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(54) Title: CRYSTALLINE FOSAMPRENAVIR CALCIUM AND PROCESS FOR THE PREPARATION THEREOF"

(57) Abstract: The present invention relates to novel crystalline form A of Fosamprenavir calcium and its process thereof.

"CRYSTALLINE FOSAMPRENAVIR CALCIUM AND PROCESS FOR THE PREPARATION THEREOF"

This application claims priority to Indian patent application No. 381/CHE/2011 filed on February 10, 2011, the contents of which are incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention relates to novel crystalline form of Fosamprenavir Calcium designated as Form A.

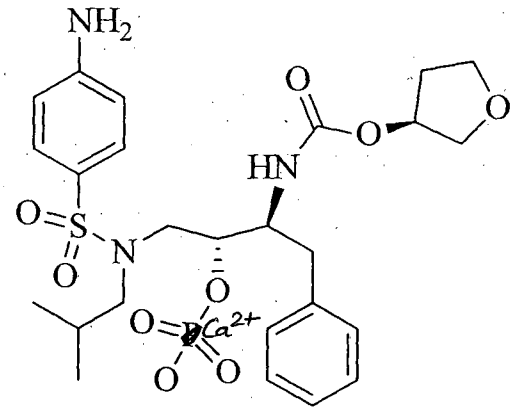
The present invention further relates to a process for the preparation of novel crystalline Form A of Fosamprenavir Calcium.

BACKGROUND OF THE INVENTION

Fosamprenavir Calcium is an antiviral compound, The chemical name of Fosamprenavir Calcium is Calcium (3S) tetrahydro-3-furanyl (1S,2R)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphono oxy)propylcarbamate. Fosamprenavir Calcium has HIV aspartyl protease inhibitory activity and is particularly well suited for inhibiting HIV-1 and HIV-2 viruses. Moreover, Calcium (3S) tetrahydro-3-furanyl (1S,2R)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphono oxy)propylcarbamate has increased solubility in the pH range of the gastro-intestinal tract compared to the HIV protease inhibitor [3S-[3R*(1R*,2S*)]]-[3-[[(4-aminophenyl)sulfonyl](2-methyl-propyl)amino]-2 -hydroxy-1-phenylmethyl)propyl]-tetrahydro-3-furanyl ester (amprenavir, 141W94). Amprenavir, which has poor solubility and is thus available as a solution in gel capsules and has a high pill burden. This new HIV protease inhibitor with its

increased solubility thus has the potential to reduce the perceived pill burden and may be formulated as a tablet.

The structure of Calcium (3S) tetrahydro-3-furanyl (1S,2R)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphono oxy)propylcarbamate is shown below as Formula I



Formula I

US 6436989B1 patent disclosed Fosamprenavir and its pharmaceutically acceptable salts, A wide range of salts of Fosamprenavir were made in this patent viz. di-sodium, di-potassium, magnesium, zinc, ethylene diamine, piperazine etc. Of these, the piperazine salt was a crystalline solid, but had the practical disadvantage of toxicity at the anticipated dose.

US 6514953B1 patent disclosed crystalline form 1 of calcium salt of (3S)-tetrahydrofuran-3-yl(1S,2R)-3-[[(4-aminophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy) propylcarbamate.

WO2010134045 publication disclosed an amorphous Fosamprenavir Calcium and process for the preparation of amorphous Fosamprenvir Calcium.

WO 2011001383 publication disclosed crystalline form II of Fosamprenavir Calcium and a process for the preparation of crystalline form II of Fosamprenavir Calcium.

WO2011085130 publication disclosed rod like amorphous, form II, form III, form IV and form P.

OBJECT AND SUMMARY OF THE INVENTION

The main object of the present invention relates to novel crystalline form of Fosamprenavir Calcium designated as Form A.

Another object of the present invention relates to a process for the preparation of Crystalline Form A of Fosamprenavir Calcium.

Yet another object of the present invention relates to crystalline Form A of Fosamprenavir Calcium characterized by an PXRD diffraction having reflections at about 3.1 ± 0.2, 4.4 ± 0.2, 5.0 ± 0.2, 6.3 ± 0.2, 7.4 ± 0.2, 8.0 ± 0.2, 2Θ.

Yet another object of the present invention relates to a process for the preparation of crystalline Fosamprenavir Calcium Form A comprising the steps of;

a) dissolving Fosamprenavir Calcium salt in a solvent or mixture of solvents,

b) heating the reaction mass,

c) removing the solvent

d) adding a second solvent or mixture of solvents; and

e) isolating crystalline form A of Fosamprenavir Calcium

Yet another object the present invention relates to a process for the preparation of crystalline Fosamprenavir calcium Form A comprising steps of;

a) suspending Fosamprenavir Calcium in a solvent or mixture of solvents,
b) heating the reaction mass,
c) removing the solvent,
d) adding a second solvent or mixture of solvents, and
d) isolating crystalline Form A of Fosamprenavir Calcium.

