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Burdwan 713 101 (IN). **BHAR, Chandan** [IN/IN]; Flat No. A-12, Sai Vihar Residency, Pashan-SUS ROAD, PASHAN, PUNE 411 021 (IN).

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(74) Agent: **FRANKS, Robert A.**; Dr. Reddy's Laboratories, Inc., Patent Prosecution Group, 200 Somerset Corporate Boulevard, 7th floor, Bridgewater, New Jersey 08807 (US).

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(71) Applicants (for all designated States except US): **DR. REDDY'S LABORATORIES LTD.** [IN/IN]; 7-1-27 Ameerpet, Hyderabad 500 016 (IN). **DR. REDDY'S LABORATORIES, INC.** [US/US]; 200 Somerset Corporate Boulevard, 7th floor, Bridgewater, New Jersey 08807 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ISLAM, Aminul** [IN/IN]; Ward No. 15, Jonaki Path, College Nagar, P. O. Bidyapara, Dist: Dhubri, Assam 783 324 (IN). **SAHADEV, Katam** [IN/IN]; Plot No. 182A, Road No. 6, R.K.H. Colony, Near Dr. A. S. Rao Nagar, ECIL-Post, Hyderabad 500 062 (IN). **REDDY, Madadi Vijaypal** [IN/IN]; C/O: Raji reddy., K H. No: 2-19-82/3, East Kalyanpuri, Uppal, Hyderabad 500 039 (IN). **KULKARNI, Raturaj Vijay** [IN/IN]; C/O V. G. Kulkarni, Near Nahata College, Mahesh nagar, Bhusawal, Dist: Jalgaon 425 201 Maharashtra (IN). **LAYEK, Mohammed, Mohosin** [IN/IN]; H. No.-168, Rasik Pur (Layek para),

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(54) Title: POLYMORPHIC FORM OF NARATRIPTAN HYDROCHLORIDE

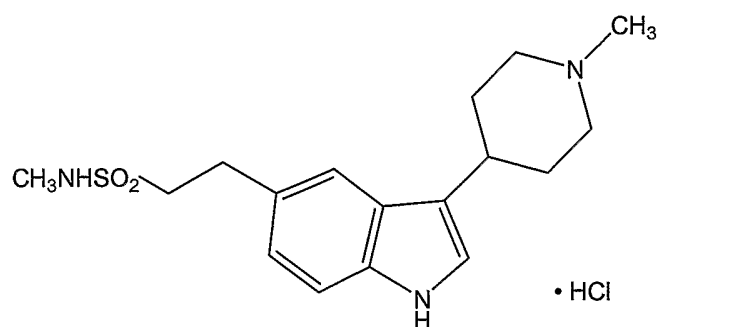
(57) Abstract: Naratriptan hydrochloride having a new crystalline form is prepared by providing a solution of naratriptan hydrochloride in a polar solvent, cooling the solution to temperatures about 0 to 20°C to form crystals, and isolating the naratriptan hydrochloride.

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POLYMORPHIC FORM OF NARATRIPTAN HYDROCHLORIDE

INTRODUCTION TO THE INVENTION

5 The present invention relates to a new crystalline form of N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride having the formula I. The present invention also relates to a process for preparing the crystalline form and a pharmaceutical composition comprising the crystalline form.



10 The compound N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride is also known by the name "natriptan hydrochloride." Naratriptan hydrochloride is the active ingredient in pharmaceutical products being sold using the trademark AMERGE, for treating migraine. The AMERGE products are tablets for oral administration, containing either 1.11 or 2.78 mg of naratriptan hydrochloride, equivalent respectively to 1 and 2.5 mg of naratriptan.

20 The new crystalline form of N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride of this invention is useful in the treatment of migraine.

