BILAYER TABLET: A NOVEL APPROACH FOR IMMEDIATE RELEASE OF TELMISARTAN AND HYDROCHLORTHAIZIDE COMBINATION.

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Abstract

The purpose of this research work was to develop a stable formulation of Antihypertensive drugs of the Telmisartan and Hydrochlorothiazide immediate release bilayer tablet and to study the dissolution profile with the reference product. The Formulation development work was initiated with wet granulation (drug layering technique) as the APIs are very static in nature and having very poor flow property. In order to improve solubility and drug release, Telmisartan is converted to its sodium salt by dissolving in aqueous solution of Sodium Hydroxide. Lactose Monohydrate and Microcrystalline Cellulose are used as diluents. Sodium Starch Glycolate is added as a superdisintegrant and Magnesium Stearate is used as the lubricant. The prepared granules are compressed into Double layer compression machine. The tablets thus formulated showed satisfactory physical parameters, and it was found to be stable and in-vitro release studies are shown that formulation (A5B5) shows Cumulative percent drug release 98.9-103.7% within 60min and matches with that of Innovator.

Keywords: Bi-layer tablets; Telmisartan; Hydrochlorothiazide.

Introduction

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain the desired drug concentration.
The tablet is the most preferred oral dosage form. The oral bioavailability of drug is dependent on disintegration, dissolution and various physiological factors. Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Superdisintegrants improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants. Traditionally, starch has been the disintegrant of choice in tablet formulation, and it is still widely used.

Bilayer tablets are prepared with one layer of drug for immediate release with second layer design to release drug later as second dose or in an extended release or for both immediate release. Bilayer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two layers. More layers are possible but the design becomes very special. Bilayer tablets are composed of two layers of granulation compressed together. They have the appearance of a sandwich because the edges of each layer are exposed.

Day-by-day’s various developed and developing countries are moving towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension and diabetes. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over monotherapy.
A low-dose combination of two different agents reduces the dose-related risk; the addition of one agent may counteract some deleterious effects of the other. Using low dosage of two different agents minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced.

Hypertension or high blood pressure is a chronic medical condition in which the blood pressure in the arteries is elevated. It is classified as either primary (essential) or secondary. About 90-95% of cases are termed "primary hypertension", which refers to high blood pressure for which no medical cause can be found. The remaining 5-10% of cases (Secondary hypertension) are caused by another conditions that affect the kidneys, arteries, heart, or endocrine system.

Telmisartan is used to treat high blood pressure (hypertension) by blocking the hormone angiotensin thereby relaxing blood vessels, causing them to widen. High blood pressure reduction helps prevent strokes, heart attacks, and kidney problems. Telmisartan is an Angiotensin Receptor Blocker (ARB) shows high affinity for the angiotensin II type 1 (AT1) receptors, has a long duration of action, and has the longest half-life of any ARB (24 hours).

The Bioavailability of Telmisartan is Poor About 45%, which due to Extensive First Pass hepatic metabolism. Hydrochlorothiazide is the diuretics of the benzothiadiazine group and has proved very important in the management of mild to moderate hypertension. It inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions. Hydrochlorothiazide is poorly water soluble drug having plasma half life of 6-8 hours. Fixed-dose combinations of ARBs with Hydrochlorothiazide are rapidly going acceptance with physician as an effective treatment option for Hypertension. ARBs plus Hydrochlorothiazide provide an effective antihypertensive therapy while promoting patient compliance with the convenience of once-daily dose. The aim of the current research work is to study the release characteristics of a Bilayer tablet containing Telmisartan and Hydrochlorothiazide in the form of immediate tablets, using a Sodium Starch Glycolate.

**Material and Method**

**Materials:** Telmisartan was obtained as a gift sample from Zyduz Cadila Ltd, India. Hydrochlorothiazide from Zyduz Cadila Ltd, India. Sodium Starch Glycolate was gifted by National Drugs and Chemicals, India. Povidone
K30 and Light Magnesium Oxide were gifted by Zim laboratories, Nagpur, India. Meglumine was purchased from Merck Pharmaceuticals.

