SOLUBILITY ENHANCEMENT OF AMISULPRIDE BY COMPLEXATION TECHNIQUE AND PREPARATION OF FAST DISSOLVING TABLET (FDT)

Thanda Venkataramudu *1, R. Arun Kumar 1, S.M. Imroz1, T. Murali Krishna2, Swamy Hanumesh 3

Dept.of Pharmaceutics,
1 Sree Vidyanikethan College of pharmacy, Tirupati, 517102, A.P, India.
2 East West College of pharmacy, Bangalore, 560091, Karnataka, India.
3 Raos College of pharmacy, Nellore, 524314, A.P, India.

ABSTRACT
The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Amisulpride, 4-Amino-N-[(2RS)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-methoxybenzamide, exhibits anti-psychotic activities by selectively binding to dopamine D(2) and D(3) receptors in the limbic system. It is used in the treatment of psychoses, paranoid, productive schizophrenias, dysthymia. However, Amisulpride (AMP) is a poorly water soluble drug, so solubility is the main constraint for oral bioavailability. An attempt has been made to increase the solubility of this drug by formulating β-cyclodextrin (β-CD) as polymer and then formulating fast dissolving tablets (FDT). Tablet formulations were prepared by direct compression technique using superdisintegrants in different concentrations. Inclusion complexes were evaluated for FT-IR, DSC and developed tablet formulations were evaluated for various pharmaceutical characteristics viz. hardness, % friability, weight variations, drug content, wetting time, disintegration time and in vitro dissolution profile. Among tablet formulations, formulation CF2 gives best disintegration and dissolution profile compared with other formulations. Results showed that β-cyclodextrin is a promising polymer for enhancing the solubility of AMP.

Keywords: Amisulpride; β-cyclodextrin; Dissolution enhancement techniques; Super disintegrants; Fast dissolving tablet.

INTRODUCTION
Fast dissolving tablets (FDTs) are solid single-unit dosage forms that are placed in mouth, allowed to disperse/dissolve in the saliva without the need of water and provides a quick onset of action. Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. FDTs are appreciated by a significant segment of population, particularly children and elderly, which have difficulty in swallowing conventional tablets or capsules (Bradoo R et al., 2001; Dobetti L, 2001; Lorenzp- Lamosa ML et al., 1997). The fast dissolving tablets are referred by various names by researchers like quick disintegrating, orally disintegrating, rapidly dissolving, mouth dissolve tablets.

Corresponding Author
Thanda Venkataramudu
Email: tvrnai16@gmail.com
Fast dissolving drug delivery system emerged from the desire to provide patient with more conventional means of taking their medication. It is difficult for many patients to swallow tablets and gelatin capsules. Hence they do not comply with prescription which results in non-compliance and ineffective therapy. In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult particularly the difficulty is experienced by pediatric and geriatric patients. Such problems can be resolved by means of mouth dissolving tablet. When placed on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

MATERIALS

Amisulpride is procured by Intas Pharmaceuticals Ltd., Ahmedabad, India. β-cyclodextrin, Ac-Di-Sol, Microcrystalline cellulose, Sodium starch glycolate, Sodium saccharine are procured by S.D. Fine Chem. Ltd, Mumbai, India.

METHODS

INCLUSION COMPLEXATION OF AMISULPRIDE WITH β-CYCLODEXTRIN (β-CD)

Methods of preparation of inclusion complex

Inclusion complexes were prepared by different methods like physical mixture and kneading method (Maski N et al., 2009; Aulton ME, 2002).

1. Physical mixture: AMP: β-CD in the different molar ratios (1:1, 1:2) was mixed for about one hour with constant triturating in glass mortar and pestle. The powders were then sifted through sieve no.85 and stored in desiccator till further use.

2. Kneading method: AMP: β-CD in different molar ratios (1:1, 1:2) was used. First cyclodextrin is added to the mortar, small quantity of distilled water is added while triturating to obtain a homogenous paste. The drug was slowly added to the paste and mixture triturated for one hour. During the process, the water content of the paste was empirically adjusted to maintain the consistency of the paste. The paste was dried at 40°C for 24 hours, pulverized by passing through sieve no. 85 and stored in a desiccator till further use.
PREPARATION OF FAST DISSOLVING TABLETS
OF INCLUSION COMPLEXES OF AMISULPRIDE
WITH β-CYCLODEXTRIN BY DIRECT
COMPRESSION METHOD

Inclusion complex of AMP: β-CD were taken and mixed with directly compressible diluent, super-ltd, Ahmedabad, India.