In yet another object, the present invention relates to a process for the preparation of crystalline Form A of Fosamprenavir Calcium comprising the steps of
a) suspending Fosamprenavir Calcium in a solvent or mixture of solvents,
b) heating the reaction mass,
c) optionally cooling the reaction mass, and
d) isolating crystalline form A of Fosamprenavir Calcium.

Yet another object the present invention relates to a process for the preparation of crystalline Fosamprenavir calcium Form A comprising steps of;
a) suspending Fosamprenavir Calcium in a solvent or mixture of solvents,
b) heating the reaction mass,
c) seeding the reaction mass, and
d) isolating crystalline Form A of Fosamprenavir Calcium.

In yet another object, the crystalline form A of Fosamprenavir Calcium prepared according to the present invention is its hydrated form having moisture content of 2.5 to 5.5%.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts the X-ray powder Diffraction (XRPD) pattern of crystalline Form A of Fosamprenavir Calcium.

Figure 2 depicts the Differential Scanning Calorimetry (DSC) thermogram of crystalline Form A of Fosamprenavir Calcium.

Figure 3 depicts the TGA thermogram of crystalline Form A of Fosamprenavir Calcium.

Figure 4 depicts the FT-IR spectra of crystalline Form A of Fosamprenavir Calcium.

Instrumentation details:

Powder X-ray Diffraction (PXRD)

The said formic acid solvate of the present invention is characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of said polymorphs of the invention were measured on Bruker AXS D8 Discover powder X-ray diffractometer equipped with a goniometer of θ/2θ configuration, Variol monochromator and Lynx-Eye detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the 2θ range of 2.0°-50.0°, 0.030° step size and 25 seconds step time.

Differential Scanning Calorimetry (DSC)

The DSC measurements were carried out on TA Q1000 of TA instruments. The experiments were performed at a heating rate of 10.0 °C/min over a temperature range of 30°C-200°C purging with nitrogen at a flow rate of 50ml/min. Standard aluminum crucibles covered by lids with three pin holes were used.

Thermo gravimetric Analysis (TGA)

TGA/DTA was recorded using the instrument TA Q5000 of TA instruments. The experiments were performed at a heating rate of 10.0 °C/min over a temperature range of 30°C-300°C purging with nitrogen at a flow rate of 25ml/min.

Infrared spectroscopy (IR)

Fourier transform infrared (FT-IR) spectra were recorded with a Perkin-Elmer spectrum one spectrometer. The samples were prepared as 1 mm thickness and 13 mm diameter KBr glassy discs by triturating 1 to 3 mg of sample with 300 mg to 400 mg of KBr and applying pressure of about 1000 lbs/sq inch. Then these discs were scanned in the spectral range of 4000 to 650 cm-1 with a resolution of 4 cm-1.

Karl-Fischer (KF)

Water content was determined on Metrohm karl-Fischer titrator (Model: 794 Basic Titrino) using pyridine free single solution (Merck, Mumbai) with sample mass between 450-550 mg.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel crystalline form of Fosamprenavir Calcium designated as Form A.

In one embodiment, the crystalline Form A of Fosamprenavir Calcium is characterized by PXRD pattern as shown in Figure1.

In another embodiment, the present invention relates to crystalline Form A of Fosamprenavir Calcium characterized by an PXRD diffraction having reflections at about 3.1 ± 0.2 2Θ, 4.4 ± 0.2 2Θ, 5.0 ± 0.2 2Θ, 6.3 ± 0.2 2Θ, 7.4 ± 0.2 2Θ, 8.0 ± 0.2 2Θ.

In yet another embodiment, the present invention relates to crystalline Form A of Fosamprenavir Calcium characterized by DSC thermogram as shown in Figure 2.

In yet another embodiment, the present invention relates to crystalline Form A of Fosamprenavir Calcium characterized by TGA/DTA thermogram as shown in Figure 3.

In yet another embodiment, the present invention relates to crystalline Form A of Fosamprenavir Calcium as a hydrate with a moisture content of 2 to 5.5%.

In yet another embodiment, the present invention relates to crystalline Form A of Fosamprenavir Calcium characterized by FT-IR spectra with characteristic absorption bands (cm^{-1}) at 3467, 3373, 3062, 1690, 1317, 1147, 991, and 751 respectively; as depicted in Figure 4.

In yet another embodiment, the process for the preparation of crystalline Fosamprenavir Calcium Form A comprising the steps of;

a) dissolving Fosamprenavir Calcium salt in a solvent or mixture of solvents,

b) heating the reaction mass,

c) removing the solvent,

d) adding a second solvent, and

e) isolating crystalline form A of Fosamprenavir Calcium

According to the present invention, Fosamprenavir Calcium is dissolved in a solvent or mixture of solvents and heated the reaction mass to obtain clear solution. Removing the solvent results in a solid which is cooled and added with a second solvent. The resultant solid is filtered and dried to afford crystalline Form A of Fosamprenavir Calcium.

