FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF AMITRIPTYLINE HYDROCHLORIDE BY DIRECT COMPRESSION TECHNIQUE

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ABSTRACT

Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablet. In the present study, an attempt has been made to prepare fast dissolving tablets of the drug Amitriptyline hydrochloride using superdisintegrants such as Croscarmellose sodium (Ac-Di-Sol), Sodium starch glycolate (Explotab) and Crospovidone by direct compression technique. The prepared tablets were evaluated for hardness, friability, wetting time, weight variation, in vitro disintegration time and in vitro dissolution study. The hardness of the tablets was in the range of 2.0 - 4.0 Kg/cm². The percentage friability of the tablets was less than one. Weight variation test results showed that the tablets were deviating from the average weight within the permissible limits of ±7.5 %. Drug content uniformity study results showed that uniform dispersion of the drug throughout the formulation i.e. 98.54% to 101.23%. Tablets containing Crospovidone (DC9) showed better disintegrating character along with the rapid release (99.83% drug within 7 minutes). No appreciable difference was found between the formulations containing other two superdisintegrants. Crospovidone was found to be better suited for the formulation of mouth dissolving tablet of Amitriptyline hydrochloride compared to other superdisintegrants used in the study.

Keywords: Fast-dissolving tablets, Amitriptyline Hydrochloride, Superdisintegrants.

INTRODUCTION

Solid dosage forms and capsules are most popular and preferred drug delivery system because of they have a high patient compliance. Many patient find difficulty to swallow tablet and hard gelatin capsule, consequently they do not take medication as prescribed. It is estimated that 50% of the population is affected by this problem which result high incidence of non-compliance and ineffective therapy¹.

The difficulty is experienced in particular by pediatric and geriatric patients, but it is applicable to people who are ill in bed and those active working patients who are busy or traveling, mentally ill, developmentally disable and patients who are uncooperative. To overcome this problem fast dissolving tablet is prepared².

Amitriptyline HCl inhibits the reuptake of norepinephiren and serotonin almost equally. These actions help in Amitriptyline HCl as an antidepressant and antipsychotic drug³.

With the view to all the above information, an attempt had been made to develop a rapidly disintegrating Amitriptyline HCl mouth dissolving tablets of which disintegrate in the oral cavity without the need of water within a matter of seconds. This will lead to the formation of suspension / solution form which can be easily swallowed, thereby improving dissolution rate and bioavailability of drug and onset of pharmacological action.

MATERIALS AND METHODS

Materials

Amitriptyline HCl was obtained as gift sample from Vasudha Pharma Chem Ltd., Hyderabad,India, Crospovidone, Croscarmellose sodium, Sodium starch glycolate and aspartame were gifted sample from Cipla, Kurkumbh,India, Lactose, Magnesium stearate was procured from S.D Fine Chemicals, Mumbai, India, were used and all other
chemicals/solvents used were analytical grade.

Method

Formulation of mouth dissolving tablets of Amitriptyline Hydrochloride

Tablet each containing 25 mg Amitriptyline Hydrochloride were prepared as per composition given in Table 1. The drug and excipients were passed through sieve (#80) to ensure the better mixing. Microcrystalline Cellulose was used as a direct compressible vehicle. Super disintegrants like Sodium Starch Glycolate, Crospovidone and Croscarmellose Sodium were used in different ratios. The powder was compressed using Rimek compression machine equipped with 8 mm round punch by direct compression technique. A minimum of 50 tablets was prepared for each batch.

Pre Compression Parameters

Angle of Repose

Angle of repose was determined using funnel method. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula

\[ \theta = \tan^{-1} \frac{h}{r} \]

Where, \( \theta \) is the angle of repose, h is height of pile; r is radius of the base of pile.

