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(54) Benevnelse **CRYSTALLINE MODIFICATIONS OF (1R, 2R)-3-(3-DIMENTHYL AMINO-1-ETHYL-2-METHYL-PROPYL) PHENOL**

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The invention relates to crystalline modifications of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol, pharmaceutical compositions comprising these modifications and use thereof.

(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol is a synthetic analgesic which is suitable for the treatment of severe to very severe, acute and chronic pain. The compound may be used here in the form of its free base or in the form of pharmaceutically acceptable salts and solvates. The preparation of the compound and salts thereof is known from EP-A-0 693 475, wherein the compound is obtained typically in the form of its salt, in the form of its hydrochloride for example.

An object of the present invention consists of making the compound (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol accessible as such, i.e. in the form of the free base, in good yields and good purity.

This object was achieved by the subject matter of the patent claims.

It was found, surprisingly, that under suitable conditions, the compound (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol can be obtained in the form of the polymorphs A, B and C described below.

These crystalline forms enable the compound (1R,2R)-3-(dimethylamino-1-ethyl-2-methylpropyl)phenol to be obtained in the form of the free base, in good yields and good purity. These forms are further characterized by good ease of handling and facilitate an exact dosage of the active ingredient.

Moreover, various polymorphs of the same pharmaceutical active ingredient differ fundamentally in their properties, whereby further advantages may arise.

Firstly, the advantages may be due to a specific physical property of a particular modification, for example in their processing and storage, such as thermodynamic stability; crystal morphology, in particular shape, size, colour; density; bulk density; hardness; deformability; calorimetric behaviour, particularly melting point; solubility

properties; in particular, intrinsic solubility rate and equilibrium solubility; hygroscopicity; relative moisture profile; stickiness etc.

Secondly, the crystalline modification may also have improved chemical properties. It is known, for example, that a lower hygroscopicity can lead to an improved chemical stability and longer shelf life of chemical compounds.

The present invention relates to a crystalline modification A of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol.

This crystalline modification A according to the invention comprises an X-ray diffraction reflection at 15.58±0.20 (2Θ), in addition at least one X-ray diffraction reflection selected from the group consisting of 28.37±0.20 (2Θ) and 34.45±0.20 (2Θ) and in addition 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, in addition to the X-ray diffraction reflection at 15.58±0.20 (2Θ) and optionally 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 optionally 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), said modification comprises in addition 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).

Preferably the crystalline modification A according to the invention can also be characterized in that, in addition to the X-ray diffraction reflection at 15.58±0.20 (2Θ) and optionally 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 optionally 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), said modification in addition 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 also be characterized in that it does not comprise one or more of the aforementioned 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).

The crystalline modification A according to the invention may also be preferably further characterized in that it does not comprise one or more of the aforementioned 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.

The crystalline modification A according to the invention in DSC investigations preferably has an endotherm with peak temperature at 75-84°C, more preferably at 76-83°C, still more preferably at 77-82°C and especially at 78-81°C.

The crystalline form A according to the invention can be further 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 of modification A.

The invention further relates to a method for preparing crystalline modification A comprising the steps of

(a) concentrating a solution of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol, wherein the solvent is methanol, ethanol, 1-propanol, 2-propanol, ethyl acetate, acetone, ethyl methyl ketone, diethyl ether, tert-butyl methyl ether, 1,4-dioxane, tetrahydrofuran, acetonitrile, dichloromethane, toluene, dimethylformamide or dimethyl sulphoxide, and

(b) storing the residue obtained according to step (a) at a temperature of > 5°C.

To prepare the crystalline modification A, firstly a solution of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol is preferably fully concentrated.

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

After the concentration, typically an oily residue preferably remains which crystallizes out after storage at a temperature of > 5°C in the form of modification A. In general, a storage period of 24 hours is sufficient.

Further processing, if required, may also be carried out by customary methods known to those skilled in the art, for example by means of filtration, washing and/or drying.

The invention further relates to a crystalline modification A of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol, which is obtainable by the method described above.

The present invention further relates to the crystalline modification B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol.

This crystalline modification B according to the invention of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol comprises an X-ray diffraction reflection at 29.06±020 (2Θ), in addition at least one X-ray diffraction reflection selected from the group consisting of 19.50±0.20 (2Θ), 35.49±0.20 (2Θ) and 40.01±0.20 (2Θ) and in addition 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 can be characterized in that, in addition to the X-ray diffraction reflection at 29.06±0.20 (2Θ) and optionally 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 optionally 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), said modification comprises in addition 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, in addition to the X-ray diffraction reflection at 29.06±0.20 (2Θ) and optionally 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 optionally 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 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), said modification 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 can also be characterized in that it does not comprise one or more of the aforementioned 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).

The crystalline modification B can also preferably be characterized in that it does not comprise one or more of the aforementioned 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.

The crystalline modification B according to the invention in DSC investigations preferably has an endotherm with peak temperature at 87-93°C, more preferably at 88-92°C, still more preferably at 89-91°C.

The crystalline form B according to the invention can also be 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 of form B.

The invention further relates to a method for preparing crystalline modification B comprising the steps of

(a) concentrating a solution of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol, wherein the solvent is methanol, ethanol, 1-propanol, 2-propanol, ethyl acetate, acetone, ethyl methyl ketone, diethyl ether, tert-butyl methyl ether, 1,4-dioxane, tetrahydrofuran, acetonitrile, dichloromethane, toluene, dimethylformamide or dimethyl sulphoxide, and

(b1) storing the residue obtained according to step (a) at a temperature of ≤ 5°C, or

(b2) suspending the residue obtained according to step (a) and stirring this suspension.

To prepare the crystalline modification B, firstly a solution of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol is preferably fully concentrated.

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

After the concentration, typically an oily residue preferably remains which crystallizes out after storage at a temperature of ≤ 5°C in the form of modification B. In general, a storage period of 24 hours is sufficient. As an alternative, the preferably oily residue can also be taken up in a suitable suspension medium and be stirred for some time. Suitable as suspension medium are particularly mixtures of one or more solvents mentioned above with water or a saturated hydrocarbon, in particular n-pentane, n-hexane or n-heptane, wherein the proportion of solvent is selected such that the residue does not go completely into solution.

