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(54) **Title:** NOVEL POLYMORPHS OF EFAVIRENZ

(57) **Abstract:** The present invention relates to novel amorphous and crystalline forms of efavirenz, processes for their preparation and pharmaceutical compositions containing them. In accordance with the present invention efavirenz crude is dissolved in acetone at 25°C - 30°C, the solution is slowly added to water for 30 minutes at 0°C - 5°C, stirred for 1 hour at the same temperature, the separated solid is filtered, washed with water and dried at 55°C - 60°C for 5 hours to give amorphous efavirenz.

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NOVEL POLYMORPHS OF EFAVIRENZ

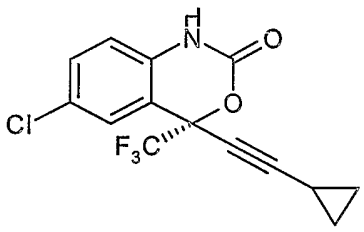
FIELD OF THE INVENTION

The present invention relates to novel polymorphs of efavirenz, processes for their preparation and pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

The present invention relates to novel polymorphs of efavirenz, processes for their preparation and pharmaceutical compositions containing them.

Pharmaceutical products with HIV reverse transcriptase (including its resistant varieties) inhibitors are described in U.S. Patent No. 5,519,021. An especially important compound among those disclosed is efavirenz, (4S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2*H*-3,1-benzoxazin-2-one. Efavirenz has the following structural formula:



This compound is used for the preparation of a medicament having nonnucleoside HIV-1 reverse transcriptase inhibiting activity that is useful in the prevention or treatment of infection by HIV and the treatment of AIDS. Efavirenz is sold commercially as SUSTIVA® by Bristol Myers Squibb.

WO patent application publication No. 98/33782 disclosed three crystalline forms, Form I (characterized by an x-ray powder diffraction patterns having peaks expressed as 2θ at 6.1, 6.4, 10.4, 10.9, 12.3, 13.2, 14.2, 15.2, 16.9, 18.4, 19.2, 20.1, 21.2, 22.3, 23.0, 24.9, 25.9, 26.3, 27.2, 28.1, 28.6, 29.1, 29.5, 30.7, 32.4 and 38.3 degrees), Form II (characterized by an x-ray powder diffraction patterns having peaks expressed as 2θ at 3.6, 6.3, 11.1, 12.8, 13.3, 14.3, 16.1, 16.9, 18.5, 19.2, 19.6, 20.6, 21.3, 22.6, 23.2, 24.4, 24.9, 26.0, 26.8,

27.6, 28.4, 29.2, 29.6, 30.6, 31.9 and 33.8 degrees) and Form III (characterized by an x-ray powder diffraction patterns having peaks expressed as 2θ at 7.2, 10.9, 13.7, 14.5, 16.7, 19.1, 19.6, 20.8, 21.7, 22.3, 22.8, 23.2, 23.9, 24.5, 24.9, 25.8, 27.0, 27.6, 29.3, 30.3, 30.7, 31.3, 33.4, 38.4 and 39.2 degrees) of efavirenz.

WO patent application publication No. 99/64405 disclosed five crystalline forms, Form 1(characterized by an x-ray powder diffraction patterns having peaks expressed as 2θ at about 6.0, 6.3, 10.3, 10.8, 14.1, 16.8, 20.0, 20.5, 21.1 and 24.8 degrees), Form 2 (characterized by an x-ray powder diffraction patterns having peaks expressed as 2θ at about 6.8, 9.2, 12.3, 16.2, 21.4, 22.7, 24.1 and 28.0 degrees), Form 3 (characterized by an x-ray powder diffraction patterns having peaks expressed as 2θ at about 7.1, 7.3, 11.0, 13.8, 20.9, 23.3, 27.9 and 33.5 degrees), Form 4 (characterized by an x-ray powder diffraction patterns having peaks expressed as 2θ at about 3.6, 6.3, 9.7, 11.0, 12.7, 13.2, 16.1, 19.2, 19.5, 20.6 and 24.3 degrees) and Form 5 (characterized by an x-ray powder diffraction patterns having peaks expressed as 2θ at about 10.2, 11.4, 11.6, 12.6, 19.1, 20.6, 21.3, 22.8, 24.8, 27.4, 28.2 and 31.6 degrees) of efavirenz.

