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(54) Title: SUBSTANTIALLY PURE MICRONIZED PARTICLES OF TELMISARTAN AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

(57) Abstract: The present invention provides micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof. Also provided are pharmaceutical compositions containing the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof.

SUBSTANTIALLY PURE MICRONIZED PARTICLES OF TELMISARTAN AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

PRIORITY

[0001] This application claims the benefit under 35 U.S.C. §119 to U.S. Provisional Application No. 60/697,153, filed July 7, 2005, and entitled "SUBSTANTIALLY PURE TELMISARTAN AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME" and to Indian Provisional Application 717/MUM/2005, filed June 20, 2005, and entitled "SUBSTANTIALLY PURE TELMISARTAN AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME", the contents of each of which are incorporated by reference herein.

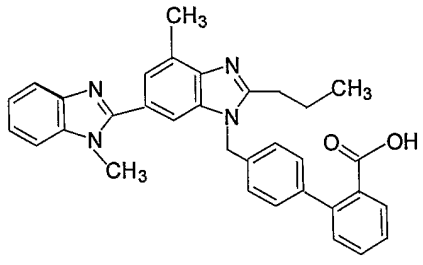
BACKGROUND OF THE INVENTION

1. Technical Field

[0002] The present invention generally relates to substantially pure micronized particles of telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof and pharmaceutical compositions containing same.

2. Description of the Related Art

[0003] Telmisartan, also known as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid, is represented by the structure of formula I.



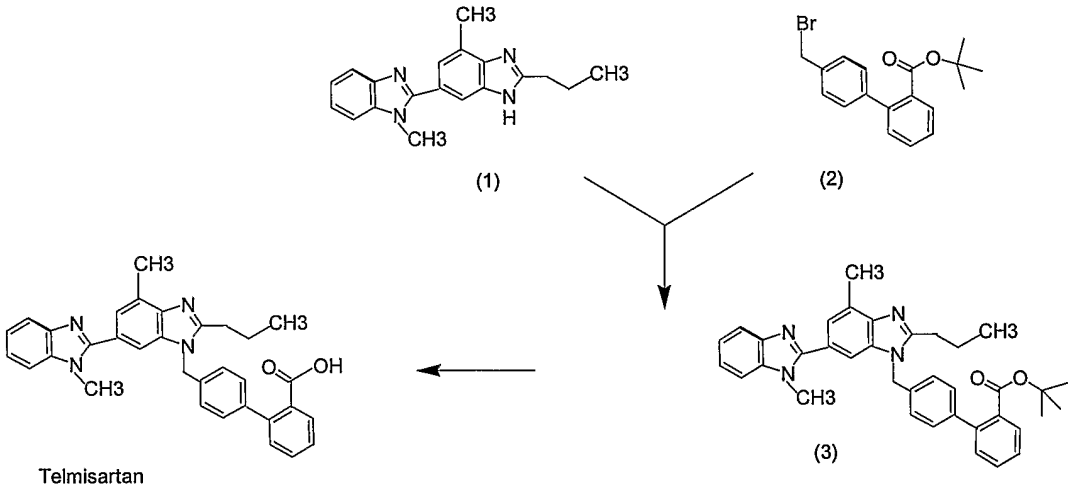
(I)

[0004] Generally, telmisartan is a non-peptide angiotensin II receptor (type AT_1) antagonist. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal

reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. Telmisartan is indicated for the treatment of hypertension. Telmisartan is sold under the trade name MICARDIS® (Boehringer Ingelheim KG CORPORATION).

[0005] U.S. Patent No. 5,591,762 ("the '762 patent") discloses a process for preparing telmisartan. The process disclosed in the '762 patent includes reacting 1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazole] (1) with 4'-(bromomethyl)[1,1'-biphenyl]-2-carboxylic acid 1,1-dimethylethyl ester (2) in a solvent optionally in the presence of an acid binding agent to produce the intermediate 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid 1,1-dimethylethyl ester (3) as generally shown in Scheme 1:

SCHEME 1



The intermediate is then hydrolyzed to provide telmisartan.

[0006] This process has been found to have several disadvantages in the commercial manufacture of a pharmaceutical composition. For example, this process is time consuming as column chromatography is required and consequently not as economical as the yield obtained is low. The process is also not eco friendly as the

effluent generated in this process is relatively high thereby resulting in a product with high organic volatile impurities.

[0007] There is an ever-present need in the pharmaceutical industry for improved pharmaceutical formulations that enhance the efficacy of poorly soluble therapeutic agents. There is especially a need for formulations that (1) enhance the absorption of poorly soluble therapeutic agents, and (2) extend the period of duration of effect of the therapeutic agents.

