Development in Formulation and Evaluation of Levodopa-Tolcapone Orally Disintegrating Tablets

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Abstract

Levodopa-Tolcapone oral disintegration tablet used in the treatment of Parkinsonism was formulated and prepared by direct compression method and evaluated. Increasing demand for more patient compliant dosage form and a novel method end up in developing orally disintegrating tablets which dissolve or disintegrates instantly on placing on buccal mucosa. It is suited for tablets undergoing high first pass metabolism in improving bioavailability with reducing dosing frequency to minimize side effect and make it more cost effective. Orally disintegrating tablets (ODTs) provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. The various formulation aspects, disintegrants employed along with various excipient developed for ODTs which include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and use of highly water soluble excipients. Evaluation, palatability studies was done for all formulation (F1-F6). Effect of superdisintegrants (such as microcrystalline cellulose, sodium starch glycolate and crospovidone) on wetting time, disintegration time, drug content, in vitro release and taste evaluation (palatability studies) was done for the formulation with the peppermint oil and evaluated for its better compliance than the other flavors used in the formulation. Taste and disintegration of optimized formulation for (F4FS) were found to be better than the marketed product.

INTRODUCTION

Advance in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being for the administration. Difficulty in swallowing is experienced by patient such as pediatric, geriatric, bedridden, disabled and mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of non-compliance and ineffective therapy. To improve the quality of life and treatment compliances of such patients fast disintegrating or orally disintegrating tablets dosage form is a better alternative for oral medication. Oral disintegrating tablets are solid dosage form containing medical substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilitate swallowing. Oral route of administration is most convenient for administering drugs for systemic effect because of ease of administration and dosage adjustments. Swallowing conventional tablets can be further hindered by conditions such as allergic reactions, and episodes of coughing. A solid dosage form containing medicinal substance, which disintegrates rapidly usually within of seconds, when placed upon the tongue also called as quick disintegrating tablet, rapid disintegrating tablet, porous tablet, mouth dissolving tablet. Tablet that to be placed in the mouth where it disperses rapidly before swallowing. Absorption through the cheek allows the drug to bypass the digestive tract for rapid systemic distribution. The first ODTs disintegrated through effervescence rather than dissolution, and were designed to make taking vitamins more pleasant for children. The ideal characteristic of oral disintegrating solid dosage form are Ease of administration, Taste of the medicament, Drug properties, Hygroscopicity, Friability, Taste masking: (sweet, salt, sour, bitter). The fast dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence the basic approach to developing fast dissolving tablet include maximizing the porous structure of the tablet, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation. This method was adapted to pharmaceutical use with the innovation of micro particles containing a drug, which would be released upon effervescence of the tablet and swallowed by the patient. Dissolution became more effective than effervescence through improved manufacturing processes and ingredients (such as the addition of mannitol to increase binding and decrease dissolution time).

In many ODT technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants.
concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases. Fast disintegration tablets can also be achieved by incorporating effervescent disintegration agents, which generates carbon dioxide. This phenomenon also resulted in partial taste masking of unacceptable taste of the drug. Super disintegrants are generally used at a low level in the solid dosage form, typically 1-10% by weight relative to the total weight of the dosage unit. Examples of super disintegrants are crosscarmelose, crospovidone, sodium starch glycolate which represents example of a cross-linked cellulose, cross-linked polymer and a cross linked starch respectively. Incorporating disintegrating agents into tablet are three types they are internal addition (intra granular), external addition (extra granular), partly internal and external. The two-step method usually produces better and more complete disintegration than the usual method of adding the disintegrants to the granulation surface only. The active ingredients must be released from the tablet are broken into small pieces and then produces a homogenous suspension is based on capillary action, high swellability, capillary action and high swellability, chemical reaction.

MATERIALS
Mannitol EZ spray, Sorbitol, Sodium starch glycolate, Avicel PH 102, Crospovidine XL-10, Citric acid anhydrous, Sodium bicarbonate, Aspartamine, Sodium stearyl fumerate, FDC blue were purchased from Modern Chemicals Pvt Ltd and all the chemicals used were of analytical grade.

METHODS
Preformualtion studies:
The pre-formulation studies like Angle of repose, Bulk density, Tapped density and Carr’s index were performed on Tolcapone-Levodopa API.

Solubility studies:
The solubility profile of Tolcapone-Levodopa was determined in 0.01 N HCl and water by using HPLC.

Formulation of Levodopa-Tolcapone orally disintegration tablets [14, 15]
Tablets were prepared by the direct compression technique. It is the easiest method to manufacture tablets and this method involves the same process as that of conventional solid dosage forms such as weighing, screening, mixing, and compression.

