ABSTRACT

Objective: Metoclopramide hydrochloride (meto) is indicated in the treatment of diabetic gastro paresis. It is also used in the treatment of pregnancy-induced morning sickness. Present work involved the development of a chrono-modulated delivery system of meto, intended to be taken at bedtime which would elicited the therapeutic response early in the morning when needed the most to prevent the symptoms of diabetic gastro paresis and morning sickness.

Methods: Immediate release tablets of meto were prepared and optimized for disintegration time and in vitro drug release. Subsequently, these tablets were compression coated using various ratios of glyceryl dibehenate and diluents. The resulting tablets were evaluated for disintegration time and in vitro drug release. Optimized formulation was subjected to accelerated stability studies for 3 mo.

Results: The optimized immediate release tablets exhibited disintegration time of 2-3 min and more than 90% drug release within 30 min. These tablets when compression coated with the optimized ratio of glyceryl dibehenate and di-calcium phosphate could delay the disintegration time to 251 min. In vitro release study of the tablets showed the lag phase of 4 h after which there was a complete drug release within 1 h. Accelerated stability studies indicated good physical and chemical stability of the formulation.

Conclusion: Chrono-modulated formulation of meto could delay the release of the drug by 4 hour. This lag in the release is expected to modulate the time of therapeutic response of meto early in the morning at 6-7 h interval after the administration of dosage form at bedtime.

Keywords: Metoclopramide hydrochloride, Chrono-modulated, Glyceryl dibehenate, Diabetic gastro paresis, Morning sickness

INTRODUCTION

Meto, a dopamine receptor antagonist, is indicated in the treatment of gastro-esophageal reflux disease, nausea and vomiting, and morning sickness during pregnancy [1, 2]. It is the only approved drug in USA for the management of diabetic gastro paresis also known as diabetic gastric stasis [3]. Diabetic gastro paresis is caused by poorly controlled type 1 and type 2 diabetes. The vagus nerve supplying to the stomach becomes damaged due to high blood glucose and lack of glucose into the cells. It is a chronic gastrointestinal disorder in which the gastric contents are not emptied in the normal way but rather at a slower rate than the usual. This results in severe digestive system symptoms like feeling of fullness very quickly upon eating, nausea, loss of appetite, abdominal pain and discomfort, bloating and heartburn. Lack of adequate gastric motility to propel the contents forward into small intestine can significantly hamper the absorption of glucose and other nutrients into the blood. Administration of anti-diabetic medicines in such a situation where there is inadequate glucose level in the blood can create serious concerns of hypoglycemia [4]. Meto stimulates the contractions of the stomach and intestine and helps to improve the gastric emptying time by acting on the dopamine receptors of the stomach and intestine. It also controls the feeling of nausea and vomiting by its action on chemo-trigger receptor zone in the brain. It helps regulate the sugar levels of diabetic patients suffering from gastro paresis by making the food available in the intestine for absorption in a manner such that the antidiabetic medications can work effectively [2].

Almost 80% of pregnant women suffer from morning sickness in the first trimester of pregnancy. They have to deal with severe nausea and bouts of vomiting in the morning which affects the appetite and eating, resulting in severe weakness and malnutrition. Oral therapy with meto is proven safe in relieving the symptoms of morning sickness [5]. Meto is available in various dosage forms like immediate release tablets, orally disintegrating tablets, solution, as well as controlled release formulations in the market. An extensive work on sustained release formulations, controlled release matrix tablets, flash release films, fast dissolving tablets, bucco-adhesive tablets, gastro-retentive delivery of meto have been reported in the literature [6-13]. However, all these formulations can exercise the therapeutic effect only after 1 to 2 h of oral administration or in a sustained manner depending on the type of dosage form. This would render the medication almost ineffective in curbing the nausea and vomiting that initiates as soon as waking up in the morning in the case of pregnant women or in preventing fluctuation in blood glucose levels of the diabetic patients suffering from gastro paresis.

Chronotherapeutic drug delivery systems are gaining importance in the field of pharmaceutical technology as these systems reduce dosing frequency, toxicity and deliver a drug that matches the circadian rhythm of that particular disease when the symptoms are maximum to worse. Chrono-modulated delivery also known as the pulsatile delivery system is typically designed for treating cardiovascular conditions, asthma, arthritis wherein the symptoms are most intense early in the morning. Hence the Chrono modulated delivery is to be administered at the bed time and expected to elicit optimum therapeutic benefits early in the morning by virtue of lag time of 4 to 5 h in the drug release. Such a delivery offers the advantage of optimum pharmacological effect when needed the most, without causing the inconvenience of waking up in the middle of the night to administer the medicine in order to have a therapeutic effect early in the morning, thus improving the patient compliance [14-16].