25 Some chemical substances exhibit polymorphism. The term polymorphism means that the substances exist in more than one form, such as one or more different crystalline forms, a noncrystalline (amorphous) form, solvates containing stoichiometric or nonstoichiometric amounts of a solvent, etc. The subject of polymorphism has become very interesting in the field of pharmaceuticals, since different polymorphic forms tend to have different stabilities, solubilities, and

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processing properties, and frequently one of polymorphic forms of a given drug may exhibit superior bioavailability and consequently show a higher activity when compared to the other polymorphs.

The existence of multiple crystalline and non crystalline solid forms of a substance also causes complications for development of pharmaceutical products, because pharmaceutical substances are required to have consistent properties and must be reproducibly manufactured in order to satisfy regulatory requirements. Polymorphism has been discussed extensively in the art, for example in the recent article by A. Goho, "Tricky Business," *Science News*, Vol. 166, pages 122-123, August 21, 2004. This article discusses the difficulty of identifying polymorphs, the present inability to predict either the existence of, or potential number of, polymorphic forms for a given compound, and the difficulties that polymorphism present to the pharmaceutical industry.

The compound N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride is discussed in U.S. Patents 4,997,841, 5,066,660, and US 4,994,483 but there is no mention of any possibility that the compound exists in different polymorphic forms. The U.S. Food and Drug Administration recommends that applicants for drug product registration investigate whether the drug substance can exist in polymorphic forms; this is discussed in the agency's draft guidance for industry entitled "ANDAs: Pharmaceutical Solid Polymorphism," which was published in December 2004. Therefore, it is always desirable to identify as many polymorphic forms as possible, in connection with product development.

SUMMARY OF THE INVENTION

In one aspect the invention provides naratriptan hydrochloride having an X-ray diffraction pattern substantially in accordance with Fig. 1.

In another aspect, the invention provides naratriptan hydrochloride having a differential scanning calorimetry curve substantially in accordance with Fig. 2

In a further aspect, the invention provides naratriptan hydrochloride having an infrared absorption spectrum substantially in accordance with Fig. 3.

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In a still further aspect, the invention provides a process for preparing a crystalline form of naratriptan hydrochloride. comprising:

- (i) providing a solution of naratriptan hydrochloride in a polar solvent;
- (ii) cooling the solution to temperatures about 0 to 20°C to form crystals;
- 5 and,
- (iii) isolating the crystalline form of naratriptan hydrochloride.

BRIEF DESCRIPTION OF THE DRAWINGS

10 Fig. 1 is an X-ray powder diffraction pattern of the new crystalline form of naratriptan hydrochloride.

Fig. 2 is a differential scanning calorimeter thermogram of the new crystalline form of naratriptan hydrochloride.

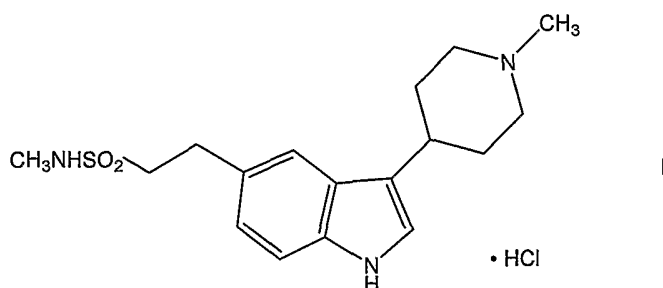
15 Fig. 3 is a Fourier transform infrared absorption spectrum of the new crystalline form of naratriptan hydrochloride.

Fig. 4 is a table showing the X-ray powder diffraction peaks and calculated d-values for the new crystalline form of naratriptan hydrochloride.

DETAILED DESCRIPTION

20

According to one aspect of the present invention, there is provided a new crystalline form of N-methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride having the formula I.



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The new crystalline form is characterized by the following data, obtained from a representative sample:

5 X-ray powder diffraction major peaks: 7.3, 9.2, 14.2, 16.6, 17.3, 17.6, 18, 18.4, 19.7, 21.1, 22.9, 23.1, 23.6, 25, and 27.8° 2 θ (a representative pattern being shown as Figure 1).

