FORMULATION AND EVALUATION OF CANDESARTAN CO-PRECIPITATE WITH HYDROPHILIC POLYMERS; PREPARATION OF ORODISPERSIBLE TABLETS

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ABSTRACT
Candesartan cilexetil is an angiotensin-receptor blocker that suffer from inadequate and variable oral bioavailability due to its poor aqueous solubility and presystemic metabolism. Therefore, the objectives of this study was to enhance candesartan cilexetil dissolution with subsequent preparation of oral dispersible tablets. The drug was precipitated from its ethanolic solution over Aerosil 200 as carrier for the deposited microcrystals. To improve surface wettability, the precipitation step was performed in presence of hydrophilic polymer. The selected polymers were polyvinylpyrrolidone 40T (PVP), hydroxypropylmethyl cellulose E5 (HPMC), Poloxamer 407 and polyethylene glycol6000 (PEG). The products were evaluated regarding dissolution pattern. Physical characterization was also evaluated for selected formulations. Thermal behaviour and X-ray powder diffraction results confirmed reduced drug crystallinity. Infra-red spectroscopy indicated drug-excipient compatibility. All formulations showed improvement in drug dissolution compared to pure drug. Presence of polymer resulted in higher initial release and dissolution efficiency. Best formulations regarding dissolution were successfully used in the preparation of oral dispersible tablets with fast drug release. Drug precipitation over carrier with large surface area in presence of hydrophilic polymer is a promising approach for enhancing dissolution rate of poorly soluble drugs.

KEYWORDS: Candesartan cilexetil, Aerosil 200, enhance dissolution rate, Orodispersible Tablets.

INTRODUCTION
Candesartan is an angiotensin-receptor blocker that may be used alone or in combination with other agents to treat hypertension. Candesartan lowers blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS). It competes with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and prevents the blood pressure increasing effects of angiotensin II.[1]

Candesartan cilexetil is an ester prodrug of its active metabolite candesartan, which owns its therapeutic effect. The ester form of the candesartan was developed to increase its lipophilicity and consequently its membrane permeability. This prodrug is rapidly and completely bioactivated by carboxylesterase enzyme after absorption to produce the pharmacologically active form.[2] Nevertheless, its bioavailability following oral administration was reported to be about 15%. Poor dissolution due to poor aqueous solubility is an important contributing factor for such low oral bioavailability.[3] In the mean time, carboxylesterases enzymes are believed to exist in the human intestinal lumen suggesting a role of premature degradation of the prodrug to the less permeable candesartan leading to significant reduction in its oral bioavailability.[4,5]

Many strategies have been conducted to improve the dissolution of Candesartan cilexetil such as the formation of inclusion complex with β-cyclodextrins[6], development of self emulsifying drug delivery system[7,8], solid dispersion with hydrophilic polymers[9] as well as mixed noisome for oral administration.[10]

Rapid disintegration with subsequent fast drug dissolution can provide promising strategy to enhance the bioavailability of this drug. The strategy will become more efficient if rapid dissolution was achieved in the oral cavity for subsequent rapid absorption from the highly vascular oral mucosa[11], thereby avoiding any possible premature degradation in the intestinal lumen. This dosage form can provide additional benefits for elderly patients who are the most vulnerable group of patients to cardiovascular disorders and can experience swallowing difficulties. Therefore patients become more
comply with the medication. They also can be administered in the absence of portable liquids. 

Accordingly, the aim of this work was to formulate orodispersible tablets with subsequent fast dissolution to avoid possible premature degradation of the Candesartan cilexetil. Rapidly dissolving solid particles of candesartan cilexetil were first produced using precipitation on solid surface. This was conducted in presence and absence of hydrophilic polymer. Optimum particles were used to develop oral dispersible tablets.