We have discovered a stable novel crystalline form of efavirenz. The novel form is at least as stable as the reported forms (Form I, Form II, Form III, Form 1, Form 2, Form 3, Form 4 and Form 5). The novel crystalline form is stable over the time and has good flow properties and so, the novel crystalline form is suitable for formulating efavirenz.

Amorphous form of efavirenz has not been reported in the prior art. So, there is a need for stable amorphous form of efavirenz for better pharmaceutical preparations.

One object of the present invention is to provide a stable novel crystalline form of efavirenz, process for preparing it and a pharmaceutical composition containing it.

Another object of the present invention is to provide a novel stable amorphous form of efavirenz, process for preparing it and a pharmaceutical composition containing it.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel amorphous form of efavirenz. The amorphous efavirenz is characterized by having broad x-ray diffraction spectrum as in figure 1.

In accordance with the present invention, a process is provided for preparation of amorphous efavirenz, which comprises:

a) precipitating from a solution of efavirenz in a C_3 - C_8 -ketonic solvent by using water as precipitating solvent at below about 15°C, and collecting the precipitated solid; and

b) drying the solid collected at about 40°C - 65°C to obtain amorphous efavirenz.

The preferable ketonic solvent is selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone and diethyl ketone; more preferable ketonic solvent is selected from acetone and diethyl ketone; and still more preferable ketonic solvent is acetone.

The solution of efavirenz in the ketonic solvent may be prepared by dissolving efavirenz in a known form or in crystalline form H1 described below in the said ketonic solvent. Alternatively, crude efavirenz may also be used in the process.

Preferably the precipitation is carried out at about 0°C - 10°C and more preferably at about 2°C - 5°C.

The precipitated solid may be collected by filtration or centrifugation.

The preferable temperature range of drying is at about 50°C - 60°C and more preferable temperature range is at about 55°C - 60°C.

Preferably the process is carried out by precipitating from a solution of efavirenz in a C_3 - C_8 -ketonic solvent, preferably acetone, by adding the said solution to water at about 0°C - 10°C and more preferably at about 2°C - 5°C; collecting the precipitated solid by filtration or centrifugation; and drying the solid collected at about 40°C - 65°C, more preferably at about 55°C - 60°C to obtain amorphous efavirenz.

The novel amorphous efavirenz is found to have better dissolution properties when compared with the known forms.

In accordance with the present invention, there is provided a novel crystalline form of efavirenz, designated as form H1, characterized by an x-ray

powder diffraction spectrum having peaks expressed as 2θ at about 5.4, 10.4, 11.6, 12.5, 15.3, 20.1, 20.8, 22.5, 23.1, 25.7, 27.9, 28.5, 28.8, 29.5, 30.2 and 38.2 degrees. Figure 2 shows typical form H1 x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of efavirenz form H1, which comprises:

a) precipitating from a solution of efavirenz in a C_1 - C_6 -alcoholic, C_3 - C_8 - ketonic solvent or a mixture thereof by using water as precipitating solvent at below about 15°C, collecting the precipitated solid;

b) drying the solid collected at about 25°C - 35°C until the water content falls in the range 2 - 10% of the solid by weight; and

c) drying the solid obtained in (b) at about 40°C - 55°C to obtain crystalline efavirenz form H1.

The preferable alcoholic solvent is selected from ethanol, n-propanol, n-butanol, isopropanol and methanol and more preferable alcoholic solvent is n-propanol.

The preferable ketonic solvent is selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone and diethyl ketone; more preferable ketonic solvent is selected from acetone and diethyl ketone; and still more preferable ketonic solvent is acetone.

The solution of efavirenz in the ketonic or alcoholic solvent may be prepared by dissolving efavirenz in a known form or in amorphous form in the said ketonic or alcoholic solvent. Alternatively, crude efavirenz may also be used in the process.

Preferably the precipitation is carried out at about 0°C - 10°C and more preferably at about 2°C - 5°C.

The precipitated solid may be collected by filtration or centrifugation.

