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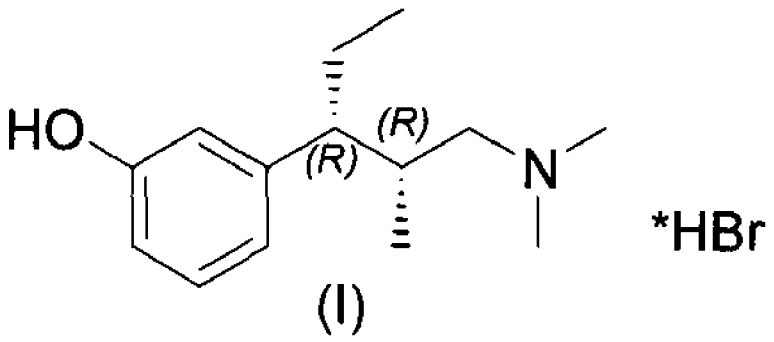
(54) Title: A NEW SOLID FORM OF TAPENTADOL AND A METHOD OF ITS PREPARATION



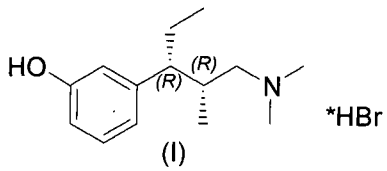
(I)

(57) Abstract: The present invention relates to a crystalline form of tapentadol hydrobromide of formula (i), chemically 3-[(1*R*,2*R*)-3-(dimethylamino)-l-ethyl-2-methylpropyl]phenol hydrobromide, which manifests the following characteristic reflection in an X-ray powder record using CuKa radiation: 14.6; 15.5; 17.9; 21.1; 21.8 ± 0.2° 2-theta, and a method of its preparation.

A new solid form of TAPENTADOL and a method of its preparation

Technical Field

The invention relates to a new crystalline form of tapentadol hydrobromide (I), chemically 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrobromide, and a method of its preparation.



(I)

Background Art

US Patent no. 6,344,558 describes a group of 1-phenyl-3-dimethylaminopropane compounds, processes of their preparations, their pharmaceutical compositions and methods of application. These compounds are used in pharmaceutical compositions as efficient analgesics. They also include tapentadol hydrochloride as a centrally acting analgesic with a dual mode of action. As an agonist of the μ-opioid receptors it prevents transmission of nerve impulses by the spinal cord and at the same time it prevents reuptake of norepinephrine in synaptic clefts.

Various processes of preparation of tapentadol, its optical isomers and pharmaceutically acceptable salts are described in the following patents: US patents 6,248,737 and 6,344,558, as well as in the following PCT applications: WO 2004/108658, WO 2005/000788, WO 2008/012046, WO 2008/012047, WO 2008/012283, WO 2011/1026314.

The EP Patent no. 0 693 475 mentions the possibility of production of pharmaceutically acceptable salts of tapentadol and similar compounds with suitable acids (such as hydrochloric, hydrobromic, sulphuric, methanesulfonic, formic, acetic, oxalic, succinic, tartaric, mandelic, fumaric, lactic, citric and the like acids), but out of this range it is only the hydrochloride that has been prepared and isolated, namely in a crystalline arrangement corresponding to form B.

US Patent application 2007/0213405 describes two crystalline forms of the hydrochloride: the above mentioned form B and form A. Each polymorph is therein characterized by X-ray powder diffraction, polymorph A being referred to as the more stable of the two forms. US 2010/272815 also describes an amorphous form of tapentadol hydrochloride.

Patent WO 2009/0149634 describes 3 different forms of tapentadol base, a process of their preparation and mentions their characterization using the X-ray powder diffraction. US patent application 2011/071120 describes preparation and characterization of several salts of tapentadol (camphorsulfonate, dibenzoyltartrate, malate, maleate and salicylate). However, the salts with high-molecular-weight acids (e.g. camphorsulfonic acid, dibenzoyltartaric acid and the like) are not suitable for pharmaceutical use as they may unacceptably increase the size of the dosage form (Handbook of Pharmaceutical Salts, Wiley, 2011, Chapter 7). Other salts may also manifest unsuitable physical-chemical properties such as a low melting point, low solubility in water or chemical or polymorphous instability.

Disclosure of Invention

The invention provides a new crystalline form of tapentadol hydrobromide, characterized by the following characteristic reflections in an X-ray powder pattern measured at 14.6; 15.5; 17.9; 21.1; 21.8 ± 0.2° 2-theta, which were measured using the CuKα radiation. This form also manifests the following other characteristic reflections: 10.2; 16.9; 24.6; 25.0; 25.4; 28.19; 29.2 and 31± 0,2° 2-theta.

The hydrobromide in accordance with this invention is characterized by the powder XRPD pattern indicated in Table 1 and the crystallographic data indicated in Table 2, which were obtained by X-ray diffraction of a monocrystal.

Tab. 1: XRPD - characteristic diffraction peaks corresponding to tapentadol hydrobromide

Pos. [°2Th.]	d-spacing [A]	Rel. Int. [%]
10.18	8.686	30.4
14.62	6.054	100.0
15.47	5.724	53.5
16.86	5.254	20.3
17.85	4.965	91.3
20.21	4.390	20.8
21.05	4.217	63.7
21.85	4.065	66.5
24.60	3.615	56.1
24.98	3.562	30.2
25.42	3.501	35.7
26.28	3.389	16.8
27.38	3.255	35.0
28.19	3.163	43.2
29.24	3.052	36.3
29.67	3.008	25.6
30.97	2.885	30.6
32.49	2.753	12.4
33.24	2.693	16.8

Tab. 2: Crystallographic data for the crystalline form of tapentadol hydrobromide

Space group	$P2_12_12_1$
a (Å)	7.0180(2)
b (Å)	12.1707(4)
c (Å)	17.7294(6)
α (°)	90
β (°)	90
γ (°)	90
V	1514.34(8)

The hydrochloride of form A, as it is designated and described in the US document no. 2007/0213405, is a highly chemically stable compound according to the said document. By comparing our new form of tapentadol hydrobromide to the already known forms we have surprisingly found out that the tapentadol hydrobromide in accordance with our invention is not only equally chemically stable as the known forms, but also considerably less hygroscopic than the described hydrochlorides. Under standard measurements form B absorbs up to 14% of weight of water at 80% relative humidity, form A absorbs 10% of water and our new

hydrobromide form absorbs only 2 to 3% of water under the same conditions. This evaluation was made based on measurements using the DVS method, wherein equilibrium hygroscopicity is determined in several sorption and desorption cycles.

