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(54) Title: LOXOPROFEN POLYMORPHS AND PROCESS FOR PREPARATION OF THE SAME

(57) Abstract: Discloses novel crystalline forms of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid (Formula II) and its sodium derivatives (Formula I) and the process for preparation thereof.

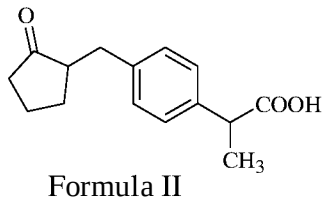
LOXOPROFEN POLYMORPHS AND PROCESS FOR PREPARATION OF THE SAME

TECHNICAL FIELD

The invention relates to novel crystalline forms of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid (Formula II) and its sodium derivatives (Formula I) and the process for preparation thereof.

BACKGROUND OF THE INVENTION

Loxoprofen is a non-steroidal anti-inflammatory drug, chemically known as a-Methyl-4-[(2-oxocyclopentyl) methyl] benzeneacetic acid and is represented by the following structure of Formula II.



Formula II

United States Patent 4,161,538 discloses the 2-oxo-compound and method of preparation of the aforesaid compounds by hydrolyzing and decarboxylating 4-(1-alkoxycarbonyl-2-oxocycloalkan-l-ylmethyl)phenyl acetic acid ester derivative or (b) reacting p-halomethylphenylacetic acid ester derivative with an enamine of cycloalkanone and hydrolyzing in the presence of mineral acids to get the resulting product as an oil. The process disclosed in this US '538 involves multiple extraction and distillation techniques which makes this process tedious and not suitable for commercial scale.

Japanese Patent Publication No. S58-004699 discloses 2-substituted propionic acid having effects as anti-inflammatory agent, analgesic activity especially, 2-[4-(2-oxocyclopentan-l-yl methyl) phenyl] propionic acid, "Loxoprofen", is commercially available as an excellent analgesic drug.

Japanese Laid-Open Patent Publication No. S62-161740 discloses the conventional preparation process includes the steps of (1) coupling reaction of 2-(p-halomethylphenyl) propionic acid ester with 2-cyclopentanone carboxylic acid ester in the presence of a base, and (2) decarboxylation and hydrolysis of ester with an acid.

In the above first coupling step, the hydrogen atom at a-position of 2-cyclopentanone carboxylic acid ester is taken off to give 2-(alkoxycarbonyl)-cyclopentenolate anion, which attacks the halomethyl group of 2-(p-halomethylphenyl) propionic acid ester to generate carbon-carbon bond so that the fundamental skeletal structure of Loxoprofen is formed.

Although above 2-(p-halomethylphenyl)propionic acid ester is relatively inexpensive, 2-cyclopentanone carboxylic acid ester is an expensive reagent. Furthermore, the reaction in the presence of base likely causes side reaction with halomethyl group of 2-(p-halomethyl)propionic acid ester.

PCT International Publication No. WO 97/47581 discloses a process for the preparation of Loxoprofen through carbonylation of p-chloromethylstyrene in the presence of a transition metal complex catalyst. The method comprises (i) carbonylation of p-chloromethylstyrene, (ii) coupling with cyclopentanone carboxylic acid ester, and (iii) decarboxylation and hydrolysis.

According to the above International Publication, p-chloromethylstyrene is liable to cause self-polymerization which also creates side products which finally affects the final product yield and purity. In addition it is required to use large quantity of solvents relative to substrate substance of p-chloromethylstyrene which is not advantageous in industrial practice.

Moreover the method disclosed in above International Publication cannot be said inexpensive because expensive cyclopentanone carboxylic acid alkyl ester is used as a starting material. All of the prior art references also do not report any crystalline polymorphs of Loxoprofen or its sodium derivatives.

Hence the most suitable and efficient method for producing crystalline forms of Loxoprofen or its derivatives has not yet been proposed. Hence, it would be desirable to provide a process for the preparation of Loxoprofen or its derivatives, which is simple, convenient and cost effective. New Crystalline forms of compounds would also be desirable for enhancing its stability & having consistent physical properties during manufacture & storage of the compound.

OBJECTIVE OF THE INVENTION

The main objective of the invention is to provide crystalline forms of Loxoprofen compound of Formula II referred as SI and S2.

Another object of the invention is o provide crystalline form of Loxoprofen sodium dihydrate compound of Formula I referred as S3.

Yet another object of the invention is to provide a process for the preparation of SI, S2 and S3 crystalline forms.

Another object of the invention is to provide a simple, cost effective process for the preparation of Loxoprofen and its pharmaceutically acceptable crystalline forms using a mixture of mineral acid and organic acid for hydrolysis.

Further object of the invention is to provide the process for the preparation of Loxoprofen which avoids multiple extraction and distillation techniques.

SUMMARY OF THE INVENTION

In one aspect, the present invention is to provide a crystalline form of 2-[4-(2-oxo-cyclopentylmethyl)-phenyl] -propionic acid compound of Formula II referred as Form SI characterized by XRD and DSC Fig. 1 & 2

In another aspect the present invention is to provide a crystalline form of 2-[4-(2-oxo-cyclopentylmethyl)-phenyl] -propionic acid compound of Formula II referred as Form S2 characterized by XRD and DSC Fig. 3 & 4.

In another aspect the present invention is to provide a crystalline form of 2-[4-(2-oxo-cyclopentylmethyl)-phenyl] -propionic acid sodium hydrate compound of Formula I referred as Form S3 characterized by XRD and DSC Fig. 5 & 6.

