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(54) **Title:** CRYSTALLINE FORMS OF CEFDINIR POTASSIUM

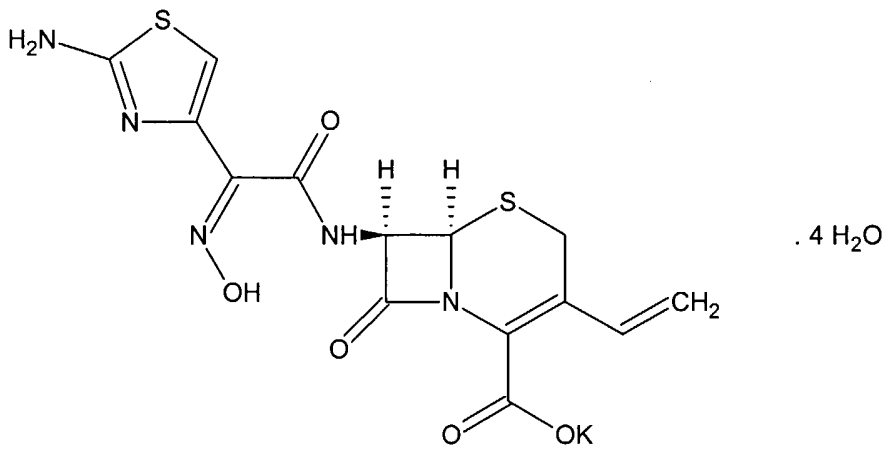
(57) **Abstract:** The present invention relates to a novel crystalline potassium salt of cefdinir - cefdinir potassium tetrahydrate, processes for its preparation, pharmaceutical compositions including cefdinir potassium tetrahydrate, and methods of treating bacterial infections using cefdinir potassium tetrahydrate. In addition, the present invention also relates to a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate, processes for its preparation, pharmaceutical compositions including the mixture, and methods of treating bacterial infections using mixtures of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate. Further it also relates to processes for preparing pure cefdinir and cefdinir potassium dihydrate from cefdinir potassium tetrahydrate.

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CRYSTALLINE FORMS OF CEFDINIR POTASSIUM

Field of Invention

The present invention relates to a novel crystalline potassium salt of cefdinir – cefdinir potassium tetrahydrate of Formula I,

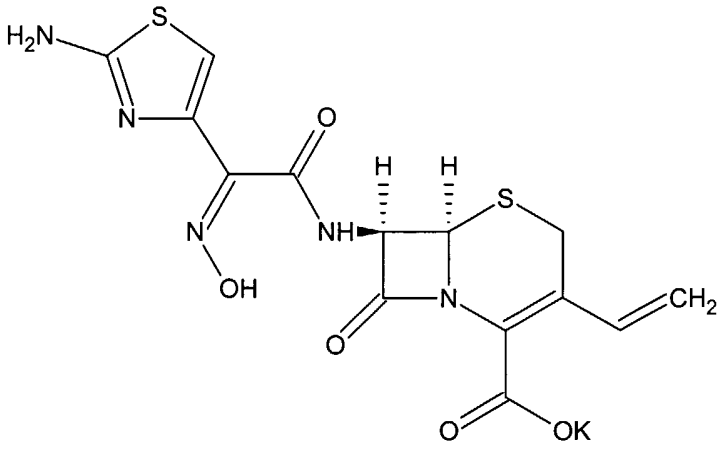


FORMULA I

processes for its preparation, pharmaceutical compositions including cefdinir potassium tetrahydrate, and methods of treating bacterial infections using cefdinir potassium tetrahydrate. In addition, the present invention also relates to a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate, processes for its preparation, pharmaceutical compositions including the mixture, and methods of treating bacterial infections using mixtures of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate. Further it also relates to processes for preparing pure cefdinir and cefdinir potassium dihydrate from cefdinir potassium tetrahydrate.

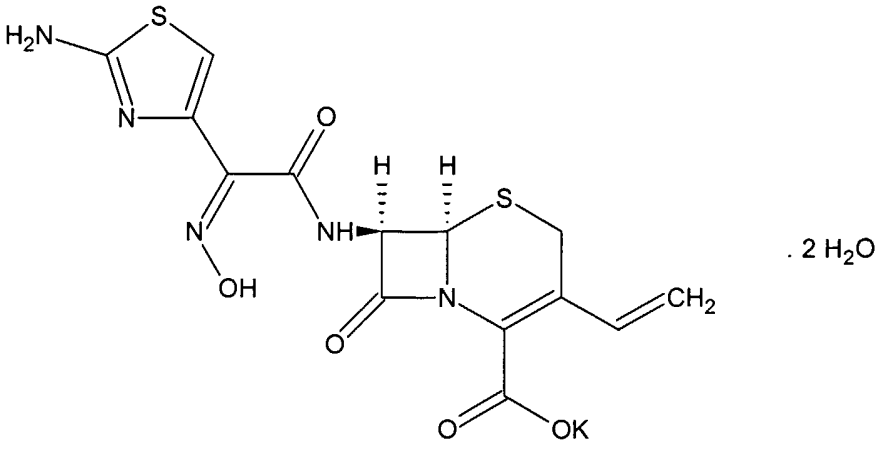
Background of the Invention

Cefdinir potassium is chemically known as potassium 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) of formula II,



FORMULA II

and is disclosed in US 4,559,334. Cefdinir is a third generation cephalosporin antibiotic for oral administration and has a broader antibacterial spectrum than other orally administrable antibiotics. Cefdinir is particularly effective against Staphylococci and Streptococci. Although US 4,559,334 describes the use of the potassium salt of cefdinir as a starting material for the synthesis of several esters of cefdinir, the synthesis or physical characteristics of cefdinir potassium have not been described at any stage. The patent describes preparation of cefdinir sodium via chromatography followed by lyophilization. The salt obtained by the given process is amorphous, hygroscopic and believed to be less than optimal for use in pharmaceutical compositions. Therefore, there is a need for pure and stable crystalline salts of cefdinir that are suitable for pharmaceutical preparations at an industrial scale; there also is a need for suitable methods for their preparation. Our Indian patent application 1242/DEL/2001 discloses preparation of cefdinir potassium dihydrate of formula III.