The temperature in step (b) may be varied over a wide range, in particular in the range from 5-25°C, also the stirring time which can range from a few minutes up to several weeks, in particular up to one week.

The invention further relates to a method for preparing crystalline modification B comprising the step of

(a) precipitating (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol from solution, wherein the solvent is methanol, ethanol, 1-propanol, 2-propanol, ethyl acetate, acetone, ethyl methyl ketone, diethyl ether, tert-butyl methyl ether, 1,4-dioxane,

tetrahydrofuran, acetonitrile, dichloromethane, toluene, dimethylformamide or dimethyl sulphoxide.

The (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol is then precipitated from the solution with the aid of 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 processing, if required, may also be carried out by customary methods known to those skilled in the art, for example by means of filtration, washing and/or drying.

The crystalline modification B may also be further obtained by cooling a melt of the crystalline modification A.

The invention further relates to a crystalline modification B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol, which is obtainable by the method described above.

Typically, modification A can be obtained by more rapid crystallization and/or at higher temperatures (possibly via the amorphous form as intermediate). Modification B may be obtained typically by slower crystallization and/or at lower temperatures (possibly by direct crystallization). The modification B is the thermodynamically most stable form, particularly in the temperature range of 5-85°C, preferably 5-50°C.

The thermodynamic stability is of significance. By using the most stable modification in a medicament, it can be specifically ensured that no polymorphic conversion of the active ingredient in the pharmaceutical formulation takes place during storage. This is advantageous since otherwise, as a consequence, conversion of a less stable modification into a stable modification can change the properties of the medicament. With respect to the pharmacological properties of a dosage form, this may result for example in a change in the solubility of the active ingredient, which is associated with a change of the release behaviour and therefore also a change in the bioavailability. Lastly, this results in an unsatisfactory storage stability of the dosage form.

The present invention also further relates to the crystalline modification C of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol.

The crystalline modification C of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol comprises 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), in addition at least one X-ray diffraction reflection 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) and in addition 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.

The crystalline modification C according to the invention in DSC investigations preferably has an endotherm with peak temperature at 75-84°C, more preferably at 76-83°C, still more preferably at 77-82°C and especially at 78-81 °C and/or an endotherm with peak temperature at 87-93°C, more preferably at 88-92°C, still more preferably at 89-91°C.

The invention further relates to a method for preparing 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-methylpropyl)phenol, wherein the suspension medium is methanol or toluene, and
(b) evaporating the suspension medium in a stream of air.

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

Subsequently, the suspension medium, optionally after cooling the suspension to room temperature, is evaporated off in a stream of air and the residue thus obtained optionally stored at room temperature.

Further processing, if required, may also be carried out by customary methods known to those skilled in the art, for example by means of filtration, washing and/or drying.

The invention further relates to a crystalline modification C of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol, which is obtainable by the method described above.

The modifications A, B and C according to the invention may also optionally form co-crystals and solvates. These are included in each case according to the invention.

The present invention also relates to a pharmaceutical composition containing the active ingredient (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol in crystalline form A, B or C and at least one pharmaceutically compatible carrier.

The pharmaceutical composition according to the invention can preferably contain one polymorph selected from the group consisting of modification A, modification B and modification C.

The pharmaceutical composition according to the invention can particularly preferably contain modification A.

Likewise, the pharmaceutical composition according to the invention can particularly preferably contain modification B.

The present invention further relates to a pharmaceutical dosage form containing a pharmaceutical composition according to the invention as described above.

The present invention also relates to a crystalline modification according to the invention of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol, namely modification A, B or C as described above, as a medicament. The invention further relates to the use of at least one crystalline modification A, B or C according to the invention of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol for preparing a medicament for treating pain, particularly acute pain and chronic pain.

In addition to 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 medicament according to the invention may typically contain further pharmaceutically compatible additives or auxiliaries such as carrier materials, fillers, solvents, diluents, dyes and/or binders.

The choice of auxiliaries and the amounts to be used of the same depend on whether the medicament is intended to be administered orally, subcutaneously, parenterally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally or topically, for example, on infections of the skin, the mucous membranes and on the eyes. For oral administration, preferred suitable preparations are in the form of tablets, coated tablets, capsules, granules, drops, juices and syrups, while for parenteral, topical and inhalation administration, solutions, suspensions, readily reconstitutable dry preparations and sprays are suitable. Crystalline forms according to the invention in a depot in dissolved form, or in a patch, optionally with addition of agents promoting skin penetration, are suitable percutaneous administration preparations. Oral or

percutaneous administrable preparation forms can delay release of the crystalline forms according to the invention.

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

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 is illustrated below by means of examples. These illustrations are merely exemplary and do not limit the general ideas of the invention.

Examples:

Abbreviations

RT	room temperature, preferably 20-25°C
TBME	tert-butyl methyl ether
EtOH	ethanol
MEK	2-butanone
THF	tetrahydrofuran
2PrOH	2-propanol
EtOAc	ethyl acetate

MeCN	acetonitrile
DMSO	dimethyl sulphoxide
DMF	dimethylformamide
IR	infrared
Min	minutes
Sec	seconds

Unless otherwise stated, solvent mixtures always refer to volume/volume.

A) Synthesis of modification A

A1)

16.689 g of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol hydrochloride (obtainable analogously to the specification according to EP A 0 693 475) were dissolved in 81 ml of distilled water in a 250 ml three-necked flask and 32% by weight aqueous sodium hydroxide solution was added until a pH of 11 had been reached (approx. 7 ml). Already after addition of a few ml, a white viscous substance precipitated out, which was dissolved in approx. 16 ml of ethyl acetate. After addition was complete, a white suspension was obtained which was stirred for 1 hour. The pH was noted here at 10 and a further 0.5 ml of aqueous sodium hydroxide solution was added. Subsequently, the precipitated base was extracted with in total 288 ml of ethyl acetate. The combined organic phases were then washed with approx. 32 ml of water, dried over magnesium sulphate and concentrated to dryness under reduced pressure on a rotary evaporator.

