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(54) Title: STABLE SOLID PHARMACEUTICAL COMPOSITION COMPRISING CANDESARTAN OR PHARMACEUTICALLY ACCEPTABLE FORMS THEREOF

(57) Abstract: The invention relates to a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms and at least one plasticizer selected from the group consisting of phthalate esters, sebacates, alginates, citrate esters, polyacrylate and polymethacrylate polymers, polymers and copolymers of ethylene, vinyl and/or acetate, various sugar alcohols, triacetin, menthol and any mixture thereof.



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STABLE SOLID PHARMACEUTICAL COMPOSITION COMPRISING
5 CANDESARTAN OR PHARMACEUTICALLY ACCEPTABLE FORMS THEREOF

Field of the invention

The present invention belongs to the field of pharmaceutical
10 industry, particularly to the field of solid pharmaceutical
compositions. Specifically, the invention relates to a
stable solid pharmaceutical composition comprising
candesartan or its pharmaceutically acceptable forms and at
least one plasticizer.

15 Background of the invention

Candesartan is a selective antagonist of subtype 1 of the
angiotensin II receptor (AT₁-antagonist). It falls in the
20 class of drugs of benzimidazole-7-carboxylic acids and
derivatives thereof. These agents exhibit a strong and more
effective hypotensive action and are less likely to cause
coughing as a side effect when compared to the class of ACE
inhibitors.

25 In general, the formulation of candesartan or its
pharmaceutically acceptable forms for effective oral
administration to a subject has hitherto been complicated
by the unique physical and chemical properties of the
30 compound. It is known that candesartan or its
pharmaceutically acceptable forms are stable against
temperature, moisture and light when they are stored

individually in the solid state while when they are incorporated into a pharmaceutical composition the decomposition of the active ingredient is observed. Up to now this problem was solved by several different ways with
5 the main stress on solving the stability problems.

A number of different types of materials and approaches has already been tried in order to find the solution for stabilizing candesartan cilexetil in a solid pharmaceutical
10 composition.

EP 546358 B1 solves the problem of decomposition of candesartan and/or its pharmaceutically acceptable salts by incorporating an oily substance having a low melting point
15 into the formulation.

WO 2005/070398 discloses the dispersing of candesartan cilexetil in a solution comprising a co-solvent and water to form a suspension.
20

A pharmaceutical formulation containing candesartan cilexetil and one or more fatty acids is disclosed in WO 2005/079751.

25 As disclosed in WO 2005/072709 and WO 2006074218 the problem could be solved by forming nanoparticles or microparticles of the drug.

WO 2005/084648 discloses the use of water-soluble polymers
30 to form a stable pharmaceutical composition of candesartan cilexetil with respect to the levels of impurities.

WO 2006/079496 discloses as a stabilizing agent a member of a group of materials known as natural gums, for example agar, xanthan gum, gum arabic (acacia), ceratonia, carrageenan.

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WO 2006/079496 further discloses that candesartan cilexetil can be de-stabilized during compression molding of tablets and for that only gentle manipulation of that step has to be undertaken. Such a gentle manipulation was defined as that
10 the main pressure during compression molding is at maximum 20 kN, preferably 10 kN.

US 2007/0014864 A, US 2007/0014853 A and US 2007/0014854 A disclose pharmaceutical granules containing an active
15 substance having poor water solubility and at least one pharmaceutically acceptable sugar.

In particular, a constant need exists for effective, orally deliverable solid pharmaceutical composition comprising
20 candesartan or its pharmaceutically acceptable forms possessing one or more of the following characteristics:

- appropriate disintegration time of the pharmaceutical composition,
- appropriate dissolution profile of the active
25 ingredient,
- appropriate processability,
- ordinary used and cost effective pharmaceutically acceptable excipients,
- appropriate economics of the technological process for
30 the preparation of the final drug product,
- appropriate chemical and physical stability of the final drug product,
- appropriate bioavailability of the final drug product,

and being prepared by the technological process of wet and dry granulation in order to:

- increase the uniformity of active ingredient distribution in the formulation,
 - 5 - densify the granulate, as for example a mixture of an active ingredient and at least one pharmaceutically acceptable excipient,
 - enhance the flow rates and rate uniformity, i.e. to improve physical characteristics,
 - 10 - reduce dust,
 - improve the appearance of the solid dosage form,
- and wherein the active substance possesses the following characteristics:
- appropriate particle size distribution,
 - 15 - appropriate solubility.

Therefore, an object underlying the present invention is to provide a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms wherein

20 the term stable composition refers to the total content of impurities originating from the decomposition of candesartan in the pharmaceutical composition and to the retained stable polymorphic form I of candesartan cilexetil.

25 Summary of the invention

In a first aspect, the present invention relates to a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms and at least one

30 plasticizer selected from the group consisting of phthalate esters, sebacates, alginates, citrate esters, polyacrylate and polymethacrylate polymers, polymers and copolymers of ethylene, vinyl and/or acetate, various sugar alcohols,

triacetin, menthol and any mixture thereof. The plasticizer is preferably selected from the group of citrate esters.

In a second aspect, the present invention relates to a
5 stable solid pharmaceutical composition comprising
candesartan or its pharmaceutically acceptable forms and at
least one plasticizer selected from the group consisting of
phthalate esters, sebacates, alginates, citrate esters,
polyacrylate and polymethacrylate polymers, polymers and
10 copolymers of ethylene, vinyl and/or acetate, various sugar
alcohols, triacetin, menthol and any mixture thereof,
wherein the total content of impurities does not exceed 10 %
area, preferably 6 % area, more preferably 4 % area and most
preferably 2 % area determined by liquid chromatography if
15 such a composition is stored for 7 days at 60 °C in a closed
vessel. The plasticizer is preferably selected from the
group of citrate esters.

In a third aspect, the present invention relates to the use
20 of a plasticizer selected from the group consisting of
citrate esters in a stable solid pharmaceutical composition
containing candesartan cilexetil as an active ingredient to
retain its stable polymorphic form I. The plasticizer is
preferably triethyl citrate.

25

In a further aspect, the present invention relates to a
process for the preparation of a stable solid pharmaceutical
composition comprising candesartan or its pharmaceutically
acceptable forms and at least one plasticizer as described
30 above by a process comprising a step selected from the group
consisting of wet granulation, dry granulation and direct
compression.

In yet another aspect, the present invention relates to a method of treating hypertension, cardiac diseases, cerebral apoplexy or renal diseases in a patient in need thereof by administering a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms according to the present invention.

Brief description of drawings

10 Figure 1: Particle size distribution of milled candesartan cilexetil material

Figure 2: Particle size distribution of unmilled candesartan cilexetil material

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Figure 3: Microscopic picture of milled candesartan cilexetil material

Figure 4: Microscopic picture of unmilled candesartan cilexetil material

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Figure 5: Comparison: Powder diffraction patterns of stable solid pharmaceutical compositions comprising candesartan cilexetil, and of candesartan cilexetil as pure substance, respectively.

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Detailed description of the invention

Therefore, an object underlying the present invention is to provide a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms. In contrast to the pharmaceutical compositions according to the prior art described above, the present invention relates to

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a stable solid pharmaceutical composition wherein the stability of candesartan or its pharmaceutically acceptable forms is achieved in a very simple way, that is by the addition of an appropriate plasticizer. The pharmaceutical composition according to the present invention offers the advantage of a low content of total impurities originating from the decomposition of candesartan and of retaining the stable polymorphic form I of candesartan cilexetil.

