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# Comparative Formulation and Evaluation of Fast Dissolving Candesartan Tablet Using Natural Superdisintegrants

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## ABSTRACT

Candesartan is used commonly for the treatment of hypertension. It has half-life of 9 hrs whereas T max is 3-4 hr. As Candesartan is water insoluble drug this adversely affects bioavailability and bioequivalence.In present study efforts are made to reduce its disintegrating time using Plantago ovata and Sodium starch glycolate as comparative superdisintegrnats.. The objective of the present study was to prepare the fast dissolving tablet of candesartan using different natural superdisintegrants like Plantago ovata, , Sodium Starch Glycolate, . Hardness, friability, weight variation, wetting time, thickness, water absorption ratio, disintegrating time, uniformity of content and in-vitro drug release were checked for evaluation purpose.

**Keywords :** Candesartan celixitil, superdisintegrants, starch glycolate, *plantago ovate*

## I. INTRODUCTION

Disintegrating agents is a substance or mixture of substances added to tablets to facilitate its break up or disintegration. Hence the therapeutic action is based on the amount of drug released from the tablet, these disintegrants which allows rapid de-aggregation of solid in to solution and followed by which absorption of the drug takes place.[3]

Oral Dispersible Tablets are "a solid dosage form containing medicinal substances, which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue..Taking geriatric patients into consideration, attempts have been made to develop a rapid dissolving tablet.These dosage forms disintegrate within 30sec with very less quantity of water. This can be achieved by addition of various superdisintegrants like Croscarmellose sodium, Crosspovidone, sodium starch glycolate [1].

Traditionally, starch has been the disintegrate of choice in tablet formulation, and it is still widely used. Starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression.

Candesartan cilexetil is a prodrug of candesartan. Candesartan cilexetil is chemically 2- Ethoxy-3-[21-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] -3 Hbenzoimidazole 4-carboxylic acid 1-cyclohexyloxycarbonyloxy ethyl ester . [2]

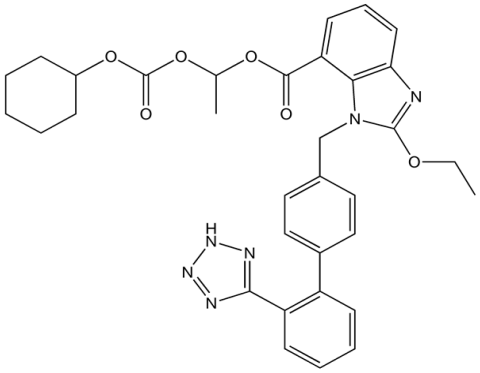


**Figure 1.** Structure of Candesartan Celixitil

Candessartan inhibits binding of angiotensin II to the AT1 – receptor. Candesartan cilexetil is hydrolyzed to candesartan during absorption from the gastrointestinal tract . The typical dose of candesartan cilexetil is 16 mg per day in patients . Compare to other ARBs Candesartan shows, has a long duration of action.. Candesartan is metabolized in Intestinal wall, Hepatic (CYP2C9) and excretion through renal (33%) and Fecal(67%) routes.

In this work; an attempt is made to formulate immediate release tablets of Candesartan using natural superdisintergrants like *plantago ovatata* and sodium starch glycolate by reducing dosing frequency and to achieve even plasma concentration profile.

## II. METHODS AND MATERIAL

### Materials

Candesartan was obtained as a gift sample from Ranbaxy Labs Ltd. All solvents were pure analytical grade purchased; Double distilled water was used throughout the experiment.

### Preparation of fast dissolving tablets of candesartan cilexetil

Fast dissolving tablets of candesartan cilexetil were prepared by direct compression. All the ingredients were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in order and compressed into tablets of 150 mg using 6 mm round punches on 10-station rotary tablet machine .A batch of 50 tablets of each formulation was prepared for all the designed formulations.

