solid-state forms of celecoxib

AND

AN IMPROVED PROCESS FOR THE PREPARATION OF CELECOXIB POLYMORPH

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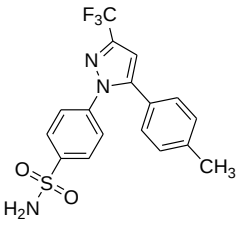
Abstract

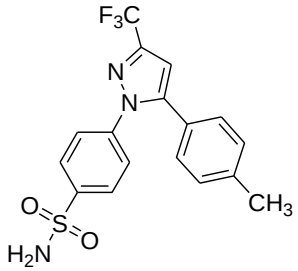
The present application provides an improved process for the preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (Celecoxib) and its purification and crystallisation to produce polymorph .



$C_{17}H_{14}F_3N_3O_2S$: 381.37

FIELD OF INVENTION

The present invention relates to “AN IMPROVED PROCESS FOR THE PREPARATION OF CELECOXIB POLYMORPH FORM”. Celecoxib is designated chemically as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The compound has the following structure:



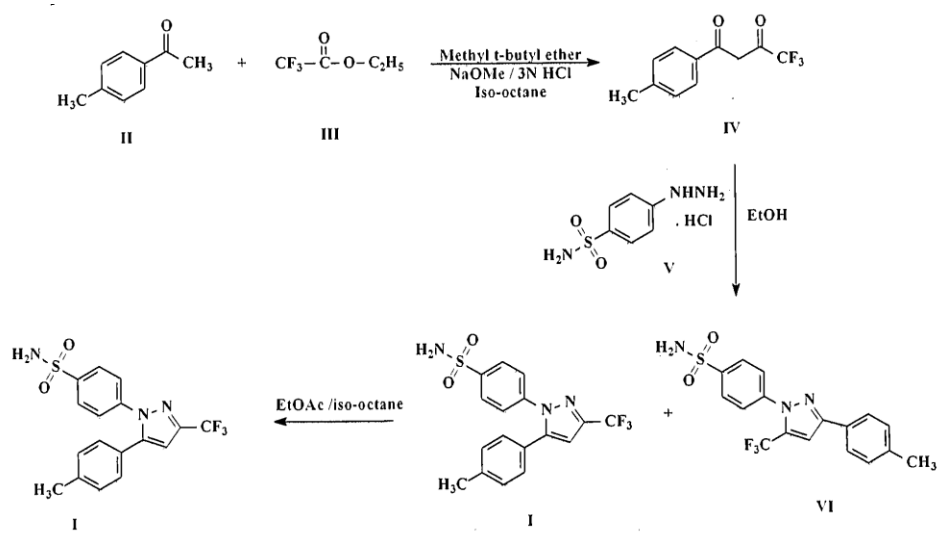
$C_{17}H_{14}F_3N_3O_2S$: 381.37 (1)

The drug is currently marketed as Celebrex® in the United States of America by Pharmacia Corporation.

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) mainly used in treatment of arthritis, pain, menstrual cramps, and colonic polyps. Celecoxib blocks the enzyme (cyclooxygenase 2) which makes prostaglandins, resulting in lowering the concentrations of prostaglandins. As a consequence, reduction in inflammation and its accompanying pain, fever, swelling and tenderness.

The manufacture of Celecoxib has been described in various patents and to cite a few references, G. D. Searl & Co. has disclosed method for preparation of Celecoxib in

US 5,466,823 which is as under:



US 5,134,142 (Matsuo et al), US 5,563,165, US 6,150,534, US 5,892,053, US 2007/0004924, US 2008/0234491, EP 1,528,058, EP 1,167,355, EP 2,246,332, WO 01/42221, WO 03/090730, WO

05/014546, WO 06/051340, WO 08/145733, and WO 2010/095024 have also described the synthesis of Celecoxib Reddy et al in their publication in Org. Process Res. Dev., 2009, 13(1), pp 98-101. have disclosed the synthesis .

