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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| (51) International Patent Classification 5 : | | (11) International Publication Number: |
|---|---|---|
| C07D 498/08, A61K 31/495<br>// (C07D 498/08, 307/00, 267/00) | A1 | WO 92/00302 |
| | | (43) International Publication Date: 9 January 1992 (09.01.92) |

(21) International Application Number: PCT/EP91/01036

(22) International Filing Date: 5 June 1991 (05.06.91)

(30) Priority data:
90112458.6 29 June 1990 (29.06.90) GB

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(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.

**Published**
*With international search report.*

(54) Title: PURE CRYSTALLINE FORM OF RIFAPENTINE

(57) Abstract

The present invention relates to the preparation of a new pure crystalline form of rifapentine, to the new pure crystalline form as such and to pharmaceutical formulations containing it.

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# PURE CRYSTALLINE FORM OF RIFAPENTINE.

The present invention relates to the preparation of a new pure crystalline form of rifapentine, to the new pure crystalline form as such and to pharmaceutical formulations containing it.

This new pure crystalline form will be called pure Form I or pure polymorphic Form I throughout this description and claims.

Rifapentine is the international non-proprietary name of an antibiotic substance which was disclosed in US Patent 4,002,752 and was found to be particularly useful in the treatment of acute pulmonary infections, see for instance M. Tsukamura et al., Kekkaku (Tuberculosis, Japan), 1986, 61/12, (633-639); P.E. Varaldo et al., Antimicrobial Agents Chemother. (USA), 1985, 27/4, (615-618); Yi Lu et al., Chin. J. Antib. (China), 1987, 12/5, (341-344) and also L.B. Heifets et al, Am. Rev. Respir. Dis 1990; 141, 626-360 which describe the bactericidal activity of rifapentine against Mycobacterium avium.

The rifapentine product which is obtained according to the process of US 4,002,752 is generally a mixture of different solid forms of rifapentine base. These different forms show different stability, formulability and bioavailability characteristics. Generally they are solvates or mixtures of solvates (depending on the "crystallization" solvent or solvents). Also an amorphous form is obtained but no pure crystalline form of rifapentine base was described or produced by this process.

WO 90/00553 describes some hydrohalides of rifapentine in pure crystalline forms.

New and stable forms of rifapentine are still needed to meet the requirements of stability both under normal storage and formulation conditions in order to optimize the preparation, formulation, storage and delivery steps in an accurate, reliable and standardized way. Moreover, a well defined and stable crystalline habit of an active principle is oftentimes a precondition and even a guarantee of a reliable and accurate bioavailability pattern that is not subject to relevant batch to batch variations.

Sometimes also the excessive hygroscopicity of an active ingredient may represent a tricky problem in storage and formulation procedures. The crystalline form of rifapentine that we describe here is not found to be particularly hydroscopic under normal handling and storage conditions.

One object of this invention is therefore a hitherto undisclosed pure crystalline Form I of rifapentine, which is easily and reliably obtained in a pure form according to the process of the invention. With "pure crystalline Form I" it is intended that the described crystalline form is a solid constituted by crystals of rifapentine containing more than 95% of the whole rifapentine present in the sample in the crystalline Form I. Such crystalline pure form does not appear to have been never described or prepared.

This pure crystalline form proves to be stable and not hygroscopic under usual storage conditions and under usual formulation handlings. This stability throughout the formulation and storage process is of importance for a reliable bioavailability of the administered dose.

As mentioned above, another object of the invention is the process for preparing rifapentine

pure crystalline Form I. The starting material of this process is a mixture of crystalline Form I and an ethanol solvate (called SII) which is in turn obtained from a crude or purified preparation of rifapentine which may be in any form including solvates and amorphous forms and their mixtures.

The starting Form I and SII mixture is transformed into pure crystalline Form I according to one of the following procedures:

a) contact with water or water-containing substances or prolonged exposure to a high degree of humidity

b) thermal treatment

Typically, the contact with water is obtained by suspending the mixture in water and then recovering pure crystalline Form I by filtration.

A typical example of water-containing substances is represented by the excipients of a wet granulation process. Also in this case the starting rifapentine material is entirely transformed into crystalline Form I but, of course, it will not be "pure" or easily purifiable but in admixture with the excipients used, which account normally for a large part of the final mixture.

Exposure to a high degree of humidity is typically obtained in a closed vessel or relatively closed vessel with a degree of relative humidity higher than 80% for at least about 24 hours. An exposure for several days to a humidity degree of about 70% does not produce any appreciable change in the starting mixture Form I + SII.

