DESIGN, PREPARE AND IN VITRO EVALUATION OF FAST DISSOLVING TABLETS OF TELMISARTAN

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ABSTRACT : The objective of the study was to formulate and evaluate fast dissolving tablet of Telmisartan. Direct compression method was used to formulate fast dissolving tablet of Telmisartan by employing amount of croscarmellose sodium and sodium starch glycolate were used as super disintegrant material along with direct compressible lactose to enhance mouth feel. The prepared batches of tablets were evaluated for hardness, friability, weight variation, disintegration time, drug content and in-vitro dissolution studies. Based on wetting time, disintegration time, the formulation containing croscarmellose sodium and sodium starch glycolate was found to be promising and tested for in-vitro drug release pattern in 6.8 phosphate buffer, short term stability and drug- super disintegrants interaction. F4 Formulation as processed excipient was found to be the best super disintegrants for the preparation of Telmisartan orally disintegrating tablets formulations. Due to it has exhibited faster disintegration time and best dissolution profile when compared to other formulations.

Keywords: Telmisartan, super disintegrants, FTIR studies, direct compression technique, in-vitro drug release studies.

I. INTRODUCTION

The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional means of taking their medication. Because of physiological changes associated with, especially, elderly and pediatrics are quite unable to swallow (Dysphagia); rather, this is a common problem of all age groups patients. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the paediatric and geriatric population, as well as other patients who prefer the convenience of easily swallowable dosage forms. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva. Recently, pharmaceutical preparations used for elderly patients have been investigated to improve the treatment compliance and quality of life of such patients. A tablet which can rapidly disintegrate in saliva (rapidly disintegrating tablet) is an attractive dosage form and a patient-oriented pharmaceutical preparation. The mouth-dissolving tablets have attracted the interest of many researchers. Many elderly patients have difficulty swallowing tablets, capsules, or powders. To alleviate this problem, these tablets are expected to dissolve or disintegrate in the oral cavity without drinking water. The disintegrated mass can slide down smoothly along the esophagus with the help of saliva, so even people who have swallowing or chewing difficulties can take it with ease. There are two different types of dispersible tablets which have to be distinguished. One dosage form disintegrates instantaneously in the mouth, to be swallowed without the need for drinking water, while the other tablet formulation can readily be dispersed in water, to form dispersion, easy to ingest by the patient. The objective of present study is to design and develop a stable solid oral dosage form of telmisartan dispersible tablets to deliver with optimum concentration of drug at desired site at specific time comparable to the innovator product with better stability, high production feasibility, and excellent patient compatibility. Solid oral dosage forms are most convenient from patient as well as from manufacturing chemist's perspective. Dispersible tablets are required to disintegrate within 3 mins in water at 15-25°C. The aim of this study is Formulation and Evaluation of Telmisartan fast dissolving tablets. Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II
receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects.\textsuperscript{7,8}

2. MATERIALS AND METHOD

2.1 MATERIALS

Telmisartan was collected as a gift sample from Hetero labs, Hyd, polymers and other excipients were purchased from AR Chemicals, Hyd.

2.2 METHODOLOGY

Compatibility studies:

The drug-polymer compatibility was ascertained by subjecting the drug and homogenates of drug and polymer to Infrared spectrophotometric study.

Fourier Transform Infrared Spectroscopy (FTIR)\textsuperscript{9,10}

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a dosage form. The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by analysing the significant changes in the shape and position of the absorbance bands. In this method individual samples as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm\(^{-1}\) in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures.

Formulation Development

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredient</th>
<th>F-1</th>
<th>F-2</th>
<th>F-3</th>
<th>F-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Telmisartan</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>2</td>
<td>Sodium starch glycolate</td>
<td>10</td>
<td>20</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Poloxomer 407</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Lactose</td>
<td>180</td>
<td>170</td>
<td>180</td>
<td>170</td>
</tr>
<tr>
<td>5</td>
<td>Aspartame</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>Magnesium stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Talc</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Total</td>
<td>400</td>
<td>400</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

Preparation technique

Direct compression method

Fast dissolving tablets of Telmisartan were prepared by direct compression. All the ingredients were passed through 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100 mg using 6mm round flat punches on 10-station rotary tablet machine (Rimek)\textsuperscript{11}.

Evaluation parameters

Precompression parameters\textsuperscript{12,13,14,15}
Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

\[
\text{Bulk density} = \frac{\text{weight of sample taken}}{\text{volume noted}}
\]

Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured.

\[
\text{Tapped density} = \frac{\text{weight of sample taken}}{\text{tapped volume}}
\]

Compressibility index

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

\[
\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100
\]

Hausner’s ratio

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

\[
\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

Angle of repose

The flow characteristics are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

\[
\tan \theta = \frac{h}{r}
\]

Evaluation of tablet

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage of 16%.

Thickness

Twenty tablets were randomly selected from each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm². Three tablets were randomly picked and hardness of the tablets were determined.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause 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. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

\[
\% F = \{1 - (W_o/W)} \times 100
\]

Drug Content

The drug content was determined by triturating tablets in a mortar and pestle. The 100 mg of sample powder was dissolved in 6.8 phosphate buffer. The solution was filtered through Whatmann filter paper. The filtrate was analyzed by U.V. spectrophotometer (LAB INDIA ) at 295 nm.

In vitro Disintegration Test

The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.

In- Vitro Release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The
dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for remaining period of time. Temperature maintained at 37±1°C. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. The solution was filtered through Whatmann filter paper. The filtrate was analyzed by U.V. spectrophotometer (Labindia) at 295 nm. The drug release was plotted against time to determine the release profile of various batches.