**Table 1.** Formulation of candesartan celixitil FDT

| **Ingrediants** | **F1 mg** | **F2 mg** | **F3 mg** | **F4 mg** | **F5 mg** | **F6 mg** | **F7 mg** | **F8 mg** |
|---|---|---|---|---|---|---|---|---|
| Candesartan celexitil | 12 | 12 | 12 | 12 | 12 | 12 | 12 | 12 |
| Dextrose | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Ferric Oxide | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 | 0.06 |
| Magnesium Stearate | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Sodium Starch Glycolate | - | - | - | - | 2.5 | 5 | 7.5 | 10 |
| Plantago Ovata | 2.5 | 5 | 7.5 | 10 | - | - | - | - |
| Microcrystalline cellulose | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Kyron T-114 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |
| Vanillin | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Camphor | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Mannitol | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| Starch | 19 | 16 | 14 | 11 | 19 | 16 | 14 | 11 |
| Total | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |

### Physicochemical property of Powder:

### 1. Loose Bulk Density (BD)

25 g of drug was weigh accurately, which was previously passed through 30 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V0). Calculate the apparent bulk density in gm/ml by the following formula

**Bulk density = Weight of powder / Bulk volume. [1]**

### 2. Tapped bulk density (TD)

25 g of drug was weigh accurately, which was previously passed through 30 # sieve and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester. The cylinder was tapped for 100 times initially and tapped volume was measured to the nearest graduated units.. The tapped bulk density was measured in gm/ml by the following formula

**Tapped Density = Weight of powder / Tapped volume[1]**

### 3. Hausner's Ratio

The hausner's ratio was determined by the following equation

**Hausner's Ratio = TD / BD [1]**

### 4.Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. The formula for Carr's Index is as below:

**Carr's Index (%) = [(TD-BD)x100]/TD [1]**

| **Sr.no** | **Carr's Index** | **Flow property** |
|---|---|---|
| 1 | 5-15 | Excellent |
| 2 | 12-18 | Good |
| 3 | 18-23 | Fair to passable |
| 4 | 23-35 | Poor |
| 5 | 33-38 | Very poor |
| 6 | >40 | extremely poor |

**Table 2.** Grading of the powders for their flow properties according to Carr's Index

**5. Angle of Repose**

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.
Ø = tan-1 h/r

| Sr. No. | Angle of Repose | Flow property |
|---|---|---|
| 1 | < 25 | Excellent |
| 2 | 25-30 | Good |
| 3 | 30-40 | Passable |
| 4 | >40 | Very Poor |

**Table 3.** Standard value of powder flow property test

**6. Solubility profile:**

Solubility studies were conducted by placing an excess amount of Candesartan (approximately 200 mg) in a 2 ml micro tube containing 1 ml of each buffer. Then, the mixture was vortexed and kept for 3 days at 37oC in a shaking water bath to facilitate the solubilization. The samples were centrifuged at 10,000 rpm for 10 min to remove the undissolved candesartan. The supernatant was taken, diluted with ethanol upto 10 times and filtered through Whatman filter paper for quantification of drug by UV spectroscopy at 224 nm.[1]

**Calibration curve of Candisartan celexetil**

**1) Preparation of standard solution:**

Candesartan cilexetil (100mg) was accurately weighed into 100ml volumetric flask and dissolved in small quantity of ethanol. The volume was made up with ethanol to get a concentration of 1000µg/ml. From this 10 ml was withdrawn and diluted to 100ml in HCl pH1.2/pH 6.8 phosphate buffers to get concentration of 100µg/ml. [1]

**2) Preparation of working solutions**

From the standard stock solution aliquots 2ml, 4ml, 6ml, 8ml and 10ml were pipetted out into 100ml volumetric flask .The volume was made up with phosphate buffer pH6.8 and HCl pH1.2 to get final concentration of 2 µg/ml, 4 µg/ml,6 µg/ml,8 µg/ml and 10µg/ml respectively .The absorbance of each concentration was measured at 224nm.Absorbance was measured at 224nm against ethanol as blank spectrophotometrically. [1]

| Concentration (µg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 2 | 0.10 |
| 4 | 0.15 |
| 6 | 0.24 |
| 8 | 0.26 |
| 10 | 0.30 |

