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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF CLOPIDOGREL BISULFATE FORM I

(57) Abstract: The present invention relates to an improved process for the preparation of Clopidogrel bisulfate Form I from clopidogrel free base. Whereas Clopidogrel free base is isolated from Clopidogrel acid addition salt.

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AN IMPROVED PROCESS FOR THE PREPARATION OF CLOPIDOGREL BISULFATE FORM I

This application claims priority to Indian patent application No. 2637/CHE/2009 filed on October 30, 2009, the contents of which are incorporated by reference in their entirety

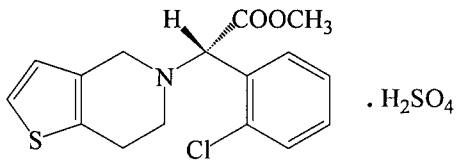
FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of Clopidogrel bisulfate Form I from clopidogrel free base. Whereas free base is isolated from Clopidogrel acid addition salts.

BACKGROUND OF THE INVENTION

Clopidogrel, having the chemical name (+)-(S)-α-(2-Chlorophenyl)-6, 7-dihydrothieno [3, 2-c] pyridin-5(4H)-acetic acid methyl ester is an antithrombotic drug. It acts as an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of glycoprotein GPIIb/IIIa complex. By inhibiting platelet aggregation, Clopidogrel reduces the chance of arterial blockage, thus preventing strokes and heart-attacks.

Clopidogrel is marketed as bisulfate salt having the following chemical structure of formula 1:



Formula 1

US 4847265 patent first discloses clopidogrel or it's salts, wherein clopidogrel is prepared from racemic clopidogrel using camphoursulfonic acid and further converted to acid addition salts.

US 6429210 patent discloses Clopidogrel bisulfate polymorphic forms I and II. This patent also discloses Clopidogrel bisulfate form I is prepared according to the process of US '265 using acetone and sulfuric acid.

US 6767913 patent discloses new polymorphic forms III, IV, V and amorphous Clopidogrel bisulfate and processes for their preparation.

US 2006/0047121 application discloses the precipitation of Clopidogrel bisulfate Form I by dissolving Clopidogrel bisulfate Form II in a C_1-C_5 carboxylic acid and by precipitating in the presence of an aliphatic or cyclic ether.

WO2004020443 application describes process for preparation of Clopidogrel bisulfate Form I, which comprises separating out crystalline Form I from the solution of Clopidogrel in the form of free base or salt in a solvent selected from the series of the primary, secondary or tertiary alcohols or their esters with carboxylic acids or optionally of mixtures thereof.

WO 2004/048385 application discloses processes for the preparation of Clopidogrel bisulfate Form I by dissolving Clopidogrel free base in ethanol followed by addition sulfuric acid and precipitated by adding an anti solvent like methyl tert-butyl ether.

These above processes were repeated in our laboratory but resulted in inconsistency of the polymorphic form, lack of reproducibility and poor yield of the product.

The present invention overcomes the problems associated with prior art processes. The present invention further directed to an improved, industrially viable, cost-effective process for the manufacturing of Clopidogrel bisulfate of polymorphic Form I.

SUMMARY OF THE INVENTION

The present invention relates to an improved process for preparation of Clopidogrel bisulfate Form I.

One aspect, the present invention provides process for the preparation of clopidogrel bisulfate form I comprising the steps of: a) dissolving Clopidogrel bisulfate in organic solvent and water, b) adding a base to get clopidogrel freebase, c) dissolving Clopidogrel free base in an organic solvent, d) optionally adding a catalyst, e) adding an ether solvent containing sulfuric acid, and f) isolating Clopidogrel bisulfate Form I.

Another aspect of the present invention provides a process for preparation of Clopidogrel free base comprising the steps of: a) dissolving Clopidogrel bisulfate in organic solvent and water, b) adding a base, and c) isolating Clopidogrel free base.

Yet another aspect of the present invention provides a process for preparation of Clopidogrel bisulfate Form I comprising the steps of: a) dissolving Clopidogrel bisulfate form II in an organic

solvent at an elevated temperature, b) cooling the solution, c) adding an ether solvent, and d) isolating Clopidogrel bisulfate Form I.

Yet another aspect of the present invention provides stable Clopidogrel bisulfate Form I during storage.

