(54) Title: NEW FORMS OF ACTIVE PHARMACEUTICAL INGREDIENT

(57) Abstract: The present invention is concerned with new polymorphic forms of entacapone, in particular new polymorphic forms α, β, γ, δ, ε, τ and the amorphous form of entacapone, processes of preparing the forms, pharmaceutical compositions containing the same, therapeutic uses thereof and methods of treatment employing the same.

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New Forms of Active Pharmaceutical Ingredient

Field of invention
The present invention is concerned with new polymorphic forms of entacapone, in particular new polymorphic forms α, β, γ, δ, ε, τ and the amorphous form of entacapone, processes of preparing the forms, pharmaceutical compositions containing the same, therapeutic uses thereof and methods of treatment employing the same.

Background of the invention
Polymorphic forms of a drug substance can have different chemical and physical properties, including melting point, chemical reactivity, apparent solubility, dissolution rate, optical and mechanical properties, vapour pressure, and density. These properties can have a direct effect on the ability to process and/or manufacture a drug substance and a drug product, as well as on drug product stability, dissolution, and bioavailability. Thus, polymorphism can affect the quality, safety, and efficacy of a drug product.

Polymorphic forms as referred to herein can include crystalline and amorphous forms as well as solvate and hydrate forms, which can be further characterised as follows.

(i) Crystalline forms have different arrangements and/or conformations of the molecules in the crystal lattice.

(ii) Amorphous forms consist of disordered arrangements of molecules that do not possess a distinguishable crystal lattice.

(iii) Solvates are crystal forms containing either stoichiometric or non-stoichiometric amounts of a solvent. If the incorporated solvent is water, the solvate is commonly known as a hydrate.

When a drug substance exists in polymorphic forms, it is said to exhibit polymorphism.

There are a number of methods that can be used to characterise polymorphs of a drug substance. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-ray powder diffraction can
also be used to support the existence of polymorphs. Other methods, including microscopy, thermal analysis (e.g., differential scanning calorimetry, thermal gravimetric analysis, and hot-stage microscopy), and spectroscopy (e.g., infrared [IR], Raman, solid-state nuclear magnetic resonance [ssNMR]) are also helpful to further characterise polymorphic forms.

Dynamic vapour sorption (DVS) is a further method for characterising a polymorphic form. DVS is a measure of the water vapour or moisture sorption of a material under varying conditions of humidity and it can be used as a measure of the hygroscopicity of a given material.

The water vapour or moisture sorption properties of pharmaceutical ingredients are recognised in the art as critical factors in determining the storage, stability, processing and application performance thereof. Moisture sorption properties are thus routinely determined for pharmaceutical materials and have traditionally been evaluated by storing samples over saturated salt solutions of established relative humidities and then regularly weighing until equilibrium is reached. However, there are a number of disadvantages associated with these methods, including: (i) the prolonged period of time taken for the samples to reach equilibrium using a static method, which can often be many days and in many cases can be several weeks; (ii) inherent inaccuracies as the samples have to be removed from the storage container to be weighed, which can cause weight loss or gain; (iii) static methods necessitate the use of large samples sizes (typically>1gm); and (iv) the highly labour intensive nature of static methods.

Drug substance polymorphic forms can exhibit different chemical, physical and mechanical properties as referred to above, including aqueous solubility and dissolution rate, hygroscopicity, particle shape, density, flowability, and compactibility, which in turn may affect processing of the drug substance and/or manufacturing of the drug product. Polymorphs can also exhibit different stabilities. The most stable polymorphic form of a drug substance is often chosen during drug development based on the minimal potential for conversion to another polymorphic form and on its greater chemical stability. However, a meta-stable form can alternatively be chosen for various reasons, including bioavailability enhancement.

Entacapone, cyan-3-(3,4-dihydroxy-5-nitrophenyl)-N,N-diethyl-2-propenamide, can be represented by the following structural formula
Entacapone acts by increasing the bioavailability of levodopa and carbidopa, by facilitating the passage of these drugs across the blood-brain barrier. Entacapone is, therefore, employed in the treatment of Parkinson's disease.

Entacapone can exist as a mixture of two geometrical isomers E and Z, as described in US5135950, which part is incorporated herein by reference. Isomer E can exist as two distinct polymorphs Form A and B. It has been found that Form B is unstable and converts to Form A, even at room temperature. In addition it has been found that isomer Z is also relatively unstable and will, under certain conditions, convert to isomer E. Polymorphically pure forms of entacapone form A, and processes for preparing them are described in US5135950. WO2005/066117 discloses polymorphic Form C and Form D of entacapone and process for preparing them. WO2005/063696 and WO2005/063695 discloses polymorphic Form C, Form D and Form E of entacapone and process for preparing them.