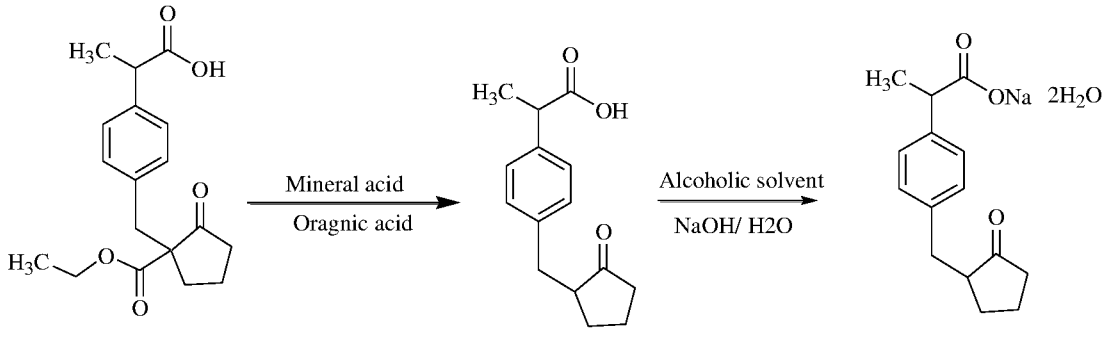
In another aspect the present invention relates to a process for the preparation of the above mentioned crystalline forms SI, S2 and S3.

In another aspect the present invention encompasses a process for the preparation of crystalline Loxoprofen and its pharmaceutically acceptable salts which comprises of the following steps:

a) Hydrolysis of the compound of Formula III using a mixture using a mixture of mineral acid and organic acid to obtain a compound of Formula II.

b) converting the compound of Formula II into its pharmaceutically acceptable salts of Formula I in the presence of methanol.

The reaction sequence of the invention can also be represented by scheme



Formula III Formula II Formula I

Scheme I

wherein the mineral acid is selected from the group comprising hydrochloric acid, trifluoro acetic acid, HF more preferably hydrochloric acid.

wherein the organic acid is selected from the group comprising acetic acid, formic acid, methane sulfonic acid, para toluene sulfonic acid more preferably acetic acid.

It has now surprisingly been found that the hydrolysis of unprotected keto-ester intermediate compound of Formula III with the mixture of mineral acid and organic acid results in Formula II followed by treatment with sodium hydroxide and water in the presence of alcoholic solvent results in formation of Formula I with higher yield.

wherein the alcoholic solvent is selected from the group comprising methanol, ethanol, butanol isopropanol, diethylene glycol, isobutanol but more preferably methanol is used.

This process is valuable as well as viable for the production of Loxoprofen with simple work up procedures to isolate the final product of Formula I with higher yield.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the X-ray powder diffraction pattern of SI crystalline form of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid compound of Formula II.

Figure 2 shows the DSC pattern of SI crystalline form of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid compound of Formula II.

Figure 3 shows the X-ray powder diffraction pattern of S2 crystalline form of (RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid compound of Formula I

Figure 4 shows the DSC pattern of S2 crystalline form of (RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid compound of Formula I.

Figure 5 shows the X-ray powder diffraction pattern of S3 crystalline form of Sodium salt of (RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid hydrate compound of Formula I.

Figure 6 shows the DSC pattern of S3 crystalline form of Sodium salt of (RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid hydrate compound of Formula I.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The first embodiment of the present invention relates to crystalline form SI of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid compound of Formula II characterized by an X-ray powder diffraction pattern having peaks expressed at 2Θ at about 14.3°, 16.5°, 16.9°, 18.4°, 18.6°, 21.1°, 21.8°, 25.4° and 27.9°.

The XRD of crystalline Form SI of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid compound of Formula II characterized is depicted in Fig 1.

In another embodiment, the present invention relates to crystalline Form SI of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid compound of Formula II characterized by melting points of T_{mp} = 111.10±1°C determined by DSC; evaluation by peak maximum; heating rate 10°C/min.

The DSC of crystalline Form SI of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid compound of Formula II characterized is depicted in Fig 2.

In another embodiment of the present invention relates to crystalline form S2 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid compound of Formula II characterized by an X-ray powder diffraction pattern having peaks expressed at 2Θ at about 14.3°, 15.7°, 16.0° , 16.5°, 16.9, 18.4°, 18.6 , 19.4°, 20.1°, 20.5°, 21.0°, 21.7°, 22.2°, 25.3°, 27.1° and 27.9°.

The XRD of crystalline Form S2 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid compound of Formula II characterized is depicted in Fig 3.

In another embodiment, the present invention relates to crystalline Form S2 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid compound of Formula II characterized by melting points of T_{mp} = 87.33±1°C determined by DSC; evaluation by peak maximum; heating rate 10°C/min.

The DSC of crystalline Form S2 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid compound of Formula II characterized is depicted in Fig 4.

In another embodiment, the present invention relates to crystalline Form S3 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid sodium dihydrate compound of Formula I characterized by an X-ray powder diffraction pattern having peaks expressed at 2Θ at about 3.5°, 7.0°, 7.3.0°, 10.3°, 10.9°, 16.6°, 17.3°, 17.5°, 18.4°, 19.5°, 19.0°, 20.7° and 22.1°.

The XRD of crystalline Form S3 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid sodium dihydrate compound of Formula I characterized is depicted in Fig 5.

In another embodiment, the present invention relates to crystalline Form S3 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid sodium dihydrate compound of Formula I characterized by melting points of T_{mp} = 76.33±1°C determined by DSC; evaluation by peak maximum; heating rate 10°C/min.

The DSC of crystalline Form S3 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid sodium dihydrate compound of Formula I characterized is depicted in Fig 6.

The invention also relates to the methods of selectively producing the crystalline Forms SI, S2 and S3.