EVALUATION PARAMETERS OF FAST
DISSOLVING TABLET

Pre compression parameters

Determination of densities

A simple test has been developed to evaluate the flowability of a powder by comparing the poured density (ρp) and tapped density (ρt) of a powder and the rate at which it packed down. Tapped density was determined by taking 20 g of the granules in 50 ml measuring cylinder and tapping it to a constant volume in a bulk density apparatus. Poured density was determined by three tap method (Lachman L et al., 1987).

% Compressibility or Carr’s index

Based on the poured density and tapped density, the % compressibility of the granules was computed using the Carr’s compressibility index (Jaimini M et al., 2007)

\[
\text{Carr’s index (\%)} = \frac{\text{Tapped density} - \text{poured density}}{\text{Tapped density}} \times 100
\]

Hausner ratio

Hausner ratio was calculated using the formula:

\[
\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Poured density}}
\]

Angle of repose

Angle of repose of the granules was determined height cone method. A funnel was fixed to a desired height and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula (Jaimini M et al., 2007).

\[
\tan \theta = \frac{2h}{D}, \quad \theta = \tan^{-1}\left(\frac{h}{r}\right)
\]

Characterization of drug and excipients

The formulation additives in concentrations used did not affect the stability and Ultraviolet absorbance of the drug.

Fourier transform infra red spectroscopy (FTIR)

The samples of AMP, β-CD and inclusion complexes were prepared in the form of KBr pellets and subjected for scanning from 4000 cm⁻¹ to 400 cm⁻¹ using FTIR spectrophotometer.

Differential Scanning Calorimetric analysis

disintegrants and other excipients in a plastic container. Table 1 gives composition of the tablet formulation. Powder blend were directly compressed using 10 mm, round-shaped flat punch in eight station tablet compression machine (Ridhdhi pharma instrument)

Approximately 2 mg of AMP, β-CD and inclusion complexes sample was taken in aluminium pan, sealed with aluminium cap and kept under nitrogen purging (atmosphere). Both the samples were scanned from 0-300°C with the scanning rate of 10°C rise/min using differential scanning calorimeter (DSC-60, Shimadzu, Japan).

Post compression parameters

Hardness

The hardness of ten tablets was found using Monsanto Hardness tester. Mean and standard deviation were computed and reported (The Indian Pharmacopoeia, 1996; Rockville MD, 2000). It is expressed in kg/cm².

Friability

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage. 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again. The % friability was then calculated using the formula:

\[
\text{% Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100
\]

Weight variation

Twenty tablets were individually weighed and average weight was calculated. The individual weight was compared to the average weight. The tablets pass the test if not more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage the percentage limit.

Wetting time

The method was applied to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 6ml of water, a tablet was put on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined (Bi Y et al., 1996; Alanzi FK, 2007).

Disintegration test

The disintegration test was carried out using USP disintegration test apparatus type II. Six tablets were
placed individually in each tube of disintegration test apparatus and discs were placed over each tablet. Distilled water was used as the medium maintained at 37°C + 0.5°C and the time taken for each tablet to disintegrate completely was recorded (Abdelbary G et al., 2004).

**Drug content uniformity**

Ten tablets were randomly selected and allowed to equilibrate with HCl acid buffer of pH 1.2 overnight and the solution was filtered (0.22 μ, Millipore) after 24 hours. Suitable dilutions were made with HCl acid buffer of pH 1.2 to get the concentration in Beer’s range. Absorbance of the solution was analyzed spectrophotometrically at 280nm against suitable blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan) and drug content per tablet was calculated.

**In-vitro dissolution study**

Dissolution study was carried out using USP dissolution test apparatus type II. The dissolution medium used was 900 ml of HCl acid buffer of pH 1.2 at 37±0.5°C. The paddle speed was kept at 50 rpm throughout the study. Aliquot of 3 ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume. After each sampling suitably diluted with 1.2 pH HCl acid buffer and analyzed spectrophotometrically at 280nm against suitable blank using UV-visible spectrophotometer (1800, Shimadzu, Kyoto, Japan).

**RESULTS**

**Fourier transformer infrared spectroscopy**

The FTIR spectra of AMP are shown in Fig 5.12. Important vibrations detected in the spectrum of AMP are -NH stretching lies in 3337 cm⁻¹. Other characteristic bands are attributed to the stretching of different group vibration: 1628 cm⁻¹ stretching of amide carbonyl, 1529 cm⁻¹ stretching of the second amide band, 1640 cm⁻¹ stretching of primary amide and 1050 cm⁻¹ stretching of –SO group. The IR spectra of β-CD showed prominent absorption bands at 2879 cm⁻¹ (for C-H stretching vibrations); and 1164 cm⁻¹, 1083 cm⁻¹ (C-H, C-O stretching vibration). The FTIR spectra of inclusion complexes seemed to be only summation of drug and β-CD spectra. This result suggested that there was no chemical interaction between drug and β-CD in their combination.

