(12) **Oversettelse av europeisk patentskrift**

(11) **NO/EP 3173400 B1**

NORGE

(19) NO

(51) Int Cl.

C07C 215/54 (2006.01)
A61K 31/137 (2006.01)
A61P 25/04 (2006.01)

Patentstyret

(21)	Oversettelse publisert	2020.01.27
(80)	Dato for Den Europeiske Patentmyndighets publisering av det meddelte patentet	2019.11.06
(86)	Europeisk søknadsnr	16203848.3
(86)	Europeisk innleveringsdag	2008.12.05
(87)	Den europeiske søknadens Publiseringsdato	2017.05.31
(30)	Prioritet	2007.12.07, EP, 07023728
(84)	Utpekte stater	AT ; BE ; BG ; CH ; CY ; CZ ; DE ; DK ; EE ; ES ; FI ; FR ; GB ; GR ; HR ; HU ; IE ; IS ; IT ; LI ; LT ; LU ; LV ; MC ; MT ; NL ; NO ; PL ; PT ; RO ; SE ; SI ; SK ; TR
(62)	Avdelt fra	EP2240431, 2008.12.05
(73)	Innehaver	Grünenthal GmbH, Zieglerstrasse 6, 52078 Aachen, Tyskland
(72)	Oppfinner	GRUSS, Michael, Hermannstr. 8, 52062 Aachen, Tyskland
(74)	Fullmektig	Orsnes Patent ApS, Forskerparken 10, 5230 ODENSE, Danmark

(54) Benevnelse **MEDICAMENTS CONTAINING CRYSTALLINE MODIFICATIONS OF (1R,2R)-3-(3-DIMETHYLAMINO-1-ETHYL-2-METHYL-PROPYL)-PHENOL**

(56) Anførte publikasjoner

EP-A- 1 612 203
EP-A- 0 693 475

Vedlagt foreligger en oversettelse av patentkravene til norsk. I hht patentloven § 66i gjelder patentvernet i Norge bare så langt som det er samsvar mellom oversettelsen og teksten på behandlingsspråket. I saker om gyldighet av patentet skal kun teksten på behandlingsspråket legges til grunn for avgjørelsen. Patentdokument utgitt av EPO er tilgjengelig via Espacenet (http://worldwide.espacenet.com), eller via søkemotoren på vår hjemmeside her: https://search.patentstyret.no/

The invention relates to medicaments for oral application containing crystalline modifications of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, and the use thereof.

(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol is a synthetic analgesic which is suitable for the treatment of severe to very severe, acute and chronic pain. The compound can in this case be used in the form of the free base thereof or in the form of pharmaceutically acceptable salts and solvates. The production of the compound and the salts thereof is known from EP-A-0 693 475, the compound normally being obtained in the form of a salt thereof, for example in the form of the hydrochloride thereof. EP 1 612 230 discloses novel crystalline forms of (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride.

It is an object of the present invention to provide the compound (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol per se, i. e., in the form of the free base, in high yields and high purity.

This object has been achieved by the subject matter of the claims.

It has surprisingly been found that under suitable conditions the compound (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol can be obtained in a crystalline form, in particular in the form of the polymorphs A, B and C described hereinafter.

These crystalline forms make it possible to obtain the compound (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol in the form of the free base, with high yields and high purity. These forms are further distinguished in that they are very easy to handle and allow an exact metering of the active ingredient.

Moreover, different polymorphs of said pharmaceutical active ingredient have fundamentally different properties, which may provide further advantages.

On the one hand, the advantages may be based on a particular physical property of a particular modification, for example in relation to the handling or storage thereof, for example thermodynamic stability; crystal morphology, in particular structure, size, colour; density; bulk density; hardness; deformability; calorimetric characteristics, in particular melting point; solubility properties, in particular intrinsic rate of dissolution and equilibrium solubility; hygroscopicity; relative moisture profile; adhesion etc.

On the other hand, the crystalline modifications may also have improved chemical properties. For example, it is known that a lower hygroscopicity can lead to improved chemical stability and longer storage lives for chemical compounds.

One aspect of the present invention therefore relates to a medicament for oral application containing a crystalline modification A of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol comprising an X-ray diffraction reflection at 15.58±0.20 (2θ), and one or more X-ray diffraction reflections selected from the group consisting of 28.37±0.20 (2Θ) and 34.45±0.20 (2θ) and additionally at least one X-ray diffraction reflection selected from the group consisting of 13.71±0.20 (2θ), 14.80±0.20 (2θ), 16.89±0.20 (2θ), 17.79±0.20 (2θ), 18.45±0.20 (2θ), 20.20±0.20 (2θ), 20.92±0.20 (2θ), 22.50±0.20 (2θ), 24.37±0.20 (2θ) and 25.33±0.20 (2θ).

Furthermore, the crystalline modification A according to the invention may be characterized in that as well as the X-ray diffraction reflection at 15.58±0.20 (2θ) and one or more X-ray diffraction reflections selected from the group consisting of 28.37±0.20 (2θ) and 34.45±0.20 (2θ) and one or more X-ray diffraction reflections selected from the group consisting of 13.71±0.20 (2θ), 14.80±0.20 (2θ), 16.89±0.20 (2θ), 17.79±0.20 (2θ), 18.45±0.20 (2θ), 20.20±0.20 (2θ), 20.92±0.20 (2θ), 22.50±0.20 (2θ), 24.37±0.20 (2θ) and 25.33±0.20 (2θ), it additionally comprises at least one X-ray diffraction reflection selected from the group consisting of 14.11±0.20 (2θ), 19.07±0.20 (2θ), 21.12±0.20 (2θ), 21.90±0.20 (2θ), 22.21±0.20 (2θ), 24.75±0.20 (2θ), 27.32±0.20 (2θ), 27.55±0.20 (2θ), 29.90±0.20 (2θ) and 30.68±0.20 (2θ).

The crystalline modification A according to the invention may also be characterized in that as well as the X-ray diffraction reflection at 15.58±0.20 (2θ) and one or more X-ray diffraction reflections selected from the group consisting of 28.37±0.20 (2θ) and 34.45±0.20 (2θ) and one or more X-ray diffraction reflections selected from the group consisting of 13.71±0.20 (2θ), 14.80±0.20(2θ) 16.89±0.20 (2θ), 17.79±0.20 (2θ), 18.45±0.20 (2θ), 20.20±0.20 (2θ), 20.92±0.20 (2θ), 22.50±0.20 (2θ), 24.37±0.20 (2θ) and 25.33±0.20 (2θ), and optionally one or more X-ray diffraction reflections selected from the group consisting of 14.11±0.20 (2θ), 19.07±0.20 (2θ), 21.12±0.20 (2θ), 21.90±0.20 (2θ), 22.21±0.20 (2θ), 24.75±0.20 (2θ), 27.32±0.20 (2θ), 27.55±0.20 (2θ), 29.90±0.20 (2θ) and 30.68±0.20 (2θ), it additionally comprises at least one X-ray diffraction reflection selected from the group consisting of 16.31±0.20 (2θ), 23.30±0.20 (2θ), 24.04±0.20 (2θ), 28.05±0.20 (2θ), 29.62±0.20 (2θ), 30.28±0.20 (2θ), 31.43±0.20 (2θ), 32.21±0.20 (2θ), 32.98±0.20 (2θ), 33.41±0.20 (2θ), 33.76±0.20 (2θ), 34.17±0.20 (2θ), 35.98±0.20 (2θ), 36.24±0.20 (2θ), 36.54±0.20 (2θ), 36.87±0.20 (2θ), 37.06±0.20 (2θ), 37.48±0.20 (2θ), 37.87±0.20 (2θ), 38.64±0.20 (2θ) and 39.48±0.20 (2θ).

Preferably, the crystalline modification A according to the invention may be characterized in that it does not comprise one or more of the following X-ray diffraction reflections selected from the group consisting of 10.93±0.20 (2θ), 12.41±0.20 (2θ), and 26.22±0.20 (2θ).

It is also preferable for the crystalline modification A according to the invention to be further characterized in that it does not comprise one or more of the following X-ray diffraction reflections selected from the group consisting of 8.10±0.20 (2θ), 10.93±0.20 (2θ), 11.83±0.20 (2θ), 12.41±0.20 (2θ), 26.22±0.20 (2θ), 26.54±0.20 (2θ) and 26.72±0.20 (2θ).

Figure 1 shows an X-ray powder diffractogram of modification A.

In DSC analyses, the crystalline modification A according to the invention preferably exhibits endothermy with a peak temperature at 75-84 ^{o}C, more preferably at 76-83 ^{o}C, even more preferably at 77-82 ^{o}C and in particular at 78-81 ^{o}C.

The crystalline form A according to the invention may further be characterized in that it comprises one or more Raman bands selected from the group consisting of 104±2 cm^{-1}, 249±2 cm^{-1}, 536±2 cm^{-1}, 724±2 cm^{-1}, 830±2 cm^{-1}, 999±2 cm^{-1}, 1283±2 cm^{-1}, 1462±2 cm^{-1}, 1584±2 cm^{-1}, 2790±2 cm^{-1}, 2839±2 cm^{-1}, 2873±2 cm^{-1}, 2933±2 cm^{-1}, 2965±2 cm^{-1} and 3045±2 cm^{-1}. Figure 2 shows a Raman spectrum for modification A.

