Title: FORMULATIONS OF CANDESARTAN

Abstract: The present invention relates to stable oral pharmaceutical formulations comprising candesartan cilexetil with an antioxidant that acts as an excellent stabilizer and to a processes for manufacturing the same, possibly together with at least one chelating agent that enhances the stability, optionally in combination with a diuretic, hydrochlorothiazide (HCTZ).
FORMULATIONS OF CANDESARTAN

The present invention relates to a stable candesartan cilexetil pharmaceutical composition that is orally administrated, comprising at least one antioxidant that acts as an excellent stabilizer, possibly together with at least one chelating agent that enhances the stability, optionally in combination with a diuretic, HCTZ. Invention also provides a practical and industrially applicable manufacturing process.

TECHNICAL BACKGROUND AND PRIOR ART

Candesartan cilexetil, a nonpeptide, is chemically described as (±)-1-[[((cyclohexyloxy) carbonyloxy) ethyl 2-ethoxy-1-[[2'-(1H-tetrazole-5-yl)]1,1'-biphenyl-4yl]-methyl]-1H-benzimidazole-7-carboxylic acid (Formula I). Candesartan cilexetil is a biphenyl tetrazole compound useful as an angiotensin II antagonist in treating circulatory system diseases such as hypertensive diseases, heart diseases (e.g. hypercardia, heart failure, cardiac infarction, etc.), strokes, cerebral apoplexy, and nephritis, among others. It is an ester prodrug of candesartan, which is chemically 2-ethoxy-1-[[2'-(1H-tetrazole-5-yl)biphenyl-4yl]-methyl]-1H-benzimidazole-7-carboxylate.

![Formula I](image)

Candesartan cilexetil is a white to off-white powder and is sparingly soluble in water and in methanol. Although candesartan cilexetil contains an asymmetric center in the ester portion of the molecule, it is sold as the racemic mixture.

In the field of hypertension therapy, angiotensin II receptor antagonists have attracted attention as effective agents for the treatment of hypertension in conjunction with angiotensin I converting enzyme (ACE) inhibitors. Candesartan cilexetil contains one chiral center at the cyclohexyloxy carbonyloxy ethyl ester group. Following oral administration, it undergoes hydrolysis at the ester link to form the active drug, candesartan, which is achiral. Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT1 subtype angiotensin II receptor antagonist. It falls in the class of benzimidazole -7-carboxylic acids and their derivatives. These agents exhibit a stronger and more effective hypotensive action when compared to other classes of ACE inhibitors.
Candesartan cilexetil is stable against temperature, moisture and light when it is alone in the solid state. However, when it is prepared into tablets and incorporated in with other ingredients, it has been observed that the active ingredient degrades over time due to deformation of crystals caused by, for example, pressure, abrasion and heat, applied in the step of granulation or molding under elevated pressure in the course of preparation.

U.S. Patent No. 5,534,534 discloses that the reduction in the content of the Candesartan cilexetil with the lapse of time in pharmaceutical compositions can be reduced by incorporating oily substances having a low melting point in these compositions. According to the patent, the oily substance is incorporated with the active component to form a stable composition that suppresses the decomposition over time that is caused by compression. The resulting composition is described as being stable with minimal crystalline disorder. The stability of pharmaceutical compositions of Candesartan cilexetil can also be correlated to various degradation products, such as desethyl Candesartan and other related substances. The levels of these related substances serve as a measure of the composition's overall stability.

**AIM OF THE INVENTION**

In the present invention, inventors attempted to find solution to the above-mentioned problems. Alternative formulation studies surprisingly revealed that some antioxidants, including the butylated hydroxyanisole (BAH) are excellent stabilizers. Presence of metal chelating agent such as citric acid enhances the stabilization performance. Investigations were conducted repeatedly to prove and secure the practical stabilizing effect of the antioxidants.

