Candesartan cilexetil belongs to angiotensin receptor antagonist therapeutic group. Its pharmacological mechanism of action is based on inhibition of angiotensin II binding to the AT1 receptors. It is used in the treatment of hypertension and in patients with heart failure who show intolerance to ACE inhibitors or in addition to treatment with ACE inhibitors [4, 9, 5, 7, 8]. Candesartan cilexetil is hydrolyzed to candesartan in during the gastrointestinal absorption [10]. Candesartan is highly bound to plasma proteins (> 99%) and does not penetrate into red blood cells. Plasma protein binding is constant when plasma concentrations are reached in the range and above recommended doses [4]. Candesartan cilexetil is an esterified form (prodrug) that is metabolized to an active metabolite with pronounced pharmacological effects. Candesartan cilexetil is a white to off-white, water-insoluble crystalline powder having a melting point of 157-160°C (Figure 1) [2].

Abstract: The present study evaluated the possibility tableting after granulation under fluid bed conditions to be used as suitable method for preparation of candesartan cilexetil-containing tablets, having a similarity factor to the reference product above 50.00. Different parameters, such as the influence of excipients, size of granules and technological regime on drug release profile were investigated in order predetermined requirements to be met.

It was found that only the mechanical addition of surfactant and change of the size of granules, used for tableting did not lead to satisfactory results. A suitable technological regime was required to achieve the biopharmaceutical requirements. The suitability of the technology was demonstrated by comparison of the tablet release profiles, obtained by different methods, in media with different pH values (pH 6.5, pH 4.5 and pH 1.2). Our results show that the addition of granulation liquid, containing 5% low substituted hydroxypropyl cellulose and 2.5% diethylene glycol mono-ethyl ether, under fluid bed conditions, led to drug release profiles, satisfied biopharmaceutical requirements in all the used media.

Key words: candesartan cilexetil, tablets, fluidized bed granulation.

Introduction

Candesartan cilexetil belongs to angiotensin receptor antagonist therapeutic group. Its pharmacological mechanism of action is based on inhibition of angiotensin II binding to the AT1 receptors. It is used in the treatment of hypertension and in patients with heart failure who show intolerance to ACE inhibitors or in addition to treatment with ACE inhibitors [4, 9, 5, 7, 8]. Candesartan cilexetil is hydrolyzed to candesartan in during the gastrointestinal absorption [10]. Candesartan is highly bound to
The aim of the present study is to investigate the possibility for production of candesartan cilexetil tablets (16 mg) using tableting after fluidized bed granulation. The proposed method has some advantages, compared to the commonly used methods, such as simplified technology leading to reduced production costs. We targeted an essential biopharmaceutical requirement stated that more than 80% of the incorporated drug should be released in a period of 60 minutes and the factor of similarity to the original product Atacand should be in the range 50-100.

Materials and methods

**Materials**

Candesartan cilexetil was purchased from Zhejiang Huahal Pharmaceuticals Co., Ltd.; diethylene glycol mono-ethyl ether was delivered from Merck. L-HPC (low substituted hydroxypropyl cellulose), lactose monohydrate, maize starch, L-HPC (low substituted hydroxypropyl cellulose), diethylene glycol mono-ethyl ether and magnesium stearate meet the requirements of the European Pharmacopoeia (Ph. Eur).

**Methods**

**Granulation and mixing:** Oystar Huttlin Mycromix quick-acting mixer-granulator and Huttlin Unilab fluidized bed apparatus equipped with nozzles of 1.2 mm were used. Flow of feed air was in the range 200-300 m³/h. Candesartan cilexetil, lactose and maize starch were mixed and transferred to the pre-heated chamber of the apparatus. After a working temperature of the mixture (38°C) was reached, a solution of L-HPC and diethylene glycol mono-ethyl ether in distilled water was added (product temperature 30-36°C).

**Drying:** Fluidized bed apparatus "Huttlin Unilab". Supply air temperature: 45-55°C. Residual moisture of the product ≤ 2.5%.

**Measurement of residual moisture:** Scale "Precisa XM 50" in 105°C.

**Calibration of the finished granules:** Sieves with a pore size of 1.0 mm and 1.5 mm.

**Characterization of the finished granules:** Tapping apparatus: "Sotax TD1", equipped with a measuring cylinder of 250 ml. Samples with volume of about 100 ml were used. The determination was made, following the requirements of European Pharmacopoeia. The following indicators were monitored: bulk volume, volume after tapping, index of compression and Hausner’s factor.