According to the present invention, fosamprenavir calcium is dissolved in a solvent selected from nitriles such as acetonitrile, propionitrile, acetone, methanol, ethanol,

butanol, water or their mixtures thereof the second solvent is selected from ester solvents such as ethyl acetate, chlorinated solvents such as dichloromethane, chloroform; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate; ethers such as methyl tertiary butyl ether, diethyl ether, dimethyl ether, diisopropyl ether; nitriles such as acetonitrile, propionitrile; water or their mixtures thereof.

In yet another object the present invention relates to a process for the preparation of crystalline Fosamprenavir calcium Form A comprising steps of;

a) suspending Fosamprenavir Calcium in a solvent or mixture of solvents,

b) heating the reaction mass,

c) removing the solvent,

d) adding a second solvent or mixture of solvents, and

d) isolating crystalline Form A of Fosamprenavir Calcium.

According to the present invention, Fosamprenavir Calcium is suspended in a solvent or mixture of solvents and heated the reaction mass to obtain clear solution. Removing the solvent completely and adding a second solvent followed by filtering the solid affords crystalline Form A of Fosamprenavir Calcium.

According to the present invention, fosamprenavir calcium is suspended in a solvent selected from nitriles such as acetonitrile, propionitrile, acetone, methanol, ethanol, butanol, water or their mixtures thereof and the second solvent is selected from chlorinated solvents such as dichloromethane, chloroform; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate; ethers such as methyl

tertiary butyl ether, diethyl ether, dimethyl ether, diisopropyl ether; nitriles such as acetonitrile, propionitrile,water or their mixtures thereof.

Yet another embodiment of the present invention relates to a process for the preparation of crystalline Form A of Fosamprenavir Calcium comprising the steps of

a) suspending Fosamprenavir Calcium in an solvent or mixture of solvents,

b) heating the reaction mass,

c) optionally cooling the reaction mass, and

d) isolating crystalline Form A of Fosamprenavir Calcium.

According to the present invention, Fosamprenavir Calcium is suspended in an organic solvent or mixture of solvents and heated the reaction mass to about 60 to 75°C. Optionally cooling the reaction mass and filtering affords crystalline Form A of Fosamprenavir Calcium.

According to the present invention, Fosamprenavir calcium is suspended in an organic solvent selected from ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone and cyclohexanone; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol, tertiary-butyl alcohol, cyclohexanol; chlorinated solvents such as dichloromethane, chloroform; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate; ethers such as diethyl ether, dimethyl ether, diisopropyl ether or their mixtures thereof.

Yet another object the present invention relates to a process for the preparation of crystalline Fosamprenavir calcium Form A comprising steps of;

a) suspending Fosamprenavir Calcium in a solvent or mixture of solvents,

b) heating the reaction mass,

c) seeding the reaction mass, and

d) isolating crystalline Form A of Fosamprenavir Calcium.

According to the present invention, Fosamprenavir Calcium is suspended in an organic solvent or mixture of solvents and heated the reaction mass to about 60 to 75 °temperature. Adding seed crystals of fosamprenavir calcium form A material and filtering affords crystalline Form A of Fosamprenavir Calcium.

According to the present invention, Fosamprenavir calcium is suspended in an organic solvent selected from ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone and cyclohexanone; alcohols such as methanol, ethanol, isopropanol, n-propanol, n-butanol, tertiary-butyl alcohol, cyclohexanol; chlorinated solvents such as dichloromethane, chloroform; hydrocarbon solvents such as toluene, xylene, n-hexane, n-heptane, cyclohexane; esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate; ethers such as diethyl ether, dimethyl ether, diisopropyl ether, water or their mixtures thereof.

According to the present invention, Fosamprenavir calcium used as input is selected from Fosamprenavir calcium form I or Fosamprenavir calcium amorphous form.

In yet another embodiment, the Fosamprenavir Calcium prepared according to the present invention is its hydrated form have a moisture content of 2 to 7% preferably 3.0 to 5.5%

In yet another embodiment, the Fosamprenavir Calcium prepared according to the present invention has a HPLC purity of more than 99% preferably more than 99.8%.

In yet another embodiment, the Fosamprenavir calcium Form A shows no significant degradation, no substantial increase in moisture content and no change in PXRD pattern when stored for 6 months at different stress conditions as mentioned below in table 1. This indicates that Fosamprenavir Calcium Form A is physically and chemically stable.

In yet another embodiment, physical and chemical stability of Fosamprenavir calcium Form A was determined by storing the samples at 40°C/75% relative humidity (RH), at 25°C/60% RH and at 5°C for 6 months. The material was analyzed by PXRD, water content by Karl Fischer and HPLC for final purity.

