FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF MEMANTINE HYDROCHLORIDE

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ABSTRACT

The aim of this research work to formulate mouth dissolving tablets of memantine hydrochloride to increase its bioavailability. Mouth dissolving tablets were prepared by direct compression technique using sublimation approach. The powder mixtures were prepared to subject both pre and post compression evaluation parameters like micromeritics properties, tablet hardness, friability, wetting time, disintegration time and in vitro drug release. The results of micromeritics studies revealed that all formulations were of acceptable to good flowability. Tablet friability and hardness indicated good mechanical strength. The F2 formulation which is having high concentration of magnesium stearate was given promising results in tablet disintegration, waiting time and gives faster dissolution rate. Crospovidone was used as a superdisintegrant for increasing of dissolution rate of tablets. The optimized formulation showed 98.64% within 10 min. The prepared tablets seem to be attractive to conventional marketed formulations.

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INTRODUCTION

New drug delivery system (NDDS) development is largely based on promoting the therapeutic efficacy [1]. While there is no doubt that new molecules are the most important components in drug formulations, the development of new drug delivery has enjoyed tremendous growth in the academia and industry [2]. One such system is fast dissolving tablet (FDT) or Orally disintegrating tablet (ODT) and their growing importance was underlined recently when European Pharmacopoeia adopted the term Orodispersible tablet as a tablet that to be placed in the oral cavity where it disperses rapidly before swallowing [3]. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of the drug is significantly greater than those observed from conventional dosage form [4]. Many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, bedridden, disabled, nauseated, or on reduced-liquid-intake diets have difficulty in swallowing conventional solid dosage forms [5-6]. Sometimes it may be difficult to swallow conventional products due to unavailability of water, mostly in the journey, allergic reactions and episodes of coughing [7]. Mouth dissolving tablets were a better alternative for oral medication in all the above conditions. Memantine is an antiparkinson agent, and it is used for the treatment of Alzheimer disease. The dissolution rate and bioavailability of a poorly soluble drug form solid dosage form depend much on formulation additive and formulation characteristics [8]. On the basis of these considerations, the present study was an attempt to formulate and evaluation of mouth dissolving tablets of memantine hydrochloride to increase its bioavailability.

EXPERIMENTAL

Materials

Memantine hydrochloride was a gift sample from MSN Labs (Hyderabad, India). All of the chemicals used for analytical grade.

Methods

Development of mouth dissolving tablet of memantine HCL

The memantine hydrochloride mouth dissolving tablet was prepared by direct compression method employing various excipients as mentioned in Table 1. Memantine hydrochloride, Microcrystalline cellulose, mannitol, crospovidone, lactose, t alc, polyvinyl pyrrolidine, sodium saccharine, sodium citrate was passed through #40 mesh and mixed well. The magnesium stearate was individually passed through #60 mesh. The blend was lubricated with magnesium stearate. The tablets were compressed using a 10 station tablet compression machine using 8 mm round shaped punches.

Formulation Characterization

Bulk density [9]

The powder sample under test was passed sufficient to complete the test through a 1.00 mm (No. 18) screen to break up agglomerates that may have formed during storage. Approximately 50 g of the test sample, M, weighed with 0.1% accuracy was introduced into a dry 250 ml graduated glass cylinder.

Tapped density

The tapped density was calculated, in g per ml by the formula:

\[
\text{Tapped density} \ (D_t) = \frac{M}{V_t}
\]

Where, \( M \) = Weight of the sample mass taken.

\( V_t \) = Tapped volume.

Compressibility index

The simplest way for measurement of powder flow is compressibility, an indication of the ease with which a material can be induced to flow is given by Compressibility index (C.I.).

Hausner ratio

The tapped density and bulk density were measured and the Hausner ratio was calculated using the formula:

\[
\text{Hausner ratio} = \frac{D_t}{D_b}
\]

Where, \( D_t \) = Tapped density

\( D_b \) = Bulk density.

