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(54) **Title:** NOVEL POLYMORPHS OF PERINDOPRIL ERBUMINE

(57) **Abstract:** Disclosed herein is a novel stable polymorph of perindopril erbumine, designated polymorph Form Theta (θ). Also disclosed is a process for its preparation and pharmaceutical compositions containing same.

NOVEL POLYMORPH OF PERINDOPRIL ERBUMINE

PRIORITY

[0001] This application claims the benefit under 35 U.S.C. §119 to Indian Provisional Application No. 1769/MUM/2006, filed on October 26, 2006, and entitled "NOVEL POLYMORPH OF PERINDOPRIL ERBUMINE", the contents of which are incorporated by reference herein.

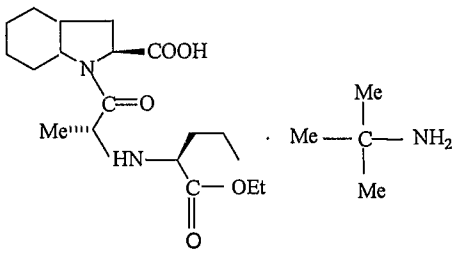
BACKGROUND OF THE INVENTION

1. Technical Field

[0002] The present invention generally relates to a novel polymorphic form of perindopril erbumine, process for its preparation and pharmaceutical compositions containing same.

2. Description of the Related Art

[0003] Perindopril erbumine, also known as (2S,3μS,7μS)-1-[(S)-N-[(S)-1-carboxy-butyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, with tert-butylamine (1:1), is represented by the structure of Formula I:



(I).

The tert-butylamine salt of perindopril, also known as perindopril erbumine, is the form commercially sold under the trade name Aceon®. Perindopril is the free acid form of perindopril erbumine and is an ethyl ester of a non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor. Perindopril is a pro-drug and is metabolized in vivo by hydrolysis of the ester group to form perindoprilat, the biologically active metabolite. Perindopril is ordinarily used to treat hypertension. Perindopril erbumine is also known as an ACE inhibitor used in the treatment of hypertension.

[0004] It is believed that perindoprilat lowers blood pressure primarily through inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyzes conversion of the inactive decapeptide, angiotensin I, to the vasoconstrictor, angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor, which stimulates aldosterone secretion by the adrenal cortex, and provides negative feedback on renin secretion. Inhibition of ACE results in decreased plasma angiotensin II, leading to decreased vasoconstriction, increased plasma renin activity and decreased aldosterone secretion. The latter results in diuresis and natriuresis and may be associated with a small increase of serum potassium.

[0005] Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as different solubility profiles, different melting point temperatures and/or different x-ray diffraction peaks. Since the solubility of each polymorph may vary, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predicable solubility profiles. It is desirable to investigate all solid state forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as, infrared spectrometry. Additionally, polymorphic forms of the same drug substance or active pharmaceutical ingredient, can be administered by itself or formulated as a drug product (also known as the final or finished dosage form), and are well known in the pharmaceutical art to affect, for example, the solubility, stability, flowability, tractability and compressibility of drug substances and the safety and efficacy of drug products. There is an ongoing need for new or purer polymorphic forms of existing drug molecules for improved drug formulations.

[0006] Various polymorphic forms of perindopril erbumine are known. See, e.g., U.S. Patent Application Publication Nos. 20030158121 and 20040029813. However, a problem associated with various known polymorphic forms of perindopril erbumine is that they can be relatively unstable over an appreciable period of time thereby resulting in the polymorphs being difficult to handle and formulate.

[0007] Accordingly, the skilled person will appreciate that, if a drug can be readily obtained in a stable crystalline form, the above problem may be solved. Thus, in the manufacture of commercially viable, and pharmaceutically acceptable, drug compositions, it is important, wherever possible, to provide drug in a substantially crystalline, and stable, form. It is to be noted, however, that this goal is not always achievable. Typically, it is not possible to predict, from molecular structure alone, what the crystallization behavior of a compound, either as such or in the form of a salt, will be. The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product such as stability. It also adds to the material that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. A new polymorphic form of perindopril erbumine has now been discovered.

SUMMARY OF THE INVENTION

[0008] In accordance with one embodiment of the present invention, perindopril erbumine in polymorph Form Theta (θ) is provided.

[0009] In accordance with a second embodiment of the present invention, perindopril erbumine in polymorph Form Theta (θ) and having a powder X-ray diffraction (XRD) pattern comprising a characteristic peak (expressed in degrees $2\theta \pm 0.2°\theta$) at about 20.46 is provided.

