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(54) Title: NOVEL CRystalline FORMS OF ABACAVIR SULFATE

(57) Abstract: The present invention relates to novel crystalline forms of abacavir sulfate, to processes for their preparation and to pharmaceutical compositions containing them.
NOVEL CRYSTALLINE FORMS OF ABACAVIR SULFATE

FIELD OF THE INVENTION

The present invention relates to novel crystalline forms of abacavir sulfate, to processes for their preparation and to pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Abacavir of formula (1):

or (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol and its salts are nucleoside reverse transcriptase inhibitors. Abacavir sulfate is a nucleoside reverse transcriptase inhibitor and used in the treatment of human immunodeficiency virus infection. Abacavir sulfate and related compounds and their therapeutic uses are disclosed in US 5,034,394.

Crystalline forms of abacavir sulfate have not been reported in the literature. Moreover, the processes described in the literature do not produce abacavir sulfate in a stable, well-defined and reproducible crystalline form.

It has now been discovered that abacavir sulfate can be prepared in three stable, well-defined and consistently reproducible crystalline forms.

The object of the present invention is to provide stable novel crystalline forms of abacavir sulfate, processes for preparing these forms and pharmaceutical compositions containing them.
DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of abacavir sulfate, designated as form I, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 8.6, 13.3, 14.8, 15.3, 17.2, 17.7, 19.3, 20.8, 21.4, 22.0, 22.9, 23.9, 25.3, 25.8 and 26.6 degrees. Figure 1 shows typical form I x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of form I abacavir sulfate. In this process, abacavir free base is dissolved in a suitable solvent, sulfuric acid is added to the solution and form I abacavir sulfate is isolated by filtration or centrifugation. The quantity of sulfuric acid per mole of abacavir free base is not critical, but 0.5 – 1.0 mole of sulfuric acid per mole of abacavir free base is preferred. The suitable solvents are ethyl acetate, acetone, diethyl ketone, methyl isobutyl ketone, n-butyl acetate, isopropyl acetate and methyl propyl ketone; and a mixture thereof. The preferably solvents are ethyl acetate and acetone.

In accordance with the present invention, there is provided a novel crystalline form of abacavir sulfate, designated as form II, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 9.3, 12.1, 17.2, 17.8, 18.4, 20.9, 21.4, 22.7, 24.4, 28.4 and 29.3 degrees. Figure 2 shows typical form II x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of form II abacavir sulfate. In this process, abacavir free base is dissolved in a suitable solvent, sulfuric acid is added and form II abacavir sulfate is isolated by filtration or centrifugation. The quantity of sulfuric acid per mole of abacavir free base is not critical, but 0.5 – 1.0 mole of sulfuric acid per mole of abacavir free base is preferred. The suitable solvents are acetonitrile, chloroform, methyl tert-butyl ether, toluene, tetrahydrofuran, dimethyl formamide, dioxane; and a mixture thereof. The preferably solvents are acetonitrile and methyl tert-butyl ether.

In accordance with the present invention, there is provided a novel crystalline form of abacavir sulfate, designated as form III, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 7.4, 8.5, 8.7, 9.4, 12.1, 13.3, 14.9, 15.2, 17.2, 17.9, 19.4, 20.8, 21.4, 22.8, 23.8, 25.2
and 26.6 degrees. Figure 3 shows typical form III x-ray powder diffraction spectrum.

In accordance with the present invention, a process is provided for preparation of form III abacavir sulfate which comprises the steps of; a) dissolving abacavir free base in an alcohol; b) adding sulfuric acid to the solution formed in (a); c) maintaining for about 15 minutes to 10 hours; d) adding diisopropyl ether; and e) isolating form III abacavir sulfate.

The suitable alcohol is methanol, isopropyl alcohol or ethanol; or a mixture thereof. The quantity of sulfuric acid per mole of abacavir free base is not critical, but 0.5 – 1.0 mole of sulfuric acid per mole of abacavir free base is preferred. After the addition of sulfuric acid, the contents are preferably maintained for about 1 to 3 hours at 10°С to 30°С. Preferably at least 20 ml of diisopropyl ether is used per 100 ml of alcohol.

Abacavir free base used in the above processes can be obtained from the previously known methods.

In accordance with the present invention, there is provided a pharmaceutical composition comprising a crystalline form of abacavir sulfate and pharmaceutically acceptable carrier or diluent. The crystalline form includes form I, form II or form III.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is a x-ray powder diffraction spectrum of form I abacavir sulfate.

Figure 2 is a x-ray powder diffraction spectrum of form II abacavir sulfate.

Figure 3 is a x-ray powder diffraction spectrum of form III abacavir sulfate.

X-Ray powder diffraction spectrum was measured on a Siemens D5000 x-ray powder diffractometer having a copper-Kα radiation.

The following examples further illustrate the present invention.

