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(54) **Title:** TAPENTADOL HYDROBROMIDE AND CRYSTALLINE FORMS THEREOF

(57) **Abstract:** The present invention provides a salt of Tapentadol, Tapentadol liydrobromide, and crystalline forms of Tapentadol hydrobromide.

TAPENTADOL HYDROBROMIDE AND CRYSTALLINE FORMS THEREOF

CROSS REFERENCE TO RELATED APPLICATION

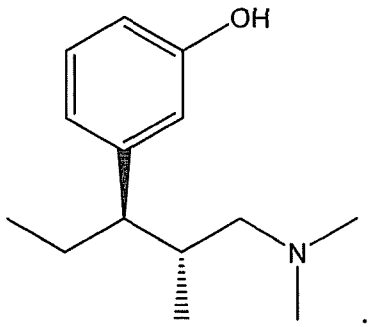
The present patent application claims the benefit of U.S. Provisional Application No. 61/392,308 filed October 12, 2010, the disclosures of which are herein incorporated by reference.

FIELD OF INVENTION

The present invention concerns the hydrobromide salt of Tapentadol, solid state forms of Tapentadol hydrobromide, processes for their preparation, and pharmaceutical compositions comprising Tapentadol hydrobromde or a solid state form thereof.

BACKGROUND OF THE INVENTION

Tapentadol, 3-[(lR,2R)-3-(dimethylamino)-l-ethyl-2-methylpropyl]phenol, has the formula:



Tapentadol is marketed under the trade name Nucynta® for the treatment of moderate to severe pain.

Tapentadol hydrochloride, its synthesis, and its use as an analgesic are disclosed in U.S. patent no. 6,248,737. European patent nos. EP1612203 and EP0693475 disclose polymorphs of Tapentadol hydrochloride (Forms A and B, respectively). International patent application publication no. WO2009/071310 discloses three polymorphic forms of Tapentadol free base. European patent no. EP 1390023 discloses pharmaceutical salts of 1-phenyl-3-dimethylamino-propane compounds and sugar substitutes. International patent application publication no. WO2008/1 10323 discloses the salts of l-phenyl-3-dimemylamino-propane and their use in treating neuropathic pain.

Different salts of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts may provide a basis for

improving formulation. Different salts of an active pharmaceutical ingredient may also give rise to a variety of polymorphs or crystalline forms.

Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule, like Tapentadol and its salts, may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviours (e.g., measured by capillary melting point, thermogravimetric analysis (TGA), or differential scanning calorimetry (DSC), as well as content of solvent in the polymorphic form), powder x-ray diffraction pattern (PXRD), infrared absorption and Raman fingerprints, and solid state NMR spectrum. The differences in physical properties have been used to distinguish polymorphic forms. One or more of these techniques may be used to distinguish different polymorphic forms of a compound. These techniques may also be used to quantify the amount of one or more crystalline forms in a mixture.

The differences in the physical properties of different salts and polymorphic forms results from the orientation and intermolecular interactions of adjacent molecules or complexes in the bulk solid. Accordingly, polymorphs are distinct solids sharing the same molecular formula yet having distinct physical properties compared to other polymorphic forms of the same compound or complex.

The discovery of new salts and polymorphic forms of Tapentadol can provide new ways to improve the synthesis and the characteristics of Tapentadol as an active pharmaceutical ingredient.

SUMMARY OF THE INVENTION

The present invention provides a salt of Tapentadol, Tapentadol hydrobromide, isolated and solid state forms of Tapentadol hydrobromide, and provides pharmaceutical compositions comprising Tapentadol hydrobromide or at least one solid state form (or solid state forms) thereof, and at least one pharmaceutically acceptable excipient.

The solid state forms of Tapentadol hydrobromide include the hydrates and solvates of Tapentadol hydrobromide.

The invention further provides the use of Tapentadol hydrobromide, and the solid state forms described below for the manufacture of a medicament for the treatment of moderate to severe pain, and provides for a method of treatment of moderate to severe pain comprising administering a therapeutically effective dose of at least one of the solid state forms described herein to a person suffering from moderate to severe pain.

