FORMULATION AND EVALUATION OF METOCLOPRAMIDE MOUTH DISSOLVING TABLETS


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ABSTRACT

The purpose of this research was to formulate mouth dissolving tablets (MDT) of Metoclopramide. Mouth dissolving tablets are designed to disintegrate and dissolve in saliva and then easily swallowed without need of water which is a major benefit over conventional dosage form. Metoclopramide is a 5 HT receptor antagonist, used to prevent nausea and vomiting. It is essential to administer antiemetic with a minimum quantity of water in order to prevent subsequent episodes of vomiting due to ingestion of water. Mouth dissolving tablets of Metoclopramide were prepared by using sodium starch Glycolate (SSG) and croscarmellose sodium (CCS) as superdisintegrants. The formulated tablets were evaluated for hardness, friability, drug content, weight variation, uniformity of dispersion, wetting time, wetting volume, in vitro dispersion time, in vitro disintegration time and in vitro drug release. The dissolution profiles of prepared tablets were compared with pure drug and marketed product. Rapid disintegration of tablets formulated in this research possibly help in administration of Metoclopramide in a more palatable form without water to prevent emesis.

Key words: Metoclopramide, Mouth dissolving Tablets (MDTs), Superdisintegrants.

INTRODUCTION

Many patients of different age groups complain of some solid conventional dosage forms such as tablets and capsules due to difficulty in swallowing (Seager H, 1998). Difficulty in swallowing (dysphagia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with those groups (Lindgreen L, Janson, 1993; Bhushan Y et al., 2000). Other categories that experience problems in using conventional oral dosage forms include the mentally ill, uncooperative and patients suffering from nausea, motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to non-availability of water. These problems led to the development of a novel type of solid oral dosage form called mouth dissolving tablet, which disintegrates/dissolves rapidly in saliva without the need of drinking water. In order to solve this problem and improve patient acceptance and compliance, the development of solid dosage forms that disintegrate rapidly or dissolve even when taken orally without water is being undertaken. Oral fast-dissintegrating dosage forms (tablet or a capsule) are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form (Ciper M, Bodmeier R, 2006) into a solution or suspension in the mouth without the need for water (Suresh B et al., 2008). The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50sec after administration (Dobetti L, 2001). The solution containing the active ingredients is swallowed, and the active ingredients are

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then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect. Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing (Koizumi K et al., 1997).

Orally disintegrating tablets are also called as orodispensible tablets, quick-disintegrating tablets, mouth-dissolving tablets, fast-disintegrating tablets, fast dissolving tablets, rapid-dissolving tablets, porous tablets, and rapimelts. Metoclopramide is a potent antiemetic Drug (Thomson Micromedex Healthcare, 2001) indicated for the treatment and/or prophylaxis of postoperative or chemotherapy or radiotherapy-induced emesis and also used in the early onset of alcoholism (Johnson BA et al., 2000). In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with glass of water; As Metoclopramide is intensely bitter, it cannot be incorporated directly into mouth dissolving tablets (MDT). The main objective behind formulation of such a dosage form will definitely get futile (Ishikawa T et al., 1999). Taste masking of the active ingredients was be done by adding sugar based diluents or by forming complex with the polymer.

MATERIALS AND METHODS

Metoclopramide was obtained as a gift sample from Sun Pharmaceuticals Ltd., Vadodara., croscarmellose sodium(yarrow chemicals, Mumbai) and Sodium starch glycolate (gift sample from micro labs, Bangalore), Mannitol, MCC, Magnesium stearate, and Aspartame from S.D Fine Chem. Mumbai.

Formulation of Mouth dissolving Tablets of Metoclopramide

Preparation of tablets by superdisintegrant addition technique

SSG and CCS were used as super disintegrants for preparation of MDTs of Metoclopramide by direct compression method. Various batches of tablet formulations prepared are shown in Table 1. Optimum combination was worked out based on powder blend properties and disintegration time of the tablets.

Preparation of powder blends for compression

Mannitol, SSG and CCS were passed through a 100 # screen prior to mixing. Metoclopramide was mixed to this blend of powder. Thereafter, flavour, aerosil, and magnesium stearate were added and mixed.