Therefore, clearly a stable physical form of entacapone is desired since it is unsatisfactory to have a form of a product that is physically unstable and can lead to a product that has uncertain or changing physical properties over time and lead to a varying performance of the active ingredient as a pharmaceutical ingredient.

Description of the invention
We have now surprisingly found by the present invention, new polymorphic forms of entacapone, including the amorphous form.

In particular, there is provided by the present invention new polymorphic forms of entacapone: polymorphic form α, polymorphic form β, polymorphic form γ, polymorphic form δ, polymorphic form ε, polymorphic form τ and the amorphous form. In addition the invention includes mixtures of the polymorphic forms which include at least 10% of one or more of the polymorphs described herein.
We present as embodiments of the invention:

A polymorphic form \( \alpha \) of entacapone characterised as having x-ray diffraction peaks (2\( \theta \)) ±0.2\(^\circ\) of one or more (preferably 2, 3, 4 or 5) of the following: 6.7\(^\circ\), 12.5\(^\circ\), 13.1\(^\circ\), 13.6\(^\circ\) and 18.4\(^\circ\). The polymorphic form \( \alpha \) may be further characterised as having one or more (preferably 2, 3, 4 or 5) additional x-ray diffraction peaks (2\( \theta \)) ±0.2\(^\circ\), selected from: 13.8\(^\circ\), 15.7\(^\circ\), 18.0\(^\circ\), 24.7\(^\circ\), and 26.1\(^\circ\).

A polymorphic form \( \alpha \) of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 1.

A polymorphic form \( \alpha \) of entacapone having an IR pattern, or substantially the same IR pattern, as shown in Figure 3.

A polymorphic form \( \alpha \) of entacapone having a differential scanning calorimetry (DSC) thermograph, or substantially the same DSC thermograph, as shown in Figure 2.

A polymorphic form \( \alpha \) of entacapone characterised as having a phase transition in a temperature range of from 146 to 158 \(^\circ\)C. Melting onset occurs at a temperature of about 164\(^\circ\)C ("about" being in particular ±0.5\(^\circ\)C).

A polymorphic form \( \beta \) of entacapone characterised as having x-ray diffraction peaks (2\( \theta \)) ±0.2\(^\circ\) of one or more (preferably 2, 3, 4 or 5) of the following: 6.5\(^\circ\), 12.9\(^\circ\), 19.5\(^\circ\), 21.9\(^\circ\) and 27.5\(^\circ\). The polymorphic form \( \beta \) of entacapone may be further characterised as having one or more (preferably 2, 3, 4 or 5) additional x-ray diffraction peaks (2\( \theta \)) ±0.2\(^\circ\), selected from: 15.8\(^\circ\), 16.6\(^\circ\), 17.2\(^\circ\), 20.1\(^\circ\), and 24.0\(^\circ\).

A polymorphic form \( \beta \) of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 4.

A polymorphic form \( \beta \) of entacapone having an IR pattern, or substantially the same IR pattern, as shown in Figure 7.
A polymorphic form $\beta$ of entacapone having a DSC thermograph, or substantially the same DSC thermograph, as shown in Figure 5.

A polymorphic form $\beta$ of entacapone characterised as having a thermo gravimetric analysis (TGA) thermogram, or substantially the same TGA thermogram, as Figure 6.

A polymorphic form $\beta$ of entacapone characterised as having a broad endothermic peak corresponding to solvent loss in a temperature range of from 58 to 88°C. A phase transition occurs at a temperature range of from 157 to 159 °C. Melting onset occurs at a temperature of about 163°C ("about" being in particular $\pm 0.5^\circ$C).

A polymorphic form $\gamma$ of entacapone characterised as having x-ray diffraction peaks (20) $\pm 0.2^\circ$ of one or more (preferably 2, 3, 4 or 5) of the following: 6.2°, 10.2°, 12.5°, 16.4° and 19.4°. The polymorphic form $\gamma$ of entacapone may be further characterised as having one or more (preferably 2, 3, 4 or 5) additional x-ray diffraction peaks (20) $\pm 0.2^\circ$ selected from: 12.2°, 16.9°, 21.3°, 21.7° and 23.4°.

A polymorphic form $\gamma$ of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 8.

A polymorphic form $\gamma$ of entacapone having an IR pattern, or substantially the same IR pattern, as shown in Figure 11.

A polymorphic form $\gamma$ of entacapone having a DSC thermograph, or substantially the same DSC thermograph, as shown in Figure 9.

A polymorphic form $\gamma$ of entacapone characterised as having a thermo gravimetric analysis (TGA) thermogram, or substantially the same TGA thermogram, as Figure 10.

