Formulation and Evaluation of Immediate Release Telmisartan Tablets using Hydrophilic Polymers

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Abstract

Aim: Telmisartan is an anti-hypertensive drug under the class of angiotensin II receptor blocker. The aim is to formulate and evaluated immediate release telmisartan tablets using hydrophilic polymers. Materials and Method: The hydrophilic polymers are polyethylene glycol 4000 (PEG-4000) and PEG-6000. Solid dispersion is prepared with polymers with different ratios 1:0.5, 1:1, 1:2 and formulated into tablets. Formulations were characterized for drug content studies, drug release studies, and drug-polymer interactions using Fourier transform infrared spectroscopy (FTIR) spectrum. Results and Discussions: Formulation containing 1:2 ratio of drug: PEG-6000 showed the best release with a cumulative release of 99.67% as compared to 74.36% for the PEG-4000. The FTIR studies showed that there is no interaction between the drug and polymer. Conclusion: Based evaluation of different parameters it was concluded that formulation of immediate release tablets of telmisartan was successfully done and F6 shows 100% at 60 min.

Key words: Immediate release tablets, polyethylene glycol-4000, polyethylene glycol-6000, solid dispersion, telmisartan

INTRODUCTION

Hypertension or high blood pressure (BP) is a medical condition, in which the BP in the arteries is persistently elevated. BP is the force of blood pushing up against the wall of blood vessels (arteries and veins). Important organs affected are heart leading to heart attack or heart failure, brain leading to stroke, kidney leading to chronic renal failure, eyes leading to bleeding in retina, loss of vision, and nerve damage.[1]

WHO rates the hypertension as one of the most important causes of premature death in worldwide. According to the WHO hypertension is a highly prevalent cardiovascular disease. In India, hypertension is the most prevalent chronic disease. The prevalence of hypertension ranges from 20% to 40% in urban adults and 12-17% among rural adults.[2]

Among all dosage, forms tablet is the most popular dosage form existing today because of its easy of self-administration, compactness and easy manufacturing and sometimes immediate onset of action and above all it is easy to maintain its stability parameters throughout the shelf life.[3] There are so many drugs are available for treatment of hypertension. Telmisartan is in the drug class of angiotensin receptor blockers and is prescribed for the treatment of high BP, reducing the risk of heart attack, stroke, or death from cardiovascular causes. 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 BP.[3] Recent studies suggest that telmisartan may also have peroxisome proliferator-activated receptor-gamma (PPARγ) agonistic properties that could potentially confer beneficial metabolic effects.[4]

In this study, telmisartan is chosen as a model drug to prepare solid dispersion because of its poor and pH dependent solubility profile and formulated into an immediate release tablet by using solid dispersion technique. For solid dispersion methods, two methods are employed, i.e., solvent evaporation

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method and fusion method. The term solid dispersion refers to a group of solid products consisting of at least two different compounds, generally hydrophobic drug and hydrophilic matrix. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles.\[^{5}\]

Chemical name of telmisartan is [4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl]methyl] 1, 1-biphenyl - 2 carboxylic acid. Telmisartan is an orally active non-peptide angiotensin II antagonist that acts on the AT1 receptor subtype. It is practically insoluble in water, so it is important to enhance the solubility of drug in dissolution medium.\[^{5}\] New studies suggest that telmisartan may also have PPARγ agonistic properties that could potentially confer beneficial metabolic effects. This observation is currently being explored in clinical trials.\[^{6,7}\]

The aim of the work is to prepare the immediate release of telmisartan tablets using hydrophilic polymers like polyethylene glycol 4000 (PEG-4000) and PEG-6000 by solvent evaporation method and fusion method.\[^{8}\]

**MATERIALS AND METHODS**

**Materials**

Telmisartan was a gift sample from Hetero Drugs Pvt Ltd., Hyderabad. PEG-4000 and PEG-6000 was obtained from Loba Chem Pvt. Ltd. Magnesium stearate and microcrystalline cellulose (MCC) were supplied from Yarrow Chem. Products, Mumbai. Talc was purchased from Merk Specialities Pvt. Limited, Mumbai.

