



(51) International Patent Classification:

A61K 9/00 (2006.01) C12Q 1/00 (2006.01)
A61K 31/395 (2006.01)

(21) International Application Number:

PCT/IB2021/054078

(22) International Filing Date:

13 May 2021 (13.05.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

202021020567 15 May 2020 (15.05.2020) IN

(71) Applicant: ATRA PHARMACEUTICALS LIMITED
[IN/IN]; Plot No. H-19, Midc, Waluj, Maharashtra, Aurangabad 431133 (IN).

(72) Inventors: KUMAR, Gidigam Prem; Plot No. H-19, Midc, Waluj, Maharashtra, Aurangabad 431133 (IN). BURMAN, Subrata Kumar; Plot No. H-19, Midc, Waluj, Maharashtra, Aurangabad 431133 (IN). DESHPANDE, Shripad Lamikant; Plot No. H-19, Midc, Waluj, Maharashtra, Aurangabad 431133 (IN). POTDAR, Umesh Dattatraya;

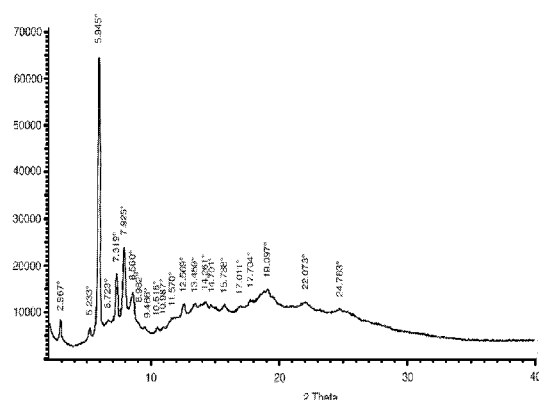
Plot No. H-19, Midc, Waluj, Maharashtra, Aurangabad 431133 (IN).

(74) Agent: BHAT, Raghavendra et al.; M/S INNOIPS, B-1104, Gracia, Kharadi, Pune 411 014, MH (IN).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: POLYMORPH OF RIFAXIMIN, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITION CONTAINING RIFAXIMIN



Angle	d Value	Rel. Intensity
2.867 °	29.75478 Å	7.3%
5.233 °	16.87444 Å	5.6%
5.945 °	14.85529 Å	100.0%
6.723 °	13.13777 Å	6.7%
7.319 °	12.08588 Å	22.3%
7.925 °	11.14701 Å	12.0%
8.589 °	10.82152 Å	15.0%
8.952 °	9.83749 Å	4.6%
9.484 °	9.33722 Å	2.3%
10.515 °	8.49581 Å	1.3%
10.967 °	8.64804 Å	1.7%
11.579 °	7.84235 Å	5.6%
12.589 °	7.03602 Å	2.0%
13.459 °	6.57343 Å	8.2%
14.251 °	6.20543 Å	5.6%
14.701 °	5.92108 Å	2.0%
15.734 °	5.77620 Å	6.4%
17.013 °	5.20862 Å	3.9%
17.704 °	5.06563 Å	7.0%
19.087 °	4.64380 Å	11.5%
22.073 °	4.02380 Å	8.8%
24.713 °	3.98636 Å	8.3%

FIGURE 1

(57) Abstract: The present invention relates to a novel polymorphic form of Rifaximin designated RV-A, method for its preparation, pharmaceutical composition containing the novel polymorphic form of Rifaximin and a method of preparing the pharmaceutical composition.

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to the identity of the inventor (Rule 4.17(i))*

Published:

- *with international search report (Art. 21(3))*
- *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

POLYMORPH OF RIFAXIMIN, PROCESS FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITION CONTAINING RIFAXIMIN

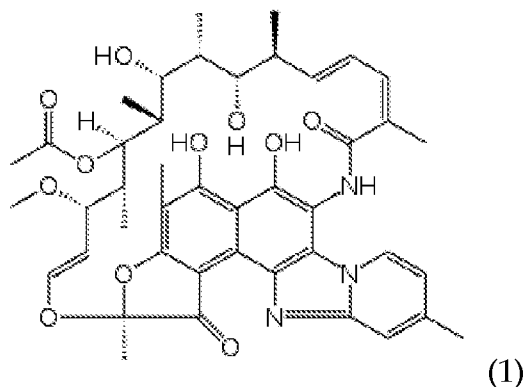
TECHNICAL FIELD

[001] The present invention relates to a novel polymorphic form of Rifaximin, method for its preparation, pharmaceutical composition containing the novel polymorphic form of Rifaximin and a method of preparing the pharmaceutical composition.

BACKGROUND

[002] Rifaximin is an antibiotic belonging to the rifamycin class. Rifaximin (1) is a non-aminoglycoside semi-synthetic, non-systemic antibiotic derived from Rifamycin, useful for the treatment of traveller's diarrhoea caused by *Escherichia coli* bacteria. Rifaximin has also been evaluated for the treatment of irritable bowel syndrome, diverticular disease, hepatic encephalopathy, pyogenic skin infections, and as an antibacterial prophylactic prior to colon surgery.

[003] Chemically, Rifaximin is (2S, 16Z, 18E, 20S, 21 S, 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 ,1 1 ,13]trienimino)- benzofuro[4,5-e]-pyrido[1 , 2-(a)]-benzimidazole-1 , 15(2H)dione, 25-acetate.



[004] WO2005044823 discloses crystalline polymorphous forms of Rifaximin (INN) antibiotic named Rifaximin alpha and Rifaximin beta, and a poorly crystalline form with a high content of amorphous content named Rifaximin gamma. These forms can be obtained by means of a crystallization process carried out by hot-dissolving the raw Rifaximin in ethyl alcohol and by causing the crystallization of the product by the addition of water at a determinate temperature and for a determinate time period. The crystallization is followed by drying carried out under controlled conditions until specific water content is reached in the end product. Also described is a composition comprising substantially amorphous Rifaximin, and a method of preparing amorphous Rifaximin. The method comprises providing dried Rifaximin; heating the Rifaximin in the presence of an alcohol to result in dissolution of the Rifaximin; precipitating and drying the precipitate to have a water content of less than 2% to form substantially amorphous Rifaximin. The disclosure further relates to Rifaximin polymorphic forms alpha, beta and gamma, the processes for their preparation and the use thereof in the manufacture of medicinal preparations for the oral or topical route.