A polymorphic form $\gamma$ of entacapone characterised as having a broad endothermic peak corresponding to solvent loss at a temperature range of from 90 to 135°C. A phase transition occurs at a temperature range of from 150 to 161 °C. Melting onset occurs at a temperature of about 164°C ("about" being in particular $\pm 0.5^\circ$C).
A polymorphic form δ of entacapone characterised as having x-ray diffraction peaks (2θ) ±0.2° of one or more (preferably 2, 3, 4 or 5) of the following: 5.9°, 15.0°, 17.8°, 18.2° and 20.3°. The polymorphic form δ of entacapone may be further characterised as having one or more (preferably 2, 3, 4 or 5) additional x-ray diffraction peaks (2θ) ±0.2°, selected from: 13.5°, 13.8°, 14.1°, 14.7° and 21.5°.

A polymorphic form δ of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 12.

A polymorphic form δ of entacapone having an IR pattern, or substantially the same IR pattern, as shown in Figure 14.

A polymorphic form δ of entacapone having a DSC thermograph, or substantially the same DSC thermograph, as shown in Figure 13.

A polymorphic form δ of entacapone characterised by a vapour sorption of about 0.09 % at 70% relative humidity (RH).

A polymorphic form δ of entacapone having a dynamic vapour sorption curve (DVS), or substantially the same DVS thermograph, as shown in Figure 15.

A polymorphic form δ of entacapone characterised as having a phase transition at a temperature range of from 148 to 150°C. Melting onset occurs at a temperature of about 163°C ("about" being in particular ±0.5°C).

A polymorphic form δ of entacapone characterised by following single crystal parameters measured by single crystal X-ray diffraction at room temperature (293(2) K) using a Bruker Nonius FR591/Kappa CCD diffractometer with CuKα radiation and atomic coordinates and equivalent isotropic displacement parameters (Table 1) at room temperature (293(2) K). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Crystal structure data at temperature of 293(2) K:

Crystal system, space group: Orthorhombic, P 2₁ 2₁ 2₁
Unit cell dimensions:

\[ a = 5.41(2) \text{ Å}; \alpha = 90.0^\circ \]
\[ b = 13.17(2) \text{ Å}; \beta = 90.0^\circ \]
\[ c = 29.88(4) \text{ Å}; \gamma = 90.0^\circ \]

5

Volume: 2913 (2) Å³
Z: 8
Calculated density: 1.39 (1) g/cm³

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<td>1.035</td>
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A polymorphic form \( \delta \) of entacapone characterised by following single crystal parameters measured by single crystal X-ray diffraction at temperature of 100 K using a Bruker Nonius FR591/Kappa CCD diffractometer with CuKα radiation and atomic coordinates and equivalent isotropic displacement parameters (Table 2) at temperature of 100 K. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Crystal structure data at temperature of 293(2) K:

Crystal system, space group: Orthorhombic, P 2₁ 2₁ 2₁
Unit cell dimensions:

\[ a = 7.18(2) \text{ Å}; \alpha = 90.0^\circ \]
\[ b = 13.10(2) \text{ Å}; \beta = 90.0^\circ \]
\[ c = 29.44(2) \text{ Å}; \gamma = 90.0^\circ \]

Volume: 2799 (2) Å³

Zₚ: 8

Calculated density: 1.45 (1) g/cm³

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A polymorphic form ε of entacapone characterised as having x-ray diffraction peaks (2θ) ±0.2° of one or more (preferably 2, 3, 4 or 5) of the following: 10.5°, 14.2°, 14.4°, 19.2° and 24.3°.

The polymorphic form δ of entacapone may be further characterised as having one or more (preferably 2, 3, 4 or 5) additional x-ray diffraction peaks (2θ)±0.2°, selected from: 16.5°, 20.4°, 21.0°, 23.3° and 26.5°.
A polymorphic form $\alpha$ of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 16.

A polymorphic form $\tau$ of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 17.

Amorphous entacapone. The amorphous form of entacapone may be further characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 18.

According to the present invention there is further provided a process of preparing new polymorphic forms of entacapone.

Typically, the process can comprise dissolving entacapone in any suitable solvent and precipitating the entacapone from solution with a suitable anti-solvent. Suitable solvents include lower alcohols (preferably ethanol, propanol or isopropanol), alkyl and cycloalkyl ketones (acetone or cyclohexanone), cyclic ethers (preferably dioxane, tetrahydrofuran (THF)), N,N-dimethylformamide (DMF), N,N-dimethyl acetamide (DMA) or dimethylsulfoxide (DMSO), and mixtures thereof and their water mixtures. Suitable antisolvents include alkanes, cycloalkanes and water.

