(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 612 203 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
01.08.2007 Bulletin 2007/31

(51) Int Cl.:
C07C 215/54 *(2006.01)* ***A61K 31/135*** *(2006.01)*
A61P 13/00 *(2006.01)*

(21) Application number: **04015091.4**

(22) Date of filing: **28.06.2004**

(54) **Crystalline forms of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride**

Kristalline Formen von (-)-(1R,2R)-3-(3-Dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochlorid

Formes cristallines de chlorhydrate de (-)-(1R,2R)-3-(3-diméthylamino-1-ethyl-2-méthylpropyl)-phénol

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR
Designated Extension States:
LT LV

(43) Date of publication of application:
04.01.2006 Bulletin 2006/01

(73) Proprietor: **Grünenthal GmbH**
52099 Aachen (DE)

(72) Inventors:
- **Fischer, Andreas, Dr.**
  52393 Hürtgenwald (DE)
- **Buschmann, Helmut, Dr.**
  08960 Sant Just Desvern Barcelona (ES)
- **Gruss, Michael, Dr.**
  52080 Aachen (DE)
- **Lischke, Dagmar**
  52459 Inden-Altdorf (DE)

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EP-B- 0 693 475

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Description

[0001] This invention relates to solid crystalline forms of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride, methods of producing same, methods of use, use as analgesics and pharmaceutical compositions containing same.

[0002] The treatment of pain conditions is of great importance in medicine. There is currently a world-wide need for additional pain therapy. The pressing requirement for a target-oriented treatment of pain conditions which is right for the patient, which is to be understood as the successful and satisfactory treatment of pain for the patients, is documented in the large number of scientific works which have recently and over the years appeared in the field of applied analgesics or on basic research on nociception.

[0003] The underlying object of the present invention was to find new solid forms of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride useful in the treatment of pain.

[0004] US Pat. Nos. 6,248,737 and 6,344,558 as well as European Patent EP 693 475 B1 disclose the substance and the synthesis of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride in example 25. As proven by X-ray diffraction the 1R,2R configuration as shown in the drawing of the structure in example 25 is correct although the configuration is reported as (-)-(1R,2S) in US 6,248,737 and (-)-(1 S,2S) in US 6,344,558 as well as in EP 693 475 B1.

[0005] It has now been surprisingly found that (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride can be produced in a reproducible manner in two different crystalline forms. The present invention provides a new form (Form A) of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride which is different from the form already known (Form B) obtained by the procedure described in example 25 of US 6,248,737 and US 6,344,558 as well as EP 693 475 B1. This new Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride is very stable at ambient conditions and therefore useful for producing a pharmaceutical composition.

[0006] The new crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride can be identified by X-ray powder diffraction. The X-ray diffraction ("XRPD") pattern is shown in Fig. 1 with the peak listing shown as Table 1.

[0007] The most important X-ray lines (2-theta values) in terms of intensity characterizing Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride showing one or a combination of the following in a powder diffraction measurement when measured using Cu K_α radiation at ambient temperature are 14.5± 0.2, 18.2±0.2, 20.4±0.2, 21.7±0.2 and 25.5±0.2.

[0008] To discriminate crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride from Form B it is more advantageous to look at the unique peaks in the X-ray diffraction diagram, i.e. e. the lines with sufficient intensity at 2-theta values, where Form B does not show lines with significant intensity. Such characteristic X-ray lines (2-theta values) for Form A in a powder diffraction pattern when measured using CuK_α radiation at ambient temperature are: 15.1±0.2, 16.0±0.2, 18.9±0.2, 20.4±0.2, 22.5±0.2, 27.3±0.2. 29.3±0.2 and 30.4±0.2

[0009] Another method to identify crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride is IR-spectroscopy. The IR-Spectrum of Form A is shown as Fig. 2 with the peak listing shown in comparism to Form B as Table 2.

[0010] In the IR-spectrum it is characteristic for crystalline Form A of (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride to show a combination of the following IR bands: 3180±4 cm^{-1}, 2970±4 cm^{-1}, 2695±4 cm^{-1} , 2115±4 cm^{-1}, 1698±4 cm^{-1}, 1462±4 cm^{-1}, 1032±4 cm^{-1} and/or 972±4 cm^{-1}.

[0011] RAMAN technique can also be used to identify of the crystalline Form A of (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride. Especially the range between 800 cm^{-1} and 200 cm^{-1}, which is shown in Fig. 3, is advantageously used also by way of RAMAN microscopy.

[0012] Crystal structure analysis of Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride showed monoclinic crystals with the following parameters of the elemental cell (length of side and angle):

a: 7,11 Å
b: 11,62 Å
c: 17,43 Å
β: 95,00°.

[0013] The elemental cell of the crystal of crystalline Form A has a volume of 1434 ± 2 $Å^3$ and a calculated density of 1.19 ± 0.01 g/cm^3.

[0014] The Invention further relates to processes for the preparation of crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride.

[0015] The process starts from crystalline Form B of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride prepared according to US Pat. Nos. 6,248,737 or 6,344,558 or European Patent EP 693 475 B1 incorpo-

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rated herein by reference.