Yet another aspect of the present invention provides a process for packaging and storing Clopidogrel bisulfate Form I with increased stability and shelf life, which includes placing Clopidogrel bisulfate Form I in a sealed container along with a moisture adsorbent.

Yet another aspect of the present invention provides packing conditions of Clopidogrel bisulfate polymorphic form I, which comprise the steps of:

a) Placing Clopidogrel bisulfate form I in innermost LDPE or HMLDPE bag under nitrogen atmosphere, twisted and tied or vacuumized nitrogen sealing,
b) Placing the innermost bag in a middle triple laminated aluminum bag under vaccumized nitrogen sealing along with a moisture adsorbent,
c) Placing the middle bag in an outer triple laminated aluminum bag under vacuumized nitrogen sealing along with a moisture adsorbent.

BRIEF DESCRIPTION OF THE FIGURES

Fig 1 shows an X-ray Diffraction diagram of Clopidogrel Bisulfate Form I.
Fig 2 shows the DSC Thermogram of Clopidogrel Bisulfate Form I.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is related to an improved process for the preparation of Clopidogrel bisulfate Form I by dissolving clopidogrel bisulfate form II in aqueous organic solvent, neutralizing the salt with a base to get clopidogrel freebase, followed by treatment with sulfuric acid in the presence of ether solvent.

In one embodiment, the present invention provides a process for preparation of Clopidogrel bisulfate Form I comprising the steps of:

a) dissolving Clopidogrel bisulfate in an organic solvent and water,
b) adding a base to get clopidogrel freebase,
c) dissolving Clopidogrel free base in a solvent,

d) adding an ether solvent containing sulfuric acid, and

e) Isolating Clopidogrel bisulfate Form I.

According to the present invention Clopidogrel bisulfate is dissolved in a mixture of an organic solvent and water at ambient temperature, neutralized with a base. Organic layer is separated; solvent is removed to get clopidogrel freebase as oil. Clopidogrel base is dissolved in solvent at ambient temperature; the resulting solution is cooled to -20 to 5°C, preferably -15 to -5°C. To this solution is added to pre-cooled solution of sulfuric acid containing ether solvent for about 45-90 min. the suspension is further stirred for about 15-24hours. The obtained solid is isolated as clopidogrel bisulfate form I

According to the present invention the organic solvent used for the dissolution of clopidogrel bisulfate is selected from chlorinated hydrocarbon solvent such as dichloromethane, aliphatic ester solvent such as ethyl acetate or mixture thereof.

According to the present invention base used for neutralization is selected from aqueous alkali metal carbonates such as sodium bicarbonate or aqueous alkali metal hydroxides such as sodium hydroxide.

According to the present invention solvent is removed to get clopidogrel freebase by distillation, or evaporation.

According to the present invention solvent used for the dissolution of clopidogrel free base is selected from ether solvents such as isopropyl ether, carboxylic acids such as acetic acid, ketone solvent such as acetone or mixture thereof.

In a preferred embodiment the ratio of carboxylic acid to the C_3 to C_6 aliphatic ketone varies from 1:5 to 5:1, preferably from 1:3 to 3:1.

The sulfuric acid is dissolved in an ether solvent, which is preferably pre-cooled to a temperature of -25°C to 0°C, more preferably to a temperature of -15°C to -10°C. The Clopidogrel solution is then added to a pre-cooled solution of sulfuric acid, the product precipitates out and the obtained solid is filtered.

Another embodiment, the present invention provides a process for preparation of Clopidogrel free base comprising the steps of:

a) dissolving clopidogrel bisulfate in an organic solvent and water,

b) adding an base,
c) optionally adding an anti-oxidant , and
d) isolating clopidogrel free base.

According to the present invention Clopidogrel bisulfate is dissolved in a mixture of an organic solvent and water at ambient temperature, neutralized with aqueous inorganic base. Organic layer is separated, optionally added catalyst and solvent is removed to get clopidogrel freebase as oil.

According to the present invention the organic solvent used for the dissolution of clopidogrel bisulfate is selected from chlorinated hydrocarbon solvent such as dichloromethane, aliphatic ester solvent such as ethyl acetate or mixture thereof.