A typical thermal treatment capable of transforming a mixture of Form I and SII into pure

crystalline Form I is represented by a treatment under reduced pressure (e.g. 0.2-0.4 mmHg, 26.6-53.3 Pa) at a temperature of 70-80°C until the transformation is complete. This transformation, under the above conditions, requires about 24-36 h.

In general a thermal treatment of a rifapentine mixture Form I + SII at a temperature between 50° and 130°C at a reduced pressure (in the range of about 0.2-0.4 mmHg) is sufficient to quantitatively transform it in pure Form I. The required time varies from a few days, typically 1 to 3 days, for the lower temperatures to a few minutes, typically 3-10 min, for the highest temperatures.

THE PHYSICAL CHARACTERISTICS OF RIFAPENTINE PURE CRYSTALLINE FORM I ARE THE FOLLOWING:

1. Solid state characterization

Form I appears as anisotropic crystals (birefringence), with an undefined habit.

Crystalline habits and phase transitions are observed with a crystallographic microscope and a Kofler hot stage microscope (HSM).

2. Thermal analysis (DSC-TG) is conducted with a Mettler TA 2000 or a Du Pont 990 thermoanalyzer and with a thermobalance (Fig. 1) and the relative data are reported in Table I. The working conditions are: gas flow $N_2$ 25 ml/min, scan speed 10°C/min, weight of sample about 4 mg.

Form I shows an endothermic peak at 172°C (due to the melting) immediately followed by the decomposition which prevents the heat of melting to be reliably

determined. At 25-110°C a desolvation endotherm, due to imbibition water, occurs.

3. The Infrared spectrum (IR) is recorded with a Perkin Elmer mod. 580 spectrophotometer in nujol mull and is reported in Fig. 2, while the assignment of the main functional bands ($cm^{-1}$) is reported in TABLE II.

TABLE I

| M.P. or Transition temperature , °C | Weight loss, % |
|---|---|
| 25 - 110 * | 4 |
| 172 ** | - |

* Imbibition water

** Melting followed by rapid decomposition

TABLE II

| | |
|---|---|
| Ansa ν OH | 3260 *,3440, 3280 |
| Furanone ν C=O | 1730 |
| Acetyl ν C=O | 1705 |
| Amide ν C=O (amide I) | 1660, 1615 |
| Amide δ NH (amide II) | 1510 |
| Acetyl ν C-O-C | 1250 |

* Narrow band of water

4. X-ray powder diffraction pattern of Form I according to ASTM, obtained with a Philips (PM 1010/77, 1049/01, 4025/10) instrument, radiation $CuK_{alpha}$, is reported in TABLE III and Fig. 3.

TABLE III

Wawe-lenghts: ALPHA 1 = 1.54051 Angström
ALPHA 2 = 1.54433
ALPHA - MEAN = 1.54178

The five strongest reflections are:

| No. | Theta degree | D Angström | Intensity |
|---|---|---|---|
| 1 | 2.95 | 14.98 | 100 |
| 9 | 6.65 | 6.65 | 49 |
| 11 | 7.9 | 5.6 | 43 |
| 7 | 5.575 | 7.93 | 40 |
| 14 | 9 | 4.92 | 34 |

TABLE III

Continued....

| No. | Theta degree | D Angström | Intensity |
|---|---|---|---|
| 1 | 2.95 | 14.98 | 100 |
| 2 | 3.4 | 13 | 28 |
| 3 | 3.85 | 11.48 | 18 |
| 4 | 4.25 | 10.4 | 11 |
| 5 | 4.575 | 9.66 | 24 |
| 6 | 5.075 | 8.71 | 31 |
| 7 | 5.575 | 7.93 | 40 |
| 8 | 6.35 | 6.97 | 9 |
| 9 | 6.65 | 6.65 | 49 |
| 10 | 7.2 | 6.15 | 11 |
| 11 | 7.9 | 5.6 | ≈3 |
| 12 | 8.15 | 5.43 | 15 |
| 13 | 8.375 | 5.29 | 27 |
| 14 | 9 | 4.92 | 34 |
| 15 | 9.4 | 4.72 | 12 |
| 16 | 9.975 | 4.45 | 12 |
| 17 | 10.4 | 4.27 | 16 |
| 18 | 10.95 | 4.05 | 16 |
| 19 | 11.4 | 3.9 | 16 |
| 20 | 11.875 | 3.74 | 19 |
| 21 | 12.275 | 3.62 | 7 |
| 22 | 13 | 3.42 | 4 |
| 23 | 14.55 | 3.06 | 4 |
| 24 | 15.2 | 2.94 | 5 |