FORMULA III

Summary of the Invention

A first aspect of the present invention provides a novel crystalline cefdinir potassium tetrahydrate of formula I. A second aspect of the present invention provides crystalline cefdinir potassium tetrahydrate having characteristic XRD as depicted in Figure I. A third aspect of the present invention provides crystalline cefdinir potassium tetrahydrate having characteristic IR as depicted in Figure II. A fourth aspect of the present invention provides crystalline cefdinir potassium tetrahydrate having characteristic DSC as depicted in Figure III. A fifth aspect of the present invention provides crystalline cefdinir potassium tetrahydrate having characteristic XRD peaks at 2θ values of 8.2 ± 0.2, 11.26 ± 0.2, 18.22 ± 0.2, 20.8 ± 0.22, 22.58 ± 0.2, 23.72 ± 0.2, 24.28 ± 0.2, 25.82 ± 0.2, 26.34 ± 0.2, 26.68 ± 0.2, 26.84 ± 0.2, 27.3 ± 0.2, 27.82 ± 0.2, 27.96 ± 0.2 and 28.62 ± 0.2

A sixth aspect of the present invention provides a process for the preparation of cefdinir potassium tetrahydrate, the process comprises crystallizing out cefdinir potassium tetrahydrate from a solution thereof in a suitable solvent followed by drying.

A seventh aspect of the present invention provides a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate. An eighth aspect of the present invention provides a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate having characteristic XRD as depicted in Figure IV. A ninth aspect of the present invention provides a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate having characteristic XRD peaks at 2θ values of 11.24 ± 0.2, 12.06 ± 0.2, 18.24 ± 0.2, 19.1 ± 0.2, 19.28 ± 0.2, 21.38 ± 0.2, 22.84 ± 0.2, 23.72 ± 0.2, 24.3 ± 0.2, 25.06 ± 0.2, 25.5 ± 0.2, 25.82 ± 0.2, 26.72 ± 0.2 and 27.96 ± 0.2.

A tenth aspect of the present invention provides a process for the preparation of a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate, the process comprising drying a wet cake of cefdinir potassium under reduced pressure at ambient temperature.

A eleventh aspect of the invention provides a process for preparing cefdinir potassium tetrahydrate from cefdinir potassium dihydrate, the process comprising keeping cefdinir potassium dihydrate in a humid atmosphere with water vapor at about 20 to 40°C for 15 to 25 hours.

A twelfth aspect of the invention provides a process for preparing cefdinir potassium dihydrate from cefdinir potassium tetrahydrate comprising air-drying cefdinir potassium tetrahydrate at above 40°C or above 50°C.

A thirteenth aspect of the invention provides a process for the manufacture of pure cefdinir characterized in that crystalline cefdinir potassium tetrahydrate is obtained from crude cefdinir, optionally recrystallized one or more times, and then converted to the free acid, i.e., cefdinir.

A fourteenth aspect of the invention provides pure cefdinir, preferably crystalline, prepared by the process of the present invention.

A fifteenth aspect of the present invention provides pharmaceutical compositions that include cefdinir potassium tetrahydrate with one or more pharmaceutically acceptable carriers and excipients. The pharmaceutical compositions include oral dosage forms such as tablets, capsules, liquid orals, suspensions and the like; and topical dosage forms such as cream, lotions, ointments and the like.

A sixteenth aspect of the present invention also provides pharmaceutical compositions that include mixtures of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate along with pharmaceutically acceptable carriers and excipients.

A seventeenth aspect of the present invention provides a method of treating bacterial infections comprising administering to a mammal in need thereof a therapeutically effective amount of cefdinir potassium tetrahydrate.

An eighteenth aspect of the present invention provides a method of treating bacterial infections comprising administering to a mammal in need thereof a therapeutically effective amount of mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate.

Accordingly, in one general aspect there is provided a crystalline cefdinir potassium tetrahydrate of formula I.

Embodiments of the crystalline cefdinir potassium tetrahydrate may include one or more of the following features. For example, the crystalline cefdinir potassium tetrahydrate may have a characteristic XRD of Figure I. The crystalline cefdinir potassium tetrahydrate has characteristic XRD peaks at 2θ values of 8.2 ± 0.2, 11.26 ± 0.2,

18.22 ± 0.2, 20.8 ± 0.22, 22.58 ± 0.2, 23.72 ± 0.2, 24.28 ± 0.2, 25.82 ± 0.2, 26.34 ± 0.2, 26.68 ± 0.2, 26.84 ± 0.2, 27.3 ± 0.2, 27.82 ± 0.2, 27.96 ± 0.2 and 28.62 ± 0.2. The crystalline cefdinir potassium tetrahydrate has a characteristic IR of Figure II. The crystalline cefdinir potassium tetrahydrate may have a characteristic DSC of Figure III.

The crystalline cefdinir potassium tetrahydrate may be present in a pharmaceutical composition that further includes one or more pharmaceutically acceptable carriers and excipients.

The crystalline cefdinir potassium tetrahydrate may be present in a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate. The mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate may have the characteristic XRD of Figure IV. The mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate may have characteristic XRD peaks at 2θ values of 11.24 ± 0.2, 12.06 ± 0.2, 18.24 ± 0.2, 19.1 ± 0.2, 19.28 ± 0.2, 21.38 ± 0.2, 22.84 ± 0.2, 23.72 ± 0.2, 24.3 ± 0.2, 25.06 ± 0.2, 25.5 ± 0.2, 25.82 ± 0.2, 26.72 ± 0.2 and 27.96 ± 0.2. The mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate may have the characteristic IR of Figure V. The mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate may be in a pharmaceutical composition that further includes one or more pharmaceutically acceptable carriers and excipients.

The mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate may be made by drying a wet cake of cefdinir potassium under reduced pressure at ambient temperature. The wet cake of cefdinir potassium may be dried at about 20 to 40°C under reduced pressure.

In another general aspect there is provided a process for the preparation of cefdinir potassium tetrahydrate of Formula I, the process including crystallizing out cefdinir potassium tetrahydrate from a solution of cefdinir potassium in a suitable solvent.

Embodiments of the process may include one or more of the following features. For example, the solution of cefdinir potassium may be obtained by adding a potassium salt of a weak acid to a suspension or solution of cefdinir in a suitable solvent. The suitable solvent may be a water miscible polar organic solvent in admixture with water. The product may be obtained by drying after crystallizing. The drying may be carried out at about 25 to 40°C.

In another general aspect there is provided a process for preparing cefdinir potassium tetrahydrate from cefdinir potassium dihydrate. The process includes keeping cefdinir potassium dihydrate in a humid atmosphere with water vapor at about 20 to 40°C for about 15 to 25 hours.

In another general aspect there is provided a process for preparing cefdinir potassium dihydrate from cefdinir potassium tetrahydrate. The process includes air-drying cefdinir potassium tetrahydrate at a temperature above 40°C.

In another general aspect there is provided a method of treating bacterial infections. The method includes administering to a mammal in need thereof a pharmaceutical composition that includes a therapeutically effective amount of cefdinir potassium tetrahydrate.

Embodiments of the method may include one or more of the following features or those described above. For example, the pharmaceutical composition may further include a therapeutically effective amount of cefdinir potassium dihydrate.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Description of the Drawings

Figure I is an X-Ray Diffraction (XRD) pattern of cefdinir potassium tetrahydrate

Figure II is an infrared (IR) spectrum of cefdinir potassium tetrahydrate

Figure III is a differential scanning calorimetry (DSC) of cefdinir potassium tetrahydrate

Figure IV is an XRD of a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate

Figure V is an IR spectrum of a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate.

Detailed Description of Invention

The inventors have now found that a potassium salt of cefdinir also may be obtained as a pure crystalline tetrahydrate using a simple and efficient process. This crystalline salt may be conveniently formulated into tablets, suspensions, injectables and

other pharmaceutical forms. Furthermore, it has been found that an efficient purification of cefdinir may be achieved by crystallizing it as cefdinir potassium tetrahydrate and then converting it back to cefdinir.

A solution of cefdinir potassium may be obtained by adding a potassium salt of a weak acid to a suspension or solution of cefdinir in a suitable solvent. The solution of cefdinir may be obtained either by dissolving cefdinir in a suitable solvent or directly from a reaction in which cefdinir is formed. Cefdinir used as the starting material may be obtained by any of the methods known in the art viz., US 4,559,334; US 4,870,168; US 6,093,814; WO 92/7840, Japanese patent applications JP 04173781, JP 01238587 and JP 02000790 (publication numbers).

Often, when the potassium salt of a weak acid is added to a suspension of cefdinir in a suitable solvent the cefdinir potassium tetrahydrate starts crystallizing out even before cefdinir has gone into solution completely. Such a process is within the meaning of the process of the present invention.

The weak acid whose potassium salt may be used for forming the potassium salt of cefdinir may be either an organic acid or an inorganic acid. Examples of suitable potassium salts include potassium acetate, potassium carbonate, potassium bicarbonate and the like.

According to the present invention, the term "suitable solvent" may be any water miscible polar organic solvent in admixture with water. Suitable water miscible polar organic solvents include ketones such as acetone and ethyl methyl ketone; lower alcohols such as methanol, ethanol, propanol, and isopropanol; nitriles such as acetonitrile; cyclic ethers such as tetrahydrofuran and dioxane; and mixtures thereof.

The crystallization may be performed at any suitable temperature depending on the solvent used. However, crystallization works well when performed at a temperature between 0 and 30°C, including the range of 5-10°C.

The isolated product may be dried in a hot air oven at about 25 to 40°C to obtain cefdinir potassium tetrahydrate. The temperature range of about 30 to 35°C works well to obtain cefdinir potassium tetrahydrate.

Cefdinir potassium tetrahydrate may be prepared by keeping cefdinir potassium dihydrate in a desiccator with water vapor at about 25 to 30°C for 20 hours, although other times may be operable.

The preparation of mixtures of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate described in the eighth aspect comprises drying of a wet cake of cefdinir potassium obtained from the reaction mixture in which cefdinir potassium is formed. The wet cake of cefdinir potassium may be dried at about 20 to 40°C under reduced pressure. A temperature range of about 25 to 30°C works well. The XRD and IR results shown in Figures IV and V, respectively, can be expected for the mixture under these conditions.

It has been observed that when cefdinir potassium tetrahydrate or cefdinir potassium dihydrate is subjected to drying at about 45 to 50°C under reduced pressure, the cefdinir loses most of the water and becomes amorphous. The amorphous form is highly unstable and picks up water at ambient temperatures and converts to a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate. When air dried at about 50°C, they convert into cefdinir potassium dihydrate.

The product described in the eleventh aspect may be obtained as crystal A as cited in US 4,935,507, which is incorporated herein by reference. Alternatively, an amorphous form of cefdinir similar to that produced by the method of US 4,559,334 may also be obtained via this purification process.

Conversion of cefdinir potassium tetrahydrate to cefdinir may be easily accomplished by suspending in water and acidifying to obtain the free acid, i.e., cefdinir.

"Crude cefdinir" is cefdinir prepared by any of the methods known in the art and which contains anti-isomer, polymeric impurities or any other impurity, which may arise during production or storage, such as degradation products. Crude cefdinir may be a solid or exist in a solvent, e.g., in a mixture resulting directly from a reaction for the synthesis of cefdinir.

Cefdinir may be obtained with a purity of 99% or more by the processes of the invention described herein.