Differential scanning calorimetry: an endotherm about 249°C (a representative curve being shown as Figure 2)

10 Infrared absorption (in KBr) peaks at about: 523, 582, 586, 638, 694, 763, 779, 807, 858, 889, 923, 955, 959, 1067, 1109, 1158, 1232, 1274, 1315, 1349, 1404, 1429, 1452, 1474, 1543, 1577, 1652, 2361, 2559, 2693, 2965, 3228 cm⁻¹ (a representative spectrum being shown as Figure 3)

15 The X-ray powder diffraction ("XRD") pattern was obtained using Cu K-alpha 1 radiation. The instrument was equipped with fine focus X-ray tube. The tube voltage and amperage were set at 50 KV and 34 mA respectively. The divergence and scattering slits were set at 1/2 degree and receiving slit at 0.15 mm. Diffracted radiation was detected by a scintillation counter detector, and a θ to 2 θ continuous scan at 3 degrees/minute from 3 to 45 degrees was used. A standard was analyzed to check the instrumental alignment, then the data were collected and analyzed using samples prepared for analysis by placing them in a standard sample holder

20 From the XRD pattern, d-values were calculated, as summarized in Fig. 4.

Differential scanning calorimetry ("DSC") was performed using a Shimadzu DSC-50 calorimeter. The sample (about 2.5 mg) was placed in an aluminum container and covered with a lid, which was not crimped. The sample was equilibrated and heated at a rate of 10°C per minute under a nitrogen atmosphere.

25 The crystalline form was also characterized by its Fourier transform infrared ("IR") spectrum in the solid state as a potassium bromide dispersion using a Perkin-Elmer 1650 Fourier transform infrared spectrophotometer.

30 It is to be understood that the XRD patterns, IR spectra and DSC curves reported herein, while reported as absolute numbers in tables and absolute positions in the figures, are intended to include the normal amount of positional variation due to experimental error, operator error, differences in equipment, technique, packing,

contamination, and the like. In general, each of the XRD values can show a variation of $\pm 0.2^\circ$. However, based on these techniques, particularly when two or more of them are used in conjugation, and using the overall spectrum and /or patterns reported in the figures, one of ordinary skill in this art will be able to identify whether
5 or not a compound is the new crystalline form of naratriptan hydrochloride in accordance with this invention.

For example, it should be kept in mind that slight variations in the observed 2θ angles values are expected, based on the specific diffractometer employed, analyst technique, and the sample preparation technique. More variation is expected for the
10 relative peak intensities, which are affected by particle sizes of the sample. Thus, identification of the exact crystalline form of a compound should be based primarily on observed 2θ angles with lesser importance attributed to relative peak intensities.

According to another feature of the present invention, there is provided a process for the preparation of the new crystalline form of N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethansulfonamide hydrochloride of the formula I, having the
15 characteristics described above, a representative embodiment comprising:

- (i) dissolving N-Methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethansulfonamide hydrochloride in a polar solvent such as methanol, ethanol, propanol, isopropanol, butanol, water, or mixtures of any two or more thereof;
- 20 (ii) crystallizing at a temperature about 0 to 10°C; and
- (iii) recovering the crystalline form product.

The starting compound can be dissolved at an elevated temperature, up to the boiling point of the solvent, to maximize the solution concentration. However, the temperature chosen for dissolving the compound must not be so high that the
25 compound degrades.

As will be appreciated by those skilled in the art, additional steps can be performed to increase product yield, and/or to enhance purity of the product. Depending on the volume of solvent used for a given quantity of starting compound, a greater or lesser amount of solvent will frequently be removed, such as by
30 evaporation, to increase solute concentration and minimize the amount of solute that remains in solution at the crystallization temperatures. Care should be taken to avoid

evaporation temperatures that affect stability of the naratriptan hydrochloride, and in most instances the evaporation temperatures can be made lower by applying a vacuum during the procedure.

Also, it sometimes will be desirable to decrease the impurity level of the solution before crystallization, such as by absorption of the impurities using an absorbent such as activated charcoal. The charcoal can be mixed with the solution, and then removed by filtration or other separation means, or the solution can be passed through a stationary bed of the charcoal.