As mentioned above, the starting material of the transformation process of the invention is represented by a mixture of rifapentine Form I and a solvate with ethanol (SII) which is conveniently referred to in this application as Form I + SII. This mixture is prepared by treating any forms of rifapentine, such as the solvates or mixtures obtained according to US 4,002,752, by the following procedure:

Rifapentine (any forms) is dissolved in a low boiling solvent, typically methylene chloride, after convenient stirring at room temperature, and preferably at about 30°C. Then ethanol is added to this solution and the volatile phase is partially removed by distilling at ambient pressure until a constant temperature of the mixture (about 75-80°C) is reached. Under these conditions all the low boiling solvent, (typically, methylene chloride) is in practice removed and the suspension that residuates contains the desired mixture rifapentine Form I + SII, which is recovered by filtration and then used as the starting material in the process of the invention.

Preferably, an equal volume of low boiling solvent and ethanol is used and, most preferably, the ratio between rifapentine (any forms) and ethanol is about 1 g per 25 ml. Ethanol is preferably 95% ethanol while the low boiling solvent is any solvent boiling between 20° and 70°C at ambient pressure which is capable of dissolving rifapentine at a temperature between room temperature and 30-35°C.

THE PHYSICAL CHARACTERISTICS OF RIFAPENTINE FORM I + SII ARE REPORTED BELOW:

1. Thermal analysis (DSC-TG) is conducted with a Mettler TA 2000 or a Du Pont 990 thermoanalyzer and with a thermobalance and the relative data are reported in Table IV. The working conditions are: gas flow $N_2$ 25 ml/min; scan speed 10°C/min, weight of sample about 4 mg.

TABLE IV

Thermal parameters of rifapentine FORM I + SII

| M.P. or Transition temperature , °C | Weight loss, % |
|---|---|
| 30°-110°C * | about 3 |
| 140°-160°C ** | about 1.3 |
| 172°C *** | - |

* = imbibition water

** = desolvation of crystallization solvent [EtOH]

*** = melting followed by decomposition

2. Infrared spectrum (IR) is recorded with a Perkin Elmer mod. 580 spectrophotometer in nujol mull; the assignments of the main functional bands ($cm^{-1}$) are reported in TABLE V.

TABLE V

Assignment of the main functional bands ($cm^{-1}$) of rifapentine FORM I + SII

| | |
|---|---|
| Ansa and ethanol ν OH | 3620 *, 3440,3380, 3280, 3120 |
| Furanone ν C=O | 1730 |
| Acetyl ν C=O | 1710, 1700 |
| Amide ν C=O (amide I) | 1680, 1660, 1615 |
| Amide δ NH (amide II) | 1500 |
| Acetyl ν C-O-C | 1250, 1245 |

* Narrow band of water

3. X-ray powder diffraction pattern of Form I + SII according to ASTM, obtained with a Philips (PW 1010/77, 1049/01, 4025/10) instrument, radiation $CuK_{alpha}$, is reported in TABLE VI.

TABLE VI

Wawe-lenghts: ALPHA 1 = 1.54051 Angström
ALPHA 2 = 1.54433
ALPHA - MEAN = 1.54178

The five strongest reflections are:

| No. | Theta degree | D Angström | Intensity |
|---|---|---|---|
| 2 | 2.88 | 15.37 | 100 |
| 1 | 2.7 | 16.36 | 95 |
| 13 | 7.9 | 5.60 | 93 |
| 10 | 6.65 | 6.65 | 83 |
| 7 | 5.1 | 8.67 | 50 |

TABLE VI

Continued....

| No. | Theta degree | D Angström | Intensity |
|---|---|---|---|
| 1 | 2.7 | 16.36 | 95 |
| 2 | 2.88 | 15.37 | 100 |
| 3 | 3.35 | 13.19 | 38 |
| 4 | 3.85 | 11.48 | 17 |
| 5 | 4.15 | 10.65 | 32 |
| 6 | 4.55 | 9.71 | 37 |
| 7 | 5.1 | 8.67 | 50 |
| 8 | 5.5 | 8.04 | 41 |
| 9 | 6.3 | 7.02 | 30 |
| 10 | 6.65 | 6.65 | 83 |
| 11 | 7.05 | 6.28 | 15 |
| 12 | 7.25 | 6.10 | 13 |
| 13 | 7.9 | 5.60 | 93 |
| 14 | 8.15 | 5.43 | 43 |
| 15 | 8.35 | 5.30 | 34 |
| 16 | 8.75 | 5.06 | 27 |

TABLE VI

Continued....