Condition	at 40°C/75%RH			at 25°C/60%RH			at 5°C		
	HPLC purity (%)	Water content (%w/w)	PXRD	HPLC purity (%)	Water content (%w/w)	PXRD	HPLC purity (%)	Water content (%w/w)	PX
Initial	99.85	4.2	Form A	99.85	4.2	Form A	99.85	4.2	For
15 days	99.84	3.5	Form A	99.85	3.7	Form A	99.85	3.6	For
1st Month	99.85	3.5	Form A	99.85	3.6	Form A	99.85	3.5	For
2nd Month	99.85	3.9	Form A	99.86	3.7	Form A	99.86	4.4	For
3rd Month	99.86	3.8	Form A	99.87	3.9	Form A	99.86	4.0	For
6th Month	99.86	3.0	Form A	99.85	3.5	Form A	99.86	3.5	For

Table -1

In yet another embodiment, the physical stability of Fosamprenavir calcium Form A was determined by storing 1.0 g of sample at 50°C and 80°C under vacuum and at 90% relative humidity (RH). The samples are tested by PXRD after 15hours and 72hours. There is no change in polymorph observed in Form A under both drying and humidity conditions. Transformation kinetics of Form A was studied by suspending 1g of Form A in appropriate solvents at 25-30°C for 15hours. The solid samples were characterized by PXRD.

Crystalline form A of Fosamprenavir Calcium is physically stable under different stress conditions. The results are shown in following Table 2.

Table 2

Condition	Duration (h)	Result
Drying at 50°C	15	Form A
	72	Form A
Drying at 80°C	15	Form A
	72	Form A
90% RH	15	Form A
	72	Form A
Slurry in n-Heptane	15	Form A
Slurry in IPE	15	Form A
Slurry in ethyl acetate	15	Form A
Slurry in acetone	15	Form A

The following examples are merely shown as representative examples of the present invention

but are not intended to be limiting.

Examples:

Example 1:

Fosamprenavir Calcium (3g) was suspended in acetonitrile (90ml) at 25 to 30 °C. The solution was heated to 70°C to get clear solution. The clear solution was stirred for 15hours at 70°C. The solid obtained was filtered and dried under vacuum at 40°C for 1hour. The product obtained was identified as Fosamprenavir Calcium novel form.

Example 2:

Fosamprenavir Calcium (1g) was suspended in acetonitrile (30ml) at 25 to 30 °C. The solution was heated to 70°C to get clear solution. To the clear solution, seeds of Fosamprenavir Calcium novel form was added and stirred for 6hours at 70°C. The solid obtained was filtered and dried under vacuum at 40°C for 1hour to afford Fosamprenavir Calcium Form A.

Example 3:

Fosamprenavir calcium (0.5g) was suspended in acetonitrile (5ml) and acetone (5 ml) at 25 to 30 °C. The solution was heated to 70°C to get clear solution. To the clear solution, seeds of Fosamprenavir calcium novel form were added and stirred for 6hours at 70°C. The solid obtained was filtered and dried under vacuum at 40°C for to afford Fosamprenavir Calcium Form A.

Example 4:

Fosamprenavir calcium (3g) was suspended in acetonitrile (60ml) at 25 to 30°C. The suspension was heated to 70°C and stirred for 15hours at 70 to 80°C. The suspension obtained was slowly cooled to 0 to 5°C and maintained for 2 to 3 hours at 0 to 5°C. The solid obtained was filtered and dried under vacuum at 40°C for 4 to 6 hours to afford crystalline Fosamprenavir calcium Form A.

Example 5:

Fosamprenavir calcium (10g) was suspended in acetonitrile (100ml) at 25 to 30°C. The suspension was heated to 70 to 80°C and stirred for 6 hours at 70 to 80°C. The suspension obtained was slowly cooled to 0 to 5°C and maintained for 2 to 3hours at 0 to 5°C. The solid obtained was filtered and dried under vacuum at 40°C for 4 to 6hours to afford crystalline Fosamprenavir calcium Form A.

Example 6:

Fosamprenavir Calcium (10g) was suspended in acetonitrile (150ml) at 25 to 30°C. The suspension was heated to 70 to 80°C and stirred for 6 hrs at 70 to 80°C. The suspension obtained was slowly cooled to 0 to 5°C and maintained for 2 to 3 hours at 0-5°C. The solid obtained was filtered and dried under vacuum at 40°C for 4 to 6 hrs to afford crystalline Fosamprenavir Calcium Form A.

Example 7:

Fosamprenavir calcium (10g) was suspended in acetonitrile (100ml) and acetone (100ml) at 25 to 30 °C. The suspension was heated to 70 to 80°C and stirred for 6hours at 70 to 80°C. The suspension obtained was slowly cooled to 0-5°C and maintained at 0-5°C for 2 to 3hours. The solid obtained was filtered and dried under vacuum at 40°C for 4 to 6hours to afford crystalline Fosamprenavir Calcium Form A.

