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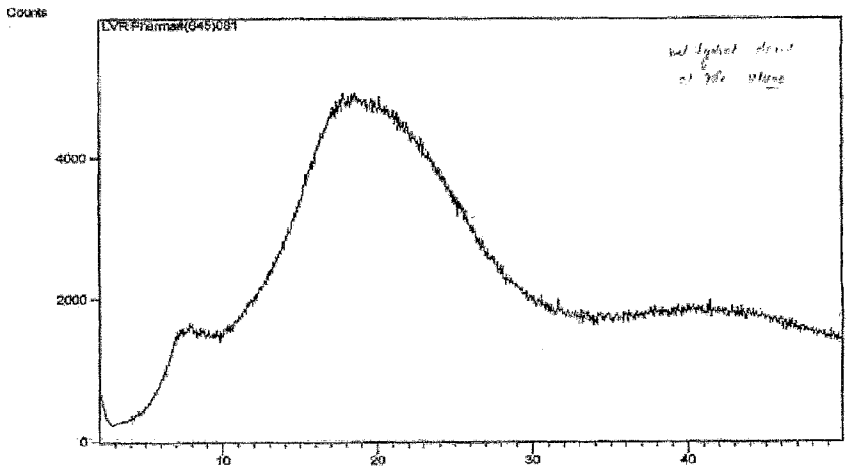
(54) Title: PROCESS FOR PREPARING AN AMORPHOUS FORM OF (2S,3S,5S)-2-(2,6- DIMETHYLPHENOXYACETYL)-AMINO-3-HYDROXY-5-(2-(1-TETRAHYDROPYRIMID-2-ONLY)-3-METHYLBUTANOYL)-AMINO-1,6-DIPHENYL HEXANE AND PRODUCT THEREOF

Figure-1



(57) Abstract: Disclosed herein is a process for preparing an amorphous form of (2S,3 S5SS)- 2-(2,6-dimethylphenoxyacetyl)-amiho-3-hydroxy-5-(2-(l-tetrahydropyrimid-2-only)- 3-methylbutanoyl)-amino-l,6-diphenyl hexane(Lopinavir), wherein lopinavir is dissolved in a solvent system, followed by removal of solvent employing drying technique and isolating the resultant pure amorphous form. Further process comprises of heating/drying the lopinavir at higher temperature to melt the solid and form uniform liquid, which is subjected to cooling arid drying to give amorphous lopinavir.

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Process For Preparing An Amorphous Form Of (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)-Amino-3-Hydroxy-5-(2-(1-Tetrahydropyrimid-2-Only)-3-Methylbutanoyl)-Amino-1,6-Diphenyl Hexane And Product Thereof

Field of the Invention

This invention, in general relates to the field of Human Immunodeficiency Virus (HIV) protease inhibitor. More particularly, the present invention provides a novel process for preparing an amorphous form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane (Lopinavir) and product thereof.

Background of the Invention

Retroviruses are those viruses which utilize a ribonucleic acid (RNA) intermediate and a RNA-dependent deoxyribonucleic acid (DNA) polymerase, reverse transcriptase, during their life cycle. Retroviruses include, but are not limited to, the RNA viruses of the Retroviridae family, and also the DNA viruses of the Hepadnavirus and Caulimovirus families.

Retroviruses cause a variety of disease states in Man, animals and plants. Some of the more important retroviruses form a pathological standpoint include human immunodeficiency viruses (HIV-1 and HIV-2) which cause Acquired Immune Deficiency Syndrome (AIDS) in man, human T-cell lymphotrophic viruses I, II, IV and V, which cause human acute cell leukemia.

Inhibitors of human immunodeficiency virus (HIV) protease have been approved for use in the treatment of HIV infection for several years. A particularly effective and recently approved HIV protease inhibitor is (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane, also known as Lopinavir.

Lopinavir is known to have ability of inhibiting HIV protease and the HIV infection. Lopinavir is particularly effective for the inhibition of HIV protease and for the inhibition of HIV infection when co administered with Ritonavir.

US 5,914,332 patent discloses a process for the preparation of lopinavir. This patent also discloses a process for the preparation of amorphous lopinavir, wherein lopinavir is crystallized from different combinations of solvents such as mixture of ethanol and water, isopropyl alcohol and water, acetone and water & acetonitrile and water to obtain amorphous lopinavir.