**SUMMARY OF THE INVENTION**

There is now provided a stable candesartan cilexetil pharmaceutical composition that is orally administrated, comprising at least one antioxidant that acts as an excellent stabilizer, possibly together with at least one chelating agent that enhances the stability, optionally in combination with a diuretic, HCTZ. This invention also provides an industrially practical and easily applicable manufacturing process.

The details of the present invention together with illustrative examples are given below.

**DETAILED DESCRIPTION OF THE INVENTION**

As it is mentioned in the preceding part, the present invention provides a new candesartan cilexetil pharmaceutical formulation that includes at least one antioxidant that is unexpectedly acts as an excellent stabilizer, possibly together with at least one
chelating agent such as citric acid that enhances the stability, optionally in combination with a diuretic, HCTZ.

The present invention is not only concerns an improved formulation of candesartan cilexetil but also yields an acceptable finished product through industrially practical and applicable manufacturing steps. More specifically, what is aimed and obtained through the present invention are to provide a composition in a tablet (or in other solid forms) and methods of manufacturing that overcome the risks associated with the degradation of the active ingredient, candesartan cilexetil, as well as effects of pressure, abrasion and heat, applied during the step of granulation or molding under elevated pressure in the course of preparation.

Apart from those, the galenic composition and the manufacturing process have therefore carefully optimized to guarantee the stability of the composition through the entire shelf-life of the drug medicine that would enable us to obtain the identical performance with that of the innovator's product, marketed under the trade name of "ATACAND®".

Moreover, the formulations of the present invention also provide synergistic relationships which have not previously been reported either. Presence of metal chelating agent such as citric acid enhances the stabilization performance.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may be a solid dosage form selected from the group that includes tablet, capsule, granule, pellet and powder. Preferably, tablet and capsule forms are employed. Most preferably, tablet form is used.

The candesartan cilexetil may be at a concentration of between about 1% to about 35% w/w, and particularly from about 2% to about 15% w/w of the total weight of the composition. The total weight of the solid composition may vary from 50 mg to 400 mg.

Among preferred antioxidants suitable for use in accordance with the present invention are included one or more of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, sodium ascorbate, calcium ascorbate, ascorbic palmitate, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-tert-butylphenol, erythorbic acid, gum guaiac, propyl gallate, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone, and tocopherols (α-tocopherol etc.) such as vitamin E, and all other vitamin E compounds, analogs and derivatives including 6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid and the like, including pharmaceutically acceptable salts and esters of these compounds and mixtures thereof. Preferably, the antioxidant is a food grade antioxidant; however any antioxidant which is generally recognized as
pharmaceutically acceptable may be used. More preferably, the antioxidant is BHA, BHT, propyl gallate and δ-Hydroxy^; 5^S-tetramethylchroman^-carboxylic acid, pharmaceutically acceptable salts or esters thereof, or mixtures thereof. Most preferably, the antioxidant is BHA. The antioxidant concentration can be in the range of about 0.0001 % to about 5%, preferably, in the range of 0.001 % to about 2% of the total weight of the composition.

Metal chelators deactivate trace metals that are free or salts of fatty acids by the formation of complex ion or coordination compounds. Synergism occurs when antioxidants are used in combination with metal chelating agents. To have maximum efficiency, primary or phenolic oxidants or their mixtures are often used in combination with various metal chelating agents.

Suitable metal chelating agents include one or more of as citric acid, ethylenediamine tetracetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like alone or in combination may be used. Preferably, citric or tartaric acid, and the most preferably, citric acid is chosen. The chelating agent concentration employed can be in the range of about 0.0 % to about 20%, preferably, in the range of 0.0% to about 5%, the most preferably, in the range of 0.0 % to about 3% of the total weight of the composition.

In addition to the above-mentioned two excipients; namely, antioxidant and metal chelating agent or their mixtures, the pharmaceutical composition may further include one or more pharmaceutically acceptable excipients. These excipients may be selected from the group that includes fillers, coating agents, binders, diluents, disintegrants, and colorants and flavoring agents.