Example 8:

Fosamprenavir Calcium (3g) was suspended in acetonitrile (15ml) and acetone (30ml) at 25-30°C. The suspension was heated to 70-80°C and stirred for 2 to 3 hours at 70 to 80°C. The suspension obtained was slowly cooled to 0 to 5°C and added acetone (30 ml) at 0 to 5°C. The solid obtained was filtered and dried under vacuum at 40°C for 4-6 hours to afford crystalline Fosamprenavir Calcium Form A.

Example 9:

Fosamprenavir calcium Form I (20g) was suspended in acetonitrile (100 ml) at 25-30°C. The suspension was heated to 70-75°C and maintained under agitation for 4hours at 70-75°C. The resulting suspension was distilled off completely to remove solvent and then kept under vacuum for 30 minutes to 1hour. The reaction mass was slowly cooled to 25-30°C, added methyl tertiary butyl ether (100 ml) and stirred for 2hours at 25-30°C. The obtained solid was filtered, washed with methyl tertiary butyl ether (50 ml), dried at 50°C under vacuum for 15hrs. The solid obtained was identified as crystalline Fosamprenavir calcium Form A.

Example 10:

Fosamprenavir calcium Form I (100g) was suspended in acetonitrile (500 ml) at 25-30°C. The suspension was heated to 70-75°C and maintained under agitation for 4 hours at 70-75°C. The resulting suspension was distilled off completely to remove solvent and then kept under vacuum for 30 minutes to 1 hour. To the reaction mass, acetonitrile (300 ml), ethyl acetate (800 ml) were added and stirred for 15 hours at 70-75°C. The suspension was slowly cooled to 0-5°C and stirred for 1hour at 0-5°C. The obtained solid was filtered, washed with ethyl acetate (200 ml) and dried at 50° under vacuum for 15 hours. The solid obtained was identified as crystalline Fosamprenavir calcium Form A.

Example 11:

Fosamprenavir calcium Form I (50g) was suspended in methanol (100 ml) and acetonitrile (200ml) at 25-30°C. The solution was heated to 40-50°C to obtain clear solution and maintained under agitation for 1hour at 45-50°C. The clear solution was filtered through hy-flo and washed with acetonitrile (50 ml). The clear solution was distilled off completely at 60-65°C to remove solvent and kept under vacuum for 30 minutes to 1 hour. To the reaction mass, acetonitile (250 ml) was added and

heated to 70-75°C. The solvent was distilled off completely and kept under vacuum for 30 minutes to 1hour. To the reaction mass, acetonitrile (150 ml), ethyl acetate (400 ml) were added and stirred for 15 hours at 70-75°C. The suspension was cooled to 0-5°C and then stirred for 1hour at 0-5°C. The obtained solid was filtered and washed with ethyl acetate (50 ml) and dried at 50°C under vacuum for 15hours. The solid obtained was identified as crystalline Fosamprenavir calcium Form A.

Example 12:

Fosamprenavir calcium amorphous form (50g) was dissolved in acetonitrile (250 ml) and water (4.0 ml) at 25-30°C. The clear solution is heated to 70-75°C and maintained under agitation for 4h at 70-75°C. The solvent was distilled off completely at 70-75°C and kept under vacuum for 030 minutes to 1 hour. The obtained solid is slowly cooled to 25-30°C and added methyl tertiary butyl ether (250 ml) and stirred for 2 hours at 25-30°C. The obtained solid was filtered, washed with methyl tertiary butyl ether (50 ml) and dried at 50°C under vacuum for 15hours. The solid obtained was identified as crystalline Fosamprenavir calcium Form A.

Example 13:

Fosamprenavir calcium amorphous form (50g) was dissolved in acetonitrile (250 ml) and water (4.0 ml) at 25-30°C. The clear solution is heated to 70-75°C and maintained under agitation the reaction mass for 4 hours at 70-75°C. The solvent was distilled off completely at 70-75°C and kept under vacuum for 30 minutes to 1 hour. The obtained solid is slowly cooled to 25-30°C and added acetonitrile (100 ml), ethyl acetate (200 ml) and stirred for 2 hours at 25-30°C. The obtained solid was filtered, washed with ethyl acetate (50 ml) and dried at 50°C under vacuum for 15 hours. The solid obtained was identified as crystalline Fosamprenavir calcium Form A.

We claim:

1) Crystalline Fosamprenavir Calcium Form A

2) Crystalline Fosamprenavir Calcium Form A, characterized by powder X-ray diffraction pattern as shown in Figure 1.

3) Crystalline Fosamprenavir calcium Form A having at least one of the characteristic peaks at 4.4 ± 0.2, 5.0 ± 0.2, 6.3 ± 0.2, 7.4 ± 0.2, 8.0 ± 0.2 2Θ.

