FORMULATION AND EVALUATION OF MUCAOAHESIVE BUCCAL TABLETS OF CANDESARTAN

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ABSTRACT

Candesartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction, and in the management of heart failure. The Mucoadhesive buccal tablets were prepared by direct compression method using carbopol 934, HPMC K4M, sodium CMC as mucoadhesive polymer. The compatibility studies of drug and excipients were performed by FT-IR spectroscopy. After examining the flow properties of the powder blends the results are found to be within prescribed limits and indicated good flowing property, hence it was subjected to tablet compression. The tablets were evaluated for post-compression parameters like weight variation, hardness, thickness, friability, drug content uniformity, Surface pH, in-vitro studies like swelling, mucoadhesive strength and drug release. Formulation (F6) containing Carbopol-934 and Sodium CMC in the ratio of (2: 3) showed good mucoadhesive strength (36.14) and maximum drug release of 98.15% in 8 hrs. Swelling increases with increase in concentration of Sodium CMC in tablets. The drug content of shown highest of 99.15 %. Surface pH was found to be 6.42. All the evaluation parameters given the positive results and comply with the standards. Stability studies were carried out on the developed formulations indicated that the formulations were stable during the study period. The results indicate that the mucoadhesive buccal tablets of Candesartan may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of candesartan through buccal mucosa.

Key Words: Mucoadhesive buccal tablets, direct compression, Hypertension, Candesartan cilexetil,

INTRODUCTION

The oral cavity is an attractive site for drug delivery due to ease of administration, avoidance of possible drug degradation in the gastrointestinal tract and first-pass metabolism. Buccal delivery system involves the admininistration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Prolonged release of the drug and increased bioavailability leads to the significant reduction in the dose and dose related side effects. Moreover buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage from the buccal cavity therefore mucoadhesive dosage forms were suggested for oral drug delivery which includes various mucoadhesive devices such as patches, tablets, films, gels, disc, and strips andointment ¹. 

Mucoadhesion is defined as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion can also be explained as the ability of synthetic orbiological macromolecules to adhere to mucosal tissues. Mucoadhesive controlled release devices can improve the effectiveness of the drug concentration between minimum effective concentration and maximum safe concentration. Also they inhibit the dilution of drug in the body fluids and allow targeting and localization of a drug at specific site. Mucoadhesive also increases the intimacy and duration of contact between a drug containing polymer and mucous surface. The combined effect of the first drug absorption and decrease in excretion rate (due to prolonged residence time) causes an increased bioavailability of the drug with smaller doses and less frequent administration. Drugs that are absorbed through the mucosal lining of tissues can enter directly into the bloodstream so that these drugs are prevented from enzymatic degradation in the GIT ².

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as First pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self-medication. The advantages of buccal drug delivery include: low enzymatic activity, painless drug administration, easy drug withdrawal ³.

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Candesartan cilexetil belongs to the class of angiotensin receptor antagonist and acts by bindingselectively and non-competitively to angiotensin II receptor type 1, thus preventing actions of angiotensin II. The drug finds most significant clinical uses in the treatment of hypertension of all grades. Candesartan cilexetil is an ester prodrug of Candesartan, which which owes its therapeutic effect. Candesartan cilexetil is white to off-white crystalline powder having melting point of 157-160°C, and is water insoluble. Candesartan acts by inhibits the binding of angiotensin II to the AT1-Receptor. Candesartan cilexetil is hydrolyzed to candesartan during absorption from gastrointestinal tract. It is used in th management of hypertension and may also be used inhe failure in patients with impaire left ventricular systolic function, either when ACE inhibitors are not tolerated, or in addition to ACE inhibitors. Candesartan cilexetil is widely used for the treatment of hypertension and heart failure in clinical application. It is available in 4 mg, 8 mg, 16 mg, 32 mg and can be used in the dose range of 8-32 mg/day.

Hence, the aim of present work is to develop a formulation and evaluation of mucoadhesive buccal tablets of Candesartan.