In another embodiment, the present invention relates to process for the preparation of crystalline Form SI of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid compound of Formula II which comprises of the following steps:

a) Dissolving l-[4-(l-carboxy-ethyl)-benzyl-2-oxo-cyclopentanecarboxylic acid methyl ester compound of formula III in acetic acid
b) Reacting step (a) with a mixture of mineral acid and an organic acid
c) Isolation of the crude product from water
d) Optionally purifying step (c) with ethyl acetate and hexane
e) Purification with Methyl-tert-butyl ether.
f) Isolation of crystalline form S1 compound of formula II

In another embodiment, the present invention relates to a process for the preparation of crystalline Form S2 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid compound of Formula II which comprises of the following steps:

a) Dissolving l-[4-(l-carboxy-ethyl)-benzyl-2-oxo-cyclopentanecarboxylic acid methyl ester compound of formula III in acetic acid
b) Reacting step (a) with a mixture of mineral acid and an organic acid
c) Isolation of the crude product from water
d) Optionally purifying step (c) with ethyl acetate and hexane
e) Purification with Methyl-tert-butyl ether and Hexane.
f) Isolation of crystalline form S2 compound of Formula II.

In another embodiment, the present invention relates to process for the preparation of crystalline Form S3 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid sodium dihydrate compound of Formula I which comprises of the following steps:

a) Dissolving the compound of Formula II in alcoholic solvent.
b) Adding aqueous sodium hydroxide to step (a)
c) Heat the reaction mass to 60-65 °C and stir the reaction for 2hrs.
d) Cool the reaction mass to 30-35°C
e) Distill off methanol and add methyl-tert-butyl ether and stir the reaction at 25-30°C
f) Filter the solid and isolate the crystalline Form S3 compound of Formula I.

The present invention is described by the following examples, which are for illustrative purpose only and should not be construed so as to limit the scope of the invention in any manner.

Example -1

Preparation of Crystalline Form SI of 2-r4-(2-Oxo-cvclopentylmethyl)-phenyll-propionic acid (Formula II)

l-[4-(l-carboxy-ethyl)-benzyl-2-oxo-cyclopentanecarboxylic acid ethyl ester (225g) and Acetic acid (562.5ml) were added into the RB flask at 30±5°C. The reaction mass was stirred for about 10±5min to get the clear solution. The reaction mass was heated to 95±2°C and to this 675ml acid mixture (Acetic acid and Cone. Hydrochloric acid) was added. Reaction was continued till to completion of stage- 1 by HPLC. The crude stage-2 was isolated from aqueous isolation followed by ethyl acetate - hexane mixture with ratio of 2:3 volumes and further purified with Methyl-tert-butyl ether (210ml) recrystallization followed by filtration at 8±2°C and dried the product at less than 40°C to get crystalline 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid (73 gm ,41 % Molar yield , HPLC purity NLT 99.7 % by area)

Figure-1 is PXRD pattern of (RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid. The following peaks are the characteristic 2-theata value with (±0.2°) at 14.3°, 16.5°, 16.9° 18.4°, 18.6°, 21.1°, 21.8°, 25.4° and 27.9°.

Figure-2 is DSC pattern of (RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid having peak value 111.10° C (±1°)

Example -2

Preparation of Crystalline Form S2 of 2-r4-(2-Oxo-cvclopentylmethyl)-phenyll-propionic acid (Formula II)

l-[4-(l-carboxy-ethyl)-benzyl-2-oxo-cyclopentanecarboxylic acid ethyl ester (300g) and Acetic acid (750ml) were added into the RB flask at 30±5°C. The reaction mass was stirred for about 10±5min to get the clear solution. The reaction mass was heated to 95±2°C and to this 900ml acid mixture (Acetic acid and Cone. Hydrochloric acid) was added. Reaction mass was

maintained for about 7.0hrs±10min. Reaction mass was cooled to 30±5°C. This reaction mass was added into pre-chilled (8±2°C) 3600ml process water. The reaction mass was stirred for 2.0hrs30min±30min at 8±2°C. Reaction mass was filtered and washed with pre-chilled (8±2°C) process water and suck dried for 3.0hrs30min±10min. To the crude product Ethyl acetate and charcoal were added and stirred for lhr, filtered through hyflo bed and concentrated at 50°C under vacuum. 10% Ethyl acetate in Hexane (1050ml) was added and stirred for lhr at 50°C. The reaction mass was cooled to 30°C and stirred for 4hrs. The product was cooled and purified with 33% Hexanes in Methyl-tert-butyl ether. During the second purification, the reaction mass was heated to 57±2°C and stirred for 60±5min. Reaction mass was cooled to 30±5°C and maintained for 4hrs. Then further cooled to 8±2°C and stirred for 2.0hrs±10min. Product filtered and washed with Hexanes-Methyl-tert-butyl ether mixer and dried the wet product at less than 40 °C under vacuum to get crystalline 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid (135 gm ,58 % Molar yield , HPLC purity NLT 99.7 % by area)

Figure-3 is PXRD pattern of (RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid. The following peaks are the characteristic 2-theata value with (±0.2°) at 14.3°, 15.7°, 16.0°,16.5°, 16.9°, 18.4°, 18.6°, 19.4°, 20.1°, 20.5° , 21.0°, 21.7°, 22.2°, 25.3°, 27.1° and 27.9°.

Figure-4 is DSC pattern of RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid having peak 87.33°C (±1°).