Stable pharmaceutical compositions may be prepared by processes known in the prior art including, for example, by comminuting, mixing, granulation (wet and dry), melting, sizing, kneading, drying, molding, immersing, coating, compression (dry or direct), etc. The coating may be carried out by known conventional methods. The coating may be applied one or more of the excipients or their mixture or mixtures with the active ingredient, candesartan cilexetil. Coating may be applied more than once and may be carried out, optionally in different sequences of the manufacturing stages, after blending with one or more pharmaceutically acceptable excipients; and maybe forming a suitable sized core or cores. Spray coating in a coating pan or fluidized bed technique may be employed. The amount of coating agent and the carrier vehicle vary upon the type of formulation and mode of administration, and is readily discernible to those of ordinary skill in the art. Suitable solvents used include one or more of ethanol, methanol, methylene
chloride, acetone, propyl alcohol, isopropyl alcohol, butyl alcohol, trichloroethane, ethylformamide, water and mixtures thereof.

The term "film coating" as used herein relates to a mixture of pharmaceutically acceptable excipients which are applied to, combined with, mixed or otherwise added to active ingredient. The said coating may be applied to a compressed tablet, beads, granules, cores or particles of active ingredient that are compressed into tablet. In the event the particle or granules are themselves film coated before being compressed into a tablet, then the film coating of the compressed tablet itself is optional.

The stable pharmaceutical composition may be a tablet or core that is coated with one or more of the functional and/or non-functional layers. The coating may be composed of one or more of the each of the followings; film forming polymer, binder and antioxidant that are employed in various proportions and possibly together with one or more of the metal chelating agent and optionally can also be included candesartan cilexetil with or without HCTZ. The HCTZ concentration employed can be in the range of about 0.0 % to about 20%, preferably, in the range of 0.0 % to about 10% of the total weight of the composition.

As coating agents one or more of the followings may be employed; hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, polyvinylpyrrolidone, ethylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose and mixtures thereof. Preferably, the coating agent is hydroxypropylcellulose or polyvinylpyrrolidone. Coating agent in a total amount of about 0.2% to about 10% by weight, preferably about 1% to about 8% by weight, of the the total weight of the composition is employed.

Suitable fillers include one or more of starch, pregelatinized starch, wheat starch, corn starch, lactose, sucrose, glucose, sorbitol, dextrates, dextrins, dextrose, fructose, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, carboxymethylcellulose calcium, microcrystallinecellulose, powdered cellulose, sodium chloride and mixtures thereof. Preferably, the filler is corn starch and lactose. Fillers in a total amount of about 30% to about 90 % by weight, preferably, about 60% to about 90% by weight of the total weight of the composition is employed.

Suitable lubricant include one or more of magnesium stearate, sodium stearyl fumarate, stearic acid, colloidal anhydrous silica, synthetic aluminum silicate, magnesium oxide, calcium stearate, talc, hydrogenated castor oil, and mixtures thereof. Most preferably, the lubricant is magnesium stearate. Lubricant in a total amount of about 0.1
% to about 3% by weight, preferably, about 0.1 % to about 1% by weight, total weight of the composition is employed.

Suitable disintegrants include one or more of croscarmellose calcium, croscarmellose sodium, crospovidone, sodium starch glycolate, colloidal silicon dioxide, starch, and mixtures thereof. Most preferably, the disintegrants is croscarmellose calcium. Suitable disintegrant in a total amount of about 0.2% to about 30% by weight, preferably, about 2 % to about 10 % by weight, is employed.

Suitable colorants and flavoring agents include any approved agents by the EMEA and FDA in an amounts less than the maximum allowable quantities for oral pharmaceutical use such as titanium oxide, and others including red iron oxide, etc or mixtures thereof.

The following examples are illustrative of the present invention and it should not be considered as limiting the scope of the invention.

**Examples:**

Compositions employed in the whole examples are depicted below in Table 1.