The invention provides a method for treating moderate to severe pain comprising administering the pharmaceutical composition comprising Tapentadol hydrobromide or at least one solid state form thereof and at least one pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a powder XRD pattern of Tapentadol hydrobromide.

Figure 2 shows a DSC thermogram of Tapentadol hydrobromide.

Figure 3 shows a powder XRD pattern of Tapentadol free base.

DETAILED DESCRIPTION OF THE INVENTION

A crystal form may be referred to herein as being characterized by graphical data "as shown in," or "as depicted in," or "substantially as depicted in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. The skilled person will understand that such graphical representations of data may be subject to small variations, e.g., in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figure disclosed herein with graphical data generated for an unknown crystal form, and confirm whether the two sets of data are characterizing the same crystal form or two different crystal forms. The crystal form characterized by the graphical data "as shown in," or "as depicted in," or "substantially as depicted in" a Figure disclosed herein includes a crystal form characterized by graphical data with small variations, which are well known to the skilled person, in comparison to the graphical data in the Figure.

A crystal form, crystalline form or polymorph may be referred to herein as pure or polymorphically pure, or substantially free of any other crystalline or polymorphic forms. As used herein in this context, the expression "substantially free" will be understood to mean that the crystalline form contains 20% or less, 10% or less, 5% or less, 2% or less, or 1% or less of any other crystalline forms of the subject compound as measured, for example, by PXRD. Thus, crystalline forms of Tapentadol salts described herein as substantially free of any other crystalline forms would be understood to contain greater than 80% (w/w), greater than 90% (w/w), greater than 95% (w/w), greater than 98% (w/w), or greater than 99% (w/w) of the subject crystalline form of Tapentadol salt. Accordingly, in some embodiments of the invention, the described crystalline form may contain from 1% to 20% (w/w), from 5%

to 20% (w/w), or from 5% to 10% (w/w) of one or more other crystal forms of the same compound.

The present invention provides Tapentadol hydrobromide. The Tapentadol hydrobromide of the present invention can be crystalline.

For example, the present invention provides a crystalline form of Tapentadol hydrobromide characterized by data selected from: a powder XRD pattern with peaks at 9.9, 14.3, 15.3, 19.1 and 20.9 ± 0.2° 2θ; apowder XRD pattern substantially as depicted in Figure 1; a DSC thermogram substantially as depicted in Figure 2; and any combinations thereof.

A person skilled in the art would be able to characterize the above form by identifying one or more characteristic peaks in a powder X-ray diffraction analysis of that form. For example, the skilled person would be able to characterize the above form by selecting one or more characteristic peaks in the diffractogram provided in Figure 1.

Reaction of Tapentadol free base with an acid does not always produce a salt which could be isolated. This was an unexpected and surprising result. One skilled in the art would expect that reaction of the free base with an acid would produce a salt that could be isolated. For example, reaction of the free base with phosphoric acid produced the phosphate salt, but it became liquid a few seconds after separation from the reaction mixture. The sulphuric acid salt of Tapentadol could not be isolated. Reaction of the free base with other acids, such as fumaric acid, oxalic acid, maleic acid, succinic acid, methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, benzoic acid, L-tartaric acid, acetic acid, citric acid and L-malic acid resulted in a bitumen. The reaction of Tapentadol free base with hydrobromic acid produced the hydrobromide salt of Tapentadol.

The Tapentadol hydrobromide salt and its crystalline forms in the present invention have advantageous properties selected from at least one of: high crystallinity, solubility, dissolution rate, morphology, thermal and mechanical stability to polymorphic conversion and/or to dehydration, storage stability, low content of residual solvent, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility, and bulk density. These properties may provide a basis for improving formulation, for example, by facilitating better processing or handling characteristics, improving the dissolution profile, or improving stability and shelf-life. They may also provide improvements to the final dosage form, for instance, if they serve to improve bioavailability, or shelf-live or storage etc.