Example -3

Preparation of Crystalline Form S3 of 2-r4-(2-Oxo-cvclopentylmethyl)-phenyll-propionic acid sodium dihydrate (Formula I)

2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid (lOOgm) was dissolved in Methanol (900 ml) at 30±5°C and stirred for 10±5min.To this, aqueous sodium hydroxide (16.2 gm) solution was added at 30±5°C and stirred for 15±5min. The reaction mass was heated to 60±5°C and maintained for l.Ohrs 45min±15min. Reaction mass was cooled to 30±5°C and filtered through filtrate membrane. The filtrate was distilled out under vacuum (NLT 700mmHg) at

NMT 45°C to get the thick mass and cooled to 30±5°C. To this crude product, Methyl-tert-butyl ether (500 ml) was added and maintained for 7.0hrs±10min. Reaction mass was filtered, washed and suck dried for 1.0hr±10min. The wet product was dried under vacuum at less than 40 °C to get crystalline 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl]-propionic acid sodium salt dihydrate (110 gm, 89 % Molar yield , HPLC purity NLT 99.9 % wt/wt , any other single max impurity NMT 0.05 % wt/wt)

Figure-5 is PXRD pattern of Sodium salt of (RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid hydrate. The following peaks are the characteristic 2-theata value with (±0.2°) at 3.5° , 7.0° , 7.3.0° , 10.3° , 10.9° , 16.6° , 17.3° , 17.5° , 18.4° , 19.5° , 19.0° , 20.7° and 22.1°

Figure-6 is DSC pattern of Sodium salt of (RS)-2-{4-[(2-oxocyclopentyl) methyl] phenyl} propionic acid hydrate having peak 76.33°C (±1.0° C).

We claim:

1. A crystalline form SI of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid (Formula II) characterized by XRD 2Θ at about 14.3°, 16.5°, 16.9°, 18.4°, 18.6°, 21.1°, 21.8°, 25.4° and 27.9°.

2. Crystalline form SI as claimed in claim 1 characterized by melting point of about 111.10°C

3. Process for preparation of crystalline Form SI of compound of Formula II as claimed in claim 1 which comprises:
   a) Dissolving l-[4-(l-carboxy-ethyl)-benzyl-2-oxo-cyclopentanecarboxylic acid methyl ester compound of formula III in acetic acid
   b) Reacting step (a) with mixture of mineral acid and organic acid
   c) Isolation of the crude product
   d) Purification with Methyl-tert-butyl ether
   e) Isolation of crystalline form S1 of compound of Formula II.

4. A crystalline form S2 of 2-[4-(2-Oxo-cyclopentylmethyl)-phenyl] -propionic acid (Formula II) characterized by XRD 2Θ at about 14.3°, 15.7°, 16.0° , 16.5°, 16.9 , 18.4°, 18.6 , 19.4°, 20.1°, 20.5°, 21.0°, 21.7°, 22.2°, 25.3°, 27.1° and 27.9°.

5. Crystalline form S2 as claimed in claim 4 characterized by melting points of about 87.33°C.

6. Process for preparation of crystalline form S2 of compound of Formula II as claimed in claim 4 which comprises:
   a) Dissolving l-[4-(l-carboxy-ethyl)-benzyl-2-oxo-cyclopentanecarboxylic acid methyl ester compound of formula III in acetic acid.
   b) Reacting step (a) with mixture of mineral acid and organic acid
   c) Isolation of the crude product

d) Purification with Methyl-tert-butyl ether and Hexane.
e) Isolation of crystalline form S2 of compound of Formula II.

7. Mineral acid as claimed in claim 3 and 6 is selected from the group comprising hydrochloric acid, trifluoroacetic acid, hydrobromic acid, hydrofluoric acid more preferably hydrochloric acid.

8. Organic acid as claimed in claim 3 and 6 is selected from the group comprising from acetic acid, para toluene sulfonic acid, formic acid, methane sulfonic acid more preferably acetic acid.

9. A crystalline form S3 of compound of Formula I characterized by XRD 2Θ at about 3.5°, 7.0°, 7.3.0°, 10.3°, 10.9°, 16.6°, 17.3°, 17.5°, 18.4°, 19.5°, 19.0°, 20.7°and 22.1°.

10. Crystalline form S3 as claimed in claim 9 characterized by melting points about 76.33°C.

11. Process for preparation of crystalline form S3 of compound of Formula I as claimed in claim 9 which comprises:

a) Dissolving the compound of Formula II in alcoholic solvent.
b) Adding aqueous sodium hydroxide to step (a)
c) Heating the reaction mass and stirring
d) Cooling the reaction mass
e) Distilling off methanol and adding methyl-tert-butyl ether and stirring
f) Filtering the solid and isolating crystalline Form S3.

12. Alcoholic solvent as claimed in claim 11 is selected from the group comprising methanol, ethanol, butanol isopropanol, diethylene glycol, isobutanol but more preferably methanol is used.