**Tableting:** The tablets were prepared using a rotary tablet machine "Kilian Pressima" equipped with 7 mm punches.

**Mechanical strength:** The measurement was conducted by using the apparatus for measuring of the mechanical strength "Sotax HT1". Ten tablets were used in the study.

**Drug release study:** Dissolution tests were carried out by using the "Sotax AT7 Smart " apparatus, equipped with 7 vessels (apparatus type II - Paddle method) at speed of 50 rpm [6].

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**Figure 1. Chemical structure of candesartan cilexetil**

![Chemical structure of candesartan cilexetil](image)
Candesartan cilexetil is poorly soluble in water. Our preliminary studies have shown that 16 mg candesartan cilexetil produce a saturated solution in 1000 ml (for pH 1.2) to 4000 ml (for pH 6.5) medium. It is essential to add surfactants in order to achieve sink conditions. In the present study, 900 ml of phosphate buffer (pH 6.5) with 0.35% Tween 20, acetate buffer pH 4.5 with 0.7% Tween 20 and 0.1 M HCL with 0.10% Sodium Lauryl Sulfate were used as a medium.

The quantity of the released candesartan cilexetil was determined using HPLC technique, apparatus Agilent 1260 Infinity. Chromatographic analysis was performed by Symetry C8 column with 150 mm x 4.6 mm internal diameter and 5μm particle size. Isocratic elution with acetonitrile (75%) and 0.1 % trifluoroacetic acid (25%) was selected with a flow rate of 1.0 ml/min. The detection wavelength was set at 254 nm. The column and the HPLC system were kept at temperature 25°C ± 1°C.

**Factor of similarity:** The calculation of the factor of similarity was made according to the requirements of Guideline on the investigation of bioequivalence (CPMP / EWP / QWP / 1401/98 / Rev1).

### Results and discussion

**Table 1: Qualitative and quantitative composition of the used excipients.**

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Composition</th>
<th>Excipients content, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>L-HPC (low substituted hydroxypropyl cellulose)</td>
<td>5.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Lactose monohydrate # 200</td>
<td>62.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Maize starch</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>L-HPC (low substituted hydroxypropyl cellulose)</td>
<td>-</td>
<td>3.0</td>
</tr>
<tr>
<td>Diethylene glycol monooethyl ether</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Distillate water</td>
<td>q.s.</td>
<td>q.s.</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>


In our previous study [1], a method of preparation of candesartan cilexetil tablets by using tableting after granulation in a fast-moving mixer granulator was described. Tablets (composition 2, Table 1) released more than 80% of the incorporated drug substance for a period of 60 minutes (curve C, Fig. 1), and their factor of similarity compared to the original product was 65.3.

Considering the promising results, obtained by using the composition 2 (using mixer granulator technology), it has been decided to further investigate the possibilities for fluid bed granulation (a method characterized by a substantial simplification of the technology). For the purpose, composition 2 (Table 1) was used as suitable composition. The granulation was performed on a Huttlin apparatus. The experimental results showed that using this method, we obtained tablets with good technological characteristics.

The release profiles are shown on Fig. 1 (curve D). Surprisingly, despite of its long disintegration time (21 min), the release rate is comparable and even higher than that of the model composition 1 which show a disintegration time of less than 3 min (Fig. 1, curve A). Obviously, in these experiments there was no correlation between the disintegration time and the tablet release rate obtained by the two different technological approaches. The impact of the granule size and the presence of surfactants were investigated to identify the factors influencing the release process.

In order candesartan cilexetil to be stabilized in tableting process and rapid decomposition of the products above the admissible norms to be prevented, it is necessary to include the stabilizing agent. Thus, we use diethylene glycol mono-ethyl ether (DEGME) as a stabilizer for our experimental composition. Moreover, this substance possesses surfactant properties, so it is used as a solubilizing agent in cosmetic products and as a co-surfactant in the preparation of microemulsions [6]. There was an expectation that diethylene glycol mono-ethyl ether included in candesartan cilexetil tablets, besides its stabilizing properties, would also improve the solubility of the substance and would possibly accelerate the release process.

