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(71) Applicant: **CIPLA LIMITED** [IN/IN]; Mumbai Central, Mumbai - 400 008 (IN).

(71) Applicant *(for MW only)*: **KING, Lawrence** [GB/GB]; A.A. Thornton & Co., 235 High Holborn, London WC1V 7LE (GB).

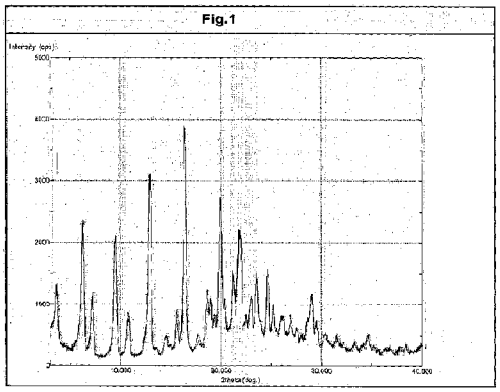
(72) Inventors: **SRINIVAS, Pathi L**; 2475/24, 7th B Main, R P C. Layout, Vijayanagar, Bangalore 560 040, Karnataka (IN). **RAO, Dharmaraj Ramachandra**; 4/403, Garden Enclave, Pokhran Road 2, Thane West, 400 601, Maharashtra (IN). **KANKAN, Rajendra Narayanrao**; 1204, Heritage, Hiranandani Gardens, Powai, Mumbai -400 076, Maharashtra (IN). **MALHOTRA, Geena**; 4 Anderson House, Opposite Mazgaon Post Office, Mazgaon, Mumbai 400 010, Maharashtra (IN). **PURANDARE, Shrinivas Madhukar**; B/25, Naperol Towers, Opposite R.A. Kidwai Road, Opposite Gyaneshwar Vidyalaya, Wadala, Mumbai-400 031, Maharashtra (IN). **RAMASUBBU, Chandrasekaran**; Bldg. No. Old No.3, New No.7; B1 First Floor, Rammiyam Foundation, Seventh Main Road, Dhandeeswaram Nagar, Velachery, Chennai 600 042 Tamil Nadu (IN). **GANGRADE, Manish**; Lok Everest Society, Building no. B3, Flat no. 1201, J.S.D. Road, Mulund-West, Mumbai 400 080, Maharashtra (IN). **KANATHALA, Shashi Rekha**; F-11 3;1, Shantivan CHS, Sector-7, Sanpada, Navi Mumbai, Mumbai 400 705, Maharashtra (IN). **JAYACHANDRAN, Jennet**; Gurukalakunnath House, Pattiam Kongatta, Pathayakunnu 670 691, Kerala (IN).

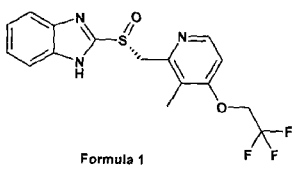
(74) Agents: **KING, Lawrence** et al.; A A THORNTON & CO, 235 High Holborn, London WC1V 7LE (GB).

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[Continued on next page]

(54) Title: GLYCEROL SOLVATE FORMS OF (R) - 2 - [[[3 -METHYL -4 (2,2, 2 - TRIFLUOROETHOXY) PYRIDIN- 2 - YL] METHYL] SULPHINYL] - 1H - BEN ZIMIDAZOLE





Formula 1

(57) Abstract: The present invention relates to novel crystalline forms of (R)-2-[[[3-methyl-4(2,2,2- trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-lH-benzimidazole (Formula 1), to processes for their preparation, to pharmaceutical compositions comprising the same and to the use of such crystalline forms for the treatment of gastrointestinal (GI) disorders.

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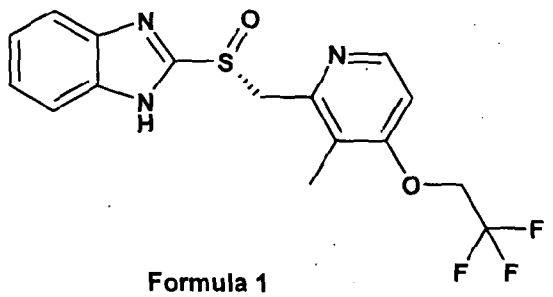
Technical field of the Invention

The present invention relates to novel crystalline forms of (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole, to processes for their preparation, to pharmaceutical compositions comprising the same and to the use of such crystalline forms for the treatment of gastrointestinal (GI) disorders.

Background of the Invention

Dexlansoprazole or (R)-lansoprazole is a member of a group of drugs called proton pump inhibitors (PPIs) that inhibit gastric acid secretion. Dexlansoprazole is used to treat heartburn caused by gastroesophageal reflux disease (GERD) and to heal erosive esophagitis (damage to the esophagus from stomach acid).

Dexlansoprazole is chemically known as (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole and is marketed as KAPIDEX®. Dexlansoprazole has the following chemical structure:



Formula 1

EP0773940B describes the preparation of (+) lansoprazole and (-) lansoprazole.

Dexlansoprazole is known to exist in different solid state forms. For example, US6462058, US6664276, US7285668 and US2007/0004779 all describe process for preparing crystalline forms of dexlansoprazole and its hydrates.

US6462058 and US7285668 disclose crystalline dexlansoprazole characterized by X-ray powder diffraction (XRD), with characteristic peaks at interplanar spacings (d) 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 & 3.11 Angtroms (Å). These patents further describe crystalline dexlansoprazole sesquihydrate characterized by XRD with characteristic peaks at interplanar spacings (d) 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 & 3.00 Å.

US7271182 describes crystalline lithium, potassium, magnesium, sodium & calcium salts of dexlansoprazole and processes for the preparation thereof. However, the process described in this patent has been found to be not reproducible as products of desired purity are not obtained upon repeated purification. Further, the obtained crystalline forms have been found to be not stable on storage.

WO2009088857 and US20100286400 disclose different hydrates of dexlansoprazole, solvates of dexlansoprazole with methanol, ethanol and isopropanol and hydrated solvates of dexlansoprazole with ethanol and isopropanol and processes for preparation thereof.

WO2009087672 and WO2009117489 disclose amorphous dexlansoprazole and a process for the preparation thereof.

WO2010079504 discloses an alkylamine salt of dexlansoprazole, a process for its preparation and pharmaceutical compositions thereof.

WO2011121546 describes a process for the preparation of amorphous alkali metal, alkaline earth metal and ammonium salts of dexlansoprazole.

WO2010056059 discloses a crystalline form of (+)-lansoprazole, whose XRD pattern comprises a peak having a 100 x I/I0 value of at least 20% at an interplanar distance (d ± 0.3A) of 17.4, 10.0, 9.6, 8.7, 7.6, 6.6, 5.7, 5.6, 5.0, 4.8, 4.4, and 4.0 Å with a melting point in the range of 151 to 156°C.

US20110009637 discloses a crystalline form of dexlansoprazole characterized by XRD with characteristic peaks at 5.7, 5.9, 7.7, 13.3, 13.5, 17.1, 17.3, 18.2, 19.3, and 20.4 °2θ.

US20100113527 and WO2010039885 disclose various crystalline forms of dexlansoprazole which are designated as Form X, Form XI, Form XII, Form XIII, and Form IX, and processes for their preparation.

WO2011092665 discloses crystalline forms of dexlansoprazole which are designated as Form A and Form B, and processes for their preparation.

WO2011139414 discloses crystalline forms of dexlansoprazole which are designated as Form B, Form C, Form D and Form E, and processes for their preparation.

WO2011020189 discloses hydrates of dexlansoprazole propylene glycolate and process for the preparation thereof.

WO2011098938 discloses dexlansoprazole 1,2-diol solvates and hydrates thereof. Examples include dexlansoprazole propylene glycol solvate, dexlansoprazole chloropropylene glycol solvate and dexlansoprazole 1,2-butanediol solvate.

One important property associated with solid state forms of drug substances is their aqueous solubility. Compounds having poor water solubility can lead to limited oral bioavailability when administered in patients. In such cases the discovery of new polymorphic forms and solvates of a pharmaceutically useful compound with better aqueous solubility, provide a significant opportunity to increase the performance characteristics of a pharmaceutical product, such as oral bioavailability and hence reduce the dosage required to be administered to the patient.

Consequently, it would be desirable to provide novel crystalline forms of dexlansoprazole having increased solubility, methods for their preparation, pharmaceutical formulations comprising the same, and methods of use thereof.

Objects of the Invention

An object of the present invention is to provide novel crystalline forms of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole and in particular novel crystalline solvates thereof. A particular object of the present invention is to provide a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole.

Another object of the present invention is to provide processes for the preparation of triol solvates of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole.

Another object of the present invention is to provide a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl- 4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1 H-benzimidazole, said composition optionally comprising one or more pharmaceutically acceptable excipients.

Another object of the present invention is to provide a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1 H-benzimidazole having improved solubility.

Another object of the present invention is to provide a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1 H-benzimidazole having a reduced dose.

Another object of the present invention is to provide a process for preparing a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1 H-benzimidazole, said composition optionally comprising one or more pharmaceutically acceptable excipients.

Another object of the present invention is to provide a method of preventing or treating GI disorders by administering a novel triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole or a pharmaceutical composition thereof.

Another object of the present invention is to provide the use of a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1 H-benzimidazole or a pharmaceutical composition thereof for the treatment of gastrointestinal disorders.

Summary of the Invention

In a first aspect, the present invention provides a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole. The triol solvate of the present invention is preferably crystalline. More preferably, the triol solvate of the present invention is a glycerol solvate. Particularly preferred glycerol solvates of the present invention are those compounds designated herein as "Form A", "Form B" and "Form C". The novel crystalline forms of the present invention are characterised by unique XRD patterns and intrinsic dissolution profiles.

The novel crystalline forms of the present invention possess certain physical and chemical properties which render them particularly suitable for pharmaceutical development, such as good solubility, permeability and bioavailability. In addition, they are suitable for bulk handling and formulation.

In a further aspect of the present invention, there is provided a process for preparing a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole. The processes of the present invention afford triol solvates of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in high purity and high yield. Advantageously, they are environmentally friendly and suitable for use on a commercial scale.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-

methyl]sulphinyl]-1H-benzimidazole, optionally comprising one or more pharmaceutically acceptable excipients.

In a further aspect of the present invention, there is provided a method for preparing a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, optionally comprising one or more pharmaceutically acceptable excipients.

In a further aspect of the present invention, there is provided method for the prevention or treatment of a GI disorder which method comprises administering a triol solvate of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole to a patient in need thereof.

In a further aspect of the present invention, there is provided a triol solvate of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole for use in the prevention or treatment of GI disorders.

Brief Description of the Drawings

Figure 1 shows an X-ray diffraction pattern of crystalline Form A of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate.

Figure 2 shows an X-ray diffraction pattern of crystalline Form B of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate.

Figure 3 shows an X-ray diffraction pattern of crystalline Form C of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate.

Figure 4 shows the intrinsic dissolution profile of crystalline Form A of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate of the present invention compared with anhydrous and sesquihydrate crystalline forms of (R)-2-[[[3-

methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, measured by a UV method.

