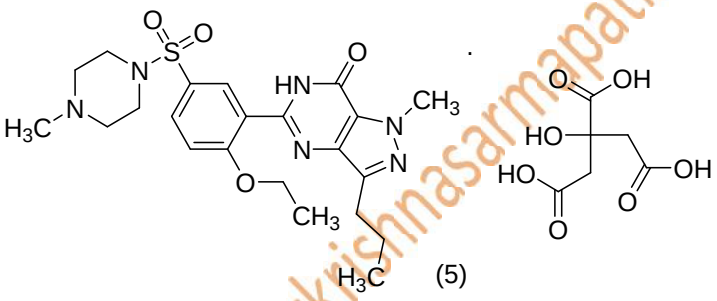
AN IMPROVED PROCESS FOR THE PREPARATION OF SILDENAFIL CITRATE (Viagra) IN ITS POLYMORPHIC FORM

Dr KrishnaSarma Pathy. Dr. Sriraman chakaravathy, Prof.Atchutha maiah,,K.v.s.sairam.

SHAKTHIBIOSCIENCE LTD MUMBAI

Abstract-

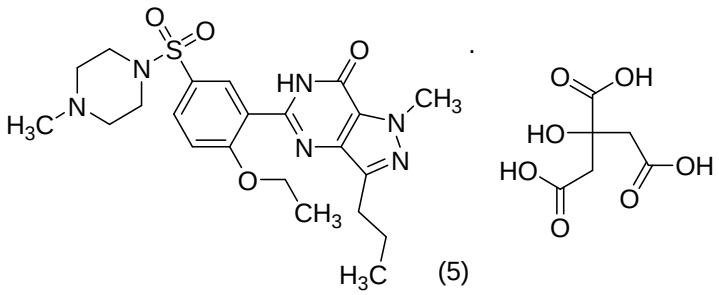
The present invention provides an improved process for preparation of 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H* –pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4methypiperazine citrate (Sildenafil Citrate) of Polymorphic form I)



(5)

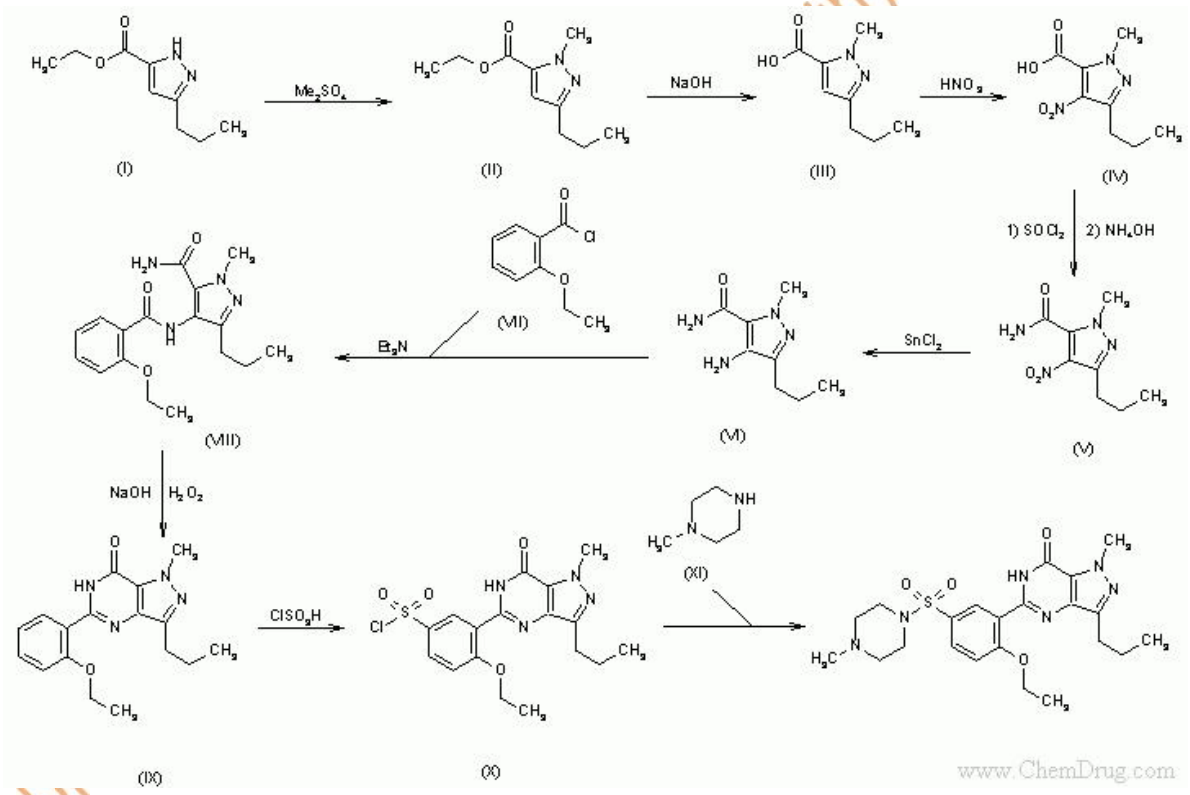
The following specification particularly describes and ascertains the nature of this invention, and the manner in which it is to be performed.