| No. | Theta degree | D Angström | Intensity |
|---|---|---|---|
| 17 | 8.95 | 4.95 | 43 |
| 18 | 9.35 | 4.74 | 12 |
| 19 | 9.36 | 4.74 | 12 |
| 20 | 9.9 | 4.48 | 21 |
| 21 | 10.4 | 4.27 | 17 |
| 22 | 10.75 | 4.13 | 7 |
| 23 | 11.05 | 4.02 | 16 |
| 24 | 11.35 | 3.91 | 22 |
| 25 | 11.65 | 3.81 | 7 |
| 26 | 11.9 | 3.73 | 22 |
| 27 | 12.25 | 3.63 | 7 |
| 28 | 13 | 3.42 | 5 |
| 29 | 13.65 | 3.26 | 5 |
| 30 | 15.15 | 2.95 | 7 |
| 31 | 16.35 | 2.73 | 4 |

A further object of this invention is to provide pharmaceutical dosage forms containing rifapentine pure crystalline Form I. These pharmaceutical dosage forms include oral solid forms such as capsules, tablets, troches, film-coated tablets, sugar-coated tablets, hard gelatin capsules, soft elastic capsules, and the like. These forms can contain the pure crystalline rifapentine Form I in powder form admixed with the usual inert excipients such as binders,

disintegrants, lubricants and preservatives. These additives are essentially the same which can be used in the formulations of similar antibiotics, e.g. rifampicin.

Other pharmaceuticals dosage forms which can be used for either oral administration or external applications include solutions, syrups, suspensions, emulsions and the like. Also in these cases the method and ingredients usually employed for the formulation of similar antibiotics, e.g. rifampicin, can be successfully utilized. Pharmaceutical dosage forms for parenteral administration are also comprised in this particular aspect of the invention. These pharmaceutical dosage forms include preparations suitable for intramuscolar or intravenous administration which optionally can be formulated as dry powder for reconstitution before use.

The rifapentine pure crystalline Form I may be also administered as medicated applications through the skin or various body orifices. Accordingly they are applied to the skin or inserted into body orifices in liquid, semi-solid or solid forms. This implies using pharmaceutical dosage forms like aerosol, ointments and suppositories.

The manufacture of the pharmaceutical dosage forms containing pure rifapentine Form I can be carried out by commonly known procedures, see for instance: Remington's Pharmaceuticals Sciences, 17 Edition, (1985) Mack Publishing Co., East, Pennsylvania 18042.

The above mentioned dosage forms show good long term stability under normal storage conditions.

EXAMPLE 1: Preparation of rifapentine polymorphic mixture Form I + SII (solvate with ethanol)

A suspension of rifapentine (2 g) in methylene chloride ($CH_2Cl_2$) (50 ml) is stirred at 30°C for 1 h until all the powder is solubilized. Then 50 ml of 95% ethanol is added and the solvents are removed by stripping at atmospheric pressure till a constant internal temperature is obtained (75-80°C).

The crystallization of rifapentine is observed at about 60°C. The final volume of the suspension is about 40-50 ml and the residual $CH_2Cl_2$ varies from 1 to 3% (gas-chromatographic determination) while the water content is in the range 2-5%.

Rifapentine is collected by filtration and washed with cold 95% ethanol.

The wet powder is dried in a static drier at 60°C under reduced pressure until a residual ethanol content less than 2% is reached (time required 6-8 hours).

The physical form of the obtained product is determined by microscopy, thermal analysis (DSC-TG), IR spectroscopy and X-ray powder diffraction. The relative data are reported in Tables IV, V and VI.

Evolved gas analysis confirmed that the solvent lost at 140-160°C was ethanol of crystallization.

EXAMPLE 2: Preparation of rifapentine pure crystalline Form I from a water suspension of rifapentine mixture Form I + SII

A suspension of rifapentine polymorphic mixture Form I + SII (1 g), obtained as described above, in about 100 ml of water is stirred for 4 hours at room temperature, than the solid is collected by filtration and washed three times with 10 ml of cold water. After drying under vacuum at 40°C, about 900 mg of rifapentine pure crystalline Form I is obtained as a powder showing small isotropic crystals with a needle habit which was analyzed by microscopy, thermal analysis (DSC-TG), IR spectroscopy and X-ray powder diffraction.

The relative data are reported in Tables I, II and III.

EXAMPLE 3: Preparation of rifapentine pure crystalline Form I by prolonged exposure of rifapentine polymorphic mixture Form I + SII to a high degree of humidity

A sample of rifapentine mixture Form I + SII is kept at room temperature at about 90% of relative humidity for 24 h. Under these conditions a complete transformation into rifapentine pure crystalline Form I is observed as shown by the physical analysis data which are in agreement with those reported above.