Figure 5 shows the intrinsic dissolution profile of crystalline Form C of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate of the present invention compared with anhydrous and sesquihydrate crystalline forms of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, measured by a UV method.

Detailed Description of the Invention

As used herein, the term "solvated" means the formation of a crystalline complex of variable stoichiometry comprising (in this invention), a compound of Formula (1) and a solvent. The term "solvate" shall be interpreted accordingly.

As used herein, the term "non-solvated" means the subject compound, i.e., the compound of Formula (1) has not formed a complex of variable stoichiometry with a solvent. A non-hydrated compound may be referred to as an anhydrate or anhydrous form.

As used herein, the phrase "substantially the same X-ray powder diffraction pattern" is understood to mean that those X-ray powder diffraction patterns having diffraction peaks with 2θ values within ± 0.2° of the diffraction pattern referred to herein are within the scope of the referred to diffraction pattern.

The present invention provides novel crystalline forms of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, methods of preparing the novel forms (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in high purity and high yield and pharmaceutical compositions comprising them.

According to a first aspect of the present invention, there is provided a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole. The triol solvate of the present invention is preferably crystalline. More preferably, the triol solvate of the

present invention is a glycerol solvate. Particularly preferred glycerol solvates of the present invention are those compounds designated herein as "Form A", "Form B" and "Form C". The novel crystalline forms of the present invention are characterised herein by reference to unique XRD patterns and intrinsic dissolution profiles. It will be appreciated that other conventional analytical methods including, but not limited to, infra-red, solid state NMR and Raman spectroscopy may also be employed to characterise the crystalline forms of the present invention.

According to a further aspect, the present invention provides (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A.

Form A may be isolated in hydrated form or anhydrous form, preferably anhydrous form. Form A has good flow characteristics.

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A is characterised by an XRD pattern with peaks at 9.48, 12.9 and 16.4 ± 0.2 °2θ. The XRD pattern may be further characterized by peaks at 6.2, 19.94, 21.82 and 24.63 ± 0.2 °2θ. The XRD pattern may comprise still further peaks at 3.64, 7.18, 10.74, 15.58, 18.52, 18.96, 20.30, 21.21, 22.99, 23.54, 25.17 and 29.02 ± 0.2 °2θ. (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A may be further characterized by an XRPD pattern with peaks at °2θ values as depicted in Table 1 below.

Table 1

Peak value (°2θ)	Relative Intensity [%]
3.64	23.0
6.20	56.4
7.18	24.9
9.47	52.8
10.74	18.7
12.90	79.1

13.44	1.4
13.57	1.7
14.47	6.7
14.90	1.5
15.58	15.0
16.40	100.0
17.73	3.9
18.52	13.0
18.96	15.6
19.33	5.4
19.94	58.7
20.30	11.2
21.21	21.0
21.82	41.2
22.40	5.5
22.99	12.8
23.54	24.4
23.86	5.5
24.63	27.3
25.17	11.5
25.51	2.4
25.98	8.3
26.18	8.2
26.92	7.2
27.59	3.1
27.96	2.8
28.52	6.4
29.02	19.9
29.05	6.4
30.37	5.1

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A may be further characterized as having substantially the same XRPD pattern with peaks at 2θ values as depicted in Figure 1.

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A may be further characterized as having an intrinsic dissolution profile substantially as shown in Table A and/or Figure 4.

The isolated (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole Form A preferably contains about 20% by weight of glycerol and is preferably in the anhydrous form.

According to a further aspect of the present invention, there is provided (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form B. Form B is substantially non-hygroscopic and has good flow characteristics.

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form B is characterised by an XRD pattern with peaks at 18.18 and 22.34 ± 0.2 °2θ. The XRD pattern may further comprise peaks at 5.60, 12.98, 13.76, 14.86, 19.73, 20.12, 20.66, 21.30, 22.88, 26.36 and 26.77 ± 0.2 °2θ. The XRD pattern may comprise still further with peaks at 7.44, 12.56, 15.94, 16.54, 16.72, 18.48, 18.87 and 23.70 ± 0.2 °2θ. (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form B may be further characterized by an XRPD pattern with peaks at °2θ values as depicted in Table 2 below.

Table 2

Peak value (°2θ)	Relative Intensity [%]
3.58	2.0

5.60	31.4
6.14	8.7
6.91	8.3
7.44	19.4
9.32	8.7
9.61	2.6
10.09	9.3
10.47	4.9
10.74	5.1
11.19	4.6
12.56	15.1
12.98	33.3
13.76	27.6
14.86	26.2
15.27	1.9
15.94	13.6
16.54	25.0
16.72	22.9
18.18	69.1
18.48	13.2
18.87	23.5
19.24	5.2
19.73	27.6
20.12	30.9
20.66	28.3
21.30	28.5
21.82	9.6
22.34	100.0
22.88	46.3
23.70	11.2

24.72	8.3
25.35	8.4
26.36	25.6
26.77	42.2
27.60	4.8
28.05	5.5
28.40	8.9
28.74	1.6
30.46	2.1

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form B may be further characterized as having substantially the same XRPD pattern with peaks at 2θ values as depicted in Figure 2.

According to a further aspect of the present invention, there is provided (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C. Form C is substantially non-hygroscopic and has good flow characteristics.

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C is characterised by an XRD pattern with peaks at 18.21, 18.88, 20.68, 22.38, 22.90 and 26.79 ± 0.2 °2θ. The XRD pattern may be further characterized by peaks at 5.63, 13.78, 14.88, 19.74, 20.32 and 26.36 ± 0.2 °2θ. The XRD pattern may comprise still further peaks at 7.48, 10.10, 13.22, 16.76, 21.33, 21.83, 23.71 and 28.42 ± 0.2 °2θ. (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C may be further characterized by an XRPD pattern with peaks at °2θ values as depicted in Table 3 below.

Table 3

S. No	Peak value (°2θ)	Relative Intensity [%]
1	5.63	40.2
2	6.93	8.4
3	7.48	20.0
4	10.10	11.7
5	11.20	5.1
6	13.22	9.1
7	13.78	34.4
8	14.88	26.4
9	16.76	20.3
10	18.21	68.7
11	18.88	62.0
12	19.74	33.3
13	20.32	34.9
14	20.68	66.4
15	21.33	20.0
16	21.83	24.3
17	22.38	100.0
18	22.90	76.3
19	23.71	17.9
20	24.19	9.7
21	25.37	10.2
22	26.36	46.3
23	26.79	75.4
24	27.58	9.4
25	28.08	6.0
26	28.42	23.9
27	30.44	3.1

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C may be further characterized as having substantially the same XRPD pattern with peaks at 2θ values as depicted in Figure 3.

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C may be further characterized as having an intrinsic dissolution profile as shown in Table B and/or Figure 5.

The isolated (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole Form C preferably contains about 20% by weight of glycerol and preferably has a water content in the range of about from 3.0 to 5.0 % w/w.

According to a further aspect of the present invention, there is provided a process for preparing a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, comprising (i) dissolving or suspending (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole or a salt or solvate thereof in a first suitable solvent; (ii) optionally adding an organic base to the solution or suspension so formed; (iii) contacting (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole with a triol; and optionally thereafter (iv) isolating the compound so formed preferably by addition of a second solvent. In a preferred embodiment, the triol is glycerol.

According to another aspect of the present invention, there is provided a process for preparing (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, comprising (i) dissolving (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in a first suitable solvent; (ii) distilling the reaction mass optionally in the presence of a base; (iii) adding glycerol; (iv) heating the resulting solution to a temperature in the range of about 25°C to about the reflux temperature of the solvent used; (v) adding a suitable second solvent; (vi) isolating (R)-2-[[[3-methyl-4-

(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A.

According to another aspect of the present invention, there is provided a process for the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, which process comprises: (i) dissolving (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in a first suitable solvent; (ii) adding a drying agent to the solution so formed; (iii) optionally adding a base; (iv) removing the first solvent, preferably under vacuum; (v) optionally stripping off the resulting residue with a further quantity of first solvent; (vi) adding glycerol and optionally a further quantity of first solvent; (vii) heating the resulting solution to a temperature in the range from about 40°C to about 60°C, preferably from about 40°C to about 50°C; (viii) adding a suitable second solvent; (ix) cooling the reaction mass to a temperature in the range from about 25°C to about 30°C and stirring the reaction mass, preferably for at least about 60 minutes; (x) isolating (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A and drying the resulting product; preferably under reduced pressure at a temperature in the range from about 20 to about 60°C, more preferably at a temperature in the range from about 30 to about 40°C, and most preferably wherein the drying step is performed for at least 8 hours.

According to another aspect of the present invention, there is provided a process for the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, which process comprises: (i) dissolving (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in a first suitable solvent; (ii) adding a drying agent to the solution so formed; (iii) removing the first solvent, preferably under vacuum; (iv) optionally stripping off the residue so formed with a further quantity of first solvent; (v) adding a further quantity of first solvent; (vi) heating the resulting solution to a temperature in the range from about 40°C to about 60°C, preferably from about 40°C to about 50°C; (vii) adding glycerol to the resulting solution; (viii) cooling the reaction mass to a temperature in the range from about 25°C to about 30°C, and adding a second solvent; (ix) cooling the reaction mass further to a temperature in the range from about 0°C to

about 5°C and stirring the reaction mass, preferably for at least about 30 minutes; (x) isolating the (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A; and (xi) drying the resulting product; preferably under reduced pressure at a temperature in the range from about 20 to about 60°C, more preferably at a temperature in the range from about 40 to about 50°C, most preferably wherein the drying step is performed for at least 12 hours.

According to another aspect of the present invention, there is provided a one pot process for the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, which process comprises: (i) combining (+)-diethyl L-tartrate, titanium (IV) isopropoxide and water with 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]thio]-1H-benzimidazole in a suitable solvent, preferably toluene and heating to the resulting mixture to a temperature in the range from about 70°C to about 75°C, preferably for a period of about 5 to about 10 minutes; (ii) cooling the reaction mixture to a temperature in the range from about 25°C to about 30°C, preferably over a period of at least 30 minutes; (iii) adding a suitable organic base, preferably diisopropylethylamine, and stirring, preferably for a period of about 30 minutes; (iv) cooling the resulting mixture to a temperature in the range from about -5°C to about 0°C; (v) adding a solution of cumene hydroperoxide (80%) in a suitable solvent, preferably toluene, preferably over a period of about 60 minutes, and maintaining the reaction for a period of at least about 2 hours; (vi) quenching the reaction by the addition of a suitable aqueous base, preferably 5% aqueous KOH solution, at a suitable temperature, preferably in the range from about -5°C to about 0°C; (vii) increasing the temperature of the reaction mixture to a temperature in the range from about 25°C to 30°C; (viii) adding an alcohol, such as methanol, ethanol or iso-propyl alcohol, preferably methanol, to the reaction mixture, and a suitable base, preferably 20% aqueous KOH solution, and stirring, preferably for about 10 to about 20 minutes, more preferably at a temperature in the range from about 30°C to 35°C; (ix) separating the organic layer and extracting with one or more a suitable solvents, preferably a mixture of 5% aqueous KOH and methanol, more preferably at a temperature in the range from about 30°C to about 35°C; (x) combining the aqueous layers and washing them with a suitable solvent, preferably dichloromethane; (xi) adjusting the pH of the aqueous solution to a pH in the range from about pH 7 to about pH 10 with a suitable acid, such as 20% acetic acid, preferably at a

temperature in the range from about 30°C to about 35°C; (xii) extracting the solid in a first suitable solvent, preferably a water immiscible solvent; (xiii) drying the resulting solution with a drying agent; (xiv) removing the solvent, preferably under vacuum, and optionally stripping off the residue so formed with a further quantity of first solvent; (xv) adding glycerol; (xvi) adding a further quantity of first solvent; (xvii) heating the resulting solution to a temperature in the range from about 40°C to about 60°C, preferably from about 40°C to about 50°C; (xviii) adding a second solvent; (xiv) cooling the reaction mass further to a temperature in the range from about 25°C to about 30°C and stirring the reaction mass, preferably for at least about 30 minutes; (xx) isolating the (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A; and (xxi) drying the resulting product; preferably under reduced pressure at a temperature in the range from about 20 to about 60°C, more preferably at a temperature in the range from about 30 to about 40°C, most preferably wherein the drying step is performed for at least 8 hours.

