FORMULATION AND EVALUATION OF FAST DISSOLVING TABLET OF ANTIHYPERTENSIVE DRUG

M. N. Karemore*, G. P. Soor, Dr. Shyamala Bhaskaran
Agnihotri College of Pharmacy, Bapuji Wadi, Ramnagar, Wardha 442001, Maharashtra, India.
Email: meghakaremore0687@gmail.com

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Abstract

The objective of this study was to formulate and evaluate fast dissolving tablets of poorly soluble Telmisartan by direct compression technique with β-cyclodextrin complexes using various superdisintegrants like croscarmellose sodium, crospovidone and sodium starch glycolate. Telmisartan is an angiotensin II receptor antagonist used in the management of hypertension. The rate of absorption and/or the extent of bioavailability for such a poorly soluble drug is controlled by rate of dissolution. Hence to enhance the solubility of drug a complex of Telmisartan was prepared with β-cyclodextrin and this complex was compressed into tablets. The prepared tablet were evaluated for weight variation, thickness, friability, hardness, assay, disintegration time, wetting time, water absorption ratio, in vitro dissolution studies, stability study and IR spectroscopy. Different formulation showed disintegration time between the range of 20 to 45 sec. Among all the formulations, formulation F1 prepared with croscarmellose sodium (5%) showed 98.64% drug release within 7 min. Thus, formulation F1 was considered as the best among the other formulations. No chemical interaction between the drug and the excipients was confirmed by FTIR studies. The stability study was conducted and the formulations were found to be stable. These results revealed that fast dissolving tablets of poorly soluble drug Telmisartan showed enhanced dissolution and hence better patient compliance.

Keywords: Fast dissolving tablet, croscarmellose sodium, crospovidone, sodium starch glycolate, Telmisartan

Introduction

The oral route of administration has wide acceptance and constitute 50-60% of total drug formulations. This trend
is still continuing since oral route is the most preferred route due to its several advantages including ease of ingestion, self-medication and most importantly, patient compliance.

The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Sometimes people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Fast dissolving tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, Orodispensible tablets, rapimelts, porous tablets, quick dissolving etc. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The technologies used for manufacturing fast-dissolving tablets are freeze-drying, spray-drying, tablet moulding, sublimation, sugar-based excipients, tablet compression and disintegration addition.

The target population for these fast dissolving dosage form have generally been pediatric, geriatric and bedridden or developmentally disabled patients. Patients with persistent nausea, who are traveling or who have little or no access to water are good candidate for fast dissolving drug delivery system.

For poorly soluble orally administered drugs, the rate of absorption is often controlled by the rate of dissolution. The rate of dissolution can be increased by increasing the surface area of available drug by various methods micronization, complexation, use of surfactant and solid dispersion. The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution.

Telmisartan is an angiotensin II receptor antagonist used in the management of hypertension. Telmisartan bind to angiotensin II type I receptor with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. In the present study, an attempt was made to develop Fast dissolving tablets of telmisartan and to investigate the effect of the superdisintegrants on the release profile of drug.
Materials

Telmisartan was obtained from Zydus Cadila Ltd. Ahamadabad as a gift sample. The Superdisintegrants obtained from Maple Biotech Ltd. Pune as a gift sample. All other excipients were obtained from S.D. Fine Chemicals Mumbai.

Method

Preparation of Telmisartan-β-cyclodextrin inclusion complex

There are various methods to prepare inclusion complex using drug and β-cyclodextrin are as follows:

1. Preparation of cyclodextrin complex by physical mixtures method.

   Drug and β-Cyclodextrin in the proportion of appropriate molar ratio (1:2 molar ratio) were mixed in a mortar for one hour.

2. Preparation of inclusion complex by kneading method

   Drug and β-Cyclodextrin in the proportion of appropriate molar ratio (1:2 molar ratio) were mixed in a mortar for one hour with small quantities of distilled water and methanol was added intermittently to get slurry like consistency. The paste was dried in the oven at the temperature of 45˚C. Dried complex were pulverized into fine powder and sifted with sieve # 80.