SUMMARY OF THE INVENTION

The present invention describes the process for the preparation of Celecoxib by a process involving condensation of 4,4,4-trifluoro-1-[4-(methyl)phenyl]-butane-1,3-dione(1) with

4-sulphonamido phenylhydrazine hydrochloride (2) in an aqueous medium to give Celecoxib (3) followed by purification in a mixture comprising of an Aromatic hydrocarbon and an aliphatic ketone to give Polymorph.

US 5,134,142 (Matsuo et al), US 5,563,165, US 6,150,534, US 5,892,053, US 2007/0004924, US 2008/0234491, EP 1,528,058, EP 1,167,355, EP 2,246,332, WO 01/42221, WO 03/090730, WO 05/014546, WO 06/051340, WO 08/145733, and WO 2010/095024 have also described the synthesis of Celecoxib Reddy et al in their publication in Org. Process Res. Dev., 2009, 13(1), pp 98-101. have disclosed the synthesis .

DETAILED DESCRIPTION OF THE DRAWINGS

Fig.1 describes the powder X-ray diffraction pattern of the Celecoxib Polymorphic

FORM

Fig.2 illustrates 2θvalues.

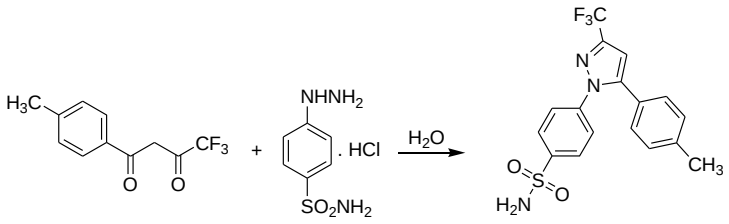
Fig.3 depicts the DSC thermogram taken at 10^{o}C /min over a temperature range of 30^{o}C to 200^{o}C for Celecoxib polymorphic FORM.

DESCRIPTION OF THE INVENTION

The present invention describes the preparation of Celecoxib by a novel process and its crystallisation to polymorphic FORM.

The present invention describes the process for the preparation of Celecoxib by a process involving condensation of 4,4,4-trifluoro-1-[4-(methyl)phenyl]-butane-1,3-dione(1) with

4-sulphonamido phenylhydrazine hydrochloride (2) in an aqueous medium to give Celecoxib (3). This is followed by crystallisation from a mixture of solvents containing Aromatic hydrocarbon and aliphatic ketone.



$C_{11}H_9F_3O_2$: 230.18 (1)

$C_6H_{10}ClN_3O_2S$: 223.68 (2)

$C_{17}H_{14}F_3N_3O_2S$: 381.37 (3)

In the condensation reaction the reactants are added in water and reactions done at ambient temperature. The crude Celecoxib is isolated by filtration.

In the for purification of Celecoxib and its crystallisation to polymorphic FORM

Preparing a solution of Crude Celecoxib in a solvent mixture comprising of of an aliphatic ketone (Acetone) and an aromatic hydrocarbon (Toluene)at reflux temperature

followed by cooling crystallisation to give crystals of Celecoxib polymorph .

The distinct advantage of the present invention over the prior art can be summarized as per below:

(1) The present process, which describes the manufacturing process of Celecoxib, which is a non-steroidal anti-inflammatory drug (NSAID), has the advantage of scaling up to the industrial level of production.
(2) The process uses safe reagents in the process which makes it for industrial scale operations.
(3) The yields in the process are higher compared to the prior art, which makes it a cost effective process.
(4) Formation of isomers are less compared with the prior art, which makes it effective to make it to the pharmacopoeial grade.

(5) Residual solvents play a very important role in the impurity profile of APIs as per the ICH Guidelines ICH Q3C (R4). In this process by carrying out the final step of condensation in the aqueous medium followed by crystallization, the residual solvents limits are well taken care of.