The (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole used in the preparation of the Form A may be in any polymorphic form or in a mixture of any polymorphic forms. For example, the (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole may be in hydrated, solvated, non-solvated or in a mixture of hydrated, solvated or non-solvated forms thereof. In a preferred embodiment, (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole is used in sesquihydrate form, which can be prepared according to known methods, for example as disclosed in US Patent No. 5948789.

According to another aspect of the present invention, there is provided a process for the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form B, which process comprises: (i) dissolving (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in a suitable first solvent; (ii) adding glycerol and a further quantity of first solvent; (iii) heating the resulting solution to a temperature in the range from about 40°C to about 60°C, preferably from about 40°C to about 50°C; (iv) adding a suitable second solvent; (v) cooling the reaction mass to a temperature in the range from about 25°C to about 30°C and stirring the reaction mass, preferably

for at least about 60 minutes; and (x) isolating (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form B and drying the resulting product; preferably under reduced pressure, most preferably wherein the drying step is performed for at least 8 hours.

The (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole used in the preparation of the Form B may be in any polymorphic form or in a mixture of any polymorphic forms. For example, the said (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole may be in hydrated, solvated, non-solvated or in a mixture of hydrated, solvated or non-solvated forms thereof. In a preferred embodiment, (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole is used in sesquihydrate form.

According to another aspect of the present invention, there is provided a process for the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C, which process comprises: (i) dissolving (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in a suitable first solvent; (ii) adding glycerol to the mixture so formed and optionally a suitable aqueous base; (iii) heating the resulting solution to a temperature in the range of about 25°C to about reflux temperature of the solvent used; (iv) adding a suitable second solvent; and (v) isolating (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C.

According to another aspect of the present invention, there is provided a process for the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C, which process comprises: (i) dissolving (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in a suitable first solvent; (ii) adding glycerol to the mixture so formed and optionally a suitable aqueous base; (iii) adding a further quantity of first solvent; (iv) heating the resulting solution to a temperature in the range from about 40°C to about 60°C, preferably from about 40°C to about 50°C; (v) adding a suitable second solvent; (v) cooling the reaction mass to a temperature in the range from

about 25°C to about 30°C and stirring the reaction mass, preferably for a duration of about 30 to about 60 minutes; and (vi) isolating (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C and drying the resulting product; preferably under reduced pressure, most preferably wherein the drying step is performed for at least 8 hours.

According to another aspect of the present invention, there is provided a process for the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C, which process comprises: (i) combining (+)-diethyl L-tartrate, titanium (IV) isopropoxide and water with 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]thio]-1H-benzimidazole in a suitable solvent, preferably toluene and heating to the resulting mixture to a temperature in the range from about 70°C to about 75°C, preferably for a period of about 5 to about 10 minutes; (ii) cooling the reaction mixture to a temperature in the range from about 25°C to about 30°C, preferably over a period of at least 30 minutes; (iii) adding a suitable organic base, preferably diisopropylethylamine, and stirring, preferably for a period of about 30 minutes; (iv) cooling the resulting mixture to a temperature in the range from about -5°C to about 0°C; (v) adding a solution of cumene hydroperoxide (80%) in a suitable solvent, preferably toluene, preferably over a period of about 60 minutes, and maintaining the reaction for a period of at least about 2 hours; (vi) quenching the reaction by the addition of a suitable aqueous base, preferably 5% aqueous KOH solution, at a suitable temperature, preferably in the range from about -5°C to about 0°C; (vii) increasing the temperature of the reaction mixture to a temperature in the range from about 25°C to 30°C; (viii) adding an alcohol, such as methanol, ethanol or iso-propyl alcohol, preferably methanol, to the reaction mixture, and a suitable aqueous base, preferably 20% aqueous KOH solution, and stirring, preferably for about 10 to about 20 minutes, more preferably at a temperature in the range from about 30°C to 35°C; (ix) separating the organic layer and extracting with one or more a suitable solvents, preferably a mixture of 5% aqueous KOH and methanol, more preferably at a temperature in the range from about 30°C to about 35°C; (x) combining the aqueous layers and washing them with a suitable solvent, preferably dichloromethane; (xi) adding a suitable water immiscible first solvent and adjusting the pH of the aqueous solution to a pH in the range from about pH 7 to about pH 10 with a suitable acid, such as 20% acetic acid, preferably at a temperature in the range from about

30°C to about 35°C; (xii) separating the organic layer and optionally washing it with 10% NaCl solution; (xiii) drying the organic layer with a suitable drying agent such as sodium sulphate, and filtering the mixture, preferably through a hyflo bed, and distilling the solution under vacuum; (xiv) dissolving the resulting residue in a further quantity of first water immiscible solvent, adding glycerol and water, said water preferably being present in an amount from about 1 to about 10% by volume, and heating the resulting mixture to a temperature in the range from about 30°C to about 50°C, preferably from about 30°C to about 45°C; (xv) cooling the reaction mass to a temperature in the range from about 25°C to about 30°C, further cooling to a temperature in the range from about 0°C to about 10°C and stirring the reaction mass, preferably for at least about 2 hours; (xvi) isolating the solid so formed; (xvii) stirring the solid in a further quantity of the first water immiscible solvent and optionally adding water, said water being present in an amount from about 1 to about 10% by volume; (xviii) heating the resulting solution to a temperature in the range from about 40°C to about 60°C, preferably from about 40°C to about 50°C and adding second suitable solvent, preferably over a period of at least about 20 minutes; (xviv) cooling the reaction mass to a temperature in the range from about 25°C to about 30°C, followed by further cooling to a temperature in the range from about 0°C to about 10°C, preferably stirring for at least 2 hours; (xx) isolating (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C and drying the resulting product; preferably under reduced pressure, most preferably wherein the drying step is performed for at least 8 hours; and (xxi) optionally purifying the resulting product by repeating steps (xi) to (xvi)

In an embodiment of the present invention, the "first solvent" used in the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Forms A, B and C is selected from the group consisting of alcohols, ketones, chloroalkanes, alkyl alkanoates or a mixture thereof. Particularly preferred solvents include methanol, ethanol, isopropanol, acetone, methyl ethyl ketone, dichloromethane (MDC), methyl acetate, ethyl acetate, butyl acetate and mixtures thereof. Most preferably, the solvent is ethyl acetate, dichloromethane or a mixture thereof.

In an embodiment of the present invention, the "second solvent" used in the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol

solvate Forms A, B and C is ethyl acetate or a suitable anti-solvent, for example a dialkyl ether, an aromatic hydrocarbon, an aromatic chlorohydrocarbon, a hydrocarbon, or a mixture thereof. Particularly preferred anti-solvents include diisopropyl ether, methyl t-butylether, toluene, xylene, chlorobenzene, 1,2-dichlorobenzene, n-pentane, n-hexane, n-heptane, cyclopentane, cyclohexane and mixtures thereof. Most preferably, the anti-solvent is n-heptane.

In an embodiment of the present invention, the drying agent is selected from the group consisting of anhydrous sodium sulphate, anhydrous magnesium sulphate, anhydrous zinc chloride and anhydrous calcium chloride. Preferably, the drying agent is anhydrous sodium sulphate.

In an embodiment of the present invention, the amount of glycerol used varies from about 5% to about 50 % w/w, preferably from about 15% to about 25% w/w.

The above-mentioned processes to prepare (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Forms A, B and C may be performed in the presence or absence of the organic base. In an embodiment, the organic base is selected from the group consisting of trialkylamines, dialkylamines, monoalkylamines, branched chain alkylamines heterocyclic bases or mixtures thereof. Particularly preferred organic bases include trimethylamine, triethylamine, tripropylamine, tributylamine, dimethylamine, diethylamine, dipropylamine, dibutylamine, monomethylamine, monoethylamine, monopropylamine, monobutylamine, diisopropylethylamine, pyridine, pyrrolidine, piperidine, morpholine, N-methyl morpholine, N-methyl piperidine, piperazine or mixtures thereof. Most preferably, the organic base is triethylamine.

The novel polymorphs (Forms A, B and C) of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole of the present invention are substantially free from other forms of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole. "Substantially free" from other forms of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole shall be understood to mean that the polymorphs of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole contain less than about 10 % by weight, preferably less than

about 5% by weight, and most preferably less than about 2% by weight, of any other form(s) of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole. Most preferably, the novel polymorphs of the present invention comprise less than about 1% by weight of other impurities, water or solvates.

The processes of the present invention may be used as a method for purifying any known form of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, as well as for the preparation of the new polymorphic forms A, B and C. Thus, in another aspect, the present invention provides the use of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, B or C as a starting material for the preparation of crystalline anhydrous (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole.

In a further embodiment of the present invention, there is provided a process for the preparation of crystalline anhydrous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, which process comprises: (i) dissolving (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazol glycerol solvate Form A, B or C in a solvent selected from the group consisting of methyl acetate, ethyl acetate, propyl acetate, butyl acetate, dichloromethane and mixtures thereof, preferably ethyl acetate; (ii) adding water to the solution so formed; (iii) isolating the organic component of the mixture and drying it using a suitable drying agent, such as anhydrous sodium sulphate; (iii) removing the organic solvent by distillation, preferably at a temperature in the range from about 40°C to about 60°C; (iv) dissolving the resulting residue in ethyl acetate; (v) adding an anti-solvent to the resulting solution, preferably at a temperature in the range from about 25°C to about 40°C, said anti-solvent selected from the group consisting of n-hexane, n-heptane, cyclohexane, diethyl ether, diisopropyl ether, methyl t-butyl ether or a mixture thereof, preferably n-heptane; (vi) isolating crystalline anhydrous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole and drying the compound so formed, preferably under reduced pressure at a temperature in the range from about 25°C to about 50°C, preferably for at least 8 hours.

In another embodiment of the present invention, there is provided the use of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, B or C in the preparation of crystalline (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate.