The lopinavir obtained by using the solvent mixtures, disclosed in the product patent have the contamination with crystalline polymeric forms. The product patent suggests that, crystallization method gives mixture of crystalline forms along with amorphous form. It is difficult to get the pure amorphous form by the solvent crystallization as given in the prior art.

Therefore, there is a need to provide a process for preparing an amorphous form of lopinavir free of any contaminations.

Objects and Summary of the Invention

It is a principal object of the present invention to provide a novel process for preparing a pure form of an amorphous (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane (Lopinavir).

It is another object of the present invention to provide a process for preparing an amorphous (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane (Lopinavir) having improved stability.

It is the further object of the present invention to provide a process for preparing an amorphous (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane (Lopinavir) in higher yield and better quality.

The above and other objects of the present invention are further attained and supported by the following embodiments described herein. However, the scope of the invention is not restricted to the described embodiments herein after.

In accordance with a preferred embodiment of the present invention, there is provided a process for preparing an amorphous form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane comprises of dissolving the 2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane in a solvent system, distilling out the remaining solvent from the resultant solution employing a drying technique and isolating the pure amorphous form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane, wherein the drying is performed employing spray drying, freeze

drying or thin film drying to obtain the resultant amorphous without any contaminations.

In accordance with another preferred embodiment of the present invention, there is provided a process for preparing an amorphous form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane comprises of heating or drying the (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane at high temperature and reduced pressure, cooling the resultant solution and isolating the pure amorphous form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane, wherein the heating/drying is performed until melt of the solid (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane to obtain pure amorphous form.

Brief Description of the Drawing:

Further objects of the present invention together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of preferred embodiments of the invention which are shown in the accompanying drawing figures, wherein:

Figure 1 is XRD pattern of lopinavir amorphous form.

Detailed Description of the Present Invention

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

The present invention relates to process for the preparation of amorphous (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane (Lopinavir), wherein lopinavir is dissolved in a solvent system, removing the solvent to get lopinavir amorphous form with higher yield and improved quality.

The solvent system according to the present invention comprises an organic solvent/s or a mixture of water and water miscible organic solvent/s or a mixture of said organic solvent/s, water and water miscible organic solvent/s.

According to the present invention, the organic solvent/s is selected from methanol, ethanol, isopropyl alcohol, acetone, tetrahydrofuran, dioxane, methyl ethyl ketone, dimethyl formamide, dimethyl acetamide or dimethyl sulfoxide or mixture thereof. Lopinavir is dissolved in a solvent to get clear solution, which is subjected to spray drying or other suitable drying technique to get lopinavir amorphous form.

According to the present invention, the water miscible organic solvent/s is selected from methanol, ethanol, isopropyl alcohol, acetone, tetrahydrofuran, dioxane, dimethyl formamide, dimethyl acetamide or dimethyl sulfoxide or mixture thereof. Lopinavir is dissolved in a mixture of water and water miscible organic solvent to get a clear solution, optionally the clear solution is treated with carbon and filtered to get a clear filtrate, which is subjected to spray drying or other suitable drying technique to get lopinavir amorphous form with better yield and improved quality as compared to the prior art.

Lopinavir, according to the process of the present invention can be dissolved in an organic solvent, mixture of water and water miscible solvents or mixtures thereof to get a clear solution. The remaining solvent is distilled out by employing the different types of drying techniques like spray drying, freeze drying or thin film drying to give amorphous lopinavir. Further, the solvent distillation can be optionally performed under reduced pressure.

Another embodiment of the present invention relates to a novel process for the preparation of lopinavir amorphous form, wherein lopinavir is heated at high temperature to melt the solid followed by cooling and drying to lopinavir amorphous form with higher yield.

A process for preparing lopinavir amorphous form comprises of heating at high temperature and reduced pressure, cooling and drying the resultant solution and isolating the pure amorphous form, wherein the temperature used for heating is in the range of 75-100°C. The temperature used for drying is in the range of 60-80° C and the resultant solution is cooled up to the temperature between 20-40°C.

According to the present invention, lopinavir is heated/dried to higher temperature to melt the solid to form the uniform liquid, which is subjected to cooling and drying to give lopinavir amorphous form.

Another aspect of the present invention is a process for the preparation of amorphous lopinavir, wherein lopinavir is subjected to drying at higher temperature, optionally under vacuum followed by cooling and isolation to give amorphous lopinavir.