Particle size distribution

Particle size distribution was determined by using a sieve shaker. Approximately weighed amount, i.e. 50 g of drug sample under study was kept at the top of the sieve, arranged in descending order of mesh size \# i.e. 1.18mm, 710µ, 500µ, 355µ, 250µ, 180µ, and the base pan. The assembly was tightly closed and allowed to vibrate for 10 min at 5 HP. The amount of power retained on each sieve and the cumulative retention was calculated. The same procedure was repeated for all formulations of placebo and drugs.

Evaluation of tablets

The formulations were evaluated for hardness, weight variation, thickness, friability, disintegration time, disintegration time in the oral cavity, in vitro dispersion time, wetting time and water absorption ratio, content uniformity, and in vitro dissolution study.
Tablet Hardness [10]

Hardness is the crushing strength of tablet which determines the ease of handling and the rigors of the transportation. For each formulation, 3 tablets were used for the study.

Weight Variation Test

The weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The table given below shows the weight variation tolerance for uncoated tablets.

Thickness

The thickness of the tablets was measured using Digital Vernier Caliper. It is expressed in mm.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause the tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dedusted and reweighed.


One tablet was placed in each of six tubes of disintegration test apparatus. Disintegration test was carried out at 37 ± 2 °C according to USP 22. Disintegration test apparatus without disc, time required for the complete passage of tablet fragments through the sieve (#10) was consider as a disintegration time of a tablet.

Disintegration Time in Oral Cavity

The disintegration time in the oral cavity of 6 human volunteers was measured by placing the tablet on the tongue until no lumps remain. It is expressed in seconds.

In-vitro Dispersion Time

In vitro dispersion time was measured by dropping tablets in a 100 ml of water and stir until completely dispersed. A Smooth dispersion is produced which passed through a sieve screen with a nominal mesh aperture of 710 μm.

Wetting Time and Water Absorption Test

Wetting time is closely related to the inner structure of tablets and to the hydrophilicity of the excipients. According to the following equation proposed by Washburn E. W., the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders. It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting time is an important step in the disintegration process to take place.

A piece of tissue paper folded twice was placed in a small petri dish (internal diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°C.

The same procedure was repeated for determining the water absorption ratio. The wetted tablet was then weighed. Water absorption ratio, R, was determined according to the following equation:

\[ R = \left( \frac{W_a - W_b}{W_a} \right) \times 100 \]

Where, \( W_a \) = Weight of tablet before study.
\( W_b \) = Weight of tablet after study.

Assay

For this 30 tablets were randomly selected from all formulations. Out of 30 tablets 10 tablets were crushed into fine powder. The powder taken equivalent to label claim was weighed accurately, dissolved in their respective media and assayed individually at respective λ max against the reagent blank. The drug content should be within 90% to 110% of the labeled claim.

Uniformity of content

Powder one tablet, shake 1 ml of dilute Hcl and 401 ml of water for 15 min, and add sufficient water to produce 100 ml and mix. Centrifuge about 15 ml and to 10 ml of the clear, supernatant liquid, add 2 ml of 1M Hcl and sufficient water to produce a solution containing about 0.005 % w/w concentrated Hcl. Measure the absorbance of the resulting solution at the max at about 254 nm.

In vitro Dissolution studies [12]

The in vitro dissolution study was carried out in USP dissolution test apparatus Type 2 (paddle). Samples were withdrawn at 1, 2, 4, 6, 8, and 10 minutes time intervals by replacing with same dissolution medium and the dissolution of the drug.
RESULTS AND DISCUSSION

Analytical development

The drugs were scanned in the range of 200 - 400 nm in UV-visible spectrophotometer to validate its absorption maxima as mentioned in the official books and the \( \lambda_{max} \) was found to the 529 nm for memantine hydrochloride.

Calibration curve

The calibration curves were plotted for memantine hydrochloride using different concentration ranges from 5-10μg/ml. The absorbances are shown in the Table 2 and the respective graphs are shown in Figure 2. Perfect linearity was observed in all cases shown by the \( R^2 \) (correlation coefficient) value indicating the absorbance vary proportionally with concentrations in the selected range obeying Beer-Lambert’s law.

