Abstract: The present invention relates to a pharmaceutical composition comprising candesartan cilexetil.
The present invention relates to a pharmaceutical composition comprising candesartan cil\textsuperscript{exetil}.

**Background of the invention**

In the field of therapy of hypertension, angiotensin II receptor antagonists have attracted attention as effective agents for the therapy of hypertension following angiotensin I converting enzyme (ACE) inhibitor. Candesartan is a selective AT\textsubscript{i} subtype angiotensin II receptor antagonist. Candesartan cil\textsuperscript{exetil} is a prodrug and is hydrolyzed to candesartan during absorption from the gastrointestinal tract. It falls in the class of benzimidazole-7-carboxylic acid and its derivatives. These agents exhibit a strong and effective hypotensive action and are less likely to cause coughing as side effect as compared to other classes of ACE inhibitors.

Candesartan eilexetil has low aqueous solubility, \textit{i.e.}, it is hydrophobic in nature. Low bioavailability of hydrophobic drugs with extremely low water solubility can be a serious problem. Different approaches have been taken to achieve a desired level of drug solubility and dissolution rate. These approaches have been based on preparations with increased surface area (micronised powders), molecular inclusion complexes (cyclodextrines and derivatives), co-precipitates with water-soluble polymers (PEG, poioxamers, PVP, HPMC) and non-electrolytes (urea, mannitol, sugars etc.), micellar solutions in surfactant systems (Cremophor\textsuperscript{TM}, Tween\textsuperscript{TM}, Gellucires\textsuperscript{TM}), and multilayer vesicles (liposomes and niosomes). Dispersed colloidal vehicles, such as oil-in-water, water-in-oil and multiple (O/W/O or W/O/W) emulsions, microemulsions and self-emulsifying compositions also have been used to improve bioavailability of poorly soluble molecules. None of these approaches has provided the efficiency for selected cases for bioavailability improvement over immediate drug release formulations.
Candesartan is stable against temperature, moisture and light when it is alone in the solid state. However when it is prepared into tablets with other ingredients, deterioration of the active ingredient has been observed over time.

U.S. Patent No. 5,534,534 discloses that deterioration of candesartan cilexetil over lime in pharmaceutical compositions can be reduced by incorporating oily substances having a low melting point in these compositions. This oily substance having a lower melting point is incorporated into the active component to form a stable composition in which decomposition can be suppressed, thus resulting in a stable composition in which the crystalline disorder is minimized.

The present invention is directed to pharmaceutical compositions comprising candesartan cilexetil wherein the pH of aqueous dispersions of the composition in water is more than 5.5. The pH of more than 5.5 provides a formulation with desirably low impurity levels.

In one aspect, a pharmaceutical composition for oral administration comprising a therapeutically effective amount of candesartan cilexetil wherein the pH of aqueous dispersions of the composition in water is more than 5.5 is provided.

In another aspect, there is provided a pharmaceutical composition for oral administration comprising a therapeutically effective amount of candesartan cilexetil wherein the pH of aqueous dispersions of the composition in water is between 5.5 - 9.

In another aspect, there is provided a pharmaceutical composition for oral administration comprising a therapeutically effective amount of candesartan cilexetil and buffering agent wherein the pH of aqueous dispersions of the composition in water is between 5.5 - 9.

In another aspect, there is provided a pharmaceutical composition of candesartan cilexetil for oral administration comprising
a) about 2-35% by weight of candesartan cilexetil;
b) about 0.005-10% by weight of buffering agent:
c) about 0.1-10% by weight of binder; and
d) about 1-10% by weight of disintegrants.

In another aspect, there is provided a process for the preparation of a pharmaceutical composition for oral administration comprising a therapeutically effective amount of candesartan cilexetil comprising:

a) blending candesartan cilexetil with other pharmaceutically acceptable excipients;
b) optionally granulating the blend;
c) lubricating the blend of step a) or granules of step b); and
d) compressing into or filling into suitable size solid dosage form,

wherein the pH of aqueous dispersions of the composition in water is between 5.5 - 9.