According to the present invention base used for neutralization is selected from alkali metal carbonates such as sodium bicarbonate or alkali metal hydroxides such as sodium hydroxide. According to the present invention solvent is removed to get clopidogrel freebase by distillation, or evaporation.

According to the present invention an anti-oxidant employed is selectged from butylated hydroxy toluene (BHT), sodium dithionite, sodium metabisulphite or resveratrol.

In yet another embodiment, the present invention provides a process for preparation of Clopidogrel bisulfate Form I comprising the steps of:

a) dissolving Clopidogrel bisulfate form II in acetic acid at an elevated temperature,
b) cooling the solution,
c) adding ether solvent,
d) isolating Clopidogrel bisulfate Form I.

According to the present invention Clopidogrel bisulfate Form II is dissolved in acetic acid at an elevated temperature, preferably at 80°C to 110°C, more preferably at 90°C to 100°C. The solution was thereafter cooled to 25-30°C. The ether solvent selected from the group consisting of diisopropyl ether, methyl tert-butyl ether, diethyl ether, preferably diisopropyl ether. The suspension is allowed to stir for a time period of 12 to 24 hours, preferably 15 to 18 hours, to enable the precipitation of free flowing white solid.

In Yet another embodiment of the present invention provides packing conditions of Clopidogrel bisulfate polymorphic form I, which comprise the steps of:

a) Placing Clopidogrel bisulfate form I in innermost LDPE or HMLDPE bag under nitrogen atmosphere, twisted and tied or vacuumized nitrogen sealing,

b) Placing the innermost bag in a middle triple laminated aluminum bag under vaccumized nitrogen sealing along with a moisture adsorbent,

c) Placing the middle bag in an outer triple laminated aluminum bag under vacuumized nitrogen sealing along with a moisture adsorbent.

According to the present invention, packaging and storing Clopidogrel bisulfate Form I with increased stability and shelf life, which includes placing Clopidogrel bisulfate Form I in a sealed container along with a moisture adsorbent.

According to the present invention, the moisture adsorbent is included to absorb any moisture which enters the packaging. Suitable moisture adsorbents which can be used in the present invention are selected from molecular sieve zeolites, high silica zeolites, having a high silica/alumina ratio of 25 or more, such as ZSM-5 (made by Mobil Oil Co., silica/alumina ratio of 400), silicalite, USY (Ultra Stable Y type).

The invention is further illustrated by the following non-limiting examples.

EXAMPLES

Example 1: Purification of Clopidogrel Bisulfate Form II

The Clopidogrel free base (73 g) was dissolved in acetone (1500 ml) at 25-30°C and cooled to 0-5°C. To this solution, conc. sulfuric acid (22.2 g) was added drop wise for 10 min at 0-5 °C followed by slowly raising the temperature to 25-30°C. The reaction mass was stirred for 15 h at 25-30 °C. The obtained solid was filtered, washed with acetone (100 ml) and dried under vacuum at 50°C for 2 hours.

Example 2: Preparation of Clopidogrel Free base from Form II

Clopidogrel bisulfate Form II (200 g) was dissolved in ethyl acetate and water [800 ml (1:1)] at 25-30°C. The clear solution was cooled to 0-5°C and pH was adjusted to 7 using saturated sodium bicarbonate solution. The organic layer was extracted with ethyl acetate (2X200 ml). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum at 40-45°C to give Clopidogrel free base as viscous oil.

Example 3: Preparation of Clopidogrel Bisulfate Form I from free base

Isopropyl ether (750 ml) and conc. sulfuric acid (7.6 g) were charged in a RB flask and cooled to -10°C to -15°C. Clopidogrel free base (25 g) was dissolved in acetic acid (25 ml) at 25-30°C and cooled to 0-5°C. This solution was added to the above pre-cooled Isopropyl ether solution drop wise for 5-10 min. The solid suspension obtained was stirred for 5 hours at -10 to -15°C and further stirring continued at 25-30 °C for 15 hours. The solid obtained was filtered, washed with isopropyl ether (3X25 ml) and dried at 50 °C for 3h. The solid was then grinded thoroughly and slurred in isopropyl ether (250 ml) for 2h at 25-30°C.The solid was filtered, washed with isopropyl ether (25 ml) and dried under vacuum at 50 °C for 15hours.

