DEVELOPMENT AND INVESTIGATION OF MATRIX TABLETS OF TELMISARTAN FOR CONTROLLED RELEASE

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ABSTRACT
The present study in the development of controlled release matrix tablets of anti-hypertensive drug Telmisartan. Hydroxy propyl methyl cellulose (HPMC) LV15 and LV5 used as a rate retarding polymer. The effect of the different proportion of the polymer and the influence of different grade of HPMC on the release rate of drug was investigated. Telmisartan release from HPMC LV15 and HPMC LV5 matrices are mainly controlled by the drug – HPMC ratio. When the influence of different grade of HPMC on the release of drug was examined, when the viscosity grade of HPMC increased there is decreased the drug release rate from matrix tablet. The tablets were prepared by direct compression methods and the prepared matrix tablets were evaluated for post-compression parameters such as hardness, friability, thickness, % weight variation, % drug content and in-vitro dissolution test.

KEYWORDS: Telmisartan, controlled release, Hydroxy propyl methyl cellulose, Dissolution.

INTRODUCTION
The oral route of drug delivery is the most popular, desirable and preferred method of administering therapeutic agents for systemic effects because it is natural, convenient for the patient, and cost effective to manufacturing process.[1] The oral controlled release drug delivery is to ensure safety and to improve efficacy of the drug as well as maintain the uniform drug level concentration. Matrix controlled release tablet formulations are the most
fashionable and straightforward to formulate on a commercial scale. The dosage release properties of matrix devices may be dependent upon the solubility of the drug in the polymer matrix.\(^2\) Hydrophilic matrix tablets have long been used as a drug delivery system. This is due to their simplicity, cost-effectiveness, reduced risk of systemic toxicity, and minimal chance of dose dumping. Matrix systems can be used to control the release of both water soluble and water insoluble drugs. HPMC is a widely used semi-synthetic hydrophilic matrix polymer that has been employed in the design of controlled release formulations due to its good compression, its ease of use, availability, very low toxicity.\(^3\) Mainly their characteristics and their ability to hydrate and form a gel layer are well known and essential to sustain and control drug release from matrices. The hydrated gel layer thickness determines the diffusion path of the drug molecules through the polymer mass in to dissolution medium.\(^4\) One approach to the manufacture of controlled release dosage forms is the direct compression of blends of drug, retardant material and additives to form a tablet in which drug is embedded in a matrix core of the retardant.\(^5\) The matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. It required fewer unit operations, less machinery, reduced number of personnel and processing time, increased product stability and production rate.\(^6\)

Telmisartan is a nonpeptide angiotensin receptor II (Type- ATI) antagonist, that cause inhibition of the action of angiotensin II on vascular smooth muscle in the symptomatic treatment of essential hypertension.\(^7\)\(^8\) High blood pressure reduction helps to prevent strokes, heart attacks, and kidney problems. Telmisartan has a long duration of action and has the longest half-life of any ARBs (24 hrs) and it have dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease.\(^9\) The objective of the present study is to prepare Telmisartan matrix tablets using different grades of HPMC and to investigate the mechanism of drug release using various kinetic models.

**MATERIALS AND METHODS**

**Materials**

Telmisartan was obtained as gift sample from Apotex research Pvt. Ltd. HPMC (LV15, LV5) was a gift sample received from shreeji chemicals. Microcrystalline cellulose, Lactose monohydrate, Magnesium stearate, Calcium sulphate dihydrate were received as gift sample
from SD fine chem limited. Silicon dioxide, Dicalcium phosphate dihydrate were received as gift sample from Rolex chemical industries. Sucrose, Dextrose was received from Thermo fisher scientific india pvt. ltd.

**Preparation of matrix tablets**

The controlled release matrix tablet formulation consisted of a drug, polymer and excipients. In all cases, the amount of the active ingredient was 80 mg and the total weight of the tablet was 300 mg. The ratios of the drug and polymer were maintained at 1:0.5, 1:1 and 1:5 levels. The compositions of various tablet formulations are given in Table-1. The drug, polymer and excipients were passed through a 100-mesh sieve and thoroughly mixed in a glass mortar for 15 minutes. The lubricant and glidants were added to the previous mixture and again mixed for 5 minutes. Then the tablets were directly compressed using a rotary tablet punching machine.