The following non-limiting examples illustrate specific embodiments of the present invention. They are, not intended to be limiting the scope of present invention in any way.

Example-1

Lopinavir (crude) 45 gm (0.071 moles) is dissolved in 135 ml of ethanol at 40-45^0 C and the solution is filtered. The filtered solution is spray dried at a feed rate of 180-720 ml/hr while drying with nitrogen at a flow rate of 350-750 lts/hr to get 35 gm pure amorphous lopinavir.

Example-2

Lopinavir (crude) 45 gm (0.071 moles) is dissolved in 90 ml of methanol at 25-30^0 C and the solution is filtered. The filtered solution is spray dried at a feed rate of 180-720 ml/hr while drying with nitrogen at flow rate of 350-750 lts/hr to get 38 gm pure amorphous lopinavir.

Example-3

Lopinavir (crude) 45 gm (0.071 moles) is dissolved in 90 ml acetone at 25-30^0 C and the solution is filtered. The filtered solution is spray dried at a feed rate of 180-

720 ml/hr while drying with nitrogen at a flow rate of 350-750 lts/hr to get 40 gm pure amorphous lopinavir.

Example-4

Lopinavir (crude) 45 gm (0.071 moles) is dissolved in 160 ml isopropyl alcohol at 25-30^0 C and the solution is filtered. The filtered solution is spray dried at a feed rate of 180-720 ml/hr while drying with nitrogen at a flow rate of 350-750 lts/hr to get 35 gm pure amorphous lopinavir.

Example-5

Lopinavir (500gm) is heated to 90^0 C, maintained at 90^0 C under vacuum, then it is cooled to 30-35^0 C under vacuum. The solid resultant obtained is milled to get the powder form. Powder form is then dried under vacuum at 90^0 C, further cooled to 30-35^0 C under vacuum to give amorphous lopinavir.

Example-6

Lopinavir hydrate (50gm) is dried at 80^0 C under vacuum and then cooled to 30-35^0 C under vacuum. The solid product is milled to get the powder form. Powdered product thus obtained is dried further under vacuum at 80^0 C and then cooled to 30-35^0 C under vacuum to give amorphous lopinavir.

While this invention has been described in detail with reference to certain preferred embodiments, it should be appreciated that the present invention is not limited to those precise embodiments. Rather, in view of the present disclosure, which describes the current best mode for practicing the invention, many modifications and variations would present themselves to those skilled in the art without departing from the scope and spirit of this invention.

We Claim:

1. A process for preparing an amorphous form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane comprising:

a) dissolving the 2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane in a solvent system;

b) distilling out the remaining solvent from the resultant solution employing a drying technique selected from spray drying, freeze drying or thin film drying; and

c) isolating the pure amorphous form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane.

2. The process according to claim 1, wherein the solvent system comprises an organic solvent/s or a mixture of water and water miscible organic solvent/s or a mixture of said organic solvent/s, water and water miscible organic solvent/s.

3. The process according to claim 2, wherein the organic solvent is selected from methanol, ethanol, isopropyl alcohol, acetone, tetrahydrofuran, dioxane, methyl ethyl ketone, dimethyl formamide or dimethylacetamide or mixture thereof.

4. The process according to claim 2, wherein the water miscible organic solvent is selected from methanol, ethanol, isopropyl alcohol, acetone, tetrahydrofuran, dioxane, dimethyl formamide, dimethyl acetamide or dimethyl sulfoxide or mixtures thereof.

5. The process according to claim 1, wherein the distillation of the solvent is carried out optionally under reduced pressure.

6. A process for preparing an amorphous form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane comprising:

a) heating the (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane at high temperature and reduced pressure;

b) cooling and drying the resultant solution; and

c) isolating the pure amorphous form of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane.

7. The process according to claim 6, wherein the temperature used for heating is in the range of 75-100^0 C.

8. The process according to claim 6, wherein the drying is carried out at a temperature range of 60-80^0 C.

9. The process according to claim 6, wherein the resultant solution is cooled up to the temperature 20-40^0 C.

10. The process according to claim 6, wherein the process is optionally carried out under vacuum.

11. The process according to claim 6, wherein the heating is performed until melting of the solid (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2-(1-tetrahydropyrimid-2-only)-3-methylbutanoyl)-amino-1,6-diphenyl hexane to form a uniform liquid.

Figure-1