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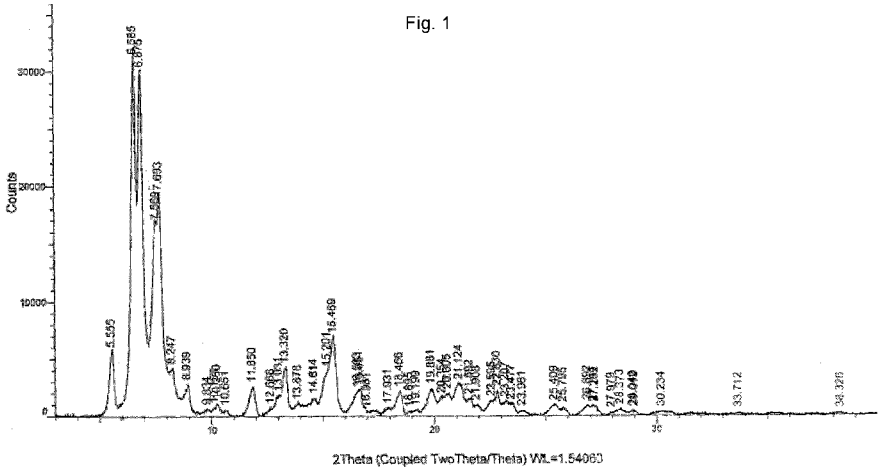
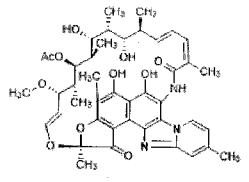
(54) Title: RIFAXIMIN CRYSTALLINE FORM

Fig. 1





(I)

(57) Abstract: The present invention relates to a process for the preparation of crystalline Form GR of Rifaximin (I). The invention also relates to crystalline Form GR of Rifaximin obtained by the process of the present invention, the said Form GR being substantially pure, stable, and characterized by X- ray powder diffraction pattern comprising of atleast five 2θ° peaks selected form 5.5, 6.6, 6.8, 7.5, 7.7, 11.8, 13.3 and 15.4 ± 0.2 2θ°. The present invention further relates to process for the preparation of substantially pure Rifaximin comprising recrystallization using mixture of alcoholic solvents.

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[Continued on next page]

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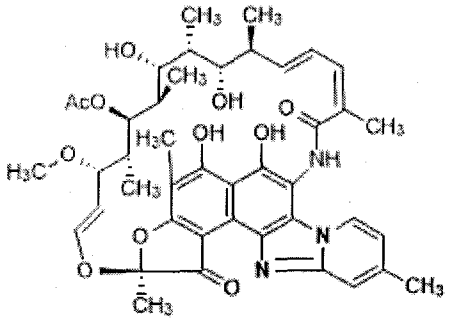
RIFAXIMIN CRYSTALLINE FORM

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation Crystalline Form GR of Rifaximin of Formula (I).



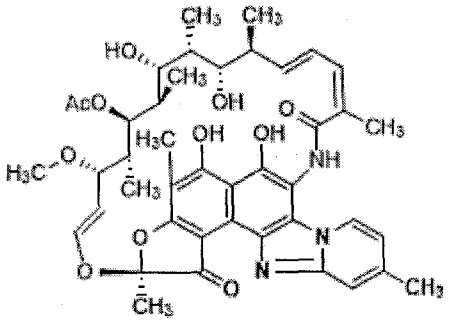
(I)

The invention also relates to crystalline Form GR of Rifaximin (I) obtained by the process of the present invention, the said Form GR being substantially pure, stable and characterized by X-ray powder diffraction pattern comprising of at least five 2θ° peaks selected from 5.5, 6.6, 6.8, 7.5, 7.7, 11.8, 13.3 and 15.4 ± 0.2 2θ°.

The present invention further relates to process for the preparation of substantially pure Rifaximin comprising recrystallization using mixture of alcoholic solvents.