In an embodiment of the present invention, there is provided a process for preparing crystalline (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate, which process comprises: (i) treating (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, B or C with water, preferably at a temperature in the range from 25°C to about 30°C, preferably for a period of about 1 to about 5 hours; (ii) isolating crystalline (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate and, optionally, drying the resulting product, preferably under reduced pressure at a temperature in the range from about 20°C to about 60°C, more preferably from about 40°C to about 50°C, for at least 8 hours.

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in amorphous form is known to be more soluble in water than the crystalline form, and consequently possesses greater bioavailability. The use of amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole is therefore generally preferred to crystalline forms in formulating pharmaceutical compositions.

The present invention provides a pharmaceutical composition comprising novel triol solvates of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole (dexlansoprazole) which are crystalline in nature yet exhibiting high aqueous solubility and improved oral bioavailability.

According to a further embodiment of the present invention, there is provided a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole and one or more pharmaceutically acceptable excipients. Preferably, the pharmaceutical composition comprises (R)-2-[[[3-methyl-4-(2,2,2-

trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate. More preferably, the pharmaceutical composition comprises (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, B or C, or a mixture of two or more of said crystalline forms.

The term "pharmaceutical composition" includes tablets (single layer, bilayer, multilayer, tablet in tablet) which may be uncoated, film coated, sugar coated, powder coated, enteric coated, seal coated, capsules (filled with powders, powders for reconstitution, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, film coated tablets, MUPS, film coated tablets MUPS, orally disintegrating MUPS, disintegrating tablets, dispersible tablets, granules, microspheres, multiparticulates or combinations thereof), sachets (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, film coated tablets, MUPS, film coated tablets MUPS, orally disintegrating MUPS, disintegrating tablets, dispersible tablets, granules, microspheres, multiparticulates or combinations thereof) and sprinkles however other dosage forms such as liquid dosage forms (liquids, liquid dispersions, suspensions, solutions, emulsions, sprays, spot-on), injection preparations, gels, aerosols, ointments, creams, controlled release formulations, lyophilized formulations, modified release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, dual release formulations etc. may also be envisaged under the ambit of the invention.

The term "modified release" means that the release of the active substance i.e. novel polymorphic forms of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, from a pharmaceutical composition is controlled in a manner to occur at a different time and/or at a different rate than that obtained from an immediate release product. The term "modified release" envisages the terms "controlled release", "delayed release", "sustained release", "extended release", "pulsatile release", "dual release" or "enteric coated" under its ambit.

Suitably, the pharmaceutical composition of the present invention is an oral dosage form, preferably that is suitable for oral or buccal administration.

Preferably, the oral dosage form is in the form of tablet (single layer, bilayer, multilayer, tablet in tablet) which may be uncoated, film coated, sugar coated, powder coated, enteric coated, seal coated; capsule [filled with powders, powders for reconstitution, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, film coated tablets, MUPS, film coated tablets MUPS, orally disintegrating MUPS or multiparticulate systems (disintegrating, film coated)], disintegrating tablets, dispersible tablets, granules, and microspheres, sachets [filled with powders, powders for reconstitution, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, film coated tablets, MUPS, film coated tablets MUPS, orally disintegrating MUPS, disintegrating tablets, dispersible tablets, granules, and microspheres, multiparticulates (disintegrating, film coated)] sprinkles exhibiting delayed release, controlled release, modified release, extended release, pulsatile release, mixed immediate release and controlled release and liquid dosage forms (liquids, liquid dispersions, suspensions, solutions, emulsions, sprays).

Preferably when the oral dosage is in the form of sachets or sprinkles it is administered by sprinkling over regular meals or with liquid or semi-solid beverages such as but not limited to juices or water.

Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving or flash melt preparations. Delayed release, controlled release, extended release or pulsatile release compositions may comprise hydrophilic, lipophilic or hydrophobic release rate controlling substances or their combinations to form matrix or reservoirs or combination of such matrix and reservoir systems.

In one embodiment, the pharmaceutical composition according to the present invention, may be administered as granules or pellets directly or filled into capsules or sachets. Preferably the granules or pellets are in a modified release form.

In another embodiment, the pharmaceutical composition according to the present invention may be administered as MUPS. Preferably the MUPS or multiparticulate systems are in a controlled release form, immediate release form, dual release form etc.

Accordingly, the pharmaceutical compositions in the form of granules, pellets and MUPS may include: (a) a core; (b) a sub coating/seal coating or separating layer coated onto the core; and (c) one or more enteric coats coated onto the sub/seal coating or separating layer.

Accordingly, the pharmaceutical compositions in the form of granules, pellets and MUPS may include: a) a core, and b) one or more seal coats.

Accordingly, the pharmaceutical compositions in the form of granules, pellets and MUPS may include: a) a core, and b) one or more enteric coats.

Accordingly, the pharmaceutical compositions in the form of granules, pellets and MUPS may include only a core.

Further, the sub coating/seal coating or separating layer over the core is preferably present in an amount from 0.5 to 20% of the composition.

Further, one or more enteric coats coated over the sub coat/seal coat or separating layer are preferably present in an amount from 2 to 30% of the composition.

The core would refer to either an inert core coated with the active or core containing the premix. The active may be coated on the inert core by techniques such as, but not limited to, powder layering, suspension coating etc. The core containing the premix may be obtained by techniques such as, but not limited to, blending, granulation, extrusion-spheronization etc.

The inert core particles that may be used for the drug layering are Non Pariel seeds (NONPARIEL-101(particle diameter- 850μm-710μm, 710-500μm and 500-355μm), NONPARIEL-103(particle diameter- 850μm-710μm, 710-500μm and 500-355μm), NONPARIEL-105(particle diameter- 850μm-710μm, 710-500μm and 300-180μm) or Celphere [CP-507 (Particle diameter-500-710μm) and CP-305 (Particle diameter 300-500μm)].

The inert core may comprise any inert/inactive material such as, but not limited to, starches, microcrystalline cellulose, sugar sphere or salt, silicon dioxide, glass beads, plastic resin particles, coarse grade silicon beads etc. A core particle containing the active material can be produced by granulating the active along with excipients such as, but not limited to, lactose, white sugar, mannitol, corn starch and crystalline cellulose using binders such as hydroxy propyl methyl cellulose, hydroxy propyl cellulose, methyl cellulose, a poly vinyl alcohol, Macrogol, gum Arabic, gelatin and starch or mixtures thereof.

The pharmaceutical composition of the present invention, comprising one or more enteric coats coated onto the sub/seal coating or separating layer, may be advantageous in modifying the release of the active ingredient.

Thus, the pharmaceutical composition of the present invention comprising one or more enteric coats coated onto the sub/seal coating or separating layer provides a pH dependant release. Accordingly, pharmaceutical composition of the present invention, comprising one or more enteric coats, controls the release of the active ingredient at different pH values. In one embodiment of the present invention, the pharmaceutical composition comprising one or more enteric coats comprises one kind of polymeric substances which is soluble in the pH range of not less than 5.

In another embodiment of the present invention, the pharmaceutical composition comprising one or more enteric coats comprises one kind of polymeric substances which is soluble in the pH range of not less than 6.

Further, the pharmaceutical composition of the present invention in the form of MUPS may include the use of additional pharmaceutically acceptable excipients.

The core may be prepared by homogenously mixing the premix and pharmaceutically acceptable excipients. The core is then formulated into small beads, pellets, granules, fine granules, mini-tablets or tablets, hard gelatin or soft gelatin capsules by conventional procedures.

The inert sub coating/seal coating or separating layer (single layered or multilayered) separates the core from an enteric coating polymer that contains free carboxyl groups, which may cause degradation and/or discoloration. The inert sub coating/seal coating or separating layer may also serve as a pH-buffering zone in which hydrogen ions diffusing from the outside toward the alkaline core can react with hydroxyl ions diffusing from the alkaline core toward the surface of the coated articles.

The inert sub coating/seal coating or separating layer can be applied to core (formulated as beads, pellets, granules, fine granules, mini-tablets or tablets, hard gelatin or soft gelatin capsules) by conventional coating procedures using aqueous, non-aqueous or hydro alcoholic solvent systems for the coating solutions or dispersions.

The enteric coats can be coated over to the inert sub coating/seal coating or separating layer by conventional coating procedures using water and/or an organic solvent for the coating solutions or dispersions.

Suitable excipients may be used for formulating the various dosage forms according to the present invention.

Stabilizers refer to any chemical, compound or material that minimizes the degradation of the active ingredient or drug by the acidic environment of the stomach. Suitable stabilizers that can be incorporated in the pharmaceutical composition of the present invention may comprise one or more, but not limited to, basic inorganic salts such as sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, potassium carbonate, potassium hydrogen carbonate, potassium hydroxide, heavy magnesium carbonate, light magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [Mg6Al2(OH)16.CO3.4H2O], and aluminum hydroxide-magnesium oxide [2.5MgO.Al2O3.xH2O], precipitated calcium carbonate, calcium hydroxide or mixtures thereof and organic compounds such as meglumine, lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, procaine or

mixtures thereof. The stabilizer is preferably present in an amount from 0.5 to 15% of the composition.

Suitable carriers, diluents or fillers for use in the pharmaceutical composition of the present invention may comprise one or more, but not limited to lactose (for example, spray-dried lactose, α-lactose, β-lactose), lactose available under the trade mark Tablettose, various grades of lactose available under the trade mark Pharmatose or other commercially available forms of lactose, lactitol, sucrose, pulverized sugars, saccharose, sorbitol, mannitol, dextrates, dextrins, dextrose, maltodextrin, croscarmellose sodium, microcrystalline cellulose (for example, microcrystalline cellulose available under the trade mark Avicel), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC), methylcellulose polymers (such as, for example, Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethyl hydroxyethylcellulose and other cellulose derivatives, starches or modified starches (including potato starch, corn starch, maize starch and rice starch) and mixtures thereof. The carriers, diluents or fillers are preferably present in an amount from 0.1 to 95% of the composition.

According to the present invention, glidants, anti-adherents and lubricants may also be incorporated in the pharmaceutical composition of the present invention, which may comprise one or more, but not limited to stearic acid and pharmaceutically acceptable salts or esters thereof (for example, magnesium stearate, calcium stearate, sodium stearyl fumarate or other metallic stearate), talc, waxes (for example, microcrystalline waxes), glycerides, light mineral oil, PEG, silica acid or a derivative or salt thereof (for example, silicates, silicon dioxide, colloidal silicon dioxide and polymers thereof, crospovidone, magnesium aluminosilicate and/ or magnesium alumino metasilicate), sucrose ester of fatty acids, hydrogenated vegetable oils (for example, hydrogenated castor oil) or mixtures thereof.

According to the present invention, suitable binders may also present in the in the pharmaceutical composition of the present invention, which may comprise one or more, but not limited to polyvinyl pyrrolidone (also known as povidone), polyethylene glycol(s), starch, modified starch

derivatives (potato starch, rice starch, corn starch, maize starch etc.), hydrolysed starch (maltodextrin), carboxymethyl starch, hydroxypropyl starch, sodium starch glycolate, acacia, alginic acid, agar, calcium carragenan, cellulose derivatives such as ethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethylcellulose, dextrin, gelatin, gum arabic, guar gum, tragacanth, sodium alginate, sucrose, pulverized sugars or mixtures thereof or any other suitable binder. The binder is preferably present in an amount from 0.1 to 5% of the composition.