Hygroscopicity is one of the properties which are monitored when suitable candidates for pharmaceutical development are looked for. Hygroscopicity, i.e. the ability of substances to bind water, plays an important role in the preparation and stability of a dosage form. If a substance only absorbs a small amount of water, it can be employed in a number of processes that are used in pharmaceutical production, for example, it can be used without problems in methods that work with water as a medium, e.g. wet granulation, without its physical-chemical properties being changed during the processing.

Another aspect of this invention provides a method of preparation of tapentadol hydrobromide. The hydrobromide is prepared from the free base of tapentadol in a suitable solvent by treatment with hydrobromic acid or hydrogen bromide, which may be either in the gaseous state or as a solution in an organic solvent. The resulting hydrobromide either directly crystallizes from the solution or the resulting solution is concentrated and/or another solvent is added as an antisolvent.

In a preferred embodiment of this invention the tapentadol base is dissolved in a solvent, which is, e.g., a C_3-C_5 ketone, C_1-C_4 alcohol, an acetic acid ester with a C_1-C_4 alcohol, *tert*-butyl methyl ether, tetrahydrofuran or dioxane, hydrobromic acid is added in an amount of 0.9 to 1.1 equivalents, or a solution of hydrobromic acid in a C_1 to C_4 alcohol is used. The resulting solution is cooled to a temperature in the range of 0 to 40°C and possibly another solvent is added as an antisolvent, which is, e.g., diethyl ether, *tert*-butyl methyl ether, ethyl acetate or diisopropyl ether. The crystallized hydrobromide is then isolated using known techniques.

The crystalline tapentadol hydrobromide is a chemically polymorphously stable form with a high melting point (183-185°C), which is preferred as compared to tapentadol hydrochloride form A, which manifests a polymorphous transformation at a relatively low temperature of ca. 45°C.

Another criterion that should be considered is solubility of the solid form of the active substance in water. This parameter was measured by adding a charge of the substance into 1 ml of water at 25°C,

tapentadol hydrobromide: 0.25 g/ml

tapentadol hydrochloride form A: > 0.4 g/ml (the form in the Palexia product made by Gruenenthal)

Tapentadol hydrobromide in accordance with our invention exhibits sufficiently high solubility in water for the active substance to be biologically available. Compared to tapentadol hydrochloride form A, which shows very good solubility in water, the relatively lower solubility of tapentadol hydrobromide may be convenient for, e.g., the preparation of a dosage form with extended release (Handbook of Pharmaceutical Salts, Wiley, 2011, Chapter 4).

Brief Description of Drawings

Fig. 1: XRPD record for tapentadol hydrobromide
Fig. 2: DSC record for tapentadol hydrobromide
Fig. 3: DVS record for tapentadol hydrobromide
Fig. 4: DSC record for tapentadol hydrochloride, Form A
Fig. 5: DVS record for tapentadol hydrochloride, Form A
Fig. 6: DSC record for tapentadol hydrochloride, Form B
Fig. 7: DVS record for tapentadol hydrochloride, Form B
Fig. 8: Crystalline structure of tapentadol hydrobromide

Examples

Samples in the examples below were characterized using the X-ray Powder Diffraction (XRPD) and Differential Scanning Calorimetry (DSC) methods.

XRPD measurement parameters: The diffraction patterns were measured using an X'PERT PRO MPD PANalytical diffractometer with a graphite monochromator, radiation used: CuKα (λ=1.542 Å), excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 - 40° 2θ, increment: 0.01° 2θ. The measurement was carried out using a flat powder sample that was placed on a Si plate. For the primary optic setting programmable divergence diaphragms with the irradiated sample area of 10 mm, Soller diaphragms 0.02 rad and an anti-dispersion

diaphragm ¼ were used. For the secondary optic setting an X'Celerator detector with the maximum opening of the detection slot, Soller diaphragms 0.02 rad and an anti-dispersion diaphragm 5.0 mm were used.

The Differential Scanning Calorimetry (DSC) records were measured with a DSC Pyris 1 device made by Perkin Elmer. The charge of the sample in a standard Al pot was between 3-4 mg and the heating-up rate was 10°C/min. The temperature program used consists of 1 minute of stabilization at the temperature of 50°C and then of heating to 250°C at the heating-up rate of 10°C/min. As the carrier gas 4.0 N_2 was used at the flow of 20 ml/min.

The Dynamic Vapour Sorption (DVS) records were measured with a DVS Advantage 1 device made by Surface Measurement Systems. The charge of the sample in a quartz dish was between 15-30 mg and the temperature in the device was 25-25.2°C. Measurement program used: the sample was loaded with two cycles with the course from the relative humidity of 0% to 90% (sorption) and then from 90% to 0% of RH (desorption). This course was repeated in the second cycle. As the carrier gas 4.0 N_2 was used at the flow of 200 sccm.

For comparison of physical-chemical properties tapentadol hydrochloride form A and hydrochloride form B were prepared in accordance with the methods described in US 2007/0213405.