Also described herein is a method for the production of crystalline modification A, comprising the steps of

(a) concentrating a solution of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol and
(b) storing the residue obtained in step (a) at a temperature of > 5 ^{o}C.

To produce crystalline modification A, a solution of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol is initially preferably fully concentrated.

Conventional organic solvents known to persons skilled in the art may be used as solvents in a solution of this type, in particular alcohols such as methanol, ethanol, 1-propanol and 2-propanol, esters such as ethyl acetate, ketones such as acetone and ethylmethyl ketone, ethers such as diethyl ether, tert-butyl methyl ether, 1,4-dioxane and tetrahydrofuran, nitriles such as acetonitrile, chlorinated hydrocarbons such as dichloromethane, aromatic hydrocarbons such as toluene, and also dimethyl formamide and dimethyl sulfoxide. Saturated hydrocarbons, such as n-pentane, n-hexane and n-heptane, and water are less suitable, the compound (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol being only poorly soluble in these substances.

The solution may also be concentrated by conventional methods known to persons skilled in the art, for example on a rotary evaporator or in an inert gas flow, in particular in an argon flow or nitrogen flow.

Normally, a preferably oily residue remains after concentration and crystallises out in the form of modification A after storage at a temperature of > 5 °C. In general, a storage time of 24 hours is sufficient.

Further work-up, where necessary, can also be carried out by conventional methods known to persons skilled in the art, for example by filtration, washing and/or drying.

Also described herein is a crystalline modification A of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol which can be obtained by the method described above.

In another aspect, the invention relates to a medicament for oral application containing crystalline modification B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol comprising an X-ray diffraction reflection at 29.06±0.20 (2θ) and one or more X-ray diffraction reflections selected from the group consisting of 19.50±0.20 (2θ), 35.49±0.20 (2θ) and 40.01±0.20 (2θ), it additionally comprises at least one X-ray diffraction reflection selected from the group consisting of 14.11±0.20 (2θ), 14.44±0.20 (2θ), 16.08±0.20 (2θ), 17.17±0.20 (2θ), 17.43±0.20 (2θ), 18.81±0.20 (2θ), 20.24±0.20 (2θ), 20.80±0.20 (2θ), 22.00±0.20 (2θ), 22.49±0.20 (2θ), 23.40±0.20 (2θ), 24.15±0.20 (2θ), 24.51±0.20 (2θ) and 29.89±0.20 (2θ).

Furthermore, the crystalline modification B according to the invention may be characterized in that as well as the X-ray diffraction reflection at 29.06±0.20 (2θ) and one or more X-ray diffraction reflections selected from the group consisting of 19.50±0.20 (2θ), 35.49±0.20 (2θ) and 40.01±0.20 (2θ) and one or more X-ray diffraction reflections selected from the group consisting of 14.11±0.20 (2θ), 14.44±0.20 (2θ), 16.08±0.20 (2θ), 17.17±0.20 (2θ), 17.43±0.20 (2θ), 18.81±0.20 (2θ), 20.24±0.20 (2θ), 20.80±0.20 (2θ), 22.00±0.20 (2θ), 22.49±0.20 (2θ), 23.40±0.20 (2θ), 24.15±0.20 (2θ), 24.51±0.20 (2θ) and 29.89±0.20 (2θ), it additionally comprises at least one X-ray diffraction reflection selected from the group consisting of 18.67±0.20 (2θ), 25.24±0.20 (2θ), 25.36±0.20 (2θ), 27.58±0.20 (2θ), 27.79±0.20 (2θ), 30.11±0.20 (2θ) and 31.00±0.20 (2θ).

The crystalline modification B according to the invention may also be characterized in that as well as the X-ray diffraction reflection at 29.06±0.20 (2θ) and one or more X-ray diffraction reflections selected from the group consisting of 19.50±0.20 (2θ), 35.49±0.20 (2θ) and 40.01±0.20 (2θ) and one or more X-ray diffraction reflections selected from the group consisting of 14.11±0.20 (2θ), 14.44±0.20 (2θ), 16.08±0.20 (2θ), 17.17±0.20 (2θ), 17.43±0.20 (2θ), 18.81±0.20 (2θ), 20.24±0.20 (2θ), 20.80±0.20 (2θ), 22.00±0.20 (2θ), 22.49±0.20 (2θ), 23.40±0.20 (2θ), 24.15±0.20 (2θ), 24.51±0.20 (2θ) and 29.89±0.20 (2θ) and optionally at least one X-ray diffraction reflections selected from the group consisting of 18.67±0.20 (2θ), 25.24±0.20 (2θ), 25.36±0.20 (2θ), 27.58±0.20 (2θ), 27.79±0.20 (2θ), 30.11±0.20 (2θ) and 31.00±0.20 (2θ), it comprises at least one X-ray diffraction reflection selected from the group consisting of 22.85±0.20 (2θ), 24.88±0.20 (2θ), 30.31±0.20 (2θ), 31.17±0.20 (2θ), 31.54±0.20 (2θ), 32.11±0.20 (2θ), 32.45±0.20 (2θ), 32.76±0.20 (2θ), 33.61±0.20 (2θ), 33.94±0.20 (2θ), 35.95±0.20 (2θ), 36.54±0.20 (2θ), 37.12±0.20 (2θ), 37.32±0.20 (2θ), 37.75±0.20 (2θ) 38.13±0.20 (2θ), 38.72±0.20 (2θ) and 39.63±0.20 (2θ).

Preferably, the crystalline modification B according to the invention is also characterized in that it does not comprise one or more of the following X-ray diffraction reflections selected from the group consisting of 10.93±0.20 (2θ), 12.41±0.20 (2θ), and 26.22±0.20 (2θ).

It is also preferable for the crystalline modification B according to the invention to also be characterized in that it does not comprise one or more of the following X-ray diffraction reflections selected from the group consisting of 8.10±0.20 (2θ), 10.93±0.20 (2θ), 11.83±0.20 (2θ), 12.41±0.20 (2θ), 26.22±0.20 (2θ), 26.54±0.20 (2θ) and 26.72±0.20 (2θ).

Figure 3 shows an X-ray powder diffractogram of form B.

In DSC analyses, the crystalline modification B according to the invention preferably exhibits endothermy with a peak temperature at 87-93 ^{o}C, more preferably at 88-92 ^{o}C, even more preferably at 89-91 ^{o}C.

The crystalline form B according to the invention is further characterized in that it comprises one or more Raman bands selected from the group consisting of 91±2 cm^{-1}, 112±2 cm^{-1}, 259±2 cm^{-1}, 381±2 cm^{-1}, 535±2 cm^{-1}, 730±2 cm^{-1}, 829±2 cm^{-1}, 999±2 cm^{-1}, 1088±2 cm^{-1}, 1173±2 cm^{-1}, 1288±2 cm^{-1}, 1445±2 cm^{-1}, 1585±2 cm^{-1}, 2790±2 cm^{-1}, 2838±2 cm^{-1}, 2869±2 cm^{-1}, 2925±2 cm^{-1}, 2952±2 cm^{-1}, 2980 cm^{-1} and 3059±2 cm^{-1}. Figure 4 shows a Raman spectrum for form B.

Also described here is a method for the production of crystalline modification B, comprising the steps of

(a) concentrating a solution of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol and
(b1) storing the residue obtained in step (a) at a temperature of ≤ 5 ^{o}C, or
(b2) suspending the residue obtained in step (a) and stirring this suspension.

To produce crystalline modification B, a solution of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol is initially preferably fully concentrated.

Conventional organic solvents known to persons skilled in the art may be used as solvents in a solution of this type, in particular alcohols such as methanol, ethanol, 1-propanol and 2-propanol, esters such as ethyl acetate, ketones such as acetone and ethylmethyl ketone, ethers such as diethyl ether, tert-butyl methyl ether, 1,4-dioxane and tetrahydrofuran, nitriles such as acetonitrile, chlorinated hydrocarbons such as dichloromethane, aromatic hydrocarbons such as toluene, and also dimethyl formamide and dimethyl sulfoxide. Saturated hydrocarbons, such as n-pentane, n-hexane and n-heptane, and water are less suitable, the compound (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol being only poorly soluble in these substances.

The solution may also be concentrated by conventional methods known to persons skilled in the art, for example on a rotary evaporator or in an inert gas flow, in particular in an argon flow or nitrogen flow.

Normally, a preferably oily residue remains after concentration and crystallises out in the form of modification B after storage at a temperature of ≤ 5 °C. In general, a storage time of 24 hours is sufficient.

Alternatively, the preferably oily residue may also be received in a suitable suspension medium and stirred for some time. Mixtures of one of the aforementioned solvents with water or a saturated hydrocarbon, in particular n-pentane, n-hexane or n-heptane, are particularly suitable as suspension media, and the proportion of solvent is to be selected in such a way that the residue is not completely dissolved.