MATERIALS AND METHODS

Materials: Candesartan cilexetil was a gift sample from (Pharonia) Pharmaceutical Chemical Company, Alexendria, Egypt. Aerosil 200, Poloxamer 407, Crosscarmelose, crosplvidone, magnesium stearate, granular mannitol, polyvinyl pyrolidone (PVP 40T), hydroxypropylmethylcellulose (HPMC E5), polyethylene glycol (PEG 6000) and Microcrystalline cellulose (Avicel PH 101), were kindly supplied by Sigma Co., Qwesna, Egypt. Ethanol purchased from El-Gommorha Chemicals Co., Egypt.

Methods

Construction of the Calibration Curve: Calibration curve of candesartan was prepared by preparing serial concentrations, in the range of 2-8 μg/ml, of pure drug in ethanol from ethanolic stock solution (1000 μg/ml). The prepared solutions were analyzed spectrophotometrically at λ max of 227nm using UV-spectrophotometer (Thermo, Evo300pc, USA) and the absorbencies obtained were recorded. The standard curve was linear (R²=0.982) over the range of the used concentrations.

Preparation of drug co-precipitate: Table 1 represents the composition of the prepared formulations. The aim of this study was to prepare drug crystals by precipitation over solid carrier with large surface area in presence of hydrophilic polymers. Aerosil 200 was used for this purpose. The drug/polymer co-precipitate were prepared according to Essa and co-workers with some modification. The selected polymers were Poloxamer 407, PVP 40T, HPMC E5 and PEG 6000. At constant carrier weight ratio, different drug: polymer ratios were used (Table 1). The drug and polymer (if any) were dissolved in the least amount of ethanol (about 30ml), aided by sonication. Aerosil 200 was then dispersed and the organic solvent was allowed to evaporate by gentle heating at 50°C over water bath, while mixing with glass rode. The drug and polymer were precipitated on the surface of the dispersed Aerosil. Precipitated drug alone was used as positive control. The precipitate was recovered, air dried and kept in a dessicator overnight to ensure removal of any residual ethanol. Each powder sample was gently sieved through a 300μm sieve and stored in a tightly closed container till use.

Characterization of the prepared formulations

Drug content: The drug content was determined by dissolving a weight equivalent to 50mg of the drug from each formulation in ethanol followed by centrifugation at 3000 rpm for 10 minutes, to remove the un-dissolved Aerosil. The clear supernatant was suitably diluted with ethanol before spectrophotometric assay.

Physical state characterization

These studies were conducted to evaluate the physical properties of the drug after precipitation and to detect any possible interaction with additives. Differential Thermal Analysis (DTA), Fourier transform infrared spectroscopy (FTIR) and X-ray diffraction were used to achieve this purpose.

Differential thermal analysis (DTA): Candesartan cilexetil, Aerosil 200, HPMC E5, PVP 40T and selected formulations were subjected to thermal analysis using differential thermal analyzer (PerkinElmer STA 6000 module, Waltham, MA). Each sample was loaded into aluminum pan which were crimped and heated at a rate of 10 °C per minute in the temperature range of 25 to 400 °C. Data analysis was conducted using Pyris software.

Table 1. The compositions of the prepared controlled precipitation systems together with the dissolution parameters represented as %amount releases after 5 minutes (Q5) and Dissolution efficiency (DE).