HPLC Purity: 99.23 %.

Example 4: Preparation of Clopidogrel Bisulfate Form I from free base

Isopropyl ether (750 ml) and sulfuric acid (7.6 g) were charged in a RB flask and cooled to -10 to -15°C. Clopidogrel free base (25 g) was dissolved in mixture of acetone (7 ml) and acetic acid (18 ml) at 25-30°C and cooled to 0-5°C. This solution was added to the above pre-cooled isopropyl ether solution in 5-10 min. The solid suspension obtained was stirred for 5 h at -10 to -15°C and further stirring continued at 25-30 °C for 15 hours. The solid obtained was filtered, washed with isopropyl ether (3X25 ml) and dried at 50 °C for 3hours. The solid was then grinded thoroughly and slurred in isopropyl ether (250 ml) for 2 hours at 25-30°C. The solid obtained was filtered, washed with isopropyl ether (25 ml) and dried under vacuum at 50 °C for 15hours.

Example 5: Preparation of Clopidogrel Bisulfate Form I from free base

Isopropyl ether (750 ml) and sulfuric acid (7.6 g) were charged in a RB flask and cooled to -10 to -15°C. Clopidogrel free base (25 g) was dissolved in mixture of acetone (12.5 ml) and acetic acid (12.5 ml) at 25-30°C in 10 min. and cooled to 0-5°C. This solution was added to the above pre-cooled isopropyl ether solution in 5-10 min. The solid suspension obtained was stirred for 5 hours at -10 to -15°C and further stirring continued at 25-30 °C for 15 hours. The solid obtained was filtered, washed with isopropyl ether (3X25 ml) and dried at 50 °C for 3hours. The solid was then grinded thoroughly and slurred in isopropyl ether (250 ml) for 2 hours at 25-30°C.The product obtained was filtered, washed with isopropyl ether (25 ml) and dried under vacuum at 50 °C for 15hours.

Example 6: Preparation of Clopidogrel Bisulfate Form I from free base

Isopropyl ether (750 ml) and sulfuric acid (7.6 g) were charged in a RB flask and cooled to -10 to -15°C. Clopidogrel free base (25 g) was dissolved in mixture of acetone (18 ml) and acetic acid (7 ml) at 25-30°C in 10 min. and cooled to 0-5°C. This solution was added to the above

pre-cooled isopropyl ether solution in 5-10 min. The solid suspension obtained was stirred for 5 hours at -10 to -15°C and further stirring continued at 25-30 °C for 15 hours. The solid obtained was filtered, washed with isopropyl ether (3X25 ml) and dried at 50 °C for 3 hours. The solid was then grinded thoroughly and slurred in isopropyl ether (250 ml) for 2 hours at 25-30°C. The solid obtained was filtered, washed with isopropyl ether (25 ml) and dried under vacuum at 50 °C for 15hours.

HPLC Purity: 99.5 %

Example 7: Preparation of Clopidogrel Bisulfate Form I from Form II

Clopidogrel Bisulfate Form II (25 g) was dissolved in acetic acid (20 ml) at 90-100°C. The clear solution was cooled to 25-30°C and isopropyl ether (750 ml) was added slowly for 3 hours. Initially gummy material formed which was stirred overnight at 25-30°C to give free flowing solid. The obtained solid was filtered, washed with isopropyl ether (2X25 ml) and dried at 50 °C for 3 hours. The solid was then grinded thoroughly and slurred in isopropyl ether (250 ml) for 2 hours at 25-30°C.The solid obtained was filtered, washed with isopropyl ether (25 ml) and dried at 50 °C for 15hours.

HPLC Purity: 99.46 %.