[0008] Accordingly, there remains a need for providing improved substantially pure, micronized particles of telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof having a relatively low content of organic volatile impurities.

SUMMARY OF THE INVENTION

[0009] In accordance with one embodiment of the present invention, substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof having an effective average particle size of less than about 300 microns is provided.

[0010] In accordance with a second embodiment of the present invention, substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof having an effective average particle size of less than about 100 microns is provided.

[0011] In accordance with a third embodiment of the present invention, substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof having an effective average particle size of less than about 60 microns is provided.

[0012] In accordance with a fourth embodiment of the present invention, substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof having an effective average particle size of less than about 15 microns is provided.

[0013] In accordance with a fifth embodiment of the present invention, a pharmaceutical composition is provided comprising substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof, having an effective average particle size of less than about 300 microns.

[0014] In accordance with a sixth embodiment of the present invention, a pharmaceutical composition is provided comprising substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof, having an effective average particle size of less than about 100 microns.

[0015] In accordance with a seventh embodiment of the present invention, a pharmaceutical composition is provided comprising substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof, having an effective average particle size of less than about 60 microns.

[0016] In accordance with an eighth embodiment of the present invention, a pharmaceutical composition is provided comprising substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof, having an effective average particle size of less than about 15 microns.

[0017] In accordance with a ninth embodiment of the present invention, substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof having a reduced level of organic impurities is provided. The reduced level of organic impurities is relative to the starting telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof.

[0018] In accordance with another embodiment of the present invention, substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof having a reduced level of at least one organic impurity selected from the group consisting of methylene dichloride, dimethyl formamide, methanol, triethyl amine and mixtures thereof is provided.

DEFINITIONS

[0019] The term "treating" or "treatment" of a state, disorder or condition as used herein means: (1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition, (2) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or (3) relieving the disease, i.e., causing

regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.

[0020] The term "therapeutically effective amount" as used herein means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated.

[0021] The term "delivering" as used herein means providing a therapeutically effective amount of an active ingredient to a particular location within a host causing a therapeutically effective blood concentration of the active ingredient at the particular location. This can be accomplished, e.g., by topical, local or by systemic administration of the active ingredient to the host.

[0022] The term "buffering agent" as used herein is intended to mean a compound used to resist a change in pH upon dilution or addition of acid of alkali. Such compounds include, by way of example and without limitation, potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dehydrate and other such material known to those of ordinary skill in the art.

[0023] The term "sweetening agent" as used herein is intended to mean a compound used to impart sweetness to a formulation. Such compounds include, by way of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

[0024] The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in granulations. Such compounds include, by way of example and without limitation, acacia alginic acid, tragacanth, carboxymethylcellulose sodium, poly (vinylpyrrolidone), compressible sugar (e.g., NuTab), ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch, combinations thereof and other material known to those of ordinary skill in the art.

[0025] When needed, other binders may also be included in the present invention. Exemplary binders include starch, poly(ethylene glycol), guar gum, polysaccharide, bentonites, sugars, invert sugars, poloxamers (PLURONIC™ F68, PLURONIC™ F127), collagen, albumin, celluloses in nonaqueous solvents, combinations thereof and the like. Other binders include, for example, poly(propylene glycol), polyoxyethylene-polypropylene copolymer, polyethylene ester, polyethylene sorbitan ester, poly(ethylene oxide), microcrystalline cellulose, poly(vinylpyrrolidone), combinations thereof and other such materials known to those of ordinary skill in the art.

[0026] The term "diluent" or "filler" as used herein is intended to mean inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of solid dosage formulations. Such compounds include, by way of example and without limitation, dibasic calcium phosphate, kaolin, sucrose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sorbitol, starch, combinations thereof and other such materials known to those of ordinary skill in the art.

[0027] The term "glidant" as used herein is intended to mean agents used in solid dosage formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Such compounds include, by way of example and without limitation, colloidal silica, calcium silicate, magnesium silicate, silicon hydrogel, cornstarch, talc, combinations thereof and other such materials known to those of ordinary skill in the art.

[0028] The term "lubricant" as used herein is intended to mean substances used in solid dosage formulations to reduce friction during compression of the solid dosage. Such compounds include, by way of example and without limitation, calcium stearate, magnesium stearate, mineral oil, stearic acid, zinc stearate, combinations thereof and other such materials known to those of ordinary skill in the art.

[0029] The term "disintegrant" as used herein is intended to mean a compound used in solid dosage formulations to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, starches such as corn starch, potato starch, pre-gelatinized and modified starched thereof, sweeteners, clays, such as bentonite,

microcrystalline cellulose (e.g. Avicel™), carsium (e.g. Amberlite™), alginates, sodium starch glycolate, gums such as agar, guar, locust bean, karaya, pectin, tragacanth, combinations thereof and other such materials known to those of ordinary skill in the art.