There is also provided a process of polymorph interconversion, which process comprises converting of a polymorphic form as prepared by the above process to a further polymorphic form. Typically, the interconversion can comprise drying of a polymorphic form in vacuo over a prolonged period of time to yield a different polymorphic form. For example, the $\beta$ form may be dried in vacuo over a prolonged period of time to yield the $\alpha$ form.

The present invention further provides, therefore, a pharmaceutical composition comprising a therapeutically effective dose of a polymorphic form of entacapone as described herein, together with a pharmaceutically acceptable carrier, diluent or excipient therefor. Excipients are chosen according to the pharmaceutical form and the desired mode of administration.

As used herein, the term “therapeutically effective amount” means an amount of a polymorphic form of entacapone according to the invention, which is capable of preventing,
ameliorating or eliminating a disease state for which administration of entacapone, such as Parkinson's disease, is indicated.

By "pharmaceutically acceptable" it is meant that the carrier, diluent or excipient is compatible with entacapone according to the invention, and not deleterious to a recipient thereof.

In another aspect the present invention also provides:

1) A polymorphic form of entacapone as described herein for use in medical therapy.
2) A polymorphic form of entacapone as described herein for use in the manufacture of a medicament for the treatment of Parkinson's disease.
3) A method of treating Parkinson's disease comprising the administration of a pharmaceutically effective amount of a polymorphic form of entacapone as described herein to a patient in need thereof.

With respect to the methods of treatment described herein, it will be understood that treatment of Parkinson's disease also includes the prevention of the disease by administering the polymorphic form of entacapone according to the invention to patients at risk of developing Parkinson's disease.

In pharmaceutical compositions for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, intratracheal, intranasal, transdermal or rectal administration, a polymorphic form of entacapone as described herein (or a mixture thereof) may be administered to animals and humans in unit forms of administration, mixed with conventional pharmaceutical carriers, for the prophylaxis or treatment of the above disorders or diseases. The appropriate unit forms of administration include forms for oral administration, such as tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, forms for sublingual, buccal, intratracheal or intranasal administration, forms for subcutaneous, intramuscular or intravenous administration and forms for rectal administration. For topical application, the polymorphic form of entacapone as described herein (or mixtures thereof) can be used in creams, ointments or lotions.
To achieve the desired prophylactic or therapeutic effect, the dose of the polymorphic form of entacapone as described herein can vary from 0.01 to 50 mg per kg of body weight per day. Each unit dose can contain from 0.1 to 1000 mg, preferably 1 to 500 mg, of the polymorphic form of entacapone described herein in combination with a pharmaceutical carrier. This unit dose can be administered 1, 2, 3, 4 or 5 times a day so as to administer a daily dosage of 0.5 to 5000 mg, preferably 1 to 2500 mg.

When a solid composition in the form of tablets is prepared, the polymorphic form of entacapone as described herein is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose, a cellulose derivative or other appropriate substances, or else they can be treated so as to have a prolonged or delayed activity and so as to release a predetermined amount of active principle continuously.

A preparation in the form of gelatin capsules can be obtained by mixing a polymorphic form of entacapone as described herein with a diluent and pouring the resulting mixture into soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir or for administration in the form of drops can contain a polymorphic form of entacapone as described herein typically in conjunction with a sweetener, which is preferably calorie-free, optionally antiseptics such as methylparaben and propylparaben, as well as a flavoring and an appropriate colour.

Water-dispersible granules or powders can contain a polymorphic form of entacapone as described herein mixed with dispersants or wetting agents, or suspending agents such as polyvinylpyrrolidone, as well as with sweeteners or taste correctors.

Rectal administration is effected using suppositories prepared with binders which melt at the rectal temperature, for example polyethylene glycols.

Parenteral administration is effected using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersants and/or wetting agents, for example propylene glycol or butylene glycol.
In another aspect of the present invention, there is also provided a polymorphic form of entacapone substantially as hereinbefore described for use in therapy.

In yet another aspect, the present invention further provides a polymorphic form of entacapone substantially as hereinbefore described, for use in the manufacture of a medicament for the treatment of a disease state prevented, ameliorated or eliminated by the administration of entacapone, such as Parkinson’s disease. In some embodiments, the present invention provides a polymorphic form of entacapone substantially as hereinbefore described, for use in the manufacture of a medicament for the treatment of Parkinson’s disease.

The present invention can be further illustrated by the following Figures and non-limiting Examples.

With reference to the Figures, these are as follows:

Figure 1 is an X-ray powder diffraction (XRPD) pattern of form α obtained by using a Philips X’Pert PRO with CuKα radiation in 2 θ=3-40 ° range.

Figure 2 is a differential scanning calorimetry (DSC) thermogram of form α obtained by using a DSC Pyris 1 manufactured by Perkin-Elmer.