A yellow oil remained in the flask, which did not crystallise even at room temperature. Crystallization was therefore initiated by scratching the flask with a spatula and the oil

crystallized out within a few minutes in the form of a yellow residue. This residue was comminuted in a mortar and an almost white crystalline solid of modification A was obtained which was characterized by ^{1}H-NMR, DSC, TG-FTIR, XRPD, Raman and HPLC.

A portion of the crystalline solid thus obtained was recrystallized as follows:
30 mg of modification A were weighed into a 20 ml vial, 6 ml of 2-propanol were added and the mixture was shaken at 30°C and 400 revolutions per minute for 4 hours. Subsequently, the solvent is evaporated off at 23°C in a stream of air. A white crystalline solid of form A was obtained.

A2)

200 mg ① according to B) were dissolved in 25 mL of acetonitrile. Subsequently, the solvent was removed under reduced pressure on the rotary evaporator. A colourless oil remained. To this oil were added approx. 1 mg of seed crystals of form A, 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)

From 3300 g of (2R,3R)-[3-(3-methoxyphenyl)-2-methylpentyl]dimethylamine hydrobromide (obtainable analogously to the specification according to EP A 0 693 475) in methylcyclohexane, 3192 g of (2R,3R)-[3-(3-methoxyphenyl)-2-methylpentyl]dimethylamine in the form of the free base were firstly obtained using 45% by weight aqueous sodium hydroxide solution (acid consumption number = 4.11 mol/kg).

18.9 kg of methanesulphonic acid and 2458 g of D,L methionine were initially charged in methylcyclohexane and then 3192 g of (2R,3R)-[3-(3-methoxyphenyl)-2-methylpentyl]dimethylamine were added and the mixture was stirred at 82°C for 18 hours. Subsequently, the mixture was diluted with 10.3 L of water at a maximum of 80°C and 9 L of methylcyclohexane were added. At a maximum of 42°C, 17.3 L of

ammonia were added thereto until the pH was 8.8. At 45°C, phase separation was effected and 3.2 g of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol were added to the organic phase at 40°C and the mixture was stirred at 36°C for 1 hour. Subsequently, the mixture was slowly cooled to 5°C and stirred for a further one hour, the precipitate formed was filtered under suction, washed with 12 L of methylcyclohexane and dried in the drying cabinet. This gave 2685 g (89.5%) of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol in the modification B.

The compound of modification B thus obtained is referred to in the experiments below with ①.

C) Synthesis of modification C

C1)

48.6 mg of modification B were suspended in 10 mL of methanol and shaken at 30°C and 400 revolutions per minute for 4 hours using a vortexer. After cooling to RT, the solvent was evaporated off at RT in a stream off air.

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 of modification A were suspended in 6 mL of toluene and shaken at 30°C and 400 revolutions per minute for 4 hours using a vortexer. After cooling to RT, the solvent was evaporated off at 23°C in a stream of air. A white solid was obtained.

The peak temperatures found in DSC investigations for the products obtained according to C1) and C2) were in the range of 78-82°C or 87-90°C and therefore in the range of the peak temperatures found for modifications A and B. The products therefore could be a mixture of forms A and B. However, the X-ray powder diffractogram shows X-ray diffraction reflections which cannot originate from a mixture of modifications A and B.

Crystallization experiments:

Example 1:

Amorphous (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)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. Within 24 hours all samples crystallized. At RT, modification A or mixtures of modification A and modification B were obtained. At lower temperatures (5°C), modification B was obtained.

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

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

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

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

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

1.6) 99.5 mg of ① were dissolved in 2 ml of THF. The solvent was removed on the 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-methylpropyl)phenol was obtained by rapid evaporation of a solution of the compound on a rotary evaporator or in a nitrogen stream. 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 solvents selected.

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

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

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

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

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

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

2.7) 96.9 mg of ① were dissolved in 1 ml of THF. The solution was filtered and the solvent was subsequently removed at RT under a high nitrogen stream. 500 µl of TBME were added to the residue thus obtained. The mixture was stirred at 5°C for a period of 2 weeks. All solid constituents were dissolved.

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

2.9) 98.5 mg of ① were dissolved in 1 ml of THF. The solution was filtered and the solvent was subsequently removed at RT under a high nitrogen stream. 500 µl of H_2O were added to the residue thus obtained. The mixture was stirred at a temperature of

5°C for a period of 1 week. The resulting crystalline residue was filtered off. A mixture of modifications A and B was obtained.

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

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

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

Example 3:

Crystallization experiments were carried out by means of vapour diffusion, in which saturated hydrocarbons and ether as precipitating agents were used. Only in one case was a crystalline precipitate, namely modification B, obtained in this case.

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

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

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

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

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

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

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

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

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

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

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

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

3.13) 200 mg of ① were dissolved in 1 ml of EtOAc. The solution was stored in a saturated cyclohexane atmosphere at RT for a period of 1 week. No precipitate was obtained. The sample was stored at 5°C for a period of 2 weeks. No precipitate was obtained.

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

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

3.16) 200 mg of ① were dissolved in 1 ml of EtOAc. The solution was stored in a saturated pentane atmosphere at RT for a period of 1 week. No precipitate was

obtained. The sample was stored at 5°C for a period of two weeks. No precipitate was obtained.

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

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

Example 4:

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

4.2) 100 mg of ① were dissolved in 0.5 ml of 1,4-dioxane. 2 ml of H_2O were added stepwise until the solution was cloudy and a sticky resin formed. The sample was stored at 5°C overnight. After scratching with a spatula, the resin crystallized out and the crystalline solid was filtered off. Modification B was obtained.

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

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

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

4.6) 100 mg of ① were dissolved in 1 ml of EtOAc. 1 ml of pentane was added stepwise until the solution was cloudy. The sample was stored at 5°C for a period of 1 week. No modification was observed.