[0030] The term "wetting agent" as used herein is intended to mean a compound used to aid in attaining intimate contact between solid particles and liquids. Exemplary wetting agents include, by way of example and without limitation, gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, (e.g., TWEEN™s), polyethylene glycols, polyoxyethylene stearates colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxyl propylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton) is another useful wetting agent, combinations thereof and other such materials known to those of ordinary skill in the art.

[0031] Most of these excipients are described in detail in, e.g., Howard C. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, (7th Ed. 1999); Alfonso R. Gennaro et al., Remington: The Science and Practice of Pharmacy, (20th Ed. 2000); and A. Kibbe, Handbook of Pharmaceutical Excipients, (3rd Ed. 2000), which are incorporated by reference herein.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0032] The present invention is directed to substantially pure micronized particles of telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof. By "substantially pure" is meant telmisartan or pharmaceutically acceptable salt, ester or derivative thereof having a purity of greater than or equal to about 98%, preferably a purity of greater than or equal to about 99% and more preferably a purity of greater than or equal to about 99.5%. In another embodiment, the substantially pure telmisartan or a

pharmaceutically acceptable salt, ester or derivative thereof can have a relatively low content of one or more organic volatile impurities.

[0033] The micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof will have a particle size of less than or equal to about 300 microns, preferably less than or equal to about 100 microns, more preferably less than or equal to about 60 microns and even more preferably less than or equal to about 15 microns. In another embodiment, substantially pure telmisartan or pharmaceutically acceptable salts, esters or derivatives thereof have an effective average particle size of less than about 300 microns as measured by light-scattering methods or other methods accepted in the art. By "an effective average particle size of less than about 300 microns" it is meant that at least 50% of the drug particles have an average particle size of less than about 300 microns when measured by light scattering or other conventional techniques. Preferably, at least 70% of the drug particles have an average particle size of less than about 300 microns, more preferably at least 90% of the drug particles have an average particle size of less than about 300 microns, and even more preferably at least about 95% of the particles have a weight average particle size of less than about 300 microns.

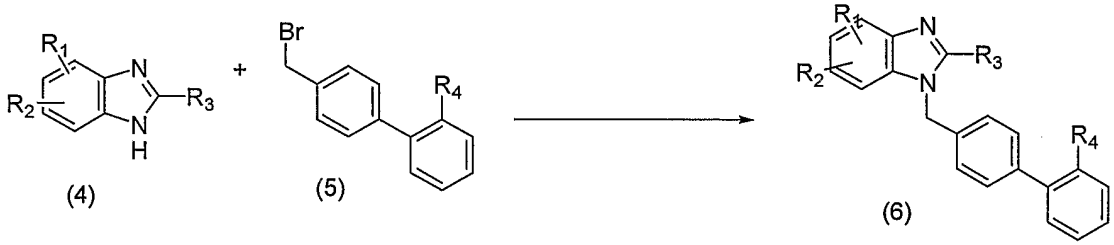
[0034] In another embodiment, substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof can have an effective average particle size of less than about 100 microns wherein the term "effective average particle size" is as defined above. In yet another embodiment, substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof can have an effective average particle size of less than about 60 microns wherein the term "effective average particle size" is as defined above. In still yet another embodiment, substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof can have an effective average particle size of less than about 15 microns wherein the term "effective average particle size" is as defined above.

[0035] The particle sizes of the telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof prepared according to the present invention can be obtained by controlling the process of particle size reduction such as, for example, by multi milling, to provide a finely divided powder, e.g., telmisartan having an effective average particle

diameter of less than about 300 microns, preferably less than about 100 microns, more preferably less than about 60 microns and even more preferably less than about 15 microns as discussed above.

[0036] In general, the substantially pure telmisartan or pharmaceutically acceptable salts, esters or derivatives thereof can be obtained, for example, via the intermediate of formula (6) as shown below. Generally, the intermediate of formula (6) can be prepared by coupling a compound of formula (4) with a compound of formula (5) in a water immiscible solvent and water, to produce a biphasic mixture, in the presence of an acid binding agent and a phase transfer catalyst to provide a compound of formula (6) as generally shown below in Scheme 2:

SCHEME 2



wherein R_1 in the 4-position is a halogen such as fluorine, chlorine or bromine atom, a C_{1-4} alkyl, a C_3-C_{12} cycloalkyl, fluoromethyl, difluoromethyl or trifluoromethyl group and R_2 represents a benzimidazol-2-yl group optionally substituted in the 1-position by the group R_a, wherein R_a denotes a substituted or unsubstituted C_{1-4} alkyl or a substituted or unsubstituted C_5-C_{30} aryl group; R_3 is a substituted or unsubstituted C_{1-5} alkyl, a substituted or unsubstituted C_{3-5} cycloalkyl group or a substituted or unsubstituted C_{1-3} alkoxy group and R_4 is a carboxylic acid ester, cyano, or a 1H-tetrazolyl group or a group which may be converted in vivo into a carboxy group.