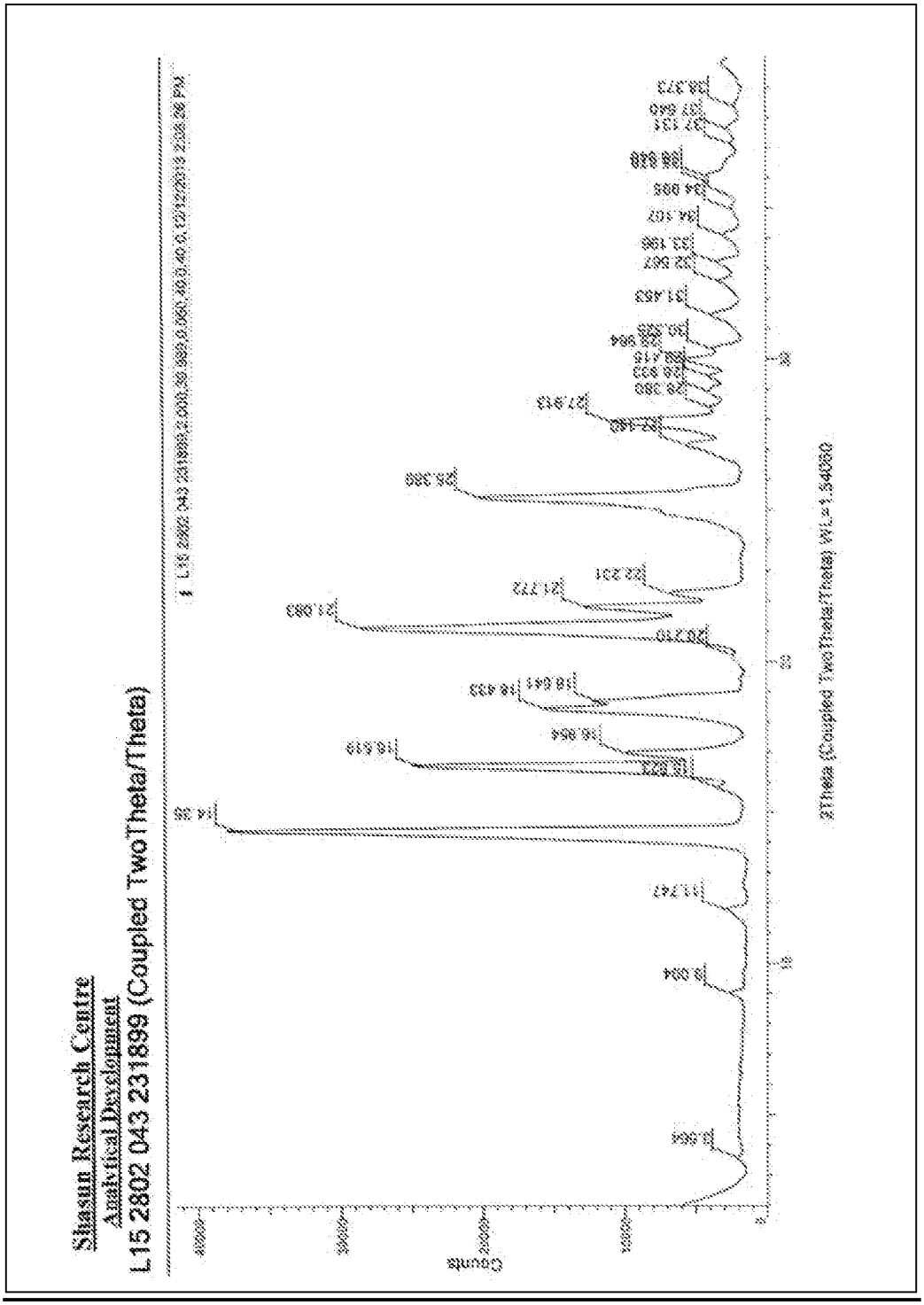
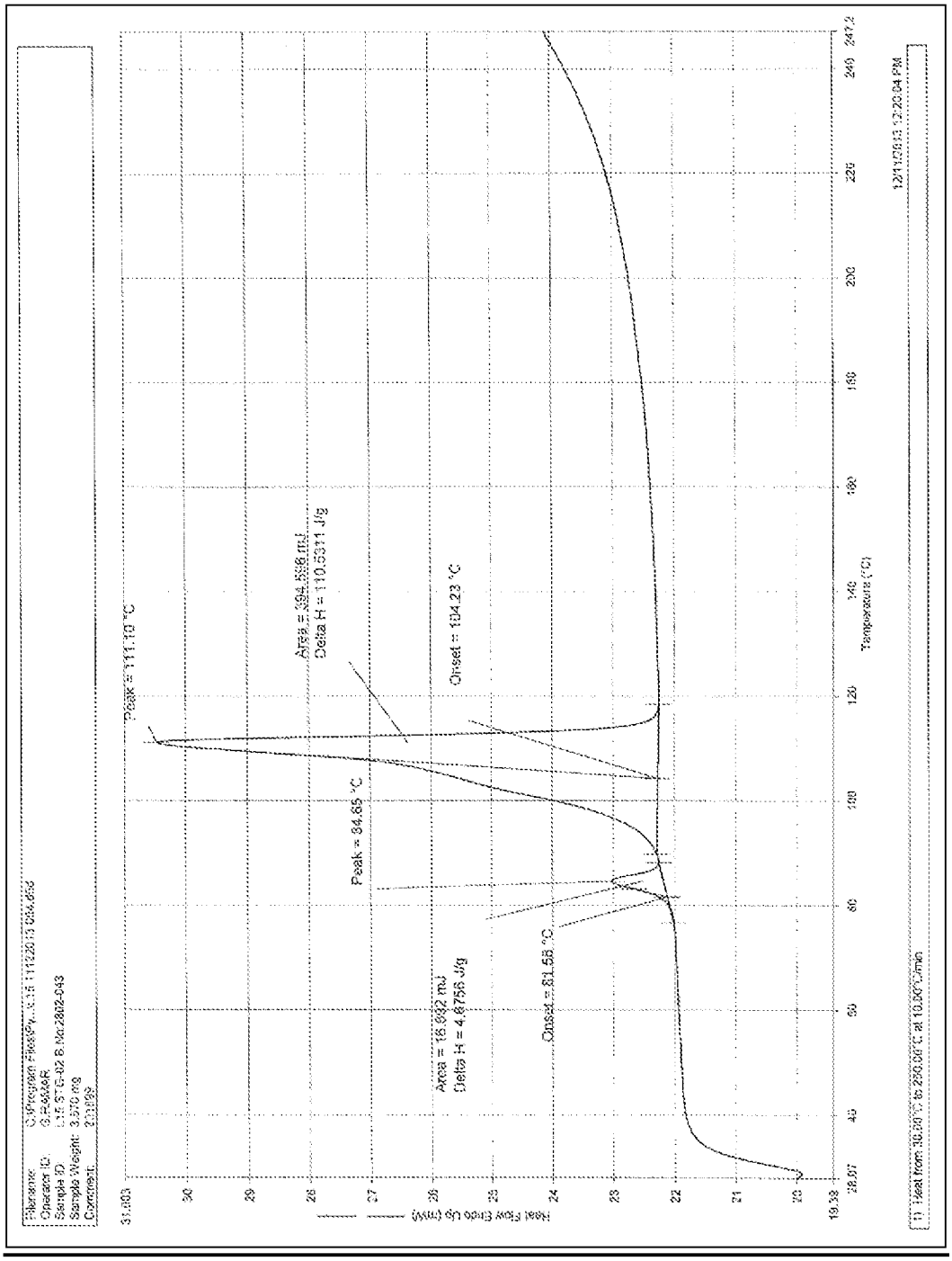

