PREPARATION AND CHARACTERIZATION OF ORODISPERSIBLE TABLETS OF CANDESARTAN CILEXETIL BY DIRECT COMPRESSION METHOD

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ABSTRACT

Objective: Candesartan cilexetil (CC) is a selective AT1 subtype angiotensin II receptor antagonist and candesartan is widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy. The objective of this study was to prepare and evaluate orodispersible tablets of candesartan cilexetil using direct compression method. The orodispersible tablets (ODT) as recently developed drug delivery system is a solution for many problems faced by patients especially the pediatric and geriatrics.

Methods: The tablets were made using different supersdiintegrant [Sodium Starch Glycolate (SSG) and Croscarmellose Sodium (CCS)], and Crospovidone (CP) at three different percentages, in addition to sweetening agent (aspartame) with microcrystalline cellulose (MCC) and mannitol as diluents. Formulated orodispersible tablets were evaluated for weight variation, friability, disintegration time, drug content, wetting time, water absorption ratio and in vitro drug release.

Results: The results show that the presence of a supersdiintegrant and MCC is desirable for orodispersion. Although all the formulations satisfied the limits of orodispersion with a dispersion time of less than 48 sec but formula (F8) that contain 10% crospovidone as supersdiintegrant with 30% MCC shows the best results regarding disintegration time of 13 sec, hardness of 3.5 kg/cm2, and fast drug release rate of 100% within 10 min, as compared with the conventional tablet (35%).

Conclusion: It can be concluded that the selected formula is good potential for preparation of orodispersible tablets of candesartan cilexetil with acceptable pharmaceutical properties.

Keywords: Candesartan cilexetil; Orodispersible tablet; Direct compression method.

INTRODUCTION

The orodispersible tablets (ODTs) as recently developed drug delivery system is a good approach to extend patency and increase marketing [1]. The ODTs combine the advantages of oral and solid dosage forms regarding patient compliance and convenience, compactness, and ease of production.

There are many terms to describe the ODTs such as melt-in-mouth, orally disintegrating tablets, Porous tablets, quick dissolving tablets, rapimelts tablets, fast dissolving drug delivery [2]. The ODTs are simply those dosage forms that disintegrate in oral cavity without need of water and it is defined by US FDA as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue".

On the other hand, European pharmacopoeia defines it as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing. The additional advantages of ODTs include; suitable for elderly, geriatric, patient with difficulty in swallowing and traveling.

Candesartan cilexetil (CC) is a selective AT1 subtype angiotensin II receptor antagonist and candesartan acts by blocking the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues such as vascular smooth muscle and the adrenal gland [3]. Candesartan is widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy [4, 5].

Candesartan is an orally active non-peptide tetrazole derivative, is chemically described as (-)-1-Hydroxyethyl2-ethoxy-1-[p-(o-H-tetrazol-5-ylphenyl) benzyl]-7- cemimidazolcarboxylate, cyclohexyl carbonate [6].

Candesartan cilexetil is an ester produrg hydrolyzed to candesartan during absorption from the gastrointestinal tract [7]. Candesartan cilexetil is marketed under the trade names Atacand® available for oral use as tablets containing 4 mg, 8 mg, 16 mg, or 32 mg of candesartan cilexetil.

The aim of this study is to prepare fast disintegrating tablet of candesartan cilexetil with optimum physical properties.

MATERIALS AND METHOD

Candesartan cilexetil was purchased from wuxi hexia chemical company, China. Crospovidone (CP) and Croscarmellose Sodium (CCS) were purchased from Pharmaceutical (Wuhan) International Co. Ltd, China. Sodium Starch Glycolate (SSG), Avicel PH 102 and aspartame were obtained from Sammara Drug Industries (SDI), Iraq. All other ingredients used were of analytical grade.

