THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

Notes > Ritonavir Polymorph
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divisional of IN/PCT/2001/00018/MUM

Also see 1638/MUMNP/2007

Section 10

"Polymorph of Ritonavir."

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The following specification particularly describes the nature of this invention and the manner in which it is to be performed:

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Polymorph of a Pharmaceutical

Technical Field

This invention relates to a novel crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane, methods for its preparation, methods for its use as a pharmaceutical agent and pharmaceutical compositions comprising the novel crystalline polymorph. This invention also relates to an amorphous form of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and methods for its preparation

Background of the Invention

Inhibitors of human immunodeficiency virus (HIV) protease have been approved for use in the treatment of HIV infection for several years. A particularly effective HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir), which is marketed as NORVIR®. Ritonavir is known to have utility for the inhibition of HIV protease, the inhibition of HIV infection, the inhibition of cytochrome P450 monooxygenase and the enhancement of the pharmacokinetics of compounds

which are metabolized by cytochrome P450 monooxygenase. Ritonavir is particularly effective for the inhibition of HIV infection when used alone or in combination with one or more reverse transcriptase inhibitors and/or one or more other HIV protease inhibitors.

Ritonavir and processes for its preparation are disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996. This patent discloses processes for preparing ritonavir which produce a crystalline polymorph of ritonavir which is termed crystalline Form I. Substantially pure Form I has the powder X-ray diffraction pattern, ^{13}C solid state nuclear magnetic resonance spectrum, the FT near infrared spectrum and the FT mid infrared spectrum which appear in FIGS. 1, 4, 6 and 8, respectively. The angular positions (two theta) of the characteristic peaks in the powder X-ray diffraction pattern of substantially pure Form I shown in FIG. 1 are 3.33° ± 0.1°, 6.76° ± 0.1°, 8.33° ± 0.1°, 14.61° ± 0.1°, 16.33° ± 0.1°, 16.76° ± 0.1°, 17.03° ± 0.1°, 18.02° ± 0.1°, 18.62° ± 0.1°, 19.47° ± 0.1°, 19.86° ± 0.1°, 20.25° ± 0.1°, 21.46° ± 0.1°, 23.46° ± 0.1° and 24.36° ± 0.1°.

Another process for the preparation of ritonavir is disclosed in U.S. Patent No. 5,567,823, issued October 22, 1996. The process disclosed in this patent also produces ritonavir as crystalline Form I.

Pharmaceutical compositions comprising ritonavir or a pharmaceutically acceptable salt thereof are disclosed in U.S. Patent Nos. 5,541,206, issued July 30, 1996; 5,484,801, issued January 16, 1996; 5,725,878, issued March 10, 1998; and 5,559,158, issued September 24, 1996 and in International Application No. WO98/22106, published May 28, 1998 (corresponding to U.S. Serial No. 08/966,495, filed November 7, 1997).

The use of ritonavir to inhibit an HIV infection is disclosed in U.S. Patent No. 5,541,206, issued July 30, 1996. The use of ritonavir in combination with one or more reverse transcriptase inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,635,523, issued June 3, 1997. The use of ritonavir in

combination with one or more HIV protease inhibitors to inhibit an HIV infection is disclosed in U.S. Patent No. 5,674,882, issued October 7, 1997. The use of ritonavir to inhibit cytochrome P450 monooxygenase and to enhance the pharmacokinetics of compounds metabolized by cytochrome P450 monooxygenase is disclosed in WO97/01349, published January 16, 1997 (corresponding to U.S. Serial No. 08/687,774, filed June 26, 1996).

It has now been unexpectedly discovered that ritonavir can be prepared as a new crystalline polymorph which is termed crystalline Form II.

All publications, issued patents and patent applications cited herein are hereby incorporated by reference.

Brief Description of the Drawings

FIG. 1 is the powder X-ray diffraction pattern of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 2 is the powder X-ray diffraction pattern of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 3 is the powder X-ray diffraction pattern of substantially pure amorphous ritonavir.