The present invention further encompasses 1) a pharmaceutical composition comprising Tapentadol hydrobromide salt, or a composition comprising at least one solid

state form of Tapentadol hydrobromide, as described above, and at least one pharmaceutically acceptable excipient; 2) the use of any one or combination of the above-described Tapentadol hydrobromide salt and its solid state forms, in the manufacture of a pharmaceutical composition; and 3) a method of treating moderate to severe pain comprising administering an effective amount of any one or combination of the above-described Tapentadol hydrobromide salt and its solid state forms to a subject in need of the treatment. The pharmaceutical composition can be useful for preparing a medicament. The present invention also provides Tapentadol hydrobromide salt or at least one of its solid state forms as described above for use as a medicament.

The Tapentadol hydrobromide and its crystalline forms of the present invention are useful for preparing different Tapentadol salts or Tapentadol free base. The above described salt of Tapentadol, Tapentadol hydrobromide, and in particular the above described crystalline forms of Tapentadol hydrobromide can be used to prepare a pharmaceutical composition. Such pharmaceutical compositions can be useful for treating pain, such as moderate to severe pain.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and processes of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention. The present invention is illustrated by the following examples, which should not be construed as limiting the scope of the present invention.

EXAMPLES

PXRD method

For PXRD characterisation, the samples were, if necessary, ground in an agate mortar and properly prepared (flatted surface in zO) on a specimen holder made from PMMA. The samples were then analyzed on a Bruker-AXS D8 Advance powder X-ray diffractometer (Bruker-AXS, Karlsruhe, Germany). The specimen holder was rotated in the zO plane at 20 rpm during measurement. The measurement conditions were as follows: Radiation: Cu Ka of wavelength 1.54A , Source 40 kV / 40 mA, divergence slit 0.6 mm, detector: Vantec-1 anti-scattering slit 5.59 mm, detector slit 10.28 mm, start angle 3°2Theta, end angle 55°2Theta,

Step 0.017° 2Theta. Raw data were evaluated using the program EVA (Brulcer-AXS, Karlsruhe, Germany).

Differential scanning calorimetry (DSC)

A Mettler Toledo 822e DSC instrument was used to record the DSC curves. A sample amount of approx. 3.6 mg was placed in the calorimeter cell and heated from 30°C to 300°C with a rate of 10°C/min and a nitrogen flow of 50 ml/min.

Example 1: Preparing of Tapentadol Free Base

Methoxy-Tapentadol hydrochloride (1 eq) was set free as Tapentadol base with 8 eq aqueous hydrobromic acid (47%) under reflux and subsequently sodium bicarbonate was added until pH 8 to 9 was reached. The solution was extracted several times with ethyl acetate. The combined organic phases were dried over sodium sulphate and distilled under reduced pressure.

Example 2: Preparation of Tapentadol hydrobromide

Tapentadol base (0.52 g, 2.35 mmol) was dissolved in acetone (5 ml) at room temperature. To this solution, aqueous hydrobromic acid (47 wt.%, 1.21 g, 7 mmol) was added and the mixture was thereafter kept in the fumehood for 3 days in an open flask. A solid precipitate formed and was separated out and filtered. The solid material was washed with acetone, and dried overnight at 40 mbars and 40°C yielding tapentadol hydrobromide 0.38 g crystals (1.3 mmol, 53.5 %yield).

Example 3: Preparation of Tapentadol free base from Tapentadol hydrobromide

To a solution of Tapentadol hydrobromide dissolved in a minimum amount of water, ethyl acetate was added. Then sodium bicarbonate was added until pH 8 to 9 was reached. The organic phase was separated. The aqueous phase was extracted several times with ethyl acetate. The combined organic phases were washed with water, dried over sodium sulphate and distilled under reduced pressure. To the oily residue, n-Hexane was added and the white solid that was formed was then filtered off.

Example 4: Preparation of Tapentadol hydrochloride from Tapentadol hydrobromide

Tapentadol hydrobromide was dissolved in acetone. Gaseous hydrogen chloride was bubbled through this clear solution, and the precipitate that formed was then filtered off.