Bulk Density

Apparent bulk density (\( \rho_b \)) was determined by pouring the blend into a graduated cylinder. The bulk volume (\( V_b \)) and weight of powder (M) was determined. The bulk density was calculated using the formula

\[ \rho_b = \frac{M}{V_t} \]

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (\( V_t \)) occupied in the cylinder and weight (M) of the blend was measured. The tapped density (\( \rho_t \)) was calculated using the following formula

\[ \rho_t = \frac{M}{V_t} \]

Carr's Compressibility Index

The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the granules was determined by Carr's compressibility index \( I \), which is calculated by using the following formula

\[ I = \frac{V_0 - V_t}{V_0} \times 100 \]

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

\[ \text{Hausner ratio} = \frac{\rho_t}{\rho_d} \]

Where \( \rho_t \) is tapped density and \( \rho_d \) is bulk density. Lower Hausner ratio \(< 1.25\) indicates better flow properties than higher ones \(>1.25\).
**Post compression parameter**

**Hardness**
The hardness of the tablet from each formulation was determined using Pfizer hardness tester\(^4\).

**Weight Variation**
Twenty tablets from each formulation were selected at a random and average weight was determined. Then individual tablets were weighed and was compared with average weight\(^4\).

**Friability**
Friability of the tablets\(^4\) was determined using Veego Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and re weighed. The friability \((f)\) is given by the formula.

\[
\text{Friability} (f) = \left(1 - \frac{W_0}{W}\right) \times 100
\]

Where \(W_0\) is weight of the tablets before the test and \(W\) is the weight of the tablet after the test

**In vitro Disintegration time**
The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of 37\(^\circ\)C ±2\(^\circ\)C and time taken for the entire tablet to disintegrate completely was noted\(^7\).

**Drug content**
Five tablets were powdered and the blend equivalent to 100 mg of Amitriptyline hydrochloride was weighed and dissolved in suitable quantity of distilled water. The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometrically at 239 nm. Each sample was analyzed in triplicate\(^8\).

**In vitro Dissolution studies\(^9\)**

*In vitro* dissolution studies for all the fabricated tablets was carried out by using USP Type II apparatus (USP XXIII Dissolution Test Apparatus) at 50 rpm in 900 ml of phosphate buffer pH 6.8, maintained at 37±0.5\(^\circ\)C. 5 ml aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and assayed spectrophotometrically at 239 nm using Shimadzu 1700 spectrophotometer. An equal volume of fresh medium, which was pre warmed at 37 \(^\circ\)C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Dissolution studies were performed in triplicate.

**Stability study\(^10, 11\)**
The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions, re-test periods and shelf lives to be established.

ICH specifies the length of study and storage conditions:

- Long term testing 25\(^\circ\)C ± 2\(^\circ\)C / 60 % RH ± 5 % for 12 months
• Accelerated testing 40°C ± 2 °C / 75 % RH ± 5 % for 6 months

In the present study, stability studies were carried out at 25°C ± 2 °C / 60 % RH ± 5 % and 40°C ± 2 °C / 75 % RH ± 5 % for a specific time period up to 30 days for the selected formulations. Tablets were evaluated for hardness, weight variation, friability, content uniformity, disintegration and drug release.

Table 1: Composition of different batches of mouth dissolving tablets of Amitriptyline Hydrochloride

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>DC0</th>
<th>DC1</th>
<th>DC2</th>
<th>DC3</th>
<th>DC4</th>
<th>DC5</th>
<th>DC6</th>
<th>DC7</th>
<th>DC8</th>
<th>DC9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>103</td>
<td>99</td>
<td>97</td>
<td>95</td>
<td>99</td>
<td>97</td>
<td>95</td>
<td>99</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Croscarmellose</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<tr>
<td>Aspartame</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Talc</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Total weight</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