FIG. 4 is the 400 MHz solid state ^{13}C nuclear magnetic resonance spectrum of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 5 is the 400 MHz solid state ^{13}C nuclear magnetic resonance spectrum of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 6 is the FT near infrared spectrum of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 7 is the FT near infrared spectrum of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 8 is the FT mid infrared spectrum of the substantially pure Form I crystalline polymorph of ritonavir.

FIG. 9 is the FT mid infrared spectrum of the substantially pure Form II crystalline polymorph of ritonavir.

FIG. 10 is the differential scanning calorimetric thermogram for substantially pure amorphous ritonavir.

Disclosure of the Invention

In accordance with the present invention, there is a novel substantially pure crystalline polymorph of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (ritonavir). For the sake of identification, this crystalline polymorph is designated as the Form II crystalline polymorph of ritonavir.

Substantially pure Form II has the powder X-ray diffraction pattern, ^{13}C solid state nuclear magnetic resonance spectrum, the FT near infrared spectrum and the FT mid infrared spectrum which appear in FIGS. 2, 5, 7 and 9, respectively. The two-theta angle positions of characteristic peaks in the powder X-ray diffraction pattern of substantially pure Form II as shown in FIG. 2 are: 8.67° ± 0.1°, 9.88° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1° 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.71° ± 0.1°and 25.38° ± 0.1°.

More preferably, substantially pure Form II is characterized by peaks in the powder X-ray diffraction pattern having two-theta angle positions as shown in FIG. 2 of:

8.67° ± 0.1°, 9.51° ± 0.1°, 9.88° ± 0.1°, 10.97° ± 0.1°, 13.74° ± 0.1°, 16.11° ± 0.1°, 16.70° ± 0.1°, 17.36° ± 0.1°, 17.78° ± 0.1°, 18.40° ± 0.1°, 18.93° ± 0.1°, 19.52° ± 0.1°, 19.80° ± 0.1°, 20.07° ± 0.1°, 20.65° ± 0.1°, 21.49° ± 0.1°, 21.71° ± 0.1°, 22.23° ± 0.1°, 25.38° ± 0.1°, 26.15° ± 0.1° and 28.62° ± 0.1°.

The substantially pure Form II crystalline polymorph of ritonavir can be prepared from amorphous ritonavir by contacting amorphous ritonavir with a C1-C3 alcohol. The method of contacting may be either by saturating the amorphous compound in the solvent at ambient temperature and then allowing the mixture to stand for an extended period of time (for example, overnight) or by dissolving the amorphous compound in the solvent at elevated temperature, preferably, at reflux, followed by cooling the solution to room temperature and isolating Form II.

In one embodiment of the process, the substantially pure Form II crystalline polymorph of ritonavir can be prepared from amorphous ritonavir by preparing a saturated solution of amorphous ritonavir in a C1-C3 alcohol at room temperature and isolating Form II which results. In practice this can be accomplished by dissolving a sufficient amount of amorphous ritonavir in the C1-C3 alcohol at elevated temperature (up to reflux) such that when the solution is allowed to cool to room temperature a saturated solution is obtained, from which Form II precipitates and can be isolated. A preferred solvent for the preparation of Form II is anhydrous ethanol. Isolation of the resulting solid provides Form II.

Substantially pure amorphous ritonavir is prepared from the Form I crystalline polymorph of ritonavir by melting Form I ritonavir and rapidly cooling the melt. Isolation of the resulting solid provides amorphous ritonavir.

Substantially pure amorphous ritonavir can also be prepared by slowly adding a solution of ritonavir Form I in a suitable solvent (methylene chloride and the like; preferably, methylene chloride) at a concentration of, preferably, about 1 g of ritonavir per about 1.5-2.0 mL of solvent (preferably, about 1 g of ritonavir/ about 1.5 mL of methylene chloride) to an anti-solvent (for example, hexane or heptane and the like; preferably, hexane) at a concentration of about 60-110 mL

of antisolvent/ g of ritonavir; preferably, about 85-90 mL of hexane/ g of ritonavir, followed by isolation (for example, by filtration) of the resulting solid.