The temperature in step (b) may vary over a wide range, in particular in the range of 5-25 °C, just like the stirring time, which may vary from a few minutes to a number of weeks, in particular up to one week.

A further aspect of the invention relates to a method for the production of crystalline modification B, comprising the step of

(a) precipitating (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol from solution.

Conventional organic solvents known to persons skilled in the art may be used to produce the (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol solution, in particular alcohols such as methanol, ethanol, 1-propanol and 2-propanol, esters such as ethyl acetate, ketones such as acetone and ethylmethyl ketone, ethers such as diethyl ether, tert-butyl methyl ether, 1,4-dioxane and tetrahydrofuran, nitriles such as acetonitrile, chlorinated hydrocarbons such as dichloromethane, aromatic hydrocarbons such as toluene, and also dimethyl formamide and dimethyl sulfoxide.

The (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol is then precipitated from the solution using media in which this compound is only poorly soluble, such as

saturated hydrocarbons, such as n-pentane, n-hexane and n-heptane, and water, for example.

Further work-up, where necessary, can also be carried out by conventional methods known to persons skilled in the art, for example by filtration, washing and/or drying.

Crystalline modification B may also be obtained by cooling a melt of crystalline modification A.

Also described herein is a crystalline modification B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol which can be obtained by the methods disclosed above.

Normally, modification A is obtained by faster crystallisation and/or at higher temperatures (probably via the amorphous form as an intermediate stage). Modification B is normally obtained by slower crystallisation and/or at lower temperatures (probably by direct crystallisation). Modification B represents the most thermodynamically stable form, in particular in the temperature range of 5-85 ^{o}C, preferably 5-50 ^{o}C.

Thermodynamic stability is important. By using the most stable modification in a medicament it may specifically be ensured that, during storage, no polymorphic conversion of the active ingredient in the pharmaceutical formulation takes place. This is advantageous because otherwise the properties of the medicament could change as a consequence of a conversion of a less stable modification into a more stable modification. In relation to the pharmacological properties of an dosage form, this could lead for example to the solubility of the active ingredient changing, accompanied by a change in the release characteristics and thus also a change in the bioavailability. Lastly, this results in inadequate storage stability of the dosage form.

A further aspect of the invention relates to a medicament for oral application containing the crystalline modification C of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol comprising at least one X-ray diffraction reflection selected from the group consisting of 10.93±0.20 (2θ), 12.41±0.20 (2θ) and 26.22±0.20 (2θ) and one or more X-

ray diffraction reflections selected from the group consisting of 8.10±0.20 (2θ), 11.83±0.20 (2θ), 26.54±0.20 (2θ) and 26.72±0.20 (2θ), additionally comprising at least one X-ray diffraction reflection selected from the group consisting of 13.71±0.20 (2θ), 14.13±0.20 (2θ), 14.82±0.20 (2θ), 15.34±0.20 (2θ), 15.59±0.20 (2θ), 16.10±0.20 (2θ) 16.43±0.20 (2θ), 16.91±0.20 (2θ), 17.32±0.20 (2θ), 17.58±0.20 (2θ), 17.82±0.20 (2θ), 18.01±0.20 (2θ), 18.46±0.20 (2θ), 19.05±0.20 (2θ), 20.23±0.20 (2θ), 20.71±0.20 (2θ), 20.94±0.20 (2θ), 21.17±0.20 (2θ), 21.90±0.20 (2θ), 22.23±0.20 (2θ), 22.52±0.20 (2θ), 23.32±0.20 (2θ), 24.12±0.20 (2θ), 24.39±0.20 (2θ), 24.92±0.20 (2θ), 25.35±0.20 (2θ), 27.33±0.20 (2θ), 27.63±0.20 (2θ), 27.84±0.20 (2θ), 28.48±0.20 (2θ), 29.64±0.20 (2θ), 29.94±0.20 (2θ), 30.54±0.20 (2θ), 30.68±0.20 (2θ), 31.03±0.20 (2θ), 31.52±0.20 (2θ), 32.29±0.20 (2θ), 32.93±0.20 (2θ), 33.66±0.20 (2θ), 35.52±0.20 (2θ), 36.05±0.20 (2θ), 36.64±0.20 (2θ), 37.54±0.20 (2θ), 38.45±0.20 (2θ), 39.15±0.20 (2θ) and 40.05±0.20 (2θ).

Figure 5 shows an X-ray powder diffractogram of form C.

In DSC analyses, the crystalline modification C according to the invention preferably exhibits endothermy with a peak temperature at 75-84 °C, more preferably at 76-83 °C, even more preferably at 77-82 °C, and in particular at 78-81 °C and/or endothermy with a peak temperature at 87-93 °C, more preferably at 88-92 °C, even more preferably at 89-91 °C.

Also described herein is a method for the production of the crystalline modification C described above, comprising the steps of

(a) shaking a suspension containing crystalline modification A and/or crystalline modification B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, and
(b) evaporating the suspension medium in an air flow.

Preferably, alcohols, in particular methanol, as well as aromatic hydrocarbons, in particular toluene, are particularly suitable suspension media.

In step a), the suspension is preferably shaken at a temperature which is above room temperature (20-25 °C), for example at a temperature in the range from > 25 to 35 °C, preferably 30±3 °C, particularly preferably 30±2 °C and in particular 30±1 °C. The shaking procedure preferably lasts for 1-6 hours, preferably 2-5 hours, even more preferably 3-4 hours.

Subsequently, the suspension medium is evaporated in an air flow, optionally after cooling the suspension to room temperature, and the resulting residue is optionally stored at room temperature.

Further work-up, where necessary, can also be carried out by conventional methods known to persons skilled in the art, for example by filtration, washing and/or drying.

Also described herein is a crystalline modification C of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol which can be obtained by the method described above.

The modifications A, B and C according to the invention may optionally also form co-crystals and solvates. These are all included within the scope of the invention.

Also described herein is a pharmaceutical composition containing the active ingredient (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol in crystalline form and at least one pharmaceutically acceptable carrier.

Preferably, the pharmaceutical composition may contain a polymorph selected from the group consisting of modification A, modification B and modification C.

It is also particularly preferable for the pharmaceutical composition to contain modification A.

It is particularly preferable for the pharmaceutical composition to contain modification B.

Also described herein is a pharmaceutical dosage form containing a pharmaceutical composition according to the invention as described above.

Also described herein is a crystalline modification according to the invention of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, in particular a crystalline modification A, B or C according to the invention as described above, as a medicament.

Also described herein is the use of at least one crystalline modification according to the invention of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, in particular a crystalline modification A, B or C according to the invention for the preparation of a drug for the treatment of pain, in particular acute pain and chronic pain.

As well as at least one crystalline form A, form B or form C according to the invention or a mixture of at least two of these forms, the drug according to the invention may, as is conventional, contain further pharmaceutically acceptable additives or excipients, such as carrier materials, fillers, solvents, thinning agents, colourings and/or binders.

The selection of the excipients and the amounts thereof to be used depend on whether the drug is to be applied orally, subcutaneously, parenterally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally or locally, for example to infections on the skin, mucous membranes and eyes. Preferably, preparations in the form of tablets, dragees, capsules, granules, drops, juices and syrups are particularly suitable for oral application, and solutions, suspensions, easily reconstitutable dry preparations and sprays for parenteral, topical and inhalative application. Crystalline forms according to the invention in a deposit in a dissolved form or in a patch, optionally along with skin penetration enhancers, are suitable preparations for percutaneous application. Preparation forms which are to be applied orally or percutaneously may release the crystalline form according to the invention in a delayed manner.

The amount of active ingredient to be administered to patients can vary and is for example dependent on the weight of the patient, the type of application, the indication and the severity of the illness.

Figure 1 shows an XRPD spectrum of crystalline modification A;

Figure 2 shows a RAMAN spectrum of crystalline modification A;

Figure 3 shows an XRPD spectrum of crystalline modification B;

Figure 4 shows a RAMAN spectrum of crystalline modification B;

Figure 5 shows an XRPD spectrum of crystalline modification C.

The invention will be illustrated with reference to examples which are merely illustrative and do not limit the scope of the invention.

Examples:

Abbreviations

RT	Room temperature, preferably 20-25 ^{o}C
TBME	tert-butyl methyl ether
EtOH	ethanol
MEK	2-butanone
THF	tetrahydrofuran
2PrOH	2-propanol
EtOAc	ethyl acetate
MeCN	acetonitrile
DMSO	dimethyl sulfoxide
DMF	dimethyl formamide
IR	infra-red
Min	minute
Sec	second

Unless otherwise specified, solvent mixtures always relate to volume/volume.