<table>
<thead>
<tr>
<th>Formula</th>
<th>Drug (gm)</th>
<th>Aerosil (gm)</th>
<th>PVP gm</th>
<th>Poloxam (gm)</th>
<th>HPMC gm</th>
<th>PEG 6000</th>
<th>Q5 (%)</th>
<th>DE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18.8±0.4</td>
<td>39±0.519</td>
</tr>
<tr>
<td>Positive control</td>
<td>0.5</td>
<td>0.25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22.5±0.7</td>
<td>33.8±7.7</td>
</tr>
<tr>
<td>F1</td>
<td>0.5</td>
<td>0.25</td>
<td>0.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>32.4±1.3</td>
<td>46.8±0.5</td>
</tr>
<tr>
<td>F2</td>
<td>0.5</td>
<td>0.25</td>
<td>0.2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>55.7±1.3</td>
<td>78.8±0.71</td>
</tr>
<tr>
<td>F3</td>
<td>0.5</td>
<td>0.25</td>
<td>-</td>
<td>0.1</td>
<td>-</td>
<td>-</td>
<td>39.9±1.2</td>
<td>50.7±1.14</td>
</tr>
<tr>
<td>F4</td>
<td>0.5</td>
<td>0.25</td>
<td>-</td>
<td>0.2</td>
<td>-</td>
<td>-</td>
<td>20.2±0.4</td>
<td>49.8±2.23</td>
</tr>
<tr>
<td>F5</td>
<td>0.5</td>
<td>0.25</td>
<td>-</td>
<td>-</td>
<td>0.1</td>
<td>-</td>
<td>64.1±0.5</td>
<td>79.9±0.3</td>
</tr>
<tr>
<td>F6</td>
<td>0.5</td>
<td>0.25</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
<td>-</td>
<td>44.2±0.8</td>
<td>57.3±1.5</td>
</tr>
<tr>
<td>F7</td>
<td>0.5</td>
<td>0.25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.1</td>
<td>43.6±1.2</td>
<td>54.3±1.13</td>
</tr>
<tr>
<td>F8</td>
<td>0.5</td>
<td>0.25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.2</td>
<td>47.4±2.2</td>
<td>58.7±0.96</td>
</tr>
</tbody>
</table>
Fourier–transform infrared spectroscopy (FTIR)
FTIR spectra was conducted for pure Candesartan cilexetil, Aerosil 200, HPMC E5, PVP 40T and selected formulations using FTIR instrument (Bruker Tensor 27, Ettlingen, Germany). Samples scanning from 5000 to 400 cm⁻¹ after compression with potassium bromide into disks using hydraulic press. Data analysis was performed using Opus IR, FT IR spectroscopy Software.

X-ray powder diffraction (XRPD)
X-ray diffractograms were obtained for pure drug, Aerosil 200, HPMC E5, PVP 40T and optimum formulations using XRPD system (Crystal Impact, Bonn, Germany). The scanning rate employed was 8°/min over a 20 range from 3 to 65°.

Table 2. Master formula for preparation of candesartan fast disintegrated tablets.

<table>
<thead>
<tr>
<th>Ingredients (mg/tablet)</th>
<th>Control tab.</th>
<th>PVP tab.</th>
<th>HPMC tab.</th>
</tr>
</thead>
<tbody>
<tr>
<td>candesartan or an equivalent formula</td>
<td>32</td>
<td>61</td>
<td>55</td>
</tr>
<tr>
<td>Mannitol (granular)</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Avicel PH101</td>
<td>90.5</td>
<td>61.5</td>
<td>67.5</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Preparation of orally dispersible tablets (ODT)
Formulations showed the best dissolution parameters were selected to prepare ODT. This process employed single punch tablet machine (Royal Artist, Kapadia Industrial Estate, BLDG, Mumbai, India) using direct compression technique. Pure drug of 32mg (control tablets) or its equivalent of co-precipitates was mixed with the excipients for 10 minutes using the bottle method. The compaction force of the tablet machine was adjusted to produce tablets having a hardness in the range of 4–5 KP using 10mm punch. Detailed compositions of the prepared tablets are presented in Table 2.