[0037] The coupling of the compound of formula 4 with the compound of formula 5 is advantageously carried out in a biphasic solvent system. Generally, a biphasic solvent system includes at least an aqueous phase and a water-immiscible phase, e.g., water and a water-immiscible solvent. Water-immiscible solvents are generally those solvents which when allowed to stand and remain undisturbed, after being initially mixed with water, separate out into a distinct layer different from the water layer. The two layers (or phases)

are typically visible to the naked eye. Suitable water-immiscible solvents include, but are not limited to, halogenated hydrocarbon solvents, aromatic hydrocarbon solvents, aliphatic hydrocarbon solvents, ketone solvents, ether solvents, and the like and mixtures thereof. Exemplary water-immiscible solvents include, but are not limited to, methylene chloride toluene, methyl isobutyl ketone, tert-butyl methyl ether, heptane, cyclohexane, n-heptane, hexane, octanol, n-decane, decalene and mixtures thereof.

[0038] The term "phase transfer catalyst" refers to a small quantity of a chemical agent that enhances the rate of a reaction between chemical species located in different phases (immiscible liquids or solid and liquid) by extracting one of the reactants, most commonly an anion, across the interface into the other phase so that reaction can proceed. The catalyst cation is not consumed in the reaction although an anion exchange does occur. Suitable phase transfer catalysts for use herein include, but are not limited to, quaternary ammonium salts substituted with a residue such as a straight or branched alkyl group having 1 to about 18 carbon atoms, phenyl lower alkyl group including a straight or branched alkyl group having 1 to 6 carbon atoms which is substituted by an aryl group and phenyl group, e.g., tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium fluoride, tetrabutylammonium iodide, tetrabutylammonium hydroxide, tetrabutylammonium hydrogen sulfate, tributylmethylammonium chloride, tributylbenzylammonium chloride, tetrapentylammonium chloride, tetrapentylammonium bromide, tetrahexylammonium chloride, benzyldimethyloctylammonium chloride, methyltrihexylammonium chloride, benzylmethyloctadecanylammonium chloride, methyltridecanylammonium chloride, benzyltripropylammonium chloride, benzyltriethylammonium chloride, phenyltriethylammonium chloride, tetraethylammonium chloride, tetramethylammonium chloride and the like; phosphonium salts substituted with a residue such as a straight or branched alkyl group having 1 to about 18 carbon atoms, e.g., tetrabutylphosphonium chloride and the like; and pyridinium salts substituted with a straight or branched alkyl group having 1 to about 18 carbon atoms, e.g., 1-dodecanylpyridinium chloride and the like.

[0039] Among these phase transfer catalysts, quaternary ammonium salts substituted with a straight or branched alkyl group having 1 to about 18 carbon atoms such