In the following section preferred embodiments are described by way of examples to illustrate the processes of the invention. These examples are not intended in any way to

limit the scope of the present invention and several variants of these examples would be evident to persons of ordinary skill in the art.

EXAMPLES

Example 1

Preparation of cefdinir potassium tetrahydrate

Potassium acetate (70 g) was added to a suspension of cefdinir (200 g) in a mixture of water (1000 ml) and acetone (1000 ml) at 25-30°C. The reaction mixture was stirred at this temperature for three hours. The reaction mixture was then cooled to 10°C and stirred for about two hours. The crystals were filtered, washed with aqueous acetone followed by acetone. The product was then dried at 25-30°C in a hot air oven to obtain 189g of the title compound, i.e., cefdinir potassium tetrahydrate.

Yield:	94.5%
Water content:	14.58%
HPLC Purity:	99.5 %
K-content (w/w):	7.7 %

Example 2

Preparation of cefdinir potassium tetrahydrate

Cefdinir potassium dihydrate (5 g, water content: 8.42%) was kept in a desiccator, saturated with water vapors, at 25 to 30°C for twenty hours to obtain cefdinir potassium tetrahydrate. The resulting cefdinir potassium tetrahydrate has an XRD pattern that matches that of the XRD pattern of Fig I.

Yield:	5.28g
Water content:	14.14%

Example 3

Preparation of a mixture of cefdinir potassium tetrahydrate and cefdinir potassium dihydrate

A wet cake of cefdinir potassium (80 g) was dried at 25 to 30°C under reduced pressure for fifteen hours to obtain 59 g of a mixture of cefdinir potassium tetrahydrate and cefdinir potassium dihydrate. The XRD pattern of the mixture is depicted in Fig IV.

Yield: 59g

Water content: 9.50%

Example 4

Preparation of pure cefdinir

Cefdinir potassium tetrahydrate (5 g, water content: 14.58%) was suspended in distilled water (150 ml) at 25 to 30°C. The pH of the mixture was adjusted to 2.4 – 2.5 by adding dilute hydrochloric acid at 25 to 30°C and stirring was continued at this temperature for two hours. The solid obtained was filtered, washed with water and dried to obtain 3.5 g of cefdinir.

Yield: 90.0%

Water content: 1.1%

HPLC Purity: 99%

Example 5

Preparation of cefdinir potassium dihydrate

Cefdinir potassium tetrahydrate (5 g, water content: 14.58%) was dried at 50-55°C in a hot air oven for about fifteen hours to get cefdinir potassium dihydrate.

Yield: 4.6g

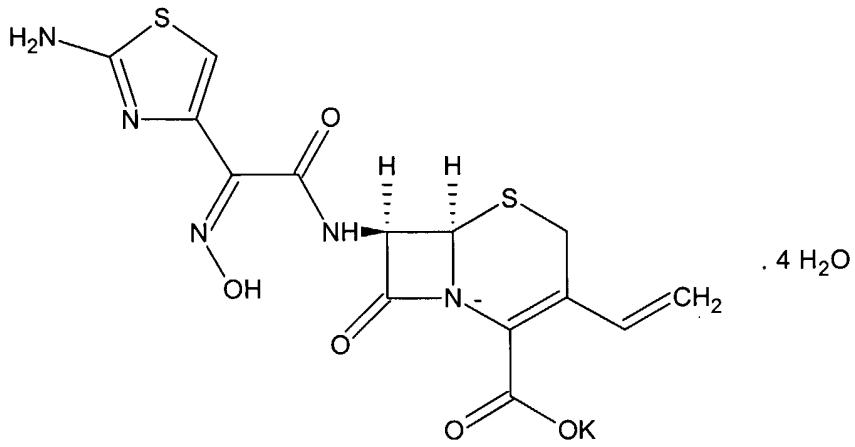
Water content: 8.4%

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. For example, therapeutically effective amounts of cefdinir potassium tetrahydrate and mixtures of cefdinir potassium tetrahydrate with cefdinir potassium dihydrate may be combined with one or more pharmaceutically acceptable carrier and excipients to form dosage forms. The dosage forms may be administered for the treatment of bacterial infections.

Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

We Claim:

1. A crystalline cefdinir potassium tetrahydrate of formula I.



Formula I

2. The crystalline cefdinir potassium tetrahydrate of claim 1, wherein the crystalline cefdinir potassium tetrahydrate has a characteristic XRD of Figure I.

3. The crystalline cefdinir potassium tetrahydrate of claim 1, wherein the crystalline cefdinir potassium tetrahydrate has characteristic XRD peaks at 2θ values of 8.2 ± 0.2,11.26 ± 0.2, 18.22 ± 0.2, 20.8 ± 0.22, 22.58 ± 0.2, 23.72 ± 0.2, 24.28 ± 0.2, 25.82 ± 0.2, 26.34 ± 0.2, 26.68 ± 0.2, 26.84 ± 0.2, 27.3 ± 0.2, 27.82 ± 0.2, 27.96 ± 0.2 and 28.62 ± 0.2.

4. The crystalline cefdinir potassium tetrahydrate of claim 1, wherein the crystalline cefdinir potassium tetrahydrate has a characteristic IR of Figure II.

5. The crystalline cefdinir potassium tetrahydrate of claim 1, wherein the crystalline cefdinir potassium tetrahydrate has a characteristic DSC of Figure III.

6. The crystalline cefdinir potassium tetrahydrate of claim 1, the crystalline cefdinir potassium tetrahydrate being in a pharmaceutical composition further comprising one or more pharmaceutically acceptable carriers and excipients.

7. The crystalline cefdinir potassium tetrahydrate of claim 1, wherein the crystalline cefdinir potassium tetrahydrate is present in a mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate.

8. The crystalline cefdinir potassium tetrahydrate of claim 7, wherein the mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate has the characteristic XRD of Figure IV.