The present invention relates to "AN IMPROVED PROCESS FOR THE PREPARATION OF SILDENAFIL CITRATE IN ITS POLYMORPHIC FORM I
Sildenafil citrate is a selective inhibitor of cyclic guanosine monophosphate (cGMP) Specific phosphodiesterase type 5 (PDE 5), commercially developed by Pfizer, Inc. as Viagra®. Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*–pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulphonyl]-4-methypiperazine citrate . The compound has the following structure:



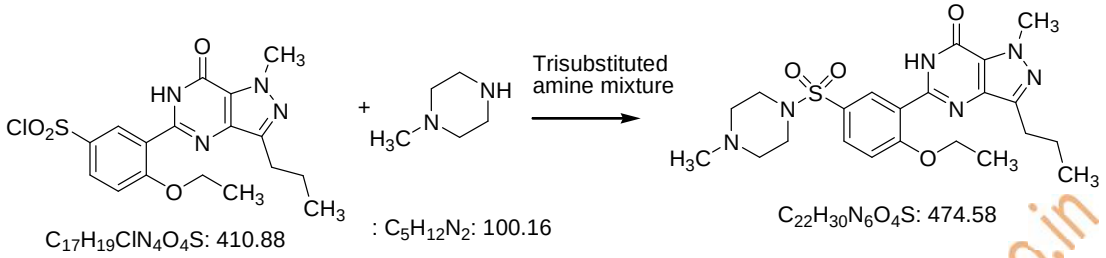
(5)

The manufacture of Sildenafil citrate has been described in various patents and to cite a few references, EP 1002798, EP 1779852, EP 0916675, US6066735, US6204383, US2010048897, WO0119827, WO122918, and WO2004072079. Amongst the various processes described, the process which has the possibility of scaling up to the Industrial scale is as below:



With respect to polymorphic forms of Sildenafil citrate, while there are no patents reported, but in a publication by A Badwan et al in the article on Sildenafil citrate, published in "Analytical profiles of Drug Substances and Excipients vol. 27, pp 339-376, describes three polymorphic forms.

The present invention describes the process for the preparation of Sildenafil citrate of Polymorphic form I as designated by us.