Formulation Development

API Characterization

The physical characteristics of the selected API such as bulk density, tapped density, Hausner ratio, compressibility index, and partial size distribution are shown in Table 3. The bulk density of all the drugs was found in the range of 0.48 - 0.52 g/ml and tapped density was 0.54 - 0.60 g/ml. The Hausner’s ratio was found in the range of 1.14 - 1.15, indicating the drugs under study have poor flow properties because Hausner’s ratio less than 1.25 indicates better flow property. The compressibility index was found in the range of 12.6 % -13.6 %. The values below 15% indicates a powder having good flow characteristics, whereas above 25% indicates poor flowability.

Evaluation of Tablets

The tablet parameters observed are given in Table 4. The tablets were compressed at the specified weight. The weights of tablets were within ± 3%, which falls within the acceptable weight variation range of ± 7.5% as per USP. Hence all formulations passed the weight variation test. Hardness of all formulations was in the range of 3.1 – 3.6 Kg/cm². The hardness of all formulations was kept constant within the above mentioned range by adjusting the compression load in order to compare the disintegration time between the formulations prepared using different excipients. The friability values of none of the formulations exceeded 0.68%. The results of friability indicate that the tablets were mechanically stable and could handle the rigors of transportation and handling. Thickness of all formulations was between 3.42 – 3.76 mm indicating fairly acceptable tableting.

Disintegration time is very important parameter of FDT, the internal structure of a tablet that is pore size distribution, water penetration into tablet and swelling of disintegrant substance are suggested to be the mechanism of disintegration. The disintegration time of formulation was satisfying because it disintegrate within 1 min. An ideal FDT should disintegrate within a minute. But the formulation No.F2 gives best disintegrating time, i.e. 17 ± 2, Sec (Figure 3 & Table 4). Percentage drug content (Assay) of Formulation No. F1 – F9 were found to be 93% w/w (Table 4) which is within the acceptable limits as per individual monograph of selected drugs. In vitro dispersion time was measured by the time taken to undergo uniform dispersion as per the British Pharmacopoeia. The rapid dispersion was observed in the Formulation No.F2 indicating direct information regarding the disintegrating nature of crosspovidone, the effect of mannitol and microcrystalline cellulose combination and the aqueous solvent. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue. Some individuals have the tendency to chew or crush the tablet after keeping in the oral cavity.

This is the reason why the disintegration time in oral cavity and the wetting values do not coincide. Even though the disintegration time in oral cavity and the wetting time values do not generally coincide, wetting time is still considered very valuable parameters to assess the disintegration time of the tablet. The wetting time of Formulation No.F1 – F9 were found in the range of 37 - 87 sec and 34-79 sec. This may be due to ability of swelling and also water absorption capacity. The water absorption ratio is closely related to the inner structure of tablets. The water absorption ratio values of formulation No. F1 – F9 were to found 12.4-16.1%.

In vitro Dissolution study

The dissolution study on Formulation No. F1 – F9 were carried out using 500 ml of respective dissolution medium as mentioned in Table No. 16 at 50 rpm using USP dissolution apparatus II (paddle). The Formulation No. F1, F2, F3, F4, F5, F6, F7, F8, F9 shows 74.32 %, 98.64 %, 67.50 %, 94.59 %, 98.10 %, 85.13 %, 70.25 %, 66.21 %, 79.72 % in 10 min respectively (Table 5 and Figure 4 and Figure 5). High dissolution resulted due to faster breakdown and rapid dispersion of the tablet. It may be due to rapid diffusion or the porous nature of the tablet. The dissolution graphs are shown in Figure respectively. By this study, an important conclusion can be drawn that Addition of super disintegration technique has improved the dissolution profile of the water soluble drugs besides expediting the disintegration time.
Figure 1: Fourier transform infrared spectra of memantine hydrochloride.

Figure 2: Calibration curve of memantine hydrochloride in pH 3.6 acetate buffer.