EXAMPLE 4: Preparation of rifapentine pure crystalline Form I by thermal treatment of rifapentine polymorphic mixture Form I + SII

When rifapentine mixture Form I + SII (particle size below 10 micrometers) is kept in an oven at a reduced pressure at the temperatures indicated below and for the reported time, its complete transformation into rifapentine pure crystalline Form I occurs.

| Pressure | Temperature (°C) | Time |
|---|---|---|
| 0.2-0.4 mmHg | 50 | 2-3 days |
| (26.6-53.3 Pa) | 70-80 | 36 h |
| | 100 | 6-10 h |
| | 130 | 5-10 min |

EXAMPLE 5: Physical stability of rifapentine pure crystalline Form I

a) Humidity

When rifapentine pure crystalline Form I is kept at room temperature at about 70% of relative humidity for 1 week the original state is maintained and no crystal modification occurs. The degree of crystallinity of Form I remains unchanged under these storage conditions.

a) Grinding

When a sample of rifapentine pure crystalline Form I is ground in a mortar or with a ballmill, the crystalline structure is broken and amorphous rifapentine is then recovered.

However, when Fitzmill or air-jet micronization is used, rifapentine pure crystalline Form I is recovered with a smaller particle size but without any significant change in its crystallinity.

EXAMPLE 6: Physical stability of rifapentine pure crystalline Form I during tablets formulation

Since physical processing can alter the crystallinity of a substance, a study was undertaken to monitor the crystallinity of rifapentine Form I in the different steps of the production of tablets.

Samples were taken during the granulation, drying, milling, blending, and tabletting process steps and their physical properties were evaluated by

DSC-TG, IR spectroscopy and X-ray powder diffraction. The results confirm that rifapentine remains in Form I throughout all of the process steps and the degree of crystallinity is virtually the same for all samples.

Tablets containing rifapentine pure crystalline Form I are currently monitored for possible changes in the degree of crystallinity on long-term stability studies. The results shows that the pure crystalline Form I in these tablets is stable and there is no change in the degree of crystallinity after 1 year at 20°C or 35°C or at 35°C and 75% relative humidity. No chemical changes were detected under the same storage conditions.

CLAIMS

1. Rifapentine pure crystalline Form I having the following characteristics:

a) Solid state characterization

Form I appears as anisotropic crystals (birefringence), with an undefined habit;

b) Thermal analysis (DSC-TG) is conducted with a Mettler TA 2000 or a Du Pont 990 thermoanalyzer and with a thermobalance (Fig. 1) and the relative data are reported in Table I; The working conditions are: gas flow $N_2$ 25 ml/min, scan speed 10°C/min, weight of sample about 4 mg,

Form I shows an endothermic peak at 172°C (due to the melting) immediately followed by decomposition which prevents the heat of melting to be reliably determined; at 25-110°C a desolvation endotherm, due to imbibition water, occurs;

c) The Infrared spectrum (IR) is recorded with a Perkin Elmer mod. 580 spectrophotometer in nujol mull and is reported in Fig. 2, while the assignment of the main functional bands ($cm^{-1}$) is reported in TABLE II;

TABLE I

| M.P. or Transition temperature , °C | Weight loss, % |
|---|---|
| 25 - 110 * | 4 |
| 172 ** | - |

* Imbibition water

** Melting followed by rapid decomposition

TABLE II

| | |
|---|---|
| Ansa ν OH | 3260 *,3440, 3280 |
| Furanone ν C=O | 1730 |
| Acetyl ν C=O | 1705 |
| Amide ν C=O (amide I) | 1660, 1615 |
| Amide δ NH (amide II) | 1510 |
| Acetyl ν C-O-C | 1250 |

* Narrow band of water

d) X-ray powder diffraction pattern of Form I according to ASTM, obtained with a Philips (PM 1010/77, 1049/01, 4025/10) instrument, radiation $CuK_{alpha}$, is reported in TABLE III and Fig. 3

TABLE III

Wawe-lenghts: ALPHA 1 = 1.54051 Angström
ALPHA 2 = 1.54433
ALPHA - MEAN = 1.54178

The five strongest reflections are:

| No. | Theta degree | D Angström | Intensity |
|---|---|---|---|
| 1 | 2.95 | 14.98 | 100 |
| 9 | 6.65 | 6.65 | 49 |
| 11 | 7.9 | 5.6 | 43 |
| 7 | 5.575 | 7.93 | 40 |
| 14 | 9 | 4.92 | 34 |

2. A process for preparing the compound of claim 1 which comprises:

a) contacting rifapentine Form I + SII with water or a water-containing substance or exposing to a high degree of humidity, or alternatively

b) subjecting rifapentine Form I + SII to thermal treatment.

