treating the diseases related to colon.

b. By producing well-disposed environment in colon for peptides and proteins when compared to upper GIT.

c. Minimizes extensive first pass metabolism of steroids

d. Prevents the gastric irritation produced by Non-steroidal anti-inflammatory drugs (NSAIDS) upon oral administration.

Factors Affecting Colon Targeted Drug Delivery:

a. Physiological factors: Gastric emptying, pH of colon, Colonic micro flora and enzymes.

b. Pharmaceutical factors: Drug candidates and Drug carriers.

Inflammatory bowel disease (IBD) is the communal terms for a group of idiopathic intestinal conditions which includes ulcerative colitis (UC) and Crohn’s disease (CD). IBD is considered to be chronic relapsing disorder allied with uncontrolled inflammation within the gastrointestinal tract which may lead to the development of colorectal cancer later in life. In IBD psychological abnormalities and the abnormalities of the sensory and motor function of the digestive tract are observed. Although it has been reported that IBD symptoms are associated with disturbances in GI motility and enhanced visceral sensitivity the pathophysiology of IBD is not fully understood. MSP is a white to yellowish white crystalline powder and used for the treatment of Gastritis, Gastro-oesophageal reflux disease, Functional dyspepsia and IBD.

Guar gum is a galactomann polysaccharide derived from the seeds of Cyamopsis tetragonolobus. It contains linear chains of 1, 4 β-D-mannopyranosyl units with α -D-galactopyranosyl units attached by 1, 6 linkages. The objective of the present research study is to develop compression coated tablets of Mosapride citrate with a view of minimizing the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of colon by employing Guar gum as a compression coat over the Mosapride citrate core tablets.

2. Materials and Methods

Materials:
Mosapride citrate was obtained as a gift sample from Sura labs, Hyderabad, Telangana and all the remaining excipients were procured from SD Fine chemicals, Mumbai, India

Method:
Direct Compression Method

Preparation of Compression Coated Mosapride Citrate Tablets:

Preparation of Mosapride Citrate Core Tablets:
Mosapride citrate core tablets were prepared by direct compression method. The drug and remaining excipients were passed through a sieve before their use in the formulation as shown in Table no. 1. All the ingredients were added according to the formulae, thoroughly mixed and then directly compressed into tablets using 6mm round, flat and plain punches on a 12 station tablet machine.

Compression Coating of Mosapride Citrate Core Tablets:
The core tablets (150 mg) were compression coated with different quantities of coating material containing Guar gum as shown in Table no.2. Half the quantity of the coating material was placed in the die cavity, the core tablet was carefully placed in the centre of the die cavity and was filled with the other half of the coating material. The coating material was compressed using 9 mm round, flat and plain punches on a 12 station tablet machine.

Table 1: Formulation Development of Core Tablet

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>15</td>
</tr>
<tr>
<td>Cross Povidone</td>
<td>15</td>
</tr>
<tr>
<td>Talc</td>
<td>3.5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2</td>
</tr>
<tr>
<td>Lactose</td>
<td>114.5</td>
</tr>
</tbody>
</table>

Total weight of Core tablet is 150mg.

Table 2: Formulation Development of Compression Tablet

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guar Gum</td>
<td>7.5</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lactose</td>
<td>136.5</td>
<td>129</td>
<td>114</td>
<td>99</td>
<td>84</td>
</tr>
</tbody>
</table>

Total weight of Compression coat is 150mg.
Total weight of final tablet (Core+ Compression coat) is 300mg.

Evaluation of Pre Compression Parameters: (9-13).

1. Angle of Repose:
The angle of repose was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured.

The angle of repose was calculated using the following equation.

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

Where ‘h’ and ‘r’ are the height and radius of the powder cone respectively.

2. **Bulk Density (BD):**

An accurately weighed powder from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The loose bulk density (BD) of powder was determined using the following formula.

\[ \text{Bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of powder}} \]

**3. Tapped bulk density (TBD):**

An accurately weighed powder from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped bulk densities (TBD) of powder blends were determined using the following formula.

\[ \text{Tapped bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of tapped powder}} \]

4. **Hausner’s Ratio:**

This indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

\[ H = \frac{D_t}{D_b} \]

Where \( H \) is the Hausner’s ratio, \( D_t \) is the tapped density of the granules and \( D_b \) is the bulk density of the powder.

5. **Carr’s Compressibility Index:**

It is a simple index that can be determined on small quantities of powder. The compressibility indices of the formulation blends were determined using Carr’s compressibility index formula.

\[ \text{Carr’s Compressibility Index} (\%) = \frac{\text{Tapped bulk density} - \text{Bulk density}}{\text{Bulk density}} \times 100 \]

**Evaluation of Post Compression Parameters: (9-13).**

1. **Weight Variation:**

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. Then each batch passes the weight variation test if not more than two of the individual tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit.

2. **Thickness:**

Ten tablets were selected randomly from each batch and thickness was measured by using Screw guage.

3. **Hardness:**

Hardness was measured by using Monsanto apparatus. For each batch ten tablets were tested. The force is measured in kilograms/cm².