The crystallization conditions are well established to give crystalline polymorph . The powder X-Ray diffraction pattern of the Celecoxib is given in Fig. 1 and 2θ values are given in table 1 of Fig.2

The differential scanning calorimeter graph of the Celecoxib polymorph under specific conditions shows the melting point around 162.7˚C. The DSC of Celecoxib is given in fig.3

The details of the invention are further illustrated in the following examples.

Example 1: Preparation of Celecoxib

In a 20 liter 3-necked flask, equipped with stirrer, thermometer and reflux condenser, deionized water(7.9 Liter)is charged and mixture of 4,4,4-trifluoro-1-[4-(methyl)phenyl]-butane-1,3-dione(1.6 Kg; 6.95×10^3mmoles) and 4-sulphonamido phenylhydrazine hydrochloride(1.7 Kg; 7.57×10^3mmoles), a resultant mixture was heated at 75˚C to 80˚C and maintained for 5 hours. The reaction mixture was cooled to 25ºC to 30ºC to give a slurry..The slurry was filtered and washed with water (3.2 liter) wet-cake was collected and further processed for purification as given below.

Purifcation and crystallisation to give Polymorph

Celecoxib wet-cake obtained in the process described above was taken into 20 liter 3-necked flask, equipped with stirrer, thermometer and reflux condenser, mixture of acetone(0.54 liter) and toluene(10.8 liter) was added and the reaction mixture was heated to 80ºC to 85ºC for 30 minutes. Activated carbon(0.3 Kg) was added and the reaction mixture was further heated to 80ºC to 85ºC. The reaction mixture was cooled to 25ºC-30 ºC. The slurry was filtered, washed with toluene and then dried at 70ºC to yield the Celecoxib polymorph compound1.35 kg (HPLC purity-99.8% & molar yield; 50.9%)

IR : 3340, 3240, 1600, 1500, , 1350, 1280, 1235, 1160, 980, 910, 840, 800, 760, 635, 560, 530 cm-1 (KBr pellet)

Proton NMR:

Solvent: DMSO d6, 300 MHz

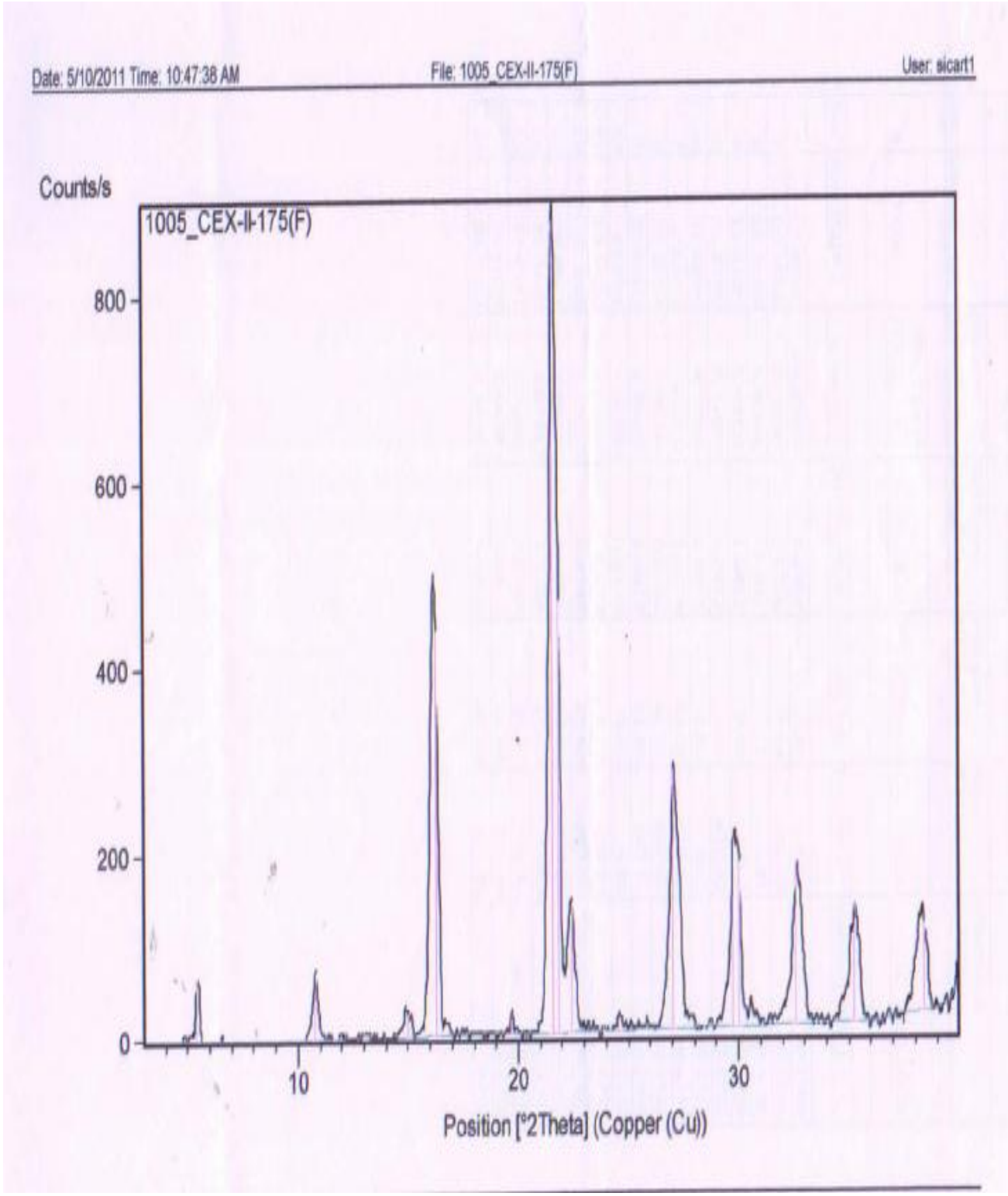
Signals	Assignment/Remarks
2.3 ppm	3 H, methyl, Singlet
3.337 and 3.329 ppm	Residual H of DMSO d6, ignore
7.20 ppm	4 H, Aromatics, multiplet
7.53 ppm	3 H, Aromatics, 1 H, H-4 (pyrazole)
8.8 ppm	1 H, Aromatic, doublet

Example 2: Preparation of Celecoxib

In a 20 liter 3-necked flask, equipped with stirrer, thermometer and reflux condenser, charge deionized water(9 Liter) and mixture of 4,4,4-trifluoro-1-[4-(methyl)phenyl]-butane-1,3-dione(1.6 Kg; 6.95×10^3mmoles) and 4-sulphonamido phenylhydrazine hydrochloride(1.7 Kg; 7.57×10^3mmoles), a resultant mixture was heated at 90˚C to 100˚C and maintained for 5 hours. The reaction mixture was cooled to 25ºC to 30ºC. The slurry was filtered and washed with water (3.2 liter) wet-cake was collected and further processed for purification as given below:

Purifcation and crystallisation to give Polymorph

Celecoxib wet-cake obtained in the process described above was taken into 20 liter 3-necked flask, equipped with stirrer, thermometer and reflux condenser, mixture of acetone(0.54 liter) and toluene (10.8 liter) was added and the reaction mixture was heated to 80ºC to 85ºC for 30 minutes. Activated carbon(0.3 Kg) was added and the reaction mixture was further heated to 80ºC to 85ºC. The reaction mixture was cooled to 25ºC-30 ºC. The separated solid was filtered, washed with toluene and then dried at 70ºC to yield the Celecoxib polymorph compound1.24 kg (HPLC purity-99.3% & molar yield; 47%)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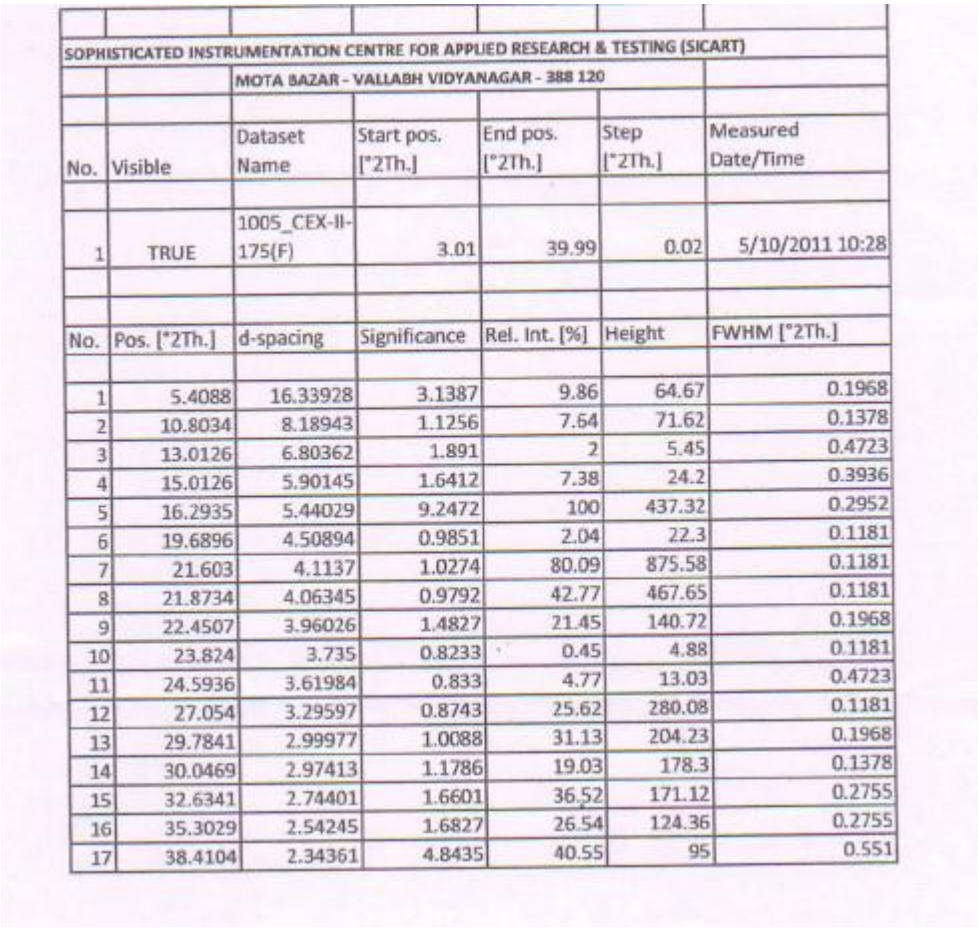
Counts/s
1005_CEX-II-175(F)
800
600
400
200
0
10
20
30
Position [°2Theta] (Copper (Cu))

Fig.1



SOPHISTICATED INSTRUMENTATION CENTRE FOR APPLIED RESEARCH & TESTING (SICART)

MOTA BAZAR - VALLABH VIDYANAGAR - 388 120

No.	Visible	Dataset Name	Start pos. [°2Th.]	End pos. [°2Th.]	Step [°2Th.]	Measured Date/Time
1	TRUE	1005_CEX-II-175(F)	3.01	39.99	0.02	5/10/2011 10:28