[005] WO2006094662 disclose crystalline polymorphous forms of Rifaximin (INN) antibiotic named Rifaximin delta and Rifaximin epsilon. These forms can be obtained by means of a crystallization process carried out by hot-dissolving the raw Rifaximin in ethyl alcohol and by causing the crystallization of the product by addition of water at a determinate temperature and for a determinate time period. The crystallization is followed by drying carried out under controlled conditions until specific water content is reached in the end product.

[006] WO 2009108730 and WO2011103120 relates to Rifaximin polymorphic, salt, hydrate, and amorphous forms, to their use in medicinal preparations, and to therapeutic methods using them. Form zeta, Form eta, Form alpha-dry, Form iota, Form iota-dry, Form iota-dry', Form beta-1, Form beta-2, Form epsilon-dry, Form B and amorphous forms of Rifaximin as well as a mesylate salt are described.

[007] WO2012156951 discloses polymorphous forms of Rifaximin namely Form kappa. The said form tends to keep its crystalline form even in the presence of moisture thereby making it more stable.

[008] WO2012109605 discloses polymorphous forms of Rifaximin namely Form Mu, Form Pis, Form Omicron, Form Zeta, Form Eta, Form Iota, and salt forms and hydrates of Rifaximin.

[009] WO2011156897 discloses polymorphous forms of Rifaximin namely substantially pure APO-I and APO-II, are provided. Rifaximin dissolved in ethyl acetate is added to heptanes to obtain form APO-I.

[0010] WO2013185211 discloses polymorphous forms of Rifaximin named APO-III and APO-IV. Also provided are novel processes for preparing the previously disclosed Rifaximin polymorphic forms APO-I and APO-II.

[0011] WO 2008155728 describes a process which provides Rifaximin in a completely amorphous form. Said process comprises the steps of dissolving crude Rifaximin in absolute ethanol while hot and then collecting after precipitation by cooling to obtain Rifaximin in amorphous form.

[0012] WO2008035109 discloses amorphous Rifaximin, methods of making it, and pharmaceutical compositions containing it. Also described are methods of converting amorphous Rifaximin to crystalline Rifaximin and vice versa.

[0013] US 20090082558 describes a stable amorphous form of Rifaximin. This form is chemically and polymorphic stable on storage and can be prepared by dissolving Rifaximin in a solvent to form a solution which is precipitated by adding an anti-solvent and isolating of the precipitated amorphous Rifaximin as an end product.

[0014] WO2006094737 and WO2012038898 describes a pharmaceutical composition comprising gastro-resistant Rifaximin microgranules.

[0015] WO2011051971 describes a solid dispersion of Rifaximin comprising Rifaximin and pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises copovidone and polyethylene glycol.

[0016] WO2012009387 describes a solid dispersion that comprises Rifaximin and one or more polymers selected from hydroxypropyl methylcellulose phthalate (HPMC-P), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), and a polymethacrylate (Eudragit® L100-55) in a specific ratio.

[0017] WO2008029208 describes polyols which stabilize polymorphous forms of Rifaximin, in particular the beta form. When polyols having at least two hydroxyl

groups are added to Rifaximin powder, polymorph beta is stable and remains stable in time independently from the environment humidity. A method to prepare formulations constituted by pure and stable polymorphous forms able to give a pharmaceutical product is also described.

[0018] WO2011005388, WO2009108814 and WO2011032085 describes use of Rifaximin for the preparation of a medication.

[0019] The present inventors have now identified a novel polymorphic form of Rifaximin, which is stable chemically and polymorphically on storage and is unaffected by external parameters such as ambient humidity.

SUMMARY

[0020] The present invention relates to a novel crystalline form of Rifaximin, namely polymorphic form of Rifaximin termed herein as Form RV-A, method for its preparation, pharmaceutical composition containing the novel polymorph of Rifaximin and a method of preparing the pharmaceutical composition.

[0021] An embodiment of the present invention provides the novel polymorphic form RV-A of Rifaximin described herein characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta (+/- 0.20 degree theta) at approximately 5.94, 7.32, 7.92, 8.56 and 19.01.

[0022] An embodiment of the present invention provides the novel polymorphic form RV-A of Rifaximin described herein characterized by a 1 % KBr FTIR spectrum comprising peaks, in terms of cm⁻¹, at approximately 3424, 2920, 1725, 1648 and 1229.

[0023] An embodiment of the present invention provides a pharmaceutical composition comprising the novel polymorphic form RV-A of Rifaximin characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta (+/- 0.20 degree theta) at approximately 5.94, 7.34, 7.93, 8.63, 13.49, 14.49 and 22.47.

[0024] An embodiment of the present invention provides the polymorphic form RV-A of Rifaximin described herein characterized by a PXRD diffractogram substantially similar to the PXRD diffractogram as depicted in Figure 1.

[0025] An embodiment of the present invention provides the polymorphic form RV-A of Rifaximin described herein characterized by a PXRD diffractogram as depicted in Figure 1.

[0026] An embodiment of the present invention provides the polymorphic form RV-A of Rifaximin described herein characterized by a FTIR spectrum substantially similar to the FTIR spectrum as depicted in Figure -2.

[0027] An embodiment of the present invention provides the polymorphic form RV-A of Rifaximin described herein characterized by a FTIR spectrum as depicted in Figure 2.

[0028] An embodiment of the present invention provides a pharmaceutical composition as an oral dosage form containing the novel polymorphic form RV-A of Rifaximin characterized by a PXRD diffractogram substantially similar to the PXRD diffractogram as depicted in Figure 3.

[0029] An embodiment of the present invention provides a pharmaceutical composition as an oral dosage form containing the novel polymorphic form RV-A of Rifaximin characterized by a PXRD diffractogram as depicted in Figure 3.

[0030] An embodiment of the present invention provides a pharmaceutical composition as an oral dosage form containing the novel polymorphic form RV-A of Rifaximin that is stable over 24 months characterized by a PXRD diffractogram substantially similar to the PXRD diffractogram as depicted in Figure 4.

[0031] An embodiment of the present invention provides a pharmaceutical composition as an oral dosage form containing the novel polymorphic form RV-A of Rifaximin that is stable over 24 months characterized by a PXRD diffractogram as depicted in Figure 4.