Example 8: Preparation of Clopidogrel Bisulfate Form I from Form II

Clopidogrel bisulfate Form II (100 g) was dissolved in dichloromethane and water [400 ml (1:1)] at 20-25°C. The clear solution was cooled to 20-25°C and pH was adjusted to 7 using saturated NaHCO3 solution. The organic layer was extracted with dichloromethane. The combined organic layers was dried over Na_2SO_4 and added butylated hydroxy toluene (0.52 g), and then concentrated under vacuum at 40-45°C to give Clopidogrel free base as viscous oil (76.6 g). This was dissolved in isopropyl ether (1149 mL) and filtered through hyflow bed and the bed was further washed with isopropyl ether (383 mL). The filtrate was cooled to -15 to -10°C and added acetone (72.7 mL) and acetic acid (3.83 mL) at the same temperature. To this added pre-cooled (0 to 5°C) solution of sulfuric acid (21.5 g) and isopropyl ether (766 mL) at -15 to -10°C for 60-90 minutes and the suspension was maintained at same temperature for 5 hours then raised to RT and maintained for 10 to 12 hours. The reaction mass was filtered and washed with isopropyl ether (2×76 mL) under nitrogen atmosphere. The solid was dried at 60-65°C in dehumidified conditions (40 ± 5% RH).

Example 9: Preparation of Clopidogrel Bisulfate Form I from Form II

Clopidogrel bisulfate Form II (100 g) was dissolved in dichloromethane and water [400 ml (1:1)] at 20-25°C. The clear solution was cooled to 20-25°C and pH was adjusted to 7

Using saturated NaHCO3 solution. The organic layer was extracted with dichloromethane.

The combined organic layers was dried over Na_2SO_4 and added butylated hydroxy toluene (0.52 g), and then concentrated under vacuum at 40-45°C to give Clopidogrel free base as viscous oil (76.6 g). This was dissolved in isopropyl ether (1149 mL) and filtered through hyflow bed and the bed was further washed with isopropyl ether (383 mL). The filtrate was cooled to -15 to -10°C and added acetone (76.6 mL) at the same temperature. To this added pre-cooled (0 to 5°C) solution of sulfuric acid (21.5 g) and isopropyl ether (766 mL) at -15 to -10°C for 60-90 minutes and the suspension was maintained at same temperature for 5 hours then raised to RT and maintained for 10 to 12 hours. The reaction mass was filtered under nitrogen atmosphere. The solid was dried at 60-65°C in dehumidified conditions (40 ± 5% RH).

Example 10: Preparation of Clopidogrel Bisulfate Form I from Form II

Clopidogrel bisulfate Form II (100 g) was dissolved in dichloromethane and water [400 ml (1:1)] at 20-25°C. The clear solution was cooled to 20-25°C and pH was adjusted to 6.5-7.5 using saturated NaHCO3 solution. The organic layer was extracted with dichloromethane (2 × 100 ml). The combined organic layers was dried over Na_2SO_4 and added butylated hydroxy toluene (0.52 g), and then concentrated under vacuum at 40-45°C to give Clopidogrel free base as viscous oil (76.6 g). This was dissolved in isopropyl ether (1149 mL) and filtered through hyflow bed and the bed was further washed with isopropyl ether (383 mL). The filtrate was cooled to -15 to -10°C and added acetic acid (76.6 mL) at the same temperature. To this added pre-cooled (0 to 5°C) solution of sulfuric acid (21.5 g) and isopropyl ether (766 mL) at -15 to -10°C for 60-90 minutes and the suspension was maintained at same temperature for 5 hours then raised to RT and maintained for 10 to 12 hours. The reaction mass was filtered and washed with isopropyl ether (2 ×76 mL) under nitrogen atmosphere. The solid was dried at 60-65°C in dehumidified conditions (40 ± 5% RH).

Example 11: Preparation of Clopidogrel Bisulfate Form I from Form II

Clopidogrel bisulfate Form II (100 g) was dissolved in dichloromethane and water [400 ml (1:1)] at 20-25°C. The clear solution was cooled to 20-25°C and pH was adjusted to 7
Using saturated NaHCO3 solution. The organic layer was extracted with dichloromethane.
The combined organic layers was dried over Na_2SO_4 and added butylated hydroxy toluene (0.52 g), and then concentrated under vacuum at 40-45°C to give Clopidogrel free base as viscous oil (76.6 g). This was dissolved in isopropyl ether (1149 mL) and filtered through hyflow bed and the bed was further washed with isopropyl ether (383 mL). The filtrate was cooled to -15 to -10°C. To this added pre-cooled (0 to 5°C) solution of sulfuric acid (21.5 g) and isopropyl ether (766 mL) at -15 to -10°C for 60-90 minutes and the suspension was maintained at same temperature for 5 hours then raised to RT and maintained for 18 to 24 hours. The reaction

mass was filtered and washed with isopropyl ether (2 ×76 mL) under nitrogen atmosphere. The solid was dried at 60-65°C in dehumidified conditions (40 ± 5% RH).