In another aspect, there is provided a process for the preparation of a pharmaceutical composition for oral administration comprising a therapeutically effective amount of candesartan cilexetil comprising:

a) dispersing candesartan cilexetil and buffering agent in water;
b) granulating the pharmaceutically acceptable excipients with dispersion of drug;
c) optionally, blending the granules with other pharmaceutically acceptable excipients;
d) lubricating the blend of step c) or granules of step b); and
e) compressing into or filling into suitable size solid dosage form,

wherein the pH of aqueous dispersions of the composition in water is between 5.5 - 9.

In another aspect, there is provided a method of treating hypertension, the method comprising orally administering to a subject in need thereof, a pharmaceutical composition comprising a therapeutically effective amount of candesartan cilexetil and buffering agent wherein the pH of aqueous dispersions of the composition in water is between 5.5 - 9.

**Detailed Description of the Invention**

The term 'candesartan cilexetil' used herein refers to a prodrug that is hydrolyzed to candesartan during absorption from the gastrointestinal tract. It may be used alone or in combination with other drugs such as hydrochlorothiazide, manindipine or other
antihypertensive drugs. Candesartan cilexetil can be present in the range of about 2% to 
about 35% w/w, more particularly about 3% to about 30% (w/w), based on the total weight of the composition.

The term "pharmaceutical composition" as used herein includes tablet, capsules, pills, granules and the like.

The buffering agent can be used in the formulation to obtain the desired pH range, which can lead to a stabilizing effect on the composition. The term "buffering agent" as used herein may include alkali metal or alkaline earth metal salt additives, which may be for example, one or more of sodium carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate, calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide. The amount of buffering agent may vary depending on the buffering capacity of the buffering agent and it may range from about 0.005-10% w/w of the final composition.

The pH of the pharmaceutical composition can be determined by taking a unit dosage of the composition containing candesartan cilexetil and dispersing or dissolving the composition in 10 to 100 ml of water.

The composition may contain pharmaceutically acceptable excipients which include, for example, fillers, binders, disintegrants, lubricants, glidants, colors and the like.

The fillers can be, for example, com starch, lactose, white sugar, sucrose, sugar compressible, sugar confectioners, glucose, sorbitol, calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, microcrystalline cellulose, silified macrortline cellulose, cellulose powdered, dextrates, dextrins, dextrose, fructose, kaolin, lactitol, mannitol, sorbitol, starch, starch pregelatinized and the like. The amount of fillers may vary from about 40-80% by weight of total composition.

Examples of binders may include, for example, methyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol pullulan, pregelatinized starch, agar, tragacanth, sodium alginate and propylene glycol A
combination of binders may also be used such as a combination of hydroxypropyl cellulose and polyvinylpyrrolidone. The amount of binder may vary from about 0.1-10% by weight of final composition.

Examples of disintegrants can include, for example, calcium carboxymethyl cellulose, pregelatinized starch, croscarrarose sodium, crospovidone, sodium starch glycolate and the like. The amount of disintegrants may vary from about 1-10% by weight of final composition.

Examples of lubricants and glidants can include, for example, colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acids, microcrystalline wax, yellow beeswax, white beeswax and the like. Their amount may vary from about 0.01-5% by weight of the final composition.

The coloring agents of the present invention may be selected from any FDA approved colors for oral use such as Ferric oxide, Tartarazine yellow. The coloring agent may be present in the dosage form or in coating over the dosage form.

The dosage form prepared by the present invention may be coated with one or more additional layers comprising film forming agents and/or pharmaceutically acceptable excipients.

The coating composition may further comprise other coating additives such as plasticizers, coloring agents, gloss producer and lubricants/glidants.

The plasticizer may be, for example, diethyl phthalate, dibutyl phthalate and triethyl citrate.