According to the present invention, suitable disintegrants may also be present in the pharmaceutical composition of the present invention, which may comprise one or more, but not limited to hydroxylpropyl cellulose (HPC), low density HPC, carboxymethylcellulose (CMC), sodium CMC, calcium CMC, croscarmellose sodium; starches exemplified under examples of fillers and also carboxymethyl starch, hydroxylpropyl starch, modified starch, crospovidone, crystalline cellulose, F-MELT® (Type C, Type M, and Type F1), sodium starch glycolate, alginic acid or a salt thereof, such as sodium alginate or their equivalents and mixtures thereof. The disintegrants are preferably present in an amount from 1 to 50% of the composition.

Suitable viscosity enhancing/thickening agents which may be used in the pharmaceutical composition of the present invention, include, but are not limited to methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxy ethyl propyl cellulose, starches (such as maize or corn starch, potato starch, rice starch, tapioca starch, and wheat starch), carboxyvinyl polymers (carbomers such as Carbopol®), carboxymethyl cellulose and salts thereof, microcrystalline cellulose and arabic gum, guar gum, and xanthan gum, and mixtures thereof. The viscosity enhancing/thickening agents is preferably present in an amount from 2 to 20% of the composition.

According to the present invention, suitable polymers that can be used in the pharmaceutical composition of the present invention include hydrophilic, hydrophobic and lipophilic polymers, and combinations thereof. Examples of polymers include, but are not limited to, cellulose ethers, e.g., hydroxypropyl methylcellulose (hypromellose or HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose, ethylcellulose, and carboxymethylcellulose sodium, polyvinylpyrrolidone,

including non-crosslinked polyvinylpyrrolidone, carboxymethylstarch, polyethylene glycols, polyoxyethylene, poloxamer (polyoxyethylene-polyoxypropylene copolymers), polyvinylalcohol, glucane (glucan), carrageenan, scleroglucane (scleroglucan), mannan, galactomannan, gellan, alginic acid and derivatives (e.g., sodium or calcium alginate, propylene glycol alginate), polyaminoacid (e.g. gelatin), methyl vinyl ether/maleic anhydride copolymers, polysaccharides (e.g. carageenan, guar gum, xanthan gum, tragacanth and ceratonia), alpha-, beta- or gamma-cyclodextrins, dextrin derivatives (e.g. dextrin), polymethacrylates (e.g. copolymers of acrylic and methacrylic acid esters containing quaternary ammonium groups), acrylic acid polymers (e.g., carbomers), shellac and derivatives thereof, cellulose acetate, cellulose butyrate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate and other acetylated cellulose derivatives etc. or combinations thereof.

Suitable lipophilic substances that can be used in the pharmaceutical composition of the present invention include, but are not limited to, waxes (e.g., carnauba wax, microcrystalline wax, beeswax, and polyethoxylated beeswax), natural fats (coconut, soya, cocoa) including modified forms such as totally or partially hydrogenated, hydrogenated castor oil, hydrogenated vegetable oil and fatty acid derivatives such as mono-, bi- and tri-substituted glycerides, phospholipids, glycerophospholipids, glyceryl palmitostearate, glyceryl behenate, glyceryl monostearate, diethyleneglycol palmitostearate, polyethyleneglycol stearate, polyethyleneglycol palmitostearate, polyoxyethylene-glycol palmitostearate, glyceryl monopalmitostearate, cetyl palmitate, fatty alcohols associated with polyethoxylate fatty alcohols, cetyl alcohol, stearic acid, saturated or unsaturated fatty acids and their hydrogenated derivatives, lecithin, cephalins, chitosan and derivatives thereof, sphingolipids, sterols such as cholesterol and its substituted derivatives etc.

According to the present invention, surfactants (amphoteric, non-ionic, cationic or anionic) may comprise of one or more, but not limited to polysorbates, sodium dodecyl sulfate (sodium lauryl sulfate), lauryl dimethyl amine oxide, docusate sodium, cetyl trimethyl ammonium bromide (CTAB) polyethoxylated alcohols, polyoxyethylene sorbitan, octoxynol, N, N–dimethyldodecylamine–N–oxide, hexadecyltrimethylammonium bromide, polyoxyl 10 lauryl ether, brij, bile salts (sodium deoxycholate, sodium cholate), polyoxyl castor oil, nonylphenol

ethoxylate cyclodextrins, lecithin, methylbenzethonium chloride, carboxylates, sulphonates, petroleum sulphonates, alkylbenzenesulphonates, naphthalenesulphonates, olefin sulphonates, alkyl sulphates, sulphates, sulphated natural oils & fats, sulphated esters, sulphated alkanolamides, alkylphenols, ethoxylated & sulphated, ethoxylated aliphatic alcohol, polyoxyethylene surfactants, carboxylic esters polyethylene glycol esters, anhydrosorbitol ester and it's ethoxylated derivatives, glycol esters of fatty acids, carboxylic amides, monoalkanolamine condensates, polyoxyethylene fatty acid amides, quaternary ammonium salts, amines with amide linkages, polyoxyethylene alkyl & alicyclic amines, N,N,N,N tetrakis substituted ethylenediamines 2- alkyl 1- hydroxyethyl 2-imidazolines, N -coco 3-aminopropionic acid/ sodium salt, N-tallow 3 -iminodipropionate disodium salt, N-carboxymethyl n dimethyl n-9 octadecenyl ammonium hydroxide, n-cocoamidethyl n-hydroxyethylglycine sodium salt or mixtures thereof.

Viscosity builders are excipients that are capable of stabilizing the formulation by increasing the viscosity of the formulation and thus preventing physical interaction of nanoparticles under the operating conditions employed.

According to the present invention, viscosity builders may comprise one or more, but not limited to derivatives of sugars, such as lactose, sucrose, saccharose, hydrolyzed starch (maltodextrin) or mixtures thereof.

Polymers or polymers blends, according to the present invention, may comprise one or more hydrophilic polymers, but not limited to cellulose derivates like hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, methylcellulose polymers hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene and carboxymethyl hydroxyethylcellulose; acrylics like acrylic acid, acrylamide, and maleic anhydride polymers, acacia, gum tragacanth, locust bean gum, guar gum, or karaya gum, agar, pectin, carrageenan, gelatin, casein, zein and alginates, carboxypolymethylene, bentonite, magnesium aluminum silicate, polysaccharides, modified starch derivatives and copolymers or mixtures thereof.

The pharmaceutical compositions, according to the present invention, may also optionally be coated, but not limited to seal coating, film coating, enteric coating or a combination thereof.

According to an embodiment of the present invention, pharmaceutical composition may be film coated with, but not limited to, ready colour mix systems (such as Opadry colour mix systems) and Kollicoat® Protect.

According to the present invention, the seal coat comprises water soluble or insoluble film forming polymeric materials, such as but not limited to, sugars, zein, cellulose derivatives such as hydroxypropyl celluloses, hydroxypropyl methylcelluloses, ethylcelluloses, and hydroxyethyl celluloses, polyvinylalcohols, providones, polyethylene glycols, poloxamers, gelatin, polylysine, polyarginine, polyglycine, polyvinylpyrrolidines, vinyl acetate copolymer, methylcellulose, carboxymethylcellulose, hypromellose, acacia and mixtures thereof to increase adherence and coherence of the seal coat.

According to the present invention, enteric coating polymers that can be used, in the pharmaceutical composition of the present invention, include, but are not limited to, cellulose acetate phthalates (CAP), hydroxypropyl methylcellulose phthalates (HPMCP), polyvinyl acetate phthalates (PVAP), hydroxypropyl methylcellulose acetate succinates (HPMCAS), cellulose acetate trimellitates, hydroxypropyl methylcellulose succinates, cellulose acetate succinates, cellulose acetate hexahydrophthalates, cellulose propionate phthalates, copolymers of methylmethacrylic acid and methyl methacrylate, copolymers of methyl acrylate, methylmethacrylate and methacrylic acid, copolymers of methylvinyl ether and maleic anhydride (Gantrez™ ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymers, natural resins such as zein, shellac and copal collophorium, carboxymethyl ethylcelluloses, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, available under the trade name EUDRAGIT® L12.5, L100, or EUDRAGIT® S12.5, S100, and several commercially available enteric dispersion systems (e.g., EUDRAGIT® L30D55, EUDRAGIT® FS30D, EUDRAGIT® L100-55, EUDRAGIT® S100, KOLLICOAT® MAE30D and 30DP (BASF), ESTACRYL® 30D, AQUATERIC® and AQUACOAT® CPD30 and

mixtures thereof. The enteric coating polymers are preferably present in an amount from 1 to 20% of the composition.

According to the present invention, plasticizers for use in the pharmaceutical composition of the present invention may comprise one or more, but are not limited to substances such as castor oil, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, polyethylene glycol, propylene glycol, triacetin, and triethyl citrate.

Examples of pH adjusting agents include, but are not limited to: sodium hydroxide, citric acid, hydrochloric acid, acetic acid, phosphoric acid, succinic acid, sodium hydroxide, potassium hydroxide, ammonium hydroxide, magnesium oxide, calcium carbonate, magnesium carbonate, magnesium aluminum silicates, malic acid, potassium citrate, sodium citrate, sodium phosphate, lactic acid, gluconic acid, tartaric acid, 1,2,3,4-butane tetracarboxylic acid, fumaric acid, diethanolamine, monoethanolamine, sodium carbonate, sodium bicarbonate, triethanolamine, or combinations thereof. The pH adjusting agents are preferably present in an amount from 0.02 to 5% of the composition.

According to the present invention, one or more pharmaceutically acceptable opacifiers such as, but not limited to, titanium dioxide (TiO2) may be used in the pharmaceutical composition covered in the present invention.

Suitable colouring agents that may be used in the pharmaceutical composition of the present invention, include but are not limited to, natural and/or artificial compounds such as FD&C colouring agents, natural juice concentrates, pigents such as titanium oxide, silicon dioxide, iron oxides such as red oxide of iron, zinc oxide and mixtures thereof.

Suitable sweetening agents that may be used in the pharmaceutical composition of the present invention, include but are not limited to, natural and/or artificial compounds, such as acesulfame, sucrose, mannitol, cyclamate, alitame, a dihydrochalcone sweetener, monellin, neohesperidin, neotame, stevia and sucralose, their pharmaceutically acceptable salts and mixtures thereof.

Suitable flavouring agents which may be used in the pharmaceutical composition of the present invention, include, but are not limited to cherry, raspberry, pineapple, black currant, strawberry flavour, caramel chocolate flavour, mint flavor and the like.

The pharmaceutical compositions, according to the present invention, may be prepared through various techniques or processes known in the art which includes, but are not limited to direct blending, direct compression, wet granulation, dry granulation, melt granulation, melt extrusion, lyophilisation, hot melt extrusion, spray drying, solution evaporation, extrusion-spheronization or combinations thereof.