[0010] In accordance with a third embodiment of the present invention, perindopril erbumine in polymorph Form Theta (θ) and having a powder XRD pattern comprising characteristic peaks (expressed in degrees $2\theta \pm 0.2°\theta$) at approximately one or more of the positions: about 9.45, about 18.20 and/or about 20.46 is provided.

[0011] In accordance with a fourth embodiment of the present invention, perindopril erbumine in polymorph Form Theta (θ) characterized by having at least one physical measurement selected from the group consisting of: a powder XRD pattern substantially in accordance with Figure 1, a Raman spectrum containing peaks at about 541.1 cm^{-1}, about 551.2 cm^{-1}, about 858.7 cm^{-1}, about 881.1 cm^{-1} and about 898.2 cm^{-1} and/or a ^{13}C solid state NMR spectrum substantially in accordance with Figure 2 is provided.

[0012] In accordance with a fifth embodiment of the present invention, a pharmaceutical composition is provided comprising a therapeutically effective amount of perindopril erbumine in polymorph Form Theta (θ).

[0013] In accordance with a sixth embodiment of the present invention, a process for preparing perindopril erbumine in polymorph Form Theta (θ) is provided comprising (a) heating a solution comprising perindopril erbumine in 1,4-dioxane at a temperature greater than or equal to about 50°C and (b) cooling and isolating perindopril erbumine in polymorph Form Theta (θ).

[0014] In accordance with a seventh embodiment of the present invention, a method of treatment is provided comprising administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of perindopril erbumine in polymorph Form Theta (θ).

[0015] The novel polymorphic form of perindopril erbumine of the present invention is generally easy to reproduce and believed to be easier to handle due to increased stability than various known polymorphic forms of perindopril erbumine.

DEFINITIONS

[0016] 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.

[0017] 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.

[0018] The term "delivering" as used herein means providing a therapeutically effective amount of an active ingredient to a particular location within a host means 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.

[0019] The term "subject" or "a patient" or "a host" as used herein refers to , mammalian animals, preferably human.

[0020] The term "stability" as used herein refers to chemical stability and solid state stability.

[0021] The term "chemical stability" as used herein means that the polymorph can be stored in an isolated form with an insignificant degree of chemical degradation or decomposition.

[0022] The term "solid state stability" as used herein means the polymorph can be stored in an isolated solid form with an insignificant degree of solid state transformation (e.g., crystallization, recrystallization, solid state phase transition, hydration, dehydration, solvatisation or desolvatisation).

[0023] Examples of "normal storage conditions" include temperatures of between minus 5 and plus 50°C and preferably between 0 and 40°C.

[0024] 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.

[0025] The term "sweetening agent" as used herein is intended to mean a compound used to impart sweetness to a preparation. 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.

[0026] The term "binders" as used herein is intended to mean substances used to cause adhesion of powder particles in tablet 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.

[0027] 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.

[0028] 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 tablets and capsules. 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.

[0029] The term "glidant" as used herein is intended to mean agents used in tablet and capsule 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.

[0030] The term "lubricant" as used herein is intended to mean substances used in tablet formulations to reduce friction during tablet compression. 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.

[0031] The term "disintegrant" as used herein is intended to mean a compound used in solid dosage forms 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.

[0032] 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,

polyvinylpyrrolidone (PVP), tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type, also known as superinone or triton), combinations thereof and other such materials known to those of ordinary skill in the art.

[0033] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0034] Figure 1 is a characteristic powder X-ray diffraction (XRD) pattern of perindopril erbumine in polymorph Form Theta (θ).

[0035] Figure 2 is a ^{13}C solid state NMR spectrum of perindopril erbumine in polymorph Form Theta (θ).

[0036] Figure 3 is a characteristic powder XRD pattern of perindopril erbumine in polymorph Form Theta (θ) after storage for five months.

[0037] Figure 4 is a characteristic powder XRD pattern of perindopril erbumine in polymorph Form Theta (θ) of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0038] One embodiment of the present invention is directed to a novel polymorph form of perindopril erbumine, designated polymorph Form Theta (θ). In one embodiment, the present invention provides perindopril erbumine in polymorph Form Theta (θ) of characterized as having a characteristic peak (expressed in degrees 2θ ± 0.2°θ) at about 20.46. In another embodiment, the present invention provides perindopril erbumine in polymorph Form Theta (θ) characterized as having characteristic peaks (expressed in degrees 2θ ± 0.2°θ) at approximately one or more of the positions: about 9.45 and about 20.46. In another embodiment, the present invention provides perindopril erbumine in polymorph Form Theta (θ) characterized as having characteristic peaks (expressed in degrees 2θ ± 0.2°θ) at approximately one or more of the positions: about 9.45, about 18.20 and about 20.46.