Sinaun Research Centre
Analytical Development
L15 2802 043 231899 (Coupled TwoTheta/Theta)
Counts
2Theta (Coupled TwoTheta/Theta) WL=1.54060

Figure-1


Peak = 111.10 °C
Area = 394.536 mJ
Delta H = 110.5311 J/g
Onset = 104.23 °C
Peak = 84.65 °C
Area = 16.692 mJ
Delta H = 4.67756 J/g
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Temperature (°C)
Heat flow Endo Up (mW)

Figure-2

SHEET 3/6

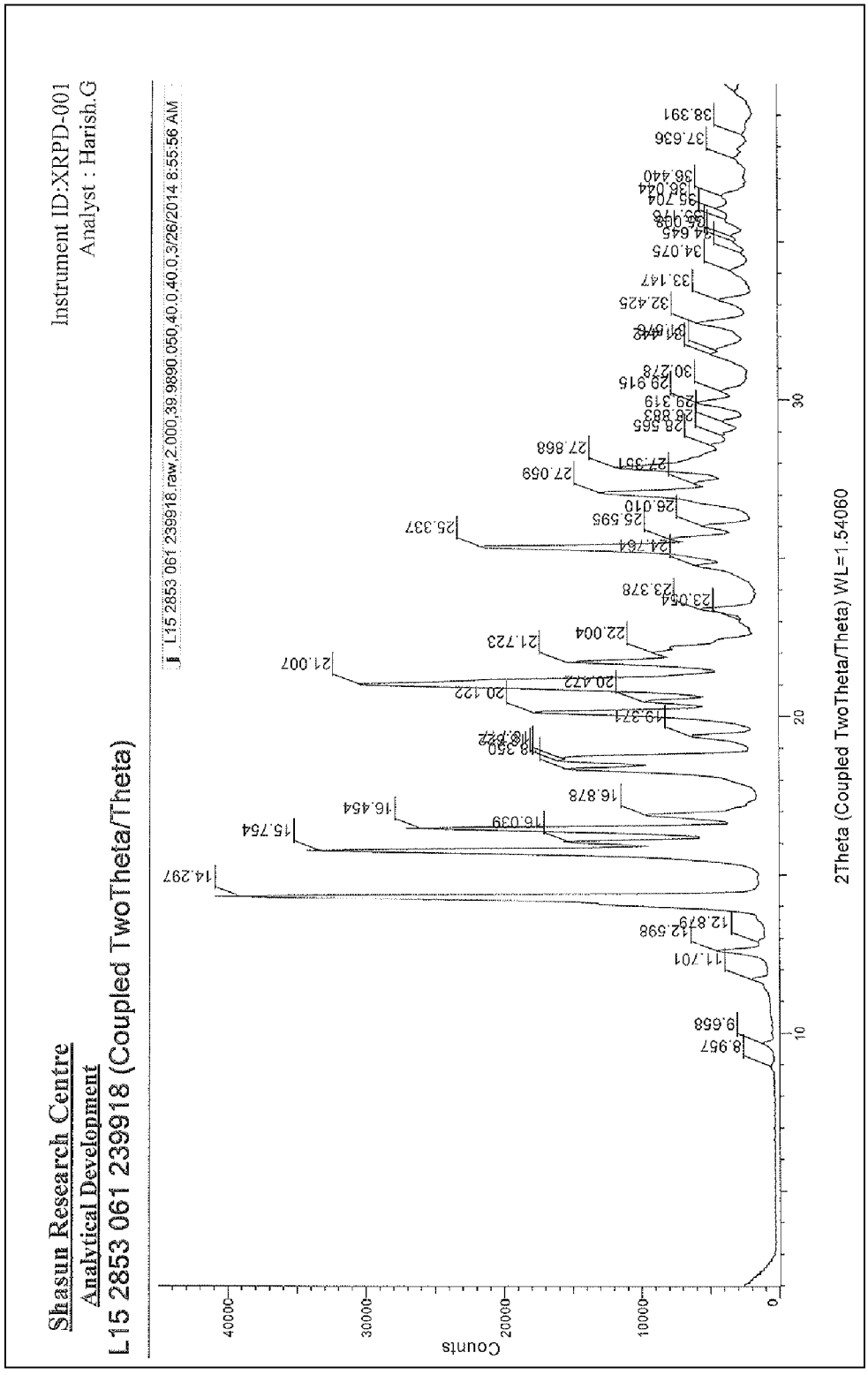

Figure-3

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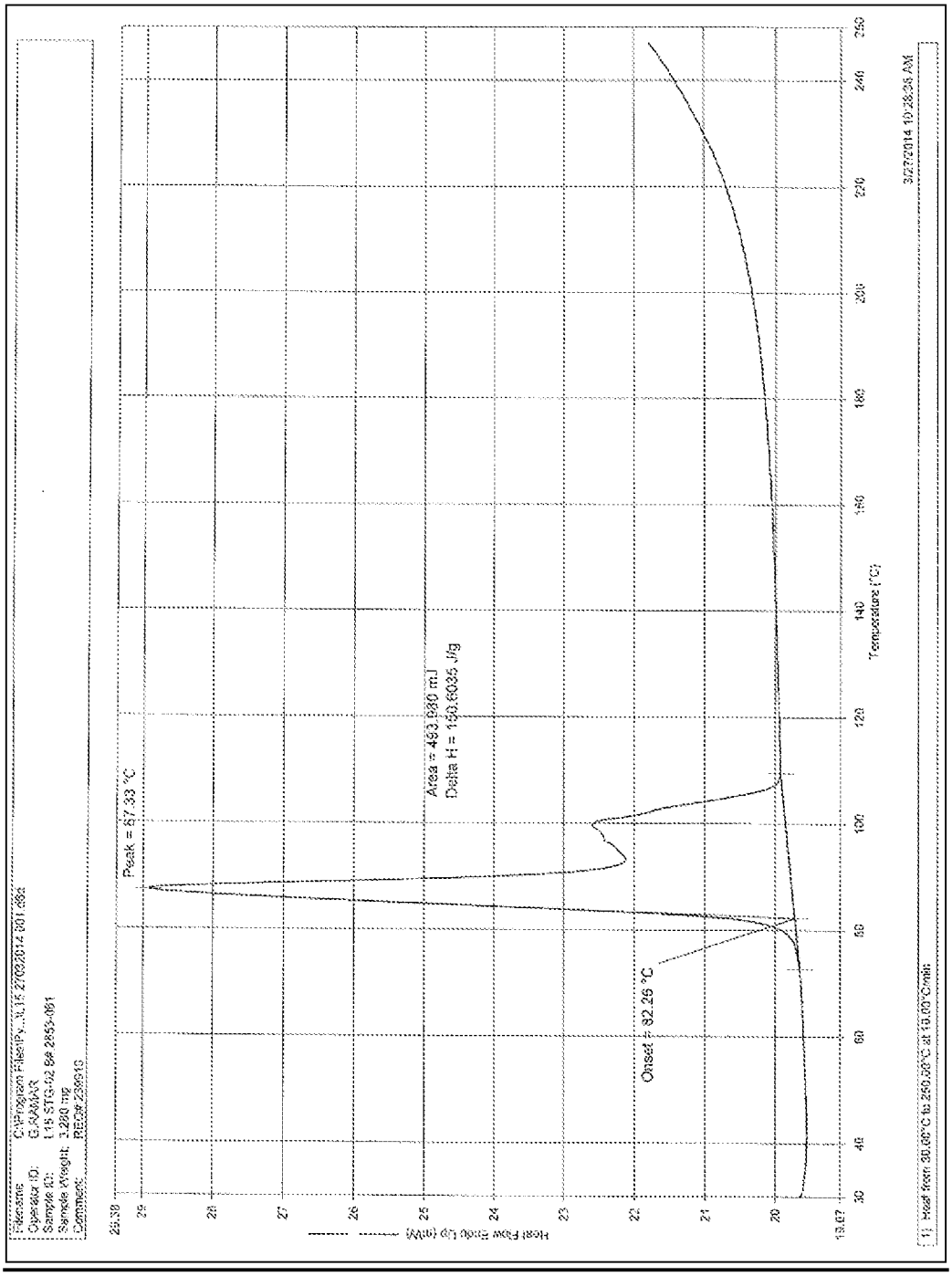
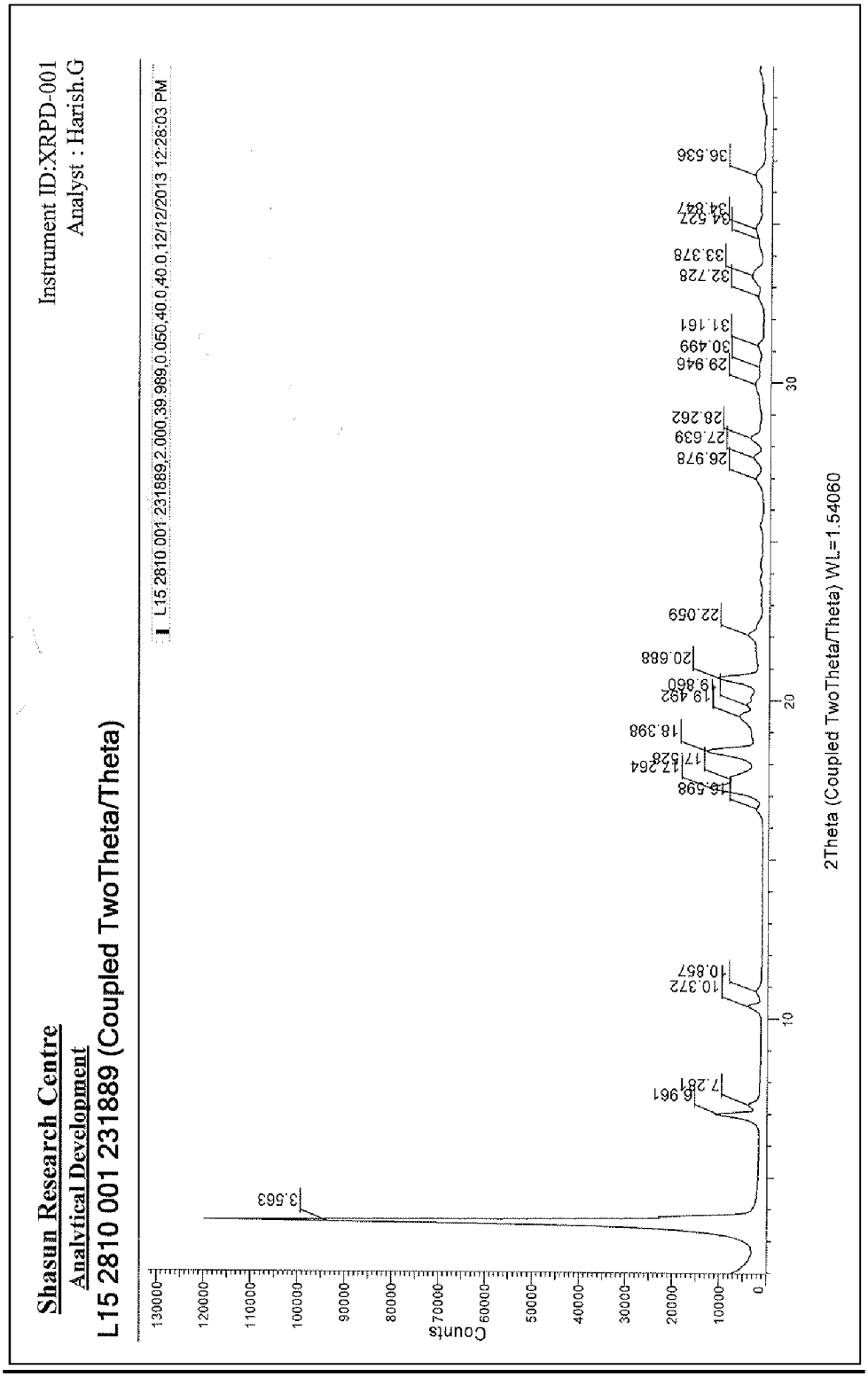