MATERIALS AND METHODS

Materials:
Candesartan cilexetil was obtained as gift sample from Micro labs, Bengaluru, India. Caribopol 934, HPMC K4M, Sodium CMC, Sodium alginate, Menthol, Talc, Lactose, Saccharin sodium were obtained from S.D fine chemicals limited, Mumbai, India. Magnesium stearate was obtained from Leo chem, S. puram, Bengaluru.

Methods:
The compatibility studies of drug and excipients were determined by FTIR studies. Both pure drug and excipients were individually analysed and further the physical mixture and formulations were also studied.

Preparation of Mucoadhesive buccal tablets of Candesartan cilexetil by direct compression method:
Mucoadhesive buccal tablets of Candesartan cilexetil were prepared by direct compression method by using as carbolopol 934, HPMC K4M, sodium CMC as mucoadhesive polymers. MCC as filler, saccharin sodium as sweetening agents, lactose as diluents, magnesium stearate as lubricant, talc used as glidants. Before going to direct compression all the ingredients were screened through sieve no.100, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and again mixed for additional 2-3 min. Before compression, hardness was adjusted and compressed into 150mg each tablets using tablet compression machine equipped with 5mm flat faced bevelled edge punches on 12 station rotary tablet machine and same hardness was used for the required number tablets. The various formulations designed were shown in Table 1.

Table 1: Formulation development of Mucoadhesive buccal tablet of Candesartan

<table>
<thead>
<tr>
<th>INGREDIENTS (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan cilexetil</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Caribopol 934</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sodium CMC</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>MCC</td>
<td>80</td>
<td>75</td>
<td>70</td>
<td>80</td>
<td>75</td>
<td>70</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Talc</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Lactose</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Saccharin sodium</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Total weight</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

Pre-Compression Parameters

Pre-compression parameters. The various Pre-compression parameters like Angle of repose, Bulk density, Tapped density, compressibility index, Hausner’s ratio and Carr’s index were studied.

Angle of Repose:: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

\[ \tan \theta = \frac{h}{r} \]

Where h and r are the height and radius of the powder cone.

Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

\[ Db= \frac{Mass\ powder}{Volume} \]

Tapped density (Dt): It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gram/ml and is given by

\[ Dt=\frac{M}{Vt} \]
Where, M - Mass of the powder
V t – Tapped volume of the powder.

Compressibility index (I) and Hausner’s ratio: Carr’s index and Hausner’s ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr’s index and Hausner’s ratio were calculated using following formula.

\[ C.I = \frac{(D_t - D_b)100}{D_t} \]

Where, \( D_t \) – Tapped density of the powder
Db – Bulk density of the powder

**Post-Compression Parameters**

The Candesartan cilexetil tablets prepared were evaluated for the following various post compression parameters:

**Organoleptic Characters**

Organoleptic characters properties such as colour, odour, taste, were evaluated for tablets from each batch were randomly selected and taste tested, colour visually compared and odour checked.

**Weight variation**

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The weight variation test is done by selecting 20 tablets randomly from each formulation after compression, weighed individually using a “Electronic weighing balance” and average weight was determined. The individual weights are compared with the average weight for the determination weight variation.

**Tablet hardness**

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using “Monsanto hardness tester”. The hardness was measured in terms of kg/cm².

**Friability**

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients. The friability was determined by using roche friabilator.

**Tablet thickness**

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using “Vernier Callipers”. It was determined by checking the thickness of ten tablets of each formulation.

**Drug content uniformity**

The tablets were tested for their drug content uniformity. At randomly selected 6 tablets from each formulation were finely powdered and dissolved in 100ml of phosphate buffer solution at pH 6.8. The solution was shaken thoroughly and the concentration of drug was determined spectrophotometrically by using SHIMADZU UV 1800 at 277nm.

**Surface pH**

The surface pH of the buccal tablets was determined Battenberg method in order to investigate the possibility of any in-vivo side effects like an acidic or alkaline pH may cause irritation to the buccal mucosa. A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping it in contact with distilled water (pH 6.5 ± 0.05) for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min.

**In-vitro swelling studies**

The degree of swelling of bio-adhesive polymers is an important factor affecting adhesive strength. For conducting the study, a tablet was weighed and placed in a petridish containing 5 ml of phosphate buffer at pH 6.8 for 12 hrs, the tablets were taken out from the petridish and excess water was removed carefully by using filter paper. The swelling Index was calculated using the following formula and results are summarized in Table 5.