Example 1

Preparation of tapentadol hydrobromide

Tapentadol base (22.7 g) was dissolved in acetone (200 ml). Then, under stirring, 47% hydrobromic acid (11.8 ml) was added dropwise. The resulting solution was cooled down to 0°C and diethyl ether (250 ml) was added dropwise under stirring. The resulting suspension was stirred at 0°C for one hour. After aspiration and washing with diethyl ether (50 ml), 23.7 g of tapentadol hydrobromide of the crystalline form corresponding to the XRPD record of Fig. 1 was obtained.

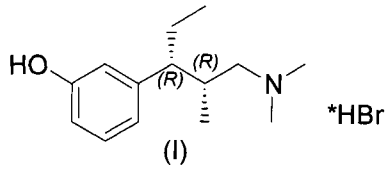
Example 2

Tapentadol base (10 g) was dissolved in 250 ml of *tert*-butyl methyl ether (MTBE) at the room temperature and a solution prepared from 5.1 ml of 48% HBr and 55 ml of methanol was

added dropwise to the solution. The resulting solution was cooled to 0°C and 30 ml of ethyl acetate were added dropwise at this temperature. The resulting mixture was cooled to -12°C within 2 hours, during it was stirred for 30 minutes. The separated crystalline fraction was aspirated through frit and washed with 2x25 ml of MTBE. The resulting product was dried at 50°C and a pressure of 12 kPa for 2 hours. 11.48 g of hydrobromide tapentadol (84%) was obtained, which manifested the XRPD pattern in accordance with Fig. 1.

CLAIMS

1. Tapentadol hydrobromide of formula I, manifesting the following characteristic reflections in an X-ray Powder Diffraction pattern measured using CuKα radiation: 14.6; 15.5; 17.9; 21.1; 21.8 ± 0.2° 2-theta.



(I)

2. Tapentadol hydrobromide in accordance with claim 1, manifesting the following other characteristic reflections 10.2; 16.9; 24.6; 25.0; 25.4; 28.19; 29.2 and 31± 0,2° 2-theta.

3. A method for the preparation of tapentadol hydrobromide as defined in claim 1, characterized in that tapentadol base is dissolved in a suitable solvent selected from a C_3-C_5 ketone, a C_1-C_4 alcohol, an acetic acid ester with a C_1-C_4 alcohol, *tert*-butyl methyl ether, tetrahydrofuran or dioxane or their mixture, hydrobromic acid or its solution in a C_1 to C_4 alcohol is added, the resulting solution is then cooled, an antisolvent is added and the crystallized tapentadol hydrobromide is isolated.

4. The method in accordance with claim 3, characterized in that hydrobromic acid is used in the range of 0.9 to 1.1 equivalents.

5. The method in accordance with claim 4, characterized in that after adding of hydrobromic acid the solution is cooled to a temperature in the range of 0 to 40°C.

6. The method in accordance with claim 3, characterized in that the antisolvent is selected from diethyl ether, *tert*-butyl methyl ether, ethyl acetate or diisopropyl ether.

7. The method in accordance with claim 3, characterized in that said suitable solvent is acetone and said antisolvent is diethyl ether.

8. Use of tapentadol hydrobromide in accordance with claim 1 for the preparation of a pharmaceutical composition.

Fig. 1:

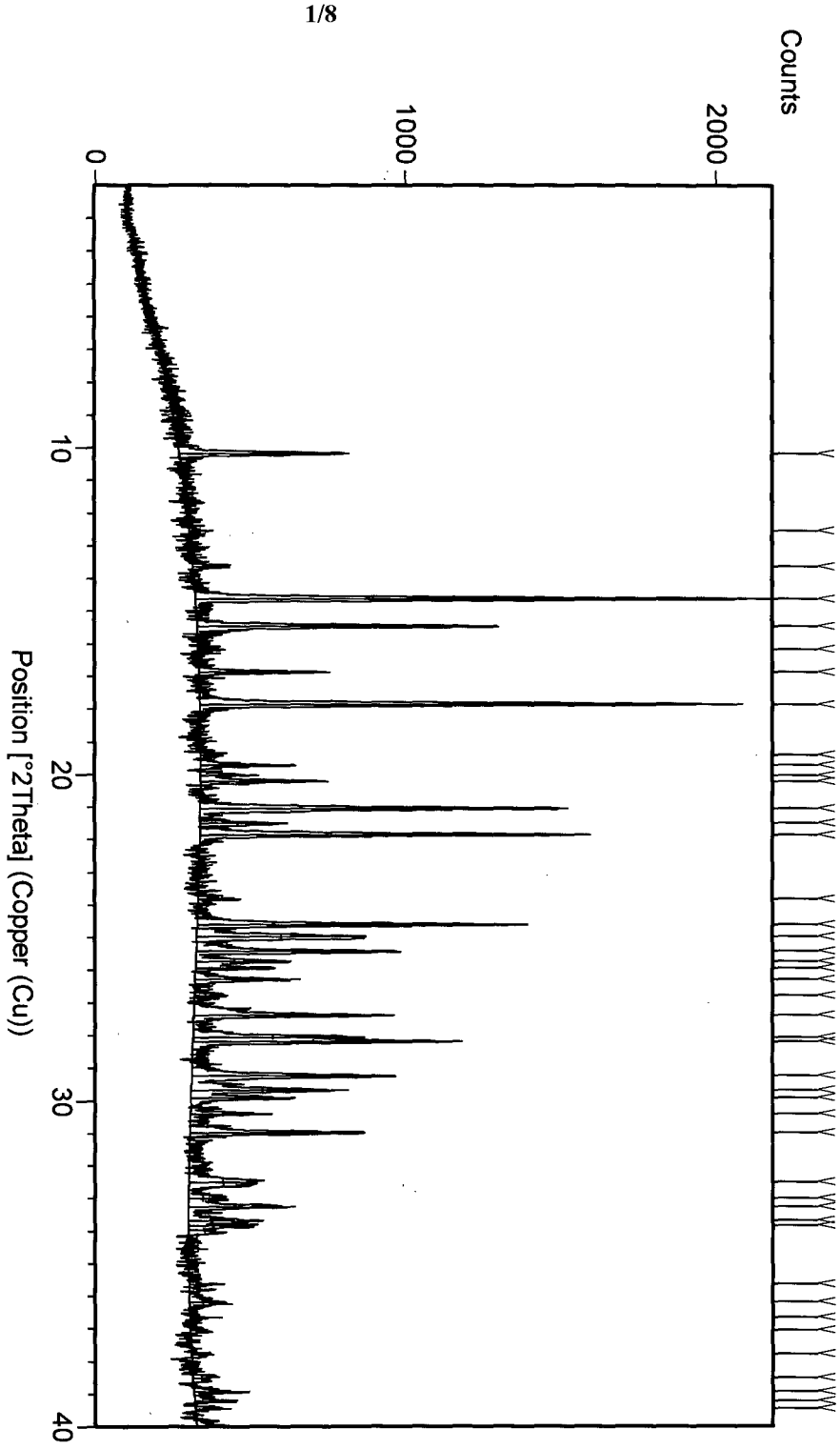
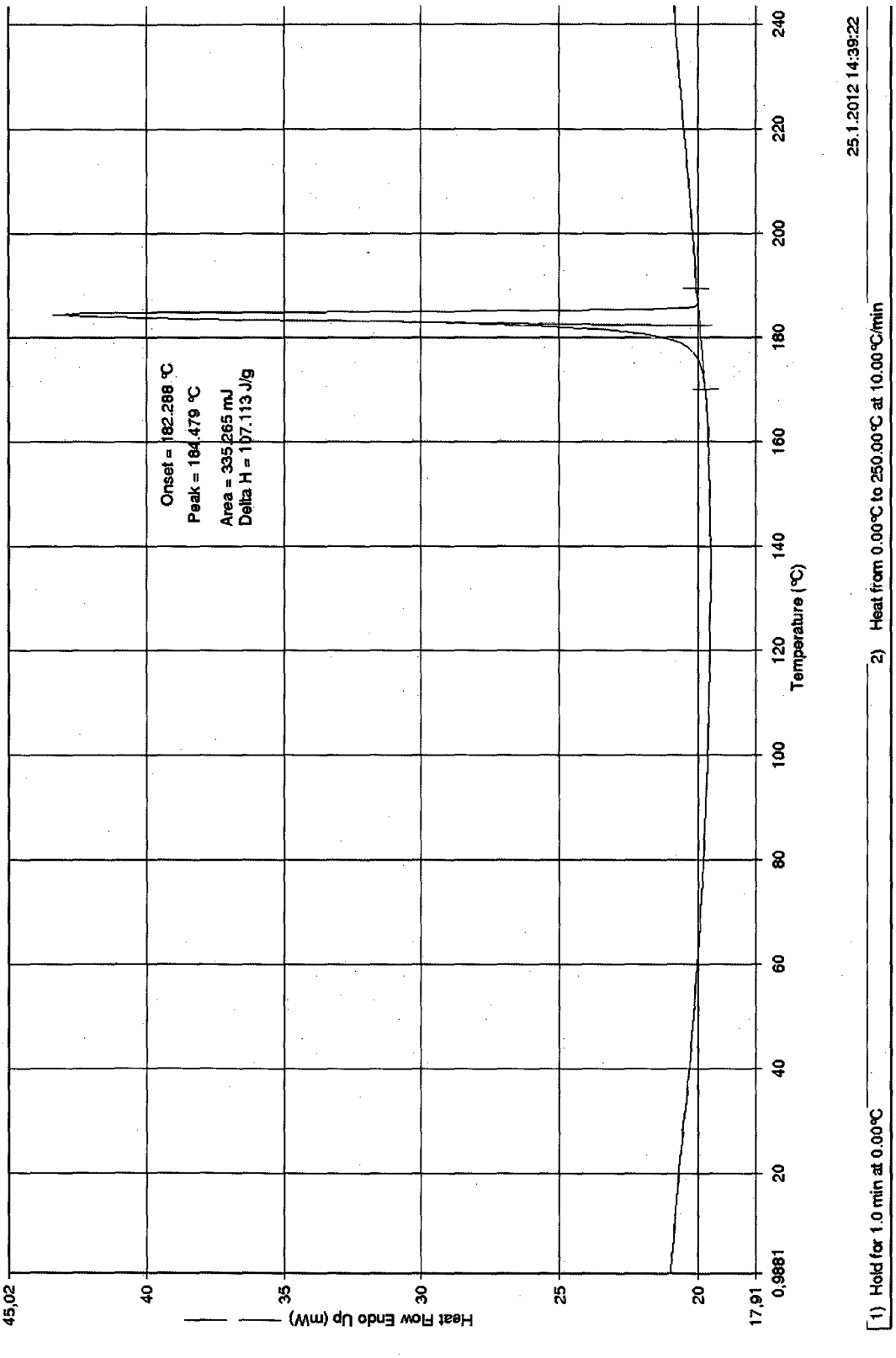