4) A process for the preparation of crystalline Fosamprenavir Calcium Form A comprising the steps of;

a) dissolving Fosamprenavir Calcium salt in a solvent or mixture of solvents

b) heating the reaction mass

c) removing the solvent

d) adding a second solvent or mixture of solvents; and

e) isolating crystalline form A of Fosamprenavir Calcium.

5) The process according to claim 4, wherein the solvent in step a is selected from acetonitrile, methanol, ethanol, butanol, acetone, water or mixtures thereof and the second solvent is selected from methyl tertiary butyl ether, acetonitrile, esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate or mixtures thereof.

6) Crystalline fosamprenavir calcium form A, characterized by a DSC thermogram as shown in Figure 2.

7) Crystalline fosamprenavir calcium form A, characterized by a TGA thermogram as shown in Figure 3.

8) Crystalline fosamprenavir calcium form A, characterized by FT-IR spectra with characteristic absorption bands (cm^{-1}) at 3467, 3373, 3062, 1690, 1317, 1147, 991, and 751.

9) Crystalline fosamprenavir calcium having at least one of the characteristics selected from;

a) Moisture content between 3 to 5.5.

b) Purity more than 99.9% by HPLC

10) A process for the preparation of crystalline Fosamprenavir calcium Form A comprising steps of;

a) suspending Fosamprenavir Calcium in a solvent or mixture of solvents,

b) heating the reaction mass,

c) removing the solvent,

d) adding a second solvent, and

d) isolating crystalline Form A of Fosamprenavir Calcium.

11) The process according to claim 10, wherein the solvent in step a is selected from acetonitrile, acetone, ethyl acetate, methanol, methyl tertiary butyl ether or their mixtures thereof and second solvent is selected form methyl tertiary butyl ether, acetonitrile, ethyl acetate, acetone, water or their mixtures thereof.

12) A process for the preparation of crystalline Form A of Fosamprenavir Calcium comprising the steps of

a) suspending Fosamprenavir Calcium in an solvent or mixture of solvents,

b) heating the reaction mass,

c) optionally cooling the reaction mass, and

d) isolating crystalline Form A of Fosamprenavir Calcium.

13) A process for the preparation of crystalline Fosamprenavir calcium Form A comprising steps of;

a) suspending Fosamprenavir Calcium in a solvent or mixture of solvents,

b) heating the reaction mass,

c) seeding the reaction mass, and

d) isolating crystalline Form A of Fosamprenavir Calcium.

14) The process according to claim 12 and 13, wherein the solvent in step a is selected from acetonitrile, acetone, ethyl acetate, methanol, methyl tertiary butyl ether or their mixtures thereof