$C_{17}H_{19}ClN_4O_4S$: 410.88

(1)

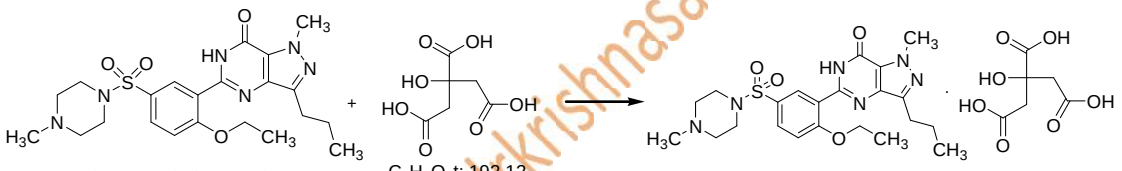
: $C_5H_{12}N_2$: 100.16

(2)

$C_{22}H_{30}N_6O_4S$: 474.58

(3)

The process is from the penultimate intermediate namely 5-(5-chlorosulphonyl-2-ethoxy phenyl) -1-methyl-3-N-propyl-1,6-dihydro-7*H*-pyrasolo-(4,3-*d*)pyrimidin-7-one, which is herein will be referred as chlorosulphonyl intermediate(1). This intermediate is condensed with N-methylpiperazine(2) in a solvent preferably of chlorinated hydrocarbon in presence of a trisubstituted amine or in presence of mixture of such amines.



$C_{22}H_{30}N_6O_4S$; 474.58

(3)

$C_6H_8O_7$t: 192.12

(4)

$C_{22}H_{30}N_6O_4S.C_6H_8O_7$;666.71

(5)

The resulting product of condensation namely Sildenafil base (3) is reacted with citric acid in an aqueous medium to give Sildenafil citrate.
The crystallization conditions are well established to give crystalline form I. The powder X-ray diffraction pattern of the Sildenafil Citrate Polymorphic form I is given in Fig. 1 and the 2θ values are given in Table 1.

The Differential scanning calorimeter graph of the Sildenafil citrate polymorph I under specific conditions shows the melting point around 197.56°C. Fig. 2 depicts a comparison of DSC thermogram scanned at 5˚C/min over a temperature range of 30˚C to 350˚C for Sildenafil citrate polymorphic form I.

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 Sildenafil citrate, which is citrate is a selective inhibitor of cyclic guanosine monophosphate(cGMP) Specific phosphodiesterase type 5 (PDE 5), 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 high which makes it a cost effective process.
(4) 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 of Sildenafil base and citric acid in the aqueous medium followed by crystallization, the residual solvents limits are well taken care of.

The details of the invention are further illustrated in the following examples.
Example 1: General preparation of Sildenafil base

In a 10 liter 3-necked flask, equipped with stirrer, thermometer and reflux condenser, Methylene dichloride (6.6Liter) was charged and 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzene-1-sulfonylchloride (823gm; 2×10^3mmoles) was added at 25-30°C. After the dissolution add N-methyl piperazine (240gm; 2.39×10^3mmoles) at 25-30°C in 15-20 minutes. Reaction mixture was stirred properly and diisopropyl ethyl amine (262.5gm; 2.03×10^3mmoles) was added, the resultant mixture was maintained at 20°C to 30°C for 2.5 hr. Methylene dichloride was distilled under atmospheric pressure. Charge deionized water (1.64 Liter) in residue and stir to form slurry, which was filtered and product was washed with deionized water (0.82 Liter) to give a wet Sildenafil base. The wet product was dried under vacuum of about 10mmHg at 65°C for 10 hrs to give Sildenafil base 827gm (HPLC purity-99.5% and Molar yield 87%).

Example 2:
In a 10 liter 3-necked flask equipped with stirrer, thermometer and reflux condenser, Methylene dichloride (6.6Liter) was charged and 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzene-1-sulfonylchloride (823gm; 2×10^3mmoles) was added at room temperature. After the dissolution add N-methyl piperazine (240gm; 2.39×10^3mmoles) at 25-30°C in 15-20 minutes. Reaction mixture was stirred properly and mixture of diisopropyl ethyl amine(335gm; 2.59×10^3mmoles) and Triethyl amine (262.5 gm; 2.59×10^3mmoles) was added, the resultant mixture was maintained at ambient temperature for 2.5 hr. Methylene dichloride was distilled under atmospheric pressure. Charge deionized water (1.64 Liter) in residue and stir to form slurry, which was filtered and product was washed with deionized water (0.82 Liter) to give a wet Sildenafil base. The wet product was dried under vacuum of about 10mmHg at 65°C for 10 hrs to give Sildenafil base 779 gm (HPLC purity-99.5% and Molar yield 82%).