4.7) 100 mg of ① were dissolved in 2.5 ml of MeOH. 3 ml of H_2O were added stepwise until the solution was cloudy and a colourless solid precipitated. The sample

was stored at RT for a period of 1 week and the solid obtained was filtered off. A crystalline powder of modification A was obtained.

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

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

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

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

4.12) 100 mg of ① were dissolved in 500 µl of EtOAc. 2 ml of pentane were added stepwise and the mixture was stirred at RT for a period of a few hours. A sticky solid was formed. The sample was stored at 5°C for a period of 3 weeks and the solid obtained was filtered off.

4.13) 100 mg of ① were dissolved in 500 µl of EtOAc. 2 ml of n-hexane were added stepwise and the mixture was stirred at RT for a period of a few hours. A sticky solid was formed. The sample was stored at 5°C for a period of 2 weeks and the solid obtained was filtered off. A crystalline powder of modification B was obtained.

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

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

Example 5:

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

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

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

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

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

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

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

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

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

5.10) The solution obtained according to Example 4.6) was stored at RT in an open vial 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-methylpropyl)phenol showed no modification on slurrying in various solvents. The formation of solvates with the solvents selected could be excluded.

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

6.2) 100 mg of ① were suspended in 500 µl of heptane/TBME. The mixture was stirred at RT for a period of 2 days and the resulting solid was filtered off. Crystalline powder of modification B was obtained.

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

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

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

Example 7:

The preparation of the amorphous modification of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol was attempted by evaporation, lyophilization or melting. All resulting samples of the amorphous modification crystallized within hours.

7.1) 150 mg of ① were dissolved in 3 ml of MeOH. The solvent was removed on the rotary evaporator. A colourless oil remained. The residue was dried under reduced pressure. Modification A was obtained.

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

7.3) 150 mg of ① were dissolved in 2 ml of 1,4-dioxane. The solvent was removed by means of freeze drying (-85°C, 0.5 mbar). A colourless residue remained which crystallized spontaneously before it was possible to carry out a PXRD analysis. Modification B with traces of modification A was obtained.

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

Example 8:

The influence of mechanical stress by grinding using a ball mill (Retsch MM200 type, agate pestle and agate mortar with 5 mm diameter) and also by pressure in the preparation of a tablet was investigated. Although pressure has no influence on the samples in the tabletting, modification A converts to modification B on grinding.

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

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

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

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

Example 9:

9.1) 20.5 mg of modification A and 20.9 mg of modification B were suspended in 200 µl of IPE. The suspension was shaken in an Eppendorf Thermomixer at RT overnight. The solid obtained was filtered off and characterized by means of FT Raman. Modification B was obtained.

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

9.3) 15 mg of modification A and 20.5 mg of modification B were suspended in 1 ml of acetone/H_2O (8:2). The suspension was stirred at 5°C for 3 days. The solid obtained was filtered off and characterized by means of FT Raman. Modification B obtained.

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

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

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

Analytics - XRPD

X-ray powder diffraction (XRPD):

XRPD investigations were carried out using a STOE Stadi P X-ray powder diffractometer in transmission geometry, in which monochromatized $CuK\alpha_1$-radiation was used by means of a germanium monocrystal. D-spacings are calculated from the 2θ values, wherein the wavelength is based on 1.54060 Å. It generally applies that the 2Θ values have an error rate of ± 0.2° in 2Θ. The experimental error in the d-spacings is therefore dependent on the position of the peak.

Modification A

Table 1 shows the peak list of modification A. The uncertainty in the 2Θ values is ± 0.2° in 2Θ, rel. I (or also RI) gives 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

2Θ	rel. I		2Θ	rel. I		2Θ	rel. I		2Θ	rel. I		2Θ	rel. I
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			

The indexing of the diffractogram of form A using the WinXPow Index (Version 2.03) program from STOE & Cie GmbH gave the following lattice constants which are in good agreement with those which were determined in the context of a single crystal structure determination:

Orthorombic, a = 12.92 Å, b = 11.98 Å, c= 8.98 Å, cell volumes 1391 $Å^3$

Modification B

Table 2 shows the peak list of modification B. The uncertainty in the 2Θ values is ± 0.2° in 2Θ, rel. I gives the relative intensity of the respective peak. 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			

2Θ	rel. I		2Θ	rel. I		2Θ	rel. I		2Θ	rel. I		2Θ	rel. I
20.24	15		25.24	5		31.17	4		36.54	4			

The indexing of the diffractogram of form B using the WinXPow Index (Version 2.03) program from STOE & Cie GmbH gave the following lattice constants which are in good agreement with those which were determined in the context of a single crystal structure determination:

Orthorombic, a = 12.54 Å, b = 12.72 Å, c= 9.10 Å, cell volumes 1400 $Å^3$

Modification C

Table 3 shows the peak list of modification C. The uncertainty in the 2Θ values is ± 0.2° in 2Θ, rel. I gives the relative intensity of the respective peak. 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			

Analytics - DSC

Differential Scanning Calorimetry (DSC): equipment names Perkin Elmer DSC 7 or Perkin Elmer Pyris 1. Unless otherwise stated, the samples were weighed into a sealed gold seal. The measurements were carried out under nitrogen stream in a temperature range from -50°C to 250°C at a heating rate of 10°C/min. The temperatures stated in the context of DSC investigations are the temperatures of the peak maxima (peak temperature T_P) unless otherwise stated. Onset temperatures of peaks are referred to as 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

Analytics - FT-Raman spectroscopy

The crystalline modifications A and B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol were characterized in each case with the aid of 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}).

Analytics - TG-FTIR

The crystalline modifications A and B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol were characterized in each case with the aid of thermogravimetric Fourier transform infrared spectroscopy (TG-FTIR).
For this purpose, the corresponding spectra were recorded using a Netzsch thermos-microbalance TG 209 and a Bruker FT-IR spectrometer Vector 22 (aluminium crucible (open or with microopening), nitrogen atmosphere, heating rate 10°C/min, 25-250°C).