Fig. 2: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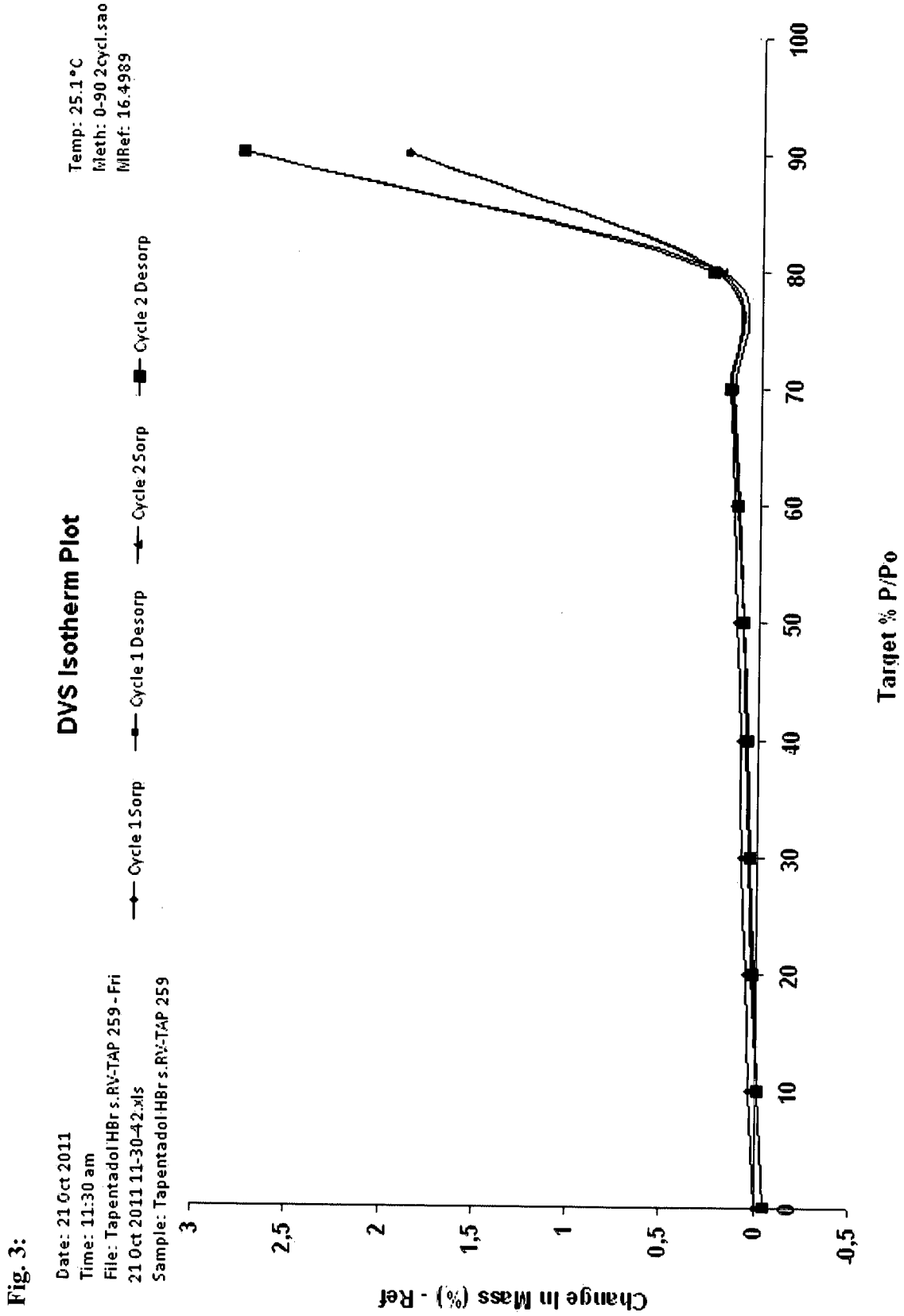
40
35
30
25
20
20
40
60
80
100
120
140
160
180
200
220
240
25.1.2012 14:39:22
1) Hold for 1.0 min at 0.00°C
2) Heat from 0.00°C to 250.00°C at 10.00°C/min

Fig. 3: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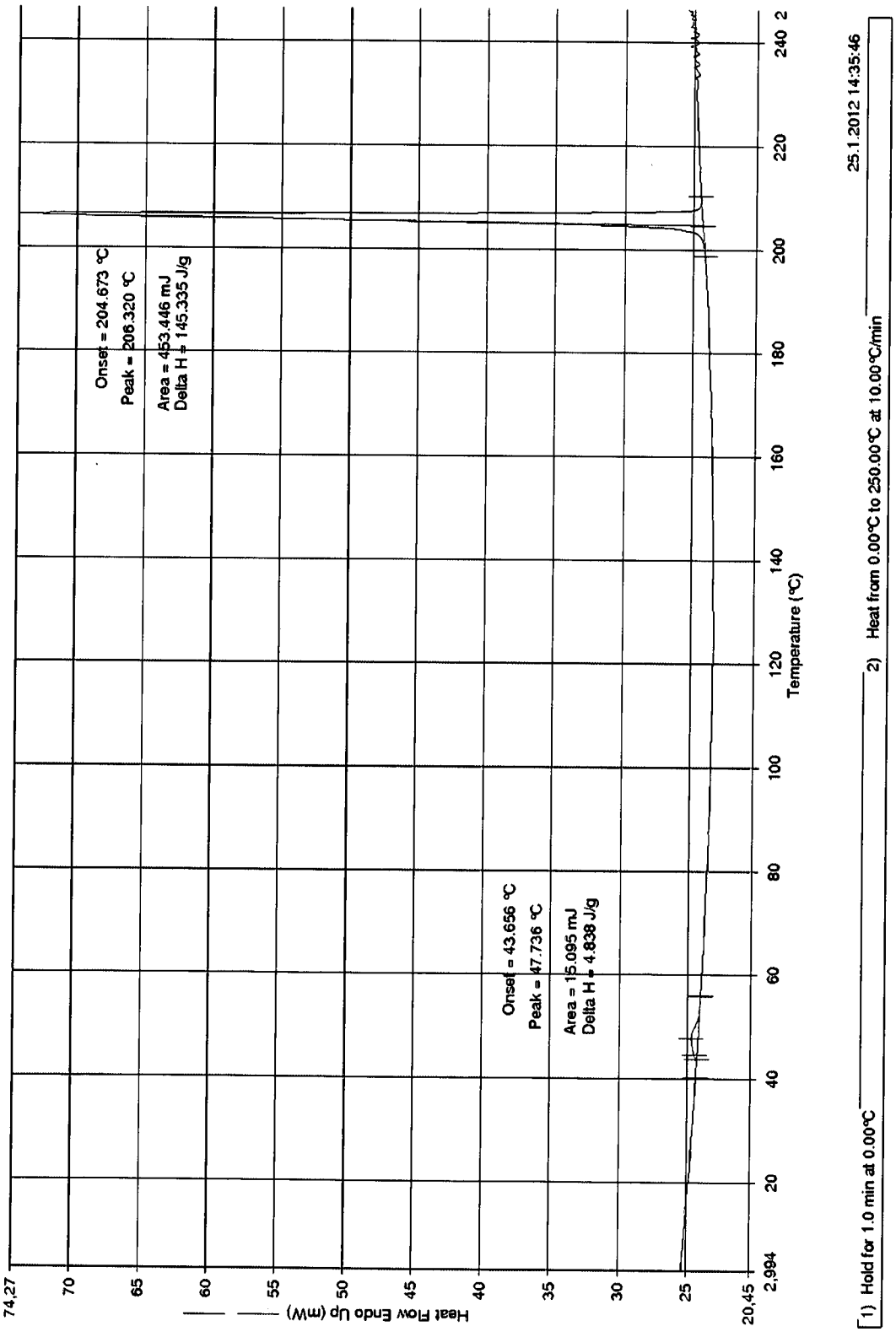
Meth: 0-90 2cycl.sao
MRef: 16.4989
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Change in Mass (%) - Ref
Target % P/Po
3
2,5
2
1,5
1
0,5
0
-0,5
0
10
20
30
40
50
60
70
80
90
100