[0039] In yet another embodiment, the perindopril erbumine in polymorph Form Theta (θ) can be characterized by having at least one, and preferably all, of the following properties: (a) an XRD substantially in accordance with Figures 1 or 4; and/or (b) a Raman spectrum containing peaks at about 541.1 cm^{-1}, about 551.2 cm^{-1}, about 858.7 cm^{-1}, about 881.1 cm^{-1} and about 898.2 cm^{-1}; and/or (c) a ^{13}C solid state NMR spectrum substantially in accordance with Figure 2.

[0040] Perindopril erbumine in polymorph Form Theta (θ) can be obtained by at least (a) heating a solution comprising perindopril erbumine in 1,4-dioxane at a temperature greater than or equal to about 50°C, and preferably greater than or equal to about 75°C; and (b) cooling and isolating perindopril erbumine in polymorph Form Theta (θ). In one embodiment, the solution of perindopril erbumine in 1,4-dioxane can be heated at a temperature ranging from about 50°C to about 150°C and preferably about 50°C to about 100°C. Generally, the heated solution will be cooled to a temperature and for a time period sufficient to crystallize the polymorph of the present invention. Preferably, the solution of perindopril erbumine in 1,4-dioxane is prepared by heating at a temperature greater than about 50°C and cooling the solution gradually until crystallization is complete. If desired, the solution may be seeded with theta (θ) crystalline form of perindopril erbumine.

[0041] Perindopril erbumine in polymorph Form Theta (θ) obtained from the processes of the present invention will be in relatively high purity, e.g., a purity greater than or equal to about 95% and preferably greater than or equal to about 99%, as measured by HPLC.

[0042] Another embodiment of the present invention relates to pharmaceutical compositions containing a therapeutically effective amount of perindopril erbumine in polymorph Form Theta (θ) of the present invention. 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, transdermal routes and the like. Oral dosage forms include, but are not limited to, tablets, pills, capsules, troches, sachets, suspensions, powders, lozenges, elixirs and the like. The perindopril erbumine in polymorph Form Theta (θ) disclosed herein also may be administered as suppositories,

ointments and suspensions, and parenteral suspensions, which are administered by other routes. However, all modes of administrations are contemplated, e.g., orally, rectally, parenterally, intranasally and topically. The most preferred route of administration of the novel perindopril erbumine in polymorph Form Theta (θ) disclosed herein is oral. The dosage forms may contain the novel perindopril erbumine in polymorph Form Theta (θ) disclosed herein as is or, alternatively, may contain perindopril erbumine in polymorph Form Theta (θ) disclosed herein as part of a composition.

[0043] The pharmaceutical compositions containing a therapeutically effective amount of perindopril erbumine in polymorph Form Theta (θ) can be combined with, for example, one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants in accordance with known and established practice. Suitable excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field, e.g., the buffering agents, sweetening agents, binders, diluents, fillers, lubricants, wetting agents and disintegrants described hereinabove.

[0044] Capsule dosages will contain the novel perindopril erbumine in polymorph Form Theta (θ) disclosed herein within a capsule which may be coated with, for example, gelatin. Tablets and powders may also be coated with, e.g., an enteric coating. The enteric coated powder forms may have coatings containing at least phthalic acid cellulose acetate, hydroxypropylmethyl cellulose phthalate, polyvinyl alcohol phthalate, carboxy methyl ethyl cellulose, 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.

[0045] 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. The tablets can be prepared according to known tableting procedures, e.g., wet granulation, dry granulation, etc.

[0046] Actual dosage levels of the novel polymorph of perindopril erbumine of the present invention may be varied to obtain an amount of the novel polymorph of perindopril erbumine of the present invention 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. The pharmaceutical compositions herein can be formulated in any release form, e.g., immediate release, sustained release, controlled release, etc.

[0047] In one embodiment, the novel polymorph of perindopril erbumine disclosed herein for use in the pharmaceutical compositions of the present invention can have a D_{50} and D_{90} particle size of less than about 300 microns, preferably less than about 200 microns, more preferably less than about 100 microns, still more preferably less than about 50 microns and most preferably less than about 20 microns. It is noted the notation D_x means that X% of the particles have a diameter less than a specified diameter D. Thus, a D_{50} of about 300 microns means that 50% of the micronized particles in a composition have a diameter less than about 300 microns. The term "micronization" used herein means any process or methods by which the size of the particles is reduced. For example, the particle sizes of the novel polymorph of perindopril erbumine of the present invention can be obtained by any milling, grinding, micronizing or other particle size reduction method

known in the art to bring the solid state form of the novel polymorph of perindopril erbumine of the present invention into any of the foregoing desired particle size range.