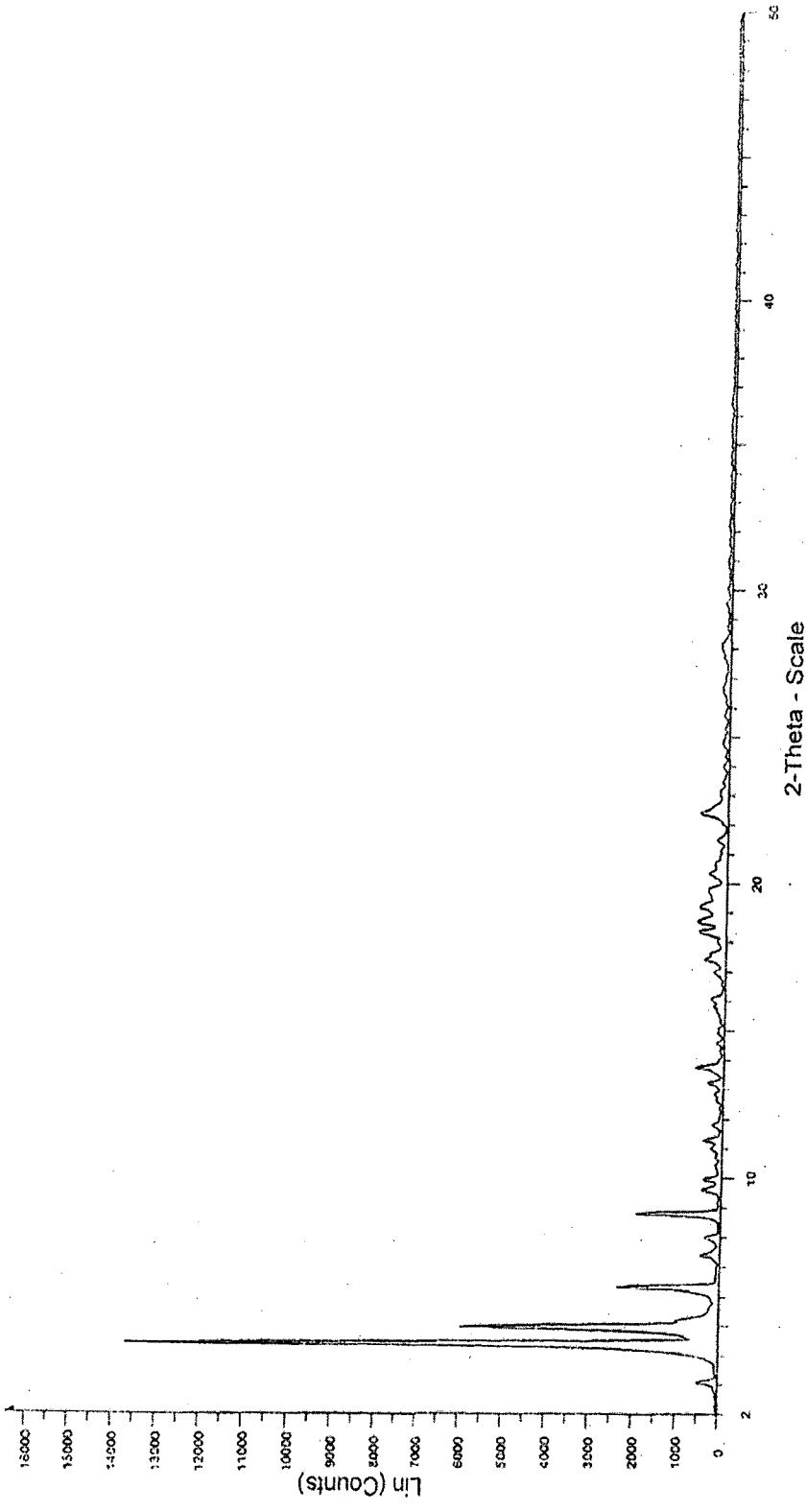

Mylan Laboratories Ltd
Lin (Counts)
2-Theta - Scale
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
11000
12000
13000
14000
15000
16000
2
10
20
30
40
50

Fig. 1 (Form A)