9. The crystalline cefdinir potassium tetrahydrate of claim 7, wherein the mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate has characteristic XRD peaks at 2θ values of 11.24 ± 0.2, 12.06 ± 0.2, 18.24 ± 0.2, 19.1 ± 0.2, 19.28 ± 0.2, 21.38 ± 0.2, 22.84 ± 0.2, 23.72 ± 0.2, 24.3 ± 0.2, 25.06 ± 0.2, 25.5 ± 0.2, 25.82 ± 0.2, 26.72 ± 0.2 and 27.96 ± 0.2.

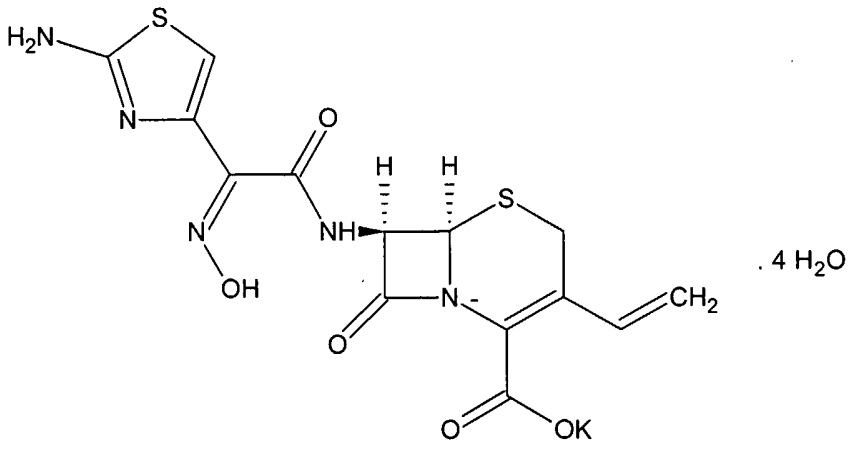
10. The crystalline cefdinir potassium tetrahydrate of claim 7, wherein the mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate has the characteristic IR of Figure V.

11. The crystalline cefdinir potassium tetrahydrate of claim 7, wherein the mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate is in a pharmaceutical composition further comprising one or more pharmaceutically acceptable carriers and excipients.

12. The crystalline cefdinir potassium tetrahydrate of claim 7, wherein the mixture of cefdinir potassium dihydrate and cefdinir potassium tetrahydrate is made by drying a wet cake of cefdinir potassium under reduced pressure at ambient temperature.

13. The crystalline cefdinir potassium tetrahydrate of claim 12, wherein the wet cake of cefdinir potassium is dried at about 20 to 40°C under reduced pressure.

14. A process for the preparation of cefdinir potassium tetrahydrate of Formula I,



Formula I

the process comprises crystallizing out cefdinir potassium tetrahydrate from a solution of cefdinir potassium in a suitable solvent.

15. The process of claim 14, wherein the solution of cefdinir potassium is obtained by adding a potassium salt of a weak acid to a suspension or solution of cefdinir in a suitable solvent.

16. The process of claim 14, wherein the suitable solvent is a water miscible polar organic solvent in admixture with water.

17. The process of claim 14, wherein the product is obtained by drying after crystallizing.

18. The process of claim 17, wherein drying is carried out at about 25 to 40°C.

19. A process for preparing cefdinir potassium tetrahydrate from cefdinir potassium dihydrate, the process comprising keeping cefdinir potassium dihydrate in a humid atmosphere with water vapor at about 20 to 40°C for about 15 to 25 hours.

20. A process for preparing cefdinir potassium dihydrate from cefdinir potassium tetrahydrate comprising air-drying cefdinir potassium tetrahydrate at a temperature above 40°C.

21. A method of treating bacterial infections comprising administering to a mammal in need thereof a pharmaceutical composition comprising a therapeutically effective amount of cefdinir potassium tetrahydrate.

22. The method of claim 21, wherein the pharmaceutical composition further comprises a therapeutically effective amount of cefdinir potassium dihydrate.