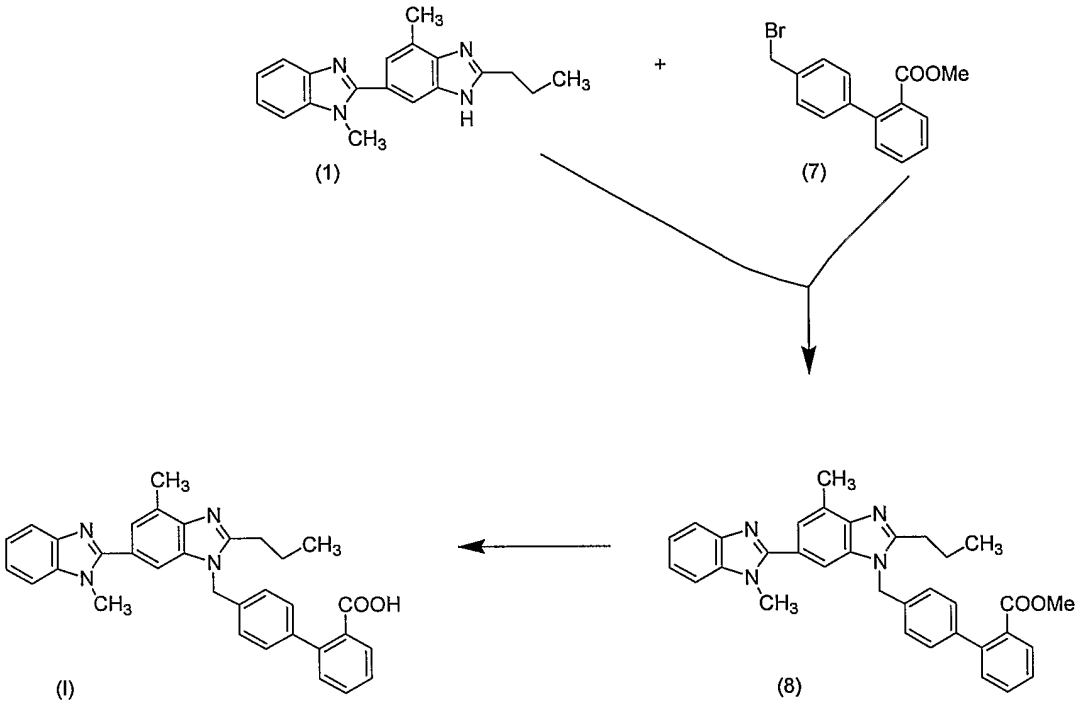
forming ions in these salts, hydroxyl ion, hydrogen sulfate ion and halogen ions are preferred, among which the chlorine ion is particularly preferred. If desired, sodium sulfite or the like may be added to the reaction system of the above-mentioned reaction for the purpose of preventing the coloration caused by oxidation. tetrabutyl ammonium bromide, tetrabutyl ammonium hydroxide, tetramethyl ammonium iodide, tetrabutyl ammonium sulfate and the like and mixtures thereof. Generally, the amount of the phase transfer catalyst employed can range from about 1% w/w to about 10% w/w and preferably from about 5% w/w to about 10% w/w.

[0040] The temperature of the reaction will ordinarily range from about 20°C to about 50°C. The time period for the reaction can range from about 2 hours to about 10 hours. The compound of formula 5 will ordinarily be present in an amount ranging from about 1 to about 1.5 moles per mole of the compound of formula 4 and preferably from about 1 to about 1.1 moles per mole of the compound of formula 4.

[0041] If desired, the reaction can be carried out in the presence of an acid binding agent. Suitable acid binding agents include, but are not limited to, alkali metal hydroxide, e.g., sodium hydroxide and potassium hydroxide, alkali metal carbonate, e.g., sodium carbonate, and the like and mixtures thereof. Generally, the acid binding agent can be employed in suitable amounts as can be determined by one skilled in the art. For example, the acid binding agent can be present in an amount ranging from about 1 molar equivalent to about 5 molar equivalent per equivalent of the compound of formula 5.

[0042] In another embodiment, substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof can be obtained by reacting 1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazole] (1) with methyl 4'-(bromomethyl)[1,1'-biphenyl]-2-carboxylate (7) in a water immiscible solvent and water, to produce a biphasic mixture, in the presence of an acid binding agent and a phase transfer catalyst to provide the intermediate methyl 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylate (8) followed by hydrolysis with one or more alkali metal hydroxides in an alcohol/water mixture to provide telmisartan of formula I as generally shown below in Scheme 3:

SCHEME 3



[0043] Following the formation of the foregoing intermediate of either formula (6) or (8), the intermediate can then be converted to telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof by techniques well known in the art. The expression "pharmaceutically acceptable salt or ester" is meant those salts or esters which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use. Representative acid additions salts include the hydrochloride, hydrobromide, sulphate, bisulphate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, mesylate, citrate, malate, maleate, fumarare, succinate, tartrate, ascorbate, glucoheptonate, lactobionate, lauryl sulphate salts and the like. Representative alkali or alkaline earth metal salts include the sodium, calcium, potassium and magnesium salts, and the like. For example, the intermediate can be hydrolyzed wherein hydrolysis is carried out in the presence of a base such as, for example, one or more alkali metal hydroxides and/or carbonates, e.g., sodium hydroxide, potassium hydroxide, potassium carbonate, and the like, and in a suitable solvent. Useful

solvents include, but are not limited to, water, alcohol, e.g., methanol, ethanol, isopropanol, etc., and the like and mixtures thereof, e.g., water/methanol. Hydrolysis can be carried out at a temperature ordinarily ranging from about 50°C to about 70°C.

[0044] The term "derivative" as used herein refers to any substance which is sufficiently structurally similar to the material which it is identified as a derivative so as to have substantially similar functionality or activity, for example, therapeutic effectiveness, as the material when the substance is used in place of the material. The functionality of any derivative disclosed herein may be determined using conventional routine methods well known to persons of ordinary skill in the art.