Pre-compression parameters: Bulk density (Dₚ) and tapped density (Dₜ) were determined for each tablet powder blend prior to compression. Fixed weight of each blend was introduced into a 10 ml measuring cylinder and the initial volume was noted and taken as bulk volume. The cylinder was tapped for 15 minutes or until fixed powder volume, this was taken as tapped volume. From these values both bulk and true densities were calculated, by dividing mass over the corresponding volume, and used in measuring compressibility index (Carr’s Consolidation Index) and Hausner ratio.[14]

Evaluation of fast disintegrating tablets
Uniformity of weight: Conducted by recording the average weight of 20 tablets of each batch and the percentage weight deviation of the individual tablets from that average was calculated. Limits for acceptance was done considering tablet weight.[15]

Tablet friability: Determined by calculating the percentage loss in weight after exposing 10 tablets to 100rpm in a friabilator (Erweka Friabilator, Western, Germany). The allowed percentage should not exceed 1%.[15]

Drug content: The test employed 10 tablets, randomly selected from tablet batch. Each tablet was crushed and dissolved in ethanol. The insoluble tablet additives were separated by centrifugation. The drug content in each tablet was determination by UV spectrophotometric assay. The accepted limit is that each tablet should contain 85 to 115% of the labelled dose, with only one tablet is allowed to deviate this limit.[15]

Disintegration test: The time taken for complete disintegration of 6 tablets placed in tablet disintegration tester (Copley Scientific NE4-cop Nottingham, UK) was determined.[15] Distilled water warmed to 37°C was used as a disintegration media.

Wetting time: A small amount of Allura red powder was carefully sprinkled over the surface of each tablet before placing the tablet over filter paper placed in a petri-dish containing 6ml of distilled water. The wetting time was taken as the time required for developing a red color on the surface of each tablet.[16]

In vitro Dissolution studies: The dissolution rate of candesartan cilexetil from different formulations (precipitated drug crystals, physical mixtures, orally dispersible tablets) was determined using the USP II dissolution apparatus (Copley, NG 42 JY, Nottingham, UK). Unprocessed pure drug was used as control for the co-precipitated samples. The dissolution medium was selected according to the FDA reported dissolution media for candesartan cilexetil dose (32mg). This medium consisted of 0.7% polysorbate 20 in 0.05M phosphate buffer adjusted to pH 6.5± 0.5. The paddle rotation was adjusted at 50 rpm and the dissolution medium (900 ml) was maintained at 37 °C ±0.5 °C. After loading 32 mg of candesartan cilexetil or its equivalent of the prepared co-precipitate powder or OD tablets in the dissolution vessels, an aliquots of 5 ml each were collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered and analyzed spectrophotometrically at 227 nm after suitable dilution, when necessary. The cumulative amount of dissolved drug (expressed as percentage of the
labeled amount) was plotted as a function of time to obtain the dissolution profiles.

STATISTICAL ANALYSIS
All experiments were conducted in triplicates and statistical analysis employed Student t-test. Results were quoted as significant where P-value is less than 0.05.

RESULTS AND DISCUSSION
Solid state characterization of drug/polymer coprecipitate: The drug content of the prepared formulations was in the acceptable range. The drug content values were in the range of 86.8 – 96.4 % w/w.

Differential thermal analysis (DTA): DTA of pure candesartan cilexetil, polymers, Aerosil 200 and selected co-precipitate (F2 and F5) are shown in Figure 1. The tested co-precipitate was selected based on the dissolution results (see below). The onset, endset and transition midpoint (Tm) of each peak were noted. The thermogram of pure drug showed two endothermic peaks. A sharp peak with onset of 162.2 °C and endset of 182 °C and Tm of 171.3 °C. This sharpness indicates the presence of the drug in its crystalline form. The second peak was very broad with Tm of 283.2 °C, indicating possible drug decomposition at elevated temperature.