<table>
<thead>
<tr>
<th>Ingredient (mg)</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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<tr>
<td>Candesartan cilexetil</td>
<td>4</td>
<td>4</td>
<td>4</td>
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<td>4</td>
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<tr>
<td>MCC PH 102</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
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<td>60</td>
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<tr>
<td>Aspartame</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Mg stearate</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>
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</tr>
<tr>
<td>Mannitol</td>
<td>116</td>
<td>106</td>
<td>96</td>
<td>116</td>
<td>106</td>
<td>96</td>
<td>116</td>
<td>106</td>
<td>96</td>
</tr>
<tr>
<td>Total weight</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>200</td>
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</table>
Formulation of candesartan cilexetil orodispersible tablets

Nine formulas (F1- F9) were prepared by direct compression method as shown in table (1). Accurately weighed quantities of active ingredient (candesartan cilexetil), superdisintegrants (SSG, CCS, and CP), sweetening agent (aspartame) with microcrystalline cellulose (MCC) and mannitol as diluents. All ingredients mixed well together using mortar and pestle for 10 min except lubricant which added later and blended for another 2 min. The final mixtures were compressed using single punch tablet machine of 9.4 mm flat face punches at compression force of 39.5 KN.

Evaluation of precompression candesartan cilexetil orodispersible formulas

Angle of repose

The funnel method was used to determine the angle of repose of the prepared powder mixture. The mixture was poured through a funnel onto a horizontal plane, fixed base diameter (D), free of vibration petri dish to form a cone.

The funnel height was maintained at approximately 2-4 cm from the tip of the granules pile in order to minimize the impact of the falling particles on the tip of the cone. The tan of angle of repose (θ) was calculated after measuring the height (H) of the cone of the granules using the following equation:

\[ \tan(\theta) = H / 0.5D \]

Hausner’s ratio and compressibility (Carr’s) index

A sample of each formula of the prepared candesartan cilexetil orodispersible powder was poured into a volumetric cylinder to occupy an initial volume (V0) and then the cylinder was subjected to a standard tapping procedure on to a solid surface until a constant volume was achieved (Vf). The compressibility index and the Hausner’s ratio are calculated using the following formulas;

\[ \text{Compressibility Index} = V_0 - V_f / V_0 \times 100 \]

Hausner’s ratio = V0 / Vf , Where, V0, Vf are the initial and final volume respectively [8].

Evaluation of tablets

Weight variation test

Twenty tablets were selected at random, individually weighed and the average weight was calculated. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by no more than 7.5% and no tablet deviates by more than 15% [9].

Hardness test

Tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks. The hardness of tablet was measured by Hardness tester TBH 125 (Erweka, Germany) and results were expressed in Kg/cm2 [10].

Friability test

The friability of the tablet was determined using Friabilator TAR 120 (Erweka, Germany). It is expressed in percentage (%). Twenty tablets were initially weighed (W0) and transferred into the Friabilator. The Friabilator was operated at 25 rpm for 4 minutes in which tablets are subjected to combined effect of shock and abrasion in a plastic chamber dropping the tablets at a height of 6 inch in each revolution. The tablets were dedusted and weighed again (W). The % Friability was then calculated by % Friability = (W0-W) / W100 [11].

Drug content uniformity test

Ten tablets were weighed and powdered. An amount of powder equivalent to 4 mg of candesartan cilexetil was dissolved in 100 ml of phosphate buffer (pH 6.8). It was shaken by mechanical means for 1 hr. Then it was filtered through a whatman filter paper. From this resulted solution 1ml was taken, diluted to 100 ml with phosphate buffer of pH 6.8 and absorbance was measured against blank at 215 nm using UV-Visible spectrophotometer (UV- 1650 PC, Shimadzu, Japan). From the absorbance values, amount of drug present in the given tablet was calculated using calibration curve. Procedure was repeated by using two or more tablets from the same formulation and the average value of all three tablets were calculated.

Wetting time and water absorption ratio

Twice folded tissue paper was placed in a petri dish having an internal diameter of 6.5 cm containing 10 ml of artificial saliva. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Three trials from each batch were performed and standard deviation was also determined [12].

Water absorption ratio (R) can be estimated by simple procedure include weighing (Wb) of the tablet prior to the placement on the Petri dish, then after recording the wetting time. The wetted tablet was removed and reweighed (Wa), the water absorption ratio was determined according to the following equation:

\[ R = 100(x (wa - wb) / wb) \]

Where wb and wa were tablet weights before and after water absorption, respectively [13, 14].