BACKGROUND OF THE INVENTION

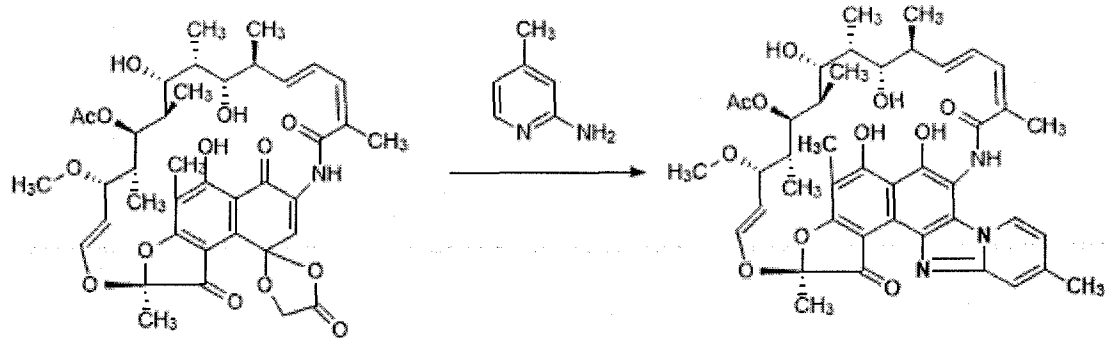
Rifaximin of formula I, is chemically known as (2S, 16Z, 18E, 20S, 21S, 22R, 23R, 24R, 25S, 26S, 27S, 28E)-5, 6, 21 , 23, 25-pentahydroxy- 27-methoxy-2, 4, 11, 16, 20, 22, 24, 26-octamethyl-2,7-(epoxypentadeca-[1 ,11 ,13]trienimino)- benzofuro[4, 5-e]- pyrido[1, 2-(alpha)]-benzimidazole-1,15(2H)dione, 25-acetate.



(I)

Egidio Marchi et.al. in the patent US 4,341,785 discloses a process for the preparation of and a method for crystallization of rifaximin using suitable solvents. However, this patent does not mention the polymorphism of rifaximin.

Vincenzo Cannata et.al. in the patent US 4,557,866 discloses process for the synthesis of pyrido- imidazo-rifamycins. The process comprises reacting the rifamycin O with a 2-aminopyridine which is shown as below Scheme I. This patent also discloses purification of Rifaximin by performing crystallization of crude Rifaximin from a 7:3 mixture of ethyl alcohol and water and followed by drying under vacuum. The crystalline form details are not disclosed.



Scheme I

G.C.Viscomi et.al. in the patent US 7,045,620 discloses that the polymorph called rifaximin form α is characterized by a water content lower than 4.5%, preferably between 2.0% and 3.0% and further by powder X-ray diffractogram which shows peaks at the values of the diffraction angles 2θ of 6.6°; 7.4°; 7.9°; 8.8°; 10.5°; 11; 1 1.8°; 12.9°; 17.6°; 18.5°; 19.7°; 21.0°; 21.1°; 22.1 °. The other polymorph called rifaximin form β is characterized by a water content higher than 4.5%, preferably between 5.0% and 6.0%, and by a powder X-ray diffractogram which shows peaks at the values of the diffraction angles 2θ of 5.4°; 6.4°; 7.0°; 7.8°; 9.0°; 10.4°; 13.1 °; 14.4°; 17.1°; 17.90°; 18.30°; 20.9° The polymorph called rifaximin γ is characterized by a powder X-ray diffractogram much poorer because of the poor crystallinity; the significant peaks are at the values of the diffraction angles 2θ of 5.0°; 7.1 °; and 8.4°.

G.C.Viscomi et.al. in US 7,923,553 discloses process for the preparation of polymorphous form rifaximin α, rifaximin β & rifaximin γ.

G.C.Viscomi et.al. in US 8,193,196 discloses two polymorphic forms of Rifaximin, designated δ characterized by x-ray powder diffraction pattern peaks at about 5.7°±0.2, 10.8°±0.2, 12.1°±0.2, and 17.0°±0.2, 2θ and ε respectively. Form δ has water content within the range from 2.5 to 6% by weight (preferably from 3 to 4.5%) and characterized by x-ray powder diffraction pattern peaks at about 8.2°±0.2, 12.4°±0.2, and 16.3°±0.2 2θ.