No.	Pos. [°2Th.]	d-spacing	Significance	Rel. Int. [%]	Height	FWHM [°2Th.]
1	5.4088	16.33928	3.1387	9.86	64.67	0.1968
2	10.8034	8.18943	1.1256	7.64	71.62	0.1378
3	13.0126	6.80362	1.891	2	5.45	0.4723
4	15.0126	5.90145	1.6412	7.38	24.2	0.3936
5	16.2935	5.44029	9.2472	100	437.32	0.2952
6	19.6896	4.50894	0.9851	2.04	22.3	0.1181
7	21.603	4.1137	1.0274	80.09	875.58	0.1181
8	21.8734	4.06345	0.9792	42.77	467.65	0.1181
9	22.4507	3.96026	1.4827	21.45	140.72	0.1968
10	23.824	3.735	0.8233	0.45	4.88	0.1181
11	24.5936	3.61984	0.833	4.77	13.03	0.4723
12	27.054	3.29597	0.8743	25.62	280.08	0.1181
13	29.7841	2.99977	1.0088	31.13	204.23	0.1968
14	30.0469	2.97413	1.1786	19.03	178.3	0.1378
15	32.6341	2.74401	1.6601	36.52	171.12	0.2755
16	35.3029	2.54245	1.6827	26.54	124.36	0.2755
17	38.4104	2.34361	4.8435	40.55	95	0.551

Fig. 2

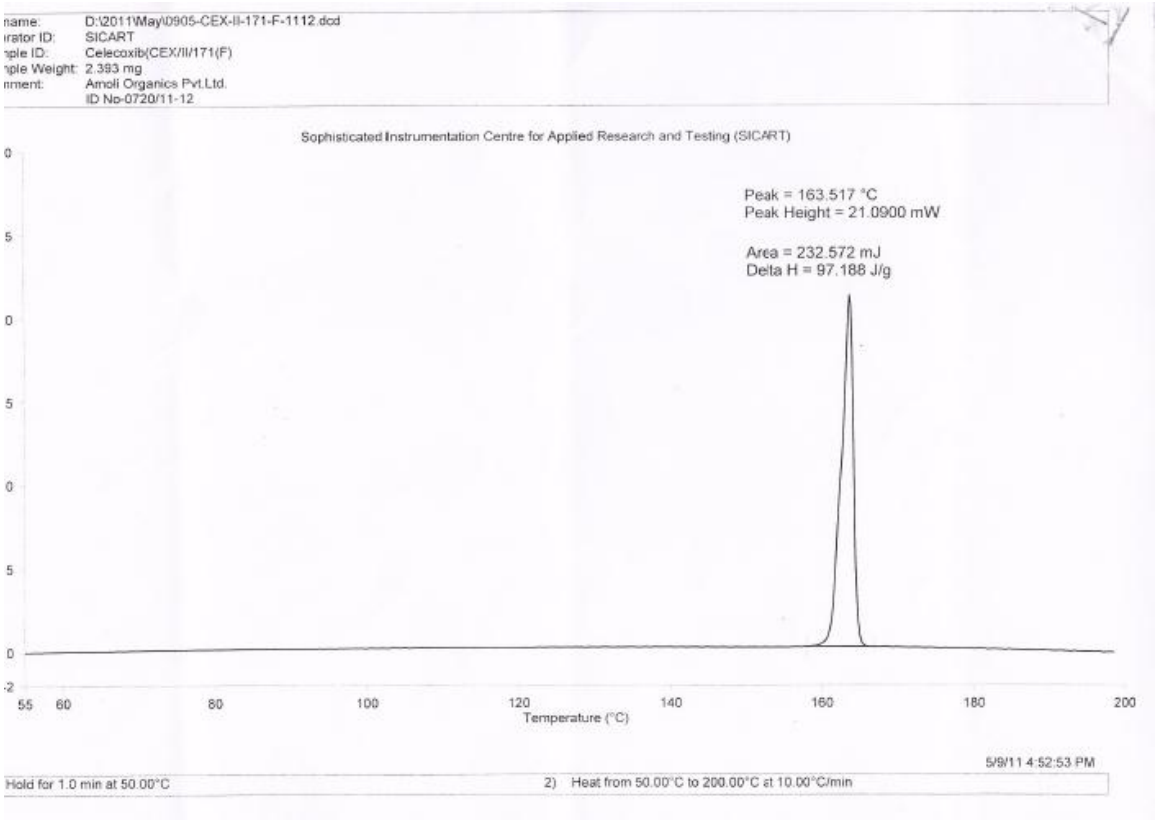


Fig.3

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