**Swelling Index (SI) = (Wt-Wo)/Wo X 100**

Where

SI= Swelling index.
Wt = Weight of tablets after time at ‘t’
Wo = Weight of tablet before placing in the beaker

**In-vitro mucoadhesive Study**

Mucoadhesive strength of the tablets was measured on a modified two-arm physical balance. The sheep buccal mucosa was used as biological membrane for the studies. The sheep mucosa was obtained from the local slaughter house and stored in krebs buffer at 4°C from the time of collection and used within 3 hrs of procurement. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8 at 37°C ± 0.5°C), so that it just touches the mucosal surface. The buccal tablets were suck to lower side of a rubber stopper. The two side of the balance were made equal before the study, by keeping a 5 gms, was removed from the right-hand pan, which lowered the
pan along with the tablet over the mucosa. The balance was kept in the position for 1 min contact time. Mucoadhesive strength was assessed in terms of weight (gm) required to detach the tablet from the membrane. Mucoadhesive strength which was measured as force of adhesion in Newton’s (Table 8) by using following formula 8.

\[
\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{100} \times 9.81
\]

**In-vitro Dissolution studies**

Dissolution testing was carried out with “Paddle type- II USP dissolution test apparatus” at rpm 50 and temperature 37±0.5°C both dissolution media and water. At each specified intervals of time 5 ml sample was withdrawn and replaced by fresh media. The samples were analytically tested to determine the concentration by UV spectroscopy method at wavelength of 277 nm. The % drug release was calculated using an equation obtained from the calibration curve 4.

**Details of Dissolution Test:**

- Dissolution test apparatus: USP type II
- Speed: 50 rpm
- Stirrer: Paddle type
- Volume of medium: 900 ml
- Volume withdrawn: 5 ml
- Medium used: phosphate buffer pH 6.8
- Temperature: 37±0.5°C
- \(\lambda_{\text{max}}\): 277 nm

Further The cumulative amount drug released from the formulations at different time intervals were subjected to various kinetic models such as zero order, first order, higuchi and korsmeyer-peppas model to characterize mechanism of drug release.

**Stability Studies**

Stability can be defined as the capacity of drug product to remain within specifications established to ensure its identity, strength, quality, and purity. The formulations were subjected to short term stability studies. The formulations were packed in aluminium foil in tightly closed container. They were then stored at 30°C 65% RH and 40°C / 75% RH for two months and evaluated for their post-compression studies.

**RESULTS AND DISCUSSION**

The compatibility studies revealed both drugs and excipients were compatible after FT IR studies, the results shown in Figure 1.

**Pre-compression evaluation parameters**

For each type of formulation blends of active pharmaceutical ingredients and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.496-0.576 g/cm³ and the tapped density between 0.560 - 0.108 g/cm³. Using the above two density data, Carr’s compressibility index were calculated. The compressibility index was found between 14.23-17.24% and the compressibility and flow ability data indicated good flow properties of all powder blends. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was range of 27.21 -29.56°. Angle of repose below 30° indicates good flow property. In the present study all powder blends showed good flow property. The results are shown in Table 2.

<table>
<thead>
<tr>
<th>Code</th>
<th>Bulk density g/cm³</th>
<th>Tapped density g/cm³</th>
<th>Carr’s index%</th>
<th>Hausner’s ratio</th>
<th>Angle of repose(°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.576±0.094</td>
<td>0.630±0.120</td>
<td>16.84±0.03</td>
<td>1.20</td>
<td>29.56±0.04</td>
</tr>
<tr>
<td>F2</td>
<td>0.530±0.101</td>
<td>0.626±0.034</td>
<td>15.49±0.094</td>
<td>1.18</td>
<td>28.19±0.067</td>
</tr>
<tr>
<td>F3</td>
<td>0.528±0.074</td>
<td>0.630±0.069</td>
<td>14.63±0.065</td>
<td>1.17</td>
<td>27.89±0.051</td>
</tr>
<tr>
<td>F4</td>
<td>0.523±0.089</td>
<td>0.632±0.091</td>
<td>17.24±0.074</td>
<td>1.20</td>
<td>27.21±0.079</td>
</tr>
<tr>
<td>F5</td>
<td>0.561±0.093</td>
<td>0.623±0.113</td>
<td>16.37±0.093</td>
<td>1.19</td>
<td>27.97±0.084</td>
</tr>
<tr>
<td>F6</td>
<td>0.496±0.112</td>
<td>0.560±0.108</td>
<td>14.23±0.034</td>
<td>1.18</td>
<td>27.61±0.099</td>
</tr>
</tbody>
</table>
Post-Compression evaluation parameters