[0016] In one embodiment of the process (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A is produced by dissolving the (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B in acetone, acetonitrile or isopropanol, optionally followed by filtering, leaving the solution to crystallize and isolating the crystals of (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A preferably by filtering again.

[0017] If acetone or acetonitrile is used it is preferred that during this process the temperature is kept below + 40 °C, more preferably below + 25°C, especially after filtering. It is further preferred that in this process between 5 mg and 1 mg, more preferably between 2.5 mg and 1.4 mg, especially between 2.0 mg and 1.4 mg (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride is dissolved per ml solvent.

[0018] The use of isopropanol is preferred, if seed crystals of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A are available. The isopropanol used preferably contains about 0.5 % per volume of water. The dissolution of the (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B in isopropanol is performed at temperatures above room temperature, preferably above 65°C but not exceeding 80 °C. After complete dissolution the heat is turned of and the seed crystals are added during a first cooling phase. Thereafter the resulting mixture is cooled down to ≤ 15 °C, preferably ≤ 10 °C and especially ≤ 5 °C.

[0019] Optionally it is possible to reduce the solvent by evaporation, preferably in an evaporator under reduced pressure. Preferably the remaining volume of the solution after evaporation should not be less than 20 % of the volume at the beginning of the process. Optionally it is also possible to add active carbon to the solution originally prepared.

[0020] In a preferred embodiment of the invention the (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A obtained by the process described above is redesolved in acetone acetonitrile or isopropanol, preferably in the solvent already used in the first step, optionally is filtered to remove any insoluble residue and, optionally after reducing the amount of solvent by evaporation, is left to crystallize.

[0021] It is preferred that in the last crystallization step the temperature is maintained at ≤ 15°C, more preferably ≤ 10°C and especially ≤ 5 °C.

[0022] In a further embodiment of the process according to the invention (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A is produced in the solid state by cooling (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form B between 24 h and 168 h to a temperature between -4°C and -80°C. It is preferred that in this process the cooling temperature is between -10°C and - 60°C, preferably between -15°C and - 50°C, especially between -25°C and -40°C and the cooling is carried out for a time between 24h and 120 h, preferably between 24h and 72 h, especially between 24 h and 48h.

[0023] This invention further relates to a new Crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride obtainable by dissolving (-)-(R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form B in acetonitrile together with active carbon, heating the solution to the boiling point, removing the active carbon by filtering, stirring the solution at a temperature below 40°C, removing insoluble residue by filtering and removing part of the solvent leaving (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystallize, redissolving the crystals so obtained in acetonitrile, removing insoluble residue by filtering and removing part of the solvent leaving (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of Form A to crystallize.

[0024] Crystalline Form A according to the invention has the same pharmacological activity as Form B but is more stable under ambient conditions. It can be advantageously used as active ingredient in pharmaceutical compositions.

[0025] Therefore the invention further relates to a pharmaceutical composition containing as active ingredient (-)-(1R, 2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride of crystalline Form A according to the invention and at least one suitable additive and/or auxiliary substance.

[0026] Such pharmaceutical composition according to the invention contains, in addition to crystalline Form A (-)-(1R. 2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride, one or more suitable additive and/or auxiliary substance such as for example carrier materials, fillers, solvents, diluents, colouring agents and/or binders, and may be administered as liquid medicament preparations in the form of injectable solutions, drops or juices, as semi-solid medicament preparations in the form of granules, tablets, pellets, patches, capsules, plasters or aerosols. The choice of the auxiliary substances, etc., as well as the amounts thereof to be used depend on whether the medicament is to be administered orally, per orally, parenterally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally, rectally or topically, for example to the skin, the mucous membranes or the eyes. For oral application suitable preparations are in the form of tablets, sugar-coated pills, capsules, granules, droplets, juices and syrups, while for parenteral, topical and inhalative application suitable forms are solutions, suspensions, readily reconstitutable dry preparations, as well as sprays. Form A in a depot form, in dissolved form or in a plaster, optionally with the addition of agents promoting skin penetration, are suitable percutaneous application preparations. Preparation forms that can be administered orally or percutaneously can provide for the delayed release of crystalline Form A according to the invention. In principle further active constituents known to the person skilled in the art may be added to the medicaments according

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to the invention.

[0027] Preferred formulations for crystalline Form A (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride according to the invention are presented in the PCT-application WO 03/035054 incorporated herein by reference.

[0028] The amount of active constituent to be administered to the patient varies depending on the patient's weight, on the type of application, medical indication and severity of the condition. Normally 0.005 to 1000 mg/kg, preferably 0.05 to 5 mg/kg of crystalline Form A according to the invention are administered.

[0029] Preferably, the crystalline Form A according to the invention is used for the treatment of pain or the treatment of urinary incontinence. Accordingly the invention also relates to the use of crystalline Form A according to the invention for the treatment of pain or the treatment of urinary incontinence.

[0030] Additionally the invention relates to a method of treatment using a sufficient amount of crystalline Form A according to the invention for the treatment of a disease, especially pain or urinary incontinence.