3. A process according to claim 2 wherein the contact with water is obtained by suspending rifapentine Form I + SII in water.

4. A process according to claim 2 wherein the exposure to a high degree of humidity is obtained by exposing rifapentine Form I + SII to a relative humidity higher than 80% for at least 24 h.

5. A process according to claim 2 wherein the thermal treatment is represented by the treatment under reduced pressure of rifapentine Form I + SII at a temperature between 50° and 130°C.

6. A process according to any one of claims 2 to 6 wherein the rifapentine Form I + SII is prepared as follows:

a) rifapentine (any forms) is dissolved in a low boiling solvent with stirring at room temperature, then

b) ethanol is added and the volatiles are partially removed by distilling at ambient pressure until a constant temperature of the residual mixture of about 75°-80°C is obtained, and

c) rifapentine Form I + SII is recovered by filtration.

7. A pharmaceutical formulation which contains rifapentine pure crystalline Form I as defined in claim 1 as an active ingredient.

8. A process for preparing a rifapentine pharmaceutical formulation which comprises admixing rifapentine pure crystalline Form I as defined in claim 1 with a pharmaceutically acceptable veichle.

9. A formulation according to claim 7 or a process according to claim 8 wherein the pharmaceutical formulation is an oral dosage form such as a tablet or a capsule.