The thermal behavior of the drug in Formula F5, drug/HPMC co-precipitate, was similar to that recorded in case of PVP 40T. This again suggests amorphous structure formation in agreement with other investigators using the same polymer with other lipophilic drugs.[18, 19]

X-ray powder diffraction (XRPD)
XRPD patterns of pure candesartan cilexetil, PVP 40T and HPMC E5, Aerosil and formulations (F2 and F5) are shown in Figure 2. Diffractograms of Aerosil, PVP 40T and HPMC E5 showed diffuse pattern characterized by the complete absence of any specific diffraction peak. These patterns indicate amorphous nature.[21]

For pure PVP 40T, the thermogram showed a broad endothermic peak beginning at 30.2 °C and ending at 94.4 °C with Tm of 54.6 (Figure 1). This broad endotherm is similar to the published thermograms for the same polymer and was attributed due to evaporation of adsorbed moisture.[17,18] Likewise, the thermal behavior of pure HPMC E5 revealed similar broad endothermic peak with Tm of 44.3 and can be similarly explained.[19] Regarding Aerosil, the thermogram reflects the amorphous nature of the material with no recognized peaks. For Formula F2, prepared using PVP 40T, the thermogram showed broad band with Tm of 45.2 °C for the polymer. The characteristic peak of the drug was abolished, indicating considerable reduction in drug crystallinity.[20] It worth noting that there was a shift in the decomposition peak to a lower Tm of at 240 °C. This may confirm amorphous form formation.

The diffraction patterns of unprocessed candesartan cilexetil showed a highly crystalline nature revealed by numerous distinctive diffraction peaks at 20 values of 5.8, 10.1, 11.9, 17.46, 18.84, 19.44, 20.46, 22.38, 23.43 and 25.29°. These 20 values are in good agreement with other published data and reflects the high crystalline nature of the drug.[21] These characteristic peaks were disappeared in the diffractograms of the tested formulations F2 and F5. This indicates reduced crystalline structure and presence of the drug in its amorphous state.

Fourier–transform infrared spectroscopy
FTIR spectra of unprocessed candesartan cilexetil, additives and the selected formulations are shown in Figure 3. The spectrum of the unprocessed drug showed the characteristic peaks recognized at 3385 cm⁻¹ for N-H stretching, 2924 cm⁻¹ for aromatic C-H stretching, 2846 cm⁻¹ for aliphatic C-H stretching. The two carbonyl groups appeared at 1710 and 1745 cm⁻¹, and N-H bending at 1603 cm⁻¹. The aromatic C-N stretching was observed at 1238 cm⁻¹ and for the aromatic C-H bending at 740 cm⁻¹. Ether C-O stretching was recorded at 1036 cm⁻¹.[19]
The FTIR spectrum of pure PVP 40T showed a characteristic band at 1658 cm\(^{-1}\) for the carbonyl group. The very broad band at 3450 cm\(^{-1}\) indicate the presence of moisture, revealing the hygroscopic nature of PVP 40T and supports the DTA findings.\(^{[22]}\) The spectrum of Aerosil showed broad peak at about 3426 and 3105 cm\(^{-1}\) that can be attributed to O-H stretching vibration modes of hydrogen bonded to OH of polymeric association and hydrogen bonded to OH intermolecular or chelate compounds. The symmetric stretching Si-O vibration of silica can be noticed at 1089 cm\(^{-1}\). The band at around 1640 cm\(^{-1}\) corresponds to H-O-H bend of crystallized water. The lower frequencies bands at around 820 and 470 cm\(^{-1}\) correspond to asymmetric Si-O stretching and Si-O bending modes, respectively.\(^{[19,23]}\)

The FTIR spectrum of pure HPMC showed the characteristic absorption bands at 3461 cm\(^{-1}\) corresponds to the OH stretching. The aliphatic C-H stretching appears at 2933 cm\(^{-1}\) and that of the aliphatic C-O stretching at 1121 cm\(^{-1}\) (Figure 2). Similar spectrum was reported by other investigators.\(^{[9,54]}\)

For FTIR spectrums of the tested formulations, the main characteristic absorption bands of the drug can be detected with no significant changes compared with the spectrum of pure drug. This suggests absence of any interaction between the drug and other additives.