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<th>Ingredient</th>
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<th>Ex. 3</th>
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<th>Ex. 5</th>
<th>Ex. 6</th>
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**Procedure:**

Antioxidant (BHA or δ-Hydroxy^-, 5,7,δ-tetramethylchroman^-carboxylic acid or α-tocopherol or Tert-butylhydroquinone) was dissolved in solvent (ethanol, water, or their mixtures) and granulation was carried out with the addition of filler(s) (lactose monohydrate...
and/or corn starch and/or microcrystalline cellulose) in either i- using a high shear mixer (Procept MIC-PRO or Collette 600) as given in examples 1, 4 and 5, or ii- using fluidized bed granulator (Vector FL-M-1 ; GEA Aeromatic) as given in examples 2, 3, 6 and 7. Wet granules were either dried in a fluidized bed drier or in a tray oven (example 3 and 4) at 60°C until the water content was reached to about 5% and passed through a screen and sized. Dried granules were coated in a fluidized bed reactor by spraying the solution of coating agent (hydroxypropylcellulose or polyvinylpyrrolidone) and candesartan cilexetil onto these granules. The coated granulates were passed through a screen and sized and then were mixed with disintegrating agent (crosscarmellose calcium or crosscarmellose calcium or sodium starch glycollate). Following to the lubrication with magnesium stearate, final samples were compressed into tablets.

In some cases, metal chelating agent (citric acid or EDTA) was dissolved together with the antioxidant in solvent (ethanol, water or mixtures) as in cases given in example 2, 5 and 6.

For the HCTZ formulation case, such as given in example 5, HCTZ was added with the candesartan simultaneously as described above. Alternatively, instead of dissolving the antioxidant and metal chelating agent in a solvent prior to initial granulation; they were blended with the fillers directly and wet granulation step was skipped.
CLAIMS

1- A solid orally administrable stable pharmaceutical composition comprising
   i- candesartan cilexetil as the active ingredient, at a concentration from 1% to 35% by weight i.e., (w/w), preferably, from 2% to 15% by weight, and
   ii- as a stabilizer, at least one antioxidant at a concentration from 0.0001 to 5% by weight, and
   iii- optionally in combination, at least one metal chelating agent, as a stabilizer-synergizer, at a concentration from 0.0 % to 20% by weight, and
   iv- optionally in combination with hydrochlorothiazide (HCTZ) in the range of about 0.0 % to about 15% by weight, of the total weight of the composition of which may vary from 50 mg to 400 mg, and
   v- in combination with other excipients including filler, coating agent, lubricant, disintegrant and colorants.

2- The composition according to claim 1 wherein pharmaceutical composition comprises a solid orally administrable dosage form selected from the group consisting of tablet, capsule, granule, pellet, beads and powder, preferably, in the tablet or capsule form and most preferably, in the tablet form.

3- The composition according to claim 1 wherein said antioxidant is selected from of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, sodium ascorbate, calcium ascorbate, ascorbic palmitate, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-tert-butylphenol, erythorbic acid, gum guaiac, propyl gallate, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone, and tocopherols (α-tocopherol etc.) such as vitamin E, and all other vitamin E compounds, analogs or derivatives including 6-Hydroxy-2,5,7,8-tetramethylchroman^4-carboxylic acid and the like, including pharmaceutically acceptable salts and esters of these compounds and mixtures thereof. More preferably, the antioxidant is BHA, BHT, propyl gallate and 6-Hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, pharmaceutically acceptable salts or esters thereof, or mixtures thereof. Most preferably, the antioxidant is BHA, BHT and 6-Hydroxy^4, 5,7,δ-tetramethylchroman^4-carboxylic acid.

4- The composition according to claim 1 wherein said metal chelating agent is selected from one or more of the group consisting of citric acid, ethylenediamine tetracetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like alone or in combination
may be used. Preferably, citric or tartaric acid, and most preferably, citric acid is employed.