Figure 3 is a Fourier transform infrared (FTIR) spectrum of form α, obtained by using a KBr pelett and Spectrum GX manufactured by Perkin-Elmer.

Figure 4 is an XRPD diffractogram of entacapone form β obtained by using a Philips X’Pert PRO with CuKα radiation in 2 θ=3-40 ° range.

Figure 5 is a DSC thermogram of form β obtained by using a DSC Pyris 1 manufactured by Perkin-Elmer.

Figure 6 is a thermogravimetric analysis (TGA) thermogram of form β obtained by using a TGA 7 manufactured by Perkin-Elmer.
Figure 7 is a FTIR spectrum of form β obtained by using a KBr pellett and Spectrum GX manufactured by Perkin-Elmer.

Figure 8 is an XRPD diffractogram of entacapone form γ obtained by using a Philips X’Pert PRO with CuKα radiation in 2Θ=3-40° range.

Figure 9 is a DSC thermogram of form γ obtained by using a DSC Pyris 1 manufactured by Perkin-Elmer.

Figure 10 is a TGA thermogram of form γ obtained by using a TGA 7 manufactured by Perkin-Elmer.

Figure 11 is a FTIR spectrum of form γ obtained by using a KBr pellett and Spectrum GX manufactured by Perkin-Elmer.

Figure 12 is an XRPD diffractogram of entacapone form δ obtained by using a Philips X’Pert PRO with CuKα radiation in 2Θ=3-40° range.

Figure 13 is a DSC thermogram of form δ obtained by using a DSC Pyris 1 manufactured by Perkin-Elmer.

Figure 14 is a FTIR spectrum of form δ obtained by using a KBr pellett and Spectrum GX manufactured by Perkin-Elmer.

Figure 15 is a dynamic vapour sorption (DVS) curve of form δ.

Figure 16 is a XRPD diffractogram of entacapone form ε obtained by using a Philips X’Pert PRO with CuKα radiation in 2Θ=3-40° range.

Figure 17 is a XRPD diffractogram of entacapone form τ obtained by using a Philips X’Pert PRO with CuKα radiation in 2Θ=3-40° range.

Figure 18 is a XRPD diffractogram of amorphous form of entacapone obtained by using a
Philips X’Pert PRO with CuKα radiation in 2 θ=3-40 ° range.

The DVS data as described herein was obtained using the Dynamic Vapour Sorption (DVS) methodology developed by Surface Measurement Systems (SMS) Ltd. for the rapid quantitative analysis of the water sorption properties of solids including pharmaceutical materials. The Surface Measurement Systems DVS instrument rapidly measures uptake and loss of moisture by flowing a carrier gas at a specified relative humidity (RH) over a sample (1 mg - 1.5 g) suspended from the weighing mechanism of a Cahn D-200 ultra sensitive recording microbalance. This particular microbalance is used because it is capable of measuring changes in sample mass lower than 1 part in 10 million and provides the long-term stability as required for the accurate measurement of vapour sorption phenomena, which may take from minutes to days to complete depending upon the sample size and material. Indeed, a major factor in determining the water sorption behaviour of materials is the need to establish rapid water sorption equilibrium, therefore the DVS instrument allows sorption behaviour to be accurately determined on very small sample sizes (typically 10 mg), thus minimising the equilibration time required.

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present invention. It will thus be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be falling within the scope of the invention.

EXAMPLES

**FORM α**

**EXAMPLE 1**

1 g of entacapone was dissolved in 3.2 ml of THF while heating. The solution was added dropwise to cold water and the obtained suspension was stirred for 2 hours. Crystals were
collected by filtration and dried in vacuo at 30 °C for 2 hours. 956 mg of entacapone form α was obtained.

EXAMPLE 2

1 g of entacapone was dissolved in 3.2 ml of THF while heating. In warm solution 19 ml of cold n-pentane was added. Obtained suspension was suctioned yielding 941 mg of entacapone form α. Product was dried at 50 °C for 15 hours.

EXAMPLE 3

1 g of entacapone was dissolved in 3.2 ml of THF while heating. In warm solution 15.4 ml of cold cyclohexane was added. Obtained suspension was suctioned yielding 920 mg of entacapone form α. Product was dried at 50 °C for 15 hours.

EXAMPLE 4

1 g of entacapone was dissolved in 3.2 ml of THF while heating. In warm solution 17.5 ml of cold n-heptane was added. Obtained suspension was suctioned yielding 927 mg of entacapone form α. Product was dried at 50 °C for 15 hours.

EXAMPLE 5

Drying of 879 mg of form β obtained according examples 8-13, at 60 °C during 17 hours under vacuo yields 585 mg of entacapone form α.