[0032] An embodiment of the present invention provides a process for the preparation of a polymorphic form RV-A of Rifaximin, the process comprising:

- a. Reacting rifamycin O with 2-amino-4-methylpyridine in a suitable solvent or a mixture of solvents, for a time between 2 – 10 hours and at a temperature between 25°C to 75°C to provide crude Rifaximin,
- b. The resulting crude Rifaximin is purified by dissolving alcohol preferable ethyl alcohol, at a temperature between 35°C and 75°C, followed by crystallization

by addition of water. The resulting suspension is stirred at a temperature between 50°C and 0°C for a duration between 2 and 24 hours,

- c. The suspension is filtered and the obtained solid is washed with water and dried under vacuum, optionally in the presence of a drying agent, at a temperature between room temperature and 75°C for a time between 2 and 24 hours.

[0033] An embodiment of the present invention provides a pharmaceutical composition as an oral dosage form.

[0034] According to one embodiment, the pharmaceutical composition may be formulated as coated or uncoated tablets, hard or soft gelatin capsules, sugar-coated pills, lozenges, wafer sheets, pellets or powders in a sealed packet.

[0035] An embodiment of the present invention provides a pharmaceutical composition as an oral dosage form, preferably in the form of a tablet.

[0036] An embodiment of the present invention provides a pharmaceutical composition in the form of tablets comprising

- i) containing Rifaximin RV-A,
- ii) pharmaceutically acceptable carriers, and optionally
- iii) a film-forming coating.

[0037] In one embodiment, the novel polymorph of Rifaximin contains less than 5% by weight total impurities.

[0038] In one embodiment, the novel polymorph of Rifaximin is at least 75% pure, or at least 80% pure, or at least 90% pure, or at least 95% pure, or at least 98% pure.

[0039] According to one embodiment, the pharmaceutical composition comprises novel polymorph of Rifaximin and a pharmaceutically acceptable carrier.

[0040] In one embodiment, the composition further comprises one or more pharmaceutically acceptable excipients. The excipients may be one or more of a diluting agent, binding agent, lubricating agent, disintegrating agent, colouring agent, flavouring agent or sweetening agent.

[0041] An embodiment of the present invention provides a process for the preparation of pharmaceutical composition that is preferably in the form of a tablet.

[0042] A further embodiment of the present invention provides a method for preparing a tablet comprising the steps of

- (i) providing novel polymorph of Rifaximin RV-A and optionally one or more further excipients
- (ii) optionally granulating the mixture of step (i) and optionally one or more further excipients
- (iii) compressing the mixture from step (i) or the granulates from step (ii) and optionally further excipients into a tablet.

[0043] According to another embodiment, presented herein, is use of novel polymorph of Rifaximin namely Form RV-A as a medicament.

[0044] According to another embodiment, presented herein, is a process for production of novel polymorph of Rifaximin namely Form RV-A.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] Drawings which illustrate embodiments of the invention are:

[0046] Figure 1: is a powder X-ray diffraction (PXRD) diffractogram of novel polymorphic form RV-A

[0047] Figure 2: is a Fourier Transform Infrared (FTIR) spectrum of novel polymorphic form RV-A

[0048] Figure 3: is a powder X-ray diffraction (PXRD) diffractogram of pharmaceutical composition containing novel polymorphic form RV-A

[0049] Figure 4: is a powder X-ray diffraction (PXRD) diffractogram of pharmaceutical composition containing novel polymorphic form RV-A taken after 24 months maintained at 30 °C and 75% relative humidity.

DETAILED DESCRIPTION

[0050] Embodiments of the present invention relates to novel polymorphic form of Rifaximin, process for the preparation of the novel polymorphic form, pharmaceutical composition containing the novel polymorphic form as well as to a process of preparing the pharmaceutical composition containing the novel polymorphic form.

[0051] As used herein "Rifaximin Form RV-A", "Form RV-A", "polymorph RV-A", "Form RV-A of Rifaximin" are used interchangeably to denote the polymorphic form of Rifaximin as further described herein by, for example, one or more peaks of a powder x-ray diffractogram, NMR, FT-IR. Rifaximin form RV-A comprises powder x-ray diffraction pattern peak positions described herein and in the figures. Rifaximin form RV-A may be identified and characterised by one or more of these parameters or peaks.

[0052] Polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore, a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as solubility profiles, melting point temperatures, hygroscopicity, particle shape, density, flowability, compatibility and/or x-ray diffraction peaks. The solubility of each polymorph may vary, thus, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predictable solubility profiles. It is desirable to investigate all solid-state forms of a drug, including all polymorphic forms, and to determine the stability, dissolution, and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as, infrared spectrometry. For a general review of polymorphs and the pharmaceutical applications of polymorphs see G. M. Wall, Pharm Manuf. 3, 33 (1986); J. K. Haleblan and W. McCrone, J Pharm. ScL, 58, 911 (1969); and J. K. Haleblan, J. Pharm. ScL, 64, 1269 (1975), all of which are incorporated herein by reference.

[0053] When used in reference to a diffractogram, a spectrum and/or data presented in a graph, the term "substantially similar" means that the subject diffractogram, spectrum and/or data presented in a graph encompasses all diffractograms, spectra and/or data presented in graphs that vary within acceptable boundaries of

experimentation that are known to a person of skill in the art. Such boundaries of experimentation will vary depending on the type of the subject diffractogram, spectrum and/or data presented in a graph, but will nevertheless be known to a person of skill in the art.

[0054] When used in reference to a peak in a PXRD diffractogram, the term "approximately" means that the peak may vary by ± 0.2 degrees 2-theta of the subject value.

[0055] When used in reference to a peak in a FTIR spectrum, the term "approximately" means that the peak may vary by ± 5 cm of the subject value.

[0056] As used herein, the term polymorph is occasionally used as a general term in reference to the forms of Rifaximin and includes within the context, salt, hydrate, polymorph and amorphous forms of Rifaximin disclosed herein. This use depends on context and will be clear to one of skill in the art.

[0057] The following example serves to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner. Depending on the nature of the methodology applied and the scale selected to display results obtained from an X-ray diffraction analysis, an intensity of a peak obtained may vary quite dramatically. For example, it is possible to obtain a relative peak intensity of 1 % when analyzing one sample of a substance, but another sample of the same substance may show a much different relative intensity for a peak at the same position. This may be due, in part, to the preferred orientation of the sample and its deviation from the ideal random sample orientation, sample preparation and the methodology applied. Such variations are known and understood by a person of skill in the art.