**Method:**

A) Preparation of bilayer tablet: **Telmisartan** Layer 1

Different trials of **Telmisartan**

**Table 1: Formulation of Telmisartan.**

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>Trials (Qty/Tab in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1</td>
</tr>
<tr>
<td><strong>PROCESS</strong></td>
<td>RMG</td>
</tr>
<tr>
<td><strong>INTRAGRANULAR PART</strong></td>
<td></td>
</tr>
<tr>
<td>Telmisartan</td>
<td>80.00</td>
</tr>
<tr>
<td>NAOH</td>
<td>4.00</td>
</tr>
<tr>
<td>Meglumine (Merck)</td>
<td>15.00</td>
</tr>
<tr>
<td>Povidone K-25</td>
<td>10.00</td>
</tr>
<tr>
<td>Purified Water</td>
<td>q.s.</td>
</tr>
<tr>
<td>Ethanol (96%) Merck</td>
<td>q.s.</td>
</tr>
<tr>
<td>Mannitol (Pearlitol SD 200)</td>
<td>291.00</td>
</tr>
<tr>
<td><strong>Total weight of intragranular material</strong></td>
<td><strong>400.00</strong></td>
</tr>
<tr>
<td><strong>EXTRAGRANULAR PART</strong></td>
<td></td>
</tr>
<tr>
<td>Mannitol (Pearlitol SD 200)</td>
<td>67.50</td>
</tr>
<tr>
<td>Sodium Stearyl Fumarate</td>
<td>10.00</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2.50</td>
</tr>
<tr>
<td><strong>Total weight</strong></td>
<td><strong>480.00</strong></td>
</tr>
</tbody>
</table>

**Procedure (Layer 1)**

**Step 1:- Preparation of drug solution**

- Required quantity of purified water was taken. Weight quantity of NAOH was added to step 1 and dissolve. Weight quantity of Telmisartan was added to step 2 under stirring and stir after complete addition to dissolve. Weight quantity of Meglumine was added to step 3 and dissolve. Weight quantity of Povidone K-25 was added to step 4 and dissolve. Finally Weight quantity of ethanol was added.
Step 2:- Top spray granulation

- Accurate quantity of Mannitol was weighed and passed through 30 no. sieve and load it to FBP top spray granulation and warm with few min. of fluidization to attain bed temp 40°C.
- Top spray granulation started using drug solution of step 1. After complete spraying granules were dry to get LOD less than 1.50% w/w.

Step 3:- Calculation for extra granular material.

Step 4:- Blending.

Intragranular material mixed with Mannitol in 2.0lit blender for 10min.

Step 5:- Lubrication.

Sodium Stearyl Fumarate shifted through sieve no. 60 and weigh, added to blend of step 4 and mix for 5min.

Step 6:- Blend ready for compression.

Antihypertensive Drug –Layer 2

B) Different trials of Hydrochlorothiazide

Table 2: Formulation of Hydrochlorothiazide.

<table>
<thead>
<tr>
<th>Telmisartan Layer composition</th>
<th>Reference formula A5</th>
<th>Reference formula A5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of Telmisartan layer</td>
<td>480.00</td>
<td>480.00</td>
</tr>
<tr>
<td>Hydrochlorothiazide Layer Composition</td>
<td>Trials (Qty/Tab in mg) (Qty/Tab in mg)</td>
<td>5,B5, Reproducible Batch</td>
</tr>
<tr>
<td>No of Trials</td>
<td>1 B1</td>
<td>2 B2</td>
</tr>
<tr>
<td>Intragranular part</td>
<td>Hydrochlorothiazide</td>
<td>25.00</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>112.80</td>
<td>113.30</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>25.00</td>
<td>25.00</td>
</tr>
<tr>
<td>Iron oxide yellow</td>
<td>0.20</td>
<td>0.20</td>
</tr>
</tbody>
</table>
**Procedure (Layer 2)**

**Step 1:** Dry mixing

1. Shift iron oxide yellow through sieve no.80 and weight exactly.
2. Mixed part quantity of lactose monohydrate and pass through sieve no 80 and then mixed with remaining qty of lactose monohydrate, Aerosil 200, Diuretic Drug 2 and pass through sieve no 30 and load it in RMG (Rapid Mixing Granulator).