**Table no.4:** Linearity data of candesartan cilexetil in buffer pH=6.4

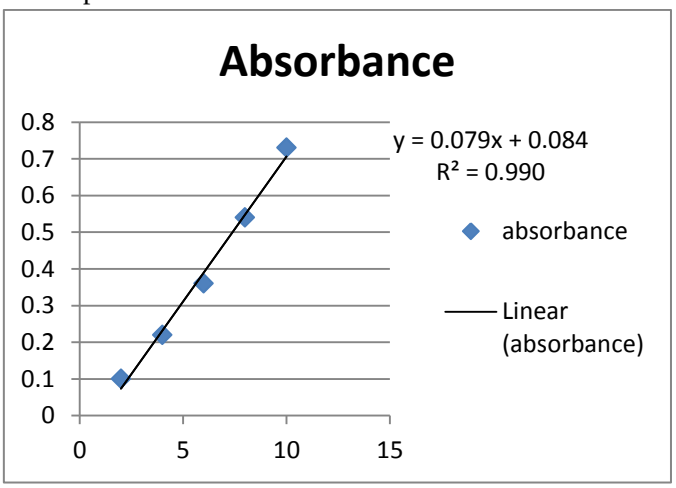



**Figure 1.** Calibration curve of Candesartan celexitil

❖ **Evaluation of Candesartan cilexetil immediate release tablet:**

**Average weight and weight variation:-**

For weight variation test JP procedure was followed. Twenty tablets were taken and their weight was determined individually and collectively using electronic balance. The average weight of the tablets was determined from collective weight. From the individual

tablets weight, the range and percentage standard deviation was calculated. Not more than 2 tablets should deviate from the average weight of tablets and the maximum percentage of deviation allowed. In direct compression of tablet, uniform weight of tablets represents appropriate powder flow and uniform die filling.[1]

| Average wt. of tablet | % deviation |
|---|---|
| 130 mg or less | ±10 |
| 130 mg | ±7.5 |
| > 130 mg | ±5 |

**Table 5:** Percentage deviation in weight variation according to USP

**Tablet Thickness:**

The thickness was measured by placing tablet between two arms of the Varnier caliper,5 tablets were taken and their thickness was measured.[2]

**Tablet Hardness**

The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.[2]

**Tablet Friability**

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (Wo) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.[2]

% Friability = 100 (Wo -W) / Wo

**In-Vitro Disintegration test**

One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±2oc and operated the apparatus for 15 minutes. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated. [1]

**In-Vitro Dissolution test:-**

**Method:** dissolution media was taken as 6.8 pH, 900ml was placed in the vessel and the USP apparatus–II (paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 + 0.5°C. Tablet was placed in the basket and placed in the vessel; the apparatus was operated for 15min at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn were withdrawn at 10, 20, 30, 40, 50 and 60 minutes; filtered and again 5ml of the fluid was replaced. . The collected samples were analyzed at 254 nm using UV- Visible spectrophotometer against the blank. [1]

**Drug Content**

10 tablets were weighed and powdered and 50 mg equivalent weight of Candesartan cilexetil was accurately weighed and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with 6.8 pH Phosphate buffer. Subsequently the solution in volumetric flask was filtered and suitable dilutions were made and analyzed at 277 nm using UV-Visible spectrophotometer (Shimadzu UV-1800). The drug content of each sample was estimated from standard curve of Candesartan cilexetil using 6.8 pH phosphate buffer.

**Wetting Time**

The method was applied to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (i.d. = 6.5 cm) containing 10 ml of pH 6.8 buffer, a tablet was put on the paper, and the time for complete wetting was measured. Three trials from each batch were performed and standard deviation was also determined.[2]

**Water absorption ratio**

The water absorption ratios of the tablet were carried out in Petri dishes with pH 6.8 phosphate buffer.