Example 12: Preparation of Clopidogrel Bisulfate Form I from free base

Clopidogrel free base (10 g) was dissolved in mixture of acetone (9.7 ml) and acetic acid (0.3 ml) at 25-30°C and cooled to 0-5°C and added butylated hydroxy toluene (0.068 g). This solution was added to a pre-cooled (-10 to -15°C) solution of isopropyl ether (300 ml) and sulfuric acid (2.7 g) over 5-10 min. The solid suspension obtained was stirred for 5 hours at -10 to -15°C and then at 25-30 °C for 15 hours. The solid obtained was filtered, washed with isopropyl ether (2×20 ml) and dried under vacuum at 50-60°C for 15hours.

Example 13: Preparation of Clopidogrel Bisulfate Form I from free base

Clopidogrel free base (50 g) was dissolved in acetone (50 ml) and cooled to 0-5°C and added butylated hydroxy toluene (0.342 g). This solution was added to a pre-cooled (-10 to -15°C) solution of isopropyl ether (1500 mL) and sulfuric acid (14 g) over 5-10 min. The solid suspension obtained was stirred for 5 hours at -10 to -15°C and then at 25-30 °C for 15 hours. The solid formed was filtered, washed with isopropyl ether (2×50 ml) and dried under vacuum at 50-60°C for 15hours.

Example14: Process for packing and storage conditions of Clopidogrel bisulfate form I.

Packing conditions: The material shall be packed in LDPE/ HMLDPE bag then twisted and tied/ vacuumised nitrogen sealing. It is then inserted in triple laminated aluminum bag and adds two silica and one molecular sieve sachet and vacuumised nitrogen sealing. Both these bags are then put into outer bag of triple laminated aluminum bag and add two silica gel sachets and one molecular sieve sachet and vacuumised nitrogen sealing.

Storage conditions: Preserve in well-closed, tight containers and store at room temperature 0 to ambient temperature.

We Claim:

1. A process for preparation of Clopidogrel bisulfate Form I comprising the steps of:
    b) dissolving Clopidogrel bisulfate in an organic solvent and water,
    c) adding an inorganic base to get clopidogrel free base,
    d) dissolving Clopidogrel free base in a solvent,
    e) adding an ether solvent containing sulfuric acid, and
    f) isolating Clopidogrel bisulfate Form I.

2) A process for preparation of Clopidogrel free base comprising the steps of:
    a) dissolving Clopidogrel bisulfate in an organic solvent and water,
    b) adding an inorganic base,
    c) optionally adding an anti-oxidant, and
    d) isolating Clopidogrel free base.

3) The process according to claim 1 or 2 wherein the organic solvent is selected from chlorinated hydrocarbon solvent such as dichloromethane, aliphatic ester solvent such as ethyl acetate or mixture thereof.

4). The process according to claims 1 or 2 wherein the inorganic base is selected from sodium carbonate, potassium carbonate, potassium bicarbonate or sodium bicarbonate.

5) The process according to claim 1, wherein solvent used in step 1(c) is selected from ether solvents such as isopropyl ether, carboxylic acids such as acetic acid, ketone solvent such as acetone or mixture thereof.

6) The process according to claim 2, where in anti-oxidant is selected from butylated hydroxy toluene (BHT), sodium dithionite, sodium metabisulphite or resveratrol.

7) A process for the preparation of Clopidogrel bisulfate Form I comprising the steps of:
    a) dissolving Clopidogrel bisulfate form II in acetic acid at an elevated temperature,
    b) cooling the solution,
    c) adding ether solvent,
    d) isolating Clopidogrel bisulfate Form I.

8) The process according to claims 1 or 7, wherein ether solvent is selected from diisopropyl ether, isopropyl ether or tert-butyl ether.

9) Process of packing Clopidogrel bisulfate polymorphic form I, which comprise the steps of:
   a) Placing Clopidogrel bisulfate form I in innermost LDPE or HMLDPE bag under nitrogen atmosphere, twisted and tied or vacuumized nitrogen sealing,
   b) Placing the innermost bag in a middle triple laminated aluminum bag under vaccumized nitrogen sealing along with a moisture adsorbent,
   c) Placing the middle bag in an outer triple laminated aluminum bag under vacuumized nitrogen sealing along with a moisture adsorbent.