Similarly, substantially pure amorphous ritonavir can also be prepared by slowly adding a solution of ritonavir Form I in a suitable solvent such as methanol or the like at a concentration of, preferably, about 1 g of ritonavir per about 1.5-2.0 mL of solvent (preferably, about 1 g of ritonavir/ about 1.5 mL of methanol) to an anti-solvent such as methyl t-butyl ether (MTBE) or the like at a concentration of about 60-150 mL of antisolvent/ g of ritonavir, preferably, about 90-110 mL of MTBE/ g of ritonavir and, most preferably, about 100 mL of MTBE/ g of ritonavir, followed by isolation (for example, by filtration) of the resulting solid.

Substantially pure amorphous ritonavir can also be prepared by slowly adding a solution of ritonavir Form I in a suitable solvent (for example, methanol and the like; preferably, methanol) at a concentration of about 1 g of ritonavir per about 1.5-2.0 mL of solvent (preferably, about 1 g of ritonavir/ about 1.6 mL of methanol) to water at about 0°C at a concentration of about 400-500 mL of water/ g of ritonavir (preferably, about 400 mL of water/ g of ritonavir), followed by isolation (for example, by filtration) and drying of the resulting solid.

Substantially pure amorphous ritonavir can also be prepared by lyophilization of a solution of ritonavir Form I. Preferred solvents are C1-C6 alcohols. A more preferred solvent is isobutanol.

Alternatively, in a preferred process, substantially pure Form II can be prepared by seeding a solution of ritonavir Form I in a suitable solvent (preferably, a C1-C3 alcohol; most preferably, ethanol) with undissolved (2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)-carbonyl)amino)-3-methylbutanamide. In a preferred method, ritonavir Form I is dissolved in ethanol (preferably, 200 proof ethanol) at a concentration of from about 150 g/ L to about 200 g/ L, preferably, about 160 g/ L. To the solution is added seed crystals of

(2S)-N-((1S)-1-Benzyl-2-((4S,5S)-4-benzyl-2-oxo-1,3-oxazolidin-5-yl)ethyl)-2-((((2-isopropyl-1,3-thiazol-4-yl)methyl)amino)carbonyl)-amino)-3-methylbutanamide in the amount of from about 0.02 g to about 0.10 g of seed crystals/ g of ritonavir. The amount of seed crystals added is such that it exceeds the saturation amount in the solvent being used so that there are undissolved seed crystals present in the ritonavir solution. The mixture is allowed to stand at a temperature of from about 0° C to about 15° C (preferably, about 5° C) for from about 12 hours to about 48 hours (preferably, about 24 hours). The resulting crystalline ritonavir Form II is isolated by filtration.

In yet another preferred alternative method, substantially pure Form II can be prepared by recrystallization of Form I or mixtures of Form I and Form II from a solution in a suitable solvent (for example, ethyl acetate or isopropyl acetate or chloroform and the like other solvents with like dielectric constant; preferably, ethyl acetate), with seeding with Form II crystals, followed by addition of an anti-solvent (for example, heptane, hexane, toluene, petroleum ether and the like other anti-solvents with like dielectric constant; preferably, heptane). The amount of seed crystals added is such that it exceeds the saturation amount in the solvent being used so that there are undissolved seed crystals present in the ritonavir solution. In a preferred method, ritonavir (Form I or a mixture of Form I and Form II) is dissolved in ethyl acetate (from about 4.0 L to about 6.0 L/kg of ritonavir) with heating (at from about 65°C to about 70°C). The solution is slowly cooled to from about 55°C to about 50°C, preferably about 52°C. Seed crystals of ritonavir Form II (from about 0.5 g of Form II seed crystals/kg of ritonavir to about 10.0 g of Form II seed crystals/kg of ritonavir, preferably about 1.25 g of Form II seed crystals/kg of ritonavir) are added and the mixture is stirred for about 1 hour at a temperature of from about 55°C to about 50°C, preferably about 52°C. The amount of seed crystals added is such that it exceeds the saturation amount in the solvent being used so that there are undissolved seed crystals