- Weigh tolcapone, mannogem, levodopa and sieve through 35 mesh and mix foe 5 min.
- Weigh Avicel, Aspartamine, Crospovidone, Citric acid anhydrous, Sodium bicarbonate, NaHCO₃, Mint Flavor, Aerosil, and FDC blue individually.
- Citric acid anhydrous, NaHCO₃, Mint Flavor was sifted through 60 #, FDC blue sifted through 80 #, and remaining excipients were sifted through 35# then added to the above mixture and mixed well.
- Sodium stearyl fumerate weighed and sifted through 35# then added to the above mixture and mixed.

Tablets was Compressed with 25 mm round punches. The above method was commonly used for preparation of each batch from F1- F6.

Precompressional studies:
The precompressional studies like Angle of repose, Carr’s index and Hausner’ ratio was performed on granules prepared with the above procedure for each batch and results are shown in Table: 4.

EVALUATION OF TABLETS [14,15,16]:
Compressed tablets were evaluated for the following parameters

Weight variation test
The weight variation was done by selecting 20 tablets randomly from each formulation and their average weight was calculated using digital balance. Individual weights of each tablet was calculated using the same and compared with the individual weights.

Hardness
The hardness of the tablets was tested by using Monsanto hardness tester.

Thickness and diameter
The thickness and diameter of the prepared tablets was measured by using Vernier calipers.

Friability:
The friability of the tablets was tested by using Roche friabilator. Accurately weighed not less than 6.5 grams of tablets, were placed in the drum. The drum was Rotated 100 times and the tablets were removed. Any loose dust from the tablets was also removed, if no tablets were cracked split or broken, the tablet weighed to the nearest milligram.

\[
\%\text{Friability} = (A-B/B) \times 100
\]

Disintegration test
The tablets were placed into each tube and the assembly was suspended in to the 100ml beaker containing water maintained at 37°C ± 2°C and operated the apparatus for 30 seconds. The assembly was removed from the liquid. The tablets were observed.

Wetting time:
Five circular tissue papers were placed in a petri dish with a 10-cm diameter. Ten milliliters of water containing eosin, a water soluble dye, was added to the petri dish. The dye solution was used to identify the complete wetting time of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petri dish at room temperature. The time required for water to reach the upper surface of the tablet and completely wet them was noted as the wetting time.

In vitro dissolution test:
Dissolution study was conducted for all the formulation using USP type-II apparatus (Electolab, Mumbai, India.). The dissolution test was performed using 500 ml of phosphate buffer.
(PH 6.8) as the dissolution medium at 50 rpm and 37°C±0.5°C. 5ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed by using UV spectrophotometer to find out λmax of the drug. Drug concentration was calculated from the standard peak and expressed as % of the drug dissolved or released.

Content uniformity test:

Five tablets were weighed and powdered, from this 10 mg equivalent of sertraline was weighed and dissolved in suitable quantity of methanol. The solution was filtered suitably through 0.45 micron filter and diluted. The drug content was analyzed using UV spectrometer at 270 nm through 0.45 micron.

Table 1. Formulation of Tablet

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>FORMULATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolcapone and Levodopa</td>
<td>F-1</td>
</tr>
<tr>
<td>-</td>
<td>250mg + 25mg</td>
</tr>
<tr>
<td>Mannitol EZ spray</td>
<td>390.5</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>-</td>
</tr>
<tr>
<td>Sodiumstarch glycolate</td>
<td>100</td>
</tr>
<tr>
<td>Avicel PH 102</td>
<td>40</td>
</tr>
<tr>
<td>Crospovidone XL-10</td>
<td>-</td>
</tr>
<tr>
<td>Citric acid anhydrous</td>
<td>22</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>25</td>
</tr>
<tr>
<td>Aspartamine</td>
<td>15</td>
</tr>
<tr>
<td>Flavor</td>
<td>3.75</td>
</tr>
<tr>
<td>Sodium stearyl fumarate</td>
<td>22.5</td>
</tr>
<tr>
<td>FDC blue</td>
<td>0.25</td>
</tr>
<tr>
<td>Total</td>
<td>950</td>
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Table 2. Drug-excipients compatibility studies

<table>
<thead>
<tr>
<th>EXCIPIENTS</th>
<th>RATIO</th>
<th>DESCRIPTION</th>
<th>Initial</th>
<th>Final</th>
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</thead>
<tbody>
<tr>
<td>API-Avicel PH 102</td>
<td>1:5</td>
<td>Creamy white coloured powder</td>
<td></td>
<td>Creamy white coloured powder</td>
</tr>
<tr>
<td>API-Mannagem</td>
<td>1:5</td>
<td>Creamy white coloured powder</td>
<td></td>
<td>Creamy white coloured powder</td>
</tr>
<tr>
<td>API+ Crospovidone XL</td>
<td>1:5</td>
<td>white coloured powder</td>
<td></td>
<td>white coloured powder</td>
</tr>
<tr>
<td>API+ Aspartamine</td>
<td>1:1</td>
<td>white coloured powder</td>
<td></td>
<td>white coloured powder</td>
</tr>
<tr>
<td>API+ peppermint oil</td>
<td>1:1</td>
<td>white coloured powder</td>
<td></td>
<td>white coloured powder</td>
</tr>
</tbody>
</table>

Table 2. API characterization

<table>
<thead>
<tr>
<th>API</th>
<th>Angle of repose</th>
<th>Bulk density</th>
<th>Tap density</th>
<th>Carr’s index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolcapone/levodopa</td>
<td>22.1</td>
<td>0.1543</td>
<td>0.2654</td>
<td>42.453</td>
</tr>
</tbody>
</table>

RESULTS AND DISCUSSION

Preformulation studies:

The pre-formulation study performed on Tolcapone-Levodopa API to find out Angle of repose, Bulk density, Tapped density and Carr’s index. The results shows all the values were in within the limit and the results are shown in Table 3.