The TG-FTIR investigations showed that both modifications decomposed above 160°C.

Analytics - DVS

The crystalline modifications A and B of (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol were characterized in each case by means of a dynamic vapour sorption (DVS). The investigations were recorded in the dynamic mode (5% relative humidity/hour).

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

Analytics – dissolution rate

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

In the first determination, a suspension of modification A or B in water was stirred without taking into account the particle size distribution. Under these conditions, the particle size influences 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 prepared and tablets were prepared for both modifications A and B. The respective form was not influenced by the tabletting, although both samples showed a dissolution rate of 0.003 mg/min cm^2. Investigation of the samples by FT-Raman showed that form A was converted into form B during the determination.

Patentkrav

1. Krystallinsk modifikasjon A av (1 R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol omfattende en røntgendiffraksjonsrefleks ved 15,58±0,20 (2Θ), i tillegg minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående av 28,37±0,20 (2Θ) og 34,45±0,20 (2Θ) og i tillegg minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående 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. Krystallinsk modifikasjon A ifølge krav 1, **karakterisert ved at** den i tillegg omfatter minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående 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. Krystallinsk modifikasjon A ifølge et av kravene 1 eller 2, **karakterisert ved at** den ikke omfatter minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående 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. Krystallinsk modifikasjon A ifølge et av kravene 1-3, **karakterisert ved at** den i DSC utviser en endotermi i området fra 75 til 84 °C.

5. Fremgangsmåte for fremstilling av den krystallinske modifikasjonen A ifølge et av kravene 1-4, omfattende trinnene
(a) å konsentrere en løsning av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol, der løsemidlet er metanol, etanol, 1-propanol, 2-propanol, eddikester, aceton, etylmetylketon, dietyleter, tert-butylmetyleter, 1,4-dioksan, tetrahydrofuran, acetonitril, diklormetan, toluen, dimetylformamid eller dimetylsulfoksid, og
(b) å lagre resten oppnådd ifølge trinn (a) ved en temperatur på >5 °C.

6. Krystallinsk modifikasjon B av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol omfattende en røntgendiffraksjonsrefleks ved 29,06±0,20 (2Θ), i

tillegg minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående av 19,50±0,20 (2Θ), 35,49±0,20 (2Θ) og 40,01±0,20 (2Θ) og i tillegg minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående 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).

7. Krystallinsk modifikasjon B ifølge krav 6, **karakterisert ved at** den i tillegg omfatter minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående 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).

8. Krystallinsk modifikasjon B ifølge et av kravene 6 eller 7, **karakterisert ved at** den ikke omfatter minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående 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).

9. Krystallinsk modifikasjon B ifølge et av kravene 6-8, **karakterisert ved at** den i DSC utviser en endotermi i området fra 87-93 °C.

10. Fremgangsmåte for fremstilling av den krystallinske modifikasjonen B ifølge et av kravene 6-8, omfattende trinnene

(a) å konsentrere en løsning av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol, der løsemidlet er metanol, etanol, 1-propanol, 2-propanol, eddikester, aceton, etylmetylketon, dietyleter, tert-butylmetyleter, 1,4-dioksan, tetrahydrofuran, acetonitril, diklormetan, toluen, dimetylformamid eller dimetylsulfoksid, og

(b1) å lagre resten oppnådd ifølge trinn (a) ved en temperatur på ≤5 °C, eller

(b2) å suspendere resten oppnådd ifølge trinn (a) og røre denne suspensjonen.

11. Fremgangsmåte for fremstilling av den krystallinske modifikasjonen B ifølge et av kravene 6-8, omfattende trinnet

(a) å utfelle (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol fra løsning, der løsemidlet er metanol, etanol, 1-propanol, 2-propanol, eddikester, aceton,

etylmetylketon, dietyleter, tert-butylmetyleter, 1,4-dioksan, tetrahydrofuran, acetonitril, diklormetan, toluen, dimetylformamid eller dimetylsulfoksid.

12. Krystallinsk modifikasjon C av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol omfattende minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående av 10,93±0,20 (2Θ), 12,41±0,20 (2Θ) og 26,22±0,20 (2Θ), i tillegg minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående av 8,10±0,20 (2Θ), 11,83±0,20 (2Θ), 26,54±0,20 (2Θ) og 26,72±0,20 (2Θ) og i tillegg minst én røntgendiffraksjonsrefleks valgt fra gruppen bestående 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).

13. Krystallinsk modifikasjon C ifølge krav 12, **karakterisert ved at** den ved DSC-undersøkelser har en endotermi med topptemperatur ved 75-84 °C og/eller en endotermi med topptemperatur ved 87-93 °C.

14. Fremgangsmåte for fremstilling av den krystallinske modifikasjonen C ifølge et av kravene 12 eller 13, omfattende trinnene

(a) å riste en suspensjon inneholdende den krystallinske modifikasjonen A og/eller den krystallinske modifikasjonen B av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol, der suspensjonsmediet er metanol eller toluen,

og

(b) å fordampe suspensjonsmediet i luftstrøm.

15. Farmasøytisk sammensetning omfattende en krystallinsk modifikasjon av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol ifølge ett eller flere av kravene 1-4, 6-9 og 12-13 samt en farmasøytisk akseptabel bærer.

16. Farmasøytisk doseringsform omfattende en farmasøytisk sammensetning ifølge krav 15.

17. Krystallinsk modifikasjon av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol ifølge ett eller flere av kravene 1-4, 6-9 og 12-13 som legemiddel.

18. Krystallinsk modifikasjon av (1R,2R)-3-(3-dimetylamino-1-etyl-2-metyl-propyl)-fenol ifølge ett eller flere av kravene 1-4, 6-9 og 12-13 for anvendelse i bekjempelse av smerte.