EXAMPLE 6

1 g of entacapone was dissolved in 3.8 ml of THF while heating. To the warm solution of entacapone 26.2 ml of cold n-hexane was added. The resulting suspension was filtered under vacuum yielding 920 mg of entacapone form α. Product was dried at 50 °C for 15 hours.

FORM β

EXAMPLE 7

1 g of entacapone was dissolved in 19 ml of an acetone/water mixture (ratio 12.5:1) and solution was heated to 60 °C. The warm solution was added to 46 ml of water/acetone mixture (ratio 24.5) seeded with 11 mg of entacapone form D. The resulting suspension was
dried under negative pressure and crystals were stirred in 47.5 ml of water for 10 min. Crystals were filtered and washed with water. 702 mg of entacapone form β was obtained.

EXAMPLE 8

1 g of entacapone was dissolved in 5 ml of DMF. The solution was added dropwise to 40 ml of strongly stirred cold water. The obtained suspension was stirred for 2 hours while maintaining temperature at 5-8 °C. Crystals were filtered and washed with 10 ml of cold water and 10 ml of diisopropyl ether, yielding 977 mg of entacapone form β.

EXAMPLE 9

1 g of entacapone was dissolved in 5 ml of DMA. The solution was added dropwise to 40 ml of cold water. The resulting suspension was stirred for 2 hours at 5-10 °C. Crystals were filtered and washed with 10 ml of cold water and with 10 ml of diisopropyl ether yielding 963 mg of entacapone form β.

EXAMPLE 10

1 g of entacapone was dissolved in 5 ml of DMSO. Solution was added dropwise to 40 ml of cold water. Obtained suspension was stirred for 2 hours at 5-10 °C. Crystals were filtered off and washed with 10 ml of cold water and with 10 ml of diisopropyl ether yielding 981 mg of entacapone form β.

EXAMPLE 11

1 g of entacapone was dissolved in 3.2 ml of THF while heating. The resulting solution was added dropwise to 25 ml of cold water. The suspension was stirred for 20 min and dried under negative pressure. 937 mg of entacapone form β was obtained.

EXAMPLE 12

1 g of entacapone was dissolved in 3.0 ml of n-propanol while heating. To the warm solution 8 ml of cold water was added. The resulting suspension was stirred for 30 min and dried under negative pressure. 873 mg of entacapone form β was obtained.
FORM ɣ
EXAMPLE 13
5 g of entacapone was suspended in 230 ml of dioxane/n-hexane mixture (1/1; v/v). The suspension was heated to 75 °C to obtain clear solution. The solution was cooled to 5 °C and the resulting suspension was stirred for 1 hour at 5 °C. The suspension was dried under negative pressure yielding 4.6 g of entacapone form ɣ.

FORM δ
EXAMPLE 14
10 1 g of entacapone was dissolved in 11 ml of cyclohexanone while heating. The solution was cooled to room temperature, filtered and added dropwise to 11 ml of n-heptane. The resulting suspension was dried under negative pressure yielding 755 mg of entacapone form δ.

EXAMPLE 15
15 2 g of entacapone was dissolved in 24 ml of cyclohexanone while heating. The solution was cooled to room temperature, filtered and added dropwise to 46 ml of n-heptane seeded with 1% of form δ. A suspension of crystals was obtained and stirred for 1 hour at room temperature. The crystals were filtered, washed with 3-4 ml of n-heptane and dried, yielding 1.508 g of entacapone form δ.

EXAMPLE 16
20 2 g of entacapone was dissolved in about 55 ml of methyl-ethyl-ketone while heating. The resulting solution was cooled to room temperature, filtered and added dropwise to about 55 ml of n-heptane seeded with 5% of form δ. The obtained suspension was dried under negative pressure, washed with 4 ml of n-heptane and dried, yielding 1.282 g of entacapone form δ.

EXAMPLE 17
25 2 g of entacapone was dissolved in 30 ml of acetone while heating. The solution was cooled to room temperature, filtered and added dropwise to about 60 ml of n-heptane seeded with 5% of form δ. The resulting suspension was dried under negative pressure, washed with 4 ml of n-heptane and dried, yielding 1.457 g of entacapone form δ.
FORM ε
EXAMPLE 18
A small container with 0.2 ml of saturated solution of entacapone in dioxane was placed in a bigger container which contained 1 ml of n-pentane. The container was sealed and during a period of a few days crystals of entacapone form ε appeared.

FORM τ
EXAMPLE 19
1 g of entacapone was dissolved in 10.5 ml of i-propanol while heating. Into the warm solution 36.8 ml of warm n-hexane was then added. The solution obtained was filtered under vacuum yielding 636 mg of entacapone form τ.