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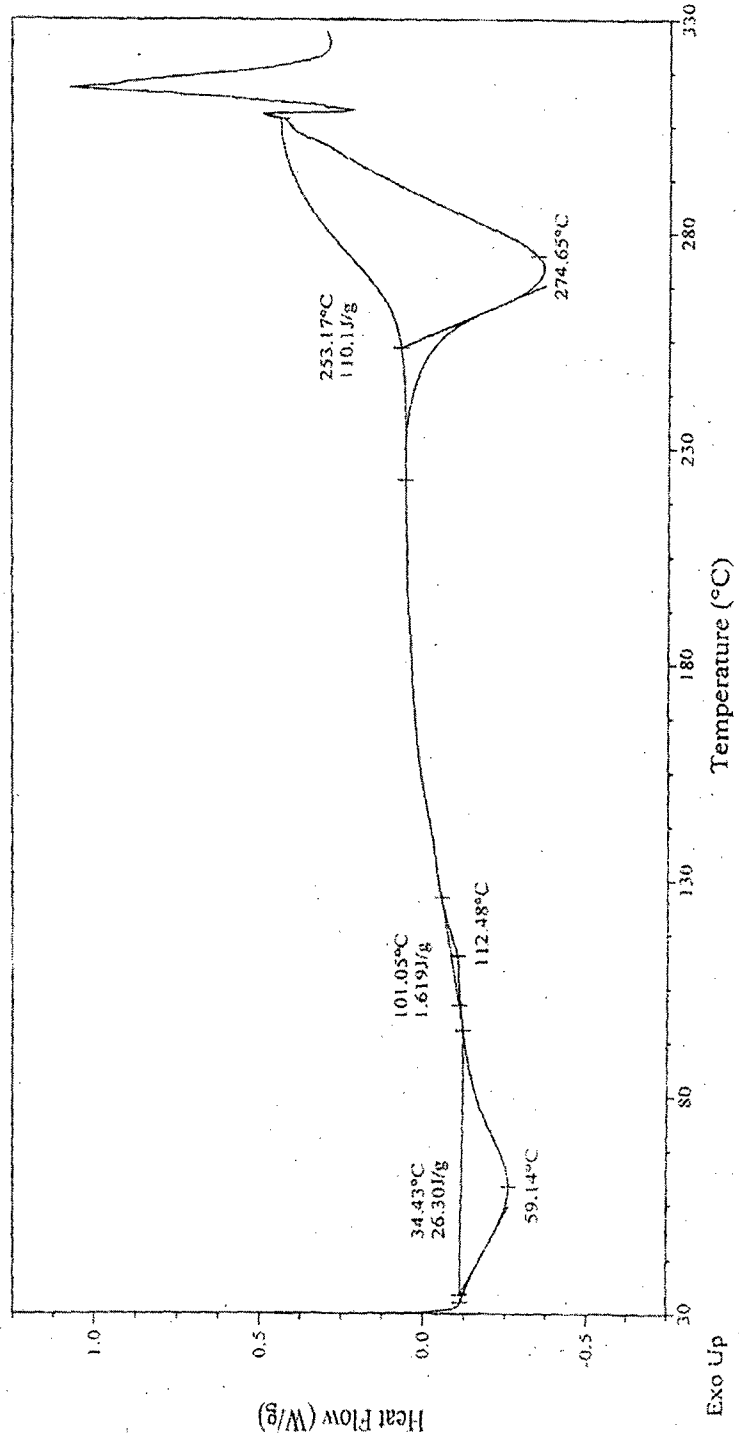
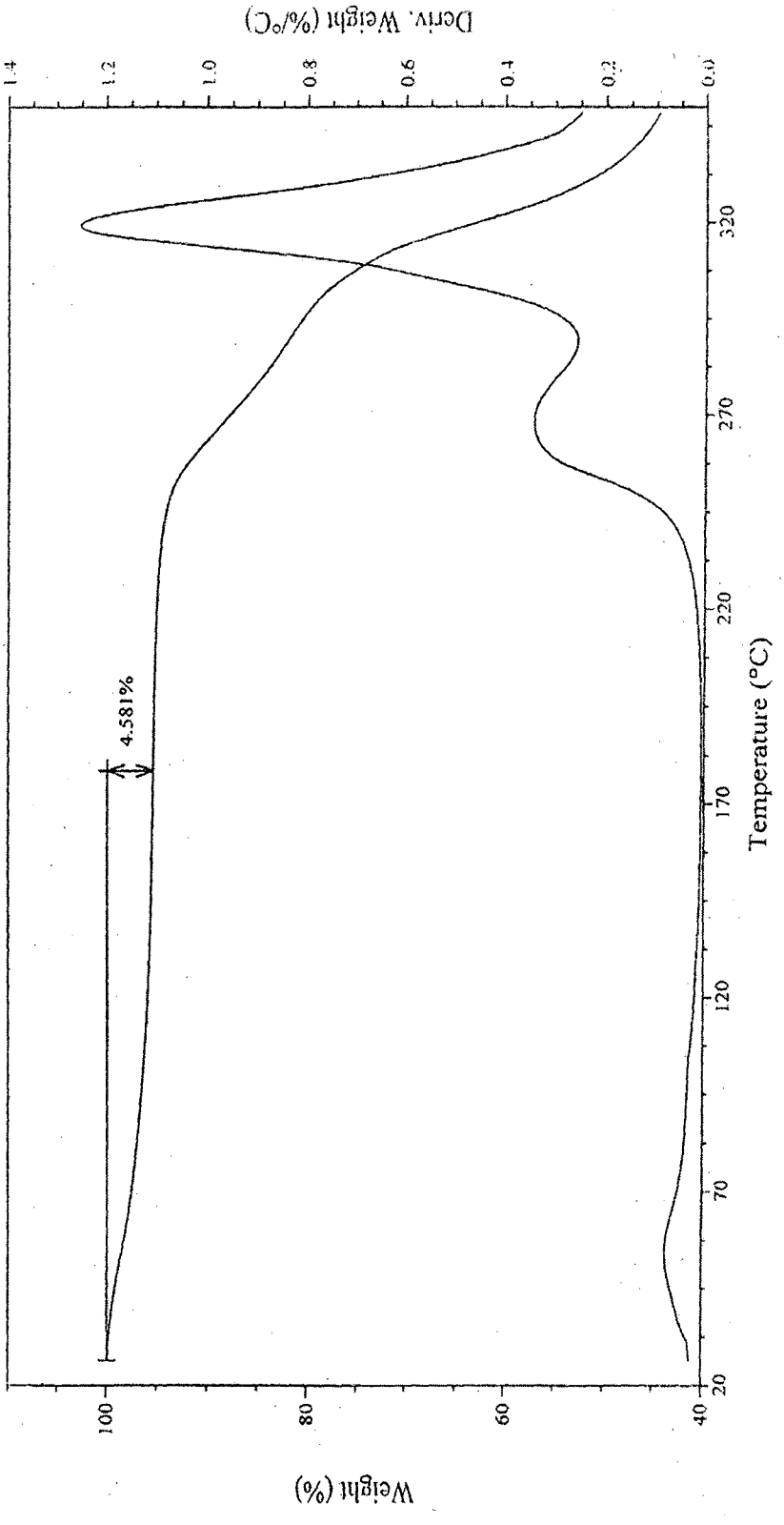


Fig 2 (DSc)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Weight (%)
Deriv. Weight (%/°C)
Temperature (°C)
4.581%
100
80
60
40
20
70
120
170
220
270
320
0.2
0.4
0.6
0.8
1.0
1.2
1.4

Fig. 3 (TGA)

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