[0058] The phrase "pharmaceutically-acceptable carrier" includes pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ, or portion of the body, to another organ, or portion of the body. Each carrier is preferably "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and

potato starch; cellulose, and its derivatives, such as hydroxypropyl methylcellulose (hypromellose), sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminium hydroxide; lubricants, such as Magnesium stearate, Zinc stearate and Glyceryl palmitostearate; surfactant, such as Sodium lauryl sulfate and Polyethene glycol, chelating agent, such as disodium EDTA; glidant, such as colloidal anhydrous silica and Talc; coating agents; coloring agents; sweetening, flavoring and perfuming agents; pyrogen- free water; isopropyl alcohol; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0059] Examples of pharmaceutically-acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetra acetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0060] Compositions containing novel Rifaximin form RV-A disclosed herein include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal, aerosol and/or parenteral administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of 100 %, this amount will range from about 1 % to about 99 % of active ingredient, preferably from about 5 % to about 70 %, most preferably from about 10 % to about 60 %.

[0061] Methods of preparing these compositions include the step of bringing into association the novel Rifaximin polymorph with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the Rifaximin polymorph with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0062] Compositions suitable for oral administration may be in the form of capsules, sachets, pills, tablets, lozenges, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles and the like, each containing a predetermined amount of the Rifaximin polymorph as an active ingredient. A compound may also be administered as a bolus, electuary or paste.

[0063] A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder such as gelatin or hydroxypropylmethyl cellulose and the like; lubricant; inert diluent; preservative; dis-integragrant such as sodium starch glycolate or cross-linked sodium carboxymethyl cellulose and the like; surface-active or dispersing agent. Moulded tablets may be made by moulding a mixture of the powdered active ingredient moistened with an inert liquid diluent in a suitable machine.

[0064] The tablets, and other solid dosage forms of the pharmaceutical compositions described herein, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical- formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres.

[0065] An embodiment of the present invention provides the novel polymorphic form RV-A of Rifaximin described herein characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta (+/- 0.20 degree theta) at approximately 5.94, 7.32, 7.92, 8.56 and 19.01.

[0066] An embodiment of the present invention provides the novel polymorphic form RV-A of Rifaximin described herein characterized by a 1 % KBr FTIR spectrum comprising peaks, in terms of cm⁻¹, at approximately 3424, 2920, 1725, 1648 and 1229.

[0067] An embodiment of the present invention provides a process for the preparation of a polymorphic form RV-A of Rifaximin, the process comprising:

- a. Reacting rifamycin O with 2-amino-4-methylpyridine in a suitable solvent or a mixture of solvents, for a time between 2 – 10 hours and at a temperature between 25°C to 75°C to provide crude Rifaximin.
- b. The resulting crude Rifaximin is purified by dissolving alcohol preferable ethyl alcohol, at a temperature between 35°C and 75°C, followed by crystallization by addition of water. The resulting suspension is stirred at a temperature between 50°C and 0°C for a duration between 2 and 24 hours.
- c. The suspension is filtered and the obtained solid is washed with water and dried under vacuum, optionally in the presence of a drying agent, at a temperature between room temperature and 75°C for a time between 2 and 24 hours.

[0068] An embodiment of the present invention provides a pharmaceutical composition as an oral dosage form, preferably in the form of a tablet.

[0069] An embodiment of the present invention provides a pharmaceutical composition in the form of tablets comprising

- i) Rifaximin RV-A,
- ii) pharmaceutically acceptable carriers, and optionally
- iii) a film forming coating agent.

[0070] The pharmaceutically acceptable carriers comprise sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as hydroxypropyl methylcellulose (hypromellose), sodium carboxymethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, ethyl cellulose, sodium starch glycolate and cellulose acetate; powdered tragacanth; malt; gelatin; talc; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol,

mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminium hydroxide; lubricants, such as Magnesium stearate, Zinc stearate, Calcium stearate, Sodium stearyl fumarate, Vegetable hydrogenated oil and Glyceryl palmitostearate; Disintegrants such as, Sodium starch glycolate and Crospovidone; Surfactant, such as Sodium lauryl sulfate and Polyethylene glycols; Chelating agent, such as disodium EDTA; Glidant, such as colloidal anhydrous silica and Talc; coating agents; coloring agents; sweetening, flavoring and perfuming agents; pyrogen- free water; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0071] An embodiment of the present invention provides a pharmaceutical composition comprising the novel polymorphic form RV-A of Rifaximin characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta (+/- 0.20 degree theta) at approximately 5.94, 7.34, 7.93, 8.63, 14.49 and 22.47.

[0072] An embodiment of the present invention provides a pharmaceutical composition comprising the novel polymorphic form RV-A of Rifaximin which is stable over 24 months even when maintained at 30°C and 75% relative humidity characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta (+/- 0.20 degree theta) at approximately 5.92, 7.35, 7.92, 8.60, 14.49 and 22.51.

[0073] Although various embodiments of the invention are disclosed herein, many adaptations and modifications may be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. Furthermore, numeric ranges are provided so that the range of values is recited in addition to the individual values within the recited range being specifically recited in the absence of the range. The word "comprising" is used herein as an open-ended term, substantially equivalent to the phrase "including, but not limited to", and the word "comprises" has a corresponding meaning. As used herein, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a thing" includes more than one such thing. Citation of references herein

is not an admission that such references are prior art to the present invention. Furthermore, material appearing in the background section of the specification is not an admission that such material is prior art to the invention.

EXAMPLES

[0074] The following examples are illustrative of some of the embodiments of the invention described herein. These examples do not limit the spirit or scope of the invention in any way.

[0075] Characterisation: The novel polymorphic form of Rifaximin was characterised by one or more of PXRD, FT-IR, ¹H NMR.

[0076] Powder X-ray diffraction (PXRD) analysis was performed using Bruker D8 Advance LYNXEYE XE-T diffractometer.

[0077] ¹H NMR spectrum Analysis: ¹H NMR was recorded on Bruker at 400 MHz, 300K and solution of the sample was made in CDCl₃.

[0078] Fourier Transform Infrared (FTIR) Analysis: The FTIR spectrum was collected at 4 cm⁻¹ resolution using a Perkin Elmer FT IR spectrum 100, Model No. C 79114 SPLIT.