The coating layers over the tablet may be applied as solution/ dispersion of coating ingredients using any technique known to those in the art such as spray coating in a coating pan or fluidized bed processor: dip coating and the like.

Example of solvents which could be used for preparing a solution/ dispersion of the coating ingredients include, for example, methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.
Examples of film forming agents can include ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methyl cellulose, carboxymethylcellulose, hydroxyethylcellulose, hydroxyethylcellulose, hydroxypropyl methyl phthalate, cellulose acetate, cellulose acetate trimellitate, cellulose acetate phthalate; waxes such as polyethylene glycol; methacrylic acid polymers such as Eudragit® RL and RS; and mixtures thereof. Alternatively, commercially available coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry® may also be used for coating.

According to one of the embodiments, the pharmaceutical composition is prepared by a process, comprising:

i) blending candesartan cilexetil with pharmaceutically acceptable excipients,

ii) optionally granulating the blend;

iii) optionally blending the granules with pharmaceutically acceptable extragranular excipients;

iv) lubricating the granules or the blend; and

v) compressing the lubricated granules or the blend into suitable sized tablets, or filling them into capsules.

A wet granulation process may be used for the preparation of the pharmaceutical composition. Wet granulation may be carried out in Rotary granulator or fluidized bed granulator. The granulating medium may comprise water or other solvents such as ethanol, isopropyl alcohol or mixtures thereof.

According to one of the embodiments, the pharmaceutical composition is prepared by wet granulation, comprising:

i) blending candesartan cilexetlii with pharmaceutically acceptable excipients;

ii) granulating the blend with a granulating fluid;
iii) optionally blending the granules with pharmaceutically acceptable extragranular excipients;
iv) lubricating the granules or the blend, and
v) compressing the lubricated granules into suitable sized tablets, or filling them into capsules.

According to one of the embodiments, the pharmaceutical composition is prepared by fluidized bed granulation, comprising:
i) dispersing binder and buffering agent in water;
ii) dispersing candesartan cilexetil into the dispersion of step i);
iii) blending intragranular pharmaceutically acceptable excipients;
iv) granulating the blend of step iii) with dispersion of candesartan in a fluidized bed granulator;
v) optionally blending the granules with pharmaceutically acceptable extragranular excipients;

Vi) lubricating the granules or the blend, and
vii) compressing the lubricated granules into suitable sized tablets, or titling them into capsules.

According to one of the embodiments, the solid pharmaceutical composition is prepared by dry granulation technique, comprising:
i) blending candesartan cilexetil with pharmaceutically acceptable excipients;
ii) granulating the blend using slugging or roller compaction;
iii) optionally blending with pharmaceutically acceptable extragranular excipients;
iv) lubricating the granules or the blend, and
v) compressing the lubricated granules into suitable sized tablets, or filling them into capsules.

According to one of the embodiments, the solid pharmaceutical composition is prepared by direct compression, comprising:
i) blending candesartan cilexetil with pharmaceutically acceptable excipients;
ii) lubricating the blend; and
iii) compressing the blend into suitable sized tablets.
The following example is illustrative of the invention, and does not limit the invention.

EXAMPLE 1

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>(wt/tablet) mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intrgranular</strong></td>
<td></td>
</tr>
<tr>
<td>Candesartan Cilexetil</td>
<td>16</td>
</tr>
<tr>
<td>Povidone K 30</td>
<td>8</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>118.5</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>10</td>
</tr>
<tr>
<td>HPC-L</td>
<td>1.8</td>
</tr>
<tr>
<td>Ferric oxide red</td>
<td>0.18</td>
</tr>
<tr>
<td>Magnesium Carbonate</td>
<td>0.02</td>
</tr>
<tr>
<td>Carboxy Methyl Cellulose Calcium</td>
<td>2</td>
</tr>
<tr>
<td>Purified Water</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>Extragranular</strong></td>
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<tr>
<td>Lactose Monohydrate</td>
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<tr>
<td>Carboxy Methyl Cellulose Calcium</td>
<td>12.5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1</td>
</tr>
<tr>
<td>Total Weight</td>
<td>200</td>
</tr>
</tbody>
</table>