Alternatively, the pharmaceutical composition according to the present invention may also comprise the drug in nano size form.

Thus, the pharmaceutical composition according to the present invention, comprising the drug in nano size form may exhibit better aqueous solubility and oral bioavailability and may, in turn, cause a reduction in the dosage of the drug.
Nanonization of hydrophobic or poorly water-soluble drug generally involves the production of drug nanocrystals through either chemical precipitation (bottom-up technology) or disintegration (top-down technology). Different methods may be utilized to reduce the particle size of the hydrophobic or poorly water soluble drug. [Huabing Chen et al., discusses the various methods to develop nanoformulations in "Nanonization strategies for poorly water-soluble drug," Drug Discovery Today, Volume 00, Number 00, March 2010].

The term "nanosize" (i.e. sub-micron) form as used herein refers to drug particles, preferably, having a D50 number average particle size of less than 2000 nm, preferably less than 1000 nm more preferably less than 500 nm, such as less than 100 nm, less than 200 nm, less than 300 nm, less than 400 nm, or less than 500 nm.

Mostly all particles have a particle size of less than or equal to about 2000 nm, preferably less than or equal to about 1000 nm.

The term "particles" as used herein refers to individual particle of drug or particles of drug or drug granules or drug compositions and/or mixtures thereof.

The nanosize particles of the present invention can be obtained by any of the process such as but not limited to milling, precipitation and homogenization.

Accordingly, milling comprises the process of reduction of the size of the particles as such in the solid form by using milling machines such as but not limited to ball mill, jet mill , planetary mill etc. Particle size reduction may also be achieved by dispersing drug particles in a liquid medium in which the drug is poorly soluble followed by applying mechanical means in the presence of grinding media to reduce the particle size of drug to the desired effective average particle size.

Accordingly, the process of precipitation involves the formation of crystalline or semi-crystalline drug nanoparticles by nucleation and the growth of drug crystals. In a typical procedure, drug molecules are first dissolved in an appropriate organic solvent such as acetone, tetrahydrofuran or N-methyl-2-pyrrolidone at a super saturation concentration to allow for the nucleation of drug seeds. Drug nanocrystals are then formed by adding the organic mixture to an antisolvent like water in the presence of stabilizers such surfactants. The choice of solvents and stabilizers and the mixing process are key factors to control the size and stability of the drug nanocrystals.

Accordingly, the process of homogenization involves passing a suspension of crystalline drug and stabilizers through the narrow gap of a homogenizer at high pressure (500–2000 bar). The pressure creates powerful disruptive forces such as cavitation, collision and shearing, which disintegrate coarse particles to nanoparticles.

Accordingly, the process of high pressure homogenization comprises drug presuspension (containing drug in the micrometer range) by subjecting the drug to air jet milling in the presence of an aqueous surfactant solution. The presuspension is then subjected to high-pressure homogenization in which it passes through a very small homogenizer gap of 25 μm which leads to a high streaming velocity. High pressure homogenization is based on the principle of cavitations (i.e., the formation, growth, and implosive collapse of vapor bubbles in a liquid).

Accordingly, the process of spray-freeze drying involves the atomization of an aqueous drug solution into a spray chamber filled with a cryogenic liquid (liquid nitrogen) or halocarbon refrigerant such as chlorofluorocarbon or fluorocarbon. The water is removed by sublimation after the liquid droplets solidify.

Accordingly, the process of supercritical fluid technology involves controlled crystallization of drug from dispersion in supercritical fluids, carbon dioxide.

Accordingly, the process of double emulsion/solvent evaporation technique involves preparation of oil/water (o/w) emulsions with subsequent removal of the oil phase through evaporation. The emulsions are prepared by emulsifying the organic phase containing drug, polymer and organic solvent in an aqueous solution containing emulsifier. The organic solvent diffuses out of the polymer phase and into the aqueous phase, and is then evaporated, forming drug-loaded polymeric nanoparticles.

Accordingly, the process of PRINT (Particle replication in non-wetting templates) involves utilization of a low surface energy fluoropolymeric mold that enables high-resolution imprint lithography, to fabricate a variety of organic particles. PRINT can precisely manipulate particle size of drug ranging from 20 nm to more than 100 nm.

Accordingly, the process of thermal condensation involves use of capillary aerosol generator (CAG) to produce high concentration condensation submicron to micron sized aerosols from drug solutions.

Accordingly, the process of ultrasonication involves application of ultrasound during particle synthesis or precipitation, which leads to smaller particles of drug and increased size uniformity.

Accordingly, the process of spray drying involves supplying the feed solution at room temperature and pumping it through the nozzle where it is atomized by the nozzle gas. The

atomized solution is then dried by preheated drying gas in a special chamber to remove water moisture from the system, thus forming dry particles of drug.

The pharmaceutical compositions of the present invention comprise the drug particles that can be manufactured by any of the types of processes as described above. The processes as describe above, however, do not limit the scope of the invention.

The pharmaceutical compositions of the present invention comprise the drug particles manufactured by any of the types of processes as described above may be formulated in dosage forms such as, but not limited to, tablets (single layer, bilayer, multilayer, tablet in tablet) which may be coated or uncoated, film coated, sugar coated, powder coated, enteric coated, seal coated; capsules (filled with powders, powders for reconstitution, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, film coated tablets, MUPS, film coated tablets MUPS, orally disintegrating MUPS, disintegrating tablets, dispersible tablets, granules, microspheres and multiparticulates or combinations thereof), soft gelatin capsules, sachets (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, film coated tablets, MUPS, film coated tablets MUPS, orally disintegrating MUPS, disintegrating tablets, dispersible tablets, granules, microspheres, multiparticulates or combinations thereof) and sprinkles however other dosage forms such as liquid dosage forms (liquids, liquid dispersions, suspensions, solutions, emulsions, microemulsions, sprays, syrups, spot-on formulations), injection preparations, gels, aerosols, ointments, creams, controlled release formulations, modified release formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations, dual release formulations etc. may also be envisaged under the ambit of the invention.

The present invention also provides a method of preventing or treating a gastrointestinal disorder, which method comprises administering a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole to a patient in need thereof. Preferably, the triol solvate is a glycerol solvate. More preferably, the pharmaceutical composition comprises (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, B or C, or a mixture thereof.

The present invention also provides the use of a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole for the prevention or treatment of a gastrointestinal disorder. Preferably, the triol solvate is a glycerol solvate. More preferably, the pharmaceutical composition comprises (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, B or C, or a mixture thereof.

The present invention also provides a pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole for use in the prevention or treatment of gastrointestinal disorders. Preferably, the triol solvate is a glycerol solvate. More preferably, the pharmaceutical composition comprises (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A, B or C, or a mixture thereof.

Preferably, the gastrointestinal disorder is selected from heartburn caused by gastroesophageal reflux disease (GERD) and erosive esophagitis.

The pharmaceutical composition, according to the present invention may further comprise or may be administered in combination with other compounds such as, but not limited to NSAIDS, antacids, anti-emetic agents, antibiotics, HMG-CoA reductase inhibitors, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and any other vasodilatory or anti-hypertensive agents or platelet aggregation inhibitors and oral anticoagulants for the treatment of for gastrointestinal disorders. In one embodiment, the pharmaceutical composition, according to the present invention, with other compounds, may be administered simultaneously, separately, or sequentially. In another embodiment, the pharmaceutical composition, according to the present invention, may be provided with other compounds in the form of a kit.

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present invention.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a propellant" includes a single propellant as well as two or more different propellants; reference to a "cosolvent" refers to a single cosolvent or to combinations of two or more cosolvents, and the like.

Experimental Procedures

Measurements of 2θ values listed herein are typically accurate to within ± 0.2 degrees unless otherwise stated. All XRD patterns were measured on a Rigaku Dmax 2200 advanced X-ray powder diffractometer fitted with a copper-K-α radiation source. The XRD patterns are expressed in terms of 2 theta values (2θ) and percentage intensity (%).

To measure the intrinsic dissolution of the (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Forms A, C, anhydrous and sesquihydrate, samples were measured to compare the influence of the different parameter setting. At appropriate time intervals, an automated sample collector removes aliquots from dissolution medium for analysis. The time interval for sampling can vary, for example, from 2 to 30 minutes, depending on the properties of the drug and dissolution medium used. Suitable dissolution equipment for these operations includes LAB INDIA DISSO 2000.

Example 1: Preparation of crystalline Form A of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate (10 g) was dissolved in ethyl acetate (200 ml), dried over anhydrous sodium sulphate. The solvent was removed, stripped off with ethyl acetate (100 ml) and the residual solid was dissolved in ethyl acetate (25 ml). Glycerol (2.5 g) was added and the reaction mass was diluted with ethyl acetate (75 ml). The reaction mixture was heated to 40°C to 45°C and n-heptane (200 ml) was added slowly at 40°C to 45°C. The reaction mass was cooled to 25°C to 30°C, and stirred for 60 minutes. The solid was isolated by filtration, washed with n-heptane (20 ml) and dried under vacuum at 25°C to 30°C for 8 to 10 hours.

Yield: 10.3 g

Enantiomeric purity: 99.58 %

HPLC purity: 99.58%

Example 2: Preparation of crystalline Form A of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate by using 25% w/w of glycerol in presence of an organic base

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate (25 g) was dissolved in ethyl acetate (375 ml), dried over anhydrous sodium sulphate. Triethylamine (0.5 ml) was added and the solvent was removed below 40°C, stripped off with ethyl acetate (250 ml) and the residual solid was dissolved in ethyl acetate (125 ml). Glycerol (6.25 g) was added and the reaction mass was diluted with ethyl acetate (125 ml). The reaction mixture was heated to 40°C to 45°C and n-heptane (500 ml) was added slowly at 40°C to 45°C. The reaction mass was cooled to 25°C to 30°C, and stirred for 60 minutes. The solid was isolated by filtration, washed with n-heptane (50 ml) and dried under vacuum at 25°C to 30°C for 8 to 10 hours.

Yield: 27.2 g

Enantiomeric purity: 99.94%

HPLC purity: 99.58%

Example 3: Preparation of crystalline Form A of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate by using 20% w/w of glycerol in presence of an organic base

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate (25 g) was dissolved in ethyl acetate (375 ml), dried over anhydrous sodium sulphate. Triethylamine (0.5 ml) was added and the solvent was removed below 40°C, stripped off with ethyl acetate (250 ml) and the residual solid was dissolved in ethyl acetate (125 ml). Glycerol (5.0 g) was added and the reaction mass was diluted with ethyl acetate (125 ml). The reaction mixture was heated to 40°C to 45°C and n-heptane (500 ml) was added slowly at 40°C to 45°C. The reaction mass was cooled to 25°C to 30°C, and stirred for 60 minutes. The solid was isolated by filtration, washed with n-heptane (50 ml) and dried under vacuum at 25°C to 30°C for 8 to 10 hours.