With this in view, the aim of the present study was to develop a chrono-modulated delivery system for meto that can be administered at bedtime and would elicit the therapeutic effect after 6-7 h, i.e. early in the morning preventing morning sickness in the case of pregnant women. In the case of diabetic patients suffering from gastro paresis, such a formulation would facilitate gastric emptying of food into intestine for absorption so that the glucose absorbed could be effectively acted upon by the antidiabetic therapy preventing hypoglycemia.

MATERIALS AND METHODS

Chemicals and reagents

Meto was procured from IPCA laboratories pvt. ltd., Mumbai, India; microcrystalline cellulose, magnesium stearate and dicalcium...
Manufacturing process
1. Meto and lactose were sifted through 30 mesh sieve. The resultant material was mixed in a blender for 10 min.
2. Microcrystalline cellulose and crospovidone XL in the case of formula F1, microcrystalline cellulose and crospovidone XL 10 in formula F2 and for formulation F3-microcrystalline cellulose, crospovidone XL 10 and colloidal silicon dioxide were sifted through 30 mesh sieve and mixed in a blender for formulation F3.
3. Magnesium stearate was sifted through 40 mesh sieve and mixed with the blend of step 1 for 10 min.
4. The blend was mixed for 3 min.
5. The lubricated blend was transferred to the hopper of the compression machine and tablets were compressed at the hardness of 2-4 kilopascals (kp) using 4.7 mm circular, biconcave, plain punches using Cadmach CMD4 single rotary compression machine.

Evaluation of tablets
Tablets of all the three batches were evaluated using following parameters.

Average weight and weight variation-20 tablets were selected randomly and weighed. The average weight of the tablets was determined. These tablets were weighed individually and the weight variation was determined.

Hardness was measured using Dr. Schleuniger hardness tester (Model 8M).

Thickness was determined using vernier caliper (Mitutoyo, 500-197-30).

Table 1: Composition of immediate release tablets of meto

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Qty in mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Meto</td>
<td>11.82</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>24.18</td>
</tr>
<tr>
<td>Lactose spray dried</td>
<td>12</td>
</tr>
<tr>
<td>Crospovidone XL</td>
<td>1.5</td>
</tr>
<tr>
<td>Crospovidone XL 10</td>
<td>-</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Disintegration time was performed as per Indian Pharmacopoeia specifications using disintegration test apparatus (Electrolab tablet disintegration test apparatus ED2L).

Assay-Tablets, 10 numbers, were powdered. Powder equivalent to 11.82 mg meto was dissolved in the diluents mentioned below, diluted suitably and subjected to assay using reverse phase HPLC (Agilent technologies 1260 Infinity).

Column-C18, 5-micron packing
Wavelength-276 nm
Flow rate-1 ml/min
Injection volume-5 microlitre
Diluent-water: acetonitrile (75:25)
Buffer solution-5.4g/litre (l) of sodium acetate in water
Mobile phase-buffer solution: acetonitrile: tetra methyl ammonium hydroxide (70:30:0.2)

In vitro release study-Tablets of the batch, F3 were subjected to in vitro drug release studies using USP Type 2 dissolution test apparatus employing 900 ml distilled water as a medium at 50 rpm for 30 min [17]. The aliquots were analyzed by High-performance liquid chromatography (HPLC) using the same method used for the assay.

Table 2: Formulae for the compression coating of meto immediate release tablets

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F4</td>
</tr>
<tr>
<td>Core tablets of F3</td>
<td>50</td>
</tr>
<tr>
<td>Glyceril dibehenate</td>
<td>127</td>
</tr>
<tr>
<td>Dicalcium phosphate</td>
<td>110</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>57</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>3</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3</td>
</tr>
</tbody>
</table>

3. The coating material was compressed around the core tablets using 9 mm circular biconcave punches set on Cadmach press coater CPC 900 machine.

Tablets were evaluated for average weight, hardness, thickness, disintegration time in a similar manner as conducted for core tablets. In vitro dissolution studies were conducted for 5 h duration, using similar conditions and apparatus as that for the immediate release tablets. The aliquots were drawn at 4, 4.5 and 5 h intervals.
Hardness challenge study

The blend of batch F9 was subjected to hardness challenge during compression. This involved compressing half the lot at lower compression pressure and rest of the lot at higher pressure.

Reproducibility trial and accelerated stability studies

Batch F10 was prepared similarly to the composition of batch F9 in order to evaluate the reproducibility and the stability profile of the formulation. The tablets were packed in aluminum foil sachets and subjected to accelerated storage conditions of 40 °C/75 % RH. Samples were evaluated at the time intervals of 1, 2 and 3 mo.

Statistical analysis

One way analysis of variance (ANOVA) was employed to assess the difference between the assay values of initial and that of stability samples using Sigma Stat software (Sigma stat 2.03, SPSS). The observed p-values of <0.05 were considered statistically significant for the test. The similar statistical test was applied to find a difference in the in vitro drug release at each time point among stability samples.