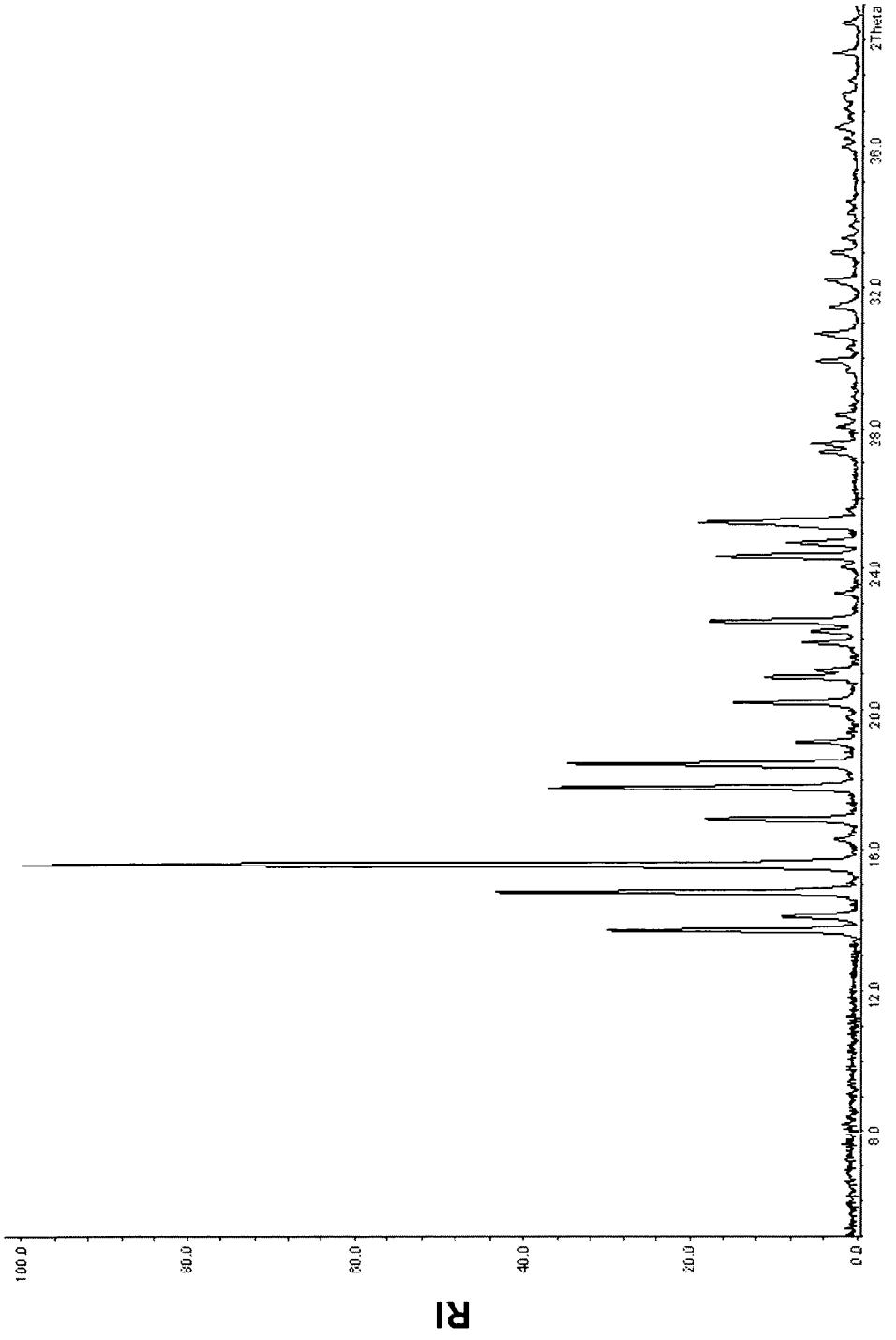

Fig.1

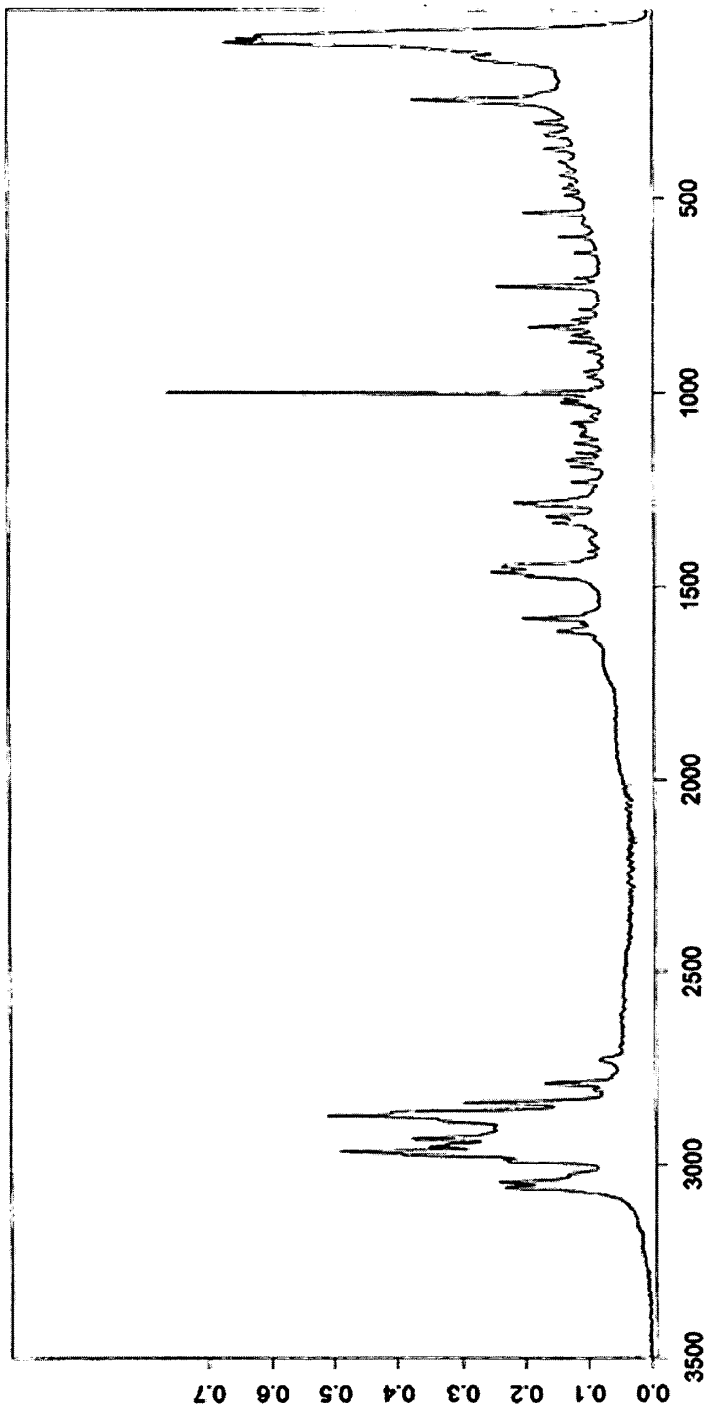