Example 5: Preparation of crystalline Tapentadol hydrobromide

Tapentadol base (0.3 g, 1.36 mmol) was suspended in 0.5 mL aqueous hydrobromic acid (47 wt.%). The suspension was warmed for 20 minutes and the warm solution was filtered. The clear solution was concentrated under reduced pressure to give an oily residue. Once at room temperature, crystals of Tapentadol hydrobromide appeared.

Example 6: Preparation of Tapentadol Hydrobromide

Tapentadol base (1 eq) was dissolved in 2-butanone at room temperature. To this solution, 1 eq of trimethylsilyl bromide and leq of water were added. Tapentadol hydrobromide crystallized overnight in an open flask resultmg in a solid form, which did not undergo polymorphic conversion.

Comparative Example 7: Preparation of Tapentadol Hydrochloride

Tapentadol base (1 eq) was dissolved in 2-butanone at room temperature. To this solution, 1 eq of trimethylsilyl chloride and leq of water were added, whereupon Tapentadol hydrochloride crystallized. Depending on ambient conditions, either polymorphic Form A or Form B or mixtures thereof were obtained.

Example 8: Preparation of Tapentadol Salts

Tapentadol base (1 eq) was dissolved in an organic solvent selected from acetone, hexane, 2-butanone, diethylether, and butanol. An acid (1 eq) selected from the table below was dissolved in the same solvent. The two solutions were combined and heated to about 60°C for about 15 minutes. The reaction was then allowed to cool to room temperature. The solvent was slowly evaporated.

The reaction of Tapentadol free base and hydrobromic acid produced the hydrobromide salt of Tapentadol. The reaction of Tapentadol free base with phosphoric acid produced the phosphate salt of Tapentadol. The phosphate salt was filtered as a solid, but became liquid a few seconds later. The sulphuric salt of Tapentadol could not be isolated. The reaction of Tapentadol free base with the other acids resulted in a bitumen.

Acids used for making Tapentadol salts		
fumaric acid	oxalic acid	maleic acid
succinic acid	methansulfonic acid	ethansulfonic acid

benzenesulfonic acid	benzoic acid	L-tartaric acid
acetic acid	citric acid	L-malic acid
sulphuric acid	phosphoric acid	hydrobromic acid

What is Claimed is:

1. Tapentadol hydrobromide.

2. The Tapentadol hydrobromide according to claim 1, wherein the Tapentadol hydrobromide is crystalline.

3. The crystalline Tapentadol hydrobromide according to claim 2, characterized by data selected from: a powder XRD partem with peaks at 9.9, 14.3, 15.3, 19.1 and 20.9 ± 0.2° 20; a powder XRD pattern as depicted in Figure 1; a DSC thermogram depicted in Figure 2; and any combination thereof.

4. A pharmaceutical composition comprising Tapentadol hydrobromide according to any of claims 1 to 3, and at least one pharmaceutically acceptable excipient.

5. A method for treating moderate to severe pain, comprising administering the pharmaceutical composition according to claim 4 to a subject suffering from the moderate to severe pain.