Fig. 4: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Area = 15.095 mJ
Delta H = 4.838 J/g
Heat Flow Endo Up (mW)
Temperature (°C)
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70
65
60
55
50
45
40
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30
25
20,45
2,994
20
40
60
80
100
120
140
160
180
200
220
240
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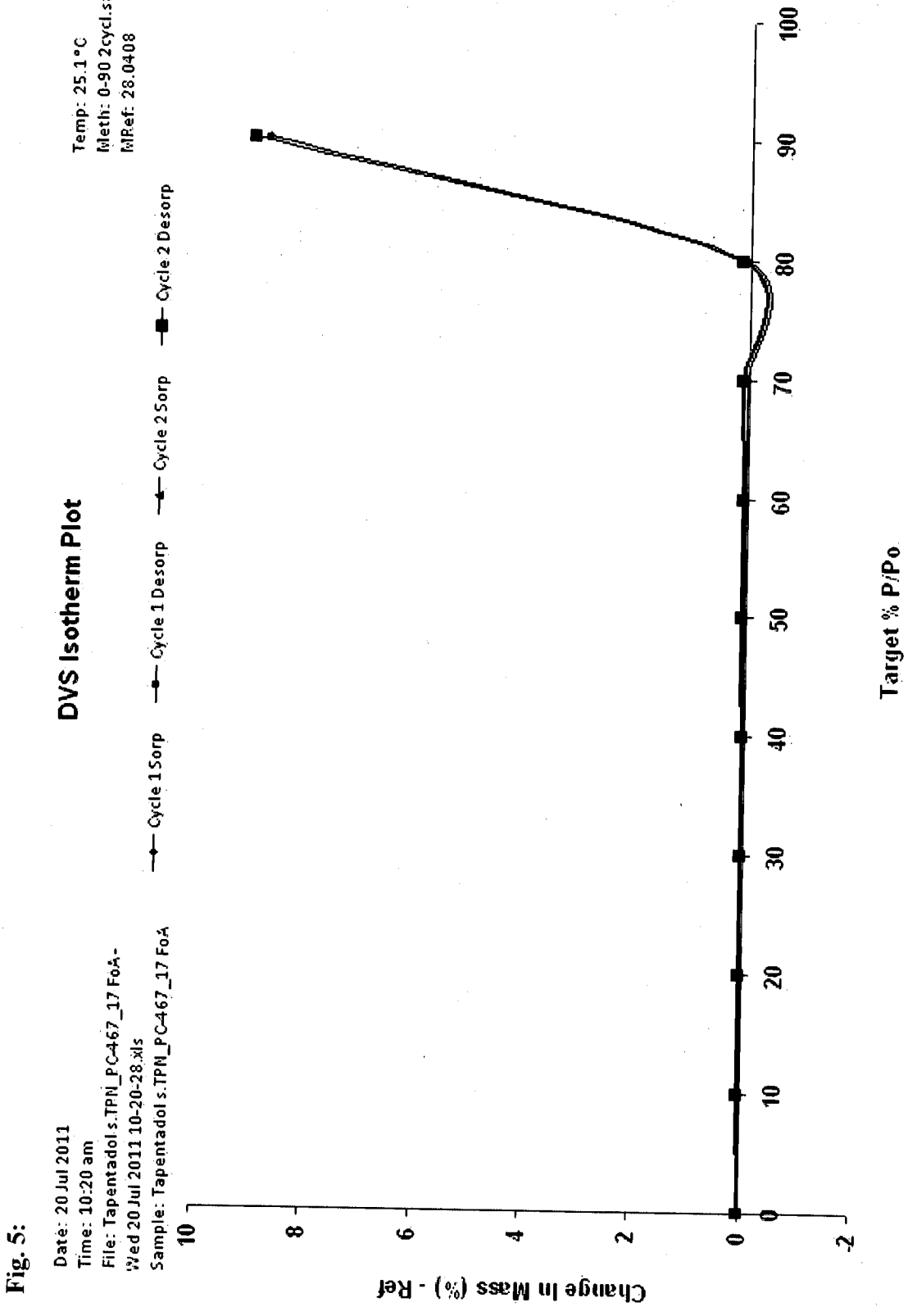
2) Heat from 0.00°C to 250.00°C at 10.00°C/min
25.1.2012 14:35:46