**Table 1: Formulation design of matrix tablet of Telmisartan.**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telmisartan</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>HPMC LV15</td>
<td>40</td>
<td>80</td>
<td>120</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMC LV5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>80</td>
<td>120</td>
</tr>
<tr>
<td>MCC</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Lactose monohydrate</td>
<td>85</td>
<td>45</td>
<td>05</td>
<td>85</td>
<td>45</td>
<td>05</td>
</tr>
<tr>
<td>Sucrose</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Dextrose</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
</tr>
<tr>
<td>Silicon dioxide</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Calcium sulphate dihydrate</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
</tr>
<tr>
<td>Dicalcium phosphate dihydrate</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
</tr>
</tbody>
</table>

**CHARACTERIZATION OF MATRIX FORMULATIONS**

- **Weight variation.**\(^{[10-12]}\)

20 tablets were collected at random and were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated using formula.

\[
\text{Percent weight variation} = \left(\frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}}\right) \times 100
\]

- **Hardness**

Hardness of the tablets was determined by using 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 the threaded bolts until the tablet fractured. Then the
final reading was recorded. The hardness was computed by deducting the initial reading from the final reading.

- **Friability**
  Twenty tablets are weighed accurately in digital balance ($W_1$). The weighed tablets are placed in the drum of Roche friabilator. The friabilator is allowed to rotate for 4mins. That is 100 revolutions. The tablets are dusted and removed from the drum. These tablets are dusted and weighed again ($W_2$). The difference between the initial weight of the tablets ($W_1$) and weight of the tablets after subjecting to friabilator ($W_2$) gives the friability of the tablet

$$F = \left( \frac{W_1 - W_2}{W_1} \right) \times 100$$

Where, $W_1$ = Weight of the tablets before

$W_2$ = Weight of the tablets after test.

- **Thickness test**
  The thickness of tablets was measured by using vernier caliper. Six tablets were used and average values were calculated.

- **Drug content uniformity**
  Five tablets were weighed and crushed in mortar & powder equivalent to 80 mg of Telmisartan was weighed and dissolved in 100 ml of phosphate buffer pH 6.8. This was the stock solution from which 1ml withdrawn and diluted to 10 ml with phosphate buffer. The absorbance was measured at wavelength 296 nm using UV-visible spectrophotometer. The drug content in each tablet was calculated using the standard calibration curve of Telmisartan in phosphate buffer pH 6.8 solution.

- **In-vitro dissolution**
  The release of Telmisartan from the CR tablet was studied in 900 ml of phosphate buffer pH 6.8 as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37° ± 0.5°c. An aliquot (1 ml) was withdrawn at specific time intervals, filtered and diluted to 10 ml with phosphate buffer pH 6.8 and drug content was determined by UV-visible spectrophotometer at 296 nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume. Dissolution studies were for a period of 12 hrs and the mean value were taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.
Release kinetic\(^{[13-14]}\)
In order to describe the kinetics of the release process of drug in all formulations, various equations were used, such as zero order rate equation, which describe the system where release rate is independent of the concentration of the dissolved species. The first order equation describes the release from the systems where dissolution rate is dependent on the concentration of the dissolving species. Higuchi equation describes the release from system where solid drug is dispersed in insoluble matrix, and the rate of drug release is related to the rate of diffusion.

In Korsmeyer-Peppas model, \(n\) is the diffusional exponent indicative of mechanism of drug release. A value of \(n = 0.45\) indicates Fickian or case I release; \(0.45 < n < 0.89\) indicates non-Fickian or anomalous release; \(n = 0.89\) indicates. The Korsmeyer Peppas equation is used to analyze whether the release of mechanism is Fickian diffusion or non-Fickian diffusion. ‘\(n\)’ value could be used to characterize different release mechanisms.

a) Zero order kinetic
It describes the system in which the drug release rate is independent of its concentration.

\[
Qt = Qo + Ko \times t
\]

Where
\(Qt\) = Amount of drug dissolved in time \(t\) and the
\(Qo\) = Initial amount of drug in the solution, which is often zero
\(Ko\) = Zero order release constant.

b) First order kinetic
It describes the drug release from the systems in which the release rate is concentration dependent.

\[
\log Qt = \log Qo + kt/2.303
\]

Where
\(Qt\) = Amount of drug released in time \(t\).
\(Qo\) = Initial amount of drug in the solution
\(k\) = First order release constant

If the first order drug release kinetic is obeyed, then a plot of \(\log (Qo - Qt)\) versus \(t\) will be straight line with a slope of \(kt/2.303\) and an intercept at \(t=0\) of \(\log Qo\).
c) **Higuchi model**
It describes the fraction of drug release from a matrix is proportional to the square root of time.