Figure-4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Instrument ID:XRPD-001
Analyst : Harish.G
L15 2810 001 231889 2.000 39.989 0.050 40.0 40.0 12/12/2013 12:26:03 PM
Counts
2Theta (Coupled TwoTheta/Theta) WL=1.54060
3.563
6.961
7.281
10.372
10.857
16.598
17.264
17.628
18.398
19.492
19.860
20.688
22.059
26.978
27.639
28.262
29.946
30.499
31.161
32.728
33.378
34.527
34.847
36.536

Figure-5

SHEET 6/6

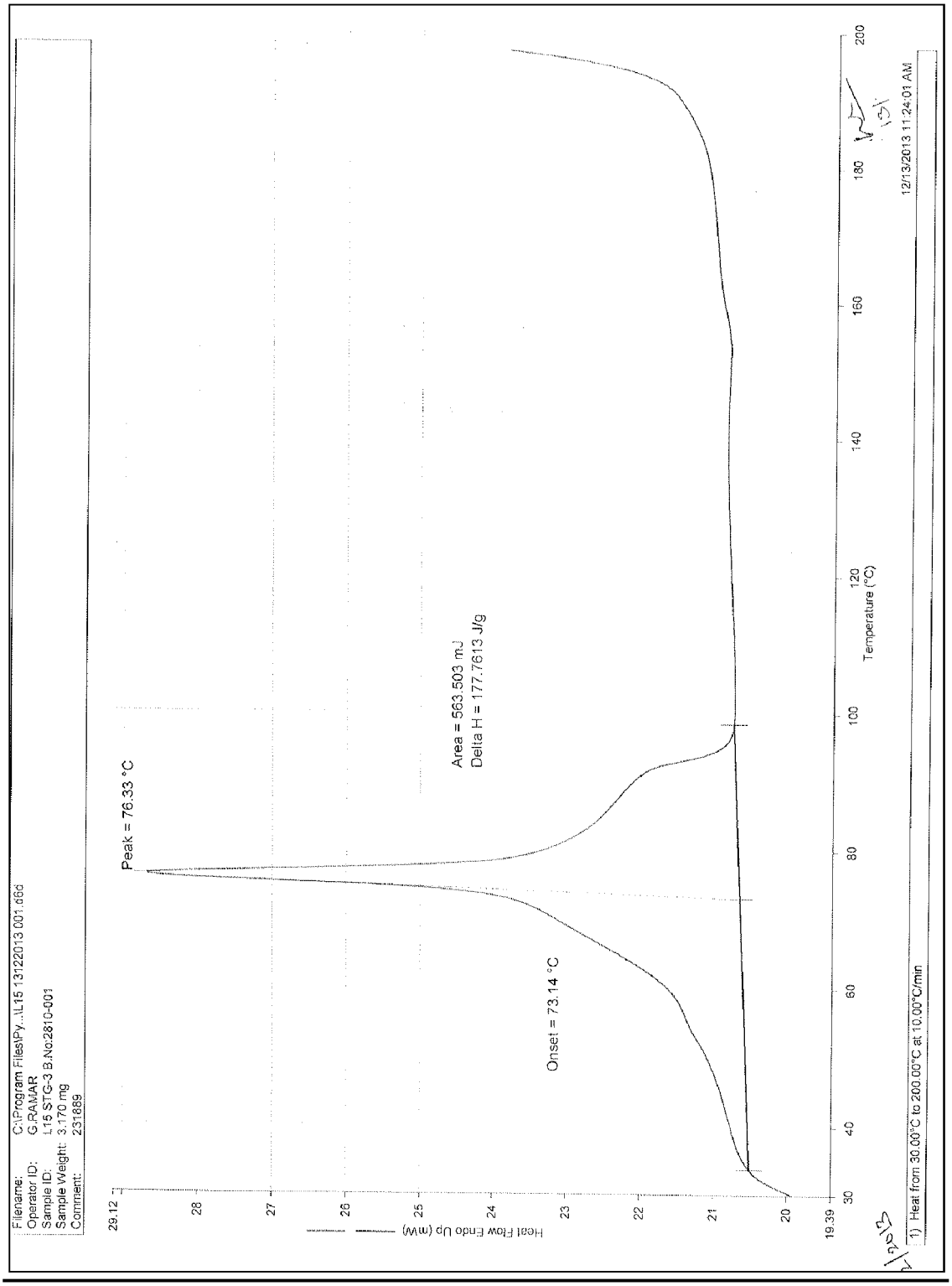

Figure-6