A) Synthesis of modification A

A1)

16.689 g (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol, hydrochloride (which can be obtained in accordance with the procedure of EP A 0 693 475) were dissolved in 81 ml distilled water in a 250 ml three-necked flask and 32 % by weight sodium hydroxide solution was added at room temperature until a pH value of 11 was reached (approx. 7 ml). Upon adding just a few ml, a tough, white substance precipitated and this substance was dissolved in approx. 16 ml ethyl acetate. After the addition was complete, a white suspension was obtained and was subsequently stirred for 1 hour. The pH value fell to 10 in the process and a further 0.5 ml sodium hydroxide solution was added. Subsequently, the precipitated base was extracted with a total of 288 ml ethyl acetate. The combined organic phases were then washed with approx. 32 ml water, dried over magnesium sulphate and concentrated in a vacuum on a rotary evaporator until dry.

A yellow oil remained in the flask and also did not crystallise at room temperature. Crystallization was then initiated by breaking the flask with a spatula and the oil crystallised within a few minutes in the form of a yellow residue. This residue was then crushed in a mortar and an off-white crystalline solid of modification A, characterized by ^{1}H-NMR, DSC, TG-FTIR, XRPD, Raman and HPLC, was obtained.

Part of the resulting crystalline solid thus obtained was recrystallised as follows:

30 mg of modification A were weighed into a 20 ml vessel, 6 ml 2-propanol were added and shaken for 4 hours at 400 rpm at 30 ^{o}C. Subsequently, the solvent was evaporated off in an air flow at 23 ^{o}C. A white crystalline solid of form A was obtained.

A2)

200 mg of (1) according to B) were dissolved in 25 ml acetonitrile. Subsequently, the solvent was removed in a vacuum on a rotary evaporator. A colourless oil remained. Approx. 1 ml seed crystals of form A were added to this oil and the sample was stored at room temperature for 2 days. A crystalline solid of form A was obtained.

B) Synthesis of modification B

B1)

3192 g of (2R,3R)-[3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethylamine were first obtained, in the form of the free base, from 3300 g (2R,3R)-[3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethylamine, hydrobromide (which can be obtained in accordance with the procedure of EP A 0 693 475) with 45 % by weight sodium hydroxide solution (acid consumption = 4.11 mol/kg).

18.9 kg of methane sulfonic acid and 2458 g D,L methionine were placed in methyl cyclohexane and then 3192 g (2R,3R)-[3-(3-methoxy-phenyl)-2-methyl-pentyl]-dimethylamine were added and the mixture was stirred at 82 °C for 18 hours. Subsequently, dilution was carried out with 10.3 l water at a maximum of 80 °C and 9 l methyl cyclohexane were added. At a maximum of 42 °C, 17.3 l ammonia were added until the pH was 8.8. A phase separation took place at 45 °C and 3.2 g (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol were added to the organic phase at 40 °C and stirred for 1 hour at 36 °C. Subsequently, after cooling slowly to 5 °C and a further hour of stirring, the precipitate which formed was filtered out by suction, washed with 12 l methyl cyclohexane and dried in a drying chamber. 2685 g (89.5 %) (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol were obtained in modification B.

The compound of modification B thus obtained will be referred to in the following as (1).

C) Synthesis of modification C

C1)

48.6 mg modification B were suspended in 10 ml methanol and shaken with a vortexer for 4 hours at 400 rpm at 30 °C. After cooling to RT, the solvent was evaporated off at RT in an air flow.

After 24 hours, the residue was present as a mixture of oil and solid. After further storage (72 hours, sealed, room temperature), a white solid was obtained.

C2)
30.23 mg modification A were suspended in 6 ml toluene and shaken with a vortexer for 4 hours at 400 rpm at 30 °C. After cooling to RT, the solvent was evaporated off at 23 °C in an air flow. A white solid was obtained.

The peak temperatures found in DSC analyses for the products obtained in accordance with C1) and C2) were in the range of 78-82 °C and 87-90 °C and thus in the range of the peak temperatures found for modifications A and B. The products could thus be a mixture of forms A and B. However, the powder diffractogram shows x-ray diffraction reflections which could not originate from a mixture of modifications A and B.

Crystallization tests:

Example 1:

Amorphous (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol was obtained by rapid evaporation of a solution of the compound on a rotary evaporator. The oily residues were stored at RT or at 5 °C. All the samples crystallised within 24 hours. Modification A or mixtures of modification A and modification B were obtained at RT. At lower temperatures (5 °C), modification B was obtained.

1.1) 109.1 mg (1) were dissolved in 2 ml TBME. The solvent was removed on a rotary evaporator. A colourless oil was obtained. The residue was stored overnight at RT. A mixture of modifications A and B was obtained.

1.2) 100 mg (1) were dissolved in 2 ml EtOH. The solvent was removed on a rotary evaporator. A colourless oil was obtained. The residue was stored overnight at RT. Modification A was obtained.

1.3) 105.6 mg (1) were dissolved in 2 ml EtOAc. The solvent was removed on a rotary evaporator. A colourless oil was obtained. The residue was stored overnight at RT. A mixture of modifications A and B was obtained.

1.4) 100.9 mg (1) were dissolved in 2 ml acetone. The solvent was removed on a rotary evaporator. A colourless oil was obtained. The residue was stored overnight at 5 °C. Modification B was obtained.

1.5) 100.0 mg (1) were dissolved in 2 ml MEK. The solvent was removed on a rotary evaporator. A colourless oil was obtained. The residue was stored overnight at 5 °C. Modification B was obtained.

1.6) 99.5 mg (1) were dissolved in 2 ml THF. The solvent was removed on a rotary evaporator. A colourless oil was obtained. The residue was stored overnight at 5 °C. Modification B was obtained.

Example 2:

Amorphous (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol was obtained by rapid evaporation of a solution of the compound on a rotary evaporator or in a nitrogen flow. The oily residues were suspended in various solvents and the mixtures thus obtained were stirred at RT or at 5 °C. No formation of solvates was observed in the selected solvents.

2.1) 96.9 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl TBME were added to the residue thus obtained. The mixture was stirred at RT for a duration of 2 weeks. All solid components were dissolved.

2.2) 104.2 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl TBME were added to the residue thus obtained. The mixture was stirred at RT for a duration of 2 weeks. All solid components were dissolved.

2.3) 99.9 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl H_2O were added to the residue thus obtained. The mixture was stirred at RT for a duration of 1 week. The resulting crystalline residue was filtered out. Modification B was obtained.

2.4) 95.3 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl IPE were added to the residue thus obtained. The mixture was stirred at RT for a duration of 2 weeks. All solid components were dissolved.

2.5) 101.7 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl H_2O/EtOH (1:1) were added to the residue thus obtained. The mixture was stirred at RT for a duration of 1 week. The resulting crystalline residue was filtered out. Modification B was obtained.

2.6) 101.0 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl acetone/EtOH (1:1) were added to the residue thus obtained. The mixture was stirred at RT for a duration of 2 weeks. Two liquid phases formed.

2.7) 96.9 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl TBME were added to the residue thus obtained. The mixture was stirred at 5 ^{o}C for a duration of 2 weeks. All solid components were dissolved.

2.8) 109.0 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl heptane/TBME (1:1) were added to the residue thus obtained. The mixture was stirred at a temperature of 5 °C for a duration of 1 week. The resulting crystalline residue was filtered out. Modification B was obtained.

2.9) 98.5 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl H_2O were added to the residue thus obtained. The mixture was stirred at a temperature of 5 °C for a duration of 1 week. The resulting crystalline residue was filtered out. A mixture of modifications A and B was obtained.

2.10) 100.7 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl IPE were added to the residue thus obtained. The mixture was stirred at 5 °C for a duration of 2 weeks. All solid components were dissolved.

2.11) 96.7 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl EtOH/H_2O (1:1) were added to the residue thus obtained. The mixture was stirred at a temperature of 5 °C for a duration of 1 week. The resulting crystalline residue was filtered out. Modification B was obtained.

2.12) 105.1 mg (1) were dissolved in 1 ml THF. The solution was filtered and subsequently the solvent was removed at RT under a strong nitrogen flow. 500 µl acetone/H_2O (1:1) were added to the residue thus obtained. The mixture was stirred at a temperature of 5 °C for a duration of 1 week. The resulting crystalline residue was filtered out. Modification B was obtained.

Example 3:

Crystallization tests were carried out by vapor diffusion, using saturated hydrocarbons and ethers as precipitants. Only in one case was a crystalline precipitate obtained, namely modification B.

3.1) 200 mg (1) were dissolved in 2 ml 2PrOH. The solution was stored at RT in a saturated n-hexane atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.2) 200 mg (1) were dissolved in 2 ml EtOAc. The solution was stored at RT in a saturated n-hexane atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.3) 200 mg (1) were dissolved in 2 ml toluene. The solution was stored at RT in a saturated n-hexane atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.4) 200 mg (1) were dissolved in 2 ml THF. The solution was stored at RT in a saturated n-hexane atmosphere for a duration of 8 weeks. The crystal precipitate which formed was filtered out. Modification B was obtained.