6. Use of Tapentadol hydrobromide according to any of claims 1 to 3 for the preparation of a pharmaceutical composition.

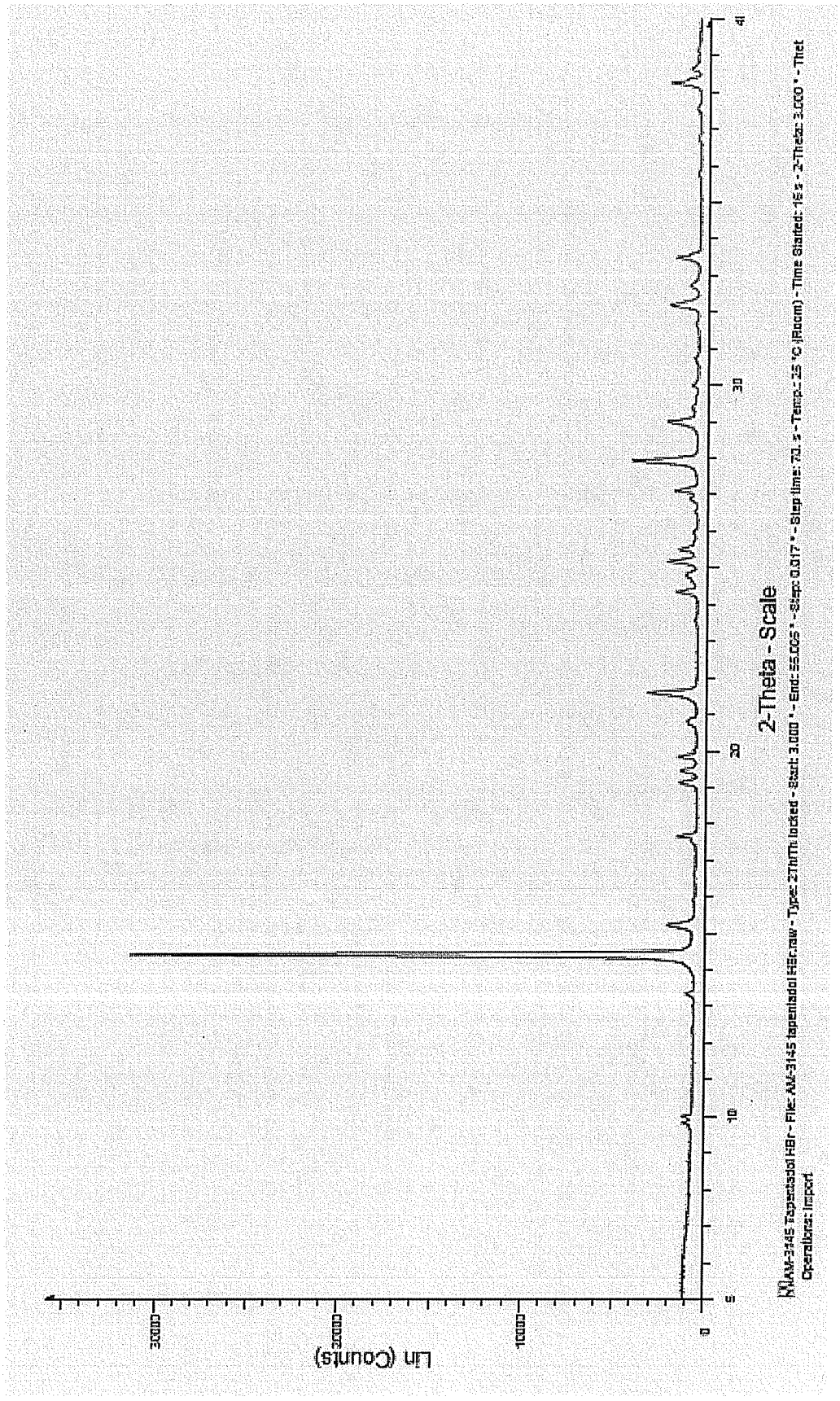
7. Use of Tapentadol hydrobromide according to any one of claims 1 to 3 for the treatment of moderate to severe pain.

8. Use of Tapentadol hydrobromide according to any one of claims 1 to 3 for the manufacture of a medicament for the treatment of moderate to severe pain.

9. Use of Tapentadol hydrobromide or at least one crystalline form thereof according to any one of claims 1 to 3 for the preparation of Tapentadol free base or a salt of the free base, wherein said salt of the free base is not Tapentadol hydrobromide.

10. Use of Tapentadol hydrobromide, or at least one crystalline form thereof, according to any one of claims 1 to 3 for the preparation of Tapentadol hydrochloride.