Organoleptic characters:
Various organoleptic properties viz. taste, colour and odour performed on all the formulations, the results found that all the formulations were sweet in taste, white in colour and odour less.

Thickness
Thickneess of all the formulations was evaluated as per the procedure and the average values was ranges between minimum of 2.12mm to maximum of 2.32mm and found to be within the allowed limit of deviation i.e. 5% of the standard value. Also the crown diameter of all the formulation was 6 mm and the results are shown in Table 3.
Table 3: Post-compression parameter

<table>
<thead>
<tr>
<th>Code</th>
<th>Weight variation (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>149.21±0.22</td>
<td>4.25±0.10</td>
<td>2.12±0.01</td>
<td>0.39±0.15</td>
<td>98.51±0.57</td>
</tr>
<tr>
<td>F2</td>
<td>148.10±0.22</td>
<td>4.30±0.09</td>
<td>2.15±0.03</td>
<td>0.56±0.11</td>
<td>95.00±0.42</td>
</tr>
<tr>
<td>F3</td>
<td>152.20±0.49</td>
<td>4.30±0.04</td>
<td>2.18±0.03</td>
<td>0.40±0.09</td>
<td>97.85±0.32</td>
</tr>
<tr>
<td>F4</td>
<td>150.10±0.41</td>
<td>4.30±0.07</td>
<td>2.12±0.02</td>
<td>0.43±0.62</td>
<td>98.79±0.27</td>
</tr>
<tr>
<td>F5</td>
<td>148.50±0.32</td>
<td>4.20±0.05</td>
<td>2.32±0.01</td>
<td>0.42±0.44</td>
<td>97.01±0.89</td>
</tr>
<tr>
<td>F6</td>
<td>149.30±0.91</td>
<td>4.25±0.03</td>
<td>2.19±0.04</td>
<td>0.50±0.53</td>
<td>99.15±0.42</td>
</tr>
</tbody>
</table>

**Hardness**

All the tablet formulations were evaluated for their hardness as per procedure and the results were shown in Table 3. All the formulations have an average hardness in between 4.20 to 4.30 kg/cm² which was found to be acceptable.

**Friability**

All the Mucoadhesive buccal tablets were evaluated for their percentage friability as per the procedure and the results are shown in Table 3. The average percentage friability for all the formulations were found between 0.39% to 0.56%, which is observed to be within the limit as per the standard (i.e. maximum 1%).

**Weight Variation**

All the formulations were evaluated for their uniformity of weight according to the procedure and the results were shown in Table 3. The maximum weight of 152.20 mg for F3 and the minimum weight of 148.10 mg for F2 formulations were observed. The maximum allowed percentage weight variation for tablets 150 mg by Indian pharmacopoeia is 7.5%, and no formulations were exceeded the limit. Thus all the formulations were found to be complying with the standards given in IP.

**Drug Content**

All the formulations were evaluated for their uniformity of drug content according to the procedure and data were shown in Table 3. The percentage drug content of all formulations was found in the range of 95.00 to 99.15% w/w. The maximum drug content of 99.15% w/w for F6 and the minimum of 95.00% w/w for F2 formulations was observed.

**Surface pH**

The surface pH of tablets of each formulation (F1 to F6) was tested and the results are provided in Table 4. The maximum and minimum pH values of the formulations were found to be 6.42 and 5.22 respectively. The acceptable pH of saliva is in the range of 5-7 and the surface pH of all tablets is within limits. Hence, the formulations may not produce any irritation to the buccal mucosa.