\[
\frac{M_t}{M_\infty} = k_H t^{1/2}
\]

Where

\(M_t\) and \(M_\infty\) = Cumulative amounts of drug release at time \(t\) and infinite time,

\(k_H\) = Higuchi dissolution constant reflecting formulation characteristics.

d) **Korsmeyer-Peppas model (Power Law)**
The power law describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

\[
\frac{M_t}{M_\infty} = k t^n
\]

Where

\(M_t\) and \(M_\infty\) = Cumulative amounts of drug release at time \(t\) and infinite time

\(k\) = Constant incorporating structural and geometrical characteristics of CR device,

\(n\) = Diffusional release exponent indicative of the mechanism of drug release for drug dissolution.

**RESULTS AND DISCUSSION**

**Physicochemical properties**

Physicochemical properties such as hardness, thickness, friability and drug content results were determined and presented in Table 2. Almost all the formulated products lied within the pharmacopoeial requirement within ±7.5% for weight variation.

Hardness of the formulated products was found in between 5.75 - 6.08 kg/cm². The thickness were found in the range of 4.11 - 4.26 mm. The friability was found in the range of 0.525 - 0.650%. The drug content values of the formulated tablets were found in between 99.1 - 99.9%.

**Table 2: Post-compression evaluation of Telmisartan matrix tablets**

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Formulation</th>
<th><strong>Weight variation</strong></th>
<th>Hardness <em>(kg/cm²)</em></th>
<th>Thickness <em>(mm)</em></th>
<th>Friability # (%)</th>
<th><strong>Drug content</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>0.302±0.38</td>
<td>5.75±0.27</td>
<td>4.26±0.12</td>
<td>0.600</td>
<td>98.76±0.7</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>0.30±0.20</td>
<td>6.00±0.31</td>
<td>4.25±0.10</td>
<td>0.632</td>
<td>99.41±0.8</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>0.299±0.22</td>
<td>5.91±0.20</td>
<td>4.18±0.07</td>
<td>0.613</td>
<td>99.9±1.4</td>
</tr>
<tr>
<td>4.</td>
<td>F4</td>
<td>0.299±0.21</td>
<td>6.00±0.31</td>
<td>4.23±0.08</td>
<td>0.650</td>
<td>99.3±1.3</td>
</tr>
</tbody>
</table>
In-vitro dissolution studies

The in-vitro dissolution characteristics of different formulation were carried out in pH 6.8 phosphate buffer. The percentages of drug released from the formulated tablets are given in Table 3.

Table 3: Dissolution profile of formulated Telmisartan tablets prepared.

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Time (hrs)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.28±0.21</td>
<td>6.08±0.37</td>
<td>4.11±0.11</td>
<td>0.525</td>
<td>99.1±1.1</td>
<td>99.4±0.6</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>28.0±0.33</td>
<td>18.25±0.22</td>
<td>12.07±0.22</td>
<td>33.9±0.25</td>
<td>24.68±0.36</td>
<td>20.76±0.22</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>34.56±0.2</td>
<td>26.0±0.55</td>
<td>24.52±0.11</td>
<td>50.7±0.23</td>
<td>38.52±0.85</td>
<td>30.97±0.61</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>60.6±0.25</td>
<td>50.2±0.75</td>
<td>45.51±0.84</td>
<td>75.7±0.36</td>
<td>65.24±0.66</td>
<td>55.04±0.85</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>82.54±0.6</td>
<td>68.12±0.71</td>
<td>63.12±0.25</td>
<td>86.9±0.45</td>
<td>83.03±0.11</td>
<td>74.87±0.28</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>91.45±0.88</td>
<td>84.20±0.22</td>
<td>80.43±0.25</td>
<td>94.7±0.22</td>
<td>89.45±0.22</td>
<td>87.4±0.25</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>97.20±0.11</td>
<td>92.8±0.35</td>
<td>87.51±0.33</td>
<td>98.9±0.74</td>
<td>94.86±0.34</td>
<td>92.9±0.23</td>
</tr>
</tbody>
</table>