4. **Friability:**

The Lab India FT1020 friability test apparatus was used to determine the friability of the Tablets. Ten pre-weighed Tablets were placed in the apparatus and was rotated at 25 rpm for 4 minutes and then the Tablets were reweighed. The percentage friability was calculated according to the following formula.

\[ \% \text{ Friability} = \frac{(W_1 - W_2) \times 100}{W_1} \]

Where \( W_1 \) = Initial weight of the 10 tablets.

\( W_2 \) = Final weight of the 10 tablets after friability.

Friability values below 1.0% are generally acceptable.

5. **Drug content (assay):**

Ten tablets were taken and powdered. Powder equivalent to one tablet was taken and dissolved in 50 ml of pH 7.2 phosphate buffer. The mixture was allowed to stand for 1 hr with intermittent sonication to ensure complete hydration of polymer and subsequent solubility of the drug. Then the volume was made up to 100ml. The mixture was filtered and 1ml of the filtrate was suitably diluted. The absorbance of solution was measured by using UV – Visible spectrophotometer (Elico SL210, India) at 272 nm. Each measurement was carried out in triplicate and the average drug content in the tablet was calculated.

6. **In vitro Dissolution studies:**

In vitro dissolution studies were conducted by using USP paddle type apparatus at a rotation speed of 50 rpm and a temperature of 37±0.5 °C. The dissolution medium consisted of 900 ml of 0.1N Hcl for first two hours, phosphate buffer pH7.2 upto 24hrs. 5ml samples were withdrawn at predetermined time intervals (1 to 24hrs) and the same volume was replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed by UV – Visible spectrophotometer (Elico SL210, India) at 272 nm. The percentage drug release was calculated using the calibration curve of the drug in 0.1N Hcl and pH7.2 phosphate buffer.

7. **Drug release kinetics and mechanism:**

To analyze the mechanism of drug release from the formulation, the dissolution profile of all the batches were fitted to Zero order, First order, Higuchi and Peppas models to ascertain the kinetic modelling of drug release.

<table>
<thead>
<tr>
<th>MODEL</th>
<th>EQUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero Order</td>
<td>( Q = K_0 t )</td>
</tr>
<tr>
<td>First order</td>
<td>( \log Q = \log Q_o + \frac{K_1 t}{2.303} )</td>
</tr>
<tr>
<td>Peppas model</td>
<td>( M_t/M_\infty \approx k t^n )</td>
</tr>
<tr>
<td>Higuchi model</td>
<td>( Q = K_3 t^{1/2} )</td>
</tr>
</tbody>
</table>

8. **Fourier Transform infrared (FTIR) Spectroscopic studies:**

Fourier Transform Infrared spectrophotometer (FTIR) was used for infrared analysis of samples to intercept the interactions of drug with polymers and other ingredients. FTIR studies were conducted for characterization of drug in tablets. The tablets were compressed and powdered. The pelletized powder along with KBr was used for FTIR studies. The IR spectra were recorded using Fourier Transform Infrared Spectrophotometer. The samples were analyzed between the wave numbers 4000 and 400 cm².
3. Results and Discussion

Wavelength was determined by scanning about 20 mg of pure drug dissolved in 0.1 N HCl in between 190-390nm and 272nm was chosen as the wavelength. Standard graph was plotted in 0.1 N HCl and 7.2 pH buffer and they showed a good linearity with an R²-values of 0.998 & 0.999 respectively. FTIR spectra revealed that there was no interaction between the drug and the excipients. The powder blend of formulations were characterized with respect to Bulk density, Tapped density, Angle of repose, Carr’s index, Hausner’s ratio and the values were shown in Table no.3. Bulk density was found in the range of 0.308±0.01 - 0.521±0.04 g/cm³. Tapped density was found in the range of 0.324±0.02 - 0.659±0.04 g/cm³. Angle of repose was found to be in the range of 25.78±0.37 - 30.21±0.81 indicating good flow ability, Carr’s index was found to be in the range of 12.84±0.14 - 15.78±0.67 indicating good flow ability and Hausner’s ratio was found to be in the range of 1.16±0.11 - 1.32±0.06 indicating fair flow properties.

### Table 3: Results For Derived and Flow Properties

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Derived properties</th>
<th>Flow properties</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bulk density</td>
<td>Tapped density</td>
</tr>
<tr>
<td>F1</td>
<td>0.521±0.04</td>
<td>0.324±0.02</td>
</tr>
<tr>
<td>F2</td>
<td>0.481±0.01</td>
<td>0.397±0.04</td>
</tr>
<tr>
<td>F3</td>
<td>0.308±0.01</td>
<td>0.472±0.01</td>
</tr>
<tr>
<td>F4</td>
<td>0.495±0.06</td>
<td>0.659±0.04</td>
</tr>
<tr>
<td>F5</td>
<td>0.492±0.07</td>
<td>0.526±0.01</td>
</tr>
</tbody>
</table>

*** All values were expressed as mean± SD.

The tablets of formulations F1-F5 were subjected to various evaluation tests such as Weight variation, hardness, Thickness, Friability and Drug content. Results were shown in Table no.4. In weight variation test, the pharmacopoeial limit of percentage deviation for the tablets of less than 324 mg is ±7.5 %. The average percentage deviation of all the formulations were found to be within the limits. The hardness ranged from 5.2± 0.5 - 6.41 ± 0.64 kg/cm². The thickness of tablets ranged from 3.48 ± 0.88 - 4.14 ± 0.80 mm. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablets. The drug content was found to be uniform in all formulations and ranged from 98.23 ± 0.89 to 101.22 ± 0.88.