Periodically, the tablets were withdrawn from the Petri dishes and weighed on electronic balance after removal of surface water by light blotting with a lab tissue for change of their weight .Water absorption ratio (R) was then determined according to the following equation:

$$R = 100 \times (wa - wb)/ wb$$

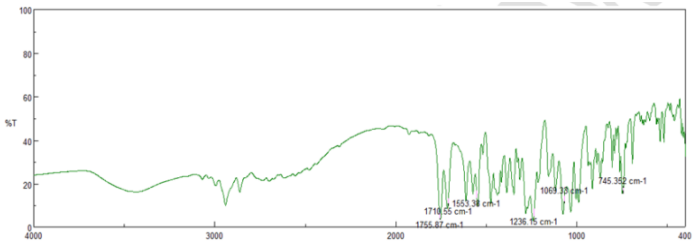
Where wb and wa were tablet weights before and after water absorption, respectivelystant weight is attained.[2]

## III. RESULT AND DISCUSSION

### FTIR Studies

Fourier transform infrared (FTIR) spectra of candesartan cilexetil and physical mixture of drug and excipients were recorded using potassium bromide KBr mixing method on FTIR instrument FTIR Study of candisartan and Excipients .FTIR studies revealed that there was no physico-chemical interaction between Candesartan cilexetil and other excipients. The pure drug Candesartan cilexetil showed characteristic absorption at 2731 cm-1, 1752cm-1, 1714cm-1, 1614 cm-1. This absorption peak at 3073 cm-1 was due to stretching of C-H bond, the peaks at 1752cm-1 and 1714cm-1 were due to two CO bonds (carbonyl group) and peak at 1614cm-1 was due to C-N bond. These peaks were present in IR scan of all formulations, so it was conformed that, presence of undisturbed drug in the formulations. Hence there were no drug-excipient interactions.

### FTIR Study of Candesartan




### FTIR Study of Candesartan and excipients

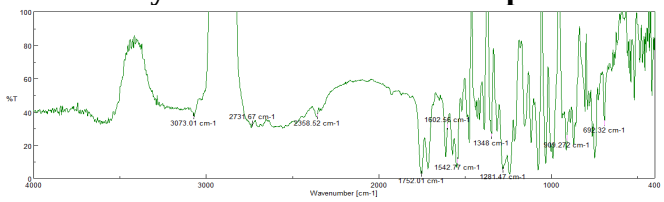



**Figure 2.** IR spectrum of Candesartan cilexetil

### ❖ Evaluation of Pre- Compression Parameters:-

The physicochemical properties and in-process parameters of all the formulation were observed and recorded. Tablet was evaluated for hardness, friability, weight variation, thickness, disintegration time, wetting time, water absorption ratio, drug content and stability study.

**Table 6.** Pre-compressional parameters of Candesartan Celixitil tablet

| | Bulk Density gm/cm$^2$ | Tapped Density gm/cm$^2$ | Carr's index | Hausner's ratio | Angle of repose($^0$) |
|---|---|---|---|---|---|
| F1 | 0.401±0.004 | 0.510±0.002 | 21.37 | 1.27 | 20.07 |
| F2 | 0.420±0.003 | 0.515±0.002 | 18.44 | 1.22 | 21.32 |
| F3 | 0.430±0.002 | 0.524±0.002 | 17.73 | 1.21 | 22.23 |
| F4 | 0.428±0.004 | 0.543±0.002 | 21.17 | 1.26 | 24.12 |
| F5 | 0.420±0.003 | 0.515±0.002 | 18.44 | 1.22 | 21.32 |
| F6 | 0.430±0.002 | 0.524±0.002 | 17.73 | 1.21 | 22.23 |
| F7 | 0.401±0.004 | 0.510±0.002 | 21.37 | 1.27 | 20.07 |
| F8 | 0.428±0.004 | 0.543±0.002 | 21.17 | 1.26 | 24.12 |