3.5) 200 mg (1) were dissolved in 2 ml 2PrOH. The solution was stored at RT in a saturated IPE atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.6) 200 mg (1) were dissolved in 2 ml EtOAc. The solution was stored at RT in a saturated IPE atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.7) 200 mg (1) were dissolved in 2 ml toluene. The solution was stored at RT in a saturated IPE atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.8) 200 mg (1) were dissolved in 2 ml THF. The solution was stored at RT in a saturated IPE atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.9) 200 mg (1) were dissolved in 2 ml 2PrOH. The solution was stored at RT in a saturated TBME atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.10) 200 mg (1) were dissolved in 2 ml EtOAc. The solution was stored at RT in a saturated TBME atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.11) 200 mg (1) were dissolved in 2 ml toluene. The solution was stored at RT in a saturated TBME atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.12) 200 mg (1) were dissolved in 2 ml THF. The solution was stored at RT in a saturated TBME atmosphere for a duration of 8 weeks. No precipitate was obtained.

3.13) 200 mg (1) were dissolved in 1 ml EtOAc. The solution was stored at RT in a saturated cyclohexane atmosphere for a duration of 1 week. No precipitate was obtained. The sample was stored at 5 ^{o}C for a duration of two weeks. No precipitate was obtained.

3.14) 200 mg (1) were dissolved in 3 ml MeCN. The solution was stored at RT in a saturated cyclohexane atmosphere for a duration of 1 week. No precipitate was obtained. The sample was stored at 5 ^{o}C for a duration of two weeks. No precipitate was obtained.

3.15) 200 mg (1) were dissolved in 1 ml DMSO. The solution was stored at RT in a saturated cyclohexane atmosphere for a duration of 3 weeks. No precipitate was obtained.

3.16) 200 mg (1) were dissolved in 1 ml EtOAc. The solution was stored at RT in a saturated pentane atmosphere for a duration of 1 week. No precipitate was obtained. The sample was stored at 5 ^{o}C for a duration of two weeks. No precipitate was obtained.

3.17) 200 mg (1) were dissolved in 3 ml MeCN. The solution was stored at RT in a saturated pentane atmosphere for a duration of 1 week. No precipitate was obtained. The sample was stored at 5 ^{o}C for a duration of two weeks. No precipitate was obtained.

3.18) 200 mg (1) were dissolved in 1 ml DMSO. The solution was stored at RT in a saturated pentane atmosphere for a duration of 3 weeks. No precipitate was obtained.

Example 4:

4.1) 100 mg (1) were dissolved in 1 ml EtOAc. 2 ml acetone were added incrementally until the solution became cloudy. The sample was stored at 5 °C for a duration of 10 days. No change was observed.

4.2) 100 mg (1) were dissolved in 0.5 ml 1,4-dioxane. 2 ml H_2O were added incrementally until the solution became cloudy and an adhesive resin was precipitated. The sample was stored at 5 °C overnight. After scratching with a spatula, the resin crystallised out and the crystalline solid was filtered out. Modification B was obtained.

4.3) 100 mg (1) were dissolved in 0.5 ml EtOAc. 6 ml heptane were added incrementally until the solution became cloudy and a colourless solid was precipitated. The sample was stored at 5 °C for a duration of 6 days and the obtained solid was filtered out. A crystalline powder was obtained.

4.4) 100 mg (1) were dissolved in 1 ml dioxane. 3 ml heptane were added incrementally until the solution became cloudy. The sample was stored at 5 °C for a duration of 1 week. No change was observed.

4.5) 100 mg (1) were dissolved in 1 ml dioxane. 11 ml iBuOAc were added incrementally. No precipitate was obtained. The sample was stored at 5 °C for a duration of 1 week. No change was observed.

4.6) 100 mg (1) were dissolved in 1 ml EtOAc. 1 ml pentane was added incrementally until the solution became cloudy. The sample was stored at 5 °C for a duration of 1 week. No change was observed.

4.7) 100 mg (1) were dissolved in 2.5 ml MeOH. 3 ml H_2O were added incrementally until the solution became cloudy and a colourless solid was precipitated. The sample was stored at RT for a duration of 1 week and the obtained solid was filtered out. A crystalline powder of modification A was obtained.

4.8) 100 mg (1) were dissolved in 500 µl 2PrOH. 3 ml H_2O were added incrementally and the mixture was stirred at RT for a duration of 5 days. The obtained solid was filtered out. A crystalline powder of modification B was obtained.

4.9) 100 mg (1) were dissolved in 500 µl EtOH. 3 ml H_2O were added incrementally and the mixture was stirred at RT for a duration of 5 days. The obtained solid was filtered out. A crystalline powder of modification B was obtained.

4.10) 100 mg (1) were dissolved in 1 ml DMF. 2 ml H_2O were added incrementally and the mixture was stirred at RT for a duration of 5 days. The obtained solid was filtered out. A crystalline powder of modification B was obtained.

4.11) 100 mg (1) were dissolved in 1 ml DMSO. 1 ml H_2O was added incrementally and the mixture was stirred at RT for a duration of 5 days. The obtained solid was filtered out. A crystalline powder of modification B was obtained.

4.12) 100 mg (1) were dissolved in 500 µl EtOAc. 2 ml pentane were added incrementally and the mixture was stirred at RT for a duration of a few hours. An adhesive solid formed. The sample was stored at 5 ^{o}C for a duration of 3 weeks and the obtained solid was filtered out.

4.13) 100 mg (1) were dissolved in 500 µl EtOAc. 2 ml n-hexane were added incrementally and the mixture was stirred at RT for a duration of a few hours. An adhesive solid formed. The sample was stored at 5 ^{o}C for a duration of 2 weeks and the obtained solid was filtered out. A crystalline powder of modification B was obtained.

4.14) 100 mg (1) were dissolved in 500 µl EtOAc. 2 ml n-heptane were added incrementally and the mixture was stirred at RT for a duration of a few hours. An adhesive solid formed. The sample was stored at 5 °C for a duration of 2 weeks and the obtained solid was filtered out. A crystalline powder of modification B was obtained.

4.15) 100 mg (1) were dissolved in 500 µl EtOAc. 2 ml cyclohexane were added incrementally and the mixture was stirred at RT for a duration of a few hours. An adhesive solid formed. The sample was stored at 5 °C for a duration of 2 weeks and the obtained solid was filtered out. A crystalline powder was obtained.

Example 5:

5.1) The solution obtained in accordance with example 2.1) was stored at RT in an open vessel in order to evaporate off the solvent. After 1 week, a crystalline solid of modification A was obtained.

5.2) The solution obtained in accordance with example 2.2) was stored at RT in an open vessel in order to evaporate off the solvent. After 1 week, a crystalline solid of modification A was obtained.

5.3) The solution obtained in accordance with example 2.4) was stored at RT in an open vessel in order to evaporate off the solvent. After 1 week, a crystalline solid of modification A was obtained.

5.4) The solution obtained in accordance with example 2.6) was stored at RT in an open vessel in order to evaporate off the solvent. After 1 week, a crystalline solid of modification A was obtained.

5.5) The solution obtained in accordance with example 2.7) was stored at RT in an open vessel in order to evaporate off the solvent. After 2 days, a crystalline solid of modification B was obtained.

5.6) The solution obtained in accordance with example 2.10) was stored at RT in an open vessel in order to evaporate off the solvent. After 2 days, a crystalline solid of modification B was obtained.

5.7) The solution obtained in accordance with example 4.1) was stored at RT in an open vessel in order to evaporate off the solvent. After 2 days, a crystalline solid of modification A was obtained.

5.8) The solution obtained in accordance with example 4.4) was stored at RT in an open vessel in order to evaporate off the solvent. After 6 days, a crystalline solid of modification A was obtained.

5.9) The solution obtained in accordance with example 4.5) was stored at RT in an open vessel in order to evaporate off the solvent. After 6 days, a crystalline solid of modification B was obtained.

5.10) The solution obtained in accordance with example 4.6) was stored at RT in an open vessel in order to evaporate off the solvent. After 6 days, a crystalline solid of modification B was obtained.

Example 6:

The crystalline modification B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol exhibited no change upon suspension in various solvents. It was possible to exclude the formation of solvates with the selected solvents.

6.1) 200 mg (1) were suspended in 500 µl TBME. The mixture was stirred at RT for a duration of 2 days and the resulting solid was filtered out. A crystalline powder of modification B was obtained.

6.2) 100 mg (1) were suspended in 500 µl heptane/TBME (1:1). The mixture was stirred at RT for a duration of 2 days and the resulting solid was filtered out. A crystalline powder of modification B was obtained.

6.3) 100 mg (1) were suspended in 500 µl H_2O. The mixture was stirred at RT for a duration of 2 days and the resulting solid was filtered out. A crystalline powder of modification B was obtained.

6.4) 100 mg (1) were suspended in 500 µl IPE. The mixture was stirred at RT for a duration of 2 days and the resulting solid was filtered out. A crystalline powder of modification B was obtained.

6.5) 100 mg (1) were suspended in 500 µl H_2O/EtOH (1:1). The mixture was stirred at RT for a duration of 2 days and the resulting solid was filtered out. A crystalline powder of modification B was obtained.