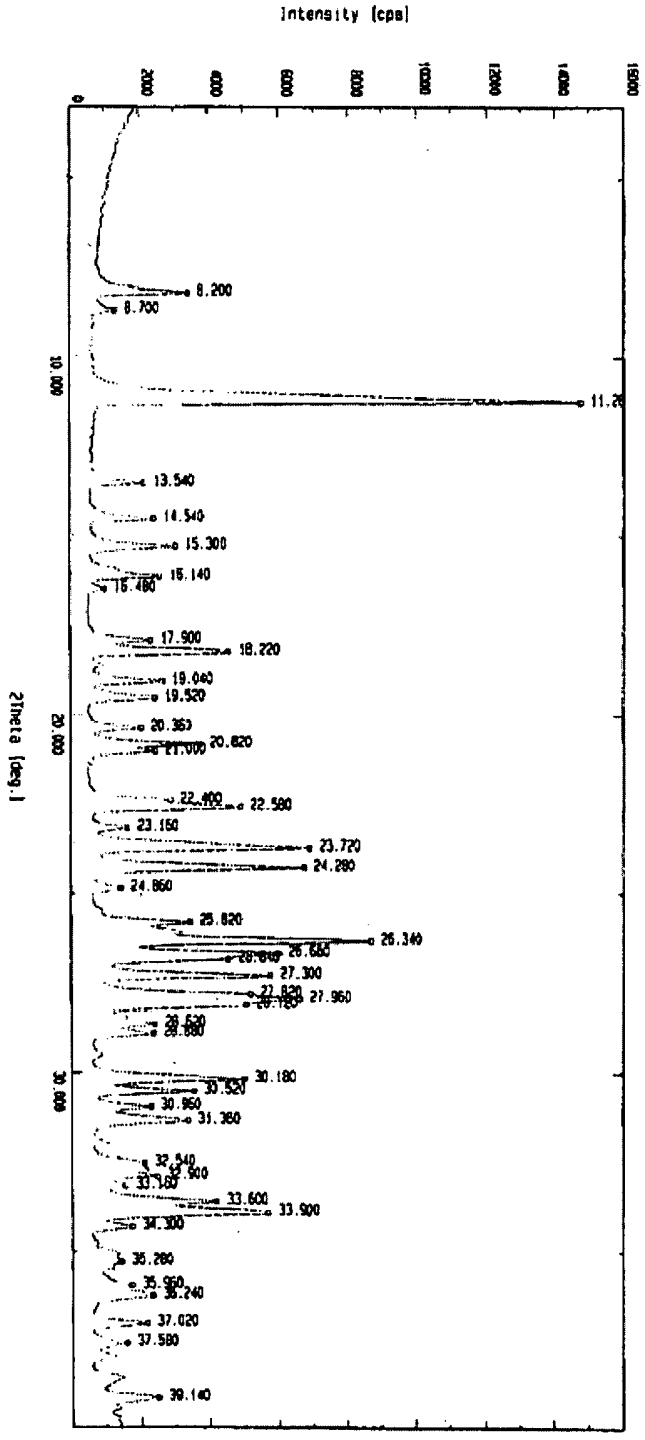

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14.540
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15.140
16.480
17.900
18.220
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20.820
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23.150
23.720
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30.960
31.360
33.600
33.900

FIGURE 1

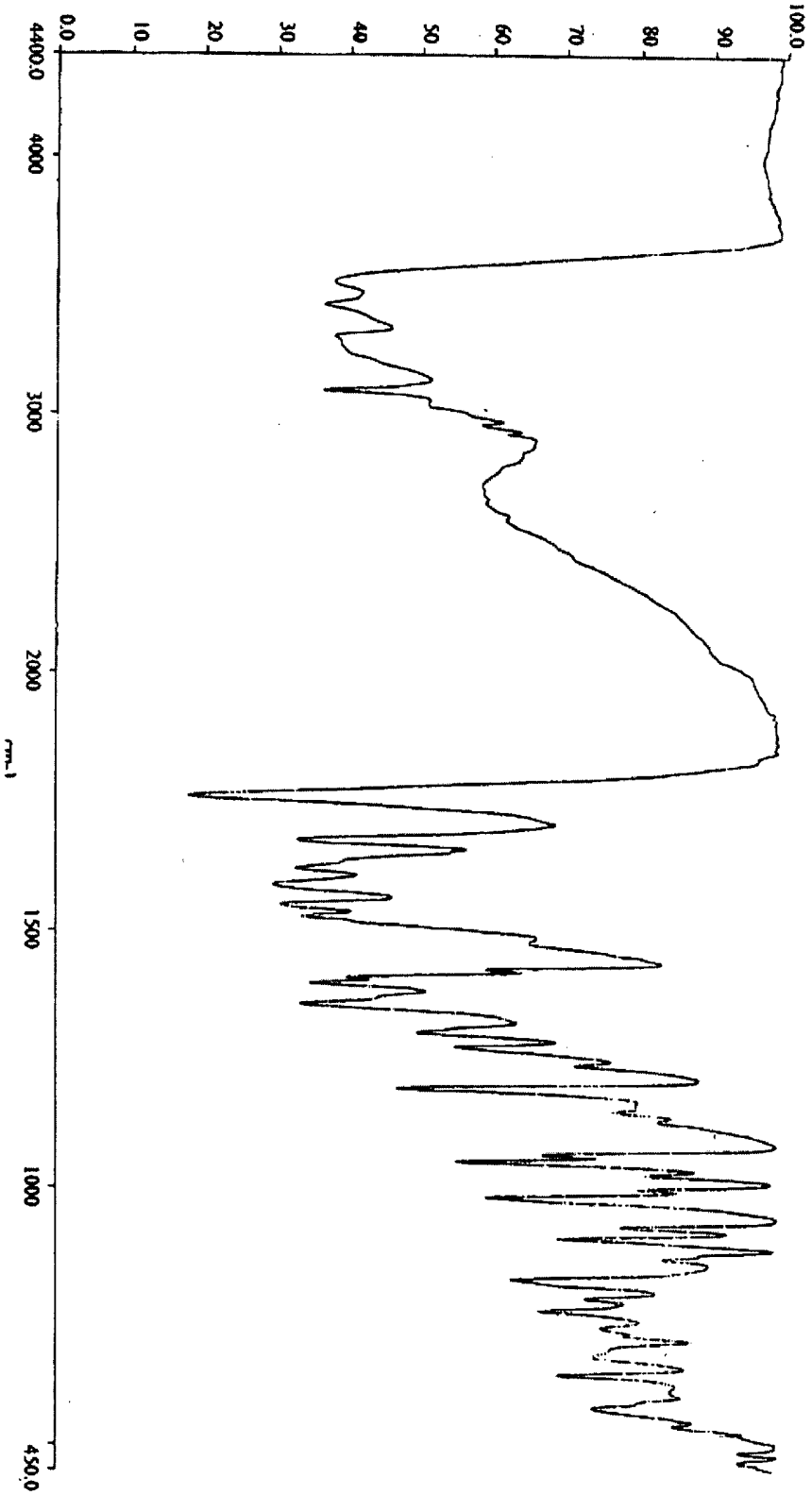

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1000
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cm-1