Figure 3: Dissolution profile of memantine hydrochloride (F2) in pH 3.6 acetate buffer.
Figure 4: Comparison of dissolution profile of memantine hydrochloride (F1, F2, F3, F4) in pH 3.6 acetate buffer.

Figure 5: Comparison of dissolution Profile of memantine hydrochloride (F5, F6, F7, F8, F9) in pH 3.6 acetate buffer.

Table 1: Formulation of mouth dissolving memantine hydrochloride tablets.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1(mg)</th>
<th>F2(mg)</th>
<th>F3(mg)</th>
<th>F4(mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine hydrochloride</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>---</td>
<td>20</td>
<td>---</td>
<td>15</td>
</tr>
<tr>
<td>Mannitol</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lactose</td>
<td>25</td>
<td>25</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Talc</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Polyvinyl Pyrrolidine</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Sodium saccharine</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>6</td>
<td>-----</td>
<td>-----</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2: Calibration data of memantine hydrochloride.

<table>
<thead>
<tr>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.07</td>
</tr>
<tr>
<td>10</td>
<td>0.8</td>
</tr>
<tr>
<td>15</td>
<td>0.9</td>
</tr>
<tr>
<td>20</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Table 3: Physical characteristics of product of formulation.

<table>
<thead>
<tr>
<th>Parameters</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>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk density (g/ml)</td>
<td>0.390</td>
<td>0.401</td>
<td>0.387</td>
<td>0.490</td>
<td>0.511</td>
<td>0.495</td>
<td>0.396</td>
<td>0.492</td>
<td>0.503</td>
</tr>
<tr>
<td>Tapped density (g/ml)</td>
<td>0.450</td>
<td>0.476</td>
<td>0.458</td>
<td>0.581</td>
<td>0.603</td>
<td>0.574</td>
<td>0.481</td>
<td>0.581</td>
<td>0.593</td>
</tr>
<tr>
<td>Compressibility Index (%)</td>
<td>13.3</td>
<td>15.7</td>
<td>15.5</td>
<td>14.43</td>
<td>15.04</td>
<td>13.76</td>
<td>19.11</td>
<td>14.21</td>
<td>13.98</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.15</td>
<td>1.18</td>
<td>1.18</td>
<td>1.17</td>
<td>1.17</td>
<td>1.17</td>
<td>1.17</td>
<td>1.17</td>
<td>1.18</td>
</tr>
<tr>
<td>Angle of repose</td>
<td>26.7</td>
<td>29.4</td>
<td>28.7</td>
<td>27.3</td>
<td>28.5</td>
<td>27.9</td>
<td>31.2</td>
<td>26.5</td>
<td>28.4</td>
</tr>
</tbody>
</table>

Table 4: Formulation details of F1–F9 (memantine hydrochloride).