**Example 1**

Abacavir free base (3.0 gm, obtained by the process described in example 21 of US 5,034,394) is dissolved in ethyl acetate (15 ml) and conc. sulfuric acid (0.3 ml) is added to the solution. Then the contents are stirred for 3 hours at 20°С and filtered to give 3.0 gm of form I abacavir sulfate.
Example 2

Abacavir free base (3.0 gm) is dissolved in acetone (20 ml) and conc. sulfuric acid (0.3 ml) is added to the solution. Then the contents are stirred for 6 hours at 25\(^\circ\)C and filtered to give 2.8 gm of form I abacavir sulfate.

Example 3

Abacavir free base (3.0 gm) is dissolved in acetonitrile (15 ml) and sulfuric acid (0.3 ml) is added to the solution. Then the contents are stirred for 2 hours at 25\(^\circ\)C and the separated solid is filtered to give 3.0 gm of form II abacavir sulfate.

Example 4

Abacavir free base (3.0 gm) is dissolved in methyl tert-butyl ether (25 ml) and sulfuric acid (0.3 ml) is added to the solution. Then the contents are stirred for 1 hours at 25\(^\circ\)C and the separated solid is filtered to give 3.0 gm of form II abacavir sulfate.

Example 5

Abacavir free base (3.0 gm) is dissolved in methanol (15 ml) and sulfuric acid (0.3 ml) is added to the solution. The contents then are cooled to 0\(^\circ\)C and diisopropyl ether (15 ml) is added. The reaction mass is stirred for 2 hours at about 25\(^\circ\)C and the separated solid is filtered to give 3.0 gm of form III abacavir sulfate.
We claim:


2. A crystalline form I abacavir sulfate as defined in claim 1, further characterized by an x-ray powder diffraction spectrum as in figure 1.

3. A process for preparation of form I abacavir sulfate as defined in claim 1, which comprises the steps of:
   a) dissolving abacavir free base in a suitable solvent;
   b) adding sulfuric acid; and
   c) isolating form I abacavir sulfate;

wherein the suitable solvent is selected from the group consisting of ethyl acetate, acetone, diethyl ketone, methyl isobutyl ketone, n-butyl acetate, isopropyl acetate and methyl propyl ketone.

4. A process according to claim 3, wherein the suitable solvent is ethyl acetate.

5. A process according to claim 3, wherein the suitable solvent is acetone.

6. A crystalline form II abacavir sulfate, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 9.3, 12.1, 17.2, 17.8, 18.4, 20.9, 21.4, 22.7, 24.4, 28.4 and 29.3 degrees.

7. A crystalline form II abacavir sulfate as defined in claim 6, further characterized by an x-ray powder diffraction spectrum as in figure 2.

8. A process for preparation of form II abacavir sulfate as defined in claim 6, which comprises the steps of:
   a) dissolving abacavir free base in a suitable solvent;
   b) adding sulfuric acid; and
   c) isolating form II abacavir sulfate;

wherein the suitable solvent is selected from the group consisting of acetonitrile, chloroform, methyl tert-butyl ether, toluene, tetrahydrofuran, dimethyl formamide and dioxane.

9. A process according to claim 8, wherein the suitable solvent is acetonitrile.

10. A process according to claim 8, wherein the suitable solvent is methyl tert-butyl ether.
11. A crystalline form III abacavir sulfate, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 7.4, 8.5, 8.7, 9.4, 12.1, 13.3, 14.9, 15.2, 17.2, 17.9, 19.4, 20.8, 21.4, 22.8, 23.8, 25.2 and 26.6 degrees.

12. A crystalline form III abacavir sulfate as defined in claim 11, further characterized by an x-ray powder diffraction spectrum as in figure 3.

13. A process for preparation of form III abacavir sulfate as defined in claim 11, which comprises the steps of:
   a) dissolving abacavir free base in an alcohol;
   b) adding sulfuric acid to the solution formed in (a);
   c) maintaining for about 15 minutes to 10 hours at about 0°C to 40°C;
   d) adding diisopropyl ether; and
   e) isolating form III abacavir sulfate;

   wherein the suitable alcohol is selected from the group consisting of methanol, isopropyl alcohol and ethanol.

14. A process according to claim 13, wherein the contents in step (c) is stirred for 1 to 3 hours at 10°C to 30°C.

15. A process according to claim 13, wherein the suitable alcohol is methanol.

16. A process according to claim 13, wherein the suitable alcohol is isopropyl alcohol.

17. A pharmaceutical composition comprising a crystalline form of abacavir sulfate and a pharmaceutically acceptable carrier or diluent.

18. A pharmaceutical composition as defined in claim 17, wherein the crystalline form is form I abacavir sulfate of claim 1.

19. A pharmaceutical composition as defined in claim 17, wherein the crystalline form is form II abacavir sulfate of claim 6.

20. A pharmaceutical composition as defined in claim 17, wherein the crystalline form is form III abacavir sulfate of claim 11.
fig. 3/3

Lin (Counts)

2-Theta - Scale
**INTERNATIONAL SEARCH REPORT**

**CLASSIFICATION OF SUBJECT MATTER**

**IPC**: C07D 473/16; A61K 31/52

According to International Patent Classification (IPC) or to both national classification and IPC

**FIELD SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

**IPC**: C07D; A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

**REGISTRY, CAPLUS, WPI, PAJ, EPO**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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