3. Preparation of inclusion complex by co-evaporation method.

   Drug and β-cyclodextrin in 1:2 molar ratio were mixed and 10 ml methanolic solution of drug was added slowly to 10 ml aqueous solution of cyclodextrin followed by stirring using magnetic stirrer at 37˚C. Resulting solution were evaporated at the temperature of 45˚C. Dried complex were pulverized into fine powder and sifted with sieve # 80.

Characterization of Telmisartan-β-Cyclodextrin Complex

1. FT-IR Spectral Analysis

   IR spectral analysis of pure telmisartan, β-cyclodextrin and telmisartan-β-cyclodextrin inclusion complex was carried out by KBr disc method.
2. Powder X-ray diffraction analysis

Powder X-ray diffraction patterns of telmisartan, β-cyclodextrin and telmisartan-β-cyclodextrin inclusion complex were determined using powder X-ray diffractometer.

3. Solubility

The solubility of telmisartan and telmisartan-β-cyclodextrin complex was checked in various solvent at room temperature using rotary/mechanical shaker. Solubility of drug was determined by saturation method. In 100 ml of solvent 100 mg of drug was added so 1000 µg/ml of solution was prepared. Drug was saturated because of insolubility in the solvent out of that 25 ml taken into 50 ml volumetric flask with the help of mechanical shaker and after shaking was completed solution was filtered through whatman filter paper and after suitable dilution absorbance was recorded and concentration of drug in solution was determined. From this concentration amount dissolved in the solvent i.e solubility was determined.

4. Dissolution study

Dissolution study of telmisartan and its complex with β-cyclodextrin was performed to evaluate drug release profile. Dissolution where performed on USP type II dissolution apparatus with 900 ml 6.8 phosphate buffer at 37°C at 50 rpm. 5ml aliquots were withdrawn at specific time interval and filtered using Whatman filter paper. Equal volume of fresh medium was replaced into dissolution medium to maintain constant volume throughout dissolution medium. Absorbance of filtered solution was checked by UV spectrophotometer at 296 nm.

5. Determination of drug content of Telmisartan-β-cyclodextrin complex

Telmisartan-β-cyclodextrin complex was evaluated for the drug content. Telmisartan-β-cyclodextrin complex equivalent to 20 mg drug was stirred with 100 ml of phosphate buffer for 60 min, then the solution was filtered and treated as stock solution containing 100 mg/ml drug. From this stock solution the concentration of 10 µg/ml was prepared and drug content was determined using calibration curve of pure telmisartan spectrophotometrically at 296 nm using phosphate buffer as blank.

Preparation of tablets containing complex of Telmisartan with β-cyclodextrin by direct compression method

The amounts of complex equivalent to 20 mg of drug was taken and then mixed with directly compressible diluent and superdisintegrants in a mortar. Magnesium stearate and talc were passed through sieve no. 80, mixed and
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blended with initial mixture in the mortar followed by compression of the blend. The formula is showed in table No.1

EVALUATION OF TELMISARTAN FAST DISSOLVING TABLETS

All the prepared tablets were evaluated for weight variation, thickness, friability, hardness, assay, disintegration time, wetting time, water absorption ratio, in vitro dissolution studies, stability study and IR spectroscopy. The result of evaluation parameters is given in Table No.2 and 3

Table No. 1: Composition of Telmisartan fast dissolving tablets.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Ingredient</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>1</td>
<td>Amount of complex equivalent to 20 mg of Telmisartan (with β-cyclodextrin)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Crosscarmellose sodium</td>
<td>7.5</td>
<td>11.25</td>
<td>15</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Crosspovidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.5</td>
<td>11.25</td>
<td>15</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Sodium starch glycolate</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.5</td>
<td>11.25</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Microcrystalline cellulose pH 102</td>
<td>11.25</td>
<td>10.12</td>
<td>9</td>
<td>11.25</td>
<td>10.12</td>
<td>9</td>
<td>11.25</td>
<td>10.12</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>Aspartame</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Magnesium Stearate</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>9</td>
<td>Talc</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>10</td>
<td>Total weight of tablet</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