<table>
<thead>
<tr>
<th>Evaluation</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>
</tr>
</thead>
<tbody>
<tr>
<td>Weight variation (mg)</td>
<td>150±2</td>
<td>150±1</td>
<td>151±1</td>
<td>150±2</td>
<td>150±1</td>
<td>149±2</td>
<td>150±2</td>
<td>151±1</td>
<td>150±2</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>3.53±</td>
<td>3.49±</td>
<td>3.51±</td>
<td>3.53±</td>
<td>3.76±</td>
<td>3.63±</td>
<td>3.57±</td>
<td>3.62±</td>
<td>3.57±</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.08</td>
<td>0.04</td>
<td>0.04</td>
<td>0.02</td>
<td>0.03</td>
<td>0.02</td>
<td>0.06</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Hardness(Kg/cm³)</td>
<td>3.3±</td>
<td>3.6±</td>
<td>3.1±</td>
<td>3.4±</td>
<td>3.6±</td>
<td>3.3±</td>
<td>3.5±</td>
<td>3.4±</td>
<td>3.6±</td>
</tr>
<tr>
<td>Disintegration time (sec)</td>
<td>26±</td>
<td>17±</td>
<td>32±</td>
<td>23±</td>
<td>41±</td>
<td>30±</td>
<td>50±</td>
<td>57±</td>
<td>49±</td>
</tr>
<tr>
<td>Disintegration time (sec)</td>
<td>1.15</td>
<td>2.1</td>
<td>1.16</td>
<td>2.15</td>
<td>2.27</td>
<td>1.19</td>
<td>2.41</td>
<td>3.16</td>
<td>2.18</td>
</tr>
<tr>
<td>Dispersion time (sec)</td>
<td>33±</td>
<td>22±</td>
<td>38±</td>
<td>28±</td>
<td>49±</td>
<td>38±</td>
<td>61±</td>
<td>68±</td>
<td>59±</td>
</tr>
<tr>
<td>Content uniformity (%)</td>
<td>96.1±</td>
<td>99.1±</td>
<td>93.2±</td>
<td>97.4±</td>
<td>94.3±</td>
<td>96.1±</td>
<td>95.1±</td>
<td>94.3±</td>
<td>95.5±</td>
</tr>
<tr>
<td>Water absorption ratio</td>
<td>13.1±</td>
<td>12.4±</td>
<td>13.1±</td>
<td>14.3±</td>
<td>13.9±</td>
<td>15.1±</td>
<td>14.8±</td>
<td>16.1±</td>
<td>15.2±</td>
</tr>
<tr>
<td>Assay (% w/w)</td>
<td>98.1</td>
<td>99.3</td>
<td>97.3</td>
<td>98.1</td>
<td>96.9</td>
<td>97.1</td>
<td>93.2</td>
<td>94.3</td>
<td>95.2</td>
</tr>
<tr>
<td>Wetting time</td>
<td>1.61</td>
<td>1.37</td>
<td>1.01</td>
<td>1.62</td>
<td>1.89</td>
<td>1.09</td>
<td>3.10</td>
<td>3.25</td>
<td>2.15</td>
</tr>
</tbody>
</table>

Table 5: In vitro Dissolution of formulation No. F1 – F9 (Memantine Hydrochloride).

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>Dissolution Medium</th>
<th>λ max</th>
<th>Cumulative % drug release (memantine hydrochloride)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 min</td>
</tr>
<tr>
<td>F1</td>
<td>pH 3.6 acetate buffer</td>
<td>229nm</td>
<td>25.67</td>
</tr>
<tr>
<td>F2</td>
<td>pH 3.6 acetate buffer</td>
<td>229nm</td>
<td>43.24</td>
</tr>
<tr>
<td>F3</td>
<td>pH 3.6 acetatebuffer</td>
<td>229nm</td>
<td>22.97</td>
</tr>
<tr>
<td>F4</td>
<td>pH 3.6 acetate buffer</td>
<td>229nm</td>
<td>37.83</td>
</tr>
<tr>
<td>F5</td>
<td>pH 3.6 acetate buffer</td>
<td>229nm</td>
<td>16.21</td>
</tr>
<tr>
<td>F6</td>
<td>pH 3.6 acetate buffer</td>
<td>229nm</td>
<td>33.78</td>
</tr>
<tr>
<td>F7</td>
<td>pH 3.6 acetate buffer</td>
<td>229nm</td>
<td>24.32</td>
</tr>
<tr>
<td>F8</td>
<td>pH 3.6 acetate buffer</td>
<td>229nm</td>
<td>13.51</td>
</tr>
<tr>
<td>F9</td>
<td>pH 3.6 acetate buffer</td>
<td>229nm</td>
<td>21.62</td>
</tr>
</tbody>
</table>

CONCLUSION

Memantine hydrochloride mouth dissolving tablet formulation was done and the direct compression method was used to punch the tablets, different excipients were used among them F2 was found to be the best formulation which showed good results for the evaluation tests. Based on the evaluation parameters like friability, dispersion test, wetting time disintegration time in the oral cavity, in vitro dissolution study, F2 was found to be optimized formulation upon its disintegration time, 61 sec and release of the drug in the dosage form was 98.64% within 10 minutes and in vitro drug release was better than other formulations.
REFERENCES