Karen S. Gushurst et.al.US 8,067,429 describes Form ζ characterized by x-ray powder diffraction pattern peaks at about 4.7 (doublet), 7.6 (doublet), and 9.5° 2-θ; or 4.7 (doublet), 7.3, and 8.2° 2-θ; or 7.6 (doublet), 8.6, and 10.5° 2-θ; or 8.2, 8.6, and 9.5° 2-θ; or 10.2 (triplet), 12.6 (quintet), and 13.2° (doublet) 2-θ; or 7.3, 10.5, and 12.9° (doublet) 2-θ; or 7.3, 7.6 (doublet), 8.2, 8.6° 2-θ; or 4.7 (doublet), 7.3, 7.6 (doublet), 9.5, and 10.5° 2-θ; or 8.2, 8.6, 9.5, 10.2 (triplet), and 10.5° 2-θ; or 8.6, 9.5, 10.2 (triplet), 10.5, and 11.2° (doublet) 2-θ; or 4.7 (doublet), 6.3, 6.4, 7.3, 7.6 (doublet), 8.2, 8.6, 9.5, 10.2 (triplet), 10.5, 11.2 (doublet), 11.9 (doublet), 12.2 (weak), 12.6 (quintet), 12.9 (doublet), 13.2° (doublet) 2-θ and Form η exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in 2θ° (+/−0.20° θ) at 6.1, 7.3, and 7.5° 2-θ; or 6.1, 7.3, and 7.9° 2-θ; or 6.1, 7.3, and 8.8° 2-θ; or 6.1, 7.3, and 12.7° 2-θ; or 6.1, 7.5, and 8.8° 2-θ; or 6.1, 7.5, and 7.9° 2-θ; or 5.3, 6.1, and 7.3° 2-θ; or 5.3, 6.1, and 7.9° 2-θ; or 5.3, 6.1, and 12.7° 2-θ; or 5.3, 6.1, and 7.5° 2-0; or 5.3, 6.1, and 8.8° 2-θ; or 6.1, 7.3, 7.5, 7.9, 8.8, and 12.7° 2-θ; or 5.3, 6.1, 7.3, 7.5, 7.9, 8.8, 12.7° 2-θ; or 5.3, 6.1, 7.3, 7.9, 8.8, and 12.7° 2-θ; or 5.3, 6.1, 7.3, 7.5, 8.8, and 12.7 ° 2-θ; or 5.3, 6.1, 7.3, 7.5, 7.9, 8.8, and 12.7 ° 2θ and polymorph Form ι exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in 2θ° (+/−0.20° θ) at 5.9±0.1; 7.9±0.1; 9.0±0.1; or 12.7±0.1; 13.9±0.1; 14.9±0.1; or 5.9±0.1; 7.9±0.1; 12.7±0.1; or 5.9±0.1; 9.0±0.1; 12.7±0.1; or 5.9±0.1; 13.9±0.1; 14.9±0.1; or 5.9±0.1; 7.9±0.1; 14.9±0.1; or 9.0±0.1; 12.7±0.1; 14.9±0.1; or 5.9±0.1; 7.9±0.1; 9.0±0.1; 14.9±0.1; or 5.9±0.1; 7.9±0.1; 9.0±0.1; 12.7±0.1; or 5.9±0.1; 7.9±0.1; 9.0±0.1; 12.7±0.1; 13.9±0.1; 14.9±0.1 and mesylate Form of rifaximin exhibits X-ray powder diffraction pattern having characteristic peaks expressed in 2θ° (+/−0.20° θ) at 5.34±0.10; 8.46±0.10; 10.95±0.10; or 5.34±0.10; 6.93±0.10; 8.46±0.10; or 5.34±0.10; 10.95±0.10; 16.23±0.10; 17.70±0.10; or 7.41±0.10; 8.46±0.10; 10.62±0.10; 10.95±0.10; or 16.23±0.10; 17.70±0.10; 17.94±0.10; 19.29±0.10; 22.77±0.10; or 16.23±0.10; 17.70±0.10; 19.29±0.10; 22.77±0.10; or 5.34±0.10; 16.23±0.10; 17.70±0.10; or 5.34±0.10; 6.93±0.10; 7.41±0.10; 8.46±0.10; 10.62±0.10; 10.95±0.10; 16.23±0.10; 17.70±0.10; 17.94±0.10;

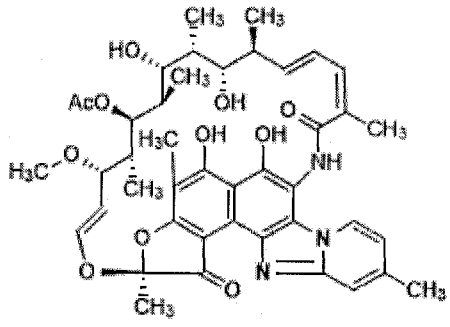
19.29±0.10; 22.77±0.10.. Further this patent discloses β-1, β-2, ε-dry and amorphous forms of Rifaximin.

Rifaximin is an important therapeautic agent for the treatment of patients with travelers' diarrhea (TD) and the reduction in risk of overt hepatic encephalopathy (HE) recurrence. Additional and improved ways of preparing new polymorphic forms of Rifaximin may provide an opportunity to improve the drug performance characteristics of such products. Hence, there exists a need for the further development of new stable crystalline form of Rifaximin and commercially viable processes for its preparation, which may be up scalable, safer for handling, less time consuming and with better and consistent quality parameters.

The inventors of this application have developed a process which provides a stable polymorphic crystalline form of Rifaximin, designated as Form GR which is stable, non-hygroscopic, and thus has easy handling properties. The process of this invention provides the crystalline Form GR of Rifaximin in substantially pure form.