The time for crystallization will vary, depending on the solution concentration, the temperature chosen, and the use of techniques such as seeding. Selection of the crystallization time for optimal yields can be determined by simple experimentation and is well within the ordinary skill in the art.

The term "pharmaceutical composition" means a composition suitable for human pharmaceutical use, comprising at least one active ingredient and at least one pharmaceutical excipient.

The pharmaceutical composition containing the crystalline form of naratriptan hydrochloride may be in the forms normally employed, such as: tablets, capsules, powders, syrups, solutions, suspensions and the like, optionally containing flavoring agents, sweeteners, etc., in suitable solid or liquid carriers or diluents; and in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 0.5 to 25 %, preferably 0.5 to 15 % by weight of active ingredient, the remainder of the composition being pharmaceutically acceptable excipients.

The crystalline form of the formula I as defined above is clinically administered to mammals, including man, via either oral, nasal, pulmonary, transdermal, parenteral, rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, or intranasal means. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection.

Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active ingredient will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired

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dosage. Thus, for oral administration, the polymorphic form can be combined with a suitable solid or liquid carrier or diluents to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavorants, sweeteners, other excipients and the like. For parental administration, the crystalline form can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds.

10 Aqueous solutions with the active ingredient dissolved in polyhydroxylated castor oil may also be used for injectable solutions. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For nasal administration, the preparation may contain the crystalline form of the present invention dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, such as propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin or preservatives such as parabenes.

Tablets, dragees or capsules having talc and / or a carbohydrate carried binder or the like are particularly suitable for any oral application. Preferably, carriers for tablets, dragees or capsules include lactose, corn starch and / or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet production method is exemplified using the following ingredients:

25	1) Active ingredient	1.1 g
	2) Lactose	123.9 g
	3) Corn starch	30 g
	4) Carboxymethyl cellulose	44 g
	5) Magnesium stearate	1 g

30 The ingredients 1 through 3 are uniformly blended with water and granulated after drying under reduced pressure. The ingredient 4 and 5 are mixed well with the

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granules and compressed by a tableting machine to prepare 1000 tablets, each containing 1.1 mg of the active ingredient.

Another typical tablet production method is exemplified using the following ingredients:

5	1) Active ingredient	2.78 g
	2) Calcium phosphate	117.22 g
	3) Lactose	40 g
	4) Corn starch	35 g
	5) Polyvinyl pyrrolidone	3.5 g
10	6) Magnesium stearate	1.5 g

The ingredients 1-4 are uniformly moistened with an aqueous solution of ingredient 5 and granulated after drying under reduced pressure. Ingredient 6 is added and granules are compressed by a tableting machine to prepare 1000 tablets, each containing 2.78 mg of the active ingredient.

15 The compound N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride can be prepared by any of a number of processes, and the present invention is not dependent on a particular synthetic method. Further, any polymorphic form of the compound is suitable for use to prepare the crystalline form of this invention. The crystallization of the polymorphic form of this invention
20 can be performed as a final step in a synthesis of the compound, and it is not always necessary to isolate a product having another polymorphic form before performing the crystallization.

Certain aspects of the invention are described in the following example, which is being provided only for purposes of illustration and is not to be construed as
25 limiting the scope of the invention in any manner.

EXAMPLE

The crystalline form of naratriptan hydrochloride was prepared by dissolving
30 90 grams of N-Methyl-3-(1-methyl-4-piperidiny)-1H-indole-5-ethanesulfonamide hydrochloride in a mixture of 1080 ml of methanol and 1620 ml of water. 9 grams of

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activated charcoal were added and the mixture was stirred for 60 to 90 minutes at a temperature 50 to 60°C, then filtered through a celite bed at 40 to 50°C to remove the charcoal. The bed was washed with 200 ml of a 2:3 mixture of methanol and water. The solution was concentrated under reduced pressure at a temperature of 40 to 50°C to a volume of 450 to 500 ml . The solution was cooled to a temperature 5 to 10°C and stirred for 40 to 60 minutes. Solids were isolated by filtration and washed with 180 ml of methanol, then dried in a vacuum oven under 500 to 600 mm Hg pressure for 3 to 5 hours at a temperature of 50 to 60°C to give 80 grams of the crystalline form of N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide hydrochloride having the XRD pattern of Fig. 1, the DSC curve of Fig. 2, and the infrared absorption spectrum of Fig. 3.