Example 3:

In a 10 liter 3-necked flask equipped with stirrer, thermometer and reflux condenser, Methylene dichloride (6.6Liter) was charged and 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzene-1-sulfonylchloride (823gm; 2×10^3mmoles) was added at room temperature. After the dissolution add N-methyl piperazine (240gm; 2.39×10^3mmoles) at 25-30°C in 15-20 minutes. Reaction mixture was stirred properly and mixture of diisopropyl ethyl amine (52.6gm; 0.406×10^3mmoles)

and Triethyl amine (164.6gm; 1.626×10^3mmoles) was added, the resultant mixture was maintained at 25˚C to 30˚C temperature for 2.5hr. Methylene dichloride was distilled under atmospheric pressure. Charge deionized water (1.64 Liter) in residue and stir to form slurry, which was filtered and product was washed with water (0.82 Liter) to give a wet Sildenafil base. The wet product was dried under vacuum of about 10mmHg at 65^{o}C for 10 hrs to give Sildenafil base 872gm (HPLC purity-99.8% and Molar yield 91.7%).

Example 4: Synthesis of Sildenafil citrate (Form I)

In a 50-liter glass assembly, deionised water (21 liter) was charged and Sildenafil base (840gm; 1.769×0^3mmoles) was added to it at room temperature. The reaction mixture was heated to 60-65˚C in 1 hr. Citric acid (370gm; 1.76×10^3mmoles) was added to the pre heated reaction mixture. The resultant mixture was further heated up and maintained at 80-85˚C, for 1hr and then charcoal treatment given at same temperature. Filter the reaction mass. Filtrate was allow to cool at 10-15˚C, resultant product obtained is filtered and washed with deionised water (0.84 Liter).Product was dried in vacuum (about 10 mm Hg) at 75^{o}C as a polymorphic form I of Sildenafil citrate salt 1.0 kg. (HPLC purity-99.9% and Molar yield 85%).

Example 5: Synthesis of Sildenafil citrate (Form I)

In a 500 liter SS reactor, 4-ethoxy-3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)benzene-1-sulfonyl chloride (30kg) was mixed with Methylene dichloride (240Liter) at 25˚C to 30˚C temperature, followed by addition of N-methyl piperazine (8.1kg) at 25-30˚C in 45-60 minutes. After addition reaction mixture was stirred properly and mixture of diisopropyl ethyl amine (2.0kg) and Triethyl amine (6.0kg) was added, the resultant mixture was maintained at 25˚C to 30˚C temperature for 3-4 hr. Methylene dichloride was distilled under atmospheric pressure. Charge deionized water (60 Liter) in residue and stir properly to form slurry, which was filtered and product was washed with deionised water (30 Liter) to give a wet Sildenafil base. The wet product was dried under vacuum of about 10mmHg to give Sildenafil base 33.0 kg (HPLC purity-99.8% and Molar yield 95%).

In a 1200 liter SS reactor, sildenafil base (30kg) was mixed with water (750Liter.) at room temperature, heat the reaction mixture to 60-65˚C. Citric acid (13.2kg) was added to the pre heated reaction mixture and the resultant mixture was further heated to 80-85˚C for 1hr, reaction mixture treated with carbon charcoal and then it was filtered. Filtrate obtained was cool to 10-15˚C, resultant product obtained is filtered and washed with deionised water. Product was dried in vacuum (about 10 mm Hg) at 75^{o}C as a polymorphic form I of Sildenafil citrate salt 35.5-36kg. (HPLC purity-99.9% and Molar yield 85%).