A person skilled in the art is aware of a number of substances defined as stabilizing agents in the pharmaceutical field, as for example natural gums, that could be used in designing a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms. We found that said substances do not provide adequate stabilization of candesartan cilexetil in a solid pharmaceutical composition.

Further, during our extensive experimental work we found that any kind of rough physical manipulation of candesartan or its pharmaceutically acceptable forms can substantially reduce its stability. We found that even the method of encapsulation can destabilize the active substance in the solid pharmaceutical composition. In order to lower the frictional forces between individual particles present in the solid composition of candesartan or its pharmaceutically acceptable forms, a person skilled in the art can try substances already known in the state of the art as tablet or capsule lubricant. Examples of said substances are calcium and magnesium stearate, sodium stearyl fumarate, stearic acid and the like. Again, we found that said substances do not provide sufficient stabilization of

candesartan or its pharmaceutically acceptable forms in a solid pharmaceutical composition as well.

Further, substances known in the art as surfactants and emulsifying agents, as for example docusate sodium, calcium steroyl-2-lactylate, benzalkonium chloride, cetrimide and sodium lauryl sulphate, and emulsifying, gelling and film-forming agents as for example hypromellose, hydroxypropyl cellulose, gelatin, pectin, alginates like sodium and potassium alginate and hypromellose acetate succinate were tested whether they lower the frictional forces between individual particles in a stable solid composition of candesartan or its pharmaceutically acceptable forms. Again we found that none of the selected substances does provide sufficient stabilization of candesartan and its pharmaceutically acceptable forms in a solid pharmaceutical composition as well.

Surprisingly, it has been found that some of the substances, known in the pharmaceutical field as plasticizers, do provide sufficient stabilization of candesartan and its pharmaceutically acceptable forms in a solid pharmaceutical composition.

The general definition used to describe plasticizers refers to pharmaceutically acceptable excipients that increase the plasticity or the ductility of the materials they are added to and that are generally applied in the preparation of film coatings for pharmaceutical dosage forms.

The term plasticizer used herein, however, refers to a pharmaceutically acceptable excipient that is added to the core of a pharmaceutical composition and not into the

coating thereof. Such a plasticizer is used to increase the plasticity and/or decrease the friction between the individual particles (constituents) of a pharmaceutical formulation on the microscopic level due to its lubrication properties.

Thus, in one aspect, the present invention relates to a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms and at least one plasticizer selected from the group consisting of phthalate esters, sebacates, alginates, citrate esters, polyacrylate and polymethacrylate polymers, polymers and copolymers of ethylene, vinyl and/or acetate, various sugar alcohols, triacetin, menthol and any mixture thereof.

The plasticizer used in the stable solid pharmaceutical composition according to the present invention may be selected from, but not limited to:

- Phthalate esters (such as for example phthalate esters like polyvinyl acetate phthalate, cellulose acetate phthalate, dibutyl phthalate, diethyl phthalate, dimethyl phthalate, hypromellose phthalate),
- Sebacates (such as for example dibutyl sebacate and diethyl sebacate),
- Alginates (such as for example sodium, potassium, propylene glycol alginate),
- Citrate esters (such as for example triethyl citrate, acetyltriethyl citrate, tributyl citrate, acetyltributyl citrate, acetyltri-2-ethylhexyl citrate),
- Polyacrylate and polymethacrylate polymers such as for example Eudragit and Plastoid polymers,

- Polymers and copolymers of ethylene, vinyl and/or acetate (such as for example polyethylene, polyvinyl alcohol, polyvinyl alcohol/polyvinyl acetate copolymer, ethylene vinyl acetate),
- 5 - Various sugar alcohols (such as for example sorbitol, xylitol),
- Various additional plasticizers (such as for example triacetin, menthol, glycofurol, sodium benzoate, sodium polyphosphate, amyl alcohol).

10

Preferably, the plasticizer is selected from the group consisting of phthalate esters, citrate esters, sebacates, polyacrylate and polymethacrylate polymers, various sugar alcohols, triacetin, menthol and any mixture thereof. More preferably, the plasticizer is selected from the group consisting of citrate esters, menthol and triacetin and any mixture thereof. Most preferably, the plasticizer is selected from the group of citrate esters. Even most preferably, the plasticizer is triethyl citrate.

20

One or more plasticizers used as a stabilizing agent in a solid pharmaceutical composition according to the present invention can be present in an amount of about less than 20% [w/w] of the final pharmaceutical composition and more preferably in an amount of about between 0.5 and 10% [w/w] of the final pharmaceutical composition.

25

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The term candesartan or its pharmaceutically acceptable forms used herein refers to a prodrug that is hydrolyzed to candesartan during absorption from the gastrointestinal tract, more particularly it refers to candesartan cilexetil. Additionally, the term candesartan or its pharmaceutically acceptable forms used herein refers to candesartan or its

pharmaceutically acceptable esters as for example cilexetil, or to its pharmaceutically acceptable salts, as for example alkaline salts or ammonium salts, preferably the active ingredient is candesartan cilexetil.

5

The concentration of candesartan or its pharmaceutically acceptable forms in the pharmaceutical composition may be between about 1 to about 99% [w/w], particularly between about 1 to about 30% [w/w] and more particularly between
10 about 1 to about 20% [w/w] determined by HPLC.

The average particle size of candesartan or its pharmaceutically acceptable forms may be between 1 and 50 μm , preferably between 1 and 40 μm , more preferably less
15 than 20 μm , determined by a laser diffraction method with a Malvern Mastersizer 2000 instrument equipped with the Hydro S dispersion unit, which is appropriate for measuring particle size distributions in the range of 20 nm to 2000 μm . Isopar L is used as dispersant. Usually, 100-800 mg of the
20 substance is dispersed in 5-10 ml of a 2% solution of epicurone (lecithin) in isopar L to get a homogeneous sample suspension. The measurement is started after adding the sample suspension into the dispersion unit, homogenizing by sonication for an appropriate time to brake-up agglomerates
25 and recirculating at a stirrer/pump speed rate of about 50-70% of maximum speed. The following particel size (D10, D50 and D90) values were measured for milled and unmilled candesartan cilexetil material:

Table 1. D10, D50 and D90 values of milled and unmilled candesartan cilexetil material

	Milled	Unmilled
Mean particle diameter	4 μ m	57/15 μ m (with ultrasonication)
D10	1.1 μ m	3.1 μ m
D50	2.8 μ m	10.5 μ m
D90	6.8 μ m	30.6 μ m
Specific surface area	7.2 m ² /g	4.2 m ² /g

5

D10/50/90 means that at least 10/50/90 % by volume of the particles have a particle size below the specified value. The good homogeneity of the respective size distribution can be taken from the size distribution profiles as shown in Figures 1 and 2. In addition, the microscopic pictures of the milled and the unmilled candesartan cilexetil material (Figures 3 and 4) confirm the homogenous size distribution especially of the milled material (Figure 3) present in the more preferred size of less than 20 μ m (cf. above).