Example 7:

Attempts were made to produce the amorphous modification of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol by evaporation, lyophilization or melting. All obtained samples of the amorphous modification crystallised within hours.

7.1) 150 mg (1) were dissolved in 3 ml MeOH. The solvent was removed on a rotary evaporator. A colourless oil remained. The residue was dried in a vacuum. Modification A was obtained.

7.2) 150 mg (1) were dissolved in 2 ml 1,4-dioxane. The solvent was removed by freeze-drier. Modification A was obtained.

7.3) 150 mg (1) were dissolved in 2 ml 1,4-dioxane. The solvent was removed by freeze-drier (−85 ^{o}C, 0.5 mbar). A colourless residue remained and crystallised spontaneously

before it was possible to perform a PXRD analysis. Modification B was obtained with traces of modification A.

7.4) 150 mg (1) were melted at 88-91 °C. The melt was frozen with dry ice. An amorphous film was obtained which crystallised within 1 hour.

Example 8:

The effect of mechanical stress from grinding with a ball mill (model Retsch MM200, agate vessel and agate ball with 5 mm diameter) and from pressure during the production of a tablet was analysed. Although the pressure during compaction had no effect on the samples, modification A was converted into modification B when ground.

8.1) A tablet was produced with 100 mg (1) on an IR tablet press (pressure 10 t, 30 min). Modification B was obtained.

8.2) A tablet was produced with 100 mg of the product of modification A according to example 5.8 on an IR tablet press (pressure 10 t, 30 min). Modification A was obtained.

8.3) 16 mg of the crystalline modification B were ground in a ball mill (shaking frequency: 30 sec^{-1}, RT) as follows: 2 × 90 min, 1 × 60 min, 2 × 30 min discontinuation. Modification B was obtained.

8.4) 15 mg of the crystalline form A were ground in a ball mill (shaking frequency: 30 sec^{-1}, RT) as follows: 2 × 90 min, 1 × 60 min, 2 × 30 min discontinuation. Modification B was obtained.

Example 9:

9.1) 20.5 mg modification A and 20.9 mg modification B were suspended in 200 µl IPE. The suspension was shaken overnight in an Eppendorf Thermomixer at RT. The

obtained solid was filtered out and characterized by FT Raman spectral analysis. Modification B was obtained.

9.2) 19.8 mg modification A and 20.5 mg modification B were suspended in 300 µl acetone/H_2O (8:2). The suspension was shaken overnight in an Eppendorf Thermomixer at RT. The resulting solid was filtered out and characterized by FT Raman spectral analysis. Modification B was obtained.

9.3) 15 mg modification A and 20.5 mg modification B were suspended in 1 ml acetone/H_2O (8:2). The suspension was stirred for three days at 5 °C. The obtained solid was filtered out and characterized by FT Raman spectral analysis. Modification B was obtained.

9.4) 20.5 mg modification A and 20.9 mg modification B were suspended in 200 µl IPE. The suspension was stirred overnight at 50 °C. The obtained solid was filtered out and characterized by FT Raman spectral analysis. Modification B was obtained.

9.5) 15 mg modification A and 15 mg modification B were suspended in 1 ml acetone/H_2O (8:2). The suspension was stirred overnight at 50 °C. The obtained solid was filtered out and characterized by FT Raman spectral analysis. Modification B was obtained.

9.6) 20.5 mg modification A and 20.9 mg modification B were suspended in 200 µl IPE. The suspension was stirred overnight at 50 °C. All solid components were dissolved. After cooling to RT, small amounts of a colourless solid were precipitated. The solvent was removed in a nitrogen flow. Modification B was obtained.

Analysis — XRPD

X-Ray Powder Diffraction (XPRD):

XRPD analyses were carried out in transmission geometry with a STOE Stadi P X-ray powder diffractometer, monochromatised $CuK\alpha_1$ radiation being used by means of a germanium monocrystal. D-distances were calculated from the 2θ values, establishing

the wavelength of 1.54060 Å. In general, the 2θ values have an error rate of ±0.2° in 2θ. The experimental error in the d-distance values is therefore dependent on the location of the peak.

Modification A

Table 1 shows the peak list for modification A. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I (or RI) is the relative intensity of the respective peak. Maximum intensity is 100.

Table 1:

2Θ	rel. I	2Θ	rel. I	2Θ	rel. I	2Θ	rel. I	2Θ	rel. I
13.71	30	20.20	15	24.75	9	30.68	5	36.24	2
14.11	9	20.92	12	25.33	18	31.43	3	36.54	1
14.80	45	21.12	5	27.32	5	32.21	4	36.87	1
15.58	100	21.90	7	27.55	6	32.98	3	37.06	2
16.31	3	22.21	6	28.05	2	33.41	2	37.48	2
16.89	18	22.50	18	28.37	3	33.76	1	37.87	1
17.79	37	23.30	3	29.62	1	34.17	1	38.64	3
18.45	34	24.04	2	29.90	5	34.45	1	39.48	2
19.07	8	24.37	17	30.28	1	35.98	2		

Indexing the diffractogram for form A with the program WinXPow Index (Version 2.03) from STOE & Cie GmbH gave the following lattice constants, which correspond well with those which were established in a monocrystal structure determination:

orthorhombic, a = 12.92 Å, b = 11.98 Å, c = 8.98 Å, cell volume 1391 $Å^3$

Modification B

Table 2 shows the peak list for modification B. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum intensity is 100.

Table 2:

2Θ	rel. I	2Θ	rel. I	2Θ	rel. I	2Θ	rel. I	2Θ	rel. I
14,11	47	20,80	30	25,36	8	31,54	1	37,12	2
14,44	35	22,00	10	27,58	9	32,11	3	37,32	2
16,08	100	22,49	17	27,79	5	32,45	1	37,75	1
17,17	42	22,85	4	29,06	19	32,76	3	38,13	1
17,43	33	23,40	26	29,89	10	33,61	2	38,72	2
18,67	5	24,15	12	30,11	5	33,94	1	39,63	3
18,81	37	24,51	31	30,31	2	35,49	2	40,01	1
19,50	1	24,88	4	31,00	6	35,95	3		
20,24	15	25,24	5	31,17	4	36,54	4		

Indexing the diffractogram for form B with the program WinXPow Index (Version 2.03) from STOE & Cie GmbH gave the following lattice constants, which correspond well with those which were established in a monocrystal structure determination: orthorhombic, a = 12.54 Å, b = 12.27 Å, c = 9.10 Å, cell volume 1400 $Å^3$

Modification C

Table 3 shows the peak list for modification C. The uncertainty in the 2θ values is ±0.2° in 2θ; rel. I is the relative intensity of the respective peaks. Maximum intensity is 100.

Table 3:

2Θ	rel. I	2Θ	rel. I	2Θ	rel. I	2Θ	rel. I	2Θ	rel. I	2Θ	rel. I
8,10	4	16,10	53	20,23	32	24,39	15	28,48	4	33,66	4
10,93	8	16,43	100	20,71	9	24,92	39	29,64	1	35,52	3
11,83	4	16,91	16	20,94	12	25,35	14	29,94	7	36,05	4
12,41	9	17,32	5	21,17	39	26,22	17	30,54	7	36,64	3
13,71	14	17,58	27	21,90	6	26,54	9	30,68	5	37,54	3
14,13	11	17,82	27	22,23	8	26,72	10	31,03	2	38,45	2
14,82	24	18,01	30	22,52	11	27,33	4	31,52	3	39,15	3
15,34	38	18,46	25	23,32	2	27,63	5	32,29	3	40,05	6
15,59	58	19,05	33	24,12	4	27,84	7	32,93	5		

Analysis — DSC

Differential Scanning Calorimetry (DSC): device reference Perkin Elmer DSC 7 or Perkin Elmer Pyris 1. Unless otherwise specified, the samples were weighed in a sealed gold crucible. The measurement took place in a nitrogen flow in a temperature range from −50 °C to 250 °C at a heating rate of 10 °C/min. The temperatures specified in relation to DSC analyses are, unless otherwise specified, the temperatures of the peak maxima (peak temperature T_P). Onset temperatures of peaks are indicated by T_O.

DSC

Modification A T_O 77.83 °C; T_P 79.46 °C; J/g 107.03

Modification B T_O 88.60 °C; T_P 89.76 °C; J/g 114.67

Modification C	T_O 78.72 °C; T_P 81.00 °C; J/g 110.74
	T_O 88.36 °C; T_P 89.17 °C; J/g 0.57

Analysis — FT Raman Spectroscopy

Crystalline modifications A and B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol were each characterized by Fourier transform (FT) RAMAN spectrometry.

For this purpose, the FT Raman spectra were recorded on a Bruker RFS100 RAMAN spectrometer (Nd-YAG 100 mW laser, excitation 1064 nm, Ge detector, 64 scans, 25-3500 cm^{-1}, resolution 2 cm^{-1}).