**Methodology**

**Construction of calibration curve**

Accurately weighed 50 mg of telmisartan pure drug was dissolved in 50 ml of hydrochloric acid (HCl) stock solution (1000 µg/ml). 10 ml was taken and make with 100 ml of 0.1 N HCl (100 µg/ml). From the above solution was subsequently diluted with 0.1 N HCl to obtain series of dilutions containing 5, 10, 15, 20, 25 and 30 µg/ml of telmisartan per ml solution. The absorbance of the above solution was measured at 296 nm using ultraviolet spectrophotometer taking 0.1 N HCl as blank. Then, a graph was plotted and shown in Figure 1.

**Method of preparation of solid dispersions**

**Solvent evaporation method**\[^{9}\]

In this method, the drug and carriers are used in different ratios (1:0.5, 1:1, 1:2). The respective amount of carrier was dissolved in methanol (10 ml), and telmisartan was added in parts with continuous stirring. The solvent was then removed by evaporation. The prepared dispersions were pulverized and sifted through sieve100# and stored in desiccators for further studies.

**Fusion method**\[^{10}\]

In this method, the polymer was weighed and melted on cooling the drug is slowly added to the polymer and allowed to evaporate under the ratios of 1:0.5, 1:1, 1:2. Formula was shown in Table 1.

**Preparation telmisartan tablets**\[^{11}\]

Telmisartan tablets were prepared by were prepared by direct comparison method employing telmisartan prepared mixture which is equivalent to 200 mg of telmisartan, MCC as a binder, lactose as diluents, magnesium stearate, and talc as lubricating agent. Formula was shown in Table 2.

**Evaluation of tablets**

**Pre-compression parameters**

**Angle of repose**\[^{12}\]

Angle is determined using funnel. The accurately weighed powder was taken in a funnel. The height of the funnel is adjusted in such a way the tip of the funnel just touches apex of the head of the blend. The powder is allowed to flow
through the funnel freely onto the surface. The diameter of the powder cone is measured, and angle of repose is calculated using the following equation.

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

Where \( h \) and \( r \) the height of the cone and radius cone base respectively.

**Bulk density**
Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. Bulk density is calculated using the following formula:

\[
\text{Bulk density} = \frac{\text{Weight of powder}}{\text{bulk volume of powder}}.
\]

**Hausner’s ratio**
The Hausner’s ratio is a number that is correlated to the flowability of a powder or granular material.

Hausner’s ratio = tapped bulk density/LB.

**Compressibility index**
The compressibility index is measure of the propensity of the powder to be compressed. As such, they are measures of the relative importance of inter-particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater inter-particulate interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility index.

**Bulk density**
It is defined as the ratio of the mass of an untapped powder sample and its volume is including the contribution of inter-particular void volume.

**Fourier transform infrared spectroscopy (FTIR) studies**
The IR spectrum of the prepared samples under dry conditions the transition minima the spectra obtain with these two polymers were compared, and the presence of additional peaks corresponding to the functional groups was noted.

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**Table 2: Formula used for formulation of telmisartan tablets**

<table>
<thead>
<tr>
<th>Materials used</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>
<th>F10</th>
<th>F11</th>
<th>F12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid dispersion (equivalent to 40 mg)</td>
<td>60</td>
<td>80</td>
<td>120</td>
<td>60</td>
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<td>120</td>
<td>60</td>
<td>80</td>
<td>120</td>
<td>60</td>
<td>80</td>
<td>120</td>
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<tr>
<td>Starch (mg)</td>
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<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<td>MCC (mg)</td>
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<td>65</td>
<td>25</td>
<td>85</td>
<td>65</td>
<td>25</td>
<td>85</td>
<td>65</td>
<td>25</td>
<td>85</td>
<td>65</td>
<td>25</td>
</tr>
<tr>
<td>Talc (mg)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<td>20</td>
</tr>
<tr>
<td>Magnesium stearate (mg)</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
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<td>15</td>
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<tr>
<td>Total Wt of tablet (mg)</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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<td>200</td>
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<td>200</td>
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<td>200</td>
</tr>
</tbody>
</table>

*All quantities are in mg, MCC: Microcrystalline cellulose

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**Post-compression parameters**

**General appearance**
The formulated tablets were assessed for its general appearance, and observations were made for shape, color, texture, and odor. The prepared tablets were found to be round shaped, smooth, and white color.