[0031] The following Examples shall further illustrate the invention without limiting it thereto.

Example 1: Master Recipe for Preparation of Form A

[0032] The master recipe is valid for a 50 ml scale.

Charge 1.9 g (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride prepared according to example 25 of European Patent EP 693 475 B1 to a 50 ml glass round bottom vessel with 3-blade overhead stirrer with baffles. Charge 25 ml isopropanol and 0.5 % (v/v) water
Stir at 800 rpm
Heat to 80 °C
Hold temperature while stirring for 10 minutes
Cool to 65 °C
Charge 0.056 g seeds (Mean Sq. Wt. CL = 58 μm^2, Median No Wt. CL = 22 μm)
Cool to 0 °C over 1 h
Filter slurry through PTFE filter column (5 μm pore size)
Dry solid material under slight vacuum until constant weight (approx. 24 h)
Repeat the same procedure with the dry solid material obtained

Example 2: Preparation of Form A (1)

[0033] (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. 32.2 mg of the thus synthesized (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was - by slight heating up to 40°C and/or agitating on an orbital shaker for 30 min - dissolved in 20 ml acetone. Following that the solution was filtered through a nylon syringe filter having a mesh of 0.20 μm and the solution was left to crystallize by slow evaporation of the solvent. Crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

Example 3: Preparation of Form A (2)

[0034] (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. 32.2 mg of the thus synthesized (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was - if necessary by agitating for e.g. 30 min - dissolved in 20 ml acetone. Following that the solution was filtered with a nylon syringe filter having a mesh of 0.20 μm and the solution was left to crystallize by slow evaporation of the solvent. In no step after and including the dissolving the temperature was allowed to rise above +25°C. Crystalline Form A of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction experiment and by RAMAN microscopic analysis.

Example 4: Preparation of Form A (3)

[0035] (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. 350 mg of the thus synthesized (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride were dissolved in 50 ml acetonitrile in a 250 ml flask. The mixture was stirred for 1.5 h on a water bath heated to 37°C $\pm$ 1°C. Any insoluble residue was removed by filtering. Of the clear solution 35 ml was removed on a rotation evaporator at 70-80 mbar and a temperature of the water bath of 30°C $\pm$ 1°C. The precipitated solid compound was filtered by vacuum. Crystalline Form A of (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-

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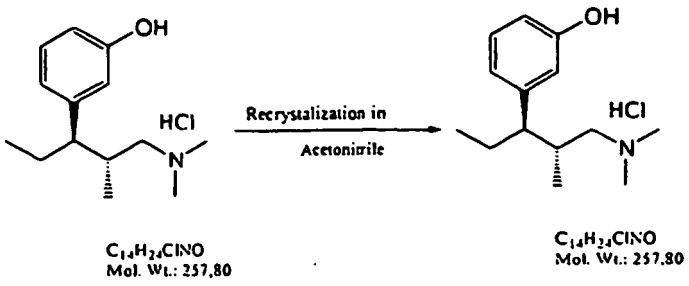
methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

Example 5: Preparation of Form A (4)

[0036] (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. The thus synthesized (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was stored for 72 h at - 40°C. Crystalline Form A of (-)-(R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

Example 6: Preparation of Form A (5)

[0037]



$C_{14}H_{24}ClNO$
Mol. Wt.: 257.80

$C_{14}H_{24}ClNO$
Mol. Wt.: 257.80

[0038] (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. 370 mg of the thus synthesized (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride were added to 40 ml acetonitrile and 100 mg active carbon in a 100 ml flask and heated to the boiling point. The active carbon was filtered off from the hot solution by means of a paper filter and the filtrate concentrated to a volume of approx. 10 ml in a rotation evaporator at 150 ± 10 mbar and 50°C. The solution was slowly rotated for 30 minutes at room temperature. Following that the solution was allowed to stand for 30 minutes at room temperature and than for 1 hour at 4°C. The Crystals are filtered by vacuum through a glass filter (276 mg yield). 266 mg of these Crystals were dissolved at room temperature in 45 ml acetonitrile, insoluble residues were removed by filtration and the solution was rotated for 1.5 h at 35-40°C at atmospheric pressure in a rotation evaporator. Than the solution was concentrated at 50°C and 150 ± 10 mbar to a volume of approx. 10 ml and then slowly rotated for 30 minutes at room temperature. Following that the flask was allowed to stand for 12 h at 4°C.
The precipitated solid is filtered by vacuum through a glass filter and dried in the air.

Yield:

[0039] 151 mg (40.8% of the theory in relation to used educt), white microcrystalline solid form

Example 7: Preparation of Form B (1)

[0040] (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was prepared according to example 25 of European Patent EP 693 475 B1. Crystalline Form B of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

Example 8: Preparation of Form B (2)

[0041] (-)-(1R,2R)-3-(3-dimethylamino-1-ethy)-2-methylpropyl)-phenol hydrochloride prepared according to one of the examples 1 to 5 was milled for at least 20 min. Then it was kept at 130°C in an oven for 80 min. Crystalline Form B of (-)-(1 R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride was generated as proven by X-ray powder diffraction and by RAMAN microscopic analysis.

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