15

The candesartan or its pharmaceutically acceptable forms present in the stable solid pharmaceutical composition according to the present invention can be prepared by any method known from the state of the art as for example disclosed in Jornal of pharmacy and pharmacology. 2005, 57, 273-285, EP 459136B1, WO 2003/014112, WO 2005/021535, WO 2005/051928, WO 2005/051929, EP 1555260 B1, WO 2006/015134, WO 2006/050922, WO 2006/063578, WO 2006/067215, WO 2006/103068, WO 2006/125592, WO 2007/074399, WO 2006/134078, WO 2007/014412, WO 2007/054965, EP 1777224, WO 2007/042161, WO 2007/048361, WO 2005/037821, WO

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2006/076710, WO 2005/111021, WO 2006/122254, PCT/EP2007/057803, PCT/EP2007/057804 and can be in any known stable polymorphic forms.

- 5 Preferably, candesartan cilexetil exists in polymorphic form I or in amorphous form, more preferably in polymorphic form I as defined by Chem. Pharm. Bull. 47(2) 182-186 (1999).

The stable solid pharmaceutical composition according to the present invention may optionally further contain one or more
10 other active ingredients. Suitable other active ingredients can include but are not limited to other angiotensin-II-receptor-antagonists, diuretics, sympathoplegic agents, Ca-channel blockers, vasodilators, ACE inhibitor, angiotensin
15 receptor antagonists, inhibitors of HMG-CoA reductase and any other pharmaceutically acceptable combination, particularly the other active agent is selected from the group consisting of, but is not limited to, angiotensin-II-receptor-antagonists, Ca-channel blockers, diuretics and
20 inhibitors of HMG-CoA reductase. When two or more other active ingredients are present in the stable pharmaceutical composition according to the present invention, they can be present in the same phase (in the intragranular phase, i.e. in the granulate, or in the extragranular phase) as
25 candesartan or its pharmaceutically acceptable forms or in a different phase as candesartan or its pharmaceutically acceptable forms. Additionally, candesartan or its pharmaceutically acceptable forms and one or more other active ingredient can be present partly in the intragranular
30 phase and partly in the extragranular phase. The concentration of candesartan or its pharmaceutically acceptable forms and of one or more other active ingredients in the pharmaceutical composition may be between about 1 to

about 99% [w/w], particularly between about 1 to about 30% [w/w] and more particularly between about 2 to about 20% [w/w] determined by HPLC.

- 5 The stable solid pharmaceutical composition according to the present invention may further include one or more pharmaceutically acceptable ingredients, i.e. excipients such as for example diluents, binders, disintegrants, surfactants and lubricants. Other and further excipients can
- 10 also be included. The term »pharmaceutically acceptable excipients« denotes that the additives are used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for the administration to patients. Pharmaceutically acceptable excipients can be solid, liquid
- 15 or semi-solid and are converted during the process into a state that allows the preparation of a stable solid pharmaceutical composition comprising candesartan or pharmaceutically acceptable forms thereof. The pharmaceutically acceptable excipient may be present in the
- 20 stable solid pharmaceutical composition according to the present invention in an amount of about 1 to about 99% [w/w], particularly from about 70 to about 99% [w/w], more particularly from about 90 to about 98% [w/w].
- 25 The particle size of the excipients used in the stable solid pharmaceutical composition according to the present invention is within the range of $D_{90} < 750 \mu\text{m}$, preferably $D_{90} < 500$, in order to ensure the homogeneity of the compression mixture as well as homogeneous granulation and
- 30 compression. D_{90} means that at least 90% by volume of the particles have a particle size below the specified value.

The diluents used in the stable solid pharmaceutical composition according to the present invention may be selected from the group consisting of, but are not limited to, microcrystalline cellulose, powdered cellulose, lactose
5 (anhydrous and monohydrate), compressible sugar, fructose, dextrates, sugar alcohols such as mannitol, sorbitol, maltitol, xylitol, lactitol, or other sugars such as saccharose, raffinose, trehalose, fructose or mixture thereof, siliconised microcrystalline cellulose, calcium
10 hydrogenphosphate, calcium carbonate, calcium lactate or any mixture thereof, preferably, microcrystalline cellulose, lactose and mannitol, or any mixtures thereof, more preferably microcrystalline cellulose and lactose.

15 The binders used in the stable solid pharmaceutical composition according to the present invention may be selected from the group consisting of, but are not limited to, polyvinylpyrrolidone, microcrystalline cellulose, hydroxyethylcellulose, hydroxypropylcellulose,
20 hydroxypropylmethylcellulose or other cellulose ethers, starch, pregelatinised starch, or polymethacrylate, or any mixtures thereof. It is preferable to use a binder with good water solubility. In view of the practical insolubility of starch in cold water, there is a strong preference for
25 binders with a very good solubility in cold water. There is a variety of binders that have a very good solubility in water, such as for example povidone of different K-values and hydroxypropylcellulose, such as for example partially substituted poly(hydroxypropyl) ether of cellulose and/or
30 low substituted poly(hydroxypropyl) ether of cellulose. Preferably, at least one binder is selected from polyvinylpyrrolidone and hydroxypropylcellulose.

The disintegrants used in the stable solid pharmaceutical composition according to the present invention may be selected from the group consisting of, but are not limited to, crospovidone, starch, pregelatinised starch, sodium strach glycollate, microcrystalline cellulose, carboxymethylcellulose sodium (CMC-Na) or calcium (CMC-Ca), cross-linked CMC-Na, polacrilin potassium, low-substituted hydroxypropylcellulose or any mixtures thereof. Preferably, at least one disintegrant is selected from cross-linked CMC-Na, starch and low-substituted hydroxypropylcellulose.

The surfactants used in the stable solid pharmaceutical composition according to the present invention may be selected from the group consisting of, but are not limited to:

1. Anionic surfactants, where the hydrophilic group carries a negative charge, such as for example carbonyl (RCOO^-), sulphonate (RSO_3^-) or sulphate (ROSO_3^-), examples include potassium laurate, $\text{CH}_3(\text{CH}_2)_{10}\text{COO}^-\text{K}^+$, and sodium lauryl sulphate, $\text{CH}_3(\text{CH}_2)_{11}\text{SO}_4^-\text{Na}^+$.
2. Cationic surfactants, where the hydrophilic group carries a positive charge (e.g., quaternary ammonium halides, $\text{R}_4\text{N}^+\text{Cl}^-$), examples include cetrimide, a mixture consisting mainly of tetradecyl (ca. 68% [w/w]), dodecyl (ca. 22% [w/w]), and hexadecyltrimethylammonium bromides (ca. 7% [w/w]), as well as benzalkonium chloride, a mixture of alkylbenzyltrimethylammonium chlorides of the general formula $[\text{C}_6\text{H}_5\text{CH}_2\text{N}^+(\text{CH}_3)_2\text{R}]\text{Cl}^-$, where R represents a mixture of the alkyls from C_8H_{17} to $\text{C}_{18}\text{H}_{37}$.
3. Ampholytic surfactants (also called zwitterionic surfactants), where the molecule contains, or can potentially contain, both a negative and a positive

charge, (e.g., sulfobetaines, $RN^+(CH_3)_2CH_2CH_2SO_3^-$), examples include N-Dodecyl-N,N-Dimethylbetaine, $C_{12}H_{25}N^+(CH_3)_2CH_2COO^-$.