In vitro disintegration time

The disintegration time of the prepared orodispersible tablet was determined using 900 ml of artificial saliva as disintegration medium at 37 ± 0.5°C. Disintegration apparatus with a basket rack assembly containing six open-ended tubes and 10-mesh screen on the bottom was used (Disintegration tester ZT 322 Erweka, Germany). A tablet was placed in each tube of the basket and the time for complete disintegration of the six tablets was recorded [15].

In vitro dissolution studies

In vitro drug release study for the selected formula of candesartan cilexetil orodispersible tablets was done using type II (paddle) dissolution apparatus DT 720 (Erweka, Germany) with the rotation speed of 50 rpm using phosphate buffer (pH 6.8) as the dissolution medium maintained at a temperature of 37 ± 0.5°C. Samples were withdrawn at predetermined time interval and filtered through Whatman filter paper, diluted suitably and analyzed at 255 nm for cumulative drug release using Shimadzu UV-Visible spectrophotometer. The dissolution experiments were conducted in triplicate [16].

Fourier transform infrared (FTIR)

Fourier Transform Infrared (FTIR) spectroscopic analysis was done to rule out any drug-excipients interaction that may occur during the formulation by direct compression method. FTIR were implanted in the range of 4000-500 cm-1 for the drug alone, the physical mixture, and tablets of selected formula [17].

Differential scanning calorimetry (DSC)

DSC studies were performed using differential scanning calorimeter [DSC 60, Shimadzu, Japan], in order to assess the thermostropic properties and thermal behaviour of pure drug (CC), mannitol, physical mixture, and selected formula (F8). About 5 mg of the sample were sealed in the aluminium pans and heated at a constant rate of 20°C /min, covering a temperature range of 50-300°C.

RESULTS AND DISCUSSION

The data obtained for precompression parameters for formulas F1-F9 such as Hausner’s ratio, Carr’s index and angle of repose are shown in table 2 found within acceptable pharmacopoeial limits. While post-compression parameters like hardness, friability, wetting time, water absorption ratio, and in vitro disintegration time are mentioned in Table 3. The tablets measured hardness was found to be in the range of 3.5 to 6.2
kg/cm². The percentage friability was less than 1% for all formulations ensuring mechanical stability of the formulated tablets. All formulations then evaluated for variation in weight and results indicated that for all formulations exhibit very low weight variation which lies within the pharmacopoeial limits i.e. ± 7.5%. The percentage drug content in all formulations were found in the range of 96.55 ± 0.82 to 101.27 ± 0.04 indicating the compliance with the pharmacopoeial limits.

According to the pharmacopoeial standards the dispersible tablet must disintegrate within 3 min. Although all formulated batches have shown disintegration time less than one minute, but formula F8 shows the shortest disintegration time (13 sec) indicating suitability of formulation for orodispersible tablets. Also evaluated for wetting time and water absorption ratio and found to be faster for the formulation F8 containing superdisintegrant crosspovidone 10% as compared to other formulations.

### Table 2: Micromeritic properties of precompression formulas of candesartan cilexetil blend powder

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Hausner’s ratio ± S.D.*</th>
<th>Carr’s index (%) ± S.D.*</th>
<th>Angle of repose (θ) ± S.D.*</th>
<th>Flow characters</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1.22±0.24</td>
<td>18.10±0.139</td>
<td>30.53±1.498</td>
<td>Passable</td>
</tr>
<tr>
<td>F2</td>
<td>1.28±0.27</td>
<td>18.8±0.181</td>
<td>31.9±0.725</td>
<td>Passable</td>
</tr>
<tr>
<td>F3</td>
<td>1.99±0.24</td>
<td>16.9±0.338</td>
<td>29.8±0.759</td>
<td>Good</td>
</tr>
<tr>
<td>F4</td>
<td>1.9±0.21</td>
<td>16.6±0.621</td>
<td>29.8±0.765</td>
<td>Good</td>
</tr>
<tr>
<td>F5</td>
<td>1.23±0.16</td>
<td>19.7±0.281</td>
<td>31.7±0.128</td>
<td>Passable</td>
</tr>
<tr>
<td>F6</td>
<td>1.27±0.06</td>
<td>18.7±0.282</td>
<td>32.3±0.123</td>
<td>Passable</td>
</tr>
<tr>
<td>F7</td>
<td>1.19±0.23</td>
<td>16.7±0.817</td>
<td>31.9±0.932</td>
<td>Passable</td>
</tr>
<tr>
<td>F8</td>
<td>1.17±0.23</td>
<td>15.3±0.823</td>
<td>26.3±0.418</td>
<td>Good</td>
</tr>
<tr>
<td>F9</td>
<td>1.21±0.17</td>
<td>17.5±0.975</td>
<td>28.1±3.461</td>
<td>Good</td>
</tr>
</tbody>
</table>