[0045] The telmisartan or pharmaceutically acceptable salt, ester or derivative thereof thus obtained can then be purified to provide a substantially pure compound. In one embodiment, telmisartan can be purified by at least dissolving telmisartan in a water-immiscible solvent follow by the addition of a suitable base and then the addition of a suitable acid. A suitable water-immiscible solvent can be a halogenated hydrocarbon solvent, e.g., methylene chloride or ethylene dichloride, a lower alcohol, e.g., methanol, ethanol or isopropanol, and the like and mixtures thereof. A suitable base includes, but is not limited to, a nitrogen-containing base, e.g., ammonia (gas or aqueous solution), triethyl amine, diisopropyl amine, dimethyl amine, monomethyl amine (gas or aqueous solution) or diisopropyl ethyl amine; an alkali metal hydroxide, e.g., sodium hydroxide or potassium hydroxide; a sodium alcoholate, e.g., sodium methoxide, sodium ethoxide or sodium isopropxide; and the like and mixtures thereof. Suitable acids include, but are not limited to, acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid and the like and mixtures thereof. If desired, the purification step can be carried out one or more times. The telmisartan or pharmaceutically acceptable salt, ester or derivative thereof thus obtained is provided in relatively high purity as discussed above and also having a relatively low content of one or more organic volatile impurities.

[0046] The micronized particles of the substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of the present invention may then be formulated into a pharmaceutical composition or dosage form. Such pharmaceutical compositions may be administered to a mammalian patient in any dosage form, e.g., liquid, powder, elixir, injectable solution, etc. Dosage forms may be adapted

for administration to the patient by oral, buccal, parenteral, ophthalmic, rectal and transdermal routes. Oral dosage forms include, but are not limited to, tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of the present invention also may be administered as suppositories, ophthalmic ointments and suspensions, and parenteral suspensions, which are administered by other routes. The dosage forms may contain the telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of the present invention as is or, alternatively, as part of a composition. The pharmaceutical compositions may further contain one or more pharmaceutically acceptable excipients as described herein.

[0047] Capsule dosages will contain the telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of the present invention within a capsule which may be coated with gelatin. Tablets and powders may also be coated with an enteric coating. The enteric-coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated capsule or tablet may have a coating on the surface thereof or may be a capsule or tablet comprising a powder or granules with an enteric-coating.

[0048] Tableting compositions may have few or many components depending upon the tableting method used, the release rate desired and other factors. For example, the compositions of the present invention may contain diluents such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents such calcium carbonate and calcium diphosphate and other diluents known to one of ordinary skill in the art. Yet other suitable diluents include waxes, sugars (e.g. lactose) and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

[0049] Other excipients contemplated by the present invention include binders such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes; disintegrants such as sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others; lubricants such as magnesium stearate, calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

[0050] Actual dosage levels of the telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of the present invention in the compositions of the invention may be varied to obtain an amount of telmisartan or pharmaceutically acceptable salt, ester or derivative thereof that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon such factors as, for example, the desired therapeutic effect, the route of administration, the desired duration of treatment, and other factors. The total daily dose of the compounds of this invention administered to a host in single or divided dose and can vary widely depending upon a variety of factors including, for example, the body weight, general health, sex, diet, time and route of administration, rates of absorption and excretion, combination with other drugs, the severity of the particular condition being treated, etc.

[0051] The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the claims.

Experimental

[0052] The purity was measured by high performance liquid chromatography under the following conditions:

Apparatus: A High Performance Liquid Chromatograph equipped with quaternary gradient pumps, variable wavelength UV detector attached with data recorder and integrator software.

Column: Superspher 100, RP-18e, 125 x 4 mm, 4 μm (Merk)

Column temperature: 40°C

Moving phase:

Solution A: 2 grams potassium dihydrogen phosphate and 3.8 grams of sodium pentane sulphonate monohydrate in water and diluted to 1000 ml with water. Adjust pH to 3 with dilute phosphoric acid, if necessary

Solution B: Methanol: Acetonitrile (200:800 v/v)

Mobile Phase:

Solution A: 2 grams potassium dihydrogen phosphate and 3.8 grams of sodium pentane sulphonate monohydrate were dissolved in water and dilute to 1000mL with water. Adjust pH to 3 with dilute phosphoric acid.

Solution B: Methanol: Acetonitrile (200: 800 v/v)

Detector: UV, 230 nm

Flow rate: 1.0 ml/min.