4. Nonionic surfactants, where the hydrophilic molecule carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene (-OCH₂CH₂O-) groups, examples include polyoxyethylated glycol monoethers (e.g. cetomacrogol), sorbitan esters (Spans®) and polysorbates (Tweens®) as well as polyoxyethylene-polyoxypropylene copolymers.

The lubricants used in the stable solid pharmaceutical composition according to the present invention may be selected from the group consisting of, but are not limited to, stearic acid or stearic acid salts (such as for example magnesium stearate), magnesium palmitate, magnesium oleate, hydrogenated vegetable oil, hydrogenated castor oil, talc, sodium stearyl fumarate, macrogols or mixtures thereof. Preferably, excipients include at least one lubricant selected from stearic acid, magnesium stearate, hydrogenated vegetable oil, hydrogenated castor oil and talc, more preferably magnesium stearate, hydrogenated castor oil and talc.

Optionally, cores/tablets can be coated with conventional materials used for film coating, i.e. as described in Pharmaceutical Coating Technology (G. Cole (ed.), 1995). Film coating formulations usually contain the following components:

- polymer(s),
- plasticizer(s),
- colourant(s)/opacifier(s),
- vehicle(s).

In the film coating suspension minor quantities of flavours, surfactants and waxes can be used.

5 The majority of the polymers used in film coating are either cellulose derivatives, such as the cellulose ethers, or acrylic polymers and copolymers. Occasionally encountered are high molecular weight polyethylene glycols, such as for example macrogols, polyvinylpyrrolidone, polyvinylalcohol
10 and waxy materials. Their function usually is to prevent bad mouth feel and/or taste and in some cases degradation, e.g. oxidation of the active ingredients and/or excipients used.

Typical cellulose ethers which may be applied as coatings
15 are hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and methylcellulose. Acrylic polymers comprise a group of synthetic polymers with diverse functionalities. Some of them can be further modified to enhance swelling and permeability by the incorporation of
20 materials such as water soluble cellulose ethers and starches in order to ensure complete disintegration/dissolution of the film.

The commonly used plasticizers can be categorized into three
25 groups:

- polyols (glycerol, propylene glycol, macrogols),
- organic esters (phthalate esters, dibutyl sebacetate, citrate esters, triacetin),
- oils/glycerides (castor oil, acetylated monoglycerides,
30 fractionated coconut oil).

Colourants/opacifiers are classified into several groups:

- organic dyes and their lakes,

- inorganic colours,
- natural colours.

Vehicles are materials that perform a necessary function in that that they provide the means of conveying the coating materials to the surface of the tablet or particle. The major classes of vehicles capable of being used are water, alcohols, ketones, esters and chlorinated hydrocarbons.

10 Different materials from each group can also be combined in defined ratios. Ready-to-use preparations, which are available on the market, can also be used as film coating suspensions.

15 Film coating suspensions can be prepared by using different solvents as for example water, alcohols, ketones, esters and chlorinated hydrocarbons, preferably water.

A composition of a coating suspension (calculated on dry material) which comprises:

- 1-99%, preferably 1-95% by weight of polymer,
- 1-50%, preferably 1-40% by weight of plasticizer,
- 0.1-20%, preferably 0.1-10% by weight of colourant/opacifier,

25 is particularly preferred.

Ingredients described as components of the coating layer, e.g. colourants, can also be incorporated in the tablet core or divided between tablet core and film coating layer.

30

The stable solid pharmaceutical composition according to the present invention can be in the form of tablets, pills, powders, lozenges, sachets, soft and hard gelatine

capsules, suppositories and the like. The dosage form is preferably suitable for oral application, more preferably it is in the form of tablets or capsules.

5 The stable solid pharmaceutical composition according to the present invention is preferably formulated in a unit dosage form, each dosage form containing about 1 to 100 mg, more usually about 1 to about 50 mg of candesartan cilexetil, preferably from about 2 to 32 mg. When one or more other
10 active ingredients are present in the stable solid pharmaceutical composition according to the present invention said other active ingredient can be present in an amount of 6.25 to 50 mg, preferably in an amount of 12.5 to 25 mg. Preferably, the stable solid pharmaceutical
15 composition according to the present invention contains 8 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide or 16 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide or 32 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide or 32 mg of candesartan
20 cilexetil and 25 mg of hydrochlorothiazide. The term »unit dosage form« refers to physically discrete units suitable as unitary dosages for human objectes and other mammals, each unit containing a predetermined quantity of candesartan cilexetil, calculated to produce the desired therapeutic
25 effect, in association with a suitable pharmaceutical acceptable excipient.

As used herein, the term stable refers to a solid pharmaceutical composition comprising candesartan or its
30 pharmaceutically acceptable forms wherein the total content of impurities originating from the decomposition of candesartan does not exceed 10 % area, preferably 6 % area, more preferably 4 % area and most preferably 2 % area

determined by liquid chromatography if such a composition is stored for 7 days at 60 °C in a closed vessel.

Therefore, another aspect of the present invention relates to a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms wherein the total content of impurities originating from the decomposition of candesartan does not exceed 10 % area, preferably 6 % area, more preferably 4 % area and most preferably 2 % area determined by liquid chromatography if such a composition is stored for 7 days at 60 °C in a closed vessel.

Further, the term stable refers to a solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms wherein candesartan or its pharmaceutically acceptable forms retain their stable polymorphic form. From the state of the art it is known that the polymorphic stability of candesartan and its pharmaceutically acceptable forms in a solid pharmaceutical composition plays an important role in designing a stable pharmaceutical composition. Namely, it is known that for example candesartan cilexetil can exist in several polymorphic forms. The most stable form is known as polymorphic form I while polymorphic form II and the amorphous form are known to be not stable enough to be used in commercial products. We found that, otherwise, stable polymorphic form I of candesartan cilexetil is structurally quite weak and is prone to deformations during any physical manipulations of candesartan cilexetil in the process of preparing a pharmaceutical composition as for example during the course of mixing of the ingredients, granulating, tableting etc. If during the course of tableting some part of otherwise stable

polymorphic form I of candesartan cilexetil undergoes amorphisation, this part of candesartan cilexetil will be degraded. Surprisingly, we found that the incorporation of one or more suitable plasticizer into the pharmaceutical composition remarkably lowers the friction between the individual particles of the constituents of the pharmaceutical composition during any physical manipulations of candesartan cilexetil. The consequence is that the crystal structure of polymorphic form I of candesartan cilexetil remains intact and so candesartan cilexetil retains its polymorphic stability during and after the course of tableting.

Surprisingly, this advantage of retainment of polymorphic form I is highly expressed in case when the plasticizer is selected from the group of citrate esters. Furthermore, while citrate esters are known to be useful as plasticizers in coating procedures, we unexpectedly found that said plasticizers are useful as plasticizers in reducing friction between the constituents of the pharmaceutical composition as well.

Therefore, another aspect of the present invention is the use of a plasticizer selected from the group consisting of citrate esters in a stable solid pharmaceutical composition containing candesartan cilexetil as an active ingredient to retain its stable polymorphic form I. The plasticizer is preferably triethyl citrate, which is widely used in the field of food additive, food packaging, cosmetics and children toys as well. It has a better biodegradability and less biochemical effects as other known plasticizers.