It has been found that the drying of precipitated product in step (a) directly at higher temperature leads to known crystalline form 1 (WO patent application publication No. 99/64405).

Preferably the drying in step (b) is carried out until the water content falls in the range 2 - 5% of the solid by weight.

The preferable temperature range of drying in step (c) is at about 40°C - 50°C and more preferably at about 40°C - 45°C.

Preferably the process is carried out by precipitating from a solution of efavirenz in a C_1 - C_6 -alcoholic solvent, preferably n-propanol or isopropanol, C_3 - C_8 -ketonic solvent, preferaly acetone or diethyl ketone, or a mixture thereof by adding the said solution to water at about 0^0C - 10^0C and more preferably at about 2^0C - 5^0C; collecting the precipitated solid by filtration or centrifugation; drying the precipitated solid at about 25^0C - 35^0C until the water content is 2 - 5%; and drying the solid obtained at about 40^0C - 55^0C, preferably at about 40^0C - 50^0C, to obtain crystalline efavirenz form H1.

Unless otherwise specified, the alkyl portion of the C_1 to C_5 -alcohol and C_3 to C_8 -ketone used can be straight or branch, unsubstituted or substituted with for example alkoxy, halogen, nitro, cyano or hydroxy groups.

The novel crystalline efavirenz form H1 is at least as stable as the reported forms (Form I, Form II, Form III, Form 1, Form 2, Form 3, Form 4 and Form 5). The novel crystalline form is stable over the time and has good flow properties and so, the novel crystalline form is suitable for formulating efavirenz.

The above novel polymorphs of efavirenz are useful for the preparation of medicaments having nucleoside HIV-1 reverse transcriptase inhibiting activity that is useful in the prevention or treatment of infection by HIV and the treatment of aids. The novel polymorphs of efavirenz can be used in pharmaceutical compositions generally in combination with at least one pharmaceutically acceptable excipient.

All the patents mentioned above are incorporated herein by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction spectrum of amorphous form of efavirenz.

Figure 2 is a x-ray powder diffraction spectrum of efavirenz form H1.

x-Ray powder diffraction spectrum was measured on a Bruker axs D8 advance x-ray powder diffractometer having a copper-Kα radiation.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitations on the scope or spirit of the invention.

Example 1

Efavirenz crude (5 gm, obtained by the process described in example 6, step A to step D, of U.S. Patent No. 5,519,021) is dissolved in acetone (20 ml) at

25°C - 30°C, slowly added to water (200 ml) for 30 minutes at 0°C - 5°C and stirred for 1 hour at the same temperature. Then the separated solid is filtered, washed with water (20 ml) and dried at 55°C - 60°C for 5 hours to give 4.5 gm of amorphous efavirenz.

Example 2

Efavirenz form 1 (10 gm, obtained by the process described in example 8 of WO patent application publication No. 99/64405) is dissolved in diethylketone (50 ml) at 25°C - 30°C, slowly added to water (350 ml) for 45 minutes at 0°C - 5°C and stirred for 2 hours at the same temperature. Then the separated solid is filtered, washed with water (50 ml) and dried at 55°C - 60°C for 5 hours to give 9.5 gm of amorphous efavirenz.

Example 3

Efavirenz crude (5 gm) is dissolved in n-propanol (20 ml) at 25°C - 30°C, slowly added to water (200 ml) for 30 minutes at 0°C - 5°C and stirred for 1 hour at the same temperature. Then the separated solid is filtered, washed with water (20 ml) and dried at 25°C - 30°C for 18 hours to obtain efavirenz as wet solid (moisture content: 2.5% by Karl fisher method). The wet solid is dried at 40°C - 45°C to give 4.4 gm of efavirenz form H1 (water content: 0.3%).

Example 4

Amorphous efavirenz (5 gm, obtained in example 1) is dissolved in isopropanol (25 ml) at 25°C - 30°C, slowly added to water (170 ml) for 30 minutes at 0°C - 5°C and stirred for 1 hour 30 minutes at the same temperature. Then the separated solid is filtered, washed with water (30 ml) and dried at 25°C - 30°C for 20 hours to obtain efavirenz as wet solid (moisture content: 3.2 % by Karl fisher method). The wet solid is dried at 40°C - 45°C to give 4.3 gm of efavirenz form H1 (water content: 0.35%).