(All quantities in mg)

Table No. 2: Evaluation of Fast dissolving tablet of Telmisartan-β-cyclodextrin complex.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Batch No.</th>
<th>Thickness (mm)</th>
<th>Weight variation (mg)</th>
<th>Friability (%)</th>
<th>Hardness (kg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>2.32</td>
<td>150 ± 5%</td>
<td>0.66</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>2.43</td>
<td>149 ± 5%</td>
<td>0.85</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>2.37</td>
<td>150 ± 5%</td>
<td>0.72</td>
<td>2.2</td>
</tr>
</tbody>
</table>
### Table No. 3: Complies as per USP specification.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Batch No.</th>
<th>Disintegration time in sec.</th>
<th>Wetting Time in sec.</th>
<th>Water Absorption Ratio (%)</th>
<th>Drug Content(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>20</td>
<td>27</td>
<td>90.01</td>
<td>99.50</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>28</td>
<td>33</td>
<td>81.08</td>
<td>99.10</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>31</td>
<td>31</td>
<td>77.63</td>
<td>98.30</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>37</td>
<td>37</td>
<td>69.93</td>
<td>97.50</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>35</td>
<td>35</td>
<td>73.02</td>
<td>97.90</td>
</tr>
<tr>
<td>6</td>
<td>F6</td>
<td>32</td>
<td>32</td>
<td>75.83</td>
<td>98.75</td>
</tr>
<tr>
<td>7</td>
<td>F7</td>
<td>34</td>
<td>34</td>
<td>74.02</td>
<td>98.30</td>
</tr>
<tr>
<td>8</td>
<td>F8</td>
<td>39</td>
<td>39</td>
<td>65.33</td>
<td>96.20</td>
</tr>
<tr>
<td>9</td>
<td>F9</td>
<td>45</td>
<td>45</td>
<td>63.08</td>
<td>95.80</td>
</tr>
</tbody>
</table>

**In-vitro Dissolution studies:**

In-vitro dissolution studies for all the fabricated tablets of telmisartan were carried out using USP apparatus type II at 50 rpm. The dissolution medium used was 6.8 phosphate buffer (900 ml) maintained at 37 ± 0.5°C.

Aliquots of dissolution media were withdrawn (5ml) at different intervals and content of telmisartan was measured by determining absorbance at 296 nm. 5ml aliquot was withdrawn at the 1min, 2min to be continued at the 1 min. intervals and filtered by whatman filter paper, suitably diluted and analyzed at 296 nm using UV - visible spectrophotometer.

An equal volume of fresh medium, which was pre-warmed at 37°C was replaced in to the dissolution medium after each sampling to maintain the constant volume throughout the test. Absorbance was taken at 296 nm.
and calculate percentage release. The results are listed in Table No.4. and the dissolution profile are shown in Fig. No. 1, 2 and 3

**Stability Study**

Stability studies of the selected formulated tablets were carried out by keeping the tablets at room temperature and at 40°C ± 2°C / 75 ± 5% RH (stability chamber) for 30days and evaluated for physical properties, drug release and drug content during the testing period. All the parameters were compared with initial formulation.