In another aspect, the present invention relates to a process for the preparation of a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms and at least one plasticizer as described
5 above by a process comprising a step selected from the group consisting of wet granulation, dry granulation and direct compression.

In yet another aspect of the present invention, there is
10 provided a method of treating hypertension, cardiac diseases, cerebral apoplexy or renal diseases in a patient in need thereof by administering a stable solid pharmaceutical composition comprising candesartan or its pharmaceutically acceptable forms according to the present
15 invention.

For a more complete understanding of the instant invention, reference is made to the following illustrative examples, although it should be clearly understood that the present invention is not limited in and way thereto.

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Example 1

Table 2. Compositions of the solid pharmaceutical composition comprising candesartan cilexetil

10

Ingredient	Composition 1	Composition 2	Comparative Composition 1	Comparative Composition 2
Candesartan cilexetil	4.0	4.0	4.0	4.0
Lactose monohydrate	90.0	90.0	96.0	96.0
Starch	20.0	20.0	20.0	20.0
Menthol		6.0		
Triethyl citrate	6.0			
Polyvinyl Alcohol			6.0	
Hydroxypropyl cellulose	4.0	4.0	4.0	4.0
Calcium carboxymethyl cellulose	5.6	5.6	5.6	5.6
Magnesium stearate	0.4	0.4	0.4	0.4

In preparation of Composition 1, hydroxypropyl cellulose and triethyl citrate were dissolved in water and candesartan cilexetil, lactose monohydrate and starch were granulated with the aqueous hydroxypropyl cellulose / triethyl citrate solution in a fluid bed granulator. In preparation of Composition 2, hydroxypropyl cellulose was dissolved in water and candesartan cilexetil, lactose monohydrate, starch

and menthol were granulated with the aqueous hydroxypropyl cellulose solution in a fluid bed granulator. In Comparative Composition 1 (WO2005/084648, example 1), hydroxypropyl cellulose and polyvinyl alcohol were dissolved in water and

5 candesartan cilexetil, lactose monohydrate and starch were granulated with the aqueous hydroxypropyl cellulose / polyvinyl alcohol solution in a fluid bed granulator. In Comparative Composition 2 (EP 546358 B1, example 1), candesartan cilexetil, lactose monohydrate and starch were

10 granulated in a fluid bed granulator with a dissolution of hydroxypropyl cellulose in water. After the granulation step has been performed, calcium carboxymethyl cellulose and magnesium stearate were added to the granules. One part of the obtained composition was compression-molded into tablets

15 and the other part was filled into capsules.

Table 3. Results of the stability test - tablets

Impurities	Composition1	Comparative Composition 1	Comparative Composition 2
Total content of impurities at the initial time of test (% area)	0.4	0.5	0.8
Total content after 7 days at 60 °C (% area)	0.8	3.2	5.9

20 Table 4. Results of the stability test - capsules

Impurities	Composition 1	Comparative Composition 1	Comparative Composition 2
Total content of impurities at the initial time of test (% area)	0.4	0.4	0.5
Total content after 7 days at 60 °C (% area)	0.8	1.0	2.0

Table 3 shows the results of the stability test of the tablets and Table 4 shows the results for the capsules. The stability tests were performed after storing the samples for 5 7 days at 60 °C. The content of the candesartan cilexetil impurities was determined by liquid chromatography:

HPLC: Agilent 1100

Data evaluation: Chemstation

10

Chromatographic conditions:

Column: Eclipse Plus-C18, 50mm x 4.6mm, 1.8 µm particles

15 **Mobile phase:**

Solvent A: 0.01M NaH₂PO₄, pH 2.5

Solvent B: acetonitrile

Gradient:

Time (min)	%A	%B
0	55	45
12	5	95
20	5	95
21	55	45
25	55	45

20

Post run: 2 min

Column temperature: 50°C

Flow rate: 1.2 ml/min

Detection: UV, 225nm

25 **Injection:** 5 µl.

As it is evident from the test results, the composition of the present invention provides a remarkable improvement in the stability of candesartan cilexetil as compared to the comparative compositions.

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Example 2

Table 5. Candesartan cilexetil compositions

Ingredient	Composition 1	Comparative Composition 3	Comparative Composition 4	Comparative Composition 5	Comparative Composition 2
Candesartan cilexetil	4.0	4.0	4.0	4.0	4.0
Lactose monohydrate	90.0	90.0	90.0	90.0	96.0
Starch	20.0	20.0	20.0	20.0	20.0
Triethyl citrate	6.0				
Gum arabic (Acacia)		6.0			
Sodium Stearyl Fumarate			6.0		
Sodium Lauryl Sulfate				6.0	
Hydroxypropyl cellulose	4.0	4.0	4.0	4.0	4.0
Calcium carboxymethyl cellulose	5.6	5.6	5.6	5.6	5.6
Magnesium stearate	0.4	0.4	0.4	0.4	0.4

10

In preparing Composition 1, hydroxypropyl cellulose was dissolved in water and candesartan cilexetil, lactose monohydrate, starch and menthol were granulated with the aqueous hydroxypropyl cellulose solution in a fluid bed granulator. In preparing Comparative Compositions 3, 4 and 5, gum arabic (Acacia) - as a representative of a natural

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gum, sodium stearyl fumarate - as a representative of a tablet or capsule lubricant, sodium lauryl sulfate - as a representative of a surfactant or an emulsifying agent were dissolved in water and candesartan cilexetil, lactose monohydrate and starch were granulated with the aqueous solution of the respective excipient in a fluid bed granulator. In preparing Comparative Composition 2 (EP 546358B1, example 1), candesartan cilexetil, lactose monohydrate and starch were granulated in a fluid bed granulator with a dissolution of hydroxypropyl cellulose in water. After the granulation step has been performed, calcium carboxymethyl cellulose and magnesium stearate were added to the granules. The obtained composition was compression-molded into tablets.

Table 6. Results of the stability test - tablets

Impurities	Composition 1	Comparative Composition 3	Comparative Composition 4	Comparative Composition 5	Comparative Composition 2
Total content of impurities at the initial time of test (% area)	0.4	0.6	0.5	0.5	0.6
Total content after 1 day at 60 °C (% area)	0.5	2.1	1.6	1.1	1.2

Table 6 shows the results of the stability test of the tablets. The stability tests were performed after storing the samples for 1 day at 60 °C. The content of the candesartan cilexetil impurities was determined by liquid chromatography as mentioned above.

As it is evident from the test results, the plasticizer of the present invention provides a remarkable improvement in

the stability of candesartan cilexetil as compared with other stabilizing agents (natural gums, lubricants and surfactants).

As it has been demonstrated in the Examples 1 and 2, a suitable plasticizer can remarkably lower the total amount of impurities originating from the decomposition of candesartan in a solid composition of candesartan cilexetil according to the present invention.

Example 3

Table 7. Composition of the stable solid pharmaceutical composition comprising candesartan cilexetil

Ingredient	Composition 1
Candesartan cilexetil	32.0
Lactose monohydrate	358.0
Starch	37.0
Triethyl citrate	6.0
Hydroxypropyl cellulose	21.0
Calcium carboxymethyl cellulose	20.0
Magnesium stearate	1.5

The stable solid pharmaceutical composition with ingredients as described in Table 7 was prepared by the same method as described in Example 1. The X-ray powder diffraction pattern was measured first at initial time and then after storage for 28 days at 40°C and 50°C for 28 days; the result is shown in Figure 5. The comparison between the powder diffraction

patterns of stable solid pharmaceutical compositions comprising candesartan cilexetil and the powder diffraction pattern of candesartan cilexetil as pure substance, respectively shows that all characteristic peaks of polymorphic form I of candesartan cilexetil are present in the composition of the present invention. The result furthermore demonstrates that polymorphic form I of candesartan cilexetil remains unchanged as there are no additional peaks emerging after storage that would indicate the presence of any other polymorph of candesartan cilexetil.