10) The process according to claim 9, wherein the moisture adsorbent is selected from molecular sieve zeolites or high silica zeolites.

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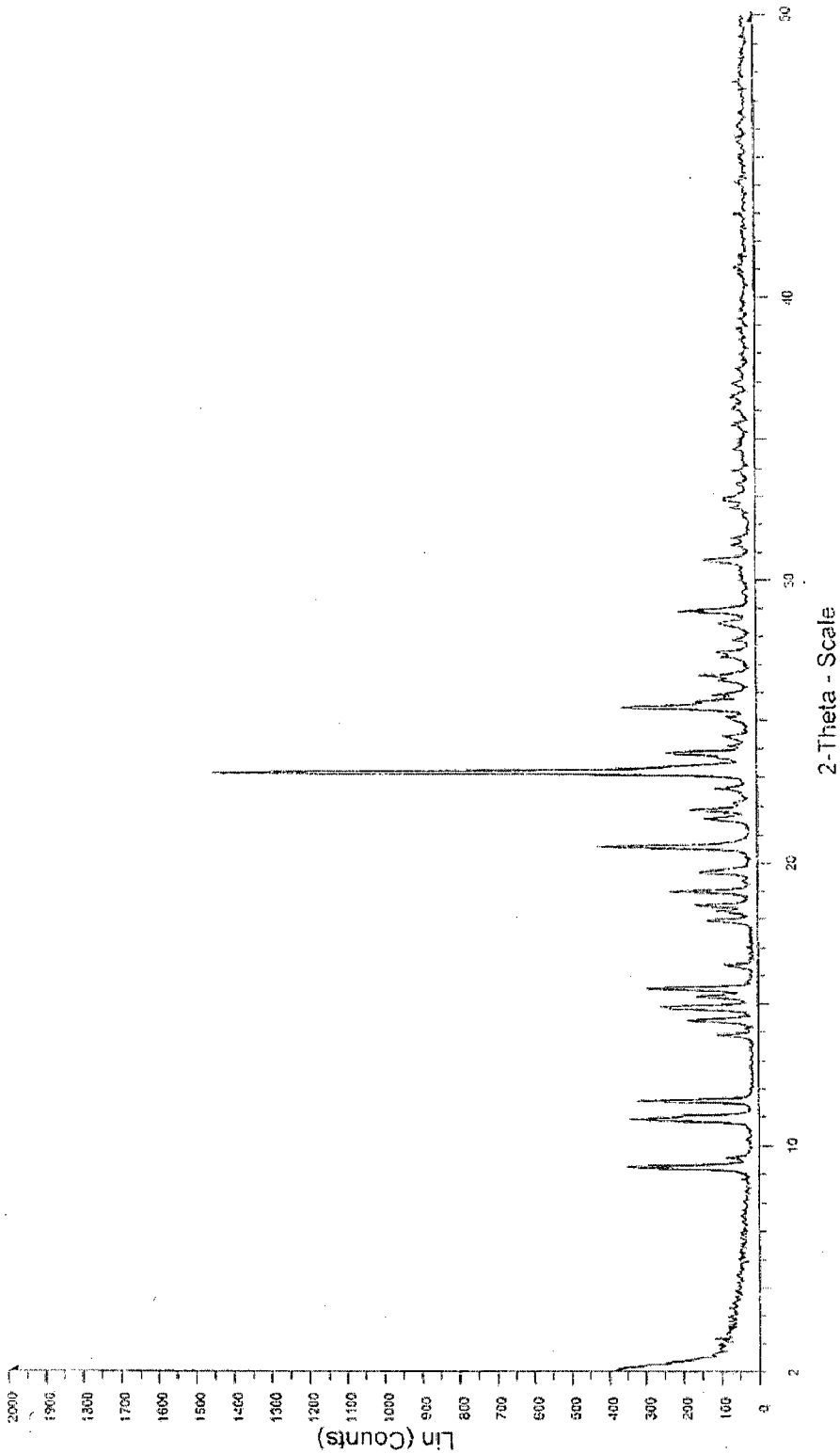