Fig. 2

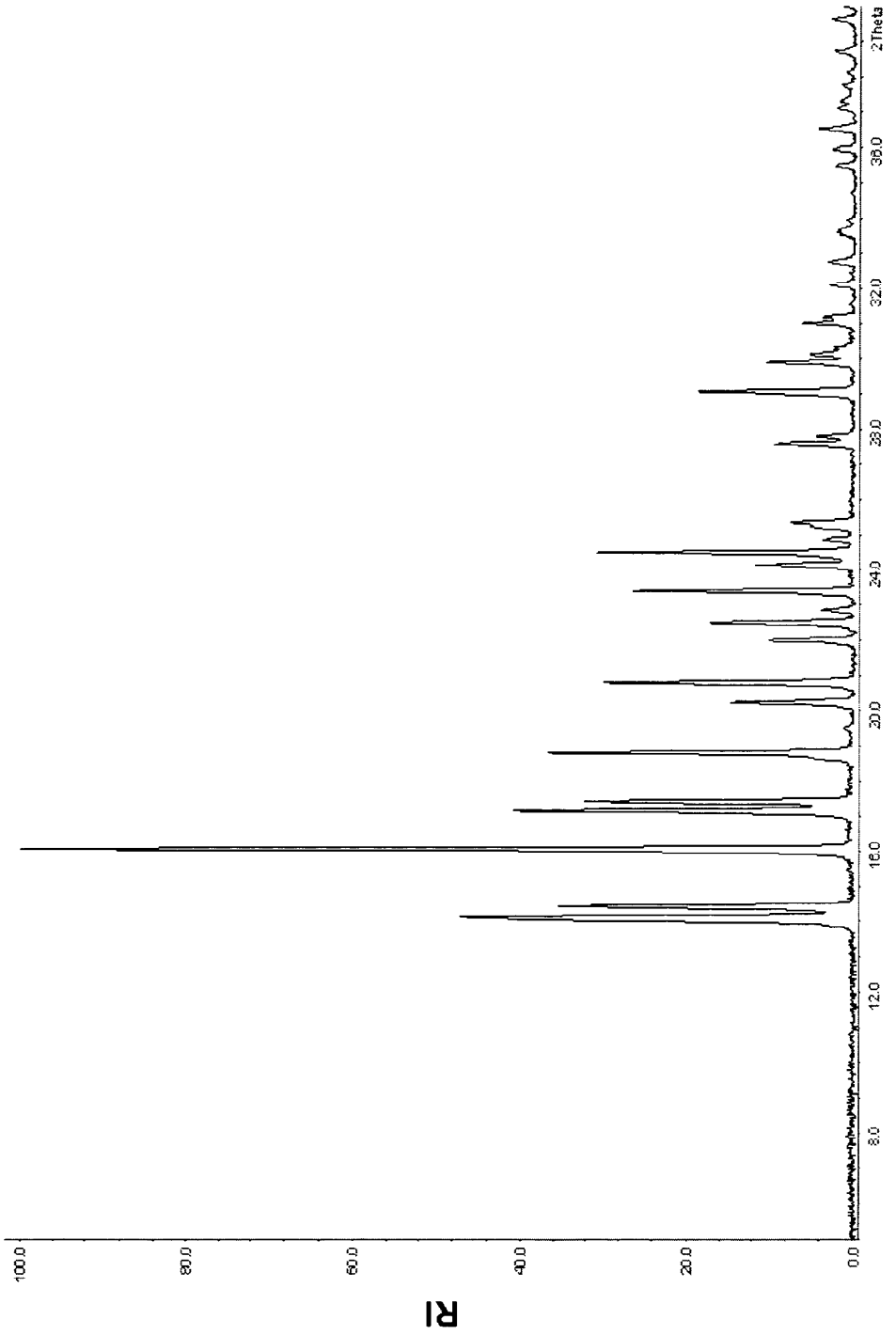

Fig. 3