Fig. 5: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MRef: 28.0408
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Change in Mass (%) - Ref
Target % P/Po
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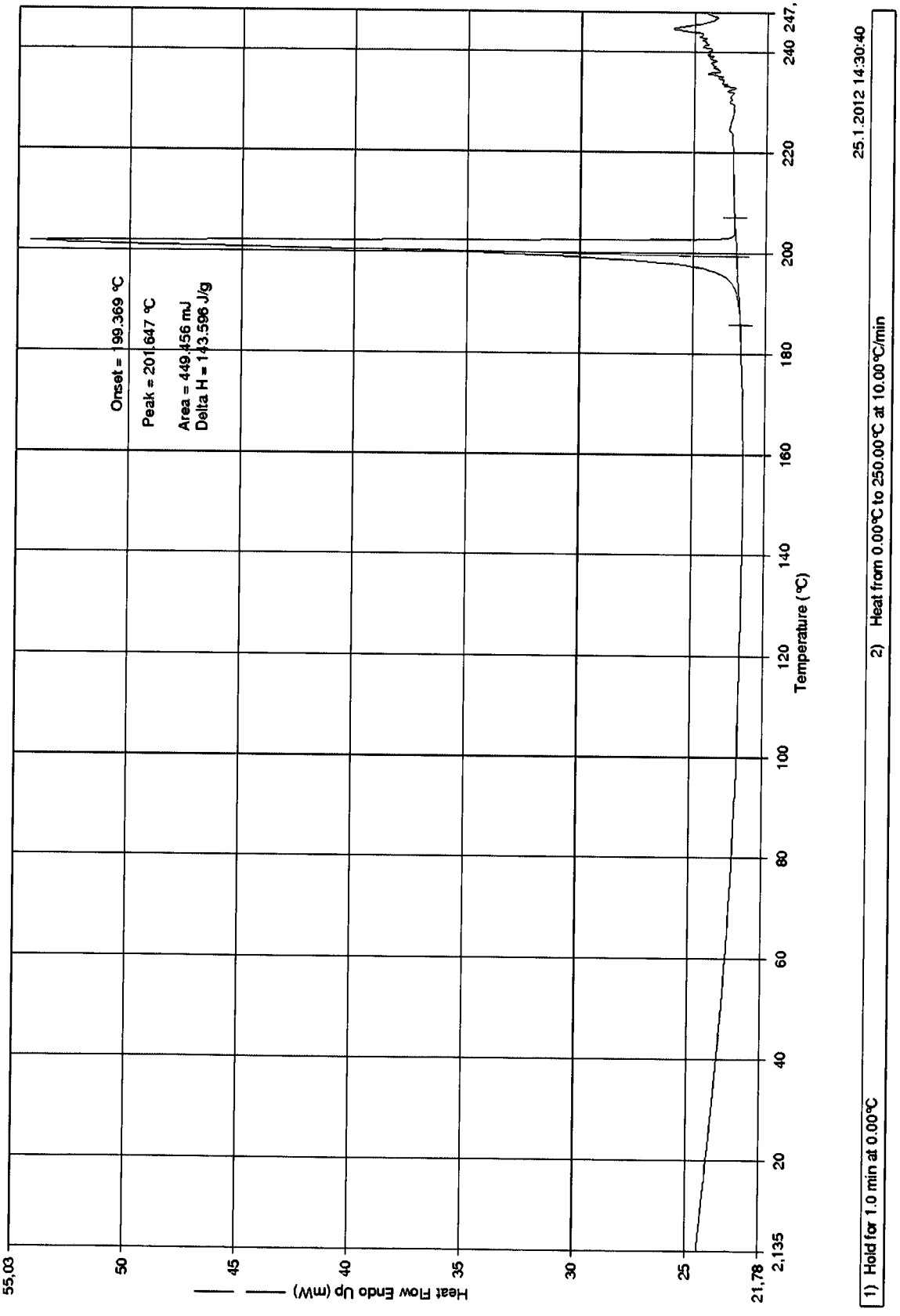
8
6
4
2
0
-2
0
10
20
30
40
50
60
70
80
90
100