Preparation of Rifaximin

[0079] To a solution of water and ethyl alcohol (100 mL, 1:1) was added rifamycin O (37.5 g) and 2-amino-4-methylpyridine (16.5 g). The reaction mass was heated at 50°C for 6 hours, then cooled to 25°C and acidified by hydrochloric acid to a pH of 2. The precipitate was filtered to provide crude Rifaximin. Crude Rifaximin (25 g) was suspended in ethyl alcohol (50 mL) and heated at 55°C so as to obtain a clear solution. To this solution was added water (20 mL) and allowed to stand to obtain crystallisation. The temperature was reduced to 0°C and maintained for 4 hours. The suspension was filtered, washed with water and dried under vacuum to obtain Rifaximin (20 g). The obtained Rifaximin form RV-A was characterised by powder X-ray diffractogram showing significant peaks at diffraction angles 2Θ of 5.94°; 7.32°; 7.92°

Mass (m/e): 786.1

¹H NMR (400 Hz, CDCl₃): δ 14.62 (s, 1H); 8.44-8.46 (d, 1H); 7.36 (s, 1H); 7.06-7.08 (s, 1H); 6.72-6.81 (dd, 1H); 6.31-6.34 (m, 1H); 5.99-6.07 (m, 2H); 4.94-5.00 (dd, 1H); 4.84-4.88 (d, 1H); 3.57-3.67 (m, 2H); 3.27 (s, 1H); 2.96 (d, 3H); 2.82-2.85 (s, 1H); 2.61 (s, 3H); 2.27 (s, 4H); 1.93-1.99 (t, 9H); 1.54-1.56 (d, 1H); 1.25-1.28 (m, 1H); 1.10-1.13 (m, 1H); 0.90-0.92 (d, 3H); 0.70-0.72 (d, 3H); 0.61-0.63 (d, 3H); 0.11-0.13 (d, 3H).

Preparation of Tablet composition:

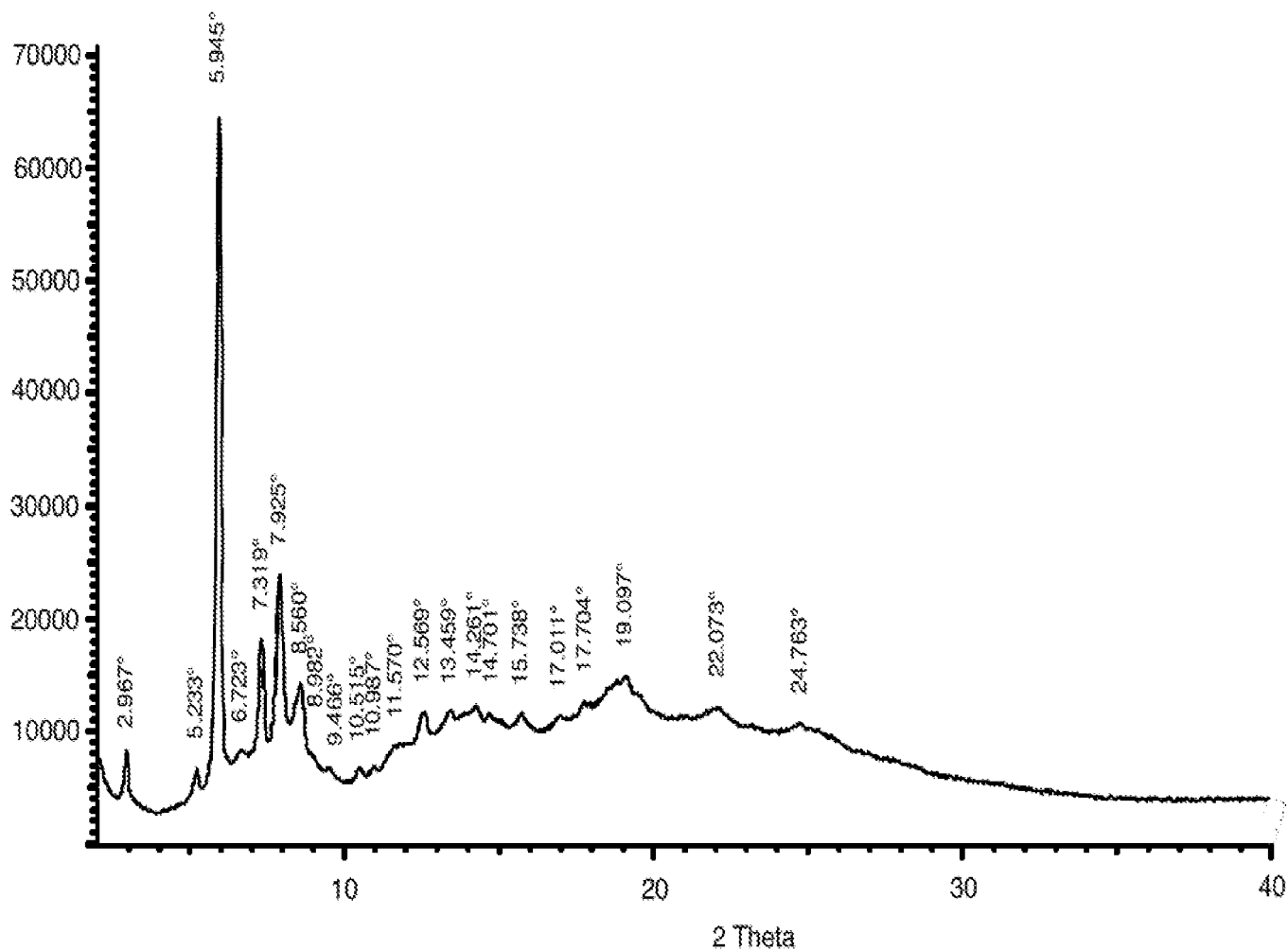
[0080] A Rifaximin composition comprising the novel polymorphic form of Rifaximin namely RV-A, microcrystalline cellulose, sodium starch glycolate, polyethylene glycol 4000, hypromellose, disodium EDTA and purified water, was mixed in a rapid mixer granulator for 15 minutes at slow speed. The blended wet mass was dried in a fluid bed dryer to obtain granules that had a moisture content of up to 4%. The granules obtained were mixed with microcrystalline cellulose, sodium starch glycolate, purified talc, colloidal anhydrous silica, glyceryl palmito stearate and magnesium stearate in a blender. The final blend was compressed on a press and the resulting tablets were film coated with instacoat Universal A05R00959 such that the resulting tablets each contain Rifaximin 555.5 mg including 1% overage and the overall tablet weight is 980 mg ±5%.