5 PROCEDURE:

1. Povidone, hydroxypropyl cellulose-L and magnesium carbonate were dissolved in water.
2. Candesartan cilexetil was dispersed in the solution of step 1.
3. Corn starch, lactose, Ferric oxide red and carboxy methyl cellulose calcium were blended.
4. The blend of step 3 was granulated with the dispersion of step 2 in the fluidized bed granulator.
5. The granules obtained in step 4 were dried and blended with carboxy methyl cellulose calcium.
6. The blend of step 5 was compressed into suitable size tablets.

The pH of the composition was determined in 100 ml of water and was found to be 7.2.

While there has been shown and described what are particular embodiments of the invention, one skilled in the pharmaceutical formulation art will appreciate that various
modifications in the formulations and process can be made without departing from the scope of the invention.
1. A pharmaceutical composition for oral administration comprising a therapeutically effective amount of candesartan cilexetil, wherein the pH of an aqueous dispersion of the composition in water is more than 5.5.

2. The pharmaceutical composition according to claim 1 wherein the pH of an aqueous dispersion of the composition in water is 5.5-9.

3. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition further comprises a buffering agent.

4. The pharmaceutical composition according to claim 3, wherein the buffering agent is selected from the group consisting of sodium carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium alurainate, calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, aluminum magnesium hydroxide and combinations thereof.

5. The pharmaceutical composition according to claim 3, wherein the buffering agent is present in an amount from about 0.05-10% by weight of the final composition.

6. The pharmaceutical composition according to claim 5 wherein the pharmaceutical composition further comprises pharmaceutically acceptable inert excipients.

7. The pharmaceutical composition according to claim 6, wherein the pharmaceutical acceptable inert excipients are selected from the group consisting of fillers, binders, disintegrants, lubricants, glidants and colorants.

8. The pharmaceutical composition according to any of the preceding claims wherein the pharmaceutical composition comprises
   a) about 2-35% by weight of candesartan cilexetil;
   b) about 0.005-10% by weight of buffering agent;
   c) about 0.1-10% by weight of binder; and
   d) about 1-10% by weight of disintegrants.

9. A process for the preparation of pharmaceutical composition for oral administration comprising a therapeutically effective amount of candesartan cilexetil comprising:
a) blending the candesartan cilexetil with pharmaceutically acceptable excipients;  
b) lubricating the blend; and  
c) compressing the lubricated blend into suitable sized tablets, or filling them into  
capsules,  
wherein the pH of an aqueous dispersion of the composition in water is more than  
5.5.

10. The pharmaceutical composition according to claim 9, wherein the blend of step a)  
is granulated by wet or dry granulation.

11. The pharmaceutical composition according to claim 10, wherein the granules are  
blended with extragranular excipients and compressed into a suitable sized tablet dosage  
form.

12. A process for the preparation of pharmaceutical composition for oral  
administration comprising a therapeutically effective amount of candesartan cilexetil  
comprising:  
a) dispersing candesartan cilexetil and other pharmaceutically acceptable  
excipients into a suitable solvent;  
b) blending intragranular pharmaceutically acceptable excipients;  
c) granulating the blend of step b) with dispersion of candesartan;  
d) blending the granules with pharmaceutically acceptable extragranular  
excipients;  
e) lubricating the granules or the blend; and  
f) compressing the lubricated granules into suitable sized tablets, or filling them  
into capsules,  
wherein the pH of an aqueous dispersion of the composition in water is more than 5.5.

13. The pharmaceutical composition according to claim 12, wherein the granulation is  
carried out in fluidized bed drier or rotary granulator.

14. The pharmaceutical composition according to claim 12, wherein the dispersion of  
step a) further comprises binder and/or buffering agent.

15. The pharmaceutical composition according to claim 1, wherein the pharmaceutical  
composition is used for treatment of hypertension.