### Table 4: Surface pH, Mucoadhesive strength, Mucoadhesive force

<table>
<thead>
<tr>
<th>Code</th>
<th>Surface pH</th>
<th>Mucoadhesive strength (G)</th>
<th>Mucoadhesive force (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5.22</td>
<td>30.20</td>
<td>2.90</td>
</tr>
<tr>
<td>F2</td>
<td>5.60</td>
<td>32.14</td>
<td>3.19</td>
</tr>
<tr>
<td>F3</td>
<td>6.34</td>
<td>34.18</td>
<td>3.17</td>
</tr>
<tr>
<td>F4</td>
<td>6.10</td>
<td>29.14</td>
<td>3.52</td>
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<tr>
<td>F5</td>
<td>6.14</td>
<td>32.17</td>
<td>2.94</td>
</tr>
<tr>
<td>F6</td>
<td>6.42</td>
<td>36.14</td>
<td>2.80</td>
</tr>
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</table>

**In-vitro drug release studies**

The drug release pattern was studied for all formulations (F1 to F6) for 10 hours and the profile is shown in Figure 2. The most important factor affecting the rate of release from buccal tablet is the drug, type of polymer and polymer ratio. The percentage cumulative drug release profile from formulations F1, F2, F3, F4,F5 and F6 at 8hrs showed 82.10%, 85.13%, 88.14%, 93.16%, 94.17% and 98.13% drug release respectively. It was concluded that by increasing the concentration of carbopol934 in the formulations (F1 to F6), the drug release rate from the tablet was found to be decreased, but when the concentration of secondary polymers HPMC K4M and Sodium CMC is increase, the drug release rate was found to be increased. This may be attributed to increased hydration followed by increased swelling of polymers with increase in concentration. The release data was fitted to various mathematical models such as zero order, first order, Higuchi, Korsmeyer-peppas and it was found that the drug release follows first order kinetics.
Figure 2: In-vitro drug release studies

Table 5: In-vitro Swelling study of Candesartan cilexetil

<table>
<thead>
<tr>
<th>Code</th>
<th>Percentage hydration</th>
</tr>
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<tr>
<td></td>
<td>1hr</td>
</tr>
<tr>
<td>F1</td>
<td>30.11</td>
</tr>
<tr>
<td>F2</td>
<td>35.15</td>
</tr>
<tr>
<td>F3</td>
<td>38.12</td>
</tr>
<tr>
<td>F4</td>
<td>45.12</td>
</tr>
<tr>
<td>F5</td>
<td>50.13</td>
</tr>
<tr>
<td>F6</td>
<td>48.23</td>
</tr>
</tbody>
</table>

Stability studies results
The formulations subjected to the stability studies and the evaluation parameters performed after the study period was shown no significant changes with respect to the initial observations. Further the results were compared and all the formulations found to be stable during the study period.

CONCLUSIONS
The Mucoadhesive buccal tablets were prepared by direct compression method using carbopol 934, HPMC K4M, sodium CMC as mucoadhesive polymer. A total of six formulations were prepared. The powder properties like angle of repose, bulk density, tapped density; Hausner’s ratio and Carr’s index of all the formulations were found to be within the standard limits. All the post-compression characteristics of the formulations like thickness, weight variation, hardness, friability, drug content and surface pH, in-vitro studies like swelling, mucoadhesive strength and drug release were found to be well within the limits of official standards. The overall studies indicated that the polymers Carbopol 934and Sodium CMC in the ratio of 2 : 3 showed satisfactory mucoadhesive properties. Among the 6 formulations, the formulation F6 using these polymers in the above ratio with drug exhibited significant swelling properties with optimum release profile. Hence it can be concluded that the formulation F6 will be useful for buccal administration for the treatment of anti-hypertensive drug. Hence the mucoadhesive buccal tablets of Candesartan may be a good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability through Buccal mucosa. The release data was showed that the drug release follows first order kinetics. Stability studies showed there were significant changes in the parameters even after the period of 60 days. From these results it was concluded that, the candesartan is suitable to develop in to Mucoadhesive buccal tablets, further clinical trials and commercial exploitation is needed for the better usefulness in the intended therapeutic treatment.

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