We claim:

1. A polymorphic form RV-A of Rifaximin.
2. The polymorphic form RV-A of Rifaximin of claim 1 characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 5.94, 7.32, 7.92, 8.56 and 19.01.
3. The polymorphic form RV-A of Rifaximin of claim 1 characterized by a PXRD diffractogram as depicted in Figure 1.
4. The polymorphic form RV-A of Rifaximin of claim 1 characterized by a 1 % KBr FTIR spectrum comprising peaks, in terms of cm^{-1} , at approximately 3424, 2920, 1725, 1648 and 1229.
5. The polymorphic form RV-A of Rifaximin of claim 1 characterized by a FTIR spectrum as depicted in Figure 2.
6. A process for the preparation of a polymorphic form RV-A of Rifaximin as claimed in claim 1, the process comprising:
 - i. reacting rifamycin O with 2-amino-4-methylpyridine in a suitable solvent or a mixture of solvents, for a time between 2 – 10 hours and at a temperature between 25°C to 75°C to provide crude Rifaximin,
 - ii. The resulting crude Rifaximin is purified by dissolving alcohol preferable ethyl alcohol, at a temperature between 35°C and 75°C, followed by crystallization by addition of water. The resulting suspension is stirred at a temperature between 50°C and 0°C for a duration between 2 and 24 hours,
 - iii. The suspension is filtered and the obtained solid is washed with water and dried under vacuum, optionally in the presence of a drying agent, at a temperature between room temperature and 75°C for a time between 2 and 24 hours.

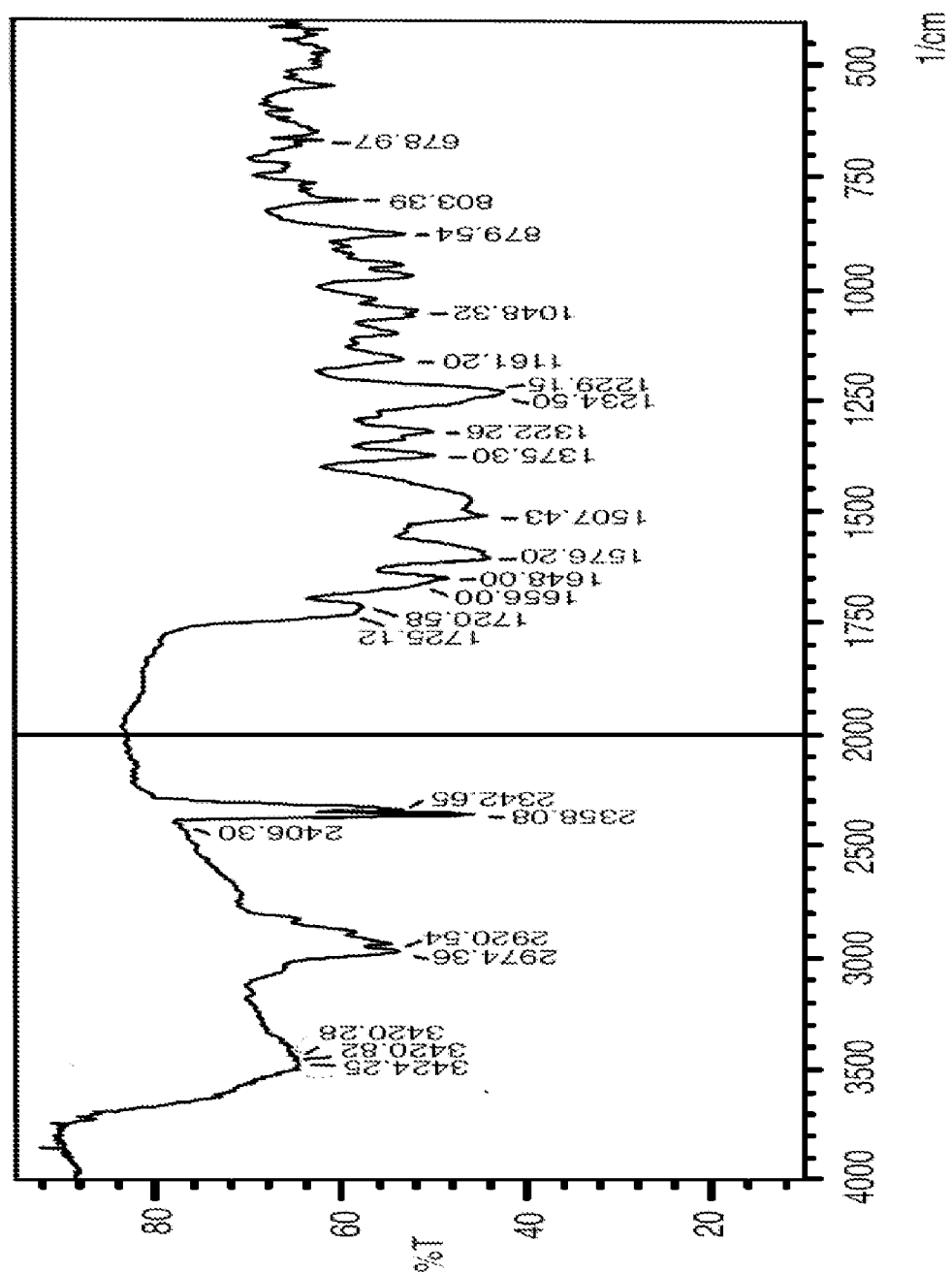
7. Pharmaceutical composition in the form of tablets comprising
 - i) Rifaximin RV-A as claimed in claim 1,
 - ii) pharmaceutically acceptable carriers, and optionally
 - iii) a film forming coating agent.
8. The pharmaceutical composition according to Claim 7, wherein the pharmaceutically acceptable carriers comprise one or more cellulose and its derivatives, selected from hydroxypropyl methylcellulose (hypromellose), sodium carboxymethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, ethyl cellulose, sodium starch glycolate, cellulose acetate; polyols selected from glycerin, sorbitol, mannitol, polyethylene glycol; lubricants selected from magnesium stearate, calcium stearate, sodium stearyl fumarate, hydrogenated vegetable oils, mineral oils and glyceryl palmitostearate; disintegrants, selected from, sodium starch glycolate, crospovidone and croscarmellose sodium; surfactant selected from sodium lauryl sulfate and polyethylene glycols; chelating agent selected from disodium EDTA; glidant selected from colloidal anhydrous silica and talc; coating solvents selected from purified water and isopropyl alcohol; coating agents; colouring agents; sweetening agents, flavouring and perfuming agents.
9. The pharmaceutical composition of claim 7 characterized by a PXRD diffractogram comprising peaks, in terms of degrees 2-theta, at approximately 5.94, 7.34, 7.93, 8.63, 14.49 and 22.47.
10. The pharmaceutical composition of claim 7 characterized by a PXRD diffractogram as depicted in Figure 3.
11. A process for the preparation of a tablet containing Rifaximin RV-A of claim 1, comprising the steps of:
 - i. providing novel polymorph of Rifaximin RV-A and optionally one or more further excipients,