We claim:

1. Amorphous efavirenz.
2. A process for preparation of amorphous efavirenz of claim 1, which comprises:

a) precipitating from a solution of efavirenz in a C_3 - C_8 -ketonic solvent by using water as precipitating solvent at below about 15^0C, and collecting the precipitated solid; and

b) drying the solid collected at about 40^0C - 65^0C to obtain amorphous efavirenz.

3. The process according to claim 2, wherein the ketonic solvent is selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone and diethyl ketone.
4. The process according to claim 3, wherein the ketonic solvent is selected from acetone and diethyl ketone.
5. The process according to claim 4, wherein the ketonic solvent is acetone.
6. The process according to claim 2, wherein the precipitation in step (a) is carried out at about 0^0C - 10^0C.
7. The process according to claim 6, wherein the precipitation is carried out at about 2^0C - 5^0C.
8. The process according to claim 2, wherein the temperature range of drying is at about 50^0C - 60^0C.
9. The process according to claim 8, wherein the temperature range is at about 55^0C - 60^0C.
10. The process according to claim 2, wherein the process is carried out by precipitating from a solution of efavirenz in a C_3 - C_8 -ketonic solvent by adding the said solution to water at about 0^0C - 10^0C, collecting the precipitated solid by filtration or centrifugation and drying the solid collected at about 40^0C - 65^0C to obtain amorphous efavirenz.
11. The process according to claim 10, wherein the ketonic solvent is acetone, the precipitation is carried out at about 2^0C - 5^0C and drying is carried out about 55^0C - 60^0C.
12. A crystalline efavirenz form H1, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 5.4, 10.4, 11.6, 12.5, 15.3, 20.1, 20.8, 22.5, 23.1, 25.7, 27.9, 28.5, 28.8, 29.5, 30.2 and 38.2 degrees.

13. A crystalline efavirenz form H1 as defined in claim 12, further characterized by a x-ray powder diffraction spectrum as in figure 2.

14. A process for preparation of efavirenz form H1 as defined in claim 12, which comprises:

a) precipitating from a solution of efavirenz in a C_1 - C_6 -alcoholic, C_3 - C_8 - ketonic solvent or a mixture thereof by using water as precipitating solvent at below about 15°C, collecting the precipitated solid;

b) drying the solid collected at about 25°C - 35°C until the water content falls in the range 2 - 10 % of the solid by weight; and

c) drying the solid obtained in (b) at about 40°C - 55°C to obtain crystalline efavirenz form H1.

15. The process according to claim 14, wherein the alcoholic solvent is selected from ethanol, n-propanol, n-butanol, isopropanol and methanol.

16. The process according to claim 15, wherein the alcoholic solvent is n-propanol.

17. The process according to claim 14, wherein the ketonic solvent is selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl tert-butyl ketone and diethyl ketone.

18. The process according to claim 17, wherein the ketonic solvent is selected from acetone and diethyl ketone.

19. The process according to claim 18, wherein the ketonic solvent is acetone.

20. The process according to claim 14, wherein the precipitation in step (a) is carried out at about 0°C - 10°C.

21. The process according to claim 20, wherein the precipitation is carried out at about 2°C - 5°C.

22. The process according to claim 14, wherein the drying in step (b) is carried out until the water content falls in the range 2 - 5% of the solid by weight.

23. The process according to claim 14, wherein the temperature range of drying in step (c) is at about 40°C - 50°C.

24. The process according to claim 23, wherein the temperature range is at about 40°C - 45°C.

25. The process according to claim 14, wherein the process is carried out by precipitating from a solution of efavirenz in a C_1 - C_6 -alcoholic solvent, C_3 - C_8 -ketonic solvent or a mixture thereof by adding the said solution to water

at about 0°C - 10°C; collecting the precipitated solid by filtration or centrifugation; drying the precipitated solid at about 25°C - 35°C until the water content is 2 - 5%; and drying the solid obtained at about 40°C - 55°C to obtain crystalline efavirenz form H1.