Fig 1

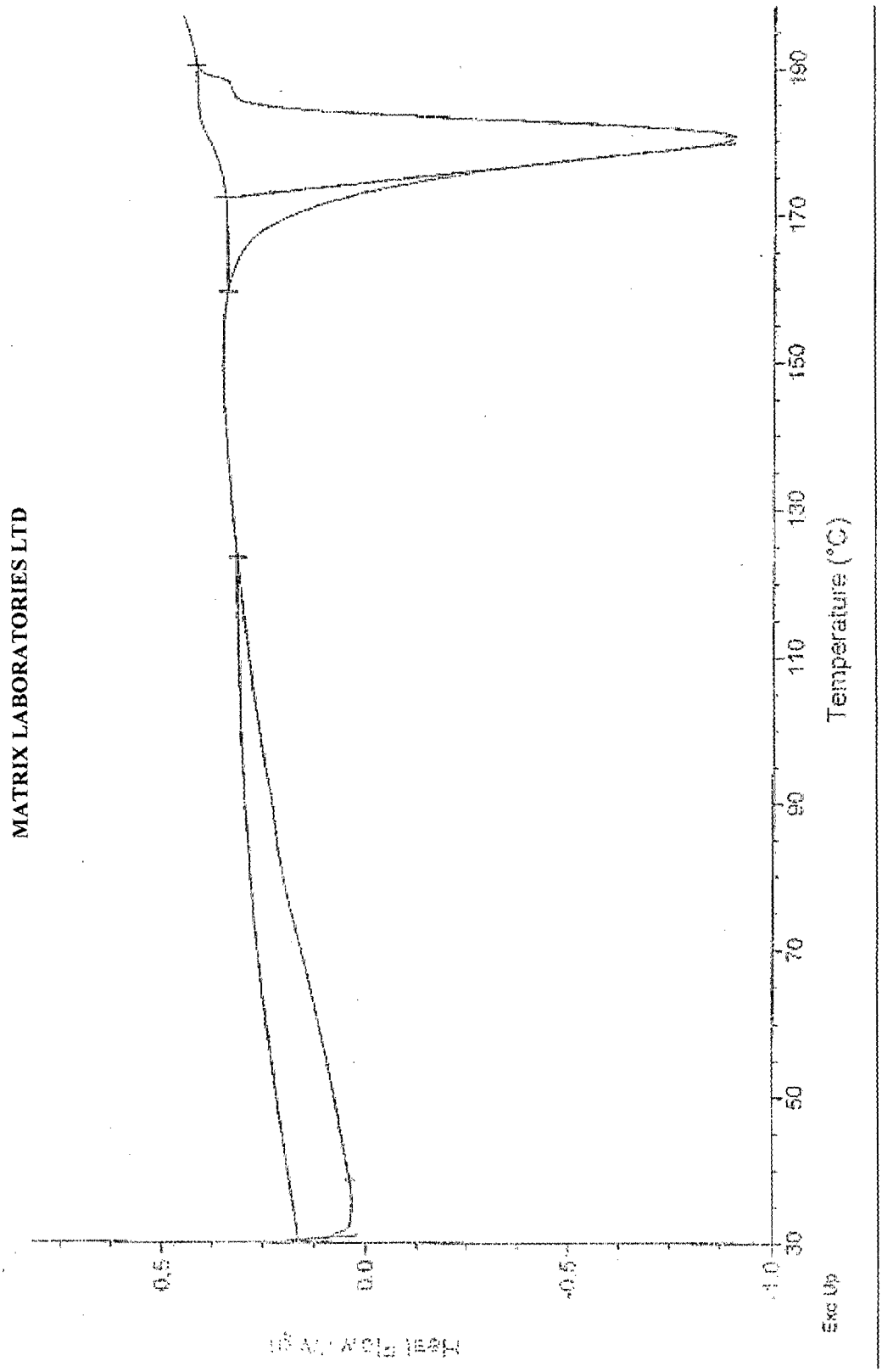
MATRIX LABORATORIES LTD
0.5
0.0
-0.5
-1.0
30
50
70
90
110
130
150
170
190
Temperature (°C)
Exo Up

Fig 2