Analysis — TG-FTIR

Crystalline modifications A and B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol were each characterized by thermogravimetric Fourier transform infrared spectroscopy (TG-FTIR). For this purpose, the appropriate spectra were recorded with a Netzsch Thermo-Microwaage TG 209 and a Bruker FT-IR spectrometer Vector 22 (aluminium crucible (open or with micro-aperture), nitrogen atmosphere, heating rate 10 °C/min, 25-250 °C).

The TG-FTIR analyses showed that both modifications decompose above 160 °C.

Analysis — DVS

Crystalline modifications A and B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol were each characterized by dynamic vapor sorption (DVS). The analyses were recorded in dynamic mode (5 % relative air humidity/hour).

The DVS cycles are reversible. At a temperature of 25 °C, changes in mass of 0.8 % for modification A and 0.3 % for modification B were found. Both modifications are not or at most slightly hygroscopic.

Analysis — Rate of Dissolution

To analyse the rate of dissolution of modifications A and B in water, two different determinations were carried out.

In the first determination, a suspension of modification A or B was in each case stirred in water, without taking into account the particle size distribution. Under these conditions, the particle size affects the result. Although form B is the more stable form at RT, it dissolves more rapidly.

In the second determination, a fresh sample of modification A was produced and tablets were produced for both modifications, A and B. Neither form was influenced by the compaction, but nevertheless, both samples exhibited a rate of dissolution of 0.003 mg/min cm^2. Analysis of the samples with FT Raman showed that form A had been converted into form B during the determination.

Patentkrav

1. Legemiddel for oral bruk som inneholder en krystallinsk modifikasjon A av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol, omfattende en røntgen-diffaksjonrefleksjon på 15,58±0.20 (2Θ), i tillegg minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 28,37±0.20 (2Θ) og 34,45±0.20 (2Θ) og i tillegg minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 13,71±0,20 (2Θ), 14,80±0,20 (2Θ), 16,89±0,20 (2Θ), 17,79±0,20 (2Θ), 18,45±0,20 (2Θ), 20,20±0,20 (2Θ), 20,92±0,20 (2Θ), 22,50±0,20 (2Θ), 24,37±0,20 (2Θ) og 25,33±0,20 (2Θ).

2. Legemidlet ifølge krav 1, **karakterisert ved at** den krystallinske modifikasjonen A i tillegg omfatter minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 14,11±0,20 (2Θ), 19,07±0,20 (2Θ), 21,12±0,20 (2Θ), 21,90±0,20 (2Θ), 22,21 ±0,20 (2Θ), 24,75±0,20 (2Θ), 27,32±0,20 (2Θ), 27,55±0,20 (2Θ), 29,90±0,20 (2Θ) og 30,68±0,20 (2Θ).

3. Legemidlet ifølge hvilket som helst av krav 1 eller 2, **karakterisert ved at** den krystallinske modifikasjonen A ikke omfatter minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 8,10±0,20 (2Θ), 10,93±0,20 (2Θ), 11,83±0,20 (2Θ), 12,41 ±0,20 (2Θ), 26,22±0,20 (2Θ), 26,54±0,20 (2Θ) og 26,72±0,20 (2Θ).

4. Legemidlet ifølge hvilket som helst av krav 1-3, **karakterisert ved at** den krystallinsk modifikasjonen A er endotermisk i området fra 75 til 84 °C i DSC.

5. Legemiddel for oral bruk som inneholder en krystallinsk modifikasjon B av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol,omfattende en røntgen-diffraksjonrefleksjon på 29,06±0,20 (2Θ), i tillegg minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 19,50±0,20 (2Θ), 35,49±0,20 (2Θ) og 40,01±0,20 (2Θ) og i tillegg minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 14,11±0,20 (2Θ), 14,44±0,20 (2Θ), 16,08±0,20 (2Θ), 17,17±0,20 (2Θ), 17,43±0,20 (2Θ), 18,81±0,20 (2Θ), 20,24±0,20 (2Θ), 20,80±0,20 (2Θ), 22,00±0,20 (2Θ), 22,49±0,20 (2Θ), 23,40±0,20 (2Θ), 24,15±0,20 (2Θ), 24,51±0,20 (2Θ) og 29,89±0,20 (2Θ).

6. Legemidlet ifølge krav 5, **karakterisert ved at** den krystallinske modifikasjonen B i tillegg omfatter minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 18,67±0,20 (2Θ), 25,24±0,20 (2Θ), 25,36±0,20 (2Θ), 27,58±0,20 (2Θ), 27,79±0,20 (2Θ), 30,11±0,20 (2Θ) og 31,00±0,20 (2Θ).

7. Legemidlet ifølge hvilket som helst av krav 5 eller 6, **karakterisert ved at** den krystallinske modifikasjonen B ikke omfatter minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 8,10±0,20 (2Θ), 10,93±0,20 (2Θ), 11,83±0,20 (2Θ), 12,41±0,20 (2Θ), 26,22±0,20 (2Θ), 26,54±0,20 (2Θ) og 26,72±0,20 (2Θ).

8. Legemidlet ifølge hvilket som helst av krav 5-7, **karakterisert ved at** den krystallinske modifikasjonen B er endotermisk i området fra 87-93 °C i DSC.

9. Legemiddel for oral bruk, som inneholder en krystallinsk modifikasjon C av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-denol, onfattende minst én røntgen-diffraksjonsrefleksjon valgt fra gruppen som består av 10,93±0,20 (2Θ), 12,41±0,20 (2Θ) og 26,22±0,20 (2Θ), ytterligere minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 8,10±0,20 (2Θ), 11,83±0,20 (2Θ), 26,54±0,20 (2Θ) og 26,72±0,20 (2Θ) og ytterligere minst én røntgen-diffraksjonrefleksjon valgt fra gruppen som består av 13,71±0,20 (2Θ), 14,13±0,20 (2Θ), 14,82±0,20 (2Θ), 15,34±0,20 (2Θ), 15,59±0,20 (2Θ), 16,10±0,20 (2Θ), 16,43±0,20 (2Θ), 16,91±0,20 (2Θ), 17,32±0,20 (2Θ), 17,58±0,20 (2Θ), 17,82±0,20 (2Θ), 18,01±0,20 (2Θ), 18,46±0,20 (2Θ), 19,05±0,20 (2Θ), 20,23±0,20 (2Θ), 20,71 ±0,20 (2Θ), 20,94±0,20 (2Θ), 21,17±0,20 (2Θ), 21,90±0,20 (2Θ), 22,23±0,20 (2Θ), 22,52±0,20 (2Θ), 23,32±0,20 (2Θ), 24,12±0,20 (2Θ), 24,39±0,20 (2Θ), 24,92±0,20 (2Θ), 25,35±0,20 (2Θ), 27,33±0,20 (2Θ), 27,63±0,20 (2Θ), 27,84±0,20 (2Θ), 28.48±0.20 (2Θ), 29.64±0.20 (2Θ), 29.94±0.20 (2Θ), 30.54±0.20 (2Θ), 30.68±0.20 (2Θ), 31,03±0,20 (2Θ), 31,52±0,20 (2Θ), 32,29±0,20 (2Θ), 32,93±0,20 (2Θ), 33,66±0,20 (2Θ), 35,52±0,20 (2Θ), 36,05±0,20 (2Θ), 36,64±0,20 (2Θ), 37,54±0,20 (2Θ), 38,45±0,20 (2Θ), 39,15±0,20 (2Θ) og 40,05±0,20 (2Θ).

10. Legemidlet ifølge krav 9, **karakterisert ved at** den krystllinske modifikatoren C er endotermisk med en topptemperatur på 75-84 °C og/eller endotermisk med en topptemperatur på 87-93 °C under DSC-tester.