FIGURE 2

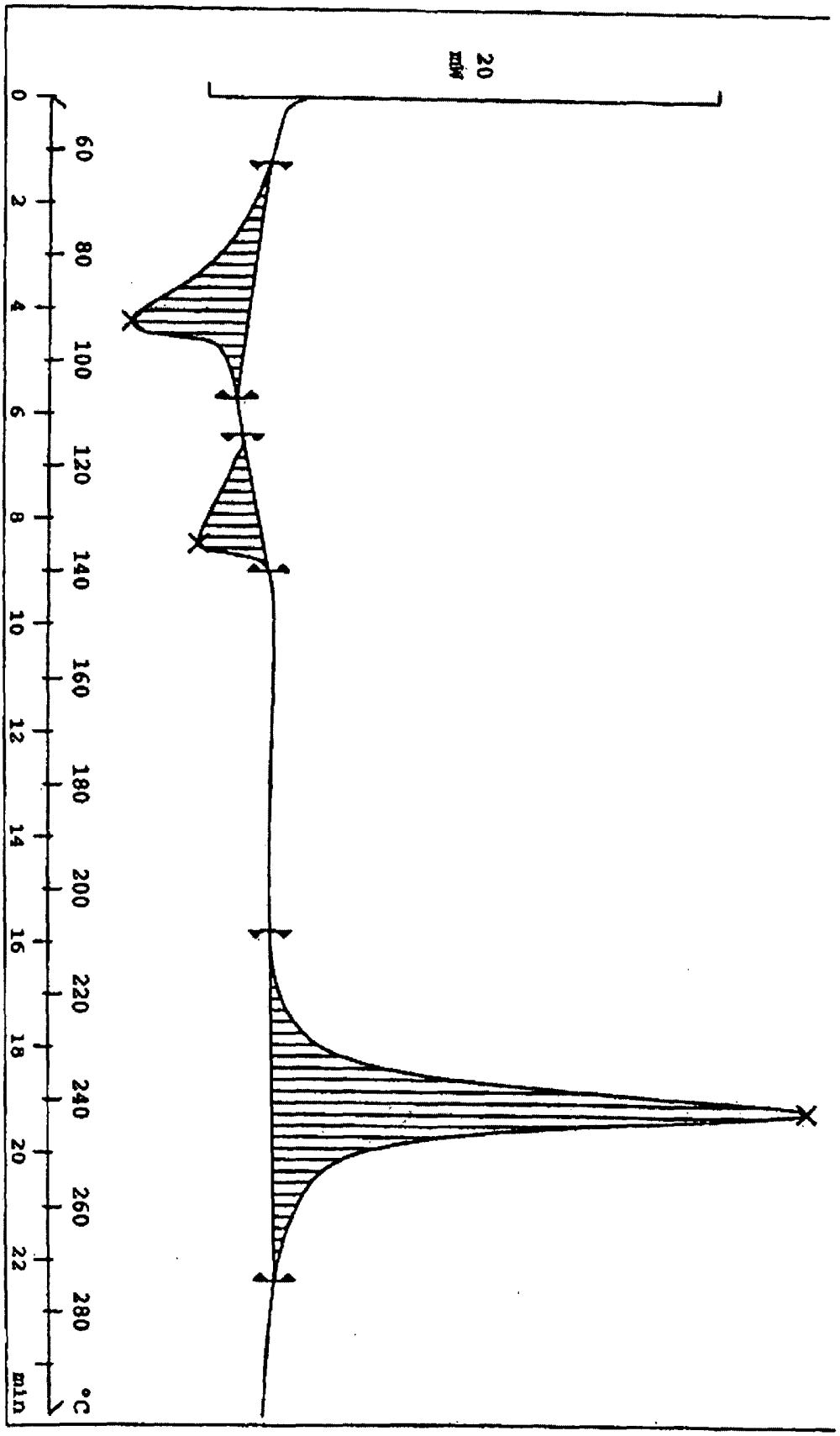

20
mW
0
2
4
6
8
10
12
14
16
18
20
22
min
60
80
100
120
140
160
180
200
220
240
260
280
°C