**In vitro drug release from the prepared microparticles**

The dissolution profiles, represented as cumulative amount of drug released versus time plots, are shown in Figure 4. Table 1 contains the dissolution parameters represented as percentage drug released after 5 minutes (Q5) and dissolution efficiency (DE). The later is computed as the area under the dissolution curve between time points \(t_1\) and \(t_2\), expressed as a percentage of the area of the rectangle described by 100\% dissolution in the same time.\(^{[25]}\) The dissolution profile of the unprocessed drug showed slow dissolution pattern (Figure 4A). The drug liberated 19\% of the loaded dose in the first 5 minutes, followed by gradual increase in the dissolved drug reaching about 50\% after 60 minutes. The calculated dissolution efficiency was 39\% (Table 1).

Precipitation of the drug from its ethanolic solution over Aerosil in presence of hydrophilic polymer largely improved drug dissolution, the intensity of which depended on polymer type and concentration. All formulations, except F4, produced significant improvement in drug dissolution as reflected by increased Q5 (P<0.05) over that for unprocessed drug and positive control (Figure 4 and Table 1). The superiority of formulations containing hydrophilic polymers could be attributed to the possible adsorption of the polymer on the microstructure of the drug microparticle surface during the solvent evaporation step. The hydrophilic polymer then undergoes rapid wettability and/or solubility upon exposure to the dissolution.

This poor dissolution behaviour reflects the hydrophobicity of the drug. A similar dissolution pattern was recorded by other investigators.\(^{[26,9]}\)

Precipitation of the drug from its ethanolic solution over Aerosil in absence of hydrophilic polymer (Positive control) slightly improved drug dissolution over unprocessed drug (Figure 4A). Though the initialy released drug was significantly higher than control (P <0.05), however the over all dissolution efficiencies were comparable. This enhanced Q5 can be explained by the presence of Aerosil providing large surface area during the precipitation step acting as a carrier upon which drug crystal would deposit. According to Noyes–Whitney equation, an increase in the surface area of a drug will result in a more rapid dissolution process.\(^{[27]}\) Thus, increased surface area led to such relatively rapid initial drug release. Moreover, the precipitation process may have a potential to produce partial change into amorphous structure with subsequent enhancement in the dissolution rate as suggested by DTA and X-ray data.

Precipitation of candesartan cilexetil over Aerosil in presence of hydrophilic polymer largely improved drug dissolution, the intensity of which depended on polymer type and concentration. All formulations, except F4, produced significant improvement in drug dissolution as reflected by increased Q5 (P<0.05) over that for unprocessed drug and positive control (Figure 4 and Table 1). The superiority of formulations containing hydrophilic polymers could be attributed to the possible adsorption of the polymer on the microstructure of the drug microparticle surface during the solvent evaporation step. The hydrophilic polymer then undergoes rapid wettability and/or solubility upon exposure to the dissolution.
It is worth noting that formulations F4 that contains poloxamer 407 at its higher concentration showed reduced Q5 compared to F3 with lower concentration (Table 1). This may be explained based on the thermoreversible gelation behavior of poloxamer copolymers.[32]

A similar result was noted for HPMC, where increasing concentration from 0.1 to 0.2 reduced drug release. This could be due to increased interaction between HPMC polymer and drug microparticle surface with possible increased thickness of the adsorbed polymer layer. This may lead to increased viscosity of the diffusion layer around the drug particles with subsequent slow drug partitioning out through it.[19]

**Characterization of fast dissolving tablets**

One reason for poor oral bioavailability of candesartan cilexetil (prodrug) is its premature degradation in the intestinal lumen by carboxylesterases enzymes to the less absorbable candesartan.[4,5] To overcome this problem, preparation of rapidly dispersible tablets in the oral cavity is a promising solution. Oral dispersible tablets with fast drug release will allow rapid absorption of considerable amount of the drug from the oral mucosa minimizing possible prodrug inactivation.