Yield: 22.1 g

Enantiomeric purity: 99.5%

HPLC purity: 99.64%

Example 4: Preparation of crystalline Form A of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate by using 15% w/w of glycerol in presence of an organic base

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate (25 g) was dissolved in ethyl acetate (375 ml), dried over anhydrous sodium sulphate. Triethylamine (0.5 ml) was added and the solvent was removed below 40°C, stripped off with ethyl acetate (250 ml) and the residual solid was dissolved in ethyl acetate (125 ml). Glycerol (3.75 g) was added and the reaction mass was diluted with ethyl acetate (125 ml). The reaction mixture was heated to 40°C to 45°C and n-heptane (500 ml) was added slowly at 40°C to 45°C. The reaction mass was cooled to 25°C to 30°C, and stirred for 60 minutes. The solid was

isolated by filtration, washed with n-heptane (50 ml) and dried under vacuum at 25°C to 30°C for 8 to 10 hours.

Yield: 16.8 g

Enantiomeric purity: 99.98%

HPLC purity: 99.71%

Example 5: Preparation of crystalline Form B of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate (25 g) was dissolved in ethyl acetate (100 ml). Glycerol (6.25 g) was added and the reaction mass was diluted with ethyl acetate (150 ml). The reaction mass was heated to 40°C to 45°C and n-heptane (500 ml) was added slowly at 40°C to 45°C. The reaction mass was cooled to 25°C to 30°C, and stirred for 60 minutes. The solid was isolated by filtration, washed with n-heptane (50 ml) and dried under vacuum at 25°C to 30°C for 8 to 10 hours.

Yield: 24.6 g

Enantiomeric purity: 99.92%

HPLC purity: 99.84%

Example 6: Preparation of crystalline Form C of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate by using 20% w/w of glycerol without organic base

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate (25.0 g) was dissolved in ethyl acetate (100 ml). Glycerol (5.0 g) was added and the reaction mass was diluted with ethyl acetate (150 ml). The reaction mass was heated to 40°C to 45°C and n-heptane (500 ml) was added slowly at 40°C to 45°C. The reaction mass was cooled to 25°C to 30°C, and stirred for 30 minutes. The solid was isolated by filtration, washed with n-heptane (50 ml) and dried under vacuum at 25°C to 30°C for 8 to 10 hours.

Yield: 27.3 g

Enantiomeric purity: 99.93%

HPLC purity: 99.83%

Example 7: Preparation of crystalline Form C of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate by using 15% w/w of glycerol without organic base

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate (25.0 g) was dissolved in ethyl acetate (100 ml). Glycerol (3.75 g) was added and the reaction mass was diluted with ethyl acetate (150 ml). The reaction mass was heated to 40°C to 45°C and n-heptane (500 ml) was added slowly at 40°C to 45°C. The reaction mass was cooled to 25°C to 30°C, and stirred for 30 minutes. The solid was isolated by filtration, washed with n-heptane (50 ml) and dried under vacuum at 25°C to 30°C for 8 to 10 hours.

Yield: 20.1 g

Enantiomeric purity: 99.95%

HPLC purity: 99.86%

Example 8: Preparation of crystalline Form C of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate by using 20% w/w of glycerol in presence of an organic base

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate (25.0 g) was dissolved in ethyl acetate (100 ml). Glycerol (5.0 g) was added followed by triethylamine (0.3 ml) and the reaction mass was diluted with ethyl acetate (150 ml). The reaction mass was heated to 40°C to 45°C and n-heptane (500 ml) was added slowly at 40°C to 45°C. The reaction mass was cooled to 25°C to 30°C, and stirred for 30 minutes. The solid was isolated by filtration, washed with n-heptane (50 ml) and dried under vacuum at 25°C to 30°C for 8 to 10 hours.

Yield: 24.3 g

Enantiomeric purity: 99.93%

HPLC purity: 99.87%

Example 9: Preparation of anhydrous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole from Form A

Crystalline Form A of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate (2.0 g) was dissolved in ethyl acetate (60 ml) and washed with water followed by brine solution (20 ml). The organic layer was dried over anhydrous sodium sulphate and distilled completely under vacuum at 40°C to 45°C. The residue was dissolved in ethyl acetate (4 ml) and treated at 25°C to 30°C with n-heptane (30 ml). The solid was isolated by filtration and dried under vacuum at 25°C to 30°C for 8 to 10 hours.
Yield: 1.6 g,

Example 10: Preparation of anhydrous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole from Form C

Crystalline Form C of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate (2.0 g) was dissolved in ethyl acetate (50 ml) and washed with water. The organic layer was dried over anhydrous sodium sulphate and distilled completely under vacuum at 40°C to 45°C. The residue was dissolved in ethyl acetate (4 ml) and treated at 25°C to 30°C with n-heptane (30 ml). The solid was isolated by filtration and dried under vacuum at 25°C to 30°C for 8 to 10 hours.
Yield: 1.7 g

Example 11: Preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate from Form A

Crystalline Form A of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate (2.0 g) was stirred in water (20 ml) for 3 hours. The solid was isolated by filtration and dried under vacuum at 40°C to 45°C under vacuum for 8 to 10 hours.
Yield: 1.48 g

Example 12: Preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate from Form C

Crystalline Form Cof (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate (2.0 g) was stirred in water (20 ml) for 3 hours. The solid was isolated by filtration and dried under vacuum at 40°C to 45°C under vacuum for 8 to 10 hours.

Yield: 1.47 g

Example 13: Preparation of crystalline Form A of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate from ethyl acetate

(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate (5.0 g) was dissolved in ethyl acetate (100 ml), dried over anhydrous sodium sulphate. The solvent was removed under vacuum at 40°C to 45°C and stripped out with ethyl acetate (40 ml). The residue was dissolved in ethyl acetate (30 ml) and glycerol (1.25 g) was added. The reaction mass was cooled to 25°C to 30°C, diluted with ethyl acetate (30 ml) and further chilled to 0°C to5°C. The reaction mass was stirred for 30 minutes, the solid was isolated by filtration and dried under vacuum at 40°C to 45°C for 12 to14 hours.

Yield: 3.6 g

Example 14: Preparation of crystalline Form A of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate

(+)-diethyl L-tartrate (3.619 g /0.0175 moles), titanium (IV) isopropoxide (2.415 g / 0.0084 moles) and water (0.06 g / 0.0033 moles) were added to toluene (75 ml) at 25°C to 30°C. The solution was stirred for 15 minutes and 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]thio]-1H-benzimidazole (10 g / 0.02829 moles) was added. The reaction mass was heated to 70°C to 75°C, maintained for 5 minutes and cooled to 25°C to 30°Cover 30 minutes. Diisopropylethylamine (2.342 g / 0.0181 moles) was added, stirred for 30 minutes and then

cooled to -5°C to 0°C. A solution of 80% cumene hydroperoxide (14.788 g/ 0.0971 moles) in toluene (10 ml) was added at -5°C to 0°C over 60 minutes. The reaction was stirred for 2 to2.5 hours at -5°C to 0°C and quenched with 5% aqueous KOH solution (50 ml) maintaining temperature at about -5°C to 0°C. The temperature of the reaction mass was raised to 25°C - 30°C and methanol was charged (25 ml). The reaction mass was basified to a pH of 12.5 to 13.0 with 20% aqueous KOH solution and stirred for 10 minutes at 30°C to 35°C. The aqueous layer was separated at 30°C to 35°C and the organic layer was extracted with a mixture of 5% aqueous KOH (30 ml) and methanol (15 ml) at 30°C to 35°C. The aqueous layers were combined and washed with MDC (3 x 30 ml) at 30°C to 35°C. The pH of the aqueous solution was adjusted to 8.5 to 9.5 with 20% acetic acid at 30°C to 35°C. The solid was extracted in ethyl acetate (2 x 50 ml). The organic layers were combined together and dried over anhydrous sulphate. The solvent was distilled completely under vacuum at 45°C and stripped off with ethyl acetate (2 x 100 ml). The residue was dissolved in ethyl acetate (37.5 ml). Glycerol (2.5 g) was added and reaction mass was diluted with ethyl acetate (75 ml). The reaction mass was heated to 43°C to 45°C and n-heptane (200 ml) was added slowly at 40°C to 45°C. The reaction mass was cooled to 25°C to 30°C, and stirred for 30 minutes. The solid was isolated by filtration, washed with n-heptane (20 ml) and dried under vacuum at 25°C to 30°C for 8 to 10 hours.

Yield: 8.0 g

HPLC purity: 98.17%

Example 15: Preparation of crystalline Form C of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate

(+)-diethyl L-tartrate (36.0 g, 0.1741 moles), titanium (IV) isopropoxide (24.0 g, 0.00835 moles) and water (0.6 g, 0.033 moles) were added to toluene (750 ml) at 25°C – 30°C. The solution was stirred for 15 minutes and added 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]thio]-1H-benzimidazole (100 g / 0.2829 moles). The reaction mass was heated to 70°C – 75°C, maintained for 5 minutes and cooled to 25°C – 30°C over 30 minutes. Diisopropylethylamine (24.0 g, 0.181 moles) was added, stirred for 30 minutes and then cooled to -5°C – 0°C. A solution of 80% cumene hydroperoxide (148 g/ 0.971 moles) in toluene (100 ml) was added at -5°C-0°C over 60 minutes. The reaction was stirred for 2-2.5 hours at -5°C –

0°C and quenched with 5% aqueous KOH solution (500 ml) maintaining temperature at about -5°C – 0°C. The temperature of the reaction mass was raised to 25°C – 30°C and methanol was charged (250 ml). The reaction mass was basified to a pH of 12.5 – 13.0 with 20% aqueous KOH solution and stirred for 10 minutes. The aqueous layer was separated and the organic layer was extracted with a mixture of 5% aqueous KOH (300 ml) and methanol (150 ml) .The aqueous layers were combined and washed with MDC. Ethyl acetate was (700 ml) was charged. The pH of the reaction mass was adjusted to 8- 9 with 20% AcOH. The organic layer was separated. Aqueous layer was extracted with ethyl acetate. The ethyl acetate layers were combined, washed with 10%NaCl solution, dried with anhydrous sodium sulphate, filtered through hyflo bed and distilled out completely under vacuum. The residue was dissolved in ethyl acetate (1000 ml). Water (7 ml) and Glycerol (25 g) were added. The reaction mass was heated to 40°C– 45°C, cooled to 25°C – 30°C, further chilled to 5°C – 10°C and maintained for 2 hours. The solid was isolated by filtration. The solid was stirred in a mixture of ethyl acetate (1000 ml) and water (1 ml) and heated to 40°C -45°C. n-Heptane (100 ml) was added slowly at 40°C – 45°C. The reaction mass was cooled to 25°C – 30°C, further chilled to 5°C – 10°C and stirred for 2 hours. The solid was isolated by filtration, washed with n-heptane (50 ml) and dried under vacuum at 25°C – 30°C for 8 – 10 hours.

Yield: 72.0 g.