The instrument was a PANalytical X'pert PRO powder diffractometer with CuK α radiation.

Example 4

Table 8. Candesartan cilexetil compositions

Ingredient	Composition 4/1 (mg)	Composition 4/2 (mg)	Composition 4/3 (mg)
Candesartan cilexetil	4.0	4.0	4.0
Lactose monohydrate	90.0	90.0	90.0
Starch	20.0	20.0	20.0
Dibutyl sebacate	6.0	6.0	6.0
Polysorbate 80	/	2.0	
Sodium lauryl sulfate	/	/	2.0
Hydroxypropyl cellulose	4.0	4.0	4.0
Calcium carboxymethyl cellulose	5.6	5.6	5.6
Magnesium stearate	0.4	0.4	0.4

In preparing Composition 4/1, hydroxypropyl cellulose was dissolved in water and dibutyl sebacate was dispersed into solution. Candesartan cilexetil, lactose monohydrate, starch
5 were granulated with the obtained dispersion in a fluid bed granulator. The obtained granulate was further processed as in Example 2.

Preparation of compositions 4/2 and 4/3:

10 Hydroxypropyl cellulose and polysorbate or sodium lauryl sulfate were dissolved in water and dibutyl sebacate was dispersed into solution. Candesartan cilexetil, lactose monohydrate, starch were granulated with the obtained dispersion in a fluid bed granulator. The obtained granulate
15 was further processed as in Example 2.

Example 5

Table 9. Candesartan cilexetil compositions

Ingredient	Composition 5/1 (mg)	Composition 5/2 (mg)	Composition 5/3 (mg)
Candesartan cilexetil	4.0	4.0	4.0
Lactose monohydrate	90.0	90.0	90.0
Starch	20.0	20.0	20.0
Diethyl phthalate	6.0	6.0	6.0
Polysorbate 80	/	2.0	
Sodium lauryl sulfate	/	/	2.0
Hydroxypropyl cellulose	4.0	4.0	4.0
Calcium carboxymethyl cellulose	5.6	5.6	5.6
Magnesium stearate	0.4	0.4	0.4

In preparing Composition 5/1, hydroxypropyl cellulose was dissolved in water and diethyl phthalate was dispersed into solution. Candesartan cilexetil, lactose monohydrate, starch were granulated with the obtained dispersion in a fluid bed granulator. The obtained granulate was further processed as in Example 2.

Preparation of compositions 5/2 and 5/3:

Hydroxypropyl cellulose and polysorbate or sodium lauryl sulfate were dissolved in water and diethyl phthalate was dispersed into solution. Candesartan cilexetil, lactose monohydrate, starch were granulated with the obtained dispersion in a fluid bed granulator. The obtained granulate was further processed as in Example 2.

Example 6

Table 10. Candesartan cilexetil compositions

Ingredient	Composition 6/1 (mg)	Composition 6/2 (mg)
Candesartan cilexetil	4.0	4.0
Lactose monohydrate	90.0	90.0
Starch	20.0	20.0
Polyvinyl acetate	6.0 ^{1,2}	6.0 ³
Hydroxypropyl cellulose	4.0	4.0
Calcium carboxymethyl cellulose	5.6	5.6
Magnesium stearate	0.4	0.4

- 5 1... Kollicoat 30SR (30% dispersion in water)
 2... weight of dry substance
 3... dry polymer is used

- 10 In preparing of Composition 6/1, hydroxypropyl cellulose was
 dissolved in water. Kollicoat 30SR was admixed to the
 obtained solution, to obtaine a dispersion containing both
 polymers. Candesartan cilexetil, lactose monohydrate, starch
 were granulated with the obtained dispersion in a fluid bed
 15 granulator. The obtained granulate was further processed as
 in Example 2.

- In preparing of Composition 6/2, hydroxypropyl cellulose and
 polyvinyl acetate were dissolved in absolute ethanole.
 20 Candesartan cilexetil, lactose monohydrate, starch were
 granulated with the obtained solurion in a fluid bed
 granulator. Obtained granulate was further processed as in
 Example 2.

CLAIMS

1. A stable solid pharmaceutical composition comprising
5 candesartan or its pharmaceutically acceptable forms and at
least one plasticizer selected from the group consisting of
phthalate esters, sebacates, alginates, citrate esters,
polyacrylate and polymethacrylate polymers, polymers and
copolymers of ethylene, vinyl and/or acetate, various sugar
10 alcohols, triacetin, menthol and any mixture thereof.
2. The stable solid pharmaceutical composition according to
claim 1 wherein the plasticizer is selected from the group
consisting of phthalate esters, citrate esters, sebacates,
15 polyacrylate and polymethacrylate polymers, various sugar
alcohols, triacetin, menthol and any mixture thereof.
3. The stable solid pharmaceutical composition according to
any preceding claims wherein the plasticizer is selected
20 from the group consisting of citrate esters, menthol and
triacetin and any mixture thereof.
4. The stable solid pharmaceutical composition according to
any preceding claims wherein the plasticizer is selected
25 from the group of citrate esters.
5. The stable solid pharmaceutical composition according to
any preceding claims wherein the plasticizer is triethyl
citrate.
- 30 6. The stable solid pharmaceutical composition according to
any preceding claims further comprising at least one
pharmaceutically acceptable ingredient selected from the

group consisting of one or more diluent, one or more binder, one or more disintegrant, one or more surfactant, one or more lubricant.

5 7. The stable solid pharmaceutical composition according to any preceding claims wherein one or more diluent is selected from the group consisting of microcrystalline cellulose, powdered cellulose, lactose, sugar, sugar alcohols, siliconised microcrystalline cellulose, calcium
10 hydrogenphosphate, calcium carbonate, calcium lactate or any mixtures thereof.

8. The stable solid pharmaceutical composition according to any preceding claims wherein one or more binder is selected
15 from the group consisting of polyvinylpyrrolidone, microcrystalline cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose or other cellulose ethers, starch, pregelatinised starch, or polymethacrylate, or any mixtures thereof.

20 9. The stable solid pharmaceutical composition according to any preceding claims wherein one or more disintegrant is selected from the group consisting of crospovidone, starch, sodium strach glycollate, microcrystalline cellulose,
25 carboxymethylcellulose sodium or calcium, cross-linked carboxymethylcellulose sodium, polacrillin potassium, low-substituted hydroxypropylcellulose or any mixtures thereof.

10. The stable solid pharmaceutical composition according to
30 any preceding claims wherein one or more surfactant is selected from the group consisting of anionic or cation surfactant, amoholytic surfactants and nonionic surfactants or any mixtures thereof.

11. The stable solid pharmaceutical composition according to any preceding claims wherein one or more lubricant is selected from the group consisting of stearic acid or
5 stearic acid salts, such as for example magnesium stearate, magnesium palmitate, magnesium oleate, hydrogenated vegetable oil, hydrogenated castor oil, talc, sodium stearyl fumarate, macrogols or any mixtures thereof.