Figure 1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2-Theta - Scale
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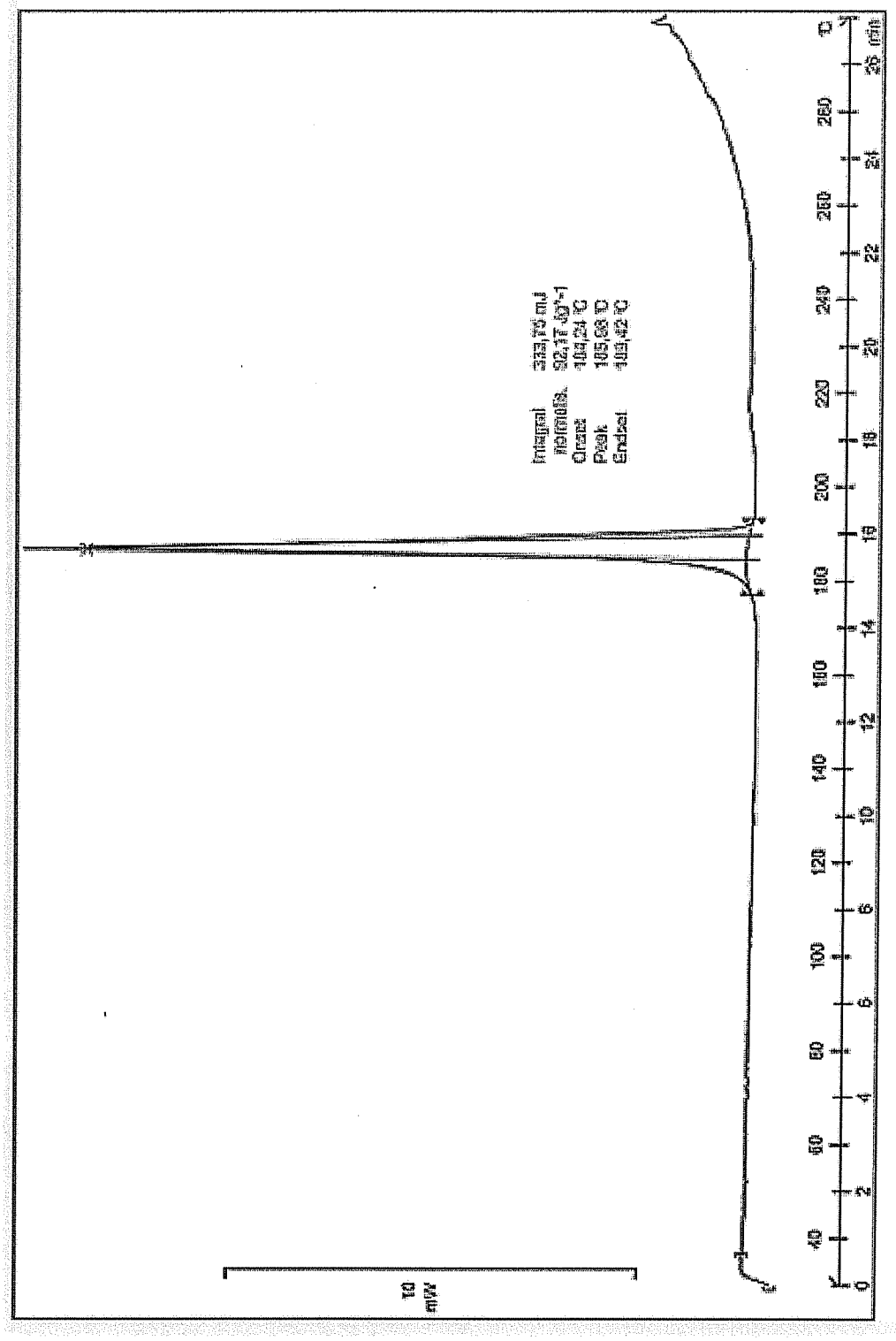
Operations: Import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normalis. 92,17 Jg^-1
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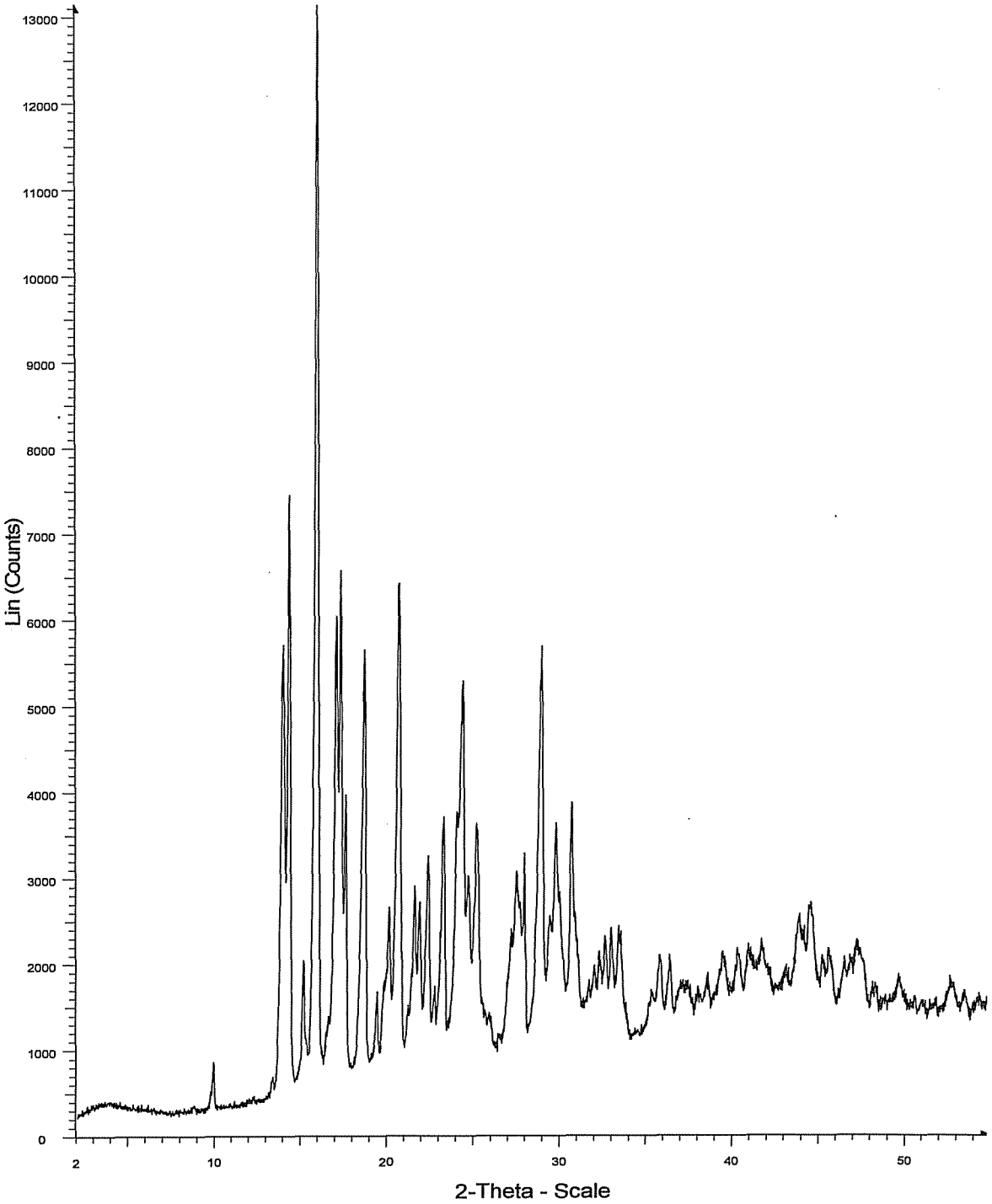
Peak 185,68 °C
Endset 188,42 °C
10 mW
exo
min
°C

Figure 2

Figure 3


Lin (Counts)
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11000
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9000
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5000
4000
3000
2000
1000
0
2
10
20
30
40
50
2-Theta - Scale

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/055893

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/137 C07C215/54 A61P29/00
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 practical, search terms used)
EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 2010/190752 Al (SCHI ENE KLAUS [DE] ET AL) 29 July 2010 (2010-07-29) page 1, paragraphs 2,3 page 2, paragraphs 31, 32	1,4-8
Y	EP 1 612 203 Al (GRUENENTHAL GMBH [DE]) 4 January 2006 (2006-01-04) cited in the application abstract page 2, paragraph 5 page 3, paragraphs 16, 24-26 page 4, paragraph 29	1-10

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2011	29/11/2011

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/055893

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/055893

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