[0048] Instruments

[0049] 1. X-Ray Powder Diffraction:

[0050] X-Ray diffraction was performed on a Philips X-Pert MPD diffractometer and analyzed as follows.

[0051] Tube anode: Cu

[0052] Generator tension: 40 kV

[0053] Tube current: 40 mA

[0054] Wavelength alpha1: 1.5406 Å

[0055] Wavelength alpha2: 1.5444 Å

[0056] Start angle [2 theta]: 5

[0057] End angle [2 theta]: 50

[0058] Time per step: 2.5 seconds

[0059] Scan step size: 0.02

[0060] 2. Raman Spectrum:

[0061] Raman Spectra were recorded on a Nicolet Almega XR Dispersive Raman Spectrometer utilizing a 633 nm He/Ne laser (100% laser power/100 µm aperture). All samples were scanned from 200–1800 cm^{-1}. Cluster analysis of the individual Raman spectra was performed in order to identify any possible polymorphic variations within the crystallized samples.

[0062] 3. Solid State NMR Analysis:

[0063] All ^{13}C solid state NMR Spectra were obtained using a Varian Unity Inova spectrometer operating as follows.

[0064] Probe: 7.5 mm MAS probe

[0065] Temperature: -20°C/253.2 K

[0066] Nucleus: 13C

[0067] Frequency: 75.398 MHz

[0068] Spectral Width: 300018.8 Hz

[0069] Acquisition Time: 50.0 ms

[0070] Recycle: 1.0 sec

[0071] No. repetitions: 4032

[0072] Cross Polarisation Experiment

[0073] Contact time: 1.00 ms

[0074] Cw decoupling

[0075] Spin-rate 5030 Hz

[0076] 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 features.

EXAMPLE 1

[0077] Preparation of perindopril erbumine in polymorph Form Theta (θ).

[0078] A sample of perindopril erbumine (89.9 mg) was dissolved in 900µl of 1,4-dioxane and heated to 95°C. The sample was cooled gradually to 25°C and then further cooled to 4-5°C. The solvent was removed and the sample dried under vacuum.

[0079] CHARACTERIZING DATA: The following characterizing data were generated for the polymorph:

[0080] The XRD of the polymorph is set forth in Figure 1 and was recorded and identified as perindopril erbumine in polymorph Form Theta (θ).

[0081] The Raman spectrum showed peak positions at about 541.1 cm^{-1}, about 551.2 cm^{-1}, about 858.7 cm^{-1}, about 881.1 cm^{-1} and about 898.2 cm^{-1}.

[0082] The ^{13}C solid state NMR spectrum of the polymorph is set forth in Figure 2.

EXAMPLE 2

[0083] Preparation of perindopril erbumine in polymorph Form Theta (θ).

[0084] A sample of perindopril erbumine (10 g) was dissolved in 100 ml of 1,4-dioxane and heated to 95°C. The reaction mass was cooled gradually to 50°C, allowed to crystallize overnight and further maintained at room temperature for 2 to 3 hours. The crystallized reaction mass was filtered and the solid was dried under vacuum at room temperature. Yield: 7.38 gm.

EXAMPLE 3

[0085] Preparation of perindopril erbumine in polymorph Form Theta (θ).

[0086] A sample of perindopril erbumine (10 g) was dissolved in 100 ml of 1,4-dioxane and heated to 95°C. The reaction mass was cooled gradually to 50°C and maintained for 10 minutes. The cooled reaction mass was filtered and dried under vacuum at room temperature. Yield: 4.2 gm.

EXAMPLE 4

[0087] Perindopril erbumine in polymorph Form Theta (θ) was stored for 5 months under normal storage conditions known to one skilled in the art. After 5 months, the XRD pattern of perindopril erbumine in polymorph Form Theta (θ) was recorded and set forth in Figure 3. As the figure shows, the XRD pattern of perindopril erbumine in polymorph Form Theta (θ) after 5 months of storage is substantially the same as the XRD pattern of perindopril erbumine in polymorph Form Theta (θ) (Figures 1 and 4) prior to storage indicating the stored perindopril erbumine in polymorph Form Theta (θ) is stable.

[0088] 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.