Evaluation of powder blend

Bulk density

Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measuring the volume and weight “as it is” (Shagufta K et al., 2007).

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of powder on mechanical tapping apparatus, which was operated for fixed number of taps until the powder bed volume reached a minimum. Using the weight of powder in a cylinder and this minimum volume, the tapped density was computed. From the results of bulk density and tapped density, Carr’s index and Hausner’s ratio were calculated to determine the flow properties.

Angle of repose

For the measurement of angle of repose, a glass funnel was secured with its tip at a given height (H) above a piece of graph paper placed on a horizontal surface. Powder was poured through the funnel until the apex of the conical pile touched the tip of the funnel. The angle of repose was calculated with the formula tan Θ = H/R, where Θ is the angle of repose and R is the radius of the conical pile.

Compressibility (Carr’s) Index

An accurate weight of formula granules was poured into a volumetric cylinder to occupy a volume (V0) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (Vf). The Carr’s index was calculated using Equation: Compressibility index = 100 × V0 –Vf

V0

Compressibility of tablets

The powder blends prepared for different batches were compressed into flat tablets, 150 mg in weight (Table 2), using 10 station tablet punching machine (Rimek, India) with flat faced punches.

EVALUATION OF TABLETS

Uniformity of weight (Weight Variation)

Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness

The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was determined using a Monsanto hardness tester.

Friability

Friability of tablets was measured by using Roche Friabilator. Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabilator at 25 rpm for 4 minutes. The tablets were dedusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. Friability below 1% was considered acceptable.
**In-vitro disintegration time**

The disintegration time was measured using dissolution apparatus USP XXIII paddle apparatus. The vessel was filled with 500 ml of water maintained at 37 °C. The paddle was rotated at 100 revolutions per minute. The tablet was placed inside the sinker and the time at which it passes completely through the mesh of sinker was taken as the disintegration of the tablet.

**Wetting time**

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a petri dish with a 10cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.

**Wetting volume**

The tablet was placed in the center of the petri dish and with the help of 5ml pipette; distilled water was added drop wise on the tablet. The volume required to completely disintegrate the tablet was noted as the wetting volume.

**Dissolution study**

The dissolution study was performed for pure drug Metoclopramide, batch and marketed conventional tablet formulation by using USP XXIII paddle apparatus. The dissolution medium was distilled water (900 mL, 37 ± 0.50C). The rate of agitation of the paddle was 50 rpm. Aliquot of dissolution medium was withdrawn at specific time interval of 5min, it was filtered and absorbance was measured spectrophotometrically at 310 nm by UV spectrophotometer (UV-1601, Shimadzu Corporation, Kyoto, Japan)

### Table 1. Formulation Of Mdts By Direct Compression Method

<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>
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<tbody>
<tr>
<td>Metoclopramide</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<td>10</td>
</tr>
<tr>
<td>SSG</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Mannitol</td>
<td>95</td>
<td>92</td>
<td>89</td>
<td>92</td>
<td>89</td>
<td>86</td>
</tr>
<tr>
<td>MCC</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Aspartame</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Magnesium stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mint flavour</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
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</tr>
</tbody>
</table>

SSG-Sodium starch glycolate, CCS-Croscarmellose sodium, MCC-Micro crystalline cellulose