AMORPHOUS FORM
EXAMPLE 20
The amorphous form of entacapone was obtained by cooling a melt of entacapone.
CLAIMS

1. A polymorphic form $\delta$ of entacapone characterised as having x-ray diffraction peaks (20) $\pm 0.2^\circ$ of one or more of the following: 5.9°, 15.0°, 17.8°, 18.2° and 20.3°.

2. A polymorphic form $\delta$ of entacapone, as claimed in claim 1, further characterised as having one or more additional x-ray diffraction peaks (20) $\pm 0.2^\circ$, selected from: 13.5°, 13.8°, 14.1°, 14.7° and 21.5°.

3. A polymorphic form $\delta$ of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 12.

4. A polymorphic form $\delta$ of entacapone having an IR pattern, or substantially the same IR pattern, as shown in Figure 14.

5. A polymorphic form $\delta$ of entacapone having a differential scanning calorimetry (DSC) thermograph, or substantially the same DSC thermograph, as shown in Figure 13.

6. A polymorphic form $\delta$ of entacapone characterised by a vapour sorption of about 0.09 % at 70% relative humidity (RH).

7. A polymorphic form $\delta$ of entacapone having a dynamic vapour sorption curve (DVS) thermograph, or substantially the same DVS thermograph, as shown in Figure 15.

8. A polymorphic form $\delta$ of entacapone characterised by following single crystal parameters as measured by single crystal X-ray diffraction at room temperature (293(2) K) using with CuK$\alpha$ radiation
   Crystal structure data at temperature of 293(2) K:
   
   **Crystal system, space group:** Orthorhombic, P 2$_1$ 2$_1$ 2$_1$
   
   **Unit cell dimensions:**
   
   \[ a = 5.41(2) \, \text{Å}; \quad \alpha = 90.0^\circ \]
   \[ b = 13.17(2) \, \text{Å}; \quad \beta = 90.0^\circ \]
   \[ c = 29.88(4) \, \text{Å}; \quad \gamma = 90.0^\circ \]
Volume: 2913 (2) Å³
Zₐ 8
Calculated density: 1.39 (1) g/cm³

9. A polymorphic form δ of entacapone characterised by following atomic coordinates and equivalent isotropic displacement parameters measured at room temperature (293(2) K)

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
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<td>0.571</td>
<td>0.426</td>
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<td>C(2)</td>
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<td>C(3)</td>
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<td>C(4)</td>
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<td>C(5)</td>
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<td>0.486</td>
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<td>C(6)</td>
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<td>0.575</td>
<td>0.464</td>
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<tr>
<td>O(2)</td>
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<td>0.422</td>
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<td>O(3)</td>
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<tr>
<td>N(3)</td>
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<td>0.496</td>
<td>0.527</td>
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<td>0.027</td>
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<td>N(1)</td>
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<td>0.850</td>
<td>0.328</td>
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<td>C(10)</td>
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<td>0.821</td>
<td>0.321</td>
<td>0.030</td>
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<tr>
<td>C(11)</td>
<td>0.266</td>
<td>0.780</td>
<td>0.274</td>
<td>0.060</td>
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<tr>
<td>C(12)</td>
<td>-0.014</td>
<td>0.952</td>
<td>0.311</td>
<td>0.028</td>
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<tr>
<td>C(13)</td>
<td>0.026</td>
<td>1.035</td>
<td>0.344</td>
<td>0.048</td>
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</table>

10. A polymorphic form δ of entacapone characterised by following single crystal parameters measured by single crystal X-ray diffraction at temperature of 100 K using CuKα radiation

Crystal structure data at temperature of 100 K:
Crystal system, space group: Orthorhombic, P 2₁ 2₁ 2₁
Unit cell dimensions:

\[ a = 7.18(2) \text{ Å}; \alpha = 90.0^\circ \]
\[ b = 13.10(2) \text{ Å}; \beta = 90.0^\circ \]
\[ c = 29.44(4) \text{ Å}; \gamma = 90.0^\circ \]

Volume: 2799 (2) Å³
$Z$

Calculated density: $1.45 (1) \text{ g/cm}^3$

11. A polymorphic form $\delta$ of entacapone characterised by following atomic coordinates and equivalent isotropic displacement parameters measured at temperature of 100 K.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
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<tbody>
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<td>C(1)</td>
<td>0.425</td>
<td>0.929</td>
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<tr>
<td>C(2)</td>
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<td>1.025</td>
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<td>C(3)</td>
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<td>1.114</td>
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<td>1.110</td>
<td>-0.027</td>
<td>0.019</td>
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<td>C(5)</td>
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<td>-0.006</td>
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<td>N(3)</td>
<td>0.165</td>
<td>1.004</td>
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<tr>
<td>O(4)</td>
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<td>1.083</td>
<td>0.050</td>
<td>0.025</td>
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<td>O(5)</td>
<td>0.117</td>
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<td>C(8)</td>
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<td>C(13)</td>
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<td>0.465</td>
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</table>

12. A polymorphic form $\alpha$ of entacapone characterised as having x-ray diffraction peaks $(2\theta) \pm 0.2^\circ$ of one or more of the following: 6.7°, 12.5°, 13.1°, 13.6° and 18.4°.