### Table 4: Evaluation of Physical Parameters of the Tablets

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Weight Variation(mg) (n=20)</th>
<th>Hardness (Kg/cm²) (n=10)</th>
<th>Thickness (mm) (n=10)</th>
<th>Friability (%) (n=10)</th>
<th>Drug content (%) (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>149.7±0.96</td>
<td>2.08±0.1</td>
<td>2.62±0.7</td>
<td>0.16±0.4</td>
<td>95.6±1.7</td>
</tr>
<tr>
<td>F1</td>
<td>305.2±0.83</td>
<td>6.08±0.37</td>
<td>3.63±0.06</td>
<td>0.23±0.07</td>
<td>98.23±0.89</td>
</tr>
<tr>
<td>F2</td>
<td>302.1±0.93</td>
<td>5.5±0.5</td>
<td>3.48±0.88</td>
<td>0.39±0.01</td>
<td>99.23±0.53</td>
</tr>
<tr>
<td>F3</td>
<td>306.6±1.48</td>
<td>5.2±0.5</td>
<td>4.14±0.80</td>
<td>0.19±0.05</td>
<td>98.65±0.78</td>
</tr>
<tr>
<td>F4</td>
<td>294.1±0.95</td>
<td>5.33±0.91</td>
<td>3.84±0.05</td>
<td>0.33±0.06</td>
<td>99.95±0.76</td>
</tr>
<tr>
<td>F5</td>
<td>298.4±1.64</td>
<td>6.41±0.64</td>
<td>3.76±0.06</td>
<td>0.24±0.07</td>
<td>101.22±0.88</td>
</tr>
</tbody>
</table>

*** All values were expressed as mean± SD.

### Table 5: Kinetics Data of All Formulations

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K₀</td>
<td>R²</td>
<td>K₁</td>
<td>R²</td>
</tr>
<tr>
<td>F1</td>
<td>9.45</td>
<td>0.9393</td>
<td>0.328</td>
<td>0.7387</td>
</tr>
<tr>
<td>F2</td>
<td>7.45</td>
<td>0.9312</td>
<td>0.222</td>
<td>0.8952</td>
</tr>
<tr>
<td>F3</td>
<td>6.011</td>
<td>0.9317</td>
<td>0.213</td>
<td>0.8934</td>
</tr>
<tr>
<td>F4</td>
<td>4.719</td>
<td>0.9294</td>
<td>0.156</td>
<td>0.8364</td>
</tr>
<tr>
<td>F5</td>
<td>3.965</td>
<td>0.9797</td>
<td>0.081</td>
<td>0.9127</td>
</tr>
</tbody>
</table>

In vitro dissolution studies of the formulations of MSP containing Guar gum (F1-F5) were carried out in 0.1N HCl for 2 hrs and in 7.2 PH buffer upto 24hrs and the Results were shown in Fig No.01.At the end of 24hr of the dissolution study, all the tablets coated with coat formulations F1-F5 were found intact. Except F1 formulation which started drug release at the end of 4hr, remaining all the formulations followed transit time of 5hrs i.e. stomach (2hrs) and small intestine (3hrs). The percentage of drug release from the formulation F1 at the...
end of 12hrs is 99.17%, F2 at the end of 16hrs is 97.42%, F3 at the end of 20hrs is 99%. F4 and F5 at the end of 24hrs is 99% and 87.24% respectively. As the concentration of polymer is increased the release rate of drug was decreased. Theoretically speaking this behaviour is expected since more amount of polymer always delays the release.

The data obtained from in vitro dissolution studies were fitted to Zero order, First order, Higuchi and Korsmeyer-Peppas equation and the results were shown in Table no.5. The Zero order plots of all the formulations were found to be high as indicated by their high regression values when compared with First order plots so all the formulations followed Zero order kinetics. All the formulations showed good correlation in Higuchi Kinetics clearly indicating that the drug release mechanism was predominantly Diffusion controlled. To confirm the exact mechanism of drug release from these tablets the data were fitted to Korsemeyer-Peppas equation. The slope values suggested that the drug release from all the formulation followed Non- Fickian diffusion (n>0.50).

4. Conclusion
The results of the present study showed that tablets formulated with Guar gum have controlled the drug release in stomach and small intestine and released maximum amount of drug in colonic envinorment. Thus we can say that tablets compression coated with Guar Gum would be potential as a formulation in delivering the drug to the colon as well as for the effective and safe therapy of IBD.

5. Acknowledgements
I would like to thank Synapse Life Sciences, Nakkalagutta, Hanamkonda, Warangal, Telangana, India, for providing all the facilities and support in carrying out this research work.

6. References