FIG. 1

TG-DSC heating curves of rifapentine Form I

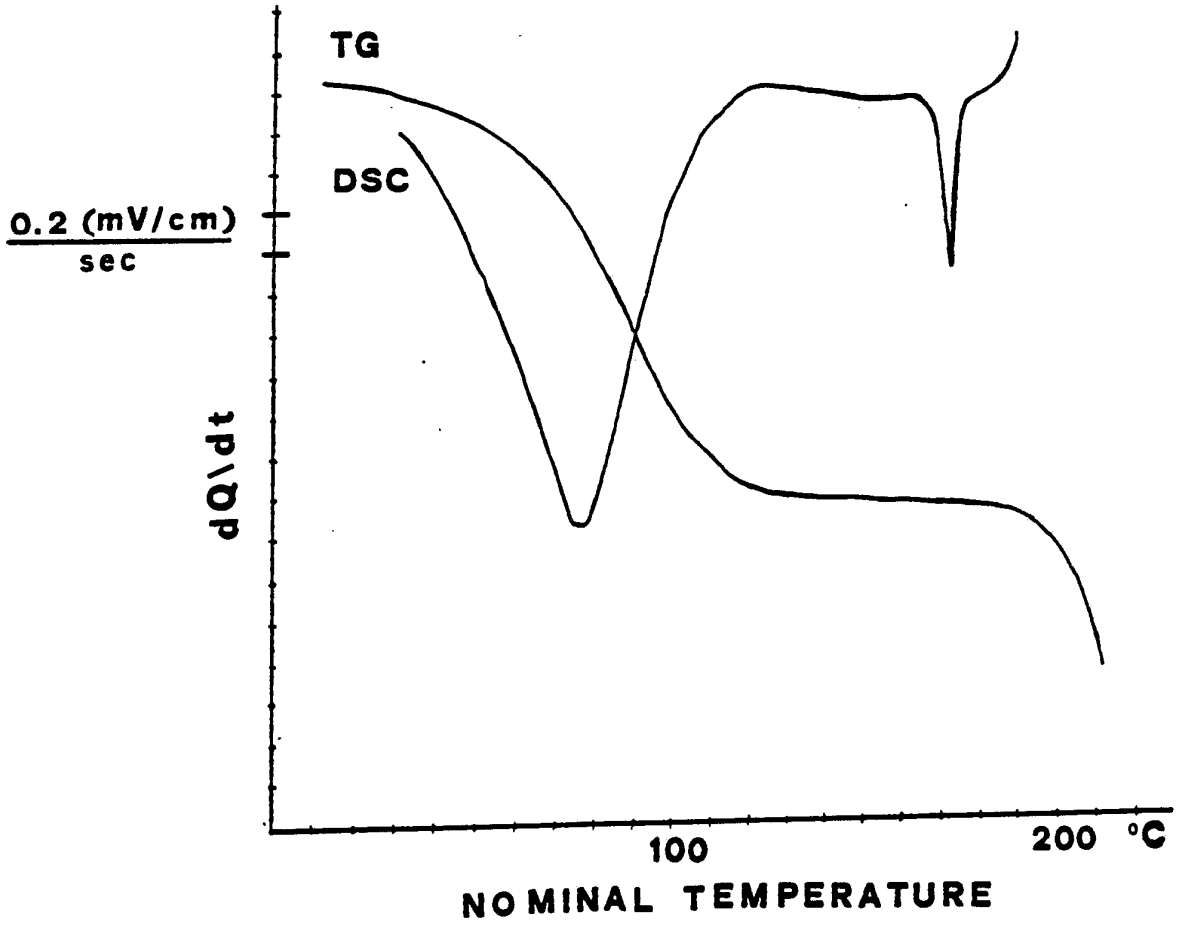
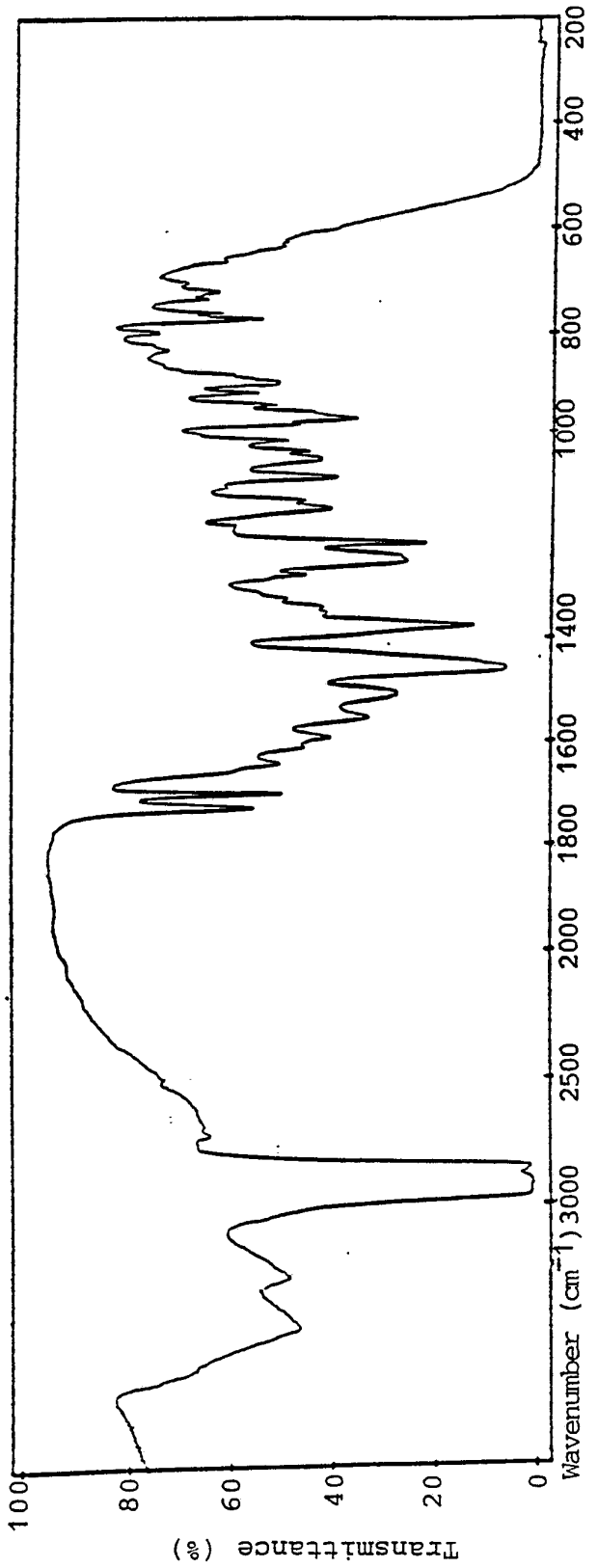