SUMMARY OF INVENTION

Particular aspects of the present invention relates to a process for the preparation of crystalline Form GR of Rifaximin (I). Crystalline Form GR of Rifaximin obtained by the process of the present invention is found to be substantially pure and stable.



(I)

In one aspect of the present invention, it relates to process for the preparation of crystalline Form GR of Rifaximin (I), characterized by X-ray powder diffraction angle peaks at 5.5, 6.6, 6.8, 7.5, 7.7, 11.8, 13.3 and 15.4 ± 0.2° 2θ comprising the steps of-

a. providing a solution of Rifaximin in a mixture of alcoholic solvent at room temperature;
b. solution obtained in step a. is maintained for a time duration ranging between 1-5 hours at a temperature ranging between 5 – 100°C;
c. stirring the solution for a time duration ranging between 1-10 hours at a temperature ranging between -10°C to 10°C;
d. separating the crystalline material.

In another aspect of the present invention relates to crystalline Form GR of Rifaximin, which is characterized by

a) X-ray powder diffraction pattern comprising of at least five 2θ° peaks selected from 5.5, 6.6, 6.8, 7.5, 7.7, 11.8, 13.3 and 15.4 ± 0.2 2θ°;

b) TGA weight loss ranging between 1-5% w/w.

In a further aspect of the present application also relates to process for the preparation of substantially pure Rifaximin comprising recrystallization using mixture of alcoholic solvent wherein mixture of alcoholic solvents is in the ratio of 1 : 10 (v/v).

Further particular aspects of the invention are detailed in the description part of the specification, wherever appropriate.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an example of X-ray powder diffraction ("XRPD") pattern of crystalline Form GR of Rifaximin.

Fig. 2 is an example of Thermogravimetric analysis ("TGA") curve of Form GR of Rifaximin.

DETAILED DESCRIPTION

As set forth herein, embodiments of the present invention provide a reproducible and efficient process for the preparation of crystalline Form GR of Rifaximin (I). Crystalline Form GR of Rifaximin obtained by the process of the present invention is found to be substantially pure and stable.

In another embodiment according to present application, it provides a process for the preparation of crystalline Form GR of Rifaximin (I), comprising the steps of:

a. providing a solution of Rifaximin in a mixture of alcoholic solvent at room temperature;
b. solution obtained in step a. is maintained for a time duration ranging between 1-5 hours at a temperature ranging between 5 – 100°C;
c. stirring the solution for a time duration ranging between 1-10 hours at a temperature ranging between -10°C to 10°C;
d. separating the crystalline material.

Individual steps of the embodiments are detailed herein below.

In the step of providing a solution according to the present invention, it comprises the source of Rifaximin that may be obtained according to any of prior disclosed processes.

In the step of providing a solution, Rifaximin as obtained is dissolved in isopropanol or in a mixture of C1-C4 alcoholic solvent. The mixture of alcoholic solvent is in the ratio of 1:10 (v/v). Stirring the reaction mass performed for not less than 10 hours at temperature ranging between 20 - 100°C.

In a particular embodiment according to present application, making solution is in the temperature range of 20 - 100°C.

In one of the particular embodiment according to present invention in step a, solvents are selected from methanol, ethanol, isopropanol, propanol, n-butanol.

In one of the particular embodiment according to present application in step a, reaction is performed at 70-85°C for 1-5 hours.

In another particular embodiment according to present invention in step a, reaction is performed at 70-85°C for 3 hours.

In yet another particular embodiment according to present invention in step a, reaction is performed at 25-35°C for 3 hours.

In a particular embodiment according to present application, solution is a mixture of Ethanol & Isopropanol or mixture of Methanol & Isopropanol.

In the Step b of present embodiment, maintaining the solution for 5 hours at a temperature ranging between 20 – 100°C.

In one of the particular embodiment according to present invention, step b is maintained for 2 hours at temperature 70-85°C.

In the Step c of present embodiment, stirring plays a very critical role in obtaining the desired characteristics of the end product i.e crystalline Form GR of Rifaximin.

In one of the particular embodiment of the present invention, solution is stirred at temperature ranging between -10°C to 10°C for 10 hours.

In another particular embodiment of the present invention, solution is stirred at temperature 0-5°C for 3 hours.

In yet another particular embodiment of the present invention, stirring is carrying out at RPM ranging from 80 – 150.

In one of the embodiment of the present invention, separating crystalline Rifaximin (I) by performing various conventional methods like distillations, filtering, drying, centrifugation etc. to obtain Form GR of Rifaximin (I).