**Weight variation test**
The weight variation test is carried out to ensure uniformity in the weight of tablets in a batch. First, the total weight of 20 tablets from each formulation is determined, and the average is calculated. The individual weight of each tablet is also determined to find out the weight variation.

\[
\% \text{ wt variation} = \left( \frac{\text{average weight of tablet} - \text{weight of each tablet}}{\text{average of tablet}} \right) \times 100.
\]

**Hardness**
Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The values are recorded and noted.

**Friability test**
About 10 previously weighed tablets were placed in the friability apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated using the following formula,

\[
\% \text{ Friability} = \left( \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \right) \times 100.
\]

**Disintegration test**
The disintegration test was done on six using Indian pharmacopeia method. At the end of the specific time lift the basket and observe that the tablets pass the test, i.e., all six units disintegrated.

**Assay**
Weighed tablets (5) were powdered using a glass mortar and pestle. An accurately weighed quantity of the tablet containing
about 250 mg of telmisartan is dissolved in methanol and taken into 100 ml of volumetric flask. Then, pipette out 10 ml of above solution than diluted up to 50 ml. From this standard solution again, 5 ml is pipette out diluted to 50 ml with 0.1 N HCl resulting solution was measured at 296 nm, and drug content was calculated against 0.1 N HCl as blank.

**In vitro dissolution study**

*In vitro* dissolution study is performed using USP type 2 apparatus (paddle) at 75 rpm. 0.1 N HCl 900 ml is used as dissolution medium which maintained at 37 ± 0.5°C. At definite time intervals, 5 ml of the fluid was withdrawn. Filtered through 0.45 µm membrane filter and again 5 ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid, and the samples were analyzed spectrophotometrically at 296 nm.

**RESULTS AND DISCUSSIONS**

**Pre-compression parameters**

About 12 formulations were prepared with different ratios addition of different ingredients. For each designed formulations powder mixed blend of drug and excipients were prepared and evaluated for various parameters.

**FTIR studies**

Pre-formulation studies for the drug-polymer interactions studied by comparing FTIR spectra of cured drug compared with the mixture of drug and with other ingredients. Telmisartan gives the characteristic peak in range nearby 3397.08/cm. The peak present in drug, excipient, other methods shows the peaks of telmisartan nearby at 3465.09, 3540.54, 3687.94/cm. The frequency of functional groups of pure drug remains unaffected by solid dispersions containing different polymers like PEG-4000 and PEG-6000 with different methods, i.e., fusion method and solvent evaporation technique. Hence, there is no interaction between drug and excipients is observed. Graphs are shown in Figures 2-8.

**Bulk density**

The bulk density of various powder sample sizes (10 g) of different ratios of drug and excipients was taken in graduated cylinder and measured with bulk density apparatus. The bulk density was found to be in the range of 0.515 ± 0.527 to 0.527 ± 0.45 kg/cm³. Results are shown in Table 3.

**Tapped density**

Tapped density of various powder sample sizes (10 g) of different ratios of drug and excipients was taken in graduated cylinder and measured with bulk density apparatus and it was found to be in the range of 0.610 ± 0.01 to 0.623 ± 0.02 g/cm³. Results are shown in Table 3.

**Compressibility index**

Compressibility index of various powder blends of 10 g prepared with different ratios of drug and excipients the compressibility index was found to be in the range of 14.56% ± 0.20% to 16.53% ± 1.6%. Results are shown in Table 3.