**Differential scanning calorimetric analysis**

The DSC thermogram of pure AMP showed sharp endothermic peaks at 126.60°C (Fig 5.8). The DSC thermogram of β-CD showed endothermic peak at 249.03°C (Fig 5.9) corresponding to its melting point. The peak of drug was absent in AMP:β-CD inclusion complexes (Fig 5.11) suggesting maximal/complete complex formation.

**Table 1: Composition of fast dissolving tablets of AMP inclusion complex**

<table>
<thead>
<tr>
<th>S. NO</th>
<th>INGREDIENTS</th>
<th>CF1</th>
<th>CF2</th>
<th>CF3</th>
<th>CF4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Inclusion complex</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>Ac-Di-Sol</td>
<td>10</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Sodium starch glycolate</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Microcrystalline cellulose</td>
<td>160</td>
<td>150</td>
<td>160</td>
<td>150</td>
</tr>
<tr>
<td>5</td>
<td>Magnesium stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Saccharin sodium</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table 2: Precompression parameters**

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Bulk density (g/cc)</th>
<th>Tapped density (g/cc)</th>
<th>Angle of repose (υ)</th>
<th>Carr’s index (%)</th>
<th>Hausner Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF1</td>
<td>0.465±0.006</td>
<td>0.540±0.02</td>
<td>24.44±0.73</td>
<td>13.88</td>
<td>1.16</td>
</tr>
<tr>
<td>CF2</td>
<td>0.465±0.006</td>
<td>0.512±0.03</td>
<td>23.50±0.71</td>
<td>9.18</td>
<td>1.10</td>
</tr>
<tr>
<td>CF3</td>
<td>0.475±0.007</td>
<td>0.526±0.01</td>
<td>25.46±0.68</td>
<td>13.50</td>
<td>1.15</td>
</tr>
<tr>
<td>CF4</td>
<td>0.455±0.006</td>
<td>0.512±0.01</td>
<td>24.94±0.53</td>
<td>11.13</td>
<td>1.13</td>
</tr>
</tbody>
</table>
Table 3: Post compression parameters

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Wetting Time (mm)</th>
<th>Hardness (Kg/cm²)</th>
<th>Friability (%)</th>
<th>Weight variation (mg)</th>
<th>Drug content (%)</th>
<th>Disintegration Ltime (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF1</td>
<td>50±1.17</td>
<td>3.7±0.11</td>
<td>0.65</td>
<td>321.13±0.94</td>
<td>99.25±0.67</td>
<td>49±1.15</td>
</tr>
<tr>
<td>CF2</td>
<td>48±0.15</td>
<td>3.8±0.20</td>
<td>0.54</td>
<td>325.06±0.41</td>
<td>99.66±0.33</td>
<td>40±0.57</td>
</tr>
<tr>
<td>CF3</td>
<td>52±1.09</td>
<td>3.7±0.11</td>
<td>0.69</td>
<td>319.13±0.30</td>
<td>99.25±0.33</td>
<td>46±0.57</td>
</tr>
<tr>
<td>CF4</td>
<td>51±1.07</td>
<td>3.6±0.20</td>
<td>0.70</td>
<td>326.13±0.11</td>
<td>97.45±0.89</td>
<td>49.3±1.15</td>
</tr>
</tbody>
</table>

Table 4: In vitro dissolution profile data of CF1, CF2, CF3 and CF4 formulations of fast dissolving tablets of AMP solid dispersion

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>CF1</th>
<th>CF2</th>
<th>CF3</th>
<th>CF4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>40.82±0.31</td>
<td>42.47±0.17</td>
<td>32.35±0.36</td>
<td>38.35±0.24</td>
</tr>
<tr>
<td>6</td>
<td>63.33±0.18</td>
<td>65.45±0.30</td>
<td>57.21±0.18</td>
<td>57.33±0.12</td>
</tr>
<tr>
<td>9</td>
<td>78.34±0.44</td>
<td>79.87±0.24</td>
<td>75.15±0.34</td>
<td>76.45±0.11</td>
</tr>
<tr>
<td>12</td>
<td>89.01±0.24</td>
<td>93.45±0.13</td>
<td>84.28±0.14</td>
<td>86.41±0.07</td>
</tr>
<tr>
<td>15</td>
<td>94.94±0.23</td>
<td>99.99±0.13</td>
<td>91.99±0.23</td>
<td>94.49±0.23</td>
</tr>
<tr>
<td>20</td>
<td>99.31±0.29</td>
<td>99.00±0.67</td>
<td>96.46±0.24</td>
<td>98.80±0.47</td>
</tr>
<tr>
<td>25</td>
<td>98.94±0.24</td>
<td>99.27±0.18</td>
<td>99.07±0.37</td>
<td>100.80±0.11</td>
</tr>
</tbody>
</table>