**Step 2:** Granulation

1. Binder solution- Dissolve weight qty of Povidone K-30 in weight quantity of purified water with continue stirring.
2. Granulate dry mix blend of step 1 using binder solution.

**Step 3:** Drying

- Dried in small FBD (fluid bed dryer) at temp 60-65°C.
- Dried up to the required LOD.
Step 4:- Milling –O.G.

Passed the dried granules through sieve no 20

Step 5:- Addition of Extragranular part.

1. Micro crystalline cellulose, Sodium starch Glycolate and Aerosil mixed and passed through sieve no.30.
2. Mix this dried mix part with Intragranular part in blender for 10 min.
3. Then added in above dried mix blend weight quantity of Magnesium Stearate (shifted through sieve no. 60) and lubricate for 3 min.

C) Physicochemical properties of prepared tablets

The weight variation of the tablets was carried out with 20 tablets using an electronic balance.

Friability was determined using 10 tablets in a Roche friabilator for 4 minutes at a speed of 100 rpm.

The hardness of 10 tablets was also evaluated using Dr. Scheleuniger hardness tester.

The thickness of the each 10 tablets was measured with a Vernier Caliper.

D) Drug Content: Procedure by HPLC

Diluent: 0.005 N Methanolic solution of Sodium hydroxide

Buffer: 2.0g/l ammonium dihydrogen phosphate. Adjust with 1M phosphoric acid to a pH of 3.0.

Mobile phase: Methanol and buffer (7:3)

Standard Solution

0.11mg/ml of USP Telmisartan RS and 0.013mg/ml of USP Telmisartan related compound ARS in diluents.

Passed the solution through a 0.45mm membrane filter

Sample Solution

Transfer not fewer than 20 tablets into a suitable volumetric flask, and add about 80% of the volume of diluent, swirl to disperse, and sonicate for about 10 min. pass the resulting solution through a 0.45mm membrane filter.

Further dilute quantitatively in mobile phase to obtain a solution having a concentration of 0.11mg/ml.
HPLC Parameters

- Detector: UV 298 nm, Column: 4.0mm × 4cm column; 5 m, packing L1, Temperature: 40 °C, Flow rate: 0.7 ml/min, Injection Volume: 5 μL

\[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{C_u} \right) \times 100 \]

Where \( r_u \) = response of Telmisartan peak from the sample solution
\( r_s \) = response of Telmisartan peak from the standard solution
\( C_s \) = concentration of USP Telmisartan RS in the standard solution (mg/ml)
\( C_u \) = nominal concentration of Telmisartan in the sample solution (mg/ml)

Acceptance criteria: 90%-110%

HPLC System

HPLC with auto sampler, UV detector, pump and in built column compartment.

In-Vitro Dissolution Studies: Dissolution Studies were carried out as per USP, Using USP dissolution apparatus type 2 with 900 ml of phosphate buffer pH 7.5 and maintained at 37 ± 0.5°C at a rotational speed of 75 rpm for 10, 15, 20, 30, 45, 60 minutes.

D) Analysis: Drug – Excipients compatibility study

DSC Study

From DSC spectra and physical parameter it was observed that there was no significant Drug- Excipients interaction, the DSC trace of API showed a sharp endothermic peak at 159°C. In the DSC trace of the mixture of API and excipients, the sharp endothermic peak observed neared to 159°C, in the majority of case. Melting endotherm of the drug was well preserved with a slight change in terms of broadening of peak or shifting towards the lower temperature. Thus these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipients, which lowers the purity of each component in the mixture and may not necessarily indicating potential incompatibility.