To evaluate the impact of diethylene glycol mono-ethyl ether on the release profile, composition 3 (Table 1) was chosen as a suitable for the test. Its content was similar to composition 1, but diethylene glycol mono-ethyl ether was not added to the granulation mixture. If diethylene glycol mono-ethyl ether is directly related to accelerated release of candesartan

Figure 1: Release profiles of candesartan cilexetil from different compositions
cilexetil, we could expect a slowing of the rate and rate of release of composition 3 (compared to the rate and release rate of composition 1 containing diethylene glycol mono-ethyl ether).

The results of the dissolution tests are presented in Fig. 2.

![Figure 2. Release profiles of tablets obtained by composition 1 (containing DEGME) and composition 3 (without DEGME).](image)

Figure 2. Release profiles of tablets obtained by composition 1 (containing DEGME) and composition 3 (without DEGME).

No significant changes in the release profiles were observed in the experiment, thus we conclude that DEGME has no direct attitude in accelerating the process.

In order to investigate the effect of granule size on drug release, composition 2 (Table 1), characterized by the highest similarity factor compared to the Atacand reference was used. The granules were divided into three fractions:< 0.3 mm, 0.3-1.0 mm; >1.0 mm. Tablets with similar mechanical strength (about 55 N) were prepared, using those three fractions. Figure 3 shows the release profiles of the tablets.

![Figure 3: Release profiles of tablets containing candesartan cilexetil, obtained by granules with different sizes.](image)
As shown in the fig. 3, there were no significant differences in the release profiles from tablets, obtained by granules sized in the range 0.3 to 1.5 mm. The similarity factor between both fractions and between fractions and the combined sample was over 55.

A comparison between tablets with the same composition (composition 2, Table 1), but prepared by different technology (tableting after granulation in a mixer granulator and in a fluidized bed conditions) was done. We found that tablets prepared after fluidized bed granulation were characterized by increased speed and release rate (Fig. 1). At the same time, the requirement for similarity in the release profiles requires a delay in the process.

For this purpose, composition 4 (Table 1) was developed, all the amount of L-HPC was incorporated into the binder solution and injected under the conditions, described above. Using this method granules with good rheological parameters were obtained (Compression Index 15.1, Hausner Factor 1.18) which allowed formulation of the tablets with the required mechanical strength. The release profiles of the tablets are shown in Fig. 4.

![Figure 4: Release profiles of tablets, obtained by composition 2 (using mixer granulator) and composition 4 (using fluidized bed conditions) in buffer with pH 6.5.](image)

The release profile of composition 4 was compared to the release profile of composition 2 (mixer granulator technology). The calculated similarity factor in this case was 57.51, which means that the release profiles at pH 6.5 were similar. Aiming to prove the suitability of the developed technology and taking into account these promising results, we decided to compare the release of both compositions 2 and 4 at pH 1.2 and at pH 4.5.

Fig. 5 compares the release profiles of the models, obtained by both methods (mixer granulator and fluidized bed) in 0.1 M HCL + 0.11% sodium lauryl sulfate medium. The obtained similarity factor was 51.20, i.e., profiles can be considered as similar.
Conclusion

The present study was aimed at investigation of the influence of the size of the granules, the presence of surfactant and the influence of technological regime on the release profiles of candesartan cilexetil tablet formulations. The obtained results showed that size of the granules and presence of surfactant do not have a significant impact on the release profiles. The speed and rate of release of the active substance...
(candesartan cilexetil) may be affected by a change in the technological regime (without changing the formulation) so that the tablets produced meet the preset requirements (release of over 80% of the active substance in 60 min and having a similarity factor to the reference product Atacand above 50.00).

Based on these studies, a technological approach to produce granules containing candesartan cilexetil using a fluidized bed apparatus has been developed. The resulting granules had good rheological characteristics. Tablets, which met the requirement to release more than 80% of the incorporated drug substance within 60 min were produced. The release profiles of the tablets obtained by tableting after fluidized bed granulation were compared to the profiles of tablets obtained after granulation in a mixer granulator. The comparison was performed in three media (pH 6.5, pH 4.5, pH 1.2) and the similarity factors were over 50, demonstrating the similarity of the profiles and the suitability of the developed technology.

References


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