13. A polymorphic form $\alpha$ of entacapone, as claimed in claim 6, further characterised as having one or more additional x-ray diffraction peaks $(2\theta) \pm 0.2^\circ$, selected from: 13.8°, 15.7°, 18.0°, 24.7°, and 26.1°.

14. A polymorphic form $\alpha$ of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 1.
15. A polymorphic form $\alpha$ of entacapone having an IR pattern, or substantially the same IR pattern, as shown in Figure 3.

16. A polymorphic form $\alpha$ of entacapone having a differential scanning calorimetry (DSC) thermograph, or substantially the same DSC thermograph, as shown in Figure 2.

17. A polymorphic form $\beta$ of entacapone characterised as having x-ray diffraction peaks $(2\theta) \pm 0.2^\circ$ of one or more of the following: $6.5^\circ$, $12.9^\circ$, $19.5^\circ$, $21.9^\circ$ and $27.5^\circ$.

18. A polymorphic form $\beta$ of entacapone, as claimed in claim 12, further characterised as having one or more additional x-ray diffraction peaks $(2\theta) \pm 0.2^\circ$, selected from one: $15.8^\circ$, $16.6^\circ$, $17.2^\circ$, $20.1^\circ$, and $24.0^\circ$.

19. A polymorphic form $\beta$ of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 4.

20. A polymorphic form $\beta$ of entacapone having an IR pattern, or substantially the same IR pattern, as shown in Figure 7.

21. A polymorphic form $\beta$ of entacapone having a differential scanning calorimetry (DSC) thermograph, or substantially the same DSC thermograph, as shown in Figure 5.

22. A polymorphic form $\beta$ of entacapone characterised as having a thermo gravimetric analysis (TGA) thermogram, or substantially the same TGA thermogram, as Figure 6.

23. A polymorphic form $\gamma$ of entacapone characterised as having x-ray diffraction peaks $(2\theta) \pm 0.2^\circ$ of one or more of the following: $6.2^\circ$, $10.2^\circ$, $12.5^\circ$, $16.4^\circ$ and $19.4^\circ$.

24. A polymorphic form $\gamma$ of entacapone, as claimed in claim 23, further characterised as having one or more additional x-ray diffraction peaks $(2\theta) \pm 0.2^\circ$ selected from: $12.2^\circ$, $16.9^\circ$, $21.3^\circ$, $21.7^\circ$ and $23.4^\circ$. 
25. A polymorphic form \( \gamma \) of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 8.

26. A polymorphic form \( \gamma \) of entacapone having an IR pattern, or substantially the same IR pattern, as shown in Figure 11.

27. A polymorphic form \( \gamma \) of entacapone having a differential scanning calorimetry (DSC) thermograph, or substantially the same DSC thermograph, as shown in Figure 9.

28. A polymorphic form \( \gamma \) of entacapone characterised as having a thermo gravimetric analysis (TGA) thermogram, or substantially the same TGA thermogram, as Figure 10.

29. A polymorphic form \( \varepsilon \) of entacapone characterised as having x-ray diffraction peaks \((2\theta) \pm 0.2^\circ\) of one or more of the following: 10.5\(^\circ\), 14.2\(^\circ\), 14.4\(^\circ\), 19.2\(^\circ\) and 24.3\(^\circ\).

30. A polymorphic form \( \varepsilon \) of entacapone, as claimed in claim 29, further characterised as having one or more additional x-ray diffraction peaks \((2\theta) \pm 0.2^\circ\) selected from: 16.5\(^\circ\), 20.4\(^\circ\), 21.0\(^\circ\), 23.3\(^\circ\) and 26.5\(^\circ\).

31. A polymorphic form \( \varepsilon \) of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 16.

32. A polymorphic form \( \tau \) of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 17.

33. Amorphous entacapone.

34. An amorphous form of entacapone characterised as having an X-ray powder diffraction pattern, or substantially the same X-ray powder diffraction pattern, as shown in Figure 18.
35. A pharmaceutical composition comprising a therapeutically effective dose of polymorphic form of entacapone according to any of claims 1 to 34, together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

36. A polymorphic form of entacapone according to any of claims 1 to 34, for use in therapy.