Fig. 6: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Delta H = 143.596 J/g
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Temperature (°C)
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21,78
2,135
25.1.2012 14:30:40
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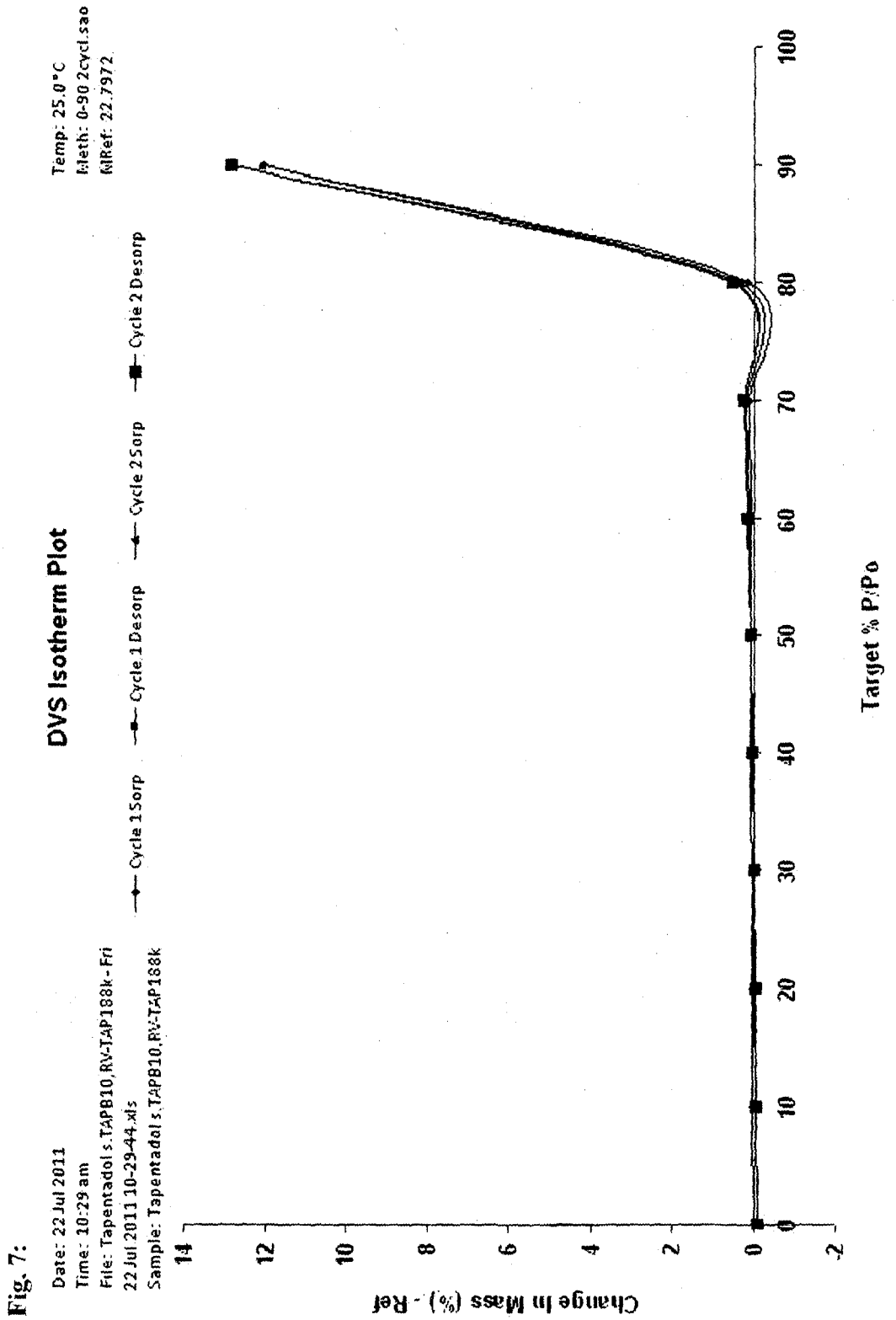
2) Heat from 0.00°C to 250.00°C at 10.00°C/min

Fig. 7: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Time: 10:29 am
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Temp: 25.0 °C
Meth: 0-90 2cycl.sao
MRef: 22.7972
Cycle 1 Sorp
Cycle 1 Desorp
Cycle 2 Sorp
Cycle 2 Desorp
Change in Mass (%) - Ref
Target % P/Po
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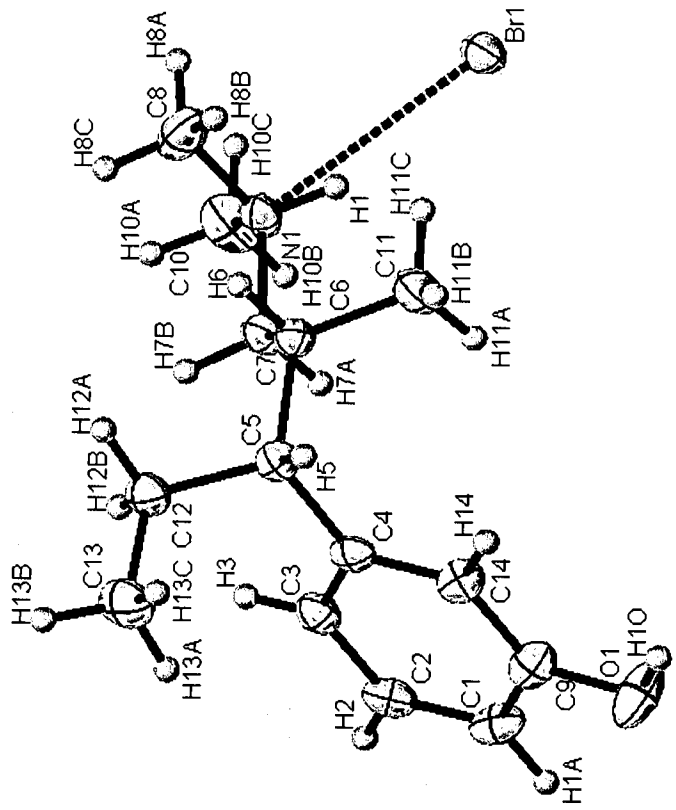
12
10
8
6
4
2
0
-2
0
10
20
30
40
50
60
70
80
90
100


Br1
H8A
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H8B
H8C
H10C
H1
H11C
H10A
C10
N1
H10B
C11
H11B
H6
C6
H11A
H7B
C7
H7A
H12A
C5
H12B
H5
C12
C4
H14
H13B
C13
H13C
H3
C3
C14
H13A
C2
O1
H10
H2
C1
C9
H1A

Fig. 8:

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000016

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/135 C07C215/62
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/010316 A1 (GRUENENTHAL GMBH [DE]; GRUSS MICHAEL [DE]; KRASZEWSKI MAGDA [DE]) 26 January 2012 (2012-01-26) Paragraph 2, page 12; pages 19-20; figure 1	1-8
A	EP 0 693 475 A1 (GRUENENTHAL GMBH [DE]) 24 January 1996 (1996-01-24) cited in the application See last paragraph, page 5	1-8
A	US 2007/213405 A1 (FISCHER ANDREAS [DE] ET AL) 13 September 2007 (2007-09-13) cited in the application claim 1	1-8

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 June 2013	11/06/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Menchaca, Roberto

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