10 12. The stable solid pharmaceutical composition according to any preceding claims further optionally comprising film coating.

13. The stable solid pharmaceutical composition according to
15 any preceding claims wherein the stable solid pharmaceutical composition is in the form of tablets, pills, powders, lozenges, sachets, soft and hard gelatine capsules or suppositories, preferably in the form of tablets or capsules.

20 14. The stable solid pharmaceutical composition according to any preceding claims wherein the total content of impurities does not exceed 10 % area, preferably 6 % area, more preferably 4 % area and most preferably 2 % area determined
25 by liquid chromatography if such a composition is stored for 7 days at 60 °C in a closed vessel.

15. A process for preparing a stable solid pharmaceutical composition according to any preceding claims comprising a
30 step selected from the group consisting of wet granulation, dry granulation and direct compression.

16. A use of a plasticizer selected from the group consisting of citrate esters in a stable solid pharmaceutical composition containing candesartan cilexetil as an active ingredient to retain its polymorphic form I.

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17. The use according to claim 15 wherein the plasticizer is triethyl citrate.

18. Stable solid pharmaceutical composition according to
10 claims 1 to 13 for use in a method of treating hypertension, cardiac diseases, cerebral apoplexy or renal diseases.

Figure 1: Particle size distribution of milled candesartan cilexetil material

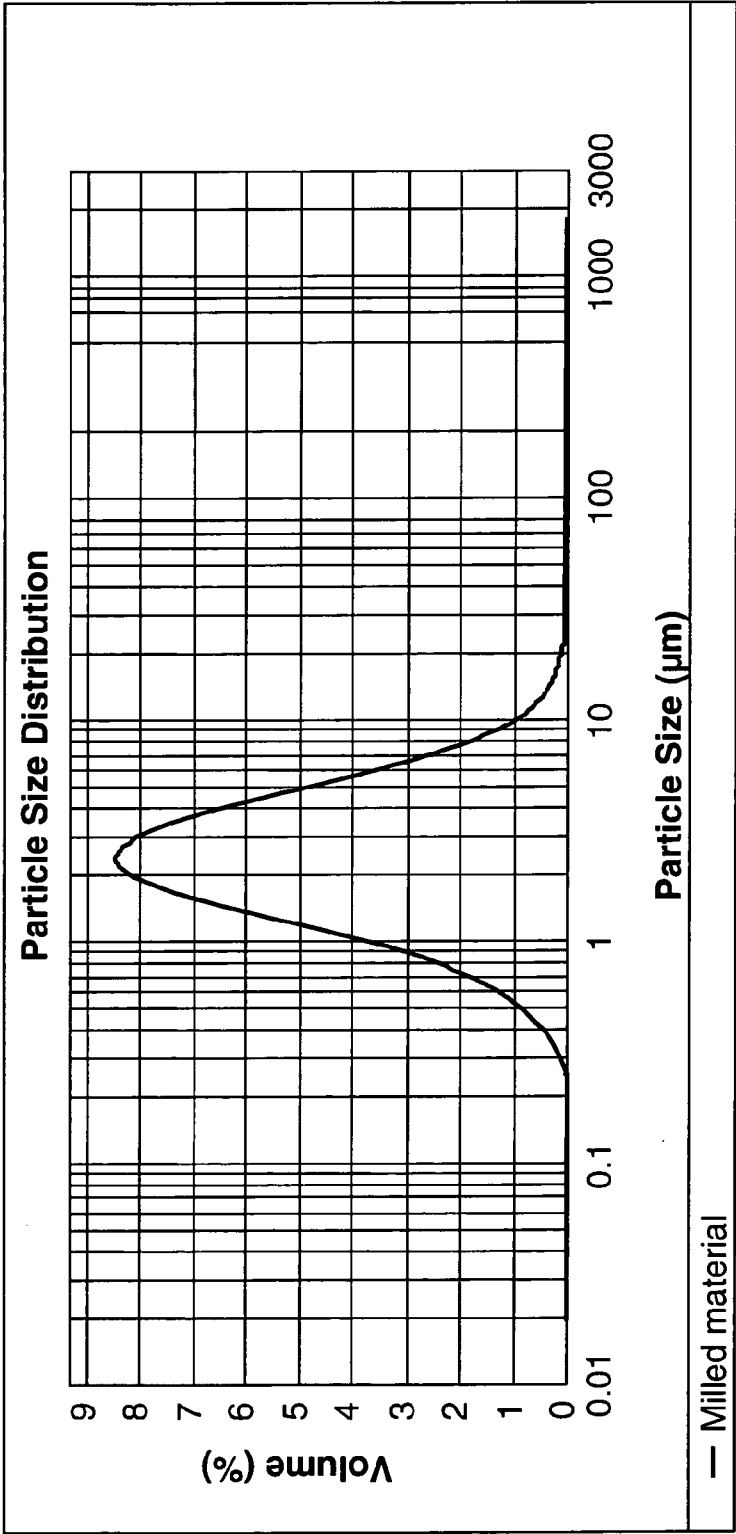


Figure 2: Particle size distribution of unmilled candesartan cilexetil material

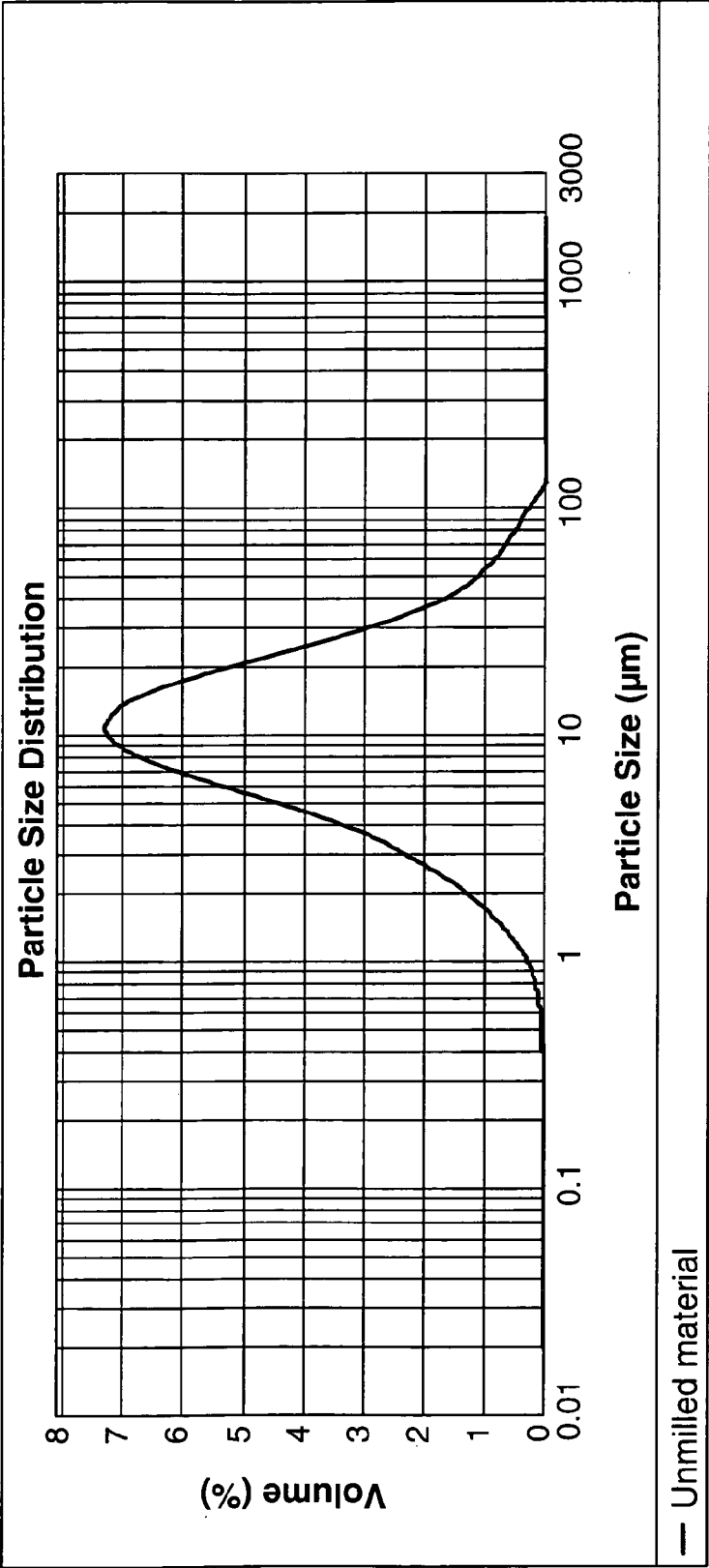


Figure 3: Microscopic picture of milled candesartan cilexetil material



Figure 4: Microscopic picture of unmilled candesartan cilexetil material

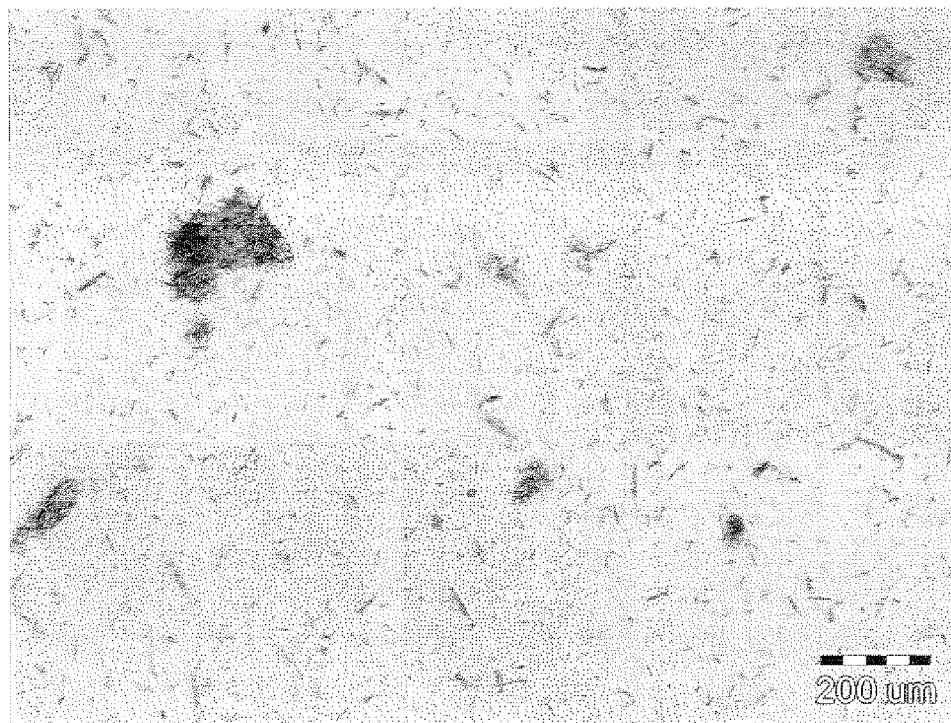
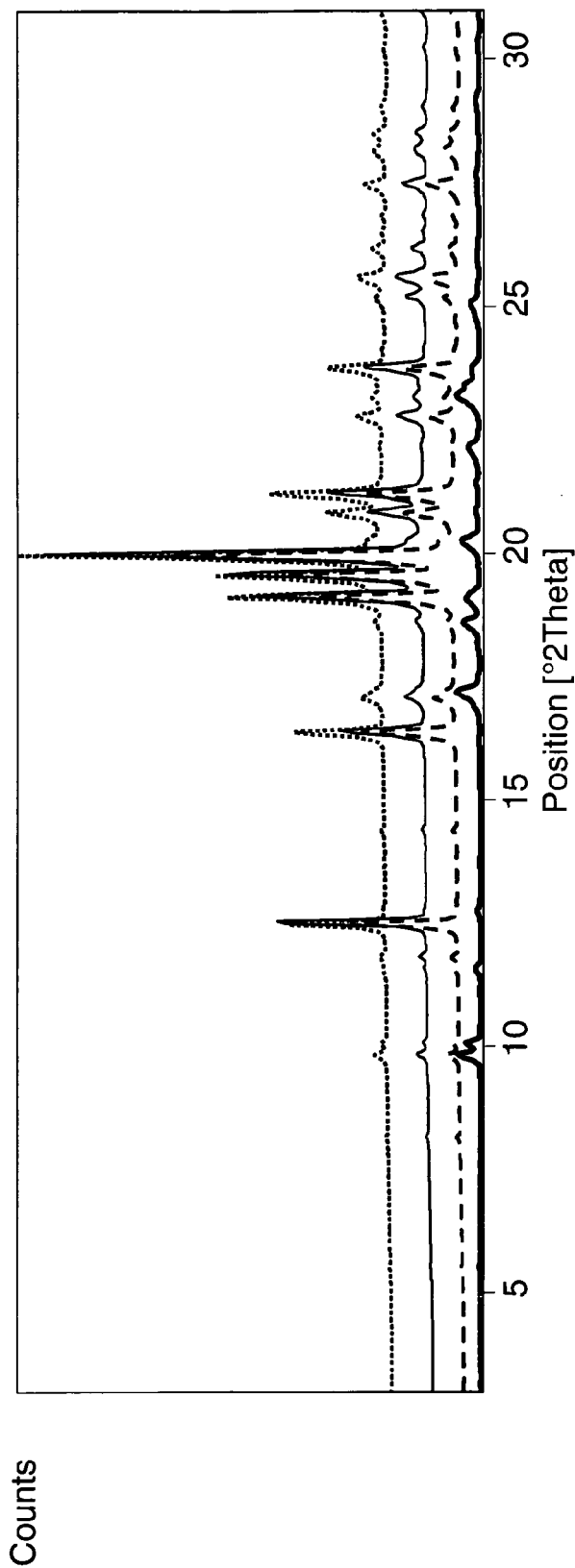


Figure 5: Comparison: Powder diffraction patterns of stable solid pharmaceutical compositions comprising candesartan cilexetil, and of candesartan cilexetil as pure substance, respectively.



- Stable solid pharmaceutical composition at initial time
- Stable solid pharmaceutical composition stored in a closed vessel at 40°C for 28 days
- Stable solid pharmaceutical composition stored in a closed vessel at 50°C for 28 days
- Candesartan cilexetil as pure substance