Table 5: STABILITY STUDIES

<table>
<thead>
<tr>
<th>Time</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
<th>Disintegration time (Sec)</th>
<th>Cumulative % drug released at the end of 15 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero month</td>
<td>3.8±0.20</td>
<td>0.54</td>
<td>99.66±0.33</td>
<td>40±0.57</td>
<td>99.99±0.13</td>
</tr>
<tr>
<td>First Month</td>
<td>3.9±0.11</td>
<td>0.52</td>
<td>98.63±0.67</td>
<td>41±1.15</td>
<td>99.94±0.52</td>
</tr>
<tr>
<td>Second Month</td>
<td>3.9±0.05</td>
<td>0.51</td>
<td>98.59±0.29</td>
<td>40±0.36</td>
<td>99.72±0.26</td>
</tr>
</tbody>
</table>

Figure 1: FTIR spectra of A) Amisulpride, B) β-cyclodextrin, C) mixture of AMP: β-CD

a

b

c
Figure 2: DSC thermogram of A) Amisulpride, B) β-cyclodextrin, C) mixture of AMP: β-CD

Figure 3: Dissolution profile of CF1, CF2, CF3 and CF4 formulations of fast dissolving tablets of AMP solid dispersion.

DISCUSSION
The values for angle of repose were found in the range of 23°-26°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.455±0.007 to 0.465±0.006 (g/cc) and 0.512±0.03 to 0.540±0.02 (g/cc) respectively. Carr’s index of the prepared blends fall in the range of 9.18% to 13.88%. Hausner ratio of the prepared blends fall in the range of 1.10 to 1.16 which is less than 1.21. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Wetting is closely related to inner structure of tablets and the hydrophilicity of excipients. The record of the wetting time was shown in Table 3. The wetting time in all the formulation was very fast. This may be due to ability of swelling and also capacity of absorption of water. MCC, starch glycolate and croscarmellose sodium absorbs water rapidly in the formulations and shows fast wetting time. This parameter also duplicates disintegration time in oral cavity as tablet is kept motionless on tongue; hence correlation between wetting time and disintegration time in oral cavity can also be made.

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data’s were shown in Table 3. The results showed that the hardness of the tablets was in range of 3.6±0.20 to 3.8±0.20 Kg/cm².
Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 3. The average weight of the tablet is approximately 325 mg; so the permissible limit is ±7.5%. The results of the test showed that, the tablet weights were within pharmacopeial limit.

Drug content uniformity study was carried out on the tablets of every batch and the data’s were shown in the Table 3. The content uniformity of all the formulations were found to be in the range of 97.45±0.89 % to 99.66±0.33 % which showed that there was uniform distribution of the drug throughout the batch.

Tablets of each batch were evaluated for percentage friability and the data’s were shown in the Table 3. The average friability of all the formulations lies in the range of 0.54 % to 0.70 % which was less than 1 % as per official requirement of IP indicating a good mechanical resistance of tablets.

Tablets of each batch were evaluated for in vitro disintegration time and the data’s were shown in the Table 3. The results showed that the disintegration time of prepared tablets were in the range of 40±0.57 to 49.3±1.15 seconds. The tablets of batch CF2 prepared using 6.5% of Ac-Di-Sol showed faster disintegration time of 40±0.57 seconds. It indicates that amongst the disintegrants used Ac-Di-Sol was better disintegrants to formulate fast dissolving tablets by direct compression method than SSG.

Finally, the tablets were evaluated for in vitro dissolution studies in simulated gastric fluid and the results were shown in the Table 4. Formulation CF2 which contain Ac-Di-Sol super-disintegrant showed more than 95% of drug release within 12 min, whereas in formulation CF3 and CF4 containing SSG super-disintegrant, more than 95% of drug release within 20 min. As the concentration of super-disintegrant of formulation CF1 was reduced to 3.0%, more than 95% of drug release within 20 min. This result exhibit a direct relationship between selection & concentration of super-disintegrants and drug release. Among the various formulations tablets of batch CF2 prepared with 6.5% Ac-Di-Sol showed complete release of drug within 15 min.

CONCLUSION
The present study is an attempt to select the best possible inclusion formulation to formulate fast dissolving tablets of AMP using super-disintegrants such as Ac-Di-Sol, sodium starch glycolate by direct compression technique. As a result of this study, it may be concluded that the complexation technique may be useful to improve solubility, dissolution rate and subsequently bioavailability of poorly soluble drug. The concept of formulating fast dissolving tablets of AMP inclusion complexes using super-disintegrants offers a suitable and practical approach in serving desired objectives of faster disintegration and dissolution characteristics.

REFERENCES
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