In a particular embodiment, separating and followed by drying wet compound at temperature 55-65°C to get crystalline Form GR of Rifaximin (I). Further, drying conditions may be employed as utilized by person skilled in the art.

Process of recovering the desired particle size crystalline Form GR of Rifaximin (I) may further require conventional steps to obtain such desired particle sizes.

According to one embodiment of the present invention provides crystalline Form GR of Rifaximin (I) is characterized by X-ray powder diffraction (XRPD) pattern substantially as depicted in Fig 1.

In another embodiment of the present invention provides crystalline Form GR of Rifaximin (I) which is characterized by TGA weight loss ranging between 1-5 % w/w.

The remaining steps of the embodiment shall be construed in line with the exemplified disclosure.

In another embodiment of the present invention provides process for the preparation of substantially pure Rifaximin comprising recrystallization using mixture of alcoholic solvent wherein mixture of alcoholic solvents is in the ratio of 1 : 10 (v/v).

Substantially pure crystalline Form GR of Rifaximin (I) obtained according to the process of the present invention results in the final API purity by HPLC of more than 99% and preferably greater than 99.5%. The purity of the Form GR of Rifaximin (I) samples was measured using Chromatography. Chromatography was performed with Waters Alliance HPLC system (MILD, USA) that consists of quaternary pump equipped with a 2695 separation module with inbuilt auto injector and 2996 photodiode array detector. The output signal was monitored and processed using chromelean software version 6.8.

In another embodiment of the present invention provides a process for preparation of Form GR of Rifaximin (I) having water content in range of 1 - 6%, preferably between 1 - 5%, as determined by the Karl Fischer method.

The crystalline Form GR of Rifaximin (I) obtained by the process of the present application may be formulated as solid compositions for oral administration in the form of capsules, tablets, pills, powders or granules. In these compositions, the active product is mixed with one or more pharmaceutically acceptable excipients. The drug substance can be formulated as liquid compositions for oral administration including solutions, suspensions, syrups, elixirs and emulsions, containing solvents or vehicles such as water, sorbitol, glycerin, propylene glycol or liquid paraffin.

In one embodiment of the present invention, it also includes premix comprising one or more pharmaceutically acceptable excipients in the range of 1 to 50% w/w with crystalline Form GR of Rifaximin (I), while retaining the amorphous form nature of the premix.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilization may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilizing agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions, which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

Pharmaceutically acceptable excipients used in the compositions comprising crystalline Form GR of Rifaximin (I) of the present application include, but are but not limited to diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, pre-gelatinized starch and the like; disintegrants such as starch, sodium starch glycolate, pregelatinized starch, Croscarmellose sodium, colloidal silicon dioxide and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

Pharmaceutically acceptable excipients used in the compositions of crystalline Form GR of Rifaximin (I) of the present application may also comprise to include the pharmaceutically acceptable carrier used for the preparation of solid dispersion, wherever utilized in the desired dosage form preparation.

The invention was further defined by reference to the following examples describing in detail by the preparation of the compounds of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES:

Example 1:

Rifaximin (4.0 gr) was dissolved in a mixture of IPA (20.0 mL) & Ethanol (4.0 mL) at 70-85°C and the mass was cooled to Room temperature (25-35°C). After 2 hours of maintenance, the mass was further cooled and stirred for 3 hrs at 0-5°C. The product was separated by filtration and dried at 55-65°C to yield the crystalline Form GR of Rifaximin.

Yield: 92%

Purity: 99.79% by HPLC;

Water Content: 4.07% by KF.

Example 2:

Rifaximin (4.0 gr) was dissolved in a mixture of IPA (12.0 mL) & Ethanol (4.0 mL) at 70-85°C and the mass was cooled to Room temperature (25-35°C). After 2 hours of maintenance, the mass was further cooled and stirred for 3 hrs at 0-5°C. The product was separated by filtration and dried at 55-65°C to yield the crystalline Form GR of Rifaximin

Yield: 84%

Purity: 99.58% by HPLC

Water Content: 4.19% by KF

Example 3:

Rifaximin (4.0 gr) was dissolved in a mixture of IPA (24.0 mL) & Ethanol (12.0 mL) at 70-85°C and the mass was cooled to Room temperature (25-35°C). After 3 hours of maintenance, the product was separated by filtration and dried at 55-65 °C to yield the crystalline Form GR of Rifaximin

Yield: 90%

Purity: 99.78% by HPLC

Water content: 3.34% by KF

Example 4:

Rifaximin (4.0 gr) crude was dissolved in a mixture of IPA (24.0 mL) & Ethanol (12.0 mL) at 70-85°C and the mass was cooled to Room temperature (25-35°C). After 2 hours of maintenance, the mass was further cooled and stirred for 3 hrs at 0-5°C. Pure Rifaximin was separated by filtration and dried at 55-65°C. Optionally the product is further subjected to the same procedure to improve purity of the product.