**Hausner’s ratio**

The Hausner’s ratio was found to be in the range of 1.170 ± 0.02 to 1.198 ±0.21. Results are shown in Table 3.

**Angle of repose**

The entire formulations were found to be in the range of 30.48 ± 0.02 to 39.23 ± 0.01 and it concludes that all
formulations are having passable flow property. Results are shown in Table 3.

**Post-compression parameters**

**General appearance**

The prepared tablets were found to be good without any tablet manufacturing defects. All prepared tablets were white in color and smooth in texture. There was no sign of picking and sticking and no lamination, chipping, capping and cracking.

**Thickness**

Thickness of the tablets was measured with the vernier calipers and it was found to be 3.00 ± 0.02 to 3.05 ± 0.01 mm with minimum deviation by which the thickness of the tablet was controlled within limits. Results are shown in Table 4.

**Weight variation test**

Tablets were prepared using direct compression technique. The 10 tablets were randomly selected and weighed individually and the results obtained in the range with acceptable weight variations as per Indian pharmacopeia (IP) specifications <7.5, i.e., 200 mg ± 7.5. Weight variation was found to be 2.2 ± 0.25 to 4.1 ± 0.25. Results are shown in Table 4.

**Hardness test**

The measured hardness of tablets of all the formulations ranged in between 2.55 ± 0.003 and 2.75 ± 0.001 kg/cm².
This ensures good handling characteristics of all batches. Results are shown in Table 4.

**Friability test**

Tablets are evaluated using Roche friabilator. Friability was found in the range of 0.29 ± 0.009 to 0.65 ± 0.02. Results are shown in Table 4.

**Disintegration time**

Disintegration was carried out according to Indian pharmacopeia. Formulations F1-F6 shows disintegration time <1 min and formulation F3 shows 31 s. For all formulations, disintegration time was found to be in the range of 31-69 s. Results are shown in Table 4.

**Assay**

Drug content of all the formulations was in the range of 98.122-102.44% of telmisartan. It complies with official specifications in IP. Results are discussed in Table 4.

**In vitro drug release**

In vitro drug release studies were conducted for the formulation using USP dissolution apparatus type-II (paddle), at 75 rpm for the formulations developed with both the polymers PEG-4000 and PEG-6000 by the fusion and solvent evaporation method in the drug: Polymer ratios of 1:0.5, 1:1, 1:2 and it is clearly shown by assigning the formulation code shown in the Table 1. The formulations with the polymer PEG-4000 and PEG-6000 (Drug: Polymer ratio 1:2) F3 and F6, respectively,
shows drug release more than 90% at the end of 60 min with the fusion method when compared to the formulations F9 and F12 solvent evaporation which are having the same drug: Polymer ratio shows drug release not more than 80% at the end of 60 min. Results are shown in Tables 5 and 6 and graphs are shown in Figures 9-12. Among the polymers of PEG-4000 and PEG-6000, the PEG-6000 shown the optimized results compared to the PEG-4000 because of its more hydrophilic nature. When compared to the methods, fusion methods are shown the optimized result 99.39% compared to the solvent evaporation 76.52% drug release because of the mechanism involved are enhanced solubilization and improved wetting property of the drug with the PEG formed at the drug crystals compared to the solvent evaporation. The immediate release tablets developed with both the methods i.e., fusion and solvent evaporation method and with different polymers PEG 4000 and PEG 6000 following first order rate kinetics and the results are shown in Table 7 and and graphs are shown in Figures 13-16.

**CONCLUSION**

The hydrophilic polymers used in formulations are PEG-4000 and PEG-6000 in the drug: Polymer ratio 1:2 in both fusion method and solvent evaporation method shows optimized results. Among these infusion method, PEG-6000 1:2 ratio shows better drug release 99.39% than PEG-4000 1:2 shows 95.23%, whereas in solvent evaporation method PEG-6000 (1:2) shows 76.52% and PEG-4000 (1:2) shows
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74.34%. FTIR studies reveal that there is no drug and polymer interactions are not taken place.