11. Legemidlet ifølge hvilket som helst av krav 1 til 10 for smertebehandling.

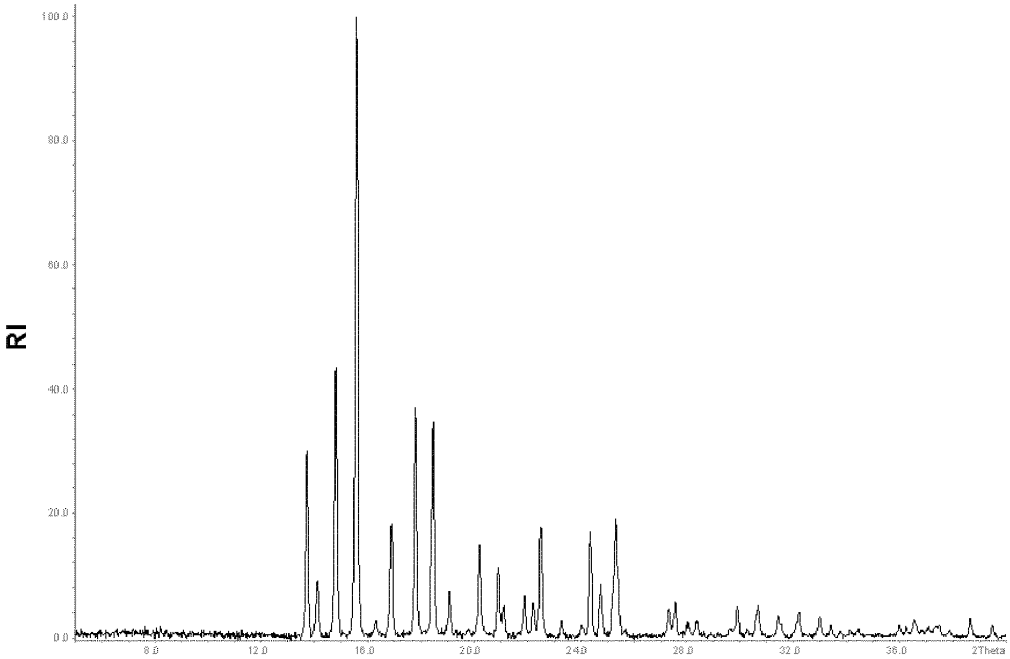
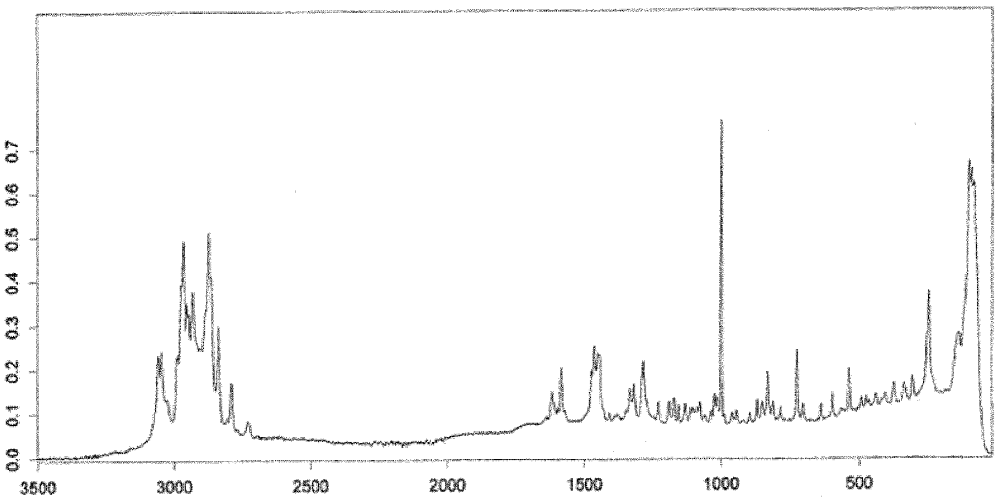

RI
100.0
80.0
60.0
40.0
20.0
0.0
8.0
12.0
16.0
20.0
24.0
28.0
32.0
36.0
2Theta

Fig.1

Fig. 2


0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
3500
3000
2500
2000
1500
1000
500

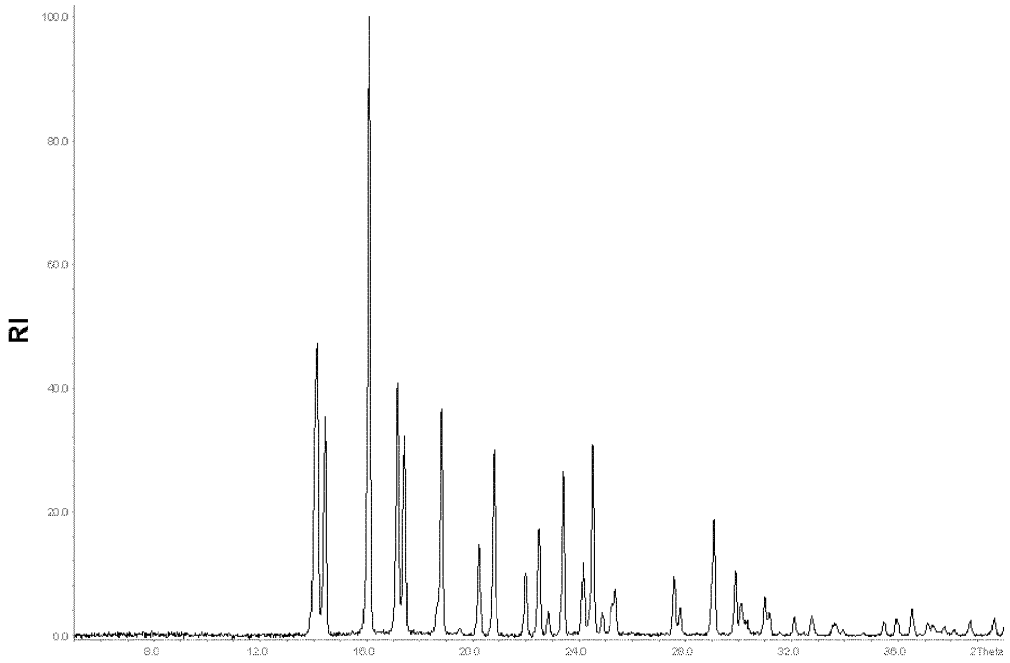
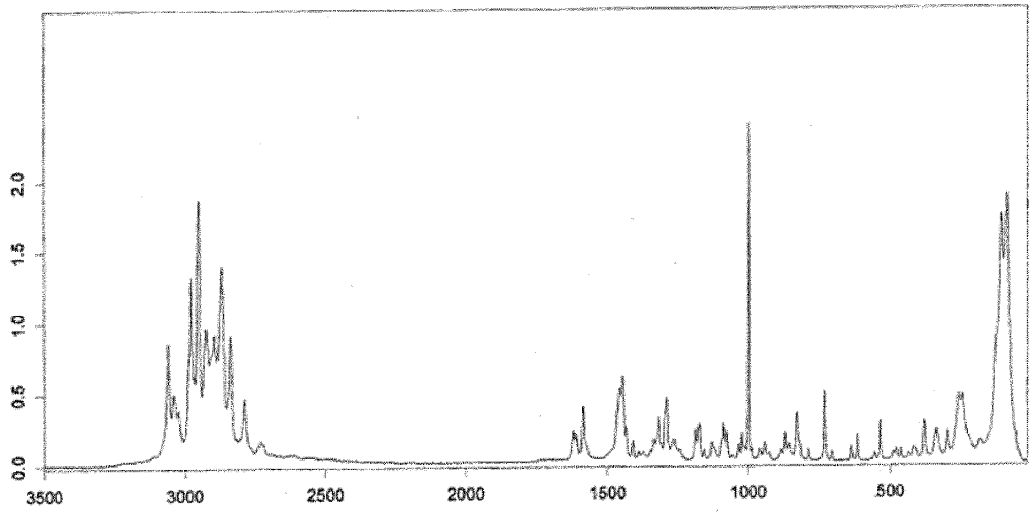

RI
100.0
80.0
60.0
40.0
20.0
0.0
8.0
12.0
16.0
20.0
24.0
28.0
32.0
36.0
2Theta

Fig. 3

Fig. 4


0.0
0.5
1.0
1.5
2.0
3500
3000
2500
2000
1500
1000
500

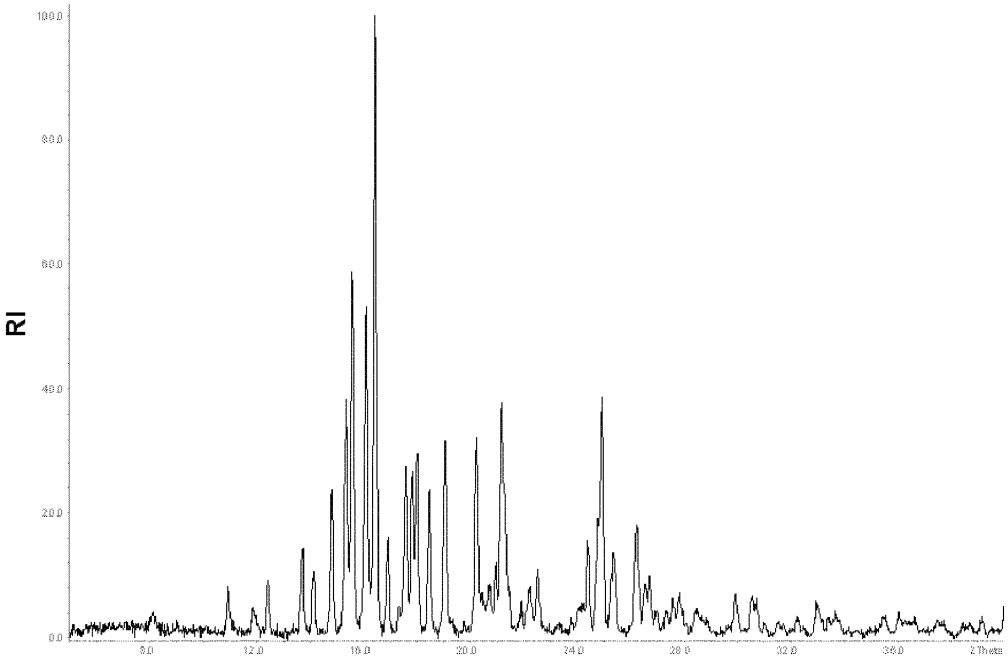


Fig. 5