*S.D. Standard deviation from mean. n=3

### Table 3: Evaluation parameters of prepared orodispersible tablets of candesartan cilexetil

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Hardness (Kg/cm²) ± S.D.*</th>
<th>Friability (%) ± S.D.*</th>
<th>Wetting times (sec) ± S.D.*</th>
<th>Water absorption ratio ± S.D.*</th>
<th>In vitro disintegration times (sec) ± S.D.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6.2±0.0529</td>
<td>0.52</td>
<td>18±1.75</td>
<td>127.6±1.63</td>
<td>20±1.12</td>
</tr>
<tr>
<td>F2</td>
<td>5.4±0.0808</td>
<td>0.41</td>
<td>40±1.51</td>
<td>172.3±0.69</td>
<td>48±1.02</td>
</tr>
<tr>
<td>F3</td>
<td>5.0±0.0802</td>
<td>0.66</td>
<td>36±2.05</td>
<td>244.0±1.72</td>
<td>43±1.98</td>
</tr>
<tr>
<td>F4</td>
<td>6.2±0.0503</td>
<td>0.43</td>
<td>18±2.11</td>
<td>123.9±1.84</td>
<td>25±2.56</td>
</tr>
<tr>
<td>F5</td>
<td>4.4±0.0901</td>
<td>0.62</td>
<td>26±1.67</td>
<td>142.24±0.99</td>
<td>34±0.36</td>
</tr>
<tr>
<td>F6</td>
<td>4.5±0.0602</td>
<td>0.63</td>
<td>19±1.65</td>
<td>142.5±1.58</td>
<td>35±2.13</td>
</tr>
<tr>
<td>F7</td>
<td>4.8±0.0550</td>
<td>0.37</td>
<td>10±2.51</td>
<td>80.86±1.36</td>
<td>14±1.88</td>
</tr>
<tr>
<td>F8</td>
<td>3.5±0.0721</td>
<td>0.72</td>
<td>06±1.41</td>
<td>98.44±0.98</td>
<td>13±0.08</td>
</tr>
<tr>
<td>F9</td>
<td>±0.909140</td>
<td>0.72</td>
<td>08±1.69</td>
<td>98.58±1.92</td>
<td>19±0.63</td>
</tr>
</tbody>
</table>

*S.D. Standard deviation from mean. n=3

The in vitro dissolution profile (Fig.1) indicated that the selected formula (F8) shows fast and complete drug release within 10 minutes in comparison to 35% of drug released from conventional marketed tablet (Atacand® 4mg tablet).

![Fig. 1: Comparison of in vitro release profile of selected formulation F8 and marketed formulation (Atacand® 4mg tablets) (n = 6)](image-url)
There is no interaction between drug and excipients as shown in FTIR (Fig. 2) and DSC thermogram (Fig. 3).

**Fig. 2**: FTIR spectra of pure drug, physical mixture, and selected formula
Overall, the results suggest that suitably formulated orodispersible tablets of candesartan cilexetil containing crospovidone 10% as a superdisintegrants (F8) can be achieved. The tablets exhibited good in vitro disintegration and wetting properties as compared to other superdisintegrants. Prepared tablets disintegrate within few seconds without need of water; thereby enhance absorption possibility may increase leading to increased bioavailability. Thus the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and increased patient compliance.

**CONCLUSION**

Candesartan cilexetil an angiotension II receptor antagonist can be used to develop the rapid disintegrating tablet successfully by direct compression techniques using selected superdisintegrants for the better patient's compliance and effective therapy. All the pre compression and post compression parameter were found to be within limit and meets the standard evaluation parameters with a slight deviation within prescribed limit. It was found that the
mannitol was the best diluent used in preparing candesartan cilexetil orodispersible tablet with fastest in vitro disintegration time. It is concluded that crosspovidone shows good disintegrating property than the most widely used superdisintegrants.

REFERENCES