FIGURE 3

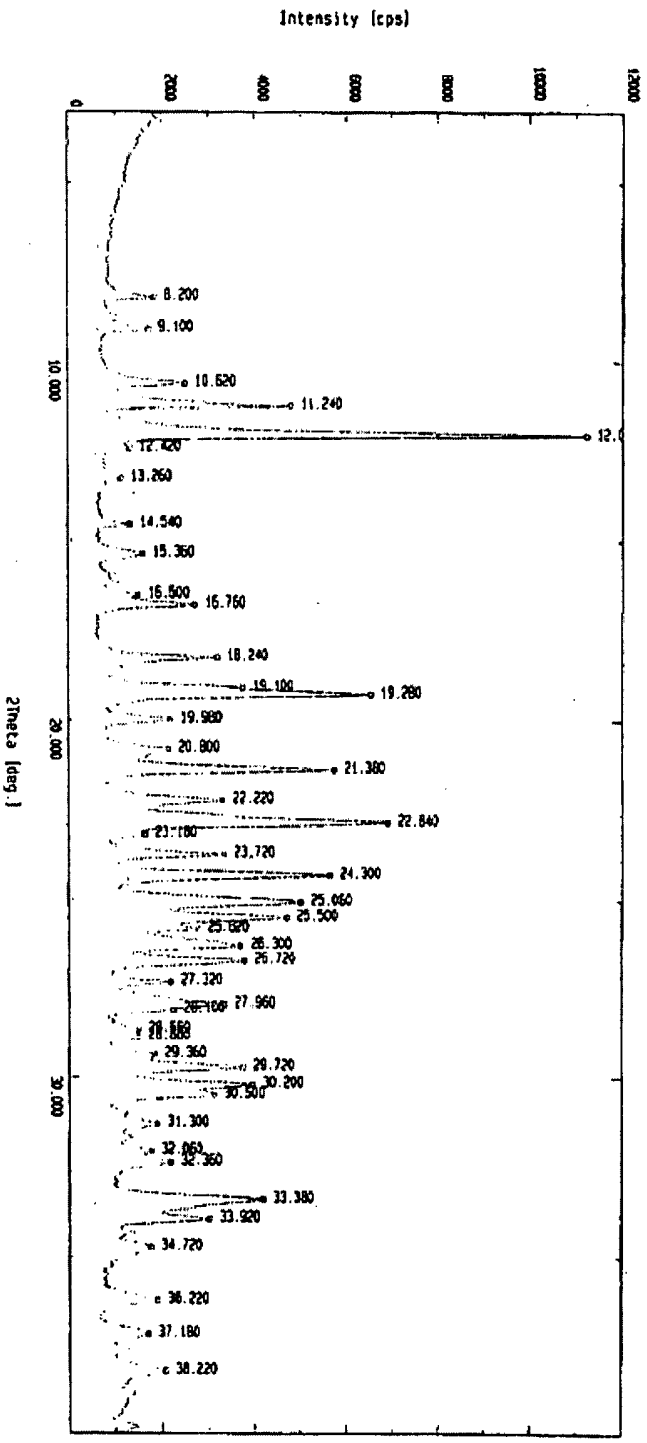

Intensity (cps)
0
2000
4000
6000
8000
10000
12000
2Theta (deg.)
10.000
20.000
30.000
8.200
9.100
10.520
11.240
12.420
13.260
14.540
15.360
16.500
16.760
18.240
19.100
19.280
19.980
20.800
21.380
22.220
22.840
23.720
24.300
25.060
25.500
26.300
26.720
27.320
27.960
29.360
29.720
30.200
30.500
31.300
32.360
33.380
33.920
34.720
36.220
37.180
38.220

FIGURE 4

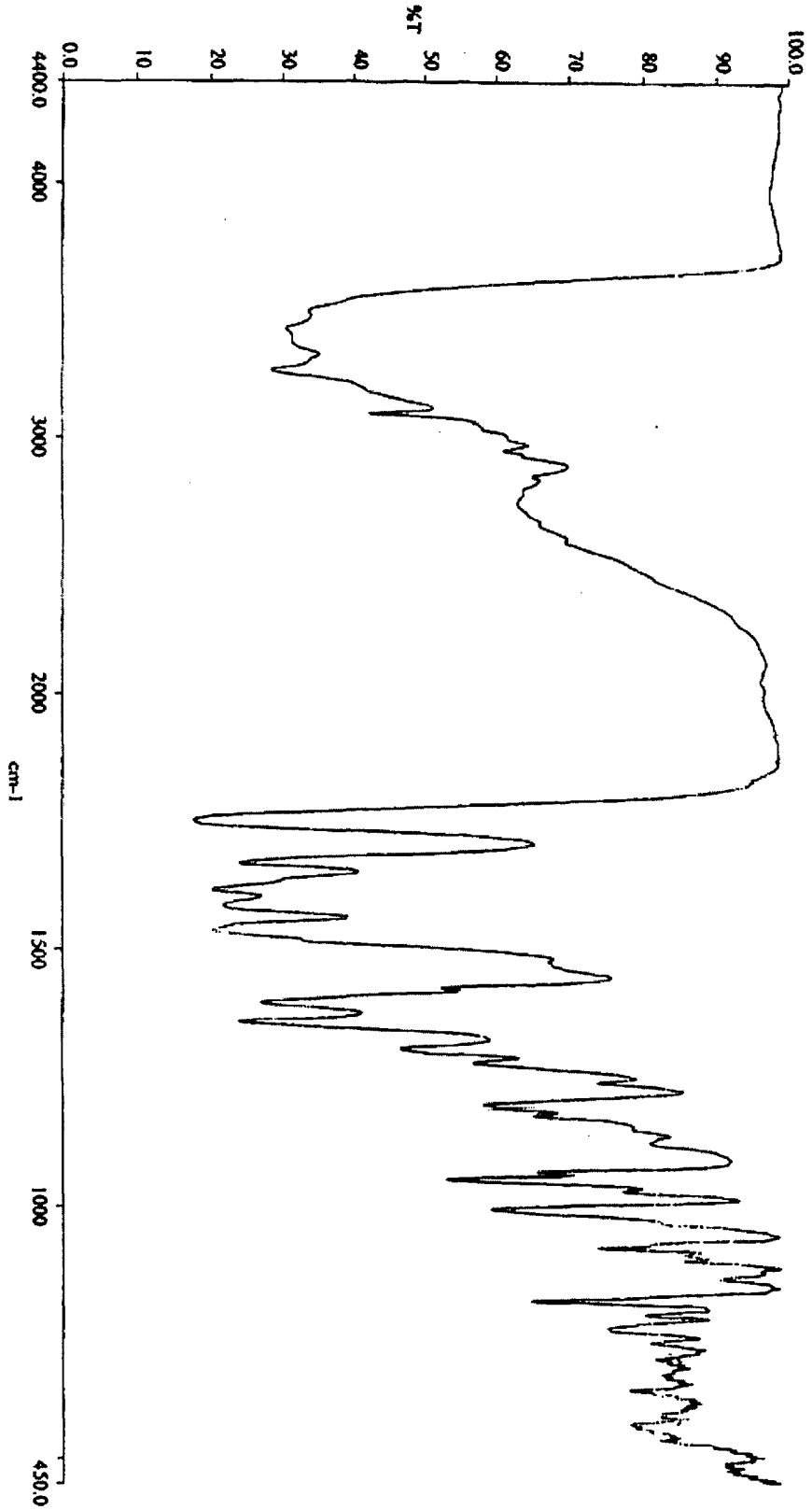

%T
0.0
10
20
30
40
50
60
70
80
90
100.0
4400.0
4000
3000
2000
1500
1000
450.0
cm-1

FIGURE 5

INTERNATIONAL SEARCH REPORT

Interr il Application No
PCT/ID2005/002858

A. CLASSIFICATION OF SUBJECT MATTER
C07D501/22 A61K31/546 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/050124 A (RANBAXY LABORATORIES LIMITED; KUMAR, YATENDRA; PRASAD, MOHAN; PRASAD,) 19 June 2003 (2003-06-19) the whole document	1
X	US 4 559 334 A (TAKAYA ET AL) 17 December 1985 (1985-12-17) cited in the application example 10	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"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

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2006	25/01/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fanni, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/002858

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

·mation on patent family members

Intern I Application No
PCT/IB2005/002858

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03050124 A	19-06-2003	AU 2002347539 A1	23-06-2003
		CN 1617875 A	18-05-2005
		EP 1458728 A1	22-09-2004
		JP 2005516011 T	02-06-2005
		US 2005080255 A1	14-04-2005
US 4559334 A	17-12-1985	NONE	