**Table No. 4: In vitro drug released study of formulation F1-F9.**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Time (min)</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>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>49.86</td>
<td>48.73</td>
<td>45.72</td>
<td>36.72</td>
<td>37.48</td>
<td>41.80</td>
<td>38.25</td>
<td>35.59</td>
<td>32.98</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>79.74</td>
<td>76.36</td>
<td>73.55</td>
<td>65.81</td>
<td>66.58</td>
<td>71.46</td>
<td>69.01</td>
<td>63.73</td>
<td>58.09</td>
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<tr>
<td>4</td>
<td>3</td>
<td>95.57</td>
<td>93.30</td>
<td>91.78</td>
<td>84.53</td>
<td>86.25</td>
<td>90.98</td>
<td>89.64</td>
<td>81.90</td>
<td>75.88</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>96.46</td>
<td>94.35</td>
<td>93.41</td>
<td>87.07</td>
<td>89.70</td>
<td>92.25</td>
<td>91.08</td>
<td>84.97</td>
<td>79.67</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>97.17</td>
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<td>88.49</td>
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<td>93.12</td>
<td>92.15</td>
<td>86.74</td>
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<td>89.52</td>
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<td>94.49</td>
<td>92.99</td>
<td>88.34</td>
<td>81.86</td>
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<tr>
<td>8</td>
<td>7</td>
<td>98.64</td>
<td>96.68</td>
<td>96.08</td>
<td>90.59</td>
<td>92.90</td>
<td>94.67</td>
<td>93.72</td>
<td>89.58</td>
<td>82.84</td>
</tr>
</tbody>
</table>

**Fig. No. 1: In Vitro Dissolution profiles formulation F1-F3**
Fig. No. 2: In Vitro Dissolution profiles of formulation F4-F6.

![Dissolution profiles of formulation containing crospovidone](image1)

Showing relationship between Time Vs % drug release

Fig. No. 3: In Vitro Dissolution profiles of formulation F7-F9.

![Dissolution profiles of formulation containing sodium starch glycolate](image2)

Showing relationship between Time Vs % drug release

Result and Discussion

The rate of dissolution can be increased by increasing the surface area of available drug by complexation with β-cyclodextrin using various methods and it was found that complex of telmisartan-β-cyclodextrin prepared with kneading method in 1:2 molar ratio showed increase in solubility of telmisartan. Powder X-ray diffraction spectroscopy showed decrease in degree of crystallinity in the given sample when complex of drug and cyclodextrin are formed and increases in amorphousness and consequently increase in solubility of drug was observed. The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution. In the present work direct compression was employed to prepare tablets. Using telmisartan-β-cyclodextrin complex, Micro crystalline cellulose and directly compressible mannitol was selected as diluent. Croscarmellose sodium, crospovidone and sodium starch glycolate were selected as superdisintegrants.
Magnesium stearate and talc were selected as lubricant and glidant respectively. Aspartame was added as a sweetening agent. Tablets were compressed individually using 8 station rotary compression machine.

Precompressional parameters, angle of repose, bulk density, tapped density, % compressibility and hausner ratio studies indicated that most of the formulation showed fair and good flow properties.

Postcompressional parameters, hardness, friability, disintegration time, wetting time, drug content and dissolution studies were studied. Friability of tablets ranged between 0.53% to 0.85%. Drug content of tablets ranged between 95.80% to 99.50%. Stability studies of the selected formulated tablets were carried out by keeping the tablets at room temperature and at 40°C ± 2°C / 75 ± 5% RH (stability chamber) for 30 days. From the stability studies it was found that formulation were stable at room temperature and at 40°C ± 2°C / 75 ± 5% RH for a period of 30 days. There was no appreciable change in physical properties, drug release and drug content during the testing period.

Tablets prepared by Croscarmellose sodium (5% concentration) as a superdisintegrant showed least disintegration time as compared with other tablets prepared by crospovidone and sodium starch glycolate. FT-IR studies revealed that, there was no interaction of the drug with the excipients used.

**Conclusion**

From this study, it was concluded that dissolution rate of poorly soluble drug, Telmisartan could be enhanced by preparing fast dissolving tablets by direct compression with β-cyclodextrin complex prepared by kneading method. Among all the formulations, formulation F1 which was prepared by direct compression with β-cyclodextrin complex using croscarmellose sodium 5% yielded better results in terms of dissolution rate.

**Acknowledgement**

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**References**

6. www.wikipedia.com
7. www.drugbank.com


**Corresponding Author:**
Megha N. Karemore*,
Plot no. 1202, Behind M.I.G. Colony,
K.D.K. College Road, Nandanwan,
Nagpur. Dist: Nagpur (M.S.) 440 009, India.
Email: meghakaremore0687@gmail.com