WHAT IS CLAIMED IS:

1. Perindopril erbumine in polymorph Form Theta (θ).

2. The perindopril erbumine in polymorph Form Theta (θ) of Claim 1, having a powder X-ray diffraction (XRD) pattern comprising a characteristic peak (expressed in degrees 2θ ± 0.2°θ) at about 20.46.

3. The perindopril erbumine in polymorph Form Theta (θ) of Claim 1, having a powder XRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) at approximately one or more of the positions: about 9.45 and about 20.46.

4. The perindopril erbumine in polymorph Form Theta (θ) of Claim 1, having a powder XRD pattern comprising characteristic peaks (expressed in degrees 2θ ± 0.2°θ) at approximately one or more of the positions: about 9.45, about 18.20 and about 20.46.

5. The perindopril erbumine in polymorph Form Theta (θ) of Claims 1-4, characterized by a XRD pattern substantially in accordance with Figure 1.

6. The perindopril erbumine in polymorph Form Theta (θ) of Claims 1-5, characterized by a Raman spectrum containing peaks at about 541.1 cm^{-1}, about 551.2 cm^{-1}, about 858.7 cm^{-1}, about 881.1 cm^{-1} and about 898.2 cm^{-1}.

7. The perindopril erbumine in polymorph Form Theta (θ) of Claims 1-6, characterized by a ^{13}C solid state NMR spectrum substantially in accordance with Figure 2.

8. The perindopril erbumine in polymorph Form Theta (θ) of Claims 1-7, having a purity of greater than or equal to about 99% as measured by HPLC.

9. A pharmaceutical composition comprising a therapeutically effective amount of perindopril erbumine in polymorph Form Theta (θ) according to any one of Claims 1-8.

10. The pharmaceutical composition of Claim 9, further comprising one or more pharmaceutically acceptable carriers, excipients, diluents or adjuvants.

11. The pharmaceutical composition of Claims 9 and 10, which is in a solid form.

12. The pharmaceutical composition of Claims 9-11, in a form of a tablet, caplet, capsule, suspension, troche or powder.

13. The pharmaceutical composition of Claims 9-12, wherein the polymorph Form Theta (θ) of perindopril erbumine is micronized polymorph Form Theta (θ) of perindopril erbumine having a particle size distribution equal to or less than about 50 microns.

14. The pharmaceutical composition of Claims 9-12, wherein the polymorph Form Theta (θ) of perindopril erbumine is micronized polymorph Form Theta (θ) of perindopril erbumine having a particle size distribution equal to or less than about 15 microns.

15. A process for preparing perindopril erbumine in polymorph Form Theta (θ) according to any one of Claims 1-8, the process comprising (a) heating a solution comprising perindopril erbumine in 1,4-dioxane at a temperature greater than or equal to about 50°C and (b) cooling and isolating perindopril erbumine in polymorph Form Theta (θ).

16. The process of Claim 15, wherein the solution of step (a) is heated to a temperature greater than or equal to about 75°C.

17. The process of Claim 15, wherein the solution of step (a) is heated to a temperature of about 50°C to about 150°C.

18. The process of Claim 15, wherein the solution of step (a) is heated to a temperature of about 50°C to about 100°C.

19. The process of Claims 15-18, wherein the step of cooling comprises cooling the solution until crystallization is complete.

20. The process of Claims 15-18, wherein the step of cooling comprises cooling the solution gradually until crystallization is complete.

21. The process of Claims 15-20, wherein perindopril erbumine in polymorph Form Theta (θ) is isolated by filtration.

22. The process of Claims 15-21, wherein the isolated perindopril erbumine in polymorph Form Theta (θ) is dried.

23. The use of perindopril erbumine in polymorph Form Theta (θ) according to any one of Claims 1-8 in the manufacture of a medicament for use as an inhibitor of angiotensin I converting enzyme.

24. The use of a pharmaceutical composition according to any one of Claims 9-14 in the manufacture of a medicament for use as an inhibitor of angiotensin I converting enzyme.