Yield: 90%

Purity: 99.50% by HPLC

Water content: 3.36% by KF

Example 5:

Rifaximin (4.0 gr) was dissolved in a mixture of IPA (24.0 mL) & Ethanol (12.0 mL) at 25-35 °C and then heated to 70-85°C. Later, the mass was cooled to 0-5°C and stirred for 3 hrs at same temperature. The product was separated by filtration and dried at 55-65 °C to yield the crystalline Form GR of Rifaximin.

Yield: 95%

Purity: 99.60% by HPLC

Water content: 4.08% by KF

Example 6:

Rifaximin (4.0 gr) was dissolved in a mixture of IPA (20.0 mL) & Methanol (4.0 mL) at 70-85°C and the mass was cooled to Room temperature (25-35°C). After 2 hours of maintenance, the mass was further cooled and stirred for 3 hrs at 0-5°C. The product was separated by filtration and dried at 55-65°C to yield the crystalline Form GR of Rifaximin.

Yield: 88%

Purity: 99.82% by HPLC

Water content: 3.74% by KF

Example 7:

Rifaximin (4.0 gr) was dissolved in a mixture of IPA (12.0 mL) & Methanol (4.0 mL) at 70-85°C and the mass was cooled to Room temperature (25-35°C). After 2 hours of maintenance, the mass was further cooled and stirred for 3 hrs at 0-5°C. The product was separated by filtration and dried at 55-65°C to yield the crystalline Form GR of Rifaximin.

Yield: 83%

Purity: 99.86% by HPLC

Water content: 3.36% by KF

Example 8:

Rifaximin (4.0 gr) was dissolved in isopropyl alcohol (20.0 mL) at 70-85°C and the mass was cooled to Room temperature (25-35°C). After 2 hours of maintenance, the mass was further cooled and stirred for 3 hrs at 0-5°C. Rifaximin was separated by filtration and dried at 55-65°C to yield the crystalline Form GR of Rifaximin.

Yield: 86%

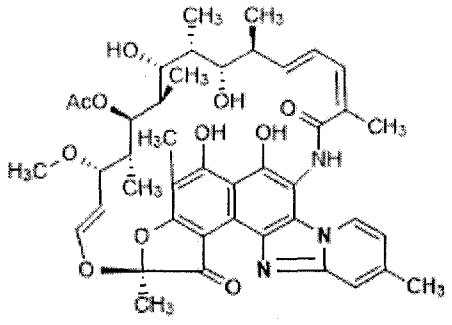
Purity: 99.52% by HPLC

Water content: 3.34% by KF

While the foregoing pages provide a detailed description of the preferred embodiments of the invention, it is to be understood that the summary, description and examples are illustrative only of the core of the invention and non-limiting. Furthermore, as many changes can be made to the invention without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

We Claim:

1) A process for the preparation of crystalline Form GR of Rifaximin (I) characterized by X-ray powder diffraction angle peaks at 5.5, 6.6, 6.8, 7.5, 7.7, 11.8, 13.3 and 15.4 ± 0.2 2θ° comprising the steps of:



(I)

a. providing a solution of Rifaximin in Isopropanol or in a mixture of alcoholic solvents at 20-100°C;
b. solution obtained in step a. is maintained for a time duration ranging between 1-5 hours at a temperature ranging between 20 – 40°C;
c. resulting mixture is stirred for a time duration ranging between 1-10 hours at a temperature ranging between -10°C to 10°C;
d. separating the crystalline material.

2) The process for the preparation of crystalline Form GR of Rifaximin (I), according to claim 1, wherein alcoholic solvent is selected from C_1-C_4 alcohol or mixture thereof.

3) The process for the preparation of crystalline Form GR of Rifaximin (I), according to claim 1, wherein C_1-C_4 alcohol selected from methanol, ethanol, isopropanol, propanol, n-butanol.

4) The process for preparing crystalline Form GR of Rifaximin (I), according to claim 2, wherein mixture of alcoholic solvents are in the ratio of 1 : 10 (v/v).

5) Crystalline Form GR of Rifaximin (I) characterized by

a. X-ray powder diffraction pattern comprising of at least five diffraction angle peaks selected form 5.5, 6.6, 6.8, 7.5, 7.7, 11.8, 13.3 and 15.4 ± 0.2 2θ°.
b. TGA weight loss ranging between 1-5%

6) Crystalline Form GR of Rifaximin (I) according to claim 5 having HPLC purity of at least 99.5 %.