Dissolution from formulated tablets

Effect of drug: polymer ratio

Drug release from the swellable matrix tablet is based on the glassy-rubbery transition of the polymer which is due to the penetration of the water into the matrix system. The primary factor of the drug release control is the interaction between the water, drug and polymer. Beside this some other variables also play a role in the release profile like drug: polymer ratio, viscosity of polymer (molecular weight) and compression force. Considering formulations F1, F2 and F3 incorporating drug and HPMC LV15 in the ratio 1: 0.5, 1:1 and 1: 1.5 respectively. The formulations F4, F5 and F6 containing drug and HPMC LV5 in the same ratio as above formulations. The most important factor affecting the rate of release of drug concentration from HPMC matrices was drug: polymer ratio of polymer. An increase in the polymer concentration causes an increase in the viscosity of the gel. This could cause a decrease in effective diffusion coefficient of the drug and thereby reducing in the drug release. In the present formulations too it was realized that the release profile decreased with increasing drug: polymer ratio. Drug release profile of formulated tablets containing HPMC LV5 and HPMC LV15 alone in different drug polymer ratio is shown in fig 1 and 2 respectively.
Effect of two viscosity grade of HPMC

It is suggested that the hydrophilic polymer such as HPMC when comes in contact with the water, it absorbs water and swells to form a gel layer which serves as a barrier to drug diffusion. The drug release process from a HPMC matrix involves water penetration into the dry matrix, hydration and gelation of the polymer, dissolution of the drug and diffusion of the dissolved drug through the resultant gel layer. Since the movement of the drug through the matrix system is predominantly diffusion controlled, which states that the process will be slower in the more viscous layer regarding drug release profiles of the formulated tablets, it was observed that there was a gradual decrease in the rate of release of the drug from the polymer (HPMC) with increase in the viscosity grade. It is show in fig 3, 4, and 5.
Fig 3: Dissolution profile of formulated products with two grades of HPMC at drug: polymer ratio 1:0.5.

Fig 4: Dissolution profile of formulated products with two grades of HPMC at drug: polymer ratio 1:1.

Fig 5: Dissolution profile of formulated products with two grades of HPMC at drug: polymer ratio 1:1.5.
Drug Release Kinetics

*In-vitro* drug release data of all formulations were fitted to Zero order, First order, Higuchi and Korsmeyer-Peppas equations to ascertain the pattern of drug release. Upon the application of different drug release model kinetics is given in and release profile represented. From the results it was found that all the formulation follows First order release kinetics. The ‘n’ values for all the formulation were found to be between 0.54 - 0.84 which indicate the anomalous transport kinetics that means the drug is released by the combined mechanism of pure diffusion controlled and swelling controlled drug release. This indicates that the release approximates non-fickian diffusion mechanism. It is showed in Table 4.

**Table 4: Best fit model for different formulations.**

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi order</th>
<th>Peppas order</th>
<th>Best Fit Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>F1</td>
<td>0.8700</td>
<td>0.9886</td>
<td>0.9721</td>
<td>0.965</td>
<td>0.5671 First order</td>
</tr>
<tr>
<td>2.</td>
<td>F2</td>
<td>0.9468</td>
<td>0.9869</td>
<td>0.9732</td>
<td>0.9463</td>
<td>0.7239 First order</td>
</tr>
<tr>
<td>3.</td>
<td>F3</td>
<td>0.9507</td>
<td>0.9879</td>
<td>0.9635</td>
<td>0.9864</td>
<td>0.8426 First order</td>
</tr>
<tr>
<td>4.</td>
<td>F4</td>
<td>0.7797</td>
<td>0.9966</td>
<td>0.9591</td>
<td>0.96</td>
<td>0.5481 First order</td>
</tr>
<tr>
<td>5.</td>
<td>F5</td>
<td>0.8541</td>
<td>0.9969</td>
<td>0.9724</td>
<td>0.9705</td>
<td>0.5882 First order</td>
</tr>
<tr>
<td>6.</td>
<td>F6</td>
<td>0.9084</td>
<td>0.9863</td>
<td>0.9745</td>
<td>0.9829</td>
<td>0.6672 First order</td>
</tr>
</tbody>
</table>

**CONCLUSION**

The present study showed that the release of Telmisartan depended on the percentage of polymer being used. It was observed that there was a linear relationship between the drug release and different viscosity grades of polymer. Thus we can infer that drug release profile decreases with increase in viscosity of polymer and with increase polymer level in the formulations. Among the two viscosity grades of HPMC used, HPMC LV15 at the drug: polymer ratio 1:1.5 showed 87.51 % over 12 hrs. Almost all formulations containing HPMC followed First order release.

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**REFERENCE**