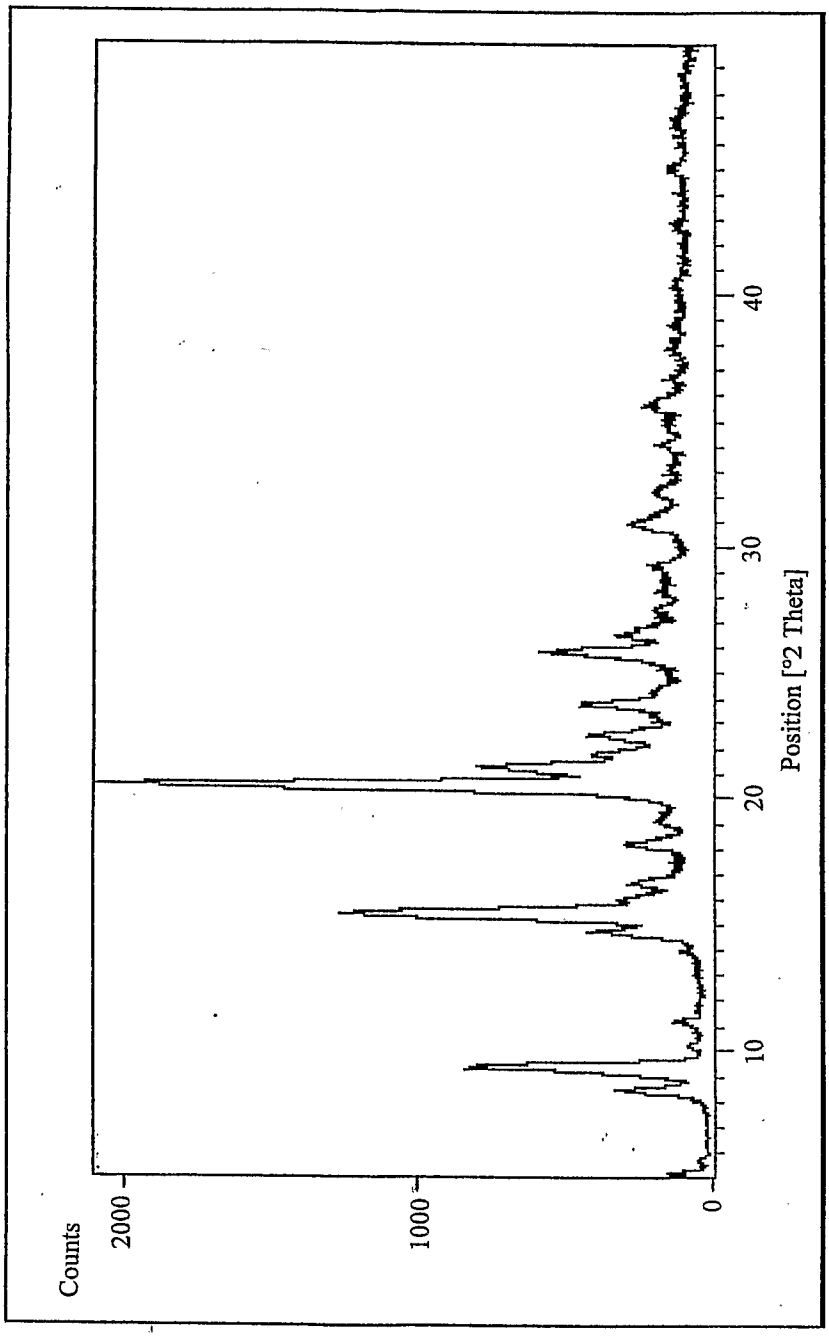


FIGURE 1

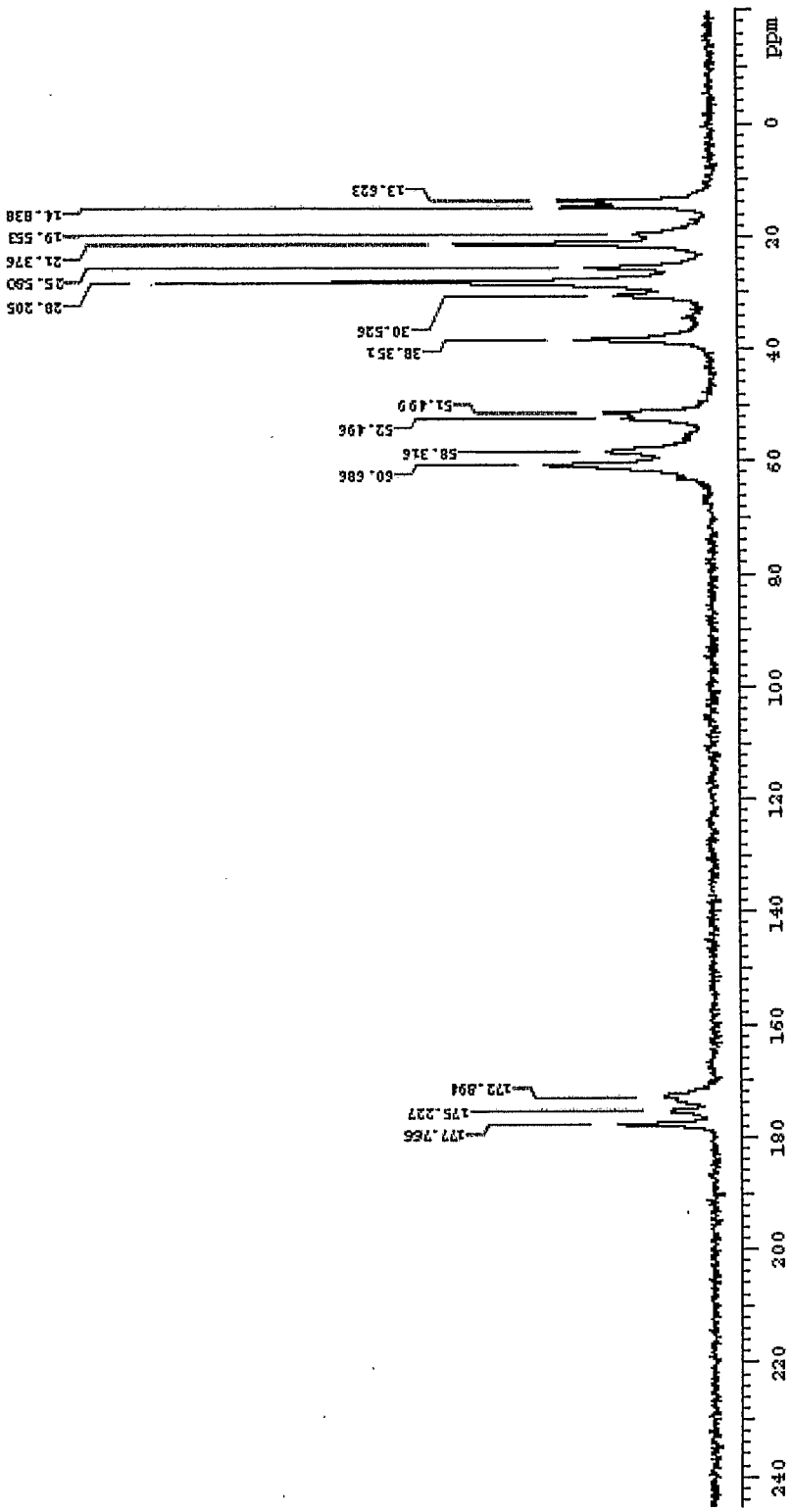

13.623
14.838
19.553
21.376
25.580
28.205
30.536
38.352
51.499
52.496
58.316
60.686
172.894
175.227
177.766
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240