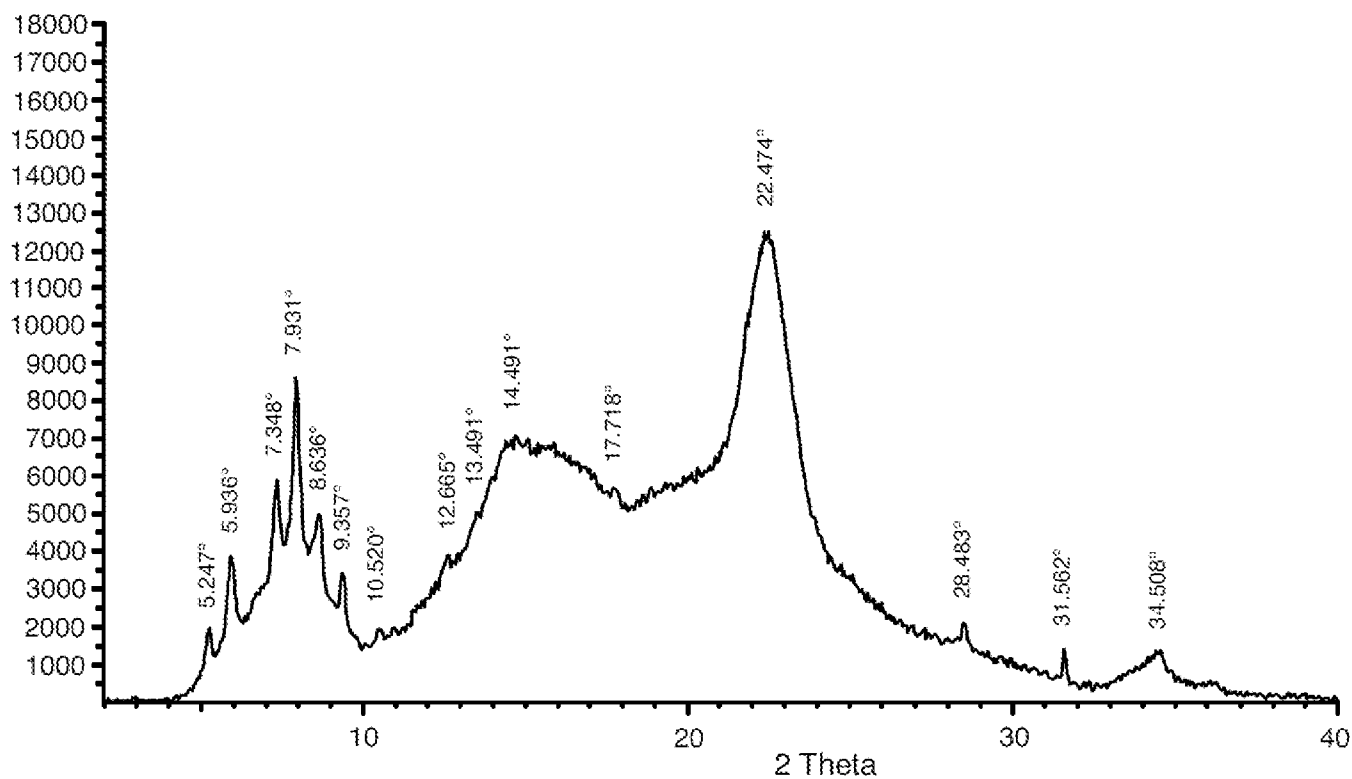
- ii. optionally granulating the mixture of step (i) and optionally one or more further excipients,
- iii. compressing the mixture from step (i) or the granulates from step (ii) and optionally further excipients into a tablet.



Angle	d Value	Rel. Intensity
2.967 °	29.75478 Å	7.3%
5.233 °	16.87444 Å	5.6%
5.945 °	14.85528 Å	100.0%
6.723 °	13.13777 Å	6.7%
7.319 °	12.06866 Å	22.9%
7.925 °	11.14701 Å	32.0%
8.560 °	10.32155 Å	15.2%
8.982 °	9.83749 Å	4.6%
9.466 °	9.33572 Å	2.3%
10.515 °	8.40681 Å	1.9%
10.987 °	8.04604 Å	1.7%
11.570 °	7.64232 Å	3.6%
12.569 °	7.03688 Å	8.5%
13.459 °	6.57343 Å	6.2%
14.261 °	6.20543 Å	8.6%
14.701 °	6.02104 Å	7.0%
15.738 °	5.62628 Å	6.4%
17.011 °	5.20803 Å	5.9%
17.704 °	5.00563 Å	7.6%
19.097 °	4.64360 Å	11.3%
22.073 °	4.02380 Å	6.8%
24.763 °	3.59252 Å	5.3%