Stability studies
The success of an effective formulation can be evaluated only through stability studies. The prepared disintegration tablets of Telmisartan were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°C and refrigerator 2-8°C for a period of 30 days.

III. RESULTS AND DISCUSSION

Compatibility Study

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Telmisartan were obtained at 3500 cm⁻¹, 1084 cm⁻¹, 3095cm⁻¹, 1745cm⁻¹.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

![Fig.1. FTIR Spectra of Telmisartan](image1)

![Fig.2. FTIR Spectra of Optimized formulation](image2)
Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm⁻¹) the drug is compatible with excipients.

**Evaluation Studies**

**Pre compression Parameters**

**Evaluation of granules**

a) **Bulk Density:** The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.512-0.528.

b) **Tapped density:** The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.611-0.629.

c) **Angle of repose:** The angle of repose for the formulated blend was carried out, It concludes that all the formulations blend was found to be in the range of 27 to 31°

d) **Compressibility index:** Compressibility index was carried out, it found between 10% to 16.9% indicating the powder blend have the required flow property for compression.

<table>
<thead>
<tr>
<th>Table 2: Results of Pre compression parameters of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B. No</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>F1</td>
</tr>
<tr>
<td>F2</td>
</tr>
<tr>
<td>F3</td>
</tr>
<tr>
<td>F4</td>
</tr>
</tbody>
</table>

**Post compression parameters**

**Weight variation**

The percentage weight variations for all formulations were tabulated in Table no. All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

**Thickness**

The thickness determined for formulated tablets were tabulated. Tablets mean thickness (n=3) were uniform in F1 to F4 formulations and were found to be in the range of 3.17mm to 3.31 mm.

**Hardness**

The measured hardness of tablets of each batch ranged between 6.5 to 7 kg/cm². This ensures good handling characteristics of all batches.

**Friability**

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

**Content Uniformity**

The percentage of drug content for F1 to F4 was found to be between 94.50% and 99.80% of Telmisartan it complies with official specifications.
Table 3 Results of Evaluation parameters of tablets

<table>
<thead>
<tr>
<th>B. No.</th>
<th>Weight variation (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>400</td>
<td>6.12</td>
<td>5.82</td>
<td>0.65</td>
<td>97.82</td>
</tr>
<tr>
<td>F2</td>
<td>399</td>
<td>6.15</td>
<td>5.65</td>
<td>0.64</td>
<td>96.42</td>
</tr>
<tr>
<td>F3</td>
<td>398</td>
<td>6.18</td>
<td>5.42</td>
<td>0.61</td>
<td>99.80</td>
</tr>
<tr>
<td>F4</td>
<td>400</td>
<td>6.23</td>
<td>5.22</td>
<td>0.60</td>
<td>95.82</td>
</tr>
</tbody>
</table>

In-vitro Dissolution Study

Table 4 In vitro release data of tablet F1 to F4

<table>
<thead>
<tr>
<th>Time</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>25.65</td>
<td>25.02</td>
<td>24.18</td>
<td>28.14</td>
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<tr>
<td>10</td>
<td>39.56</td>
<td>38.25</td>
<td>37.81</td>
<td>36.58</td>
</tr>
<tr>
<td>15</td>
<td>44.28</td>
<td>43.45</td>
<td>42.58</td>
<td>44.27</td>
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<tr>
<td>20</td>
<td>69.35</td>
<td>68.57</td>
<td>67.84</td>
<td>66.28</td>
</tr>
<tr>
<td>25</td>
<td>78.56</td>
<td>77.19</td>
<td>78.29</td>
<td>79.14</td>
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<tr>
<td>30</td>
<td>89.25</td>
<td>88.27</td>
<td>90.96</td>
<td>96.88</td>
</tr>
</tbody>
</table>

Fig.3. Dissolution Profile of formulations (F1 to F4)

Stability Studies
There was no significant change in physical and chemical properties of the tablets of formulation F-4 after 3 months. Parameters quantified at various time intervals were shown

Table no: 5 Results of stability studies of optimized formulation F-4

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Parameters</th>
<th>Initial</th>
<th>1st Month</th>
<th>2nd Month</th>
<th>3rd Month</th>
<th>Limits as per Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-4</td>
<td>25°C/60% RH % Release</td>
<td>96.88</td>
<td>96.87</td>
<td>96.85</td>
<td>96.82</td>
<td>Not less than 85 %</td>
</tr>
<tr>
<td>F-4</td>
<td>30°C/75% RH % Release</td>
<td>96.88</td>
<td>96.84</td>
<td>96.82</td>
<td>96.81</td>
<td>Not less than 85 %</td>
</tr>
<tr>
<td>F-4</td>
<td>40°C/75% RH % Release</td>
<td>96.88</td>
<td>96.81</td>
<td>96.80</td>
<td>96.80</td>
<td>Not less than 85 %</td>
</tr>
</tbody>
</table>

IV. CONCLUSION

The aim of the present study was to develop an optimized formula for fast disintegrating tablet containing Telmisartan. Pre-formulation studies it was decided to prepare fast dissolving tablets prepared by direct compression method. In the formulation of sodium starch glycolate, and croscarmellose were used as super disintegrants. Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner’s ratio. The compressed tablets were also evaluated for weight variation, hardness, friability, drug content, disintegration time, wetting time, in vitro drug release and stability studies. In the above studies F4 formulation showed promising results. It was further supported by FTIR analysis which showed that F4 had no interaction with excipients. The stability studies were carried out for the optimized batch F4 for 90 days and it showed acceptable results. So F4 formulation was considered as the optimized formulation.

REFERENCES

5. 5th ed. 1.0. Strasbourg, France: 2005. European Pharmacopoeia 5.0; p. 628.]