Solubility studies

The solubility profile of Tolcapone-levodopa is determined in .01 N Hcl and water by using HPLC and solubility was better in the given pH of water and 0.01.

Formulation of Levodopa-Tolcapone orally disintegration tablets

Tablets were prepared by the direct compression technique. Totally six batches of tablets were prepared by changing the various ingredients and various concentration. The six formulations with their formula are shown in Table 1.
Table 4. Evaluated Results of Precompressional and Post compressional Parameters

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>F-1</th>
<th>F-2</th>
<th>F-3</th>
<th>F-4</th>
<th>F-5</th>
<th>F-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose</td>
<td>17.32</td>
<td>26.59</td>
<td>29.85</td>
<td>26.56</td>
<td>32.53</td>
<td>28.28</td>
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<tr>
<td>Carr’s index</td>
<td>30.60</td>
<td>29.55</td>
<td>27.49</td>
<td>29.36</td>
<td>30.91</td>
<td>31.64</td>
</tr>
<tr>
<td>Hausner’ ratio</td>
<td>1.44</td>
<td>1.41</td>
<td>1.41</td>
<td>1.37</td>
<td>1.40</td>
<td>1.46</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>5.00</td>
<td>5.05</td>
<td>5.02</td>
<td>5.04</td>
<td>5.03</td>
<td>5.06</td>
</tr>
<tr>
<td>Hardness (kg/cm²)(aver)</td>
<td>6.2</td>
<td>5.5</td>
<td>6.4</td>
<td>5.5</td>
<td>5.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.07</td>
<td>0.06</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.75</td>
</tr>
<tr>
<td>Disintegration time (sec)</td>
<td>30-40</td>
<td>25-50</td>
<td>15-20</td>
<td>10-15</td>
<td>15-20</td>
<td>60-120</td>
</tr>
<tr>
<td>Wetting time (sec)</td>
<td>23</td>
<td>28</td>
<td>24</td>
<td>18</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>% Drug release In 45 min</td>
<td>102.12</td>
<td>95.81</td>
<td>97.89</td>
<td>99.89</td>
<td>99.90</td>
<td>99.47</td>
</tr>
<tr>
<td>Content uniformity</td>
<td>94.65</td>
<td>96.8</td>
<td>96.8</td>
<td>102.8</td>
<td>99.7</td>
<td>96.7</td>
</tr>
</tbody>
</table>

Precompressional studies:
The precompressional studies like Angle of repose 17.32, 26.59, 26.85, 26.56 Carr’s index and Hausner’ ratio was performed on granules and the results are shown in Table 4.

EVALUATION OF TABLETS

Weight variation test
The test results on weight variation of the tablets shows, that all the tablets were not showing much variation in weight.

Hardness
The hardness of the tablets was tested by using Monsanto hardness tester and the formulations F4 and F5 shows better results when compared to all other formulations. The results are shown in Table 4.

Thickness and diameter
The thickness and diameter of the prepared tablets was measured by using Vernier calipers. The values are within the normal limit and the formulations F4 and F5 shows better results when compared to all other formulations. The results are shown in Table 4.

Friability:
The friability of the tablets was tested by using Roche friabilator and the results shows that all the values are within the normal limit and the formulations F4 and F5 shows better results when compared to all other formulations. The results are shown in Table 4.

Disintegration test:
The disintegration test for each batch was performed and it was noted that the formulations F4 and F5 shows better results when compared to all other formulations. The results are shown in Table 4.

Wetting time:
The wetting time for all the formulation were within the limit and the formulations F4 and F5 shows better results when compared to all other formulations. The results are shown in Table 4.

In vitro dissolution test:
Dissolution study was conducted for all the formulations and it was noted that the formulations F4 and F5 showed drug release of 99.89, 99.90% respectively with better disintegrating capacity.

CONCLUSION:
Six different groups (F1, F2, F3, F4, F5 & F6) of formulations with various concentrations of tablet excipients were prepared with each group containing three different formulations. Among the six formulation F-4 & F-5 were the better than other formulations and marketed formulation. Taste evaluation was done with various parameters and the results were satisfied. The above study results show that the direct compression was more preferred economical and includes less procedure steps than other methods.

REFERENCES