### Table 2. Pre-Compressional Evaluation Parameters

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Bulk Density (gm/ml)</th>
<th>Tapped Density(gm/ml)</th>
<th>Angle of Repose ( Θ )</th>
<th>Carr’s Index</th>
<th>Hausner ratio</th>
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<tbody>
<tr>
<td>F₁</td>
<td>0.58±0.067</td>
<td>0.66±0.075</td>
<td>27.06±1.67</td>
<td>0.12</td>
<td>1.13</td>
</tr>
<tr>
<td>F₂</td>
<td>0.61±0.046</td>
<td>0.69±0.064</td>
<td>24.17±1.75</td>
<td>0.11</td>
<td>1.13</td>
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<tr>
<td>F₃</td>
<td>0.64±0.047</td>
<td>0.72±0.047</td>
<td>24.51±1.42</td>
<td>0.11</td>
<td>1.12</td>
</tr>
<tr>
<td>F₄</td>
<td>0.59±0.023</td>
<td>0.67±0.087</td>
<td>26.49±1.63</td>
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<td>1.13</td>
</tr>
<tr>
<td>F₅</td>
<td>0.62±0.046</td>
<td>0.69±0.064</td>
<td>24.71±1.23</td>
<td>0.10</td>
<td>1.11</td>
</tr>
<tr>
<td>F₆</td>
<td>0.63±0.023</td>
<td>0.66±0.084</td>
<td>24.62±0.89</td>
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### Table 3. Post-Compressional Evaluation Parameters

<table>
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<tr>
<th>Batch</th>
<th>Weight Variation (%)</th>
<th>Hardness (Kg/cm²)</th>
<th>Friability (%)</th>
<th>In-vitro Disintegration Time (seconds)</th>
<th>Wetting time (seconds)</th>
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<tbody>
<tr>
<td>F₁</td>
<td>150.5</td>
<td>3.76</td>
<td>0.5±0.14</td>
<td>27</td>
<td>45</td>
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<tr>
<td>F₂</td>
<td>150.5</td>
<td>3.70</td>
<td>0.6±0.17</td>
<td>25</td>
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<td>F₃</td>
<td>149.6</td>
<td>3.76</td>
<td>0.7±0.16</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>F₄</td>
<td>150.0</td>
<td>3.24</td>
<td>0.6±0.12</td>
<td>23</td>
<td>45</td>
</tr>
<tr>
<td>F₅</td>
<td>150.1</td>
<td>3.66</td>
<td>0.7±0.17</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>F₆</td>
<td>150.1</td>
<td>3.24</td>
<td>0.7±0.18</td>
<td>17</td>
<td>36</td>
</tr>
</tbody>
</table>
RESULTS AND DISCUSSION

The present research was undertaken to formulate the mouth dissolving tablets of Metoclopramide. Mouth dissolving tablets of Metoclopramide by direct compression method using sodium starch glycolate and croscarmellose sodium as superdisintegrants. The primary requirement for both dosage forms is quicker disintegration. The results obtained by evaluating the powder blends of drug and excipients is shown in Table 2. Values for angle of repose were found in the range of 24 to 27° showing that the blend of powder was free flowing and can be used for direct compression. The value for Carr’s index was less than 1, indicating that all the batches of powder blends were having good compressibility. The results for evaluation of different batches of Metoclopramide mouth dissolving tablets prepared by direct compression technique were within the limits for uncoated tablets as per Indian Pharmacopoeia. Hardness of tablets was found to be in range of 3.24 to 3.76 kg/cm². Friability was observed between 0.5 to 0.7%. Thus the hardness and friability data indicates good mechanical resistance of tablets. In-vitro disintegration time for different batches was 17 to 27 seconds. When the amount of SSG increased up to 6% per tablet, the disintegration time decreased. Wetting time is determined to get idea of wetting lag time before disintegration and also found that as the wetting time decreased disintegration time also decreased (Fig 1). Thus these results indicate that these tablets would disintegrate almost instantaneously when they will come in contact with even slight quantity of saliva in the mouth. By the mechanism of swelling SSG and CCS shows their disintegration effect. The formulation (F₃) having 6% of SSG showed best results when compared to other formulations. It was seen that almost 90% of drug was released in first fifteen minutes (Fig 2). Thus the release rate of Metoclopramide was significantly enhanced by formulating MDT using superdisintegrants.

CONCLUSION

Mouth dissolving tablets Metoclopramide were prepared by direct compression method using sodium starch glycolate and croscarmellose sodium as superdisintegrants. The tablets disintegrated rapidly and had acceptable hardness and friability. In vitro drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the superdisintegrant based mouth dissolving tablets of Metoclopramide would be quite effective in emesis, providing quick onset of action without need of water for administration.

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