5- The composition according to claim 1 wherein said excipients include one or more of the followings:

i- Filler in a total amount of about 30% to about 90% by weight, preferably about 60% to about 90% by weight, of the composition and selected from one or more of the group consisting of starch, pregelatinized starch, wheat starch, corn starch, lactose, sucrose, glucose, sorbitol, dextrates, dextrins, dextrose, fructose, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, carboxymethylcellulose calcium, microcrystallinecellulose, powdered cellulose and sodium chloride, is employed.

ii- Coating agent in a total amount of about 0.2% to about 10% by weight, preferably about 1% to about 8% by weight, of the composition and selected from one or more of the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, polyvinylpyrrolidone, ethylcellulose, carboxymethylcellulose, hydroxyethylcellulose and hydroxyethylcellulose or mixtures thereof, is employed.

iii- Lubricant in a total amount of about 0.1% to about 3% by weight, preferably about 0.1% to about 1% by weight, of the composition and selected from one or more of the group consisting of magnesium stearate, sodium stearyl fumarate, stearic acid, colloidal anhydrous silica, synthetic aluminum silicate, magnesium oxide, calcium stearate, talc and hydrogenated castor oil, is employed.

iv- Disintegrant in a total amount of about 0.2% to about 30% by weight, preferably about 2% to about 10% by weight, include one or more of croscarmellose calcium, croscarmellose sodium, crospovidone, sodium starch glycolate, colloidal silicon dioxide and starch. Preferably, croscarmellose calcium and/or crospovidone are employed.

6- A process for manufacturing of the composition of any of the preceding claims comprises one or more of the following steps; antioxidant and filler addition, granulation, drying, screening, coating, sizing, disintegrant addition, lubrication and compression. Optionally, metal chelating agent and/or HCTZ addition steps are also involved.

7- The process for manufacturing of the composition of any of the preceding claims comprises a "film coating" as used herein relates to a mixture of coating agent which is applied to, combined with, mixed or otherwise added to active ingredient. The said
coating may be applied to a compressed tablet, beads, granules, cores or particles of active ingredient that are compressed into tablet. In the event the particle or granules are themselves film coated before being compressed into a tablet, then the film coating of the compressed tablet itself is optional.

The process for manufacturing of the composition of any of the preceding claims comprises a film coating step that is carried out either using fluidized bed coating or pan-coating techniques. Preferably, fluidized bed coating technique is applied that involves spraying a solution of film coating mixture, optionally in combination with HCTZ.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<tr>
<td>A</td>
<td>WO 2005/084648 A1 (RANBAXY LAB LTD [IN]; SINGH ROMI BARAT [IN]; KARANTH GIRISH [IN]; PRAS) 15 September 2005 (2005-09-15) page 1, line 22 - line 25 page 3, line 20 - line 22 page 4, line 7 - line 15 examples</td>
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<td>WO 2005/070398 A1 (RANBAXY LAB LTD [IN]; SINGH ROMI BARAT [IN]; KARANTH GIRISH K [IN]; PR) 4 August 2005 (2005-08-04) claim 1; examples</td>
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<td>WO 2006/079496 A1 (LEK PHARMACEUTICALS D D [SL]; JERALA-STRUKELO JZENKA [SI]; LEGEN IGOR) 3 August 2006 (2006-08-03) page 4; examples</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date

'X' document of particular relevance, the claimed invention cannot be considered to involve the inventive step when the document is taken alone

'Y' document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is taken together with one or more other such documents, such combination being obvious to the person skilled in the art

A* document member of the same patent family

Date of the actual completion of the International search

12 July 2007

Date of mailing of the International search report

18/07/2007

Authorised officer

Boulois, Denis
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<td>WO 2005/079751 A (RANBAXY LAB LTD [IN]; SINGH ROMI BARAT [IN]; KARANTH GIRISH K [IN]; PR) 1 September 2005 (2005-09-01) page 1, line 7 - line 17 page 4, line 9 - line 24 examples</td>
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