The table of Fig. 4 was prepared to summarize the data from the XRD pattern, and includes calculated d-spacing values for the new crystalline form.

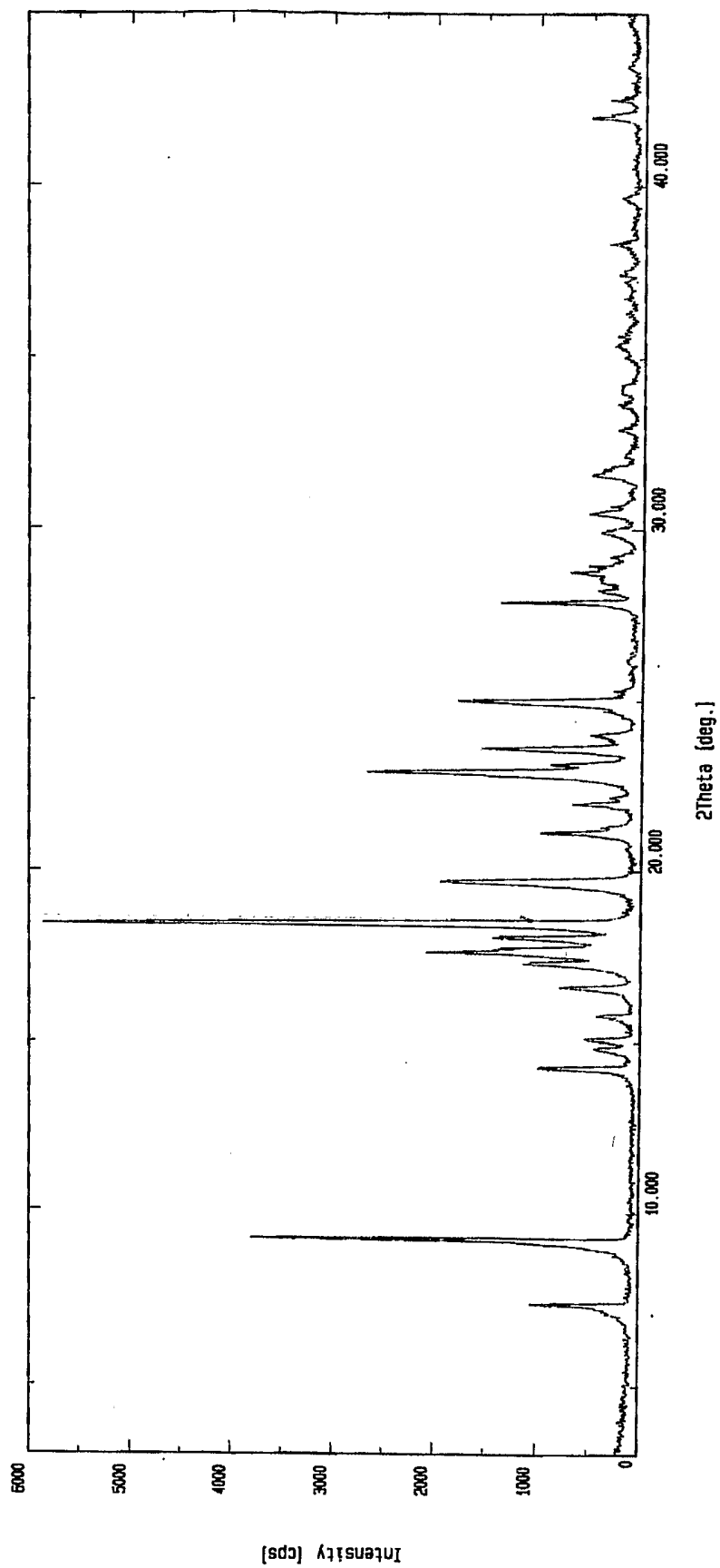
CLAIMS:

1. Naratriptan hydrochloride having an X-ray diffraction pattern substantially in accordance with Fig. 1.
2. The naratriptan hydrochloride according to claim 1, having X-ray powder diffraction comprising peaks at about 7.3, 9.2, 14.2, 16.6, 17.3, 17.6, 18, 18.4, 19.7, 21.1, 22.9, 23.1, 23.6, 25, and $27.8 \pm 0.2^\circ 2\theta$.
3. Naratriptan hydrochloride having a differential scanning calorimetry curve substantially in accordance with Fig. 2
4. Naratriptan hydrochloride having an infrared absorption spectrum substantially in accordance with Fig. 3.
5. A process for preparing naratriptan hydrochloride according to claim 1. comprising:
 - (i) providing a solution of naratriptan hydrochloride in a polar solvent;
 - (ii) cooling the solution to temperatures about 0 to 20°C to form crystals;and,
 - (iii) isolating the naratriptan hydrochloride.
6. The process according to claim 5, wherein the polar solvent comprises an alcohol.
7. The process according to claim 5, wherein the polar solvent comprises methanol.
8. The process according to claim 5, wherein the solvent comprises a mixture of methanol and water.

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9. A pharmaceutical composition comprising naratriptan hydrochloride according to claim 1, and at least one pharmaceutical excipient.
10. A pharmaceutical composition comprising naratriptan hydrochloride prepared according to claim 5, and at least one pharmaceutical excipient.