Direction compression method was used to formulate the tablets. All formulations show acceptable flow properties and

Table 3: Pre-compression parameters of formulations (F1-F12)

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Mean±SD (n=3)</th>
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<tbody>
<tr>
<td></td>
<td>Bulk density (g/ml)</td>
</tr>
<tr>
<td>F1</td>
<td>0.515±1.47</td>
</tr>
<tr>
<td>F2</td>
<td>0.523±0.45</td>
</tr>
<tr>
<td>F3</td>
<td>0.518±0.25</td>
</tr>
<tr>
<td>F4</td>
<td>0.517±1.05</td>
</tr>
<tr>
<td>F5</td>
<td>0.525±0.99</td>
</tr>
<tr>
<td>F6</td>
<td>0.523±0.36</td>
</tr>
<tr>
<td>F7</td>
<td>0.527±0.45</td>
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<tr>
<td>F8</td>
<td>0.516±0.24</td>
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<tr>
<td>F9</td>
<td>0.522±0.25</td>
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<td>F10</td>
<td>0.526±0.65</td>
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<tr>
<td>F11</td>
<td>0.522±0.34</td>
</tr>
<tr>
<td>F12</td>
<td>0.525±0.11</td>
</tr>
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</table>

SD: Standard deviation

Table 4: Post-compression parameters of telmisartan tablets (F1-F12)

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Mean±SD (n=3)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Weight variation</td>
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<tr>
<td>F1</td>
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<tr>
<td>F2</td>
<td>2.5±0.36</td>
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<tr>
<td>F3</td>
<td>3.5±0.26</td>
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<tr>
<td>F4</td>
<td>2.2±0.25</td>
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<tr>
<td>F5</td>
<td>4.1±0.25</td>
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<tr>
<td>F6</td>
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<td>F7</td>
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<tr>
<td>F8</td>
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<tr>
<td>F9</td>
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<td>F10</td>
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<td>F11</td>
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<tr>
<td>F12</td>
<td>2.6±0.25</td>
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SD: Standard deviation

Table 5: In vitro drug release profile of formulations (F1-F12)

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<tr>
<th>Time (min)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
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</tr>
<tr>
<td>5</td>
<td>9.23±0.04</td>
<td>11.69±0.02</td>
<td>15.38±0.3</td>
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<td>12.81±0.03</td>
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<tr>
<td>10</td>
<td>26.8±0.2</td>
<td>29.06±0.32</td>
<td>30.81±0.056</td>
<td>22.81±0.06</td>
<td>32.61±0.04</td>
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<tr>
<td>20</td>
<td>36.9±0.36</td>
<td>53.89±0.02</td>
<td>52.89±0.045</td>
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<td>58.01±0.03</td>
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<tr>
<td>30</td>
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<td>68.03±0.14</td>
<td>79.32±0.065</td>
<td>46.09±0.03</td>
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<td>45</td>
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<td>72.81±0.02</td>
<td>80.67±0.12</td>
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<td>82.09±0.07</td>
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<tr>
<td>60</td>
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<td>95.23±0.35</td>
<td>72.64±0.15</td>
<td>91.69±0.02</td>
<td>99.39±0.22</td>
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</tbody>
</table>

74.34%. FTIR studies reveal that there is no drug and polymer interactions are not taken place.

Direction compression method was used to formulate the tablets. All formulations show acceptable flow properties and
pre-compression parameters such as angle of repose, bulk density, tapped density, compressibility index, and Hausner’s ratio. The post-compression parameters such as hardness, friability, disintegration time, and weight variation are found to be within the IP limits. The drug content of all tablets was found to be 98.12-102.44% within the limit.
Based on above discussed parameters, it was concluded that formulation of immediate release tablets of telmisartan was successfully done and F6 shows 100% at 60 min with the fusion method.

**ACKNOWLEDGMENT**

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**REFERENCES**

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