Table 2: Evaluation of Mixed Blend of Drug and Excipients

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Angle of repose (θ)</th>
<th>Bulk density (g/cm³)</th>
<th>Tapped density (g/cm³)</th>
<th>Hausner's ratio</th>
<th>Compressibility index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC0</td>
<td>25.11</td>
<td>0.454</td>
<td>0.522</td>
<td>1.14</td>
<td>13.03</td>
</tr>
<tr>
<td>DC1</td>
<td>23.42</td>
<td>0.451</td>
<td>0.542</td>
<td>1.201</td>
<td>17.01</td>
</tr>
<tr>
<td>DC2</td>
<td>24.14</td>
<td>0.459</td>
<td>0.539</td>
<td>1.173</td>
<td>14.18</td>
</tr>
<tr>
<td>DC3</td>
<td>24.30</td>
<td>0.438</td>
<td>0.523</td>
<td>1.194</td>
<td>16.28</td>
</tr>
<tr>
<td>DC4</td>
<td>25.01</td>
<td>0.447</td>
<td>0.539</td>
<td>1.205</td>
<td>17.01</td>
</tr>
<tr>
<td>DC5</td>
<td>26.56</td>
<td>0.473</td>
<td>0.565</td>
<td>1.194</td>
<td>16.31</td>
</tr>
<tr>
<td>DC6</td>
<td>25.76</td>
<td>0.46</td>
<td>0.553</td>
<td>1.202</td>
<td>16.79</td>
</tr>
<tr>
<td>DC7</td>
<td>25.17</td>
<td>0.427</td>
<td>0.508</td>
<td>1.189</td>
<td>15.93</td>
</tr>
<tr>
<td>DC8</td>
<td>25.11</td>
<td>0.478</td>
<td>0.567</td>
<td>1.186</td>
<td>15.72</td>
</tr>
<tr>
<td>DC9</td>
<td>26.56</td>
<td>0.442</td>
<td>0.537</td>
<td>1.21</td>
<td>17.68</td>
</tr>
</tbody>
</table>

Fig. 1: Comparative dissolution profile of Amitriptyline hydrochloride tablets containing different superdisintegrants DC0, DC1, DC2 & DC3
Table 3: Evaluation of tablets

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Weight Variation (mg)</th>
<th>Hardness Kg/cm² ± SD</th>
<th>Thickness (mm) ± SD</th>
<th>Friability (%)</th>
<th>Drug content (%) ± SD</th>
<th>In vitro disintegration time (sec) ± SD</th>
<th>Water absorption ratio (Sec)</th>
<th>Wetting time (Sec)</th>
<th>% Drug release</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC0</td>
<td>199–205 (within the IP limit of ±7.5%)</td>
<td>4.1±0.311</td>
<td>3.71±0.010</td>
<td>0.42</td>
<td>99.18±0.72</td>
<td>242±0.73</td>
<td>83.01±0.26</td>
<td>61±0.263</td>
<td>97.13</td>
</tr>
<tr>
<td>DC1</td>
<td>3.4±0.401</td>
<td>3.70±0.030</td>
<td>0.52</td>
<td>99.81±1.07</td>
<td>39±0.90</td>
<td>72.3±0.31</td>
<td>25±0.201</td>
<td>97.70</td>
<td></td>
</tr>
<tr>
<td>DC2</td>
<td>3.2±0.209</td>
<td>3.73±0.012</td>
<td>0.56</td>
<td>98.54±0.50</td>
<td>23±0.68</td>
<td>77.64±0.54</td>
<td>12±0.324</td>
<td>97.72</td>
<td></td>
</tr>
<tr>
<td>DC3</td>
<td>3.2±0.216</td>
<td>3.73±0.040</td>
<td>0.67</td>
<td>99.12±0.72</td>
<td>20±0.64</td>
<td>75.15±0.11</td>
<td>17±0.496</td>
<td>98.78</td>
<td></td>
</tr>
<tr>
<td>DC4</td>
<td>3.6±0.513</td>
<td>3.70±0.011</td>
<td>0.71</td>
<td>99.30±0.27</td>
<td>24±0.71</td>
<td>68.15±0.31</td>
<td>19±0.406</td>
<td>99.01</td>
<td></td>
</tr>
<tr>
<td>DC5</td>
<td>3.2±0.291</td>
<td>3.71±0.035</td>
<td>0.63</td>
<td>101.23±0.39</td>
<td>22±0.27</td>
<td>68.77±0.45</td>
<td>17±0.496</td>
<td>98.90</td>
<td></td>
</tr>
<tr>
<td>DC6</td>
<td>3.4±0.316</td>
<td>3.71±0.053</td>
<td>0.60</td>
<td>101.03±0.73</td>
<td>31±0.55</td>
<td>59.25±0.78</td>
<td>12±0.324</td>
<td>99.12</td>
<td></td>
</tr>
<tr>
<td>DC7</td>
<td>3.5±0.263</td>
<td>3.73±0.025</td>
<td>0.68</td>
<td>98.63±0.44</td>
<td>23±0.94</td>
<td>70.17±0.70</td>
<td>10±0.201</td>
<td>99.56</td>
<td></td>
</tr>
<tr>
<td>DC8</td>
<td>3.9±0.315</td>
<td>3.70±0.013</td>
<td>0.42</td>
<td>99.50±0.34</td>
<td>18±0.57</td>
<td>68.79±0.32</td>
<td>14±0.263</td>
<td>99.01</td>
<td></td>
</tr>
<tr>
<td>DC9</td>
<td>3.7±0.277</td>
<td>3.70±0.033</td>
<td>0.47</td>
<td>99.96±0.77</td>
<td>13±0.76</td>
<td>57.77±0.55</td>
<td>9±0.413</td>
<td>99.83</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2: Comparative dissolution profile of Amitriptyline hydrochloride tablets containing different superdisintegrants DC0, DC4, DC5 & DC6