FIG. 2

IR spectrum of rifapentine Form I in nujol mull



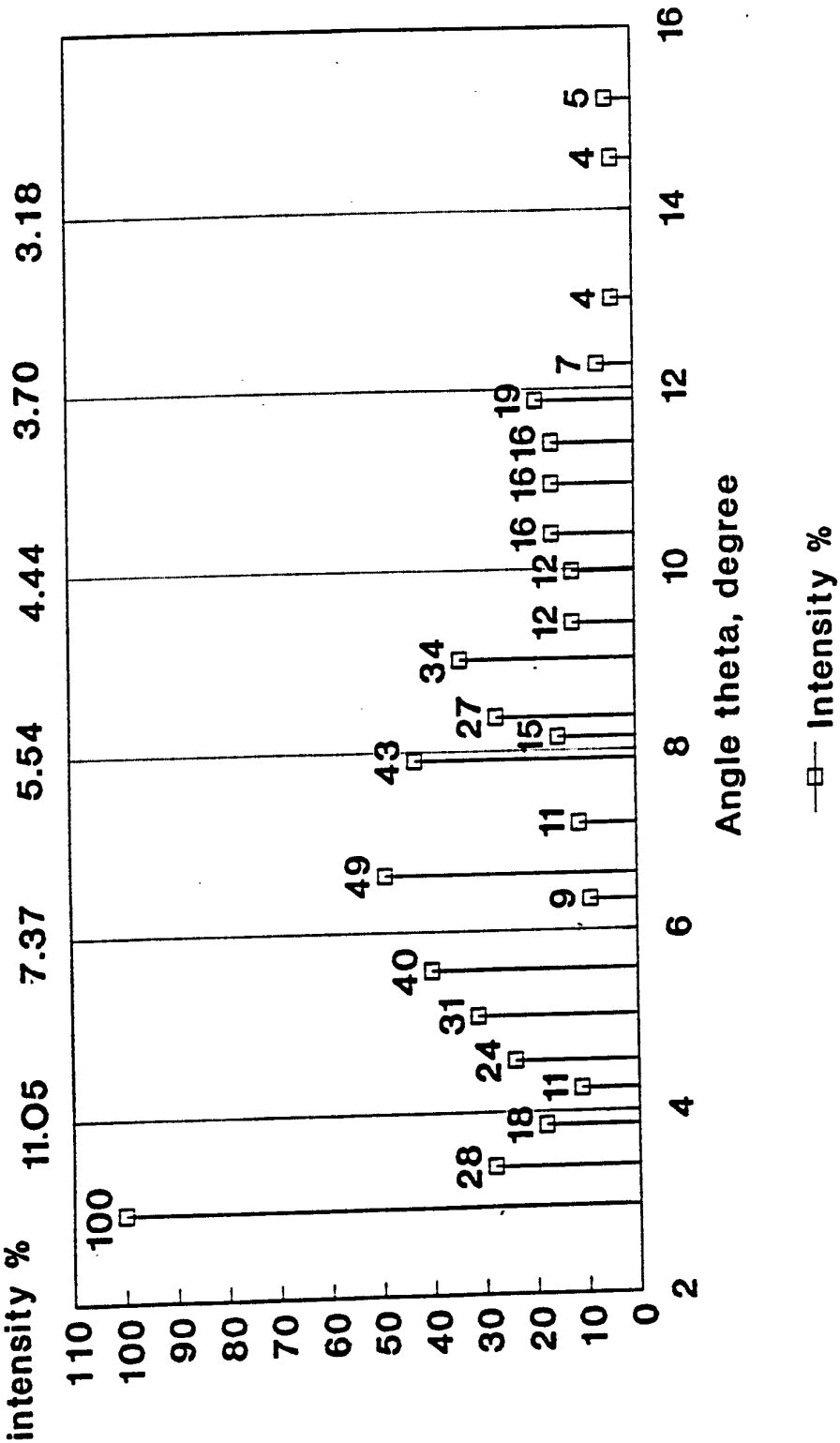



FIG. 3 X-ray diffraction pattern of rifapentine Form I

# INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01036

## I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 498/08 A 61 K 31/495 //(C 07 D 498/08 C 07 D 307:00 C 07 D 267:00 )

## II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl.5 | C 07 D 498/00 A 61 K 31/00 |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

## III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document,[11] with indication, where appropriate, of the relevant passages[12] | Relevant to Claim No.[13] |
|---|---|---|
| Y | US,A,4002752 (R. CRICCHIO et al.) 11 January 1977, see claims 1,8; column 2, example 1 (cited in the application) --- | 1,7 |
| Y | CHEMICAL ABSTRACTS, vol. 112, no. 20, 14 May 1990 (Columbus, Ohio, US), R. LU et al.: "Crystal modification of rifandin", see page 410, abstract no. 185647p, & Kangshengsu 1989, 14(5), pages 301-306 --- | 2,4,5 |
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° Special categories of cited documents :[10]

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

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

"&" document member of the same patent family

## IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 26-08-1991 | 18 OCT 1991 |
| International Searching Authority | Signature of Authorized Officer |
| EUROPEAN PATENT OFFICE | MISS D. S. KOWALCZYK |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

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This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 20/09/91
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