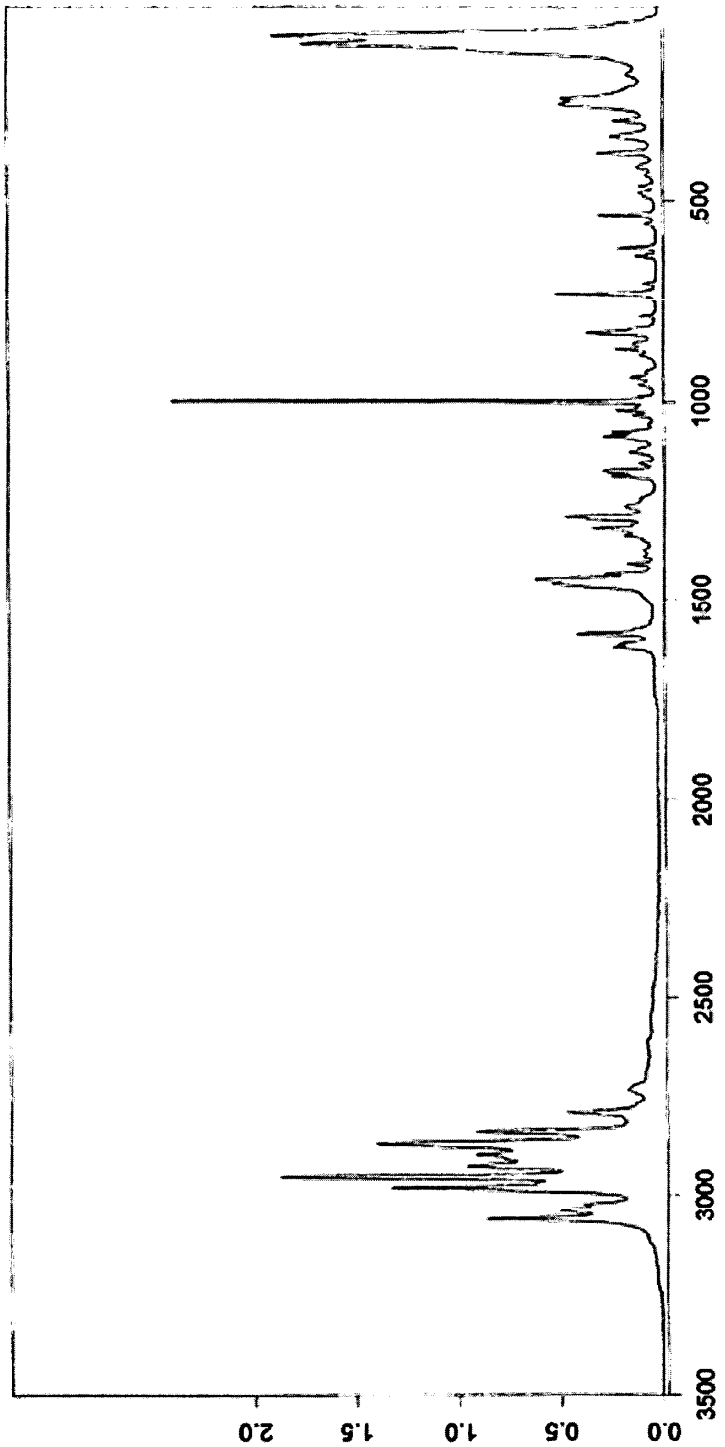

Fig. 4

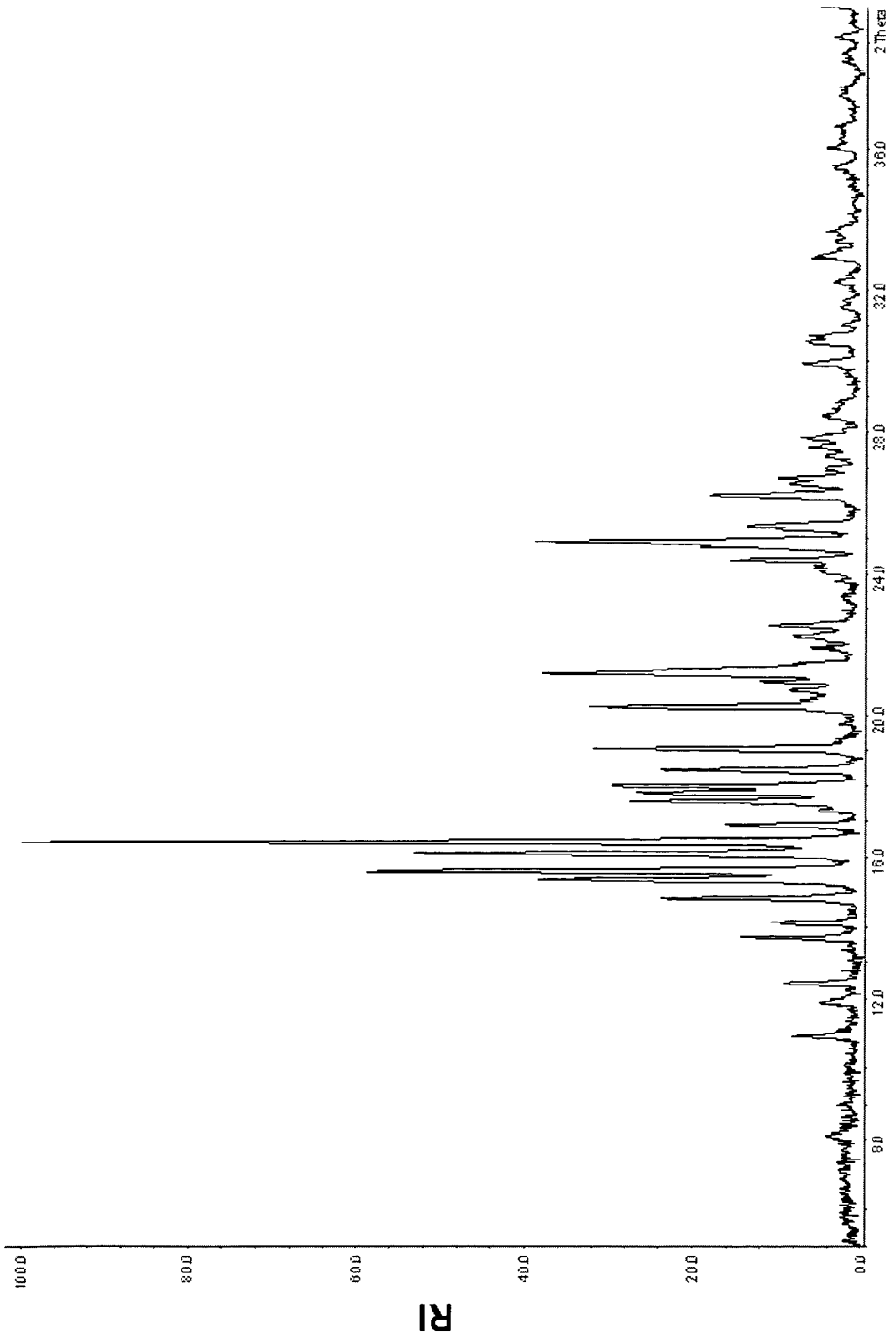

Fig. 5