Fig. 3: Comparative dissolution profile of Amitriptyline hydrochloride tablets containing different superdisintegrants DC0, DC7, DC8 & DC9
RESULTS AND DISCUSSION

Nine formulations of Amitriptyline Hydrochloride were prepared with concentration of three superdisintegrants: Sodium Starch glycolate, Croscarmellose sodium, Crospovidone and microcrystalline cellulose were used as a direct compressible vehicle. For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique. Bulk density was found in the range of 0.427-0.478 g/cm³ and the tapped density between 0.508-0.567 g/cm³ (Table II). Using these two density data Hausner’s ratio and compressibility index was calculated. The powder blend of all the formulations had Hausner’s ratio of 1.2 or less indicating good flowability. The compressibility index was found between 13.03 and 17.68 % and the compressibility - flowability correlation data¹² indicated a fairly good flowability of the blend. The good flowability of blend was also evidenced with angle of repose (range of 23 – 27 °), which is below 40 ° indicating good flowability.

Tablets were prepared using direct compression technique. Thickness of the tablets was measured by screw gauge by picking tablets randomly from all the batches. The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 3.70 ± 0.013 mm to 3.73 ± 0.040 mm. The standard deviation values indicated that all the formulations were within the range. Since the powder material was free flowing, tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variations as per pharmaceutical specifications. The drug content was found in the range of 98.54 – 101.23 % (acceptable limit) and the hardness of the tablets between 3.0 – 4.0 kg/cm² (Table III). Friability of the tablets was found below 1 % indicating a good mechanical resistance of tablets. Wetting time is closely related to the inner structure of the tablet. This showed that wetting process was very rapid in almost all formulations. This may be due to ability of swelling and also capacity of water absorption and causes swelling. The in-vitro dispersion time is measured by the time taken to undergo uniform dispersion. Rapid dispersion within few minutes was observed in all the formulations. The results showed that tablet containing Crospovidone having low dispersion time as compare to other superdisintegrants. The dispersion time increases as the concentration of superdisintegrants increases. The in vitro disintegration time of the tablets was found to be less than 60 sec. All the formulations showed enhanced dissolution rate as compared to Amitriptyline hydrochloride with out superdisintegrants. The maximum increase in the dissolution rate was observed with crospovidone amongst the three superdisintegrants. The order of enhancement of the dissolution rate with various superdisintegrants found to be Crospovidone >Cross carmellose>Sodium starch glycolate.

Stability study shows no significant changes in values during one-month study.

CONCLUSION

It was concluded that mouth-dissolving tablets of Amitriptyline hydrochloride can be successfully prepared by direct compression technique using selected superdisintegrants for the better patient compliance and effective therapy.

ACKNOWLEDGEMENTS

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Kurkumbh (India) for providing gift sample of Amitriptyline Hydrochloride and Crospovidone, Croscarmellose sodium, Sodium starch glycolate, aspartame, respectively.

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