7) A process for the preparation of substantially pure Rifaximin (I) comprising recrystallization using mixture of alcoholic solvent wherein mixture of alcoholic solvents is in the ratio of 1 : 10 (v/v).

Figure 01 of 02

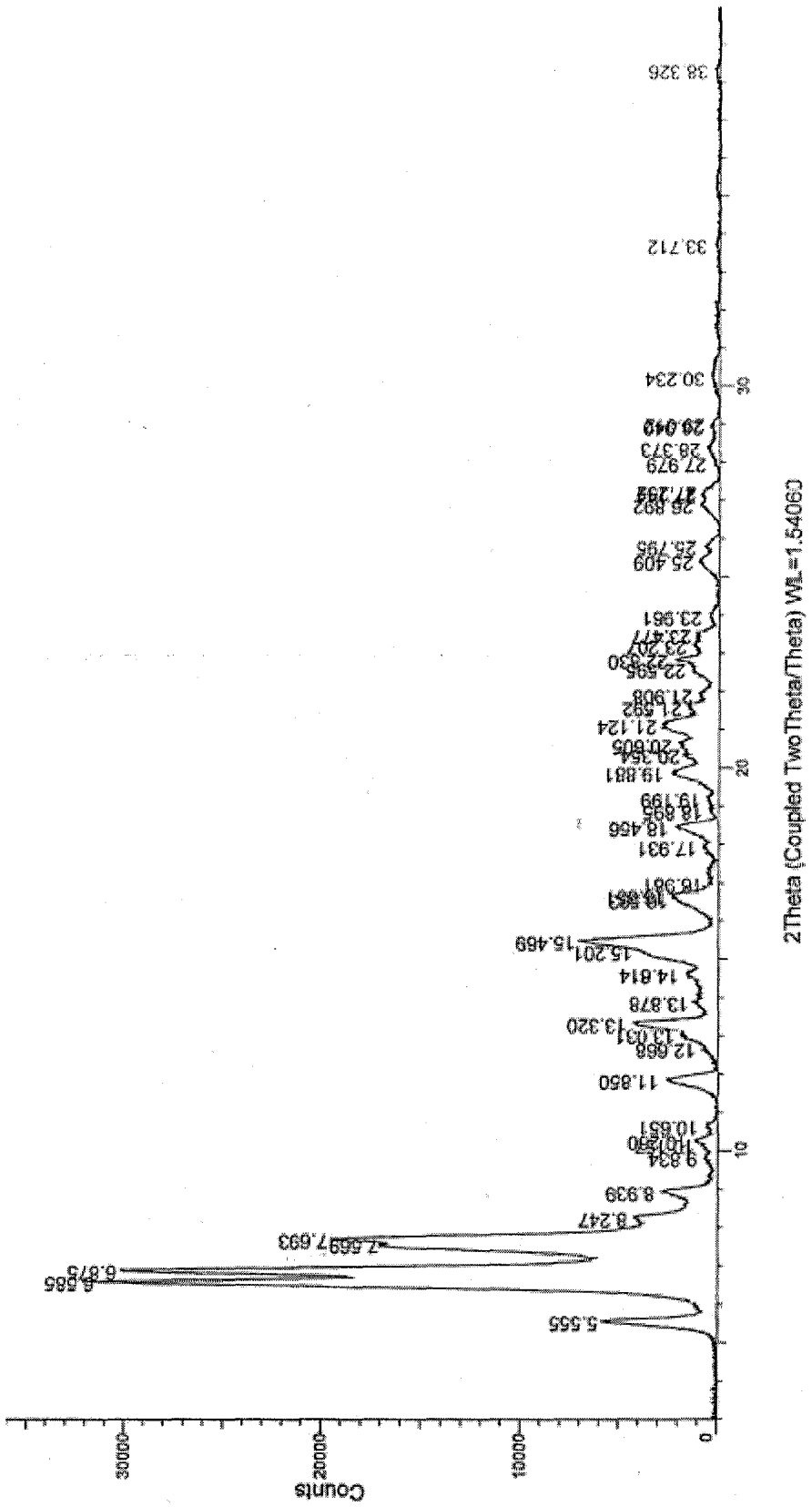
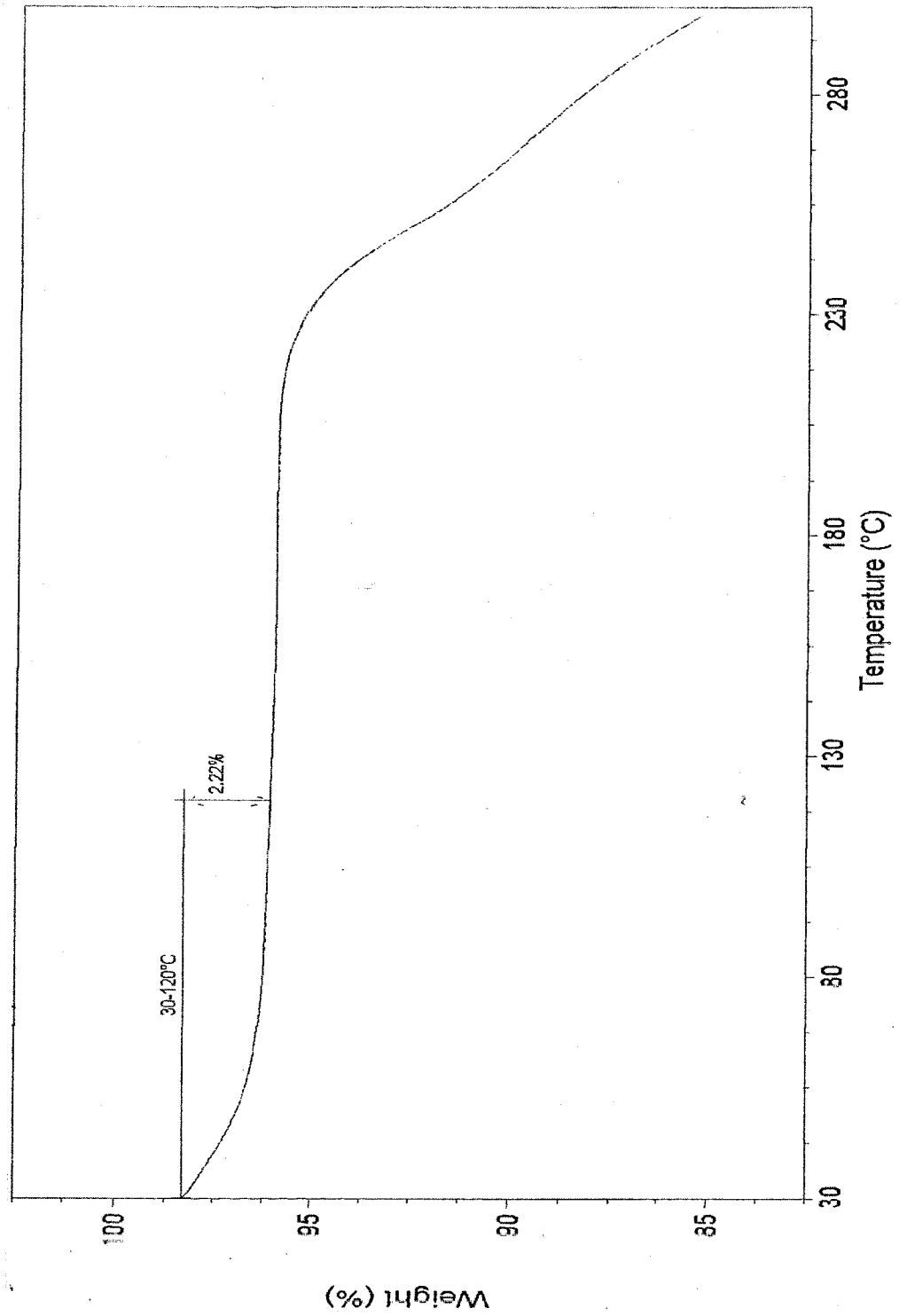


Figure 02 of 02



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2018/050920

A. CLASSIFICATION OF SUBJECT MATTER
C07D498/22 Version=2018.01

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 practicable, search terms used)

TotalPatent One

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2015159275 A2; GRANULES INDIA LIMITED; 22-10-2015 (22 October 2015). Claims 15-20	1-4, 7
X	WO2017021975 A1; MSN LABORATORIES PRIVATE LIMITED; 09-02-2017 (09 February 2017). Whole document	1-4, 7
A	US20090082558 A1; APOTEX PHARMACHEM INC; 26-03-2009 (26 March 2009). Whole document	5, 6

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

☒ See patent family 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 application or patent but published on or after the international filing date

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"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
31-05-2018	31-05-2018

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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2018/050920

Citation	Pub.Date	Family	Pub.Date
WO 2015159275 A2	22-10-2015	CA 2946101 A1	22-10-2015
		EP 3134415 A2	01-05-2017
		US 9765088 B2	19-09-2017
WO 2017021975 A1	09-02-2017	IN 4109CHE2015 A	02-10-2017