FIGURE 2

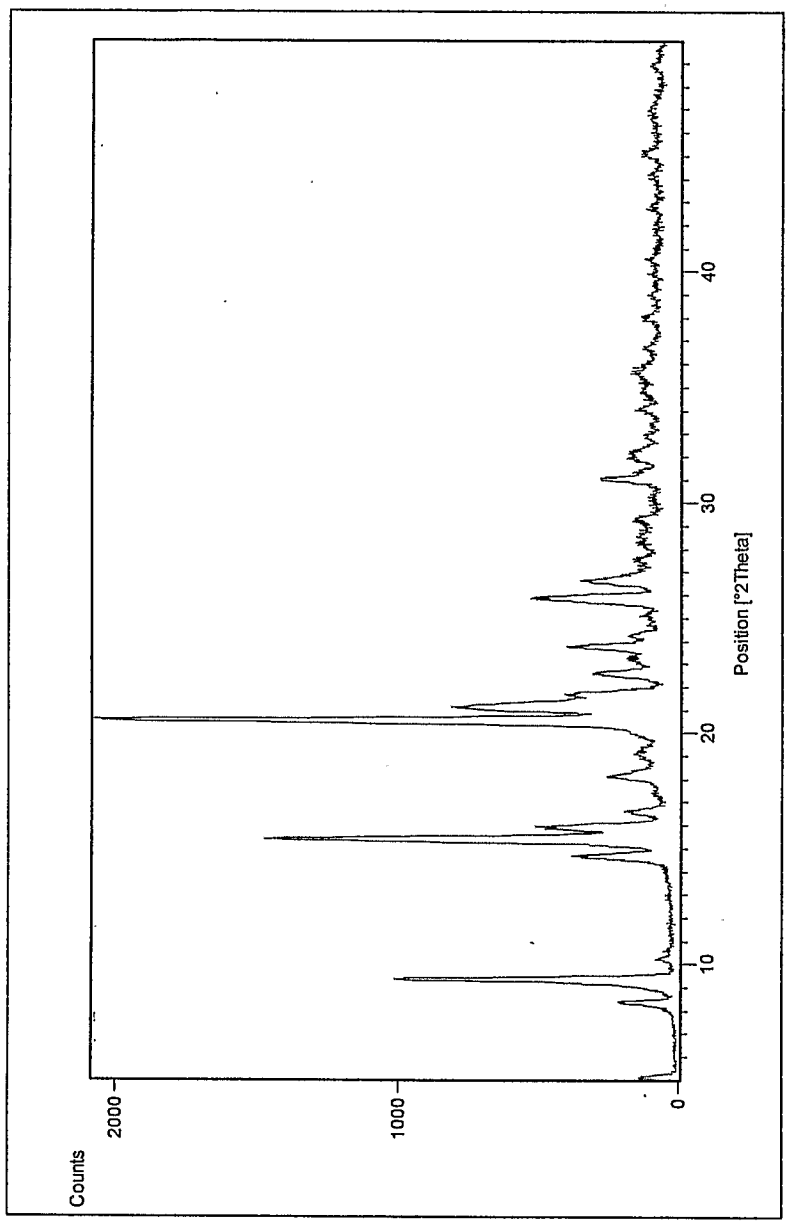


FIGURE 3

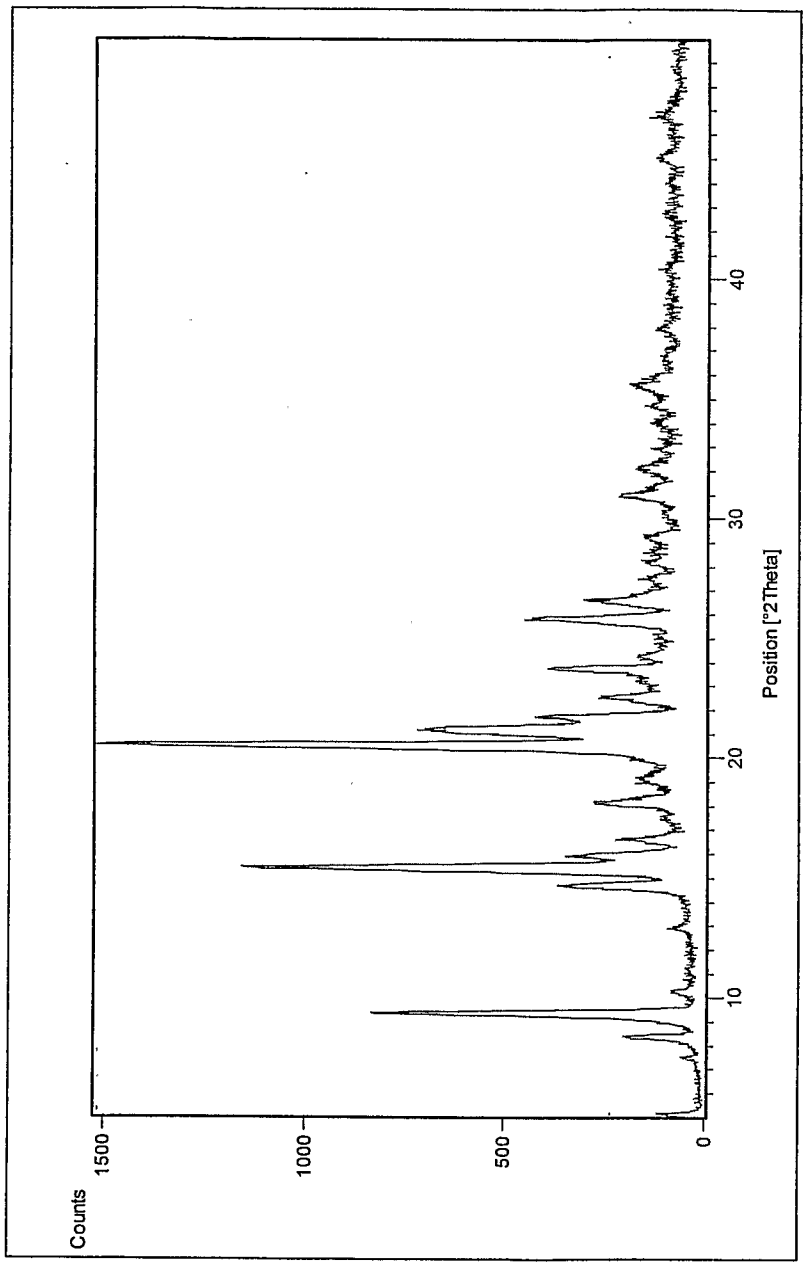


FIGURE 4