***[F1-F4=PGO ; F5- F8=SSG]**

### ❖ EVALUATION OF POST -COMPRESSION PARAMETERS:-

**Table 7.** Post-compression parameters of Candesartan Celixitil tablet.

***[F1-F4=PGO ; F5- F8=SSG]**

| Batch | Avg.Tab.wt. mg | Thickness (mm) | Hardness kg/cm$^2$ | Friability (%) |
|---|---|---|---|---|
| F1 | 150±3 | 2.7±0.03 | 3.3±0.05 | 0.57 |
| F2 | 151±2 | 2.5±1.43 | 3.2±0.05 | 0.40 |
| F3 | 148±3 | 2.4±0.03 | 3.7±0.05 | 0.67 |
| F4 | 149±3 | 2.8±0.2 | 3.1±0.05 | 0.38 |
| F5 | 146±2 | 2.3±0.02 | 3±0.05 | 0.22 |
| F6 | 150±3 | 2.2±0.12 | 3.3±0.05 | 0.35 |
| F7 | 149±1 | 2.9±0.16 | 3.1±0.05 | 0.4 |
| F8 | 148±3 | 2.8±0.2 | 3.7±0.05 | 0.23 |

**Table 8.** Disintegration, wetting time, water absorption ratio and drug content of candesartan cilexetil FDT.

| Batch | In-Vitro dispersion | Water absorption ratio | Wetting time | Drug content |
|---|---|---|---|---|
| F1 | 62±1.01 | 57±1.43 | 59±1.17 | 99.56± 1.69 |
| F2 | 47±1.13 | 70±1.59 | 43±1.10 | 56.81 ±0.25 |
| F3 | 31±2.24 | 80±1.11 | 29±1.29 | 99.74 ±1.21 |
| F4 | 20±1.52 | 83±1.15 | 18±1.11 | 81.25 ±1.76 |
| F5 | 60±1.26 | 49±1.33 | 58±1.41 | 99.48 ±0.82 |
| F6 | 44±1.35 | 54±1.07 | 41±1.23 | 99.31±0.98 |
| F7 | 35±1.17 | 67±1.18 | 32±1.32 | 99.12±1.58 |
| F8 | 25±1.61 | 71±1.32 | 21±2.121.69 | 100.20±1.61 |

***[F1-F4=PGO ; F5- F8=SSG]**

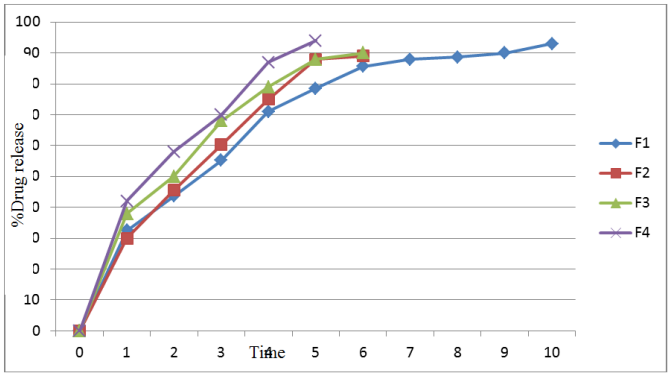



**Figure 3.** In vitro dissolution test for tablet formulations.

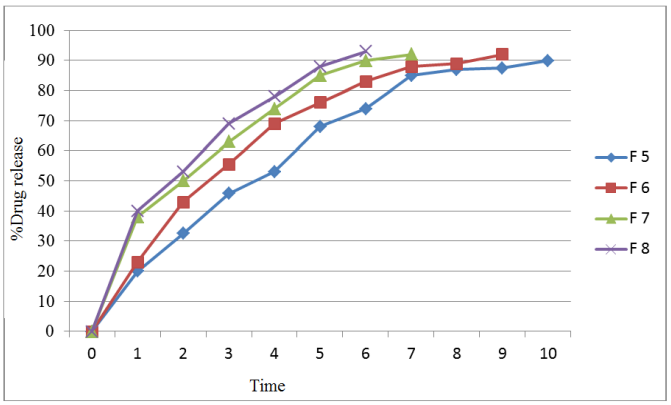



**Figure 4.** In vitro dissolution test for tablet formulations

## IV. CONCLUSION

Tablet formulation F4 showed maximum dissolution in short time period of 5 mins. Formulation of F4 batch was superior as compare to other batches. It can be concluded that fast dissolving tablets with improved dissolution of cilexetil could be prepared by using natural superdisintegrant like Plantago ovata .

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