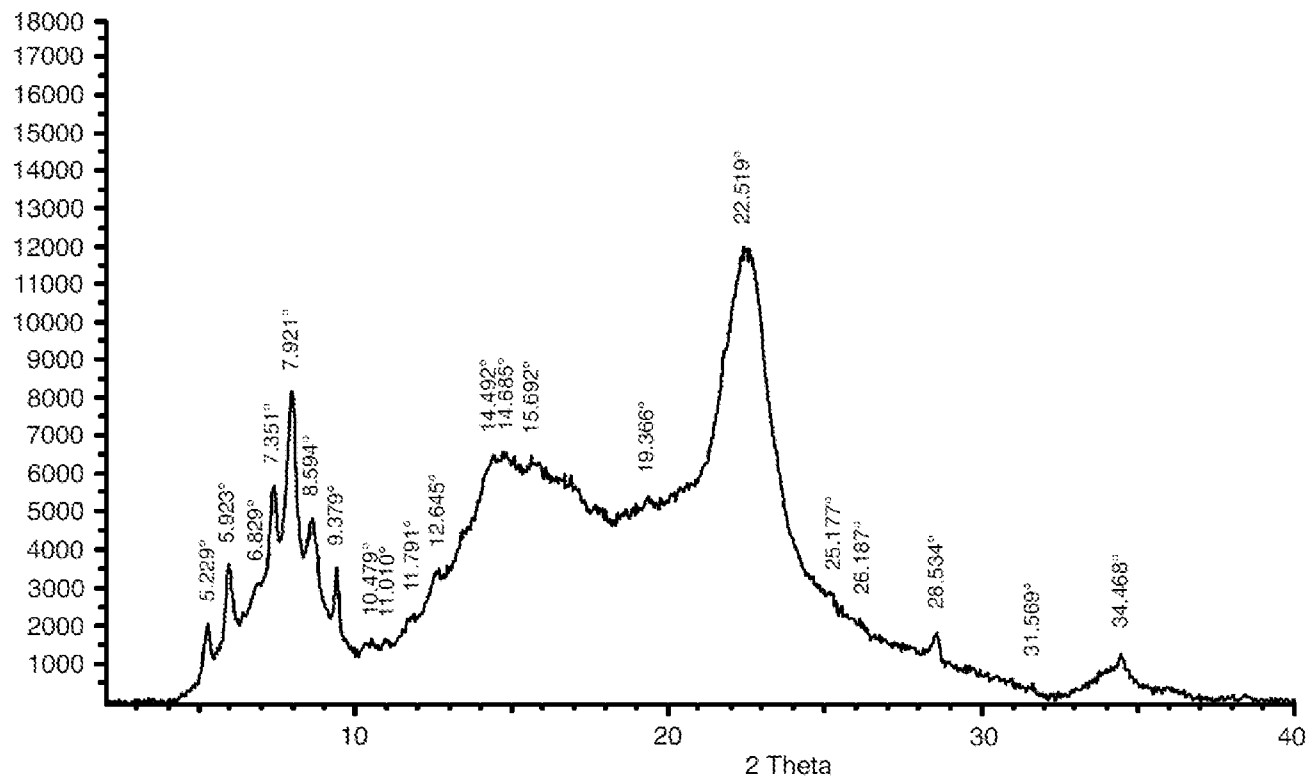
FIGURE 1

**FIGURE 2**



Index	Angle	d Value	Rel. Intensity
1	5.247 °	16.82912 Å	15.8%
2	5.936 °	14.87634 Å	30.4%
3	7.348 °	12.02031 Å	46.8%
4	7.931 °	11.13811 Å	69.0%
5	8.636 °	10.23034 Å	39.6%
6	9.357 °	9.44369 Å	27.5%
7	10.520 °	8.40266 Å	15.5%
8	12.665 °	6.98374 Å	30.0%
9	13.491 °	6.55779 Å	40.0%
10	14.491 °	6.10749 Å	55.4%
11	17.718 °	5.00171 Å	45.5%
12	22.474 °	3.95301 Å	100.0%
13	28.483 °	3.13122 Å	17.3%
14	31.562 °	2.83239 Å	11.8%
15	34.508 °	2.59701 Å	11.5%

FIGURE 3



Index	Angle	d Value	Rel. Intensity
1	5.229 °	16.88515 Å	17.7%
2	5.923 °	14.90923 Å	30.7%
3	6.829 °	12.93388 Å	26.2%
4	7.351 °	12.01549 Å	47.6%
5	7.921 °	11.15196 Å	68.6%
6	8.594 °	10.28090 Å	40.3%
7	9.379 °	9.42167 Å	29.7%
8	10.479 °	8.43555 Å	14.7%
9	11.010 °	8.02986 Å	14.0%
10	11.791 °	7.49959 Å	19.5%
11	12.645 °	6.99459 Å	29.9%
12	14.482 °	6.10704 Å	53.6%
13	14.685 °	6.02753 Å	55.2%
14	15.692 °	5.64260 Å	52.7%
15	19.366 °	4.57965 Å	45.4%
16	22.519 °	3.94512 Å	100.0%
17	25.177 °	3.53436 Å	24.9%
18	26.187 °	3.40032 Å	17.8%
19	28.534 °	3.12574 Å	15.6%
20	31.569 °	2.83179 Å	4.5%
21	34.468 °	2.59998 Å	10.9%

FIGURE 4

SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/054078

A. CLASSIFICATION OF SUBJECT MATTER

A61K9/00, A61K31/395, C12Q1/00 Version=2021.01

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)

A61K, C12Q

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)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2005044823 A2 (ALFA WASSERMANN SPA) 19 June 2005 (19-05-2005); see abstract, description pages 6-22; claims 1-12	1-11
Y	WO2011156897 A2 (APOTEX PHARMACHEM INC) 22 December 2011 (22-12-2011); see abstract, description pages 3-14; claims 1-29	1-11
Y	WO2013185211 A1 (APOTEX PHARMACHEM INC) 19 December 2013 (19-12-2013); see abstract, description pages 3-32; claims 1-57	1-11
Y	Sudha R. Vippagunta et al; 'Crystalline solids'; Advanced Drug Delivery Reviews, 2001, 48, 3-26; Whole Document	1-11
Y	Lian Yu; 'Amorphous pharmaceutical solids: preparation, characterization and stabilization'; Advanced Drug Delivery Reviews 2001, 48, 27-42; Whole Document	1-11
Y	WO2008035109 A1 (CIPLA LTD [IN]) 27 March 2008	



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

"D" document cited by the applicant in the international application

"E" earlier application or patent 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

"I" 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

12-08-2021

Date of mailing of the international search report

12-08-2021

Name and mailing address of the ISA/

Indian Patent Office
Plot No.32, Sector 14, Dwarka, New Delhi-110075
Facsimile No.

Authorized officer

Dr. Sagar Khan

Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2021/054078

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	(27-03-2003); see abstract, description pages 9-50; claims 1-23	1-11

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2021/054078

Citation	Pub.Date	Family	Pub.Date
WO 2005044823 A2	19-05-2005	US 8173801 B2	08-05-2012
		CA 2538546 A	19-05-2005
		EP 1676848 A1	28-01-2009
		JP 2011046738 A	10-03-2011
		AU 2004287601 B2	26-02-2009
WO 2011156897 A2	22-12-2011	CA 2802874 A1	22-12-2011
		EP 2582707 A4	08-01-2014
		US 2013090348 A1	11-04-2013
WO 2013185211 A1	19-12-2013	CA 2876737 A1	19-12-2013
		US 2015284407 A1	08-10-2015