The powder X-Ray diffraction is given in Figure 1.

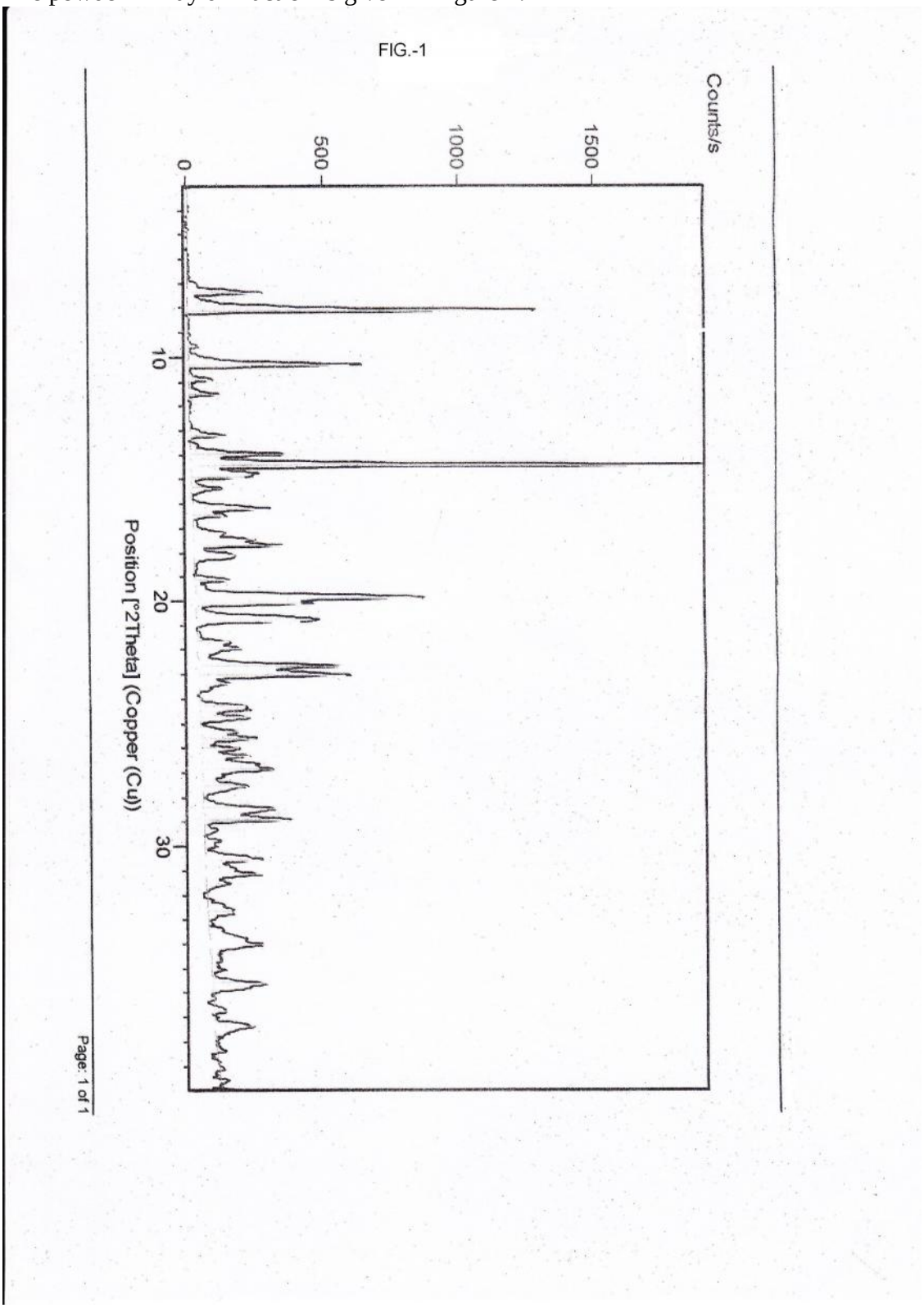
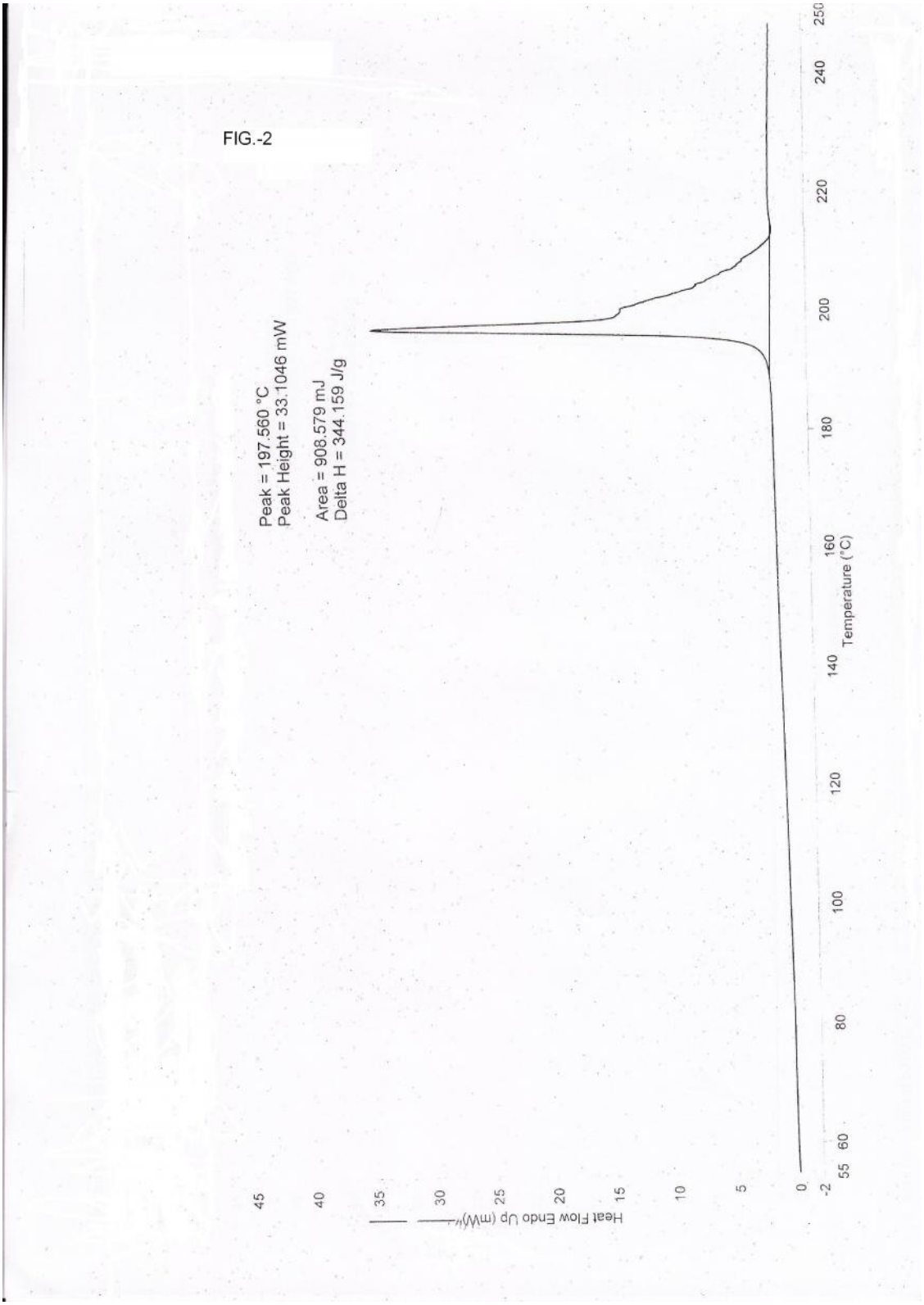