RESULTS AND DISCUSSION

Preparation of immediate release core tablets of meto

The aim of the present study was to develop the chrono-modulated delivery system for meto using compression coating technique. For this, core tablets containing the drug needed to be developed initially which would release the drug immediately upon dissolving the external barrier coat. Immediate release tablets of meto were hence prepared by direct compression technique.

The powder blend of formula F1 lacked appropriate flow properties which resulted in poor flow from the hopper onto the feed frame. Also, the tablet surface appeared slightly rough. It was required to improve the flow of the powder blend and improve the appearance. Magnesium stearate concentration was increased to 1.5 % and finer grade of the flow of the powder blend and improve the appearance. Magnesium stearate concentration was increased to 1.5 % and finer grade of the formulation. The tablets were packed in aluminum foil sachets and subjected to accelerated storage conditions of 40 °C/75 % RH. Samples were evaluated at the time intervals of 1, 2 and 3 mo.

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Accelerated stability studies

Stability samples of batch F10, when evaluated at various time intervals, showed no significant difference in appearance, hardness or other physical traits as compared to initial samples (table 6).

Table 5: Hardness challenge studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tablets of F9 with low hardness</th>
<th>Tablets of F9 with High Hardness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight (mg)</td>
<td>348.5±1.9</td>
<td>351.5±1.8</td>
</tr>
<tr>
<td>Hardness (kp)</td>
<td>1.5–2.5</td>
<td>6-7</td>
</tr>
<tr>
<td>Disintegration time (min)</td>
<td>173</td>
<td>267</td>
</tr>
<tr>
<td>Drug release at 4 h (%)</td>
<td>38±±2.5</td>
<td>0</td>
</tr>
<tr>
<td>Drug release at 4.5 h (%)</td>
<td>89±±5.6</td>
<td>59.6±±3.6</td>
</tr>
<tr>
<td>Drug release at 5 h (%)</td>
<td>108±±2.2</td>
<td>86±±0.5</td>
</tr>
</tbody>
</table>

Values of drug release are represented as mean±standard deviation, n=6

Accelerated stability studies

Stability samples of batch F10, when evaluated at various time intervals, showed no significant difference in appearance, hardness or other physical traits as compared to initial samples (table 6).

Table 6: Evaluation of stability samples of batch F10

<table>
<thead>
<tr>
<th>Test</th>
<th>Specification</th>
<th>Initial</th>
<th>1 mo</th>
<th>2 mo</th>
<th>3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>White to off-white coloured circular, biconvex tablets</td>
<td>White to off-white coloured circular, biconvex tablets</td>
<td>White to off-white coloured circular, biconvex tablets</td>
<td>White to off-white coloured circular, biconvex tablets</td>
<td>White to off-white coloured circular, biconvex tablets</td>
</tr>
<tr>
<td>Average weight (mg)</td>
<td>350 m±3%</td>
<td>99.8±±0.7</td>
<td>100.3±±1.7</td>
<td>99.3±±1.1</td>
<td>99.1±±2.0</td>
</tr>
<tr>
<td>Hardness (kp)</td>
<td>3–7kp</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Disintegration time (min)</td>
<td>230–300 min</td>
<td>65.8±±4.1</td>
<td>63.9±±2.7</td>
<td>66.4±±3.5</td>
<td>62.6±±3.2</td>
</tr>
<tr>
<td>Assay (mg)</td>
<td>90–110%</td>
<td>97.2±±3.8</td>
<td>93.2±±1.4</td>
<td>95.2±±2.5</td>
<td>91.5±±1.9</td>
</tr>
<tr>
<td>Drug release</td>
<td>4 h: NMT 10%</td>
<td>97.2±±3.8</td>
<td>93.2±±1.4</td>
<td>95.2±±2.5</td>
<td>91.5±±1.9</td>
</tr>
<tr>
<td></td>
<td>4.5 h: NLT 50%</td>
<td>65.8±±4.1</td>
<td>63.9±±2.7</td>
<td>66.4±±3.5</td>
<td>62.6±±3.2</td>
</tr>
<tr>
<td></td>
<td>5 h: NLT 85%</td>
<td>97.2±±3.8</td>
<td>93.2±±1.4</td>
<td>95.2±±2.5</td>
<td>91.5±±1.9</td>
</tr>
</tbody>
</table>

Values of assay and drug release are represented as mean±standard deviation, n=3, n=6 respectively

Acknowledgment

Authors would like to acknowledge Gattefosse India Pvt. Ltd for generously providing the gift sample of glyceryl dibehenate.

CONFLICT OF INTERESTS

Declare none

REFERENCES


How to cite this article