26. The process according to claim 25, wherein the alcoholic solvent is n-propanol or isopropanol, ketonic solvent is acetone or diethyl ketone, the precipitation is carried out at about 2°C - 5°C and drying is carried out about 40°C - 50°C.

27. A pharmaceutical composition comprising amorphous efavirenz of claim 1 and a pharmaceutically acceptable excipeint.

28. A pharmaceutical composition comprising crystalline efavirenz form H1 of claim 14 and a pharmaceutically acceptable excipeint.

Fig. 1

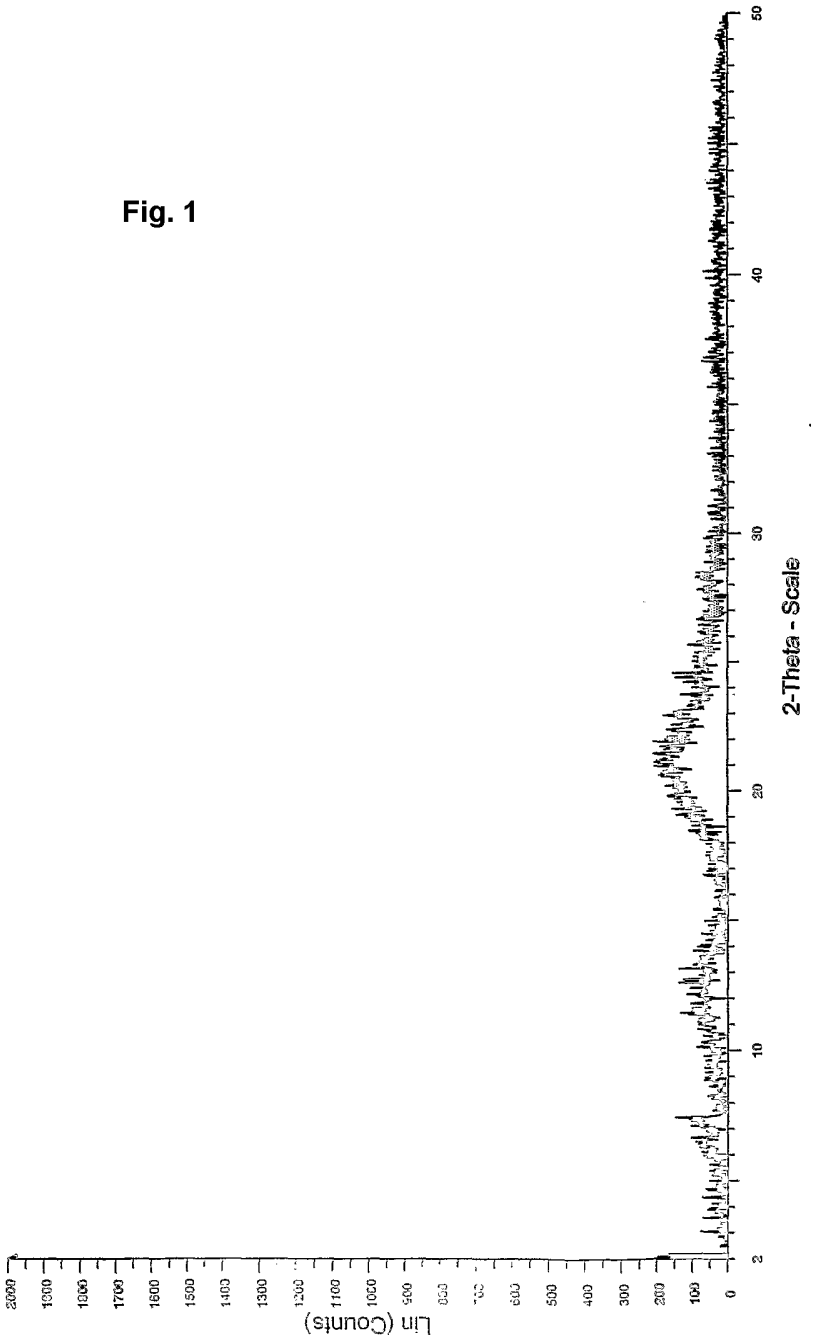


Fig. 2