Results and discussions:

1) Tablet Characteristics

Telmisartan was converted to its sodium salt by dissolving in aqueous solution of Sodium Hydroxide, in order to improve solubility and drug release of Telmisartan from the formulation. Hydrochlorothiazide is a yellow colour.
Microcrystalline Cellulose, Lactose Monohydrate and Maize Starch are used as diluents. Sodium Starch Glycolate is added as a disintegrating agent. Povidone K30 is used as binder. Light Magnesium Oxide is used as alkalizing agent. Magnesium Stearate is used as the lubricant. The tablet of different formulation was subjected to various evaluation tests such as weight variation, hardness, thickness, friability, and drug content. The results of these parameters are given in Table 3.

The Physico-chemical properties have been studied. Based on the result obtained, all the formulations of Telmisartan and Hydrochlorothiazide were having properties within the standard limits.

Table 3: Physical parameters* of prepared batches for bilayer tablet.

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Wt. of total tab. (mg)</th>
<th>Wt. of ‘A Part’(mg)</th>
<th>Wt. of ‘B Part’(mg)</th>
<th>Hardness total tab (kp)</th>
<th>Hardness ‘A Part’ (kp)</th>
<th>Hardness ‘B Part’ (kp)</th>
<th>Total Thickness</th>
<th>D.T. total tab (min)</th>
<th>D.T. ‘A Part’ (min)</th>
<th>D.T. ‘B Part’ (min)</th>
<th>Friability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A5B1</td>
<td>682.5</td>
<td>478.2 (476-483)</td>
<td>204.3 (202-206)</td>
<td>10.3 (8.7-11.5)</td>
<td>3.5 (3.0-4.0)</td>
<td>6.25-6.30</td>
<td>8</td>
<td>20 sec</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5B2</td>
<td>683.0</td>
<td>483.2 (481-485)</td>
<td>199.8 (197-203)</td>
<td>9.7 (8.3-10.8)</td>
<td>3.3 (3.0-3.8)</td>
<td>6.15-6.20</td>
<td>8</td>
<td>min 25 sec</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5B3</td>
<td>685.1</td>
<td>480.7 (478-482)</td>
<td>204.4 (202-206)</td>
<td>10.6 (9.0-11.8)</td>
<td>3.8 (3.4-4.2)</td>
<td>6.10-6.18</td>
<td>8</td>
<td>min 45 sec</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5B4</td>
<td>682.2</td>
<td>482.3 (480-484)</td>
<td>199.9 (196-203)</td>
<td>10.2 (9.3-11.0)</td>
<td>3.7 (3.3-4.0)</td>
<td>6.13-6.20</td>
<td>8</td>
<td>min 50 sec</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A5B5</td>
<td>681.3</td>
<td>480.2 (477-485)</td>
<td>201.1 (200-203)</td>
<td>9.8 (9.0-11.0)</td>
<td>3.9 (3.6-4.2)</td>
<td>6.09-6.15</td>
<td>8</td>
<td>min 30 sec</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Mean of three determination DT- Disintegration time

2) **Drug Content**

The formulation (A5B5) shows the maximum Drug Content (i.e. T5-99.10% and H5-99.37%).

3) **Drug release**

*In-Vitro* Dissolution Studies

Dissolution sample were analyzed by UV Spectrophotometer meter. From *in vitro* drug release profile, Formulation A5B5 shows Cumulative percent drug release 99.0-103.6% within 60min and matches with that of Innovator, so Formulation A5B5 was declared as an Optimized formulation.
Table 4: Cumulative percent drug release profile of Bilayer tablet

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Innovator ‘A’</th>
<th>Innovator ‘B’</th>
<th>A5B1</th>
<th>A5B2</th>
<th>A5B3</th>
<th>A5B4</th>
<th>A5B5</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>48.0</td>
<td>90.0</td>
<td>47.0</td>
<td>85.0</td>
<td>43.0</td>
<td>83.0</td>
<td>40.3</td>
</tr>
<tr>
<td>20</td>
<td>69.9</td>
<td>99.1</td>
<td>78.0</td>
<td>91.0</td>
<td>74.0</td>
<td>94.8</td>
<td>72.8</td>
</tr>
<tr>
<td>30</td>
<td>87.3</td>
<td>99.1</td>
<td>93.0</td>
<td>91.7</td>
<td>94.0</td>
<td>95.0</td>
<td>95.0</td>
</tr>
<tr>
<td>45</td>
<td>99.4</td>
<td>99.4</td>
<td>100.1</td>
<td>91.5</td>
<td>97.8</td>
<td>95.2</td>
<td>98.3</td>
</tr>
<tr>
<td>60</td>
<td>102.1</td>
<td>100.3</td>
<td>100.0</td>
<td>91.0</td>
<td>98.0</td>
<td>95.2</td>
<td>102.5</td>
</tr>
</tbody>
</table>