Based on the in vitro dissolution studies formulations F2 and F5, prepared using PVP 40T and HPMC respectively, were selected to prepare oral dispersible tablets as they showed the highest Q5. Tablets were prepared using 32mg of unprocessed drug (control tablet) or an equivalent amount of each formulation (Table 2). Tablets were prepared by direct compression method, after using suitable formulation aids, according to compositions shown in Table 2.

To ensure dose uniformity among tablets, the flow properties of each powder mixture was evaluated prior to compaction. The results of powder flowability are shown in Table 3. For Carr’s Index, powders with values between 5 and 18 are considered to have good flow properties. For Hausner ratio, values less than 1.25 would indicate free flowing powders where values more than 1.25 reflects bad flowability.[13] All formulations, showed a good powder flow properties and were suitable for manufacture of tablets, with a good correlation between Carr's compressibility and Hausner ratio values. Such good flow properties resulted in uniform tablet weight that complied with the US pharmacopeial requirements with a deviation from average weight being less than 2%.

The drug content uniformity ranged from 97.8% to 98.1% of the labeled dose. Tablet hardness were in the average of 5.0 kp, with tablet friability less than 1% (Table 3). These results are satisfactory according to the acceptance criteria of the US pharmacopeia.[15]

The results of dissolution studies indicated the superiority of HPMC at the two concentrations and PVP 40T at the higher concentration over other polymers in improving dissolution parameters (Table 1). Similar findings was reported where PVP 40T was better than Poloxamer 188 and PEG6000 in improving dissolution of domperidone.[31]
Table 3. Results of powder flowability, tablet quality control tests, together with in vitro dissolution parameters of oral dispersible tablets represented as percentage drug released after 5 min (Q5) and dissolution efficiency (DE).

<table>
<thead>
<tr>
<th>Powder Flowability</th>
<th>Content uniformity (%)</th>
<th>Disintegration time (sec)</th>
<th>Friability (%)</th>
<th>Hardness</th>
<th>Wetting time (Sec)</th>
<th>Q5</th>
<th>DE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carr’s Index</td>
<td>Hausner ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cont tab.</td>
<td>19.3</td>
<td>1.24</td>
<td>98.1±1.8</td>
<td>28.3±2.0</td>
<td>0.28</td>
<td>5.22</td>
<td>36±2</td>
</tr>
<tr>
<td>PVP tab.</td>
<td>14.0</td>
<td>1.16</td>
<td>97.9±2</td>
<td>10.0±1.8</td>
<td>0.02</td>
<td>5.21</td>
<td>19.3±0.6</td>
</tr>
<tr>
<td>HPMC tab.</td>
<td>18.0</td>
<td>1.23</td>
<td>97.9±1.8</td>
<td>8.75±1.25</td>
<td>0.33</td>
<td>5.3</td>
<td>16.6±1.9</td>
</tr>
</tbody>
</table>

All formulations showed rapid disintegration time that ranged from 10 to 28 seconds, for PVP Tab and control Tab respectively. Such rapid disintegration could be due to the presence of super-disintegrants that swells and break tablets apart. The recorded disintegration time values are acceptable taking into consideration the FDA specification of orodispensible tablets which recommends a disintegration time of approximately less than or equal to 30 seconds.[34] For wetting time test, PVP Tab and HPMC Tab showed a time of 19 and 16 seconds, respectively. The control Tab showed a longer time of about 39 seconds. This could be attributed to the presence of hydrophilic polymers in the former tablet types that would increase tablet wettability.

4. CONCLUSION
Precipitation over Aerosol in presence of hydrophilic polymers improved the dissolution rate of candesartan cilexetil. Such improvement depended largely on polymer type and concentration. Adsorption of polymer chains and amorphous drug microparticles on the large surface area of the carrier explains such enhancement. The developed drug microparticles were successfully formulated as oral dispersible tablets with rapid dissolution of candesartan cilexetil. This is expected to increase drug bioavailability by avoiding premature degradation in the intestinal lumen to the less absorbed form.

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