Injection Volume: 10µL

Retention time: about 9.9 min

[0053] The level of organic impurities were measured under the following conditions:

Instrument:	Gas chromatograph equipped with FID detector and headspace.
Instrument:	Agilent 6890 plus gas chromatograph equipped with FID detector and Gerstel Headspace.
Column:	Rtx-624, 75 m x 0.53 mm ID, 3 µm
Column Temp.:	40°C (hold for 10 minutes) to 240°C @ 20°C/minute, hold at 240°C for 5 minutes
Injector/detector:	250°C/300°C
Carrier gas:	Nirogen @ 30cm/sec, linear velocity
Split Ratio:	(2:1)

Head Space Parameters:

Incubation Temperature:	95°C
Incubation Time:	30 minutes
Agitation Speed:	600 rpm
Syringe Temperature:	115°C
Injection Volume:	1 ml

EXAMPLE 1

[0054] Preparation of Methyl 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylate

[0055] 1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazole] (40 g) in methyl isobutyl ketone ("MIBK", 160 ml) was placed in a vessel and a potassium hydroxide solution (36.8 g KOH in 200 ml water) was added. Methyl 4'-(bromomethyl)[1,1'-biphenyl]-2-carboxylate (44 g) and tert-butyl ammonium bromide (4 g) were added. The reaction mixture was stirred for 2 hours at 25 – 30°C and then filtered and washed with MIBK (40 ml). The material was dried at 60 – 65°C.

Dry wt. 78 grams

[0056] Preparation of Telmisartan

[0057] Methyl 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylate (45 g) in methanol (225 ml) were charged to a reaction vessel. A potassium hydroxide solution (19 g KOH in 55 ml water) was added and the reaction mass was heated to reflux for 3 hours. The reaction mass was cooled to 25°C and the pH was adjusted to 6 using dilute HCl. The solid obtained was filtered and dried (37 g). The dried solid was taken in a combination of dichloromethane and methanol (8 vol. to 2 vol). The insolubles were filtered and the reaction mass was concentrated in methylene dichloride and the solid was isolated from methanol. The isolated solid was dried, charged in N,N'-dimethyl formamide (150 ml) and heated to provide a clear solution. The solution was filtered and a clear filtrate was obtained and cooled to remove precipitate of product. The product was filtered and dried.

Dry wt. 29 grams

HPLC purity- 99.6%

[0058] Purification to reduce organic volatile impurities

[0059] The solid obtained was dried and taken in a mixture of (1:1) methanol:water and dissolved by addition of triethylamine, charcoalized and precipitated by addition of acetic acid. The obtained solid was filtered, washed with water and dried to provide pure telmisartan having reduced level of organic volatile impurities and reduced particle size.

HPLC Purity -99.6%

The level of organic volatile impurities are as follows:

Methylene dichloride - Less than about 25 parts per million (ppm)

Dimethyl formamide - Less than about 25 ppm

Methanol - Less than about 25 ppm

Triethyl Amine - Less than about 150 ppm

Overall level of organic volatile impurities: less than 500 ppm

EXAMPLE 2

[0060] Reduction of particle size and particle size distribution of Telmisartan

[0061] Telmisartan obtained from Example 1 was fine-milled by being passed through a multi mill at a rotation rate of 750 to 1500 rotations per minute (RPMs) and a feed rate of 15 to 25 kg/hr to where 90% of the telmisartan particles had a diameter of about 100 microns and the remaining 10% of the telmisartan particles had a diameter below 100 microns.

EXAMPLE 3

[0062] Reduction of particle size and particle size distribution of Telmisartan

[0063] Telmisartan obtained from Example 1 was micronized by being passed through an air jet mill at a feed rate of 1 kg/hr, a feed air pressure of 6 kg, a grinding air pressure of 4 kg to where 90% of the telmisartan particles have a diameter of less than about 15 microns.

[0064] It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the features and advantages appended hereto.

WHAT IS CLAIMED IS:

1. Substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof having an effective average particle size of less than about 300 microns.

2. The substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof of Claim 1, having a purity of greater than or equal to about 98%.

3. The substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof of Claim 1, having a purity of greater than or equal to about 99%.

4. The substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof of Claim 1, having a purity of greater than or equal to about 99.5%.

5. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, having an effective average particle size of less than about 100 microns.

6. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, having an effective average particle size of less than about 60 microns.

7. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, having an effective average particle size of less than about 15 microns.

8. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 50% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 300 microns.

9. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 70% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 300 microns.

10. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 90% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 300 microns.

11. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 95% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 300 microns.

12. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 50% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 100 microns.

13. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 70% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 100 microns.

14. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 90% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 100 microns.

15. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 95% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 100 microns.

16. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 50% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 60 microns.

17. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 70% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 60 microns.

18. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 90% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 60 microns.

19. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 95% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 60 microns.

20. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 50% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 15 microns.

21. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 70% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 15 microns.

22. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 90% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 15 microns.

23. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-4, wherein at least about 95% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 15 microns.

24. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-23, further characterized by having a reduced level of one or more organic impurity relative to the starting telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof.

25. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 1-23, further characterized by having a reduced level of at least one impurity selected from the group consisting of methylene dichloride, dimethyl formamide, methanol, triethyl amine and mixtures thereof.

26. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claims 24 and 25, having less than or equal to about 25 parts per million (ppm) of methylene dichloride, less than or equal to about 25 ppm of dimethyl formamide, less than or equal to about 25 ppm of methanol and less than or equal to about 150 ppm of triethyl amine.

27. A pharmaceutical composition comprising a therapeutically effective amount of micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof, wherein the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 300 microns.

28. The pharmaceutical composition of Claim 27, wherein the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 100 microns.

29. The pharmaceutical composition of Claim 27, wherein the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 60 microns.

30. The pharmaceutical composition of Claim 27, wherein the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 15 microns.

31. The pharmaceutical composition of Claim 27, wherein at least about 50% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 300 microns.

32. The pharmaceutical composition of Claim 27, wherein at least about 70% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 300 microns.

33. The pharmaceutical composition of Claim 27, wherein at least 90% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 300 microns.

34. The pharmaceutical composition of Claim 27, wherein at least 95% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 300 microns.

35. The pharmaceutical composition of Claim 27, wherein at least about 50% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 100 microns.

36. The pharmaceutical composition of Claim 27, wherein at least about 70% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 100 microns.

37. The pharmaceutical composition of Claim 27, wherein at least 90% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 100 microns.

38. The pharmaceutical composition of Claim 27, wherein at least 95% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 100 microns.

39. The pharmaceutical composition of Claim 27, wherein at least about 50% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 60 microns.

40. The pharmaceutical composition of Claim 27, wherein at least about 70% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 60 microns.

41. The pharmaceutical composition of Claim 27, wherein at least 90% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 60 microns.

42. The pharmaceutical composition of Claim 27, wherein at least 95% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 60 microns.

43. The pharmaceutical composition of Claim 27, wherein at least about 50% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an effective average particle size of less than about 15 microns.

44. The pharmaceutical composition of Claim 27, wherein at least about 70% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 15 microns.

45. The pharmaceutical composition of Claim 27, wherein at least 90% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 15 microns.

46. The pharmaceutical composition of Claim 27, wherein at least 95% of the micronized particles of substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof have an average particle size of less than about 15 microns.

47. The pharmaceutical composition of Claims 27-46, wherein the substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof has a purity of greater than or equal to about 98%.

48. The pharmaceutical composition of Claims 27-46, wherein the substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof has a purity of greater than or equal to about 99%.

49. The pharmaceutical composition of Claims 27-46, wherein the substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof has a purity of greater than or equal to about 99.5%.

50. The pharmaceutical composition of Claims 27-46, wherein the substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof has a reduced level of one or more organic impurity relative to the starting telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof.

51. The pharmaceutical composition of Claims 27-46, wherein the substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof has a reduced level of at least one impurity selected from the group consisting of methylene dichloride, dimethyl formamide, methanol, triethyl amine and mixtures thereof.

52. The pharmaceutical composition of Claims 50 and 51, wherein the substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof has less than or equal to about 25 parts per million (ppm) of methylene dichloride, less than or equal to about 25 ppm of dimethyl formamide, less than or equal to about 25 ppm of methanol and less than or equal to about 150 ppm of triethyl amine.

53. The pharmaceutical composition of Claims 27-52, further comprising at least one pharmaceutically acceptable excipient.

54. The pharmaceutical composition of Claims 27-53, which is a tablet or capsule.

55. The pharmaceutical composition of Claims 27-53, in the form of a powder suspension in a liquid.

56. Substantially pure telmisartan or a pharmaceutically acceptable salt, ester or derivative thereof and having a reduced level of organic impurities.

57. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claim 56, wherein the reduced level of at least one impurity is selected from the group consisting of methylene dichloride, dimethyl formamide, methanol, triethyl amine and mixtures thereof.

58. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claim 56, having less than or equal to about 25 parts per million (ppm) of methylene dichloride, less than or equal to about 25 ppm of dimethyl formamide, less than or equal to about 25 ppm of methanol and less than or equal to about 150 ppm of triethyl amine.

59. The substantially pure telmisartan or pharmaceutically acceptable salt, ester or derivative thereof of Claim 57, having less than or equal to about 25 parts per million (ppm) of methylene dichloride, less than or equal to about 25 ppm of dimethyl formamide, less than or equal to about 25 ppm of methanol and less than or equal to about 150 ppm of triethyl amine.