FIG. 1



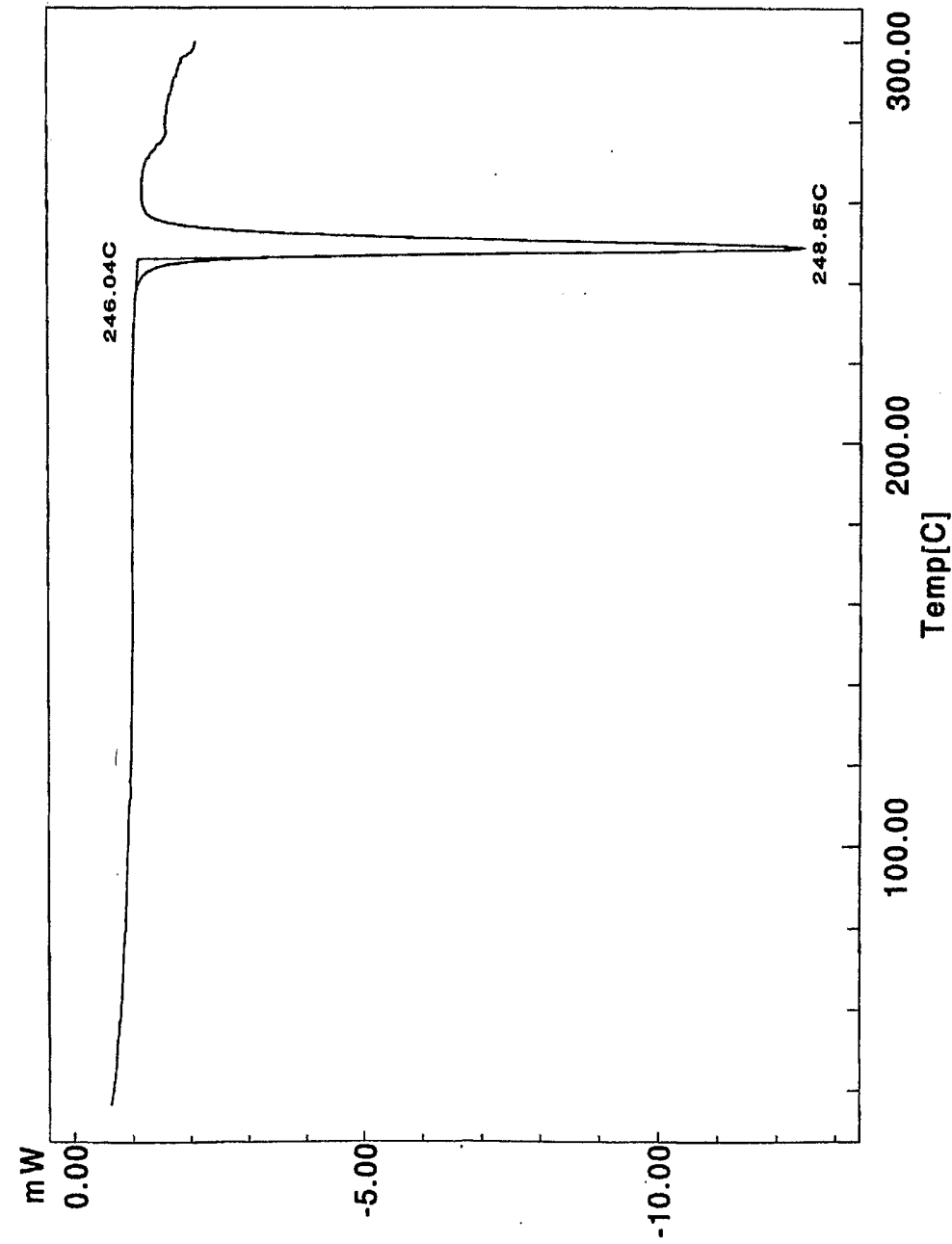


FIG. 2

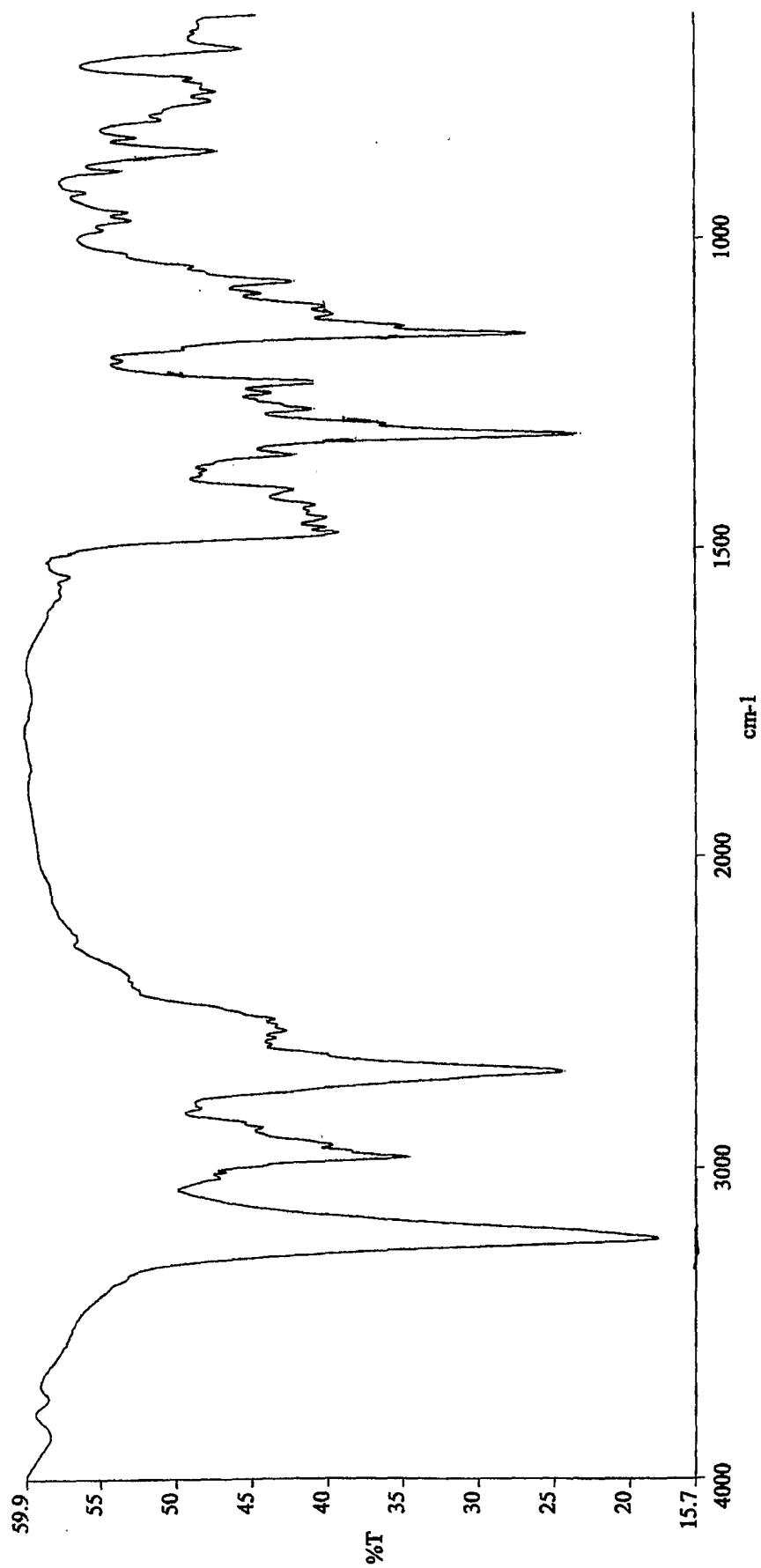


FIG. 3

FIG. 4

Peak No.	2Theta	FWHM	d-value	Intensity	I/Io	Peak No.	2Theta	FWHM	d-value	Intensity	I/Io
1	7.340	0.118	12.0938	957	17	31	32.900	0.141	2.7201	138	2
2	9.180	0.118	9.6255	3555	63	32	33.640	0.141	2.6620	127	2
3	14.220	0.165	6.2233	930	16	33	34.200	0.353	2.6196	134	2
4	14.800	0.165	5.9806	366	6	34	35.040	0.118	2.5587	107	2
5	15.080	0.165	5.8702	463	8	35	35.400	0.165	2.5335	171	3
6	15.780	0.118	5.5114	346	6	36	36.740	0.118	2.4442	116	2
7	16.580	0.141	5.3424	688	12	37	37.240	0.141	2.4125	110	2
8	17.280	0.165	5.1275	1023	18	38	37.460	0.118	2.3988	123	2
9	17.580	0.118	5.0407	1949	34	39	38.300	0.118	2.3481	220	4
10	18.020	0.141	4.9186	1339	24	40	39.560	0.282	2.2707	140	2
11	18.440	0.165	4.8075	5657	100	41	41.960	0.118	2.1514	452	8
12	19.560	0.188	4.5118	1871	33	42	42.480	0.118	2.1262	239	4
13	21.120	0.118	4.2031	927	16						
14	21.980	0.141	4.0405	514	9						
15	22.880	0.141	3.8836	2584	46						
16	23.140	0.118	3.8406	703	12						
17	23.580	0.165	3.7699	1359	24						
18	24.000	0.141	3.7048	412	7						
19	24.960	0.165	3.5645	1662	29						
20	25.320	0.118	3.5146	128	2						
21	27.660	0.141	3.1997	1133	20						
22	28.220	0.141	3.1597	345	6						
23	28.500	0.165	3.1293	321	6						
24	28.720	0.118	3.1058	526	9						
25	28.920	0.118	3.0848	395	7						
26	29.200	0.141	3.0558	217	4						
27	29.920	0.235	2.9839	327	6						
28	30.480	0.165	2.9304	439	8						
29	31.580	0.141	2.8307	400	7						
30	31.800	0.118	2.8117	230	4						