Table 1: A table for 2θ Values of Sildenafil citrate polymorphic form I

No.	Pos. [°2Th.]	d-spacing	Significance	Rel. Int. [%]	Height	FWHM [°2Th.]
1	7.3764	11.98471	6.2702	20.43	268.55	0.1968
2	8.1127	10.8985	8.2537	67.21	1262.36	0.1378
3	9.5327	9.27806	1.0402	1.65	36.19	0.1181
4	10.3293	8.56425	7.2082	35.73	587.13	0.1574
5	10.9047	8.11361	1.1678	3.71	81.21	0.1181
6	11.4934	7.69927	1.6423	4.93	108.04	0.1181
7	13.1887	6.71317	2.474	6.71	125.94	0.1378
8	13.9689	6.33994	2.7846	18.33	344.26	0.1378
9	14.4271	6.13961	9.0055	100	1878.24	0.1378
10	14.9079	5.94267	0.8893	7.38	194.15	0.0984
11	15.3464	5.77383	1.0773	4.82	105.62	0.1181
12	16.1917	5.47426	1.5703	12.65	277.21	0.1181
13	16.483	5.37816	1.4703	5.98	112.35	0.1378
14	17.1452	5.17192	1.4148	7.74	113.04	0.1771
15	17.4416	5.08469	0.845	10.21	223.67	0.1181
16	17.6803	5.01656	2.0602	14.99	328.43	0.1181
17	18.0743	4.90808	0.8691	9.4	154.41	0.1574
18	19.1325	4.63896	4.4349	10.38	124.04	0.2165
19	19.8725	4.46784	10.8052	81.97	829.02	0.2558
20	20.123	4.41278	2.7797	20.47	384.52	0.1378
21	20.8422	4.26212	3.8423	25.86	377.8	0.1771
22	21.664	4.10225	1.3778	6.84	112.38	0.1574
23	21.934	4.05236	0.8037	7.22	158.1	0.1181
24	22.6644	3.92339	2.6455	28.17	529.09	0.1378
25	23.0446	3.85952	4.2792	32.63	536.27	0.1574
26	23.3581	3.80843	0.8911	6.1	114.54	0.1378
27	24.2522	3.67001	1.048	10.05	165.16	0.1574
28	24.7131	3.6026	1.7664	11.03	181.25	0.1574
29	25.2918	3.52147	0.8595	6.37	139.48	0.1181
30	25.5938	3.4806	3.209	14.95	196.52	0.1968
31	25.998	3.42739	1.2909	7.27	136.6	0.1378
32	26.2996	3.38876	1.3513	7.83	171.58	0.1181
33	26.8428	3.32142	1.1524	13.69	257.13	0.1378
34	27.5147	3.24181	2.7231	17.37	163.15	0.2755

35	28.4299	3.1395	1.2032	13.87	260.47	0.1378
36	28.9019	3.08929	4.2121	21.23	310.21	0.1771
37	30.5636	2.92501	1.0596	9.27	203.03	0.1181
38	31.1155	2.87438	1.7024	11.28	211.91	0.1378
39	32.6723	2.7409	4.1483	19.55	91.79	0.551
40	33.99	2.63759	0.987	10.44	196.01	0.1378
41	35.6268	2.52008	1.0154	10.52	197.55	0.1378
42	36.7513	2.44551	1.4549	4.56	42.78	0.2755
43	37.3712	2.40636	2.3269	14.87	139.66	0.2755

FIG.-2


Peak = 197.560 °C
Peak Height = 33.1046 mW
Area = 908.579 mJ
Delta H = 344.159 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
45
40
35
30
25
20
15
10
5
0
-2
55
60
80
100
120
140
160
180
200
220
240
250