Fig 2: Cumulative percent drug release for Telmisartan and Innovator.

Fig 3: Cumulative percent drug release for HCTZ and Innovator

4) DSC thermal analysis

The DSC thermal analysis spectra of Telmisartan and Drug with other excipients are shown in Fig 4, 5, 6, 7 and 8.

1) Drug (Telmisartan)
Fig 4: Thermal analysis spectra of Telmisartan.

2) Drug + Povidone

![Thermal analysis spectra of Drug + Povidone](image1)

Fig 5: Thermal analysis spectra of Drug + Povidone

3) Drug + Meglumine

![Thermal analysis spectra of Drug + Meglumine](image2)

Fig 6: Thermal analysis spectra of Drug + Meglumine

4) Drug + Mixture of all excipients

![Thermal analysis spectra of Mixture of Drug with all excipients](image3)

Fig 7: Thermal analysis spectra of Mixture of Drug with all excipients

5) Drug (Hydrochlorothiazide)
Fig 8: Thermal analysis spectra of Hydrochlorothiazide

5) Stability Study

At different storage condition

Drug - excipients compatibility study were carried out at initial day, 40°C / 75% RH in open vials for 15 days and 30 days and at 40°C / 75% RH in closed vials for 30 days and samples were also exposed to 50°C for 15 days and 30 days. Study was carried out using HPLC method using Empower 2 software. Telmisartan and Hydrochlorothiazide was found to be stable with all the excipients used within present study without any physical, chemical or therapeutic incompatibility. Based on these results, excipients such as Mannitol, Meglumine, SSF, Povidone K30, and Magnesium stearate, NaoH Pellets, Lactose Monohydrate, Ferric oxide yellow has been used in present study.

Preformulation study protocol for Telmisartan and Hydrochlorothiazide at different storage condition is given in Table 5

Table-5: Preformulation study protocol for Telmisartan and Hydrochlorothiazide at different storage condition.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Blend composition</th>
<th>Ratio (API: Exc.)</th>
<th>Storage Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>40°C /75% RH(open)</td>
</tr>
<tr>
<td>1</td>
<td>Drug-1 A + Sodium Hydroxide</td>
<td>1:0.1</td>
<td>2W,4W</td>
</tr>
<tr>
<td>2</td>
<td>Drug-1 A + Meglumine</td>
<td>1:0.3</td>
<td>2W,4W</td>
</tr>
<tr>
<td>3</td>
<td>Drug-1 A + Povidone K25</td>
<td>1:0.5</td>
<td>2W,4W</td>
</tr>
<tr>
<td>4</td>
<td>Drug-1 A + Magnesium Stearate</td>
<td>1:0.15</td>
<td>2W,4W</td>
</tr>
<tr>
<td>5</td>
<td>Drug-2 B + Lactose</td>
<td>1:15</td>
<td>2W,4W</td>
</tr>
<tr>
<td>6</td>
<td>Drug-2 B + MCC</td>
<td>1:10</td>
<td>2W,4W</td>
</tr>
<tr>
<td>7</td>
<td>Drug-2 B + Sodium starch glycolate</td>
<td>1:1</td>
<td>2W,4W</td>
</tr>
</tbody>
</table>
Conclusion

In the present study we can conclude that immediate release Bilayer tablets of Telmisartan & Hydrochlorothiazide (80+25) mg were successfully prepared by drug layering method and Superdisintegrant using Sodium Starch Glycolate and their evaluation were carried out. Drug release from the developed formulations matched with Innovator and also found to be stable formula.

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