Example 16: Preparation of crystalline Form C of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate

(+)-diethyl L-tartrate (36.0 g, 0.1741 moles), titanium (IV) isopropoxide (24.0 g, 0.00835 moles) and water (0.6 g, 0.033 moles) were added to toluene (750 ml) at 25°C – 30°C. The solution was stirred for 15 minutes and added 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl]thio]-1H-benzimidazole (100 g / 0.2829 moles). The reaction mass was heated to 70°C – 75°C, maintained for 5 minutes and cooled to 25°C – 30°C over 30 minutes. Diisopropylethylamine (24.0 g, 0.181 moles) was added, stirred for 30 minutes and then cooled to -5°C– 0°C. A solution of 80% cumene hydroperoxide (148 g/ 0.971 moles) in toluene (100 ml) was added at -5°C – 0°C over 60 minutes. The reaction was stirred for 2-2.5 hours at -5°C – 0°C and quenched with 5% aqueous KOH solution (500 ml) maintaining temperature at about -

5°C– 0°C. The temperature of the reaction mass was raised to 25°C – 30°C and methanol was charged (250 ml). The reaction mass was basified to a pH of 12.5 – 13.0 with 20% aqueous KOH solution. The aqueous layer was separated and the organic layer was extracted with a mixture of 5% aqueous KOH (300 ml) and methanol (150 ml).The aqueous layers were combined and washed with MDC. MDC was (700 ml) was charged. The pH of the reaction mass was adjusted to 8- 9 with 20% AcOH. The organic layer was separated. Aqueous layer was extracted with MDC. The organic layers were combined, washed with water, dried with anhydrous sodium sulphate, filtered through hyflo bed and distilled out completely under vacuum. The residue was dissolved in ethyl acetate (1000 ml). Water (7 ml) and Glycerol (25 g) were added. The reaction mass was heated to 30°C – 35°C, cooled to 25°C – 30°C, further chilled to 5°C – 10°C and stirred for 2 hours. The solid was isolated by filtration and washed with n-Heptane (50 ml). The wet solid was stirred in ethyl acetate (1000 ml) and heated to 40°C – 45°C. n-Heptane (100 ml) was added slowly at 40°C – 45°C. The reaction mass was cooled to 25°C – 30°C, further chilled to 5°C -10°C and stirred for 2 hours. The solid was isolated by filtration, washed with n-heptane (100 ml) and dried under vacuum at 25°C– 30°C for 8 – 10 hours.

Purification:-

The solid was stirred in MDC (700 ml) and water (500 ml). The pH of the reaction mass was adjusted to 8-9 with 20% AcOH solution (75 ml). The organic layer was separated, washed with water, filtered through hyflo bed and distilled out completely under vacuum. The residue was dissolved in ethyl acetate (700 ml). Water (4.9ml) and Glycerol (17.5g) were added. The reaction mass was heated to 30°C – 35°C, added n-Heptane (70 ml), cooled to 25°C – 30°C, further chilled to 5°C – 10°C and stirred for 2 hours. The solid was isolated by filtration and washed with n-Heptane (70 ml) and dried under vacuum at 25°C – 30°C for 8 – 10 hours.

Yield: 68.0 g

Comparative Intrinsic Dissolution Study

Example 17 - Preparation of tablet

General process for preparing tableting mixture comprising (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate:-

A tableting mixture (50 mg) comprising solely (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate prepared according to any of the examples 1 to 16 (i.e. with no excipients) was prepared and compressed to a pellet using a manual hand press operating at a compression pressure of 1 tonnes for 1 minute.

General process for preparing tableting mixture comprising (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole :-

Similarly, a tableting mixture (50 mg) comprising solely (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in anhydrous or sesquihydrate form each was prepared and compressed to a pellet using a manual hand press operating at a compression pressure of 1 tonnes for 1 minute.

In-vitro dissolutions studies were performed on the 50 mg pellet in a LAB INDIA DISSO 2000.

The pellet was fixed in a PFTE holder, such that only the pellet surface came into contact with the dissolution medium. The PFTE loaded holder was placed in the dissolution vessel containing 900 ml of 2% SLS in Phosphate buffer pH 7.5 at 37±0.5°C. One pellet was measured for each run of the design of the experiments. Stirring was performed with a paddle rotating at 100 rpm. The dissolution was followed up to 360min and the concentration of active ingredient, (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, dissolved in the test medium was determined by removing samples of 10 ml at the specified time.

The concentration of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole was quantified by UV method at a maximum wavelength of 286 nm and 650nm under conditions as specified:

Standard Preparation: 15 mg (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole sesquihydrate dissolved to 50 ml with methanol 2 ml of this solution diluted to 50 ml with dissolution medium.

Sample Aliquot: 10 ml of aliquot further diluted to 50 ml with dissolution medium.

The percentage of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole released from the glycerol solvate Form A as well as from the anhydrous and sesquihydrate forms of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole was plotted against time, as shown in Figure 4. The intrinsic dissolution rate was derived from the slope of this curve. Table A shows the results in tabular form.

Table A: Intrinsic Dissolution Profile of Crystalline Form A of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate with Prior Art anhydrous and sesquihydrate Forms

Time in minutes	% Release of Form A	% Release of Anhydrous Form	% Release of Sesquihydrate Form
20	7	6	6
40	13	11	11
60	19	15	15
80	24	19	20
100	29	24	24
120	34	29	30
140	39	32	33
160	44	36	37
180	48	41	41
200	53	45	45

220	57	48	49
240	62	52	53
260	66	56	57
280	70	59	60
300	74	63	64
320	79	67	68
340	80	71	72
360	80	75	75

When compared with known anhydrous and seaquihydrate forms of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole, the new form A exhibited a superior rate of dissolution as shown in Table A. The peak dissolution of 79.0 % was achieved at 320 mins for the new Form A; whereas, at the same time, 67.0 % and 68.0% were achieved for anhydrous and sesquihydrate forms respectively.

Example 18

The percentage of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole released from the glycerol solvate Form C as well as from the anhydrous and sesquihydrate forms of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole was plotted against time, as shown in Figure 5. The intrinsic dissolution rate was derived from the slope of this curve. Table B shows the results in tabular form.

Table B: Intrinsic Dissolution Profile of Crystalline Form C of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate with Prior Art anhydrous and sesquihydrate Forms

Time in minutes	% Release of Form C	% Release of Anhydrous Form	% Release of Sesquihydrate Form
20	7	6	6
40	13	11	11
60	19	15	15
80	23	19	20
100	29	24	24
120	33	29	30
140	38	32	33
160	42	36	37
180	47	41	41
200	52	45	45
220	56	48	49
240	60	52	53
260	64	56	57
280	68	59	60
300	72	63	64
320	76	67	68
340	79	71	72
360	81	75	75

When compared with known anhydrous and seaquihydrate forms of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy) pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole; the new form C exhibited a superior rate of dissolution as shown in Table B. The peak dissolution of 76.0 % was achieved at 320 mins for the new Form C; whereas, at the same time, 67.0 % and 68.0% were achieved for anhydrous and sesquihydrate forms respectively.

Example 19 – Delayed released capsules

Sr. No	Ingredients	Mg/Capsule
	Dry Mix	
1	(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate	74.94
2	Light Magnesium Carbonate	16.00
3	Pulverised Sugar	13.06
4	Low substituted Hydroxypropyl cellulose	12.00
5	Sugar spheres	60.00
	TOTAL	**176.00**
	Binder	
6	Hydroxypropyl Cellulose	1.80
7	Purified Water	q.s
	TOTAL	**177.80**
	Seal Coating	
8	Hydroxypropylmethyl Cellulose	11.50
9	Purified Talc	5.20
10	Titanium dioxide	6.30
11	Purified Water	q.s
	TOTAL	**200.80**
	Enteric Coating I	
12	Seal coated pellets	50.20
13	Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion	15.00
14	Triethyl Citrate	1.50
15	Polysorbate 80	0.55
16	Purified Talc	1.95
17	Titanium dioxide	1.50
18	Purified Water	q.s
	TOTAL	**70.70**
	Enteric Coating II	
19	Seal coated pellets	150.60

20	Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)	7.52
21	Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)	22.60
22	Triethyl citrate	3.01
23	Purified talc	7.52
24	Isopropyl alcohol	q.s
25	Purified Water	q.s
	TOTAL	**191.25**
	Blending	
26	Enteric coated pellets I	70.70
27	Enteric coated pellets II	191.25
28	Purified Talc	1.05
	TOTAL	**263.00**

Process:

1. (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate, light magnesium carbonate, pulverised sugar and low substituted hydroxypropyl cellulose were blended together to produce a dry mix and loaded on sugar spheres in a coating machine using a binder to form drug loaded pellets.

2. The drug loaded pellets obtained in step (1) were seal coated using HPMC, talc and titanium dioxide and part of the seal coated pellets were enteric coated using Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) dispersion to form Enteric coated pellets I.

3. Remaining part of the seal coated pellets were then enteric coated using Methacrylic Acid - Methyl Methacrylate Copolymer (1:1) dispersion and Methacrylic Acid - Methyl Methacrylate Copolymer (1:2) dispersion to form Enteric coated pellets II.

4. The enteric coated pellets obtained in step (2) and (3) were blended with talc and filled in a capsules.

Example 20 - ODT MUPS

Sr. No	Ingredients	Mg/Capsule
	Dry Mix	
1	(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate	74.94
2	Light Magnesium Carbonate	16.00
3	Pulverised Sugar	13.06
4	Low substituted Hydroxypropyl cellulose	12.00
5	Sugar spheres	60.00
	TOTAL	**176.00**
	Binder	
6	Hydroxypropyl Cellulose	1.80
7	Purified Water	q.s
	TOTAL	**177.80**
	Seal Coating	
8	Hydroxypropylmethyl Cellulose	11.50
9	Purified Talc	5.20
10	Titanium dioxide	6.30
11	Purified Water	q.s
	TOTAL	**200.80**
	Enteric Coating I	
12	Seal coated pellets	50.20
13	Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion	15.00
14	Triethyl Citrate	1.50
15	Polysorbate 80	0.55
16	Purified Talc	1.95
17	Titanium dioxide	1.50
18	Purified Water	q.s
	TOTAL	**70.70**
	Enteric Coating II	
19	Seal coated pellets	150.60

20	Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)	7.52
21	Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)	22.60
22	Triethyl citrate	3.01
23	Purified talc	7.52
24	Isopropyl alcohol	q.s
25	Purified Water	q.s
	TOTAL	**191.25**
	Blending	
26	Microcrystalline cellulose	145.00
27	Mannitol	150.60
28	Crospovidone	30.00
29	F - Melt® (Type C)	140.45
30	Aspartame	10.00
31	Strawberry flavour	10.00
32	Colloidal Silicon Dioxide	8.00
33	Magnesium stearate	4.00
	TOTAL	**760**

Process:

1. (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate, light magnesium carbonate, pulverised sugar and low substituted hydroxypropyl cellulose were blended together to produce a dry mix and loaded on sugar spheres in a coating machine using a binder to form drug loaded pellets.

2. The drug loaded pellets obtained in step (1) were seal coated using HPMC, talc and titanium dioxide and a part of the seal coated pellets obtained in step (2) were enteric coated Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) dispersion to form Enteric coated pellets I.

3. Remaining part of seal coated pellets were then enteric coated using Methacrylic Acid - Methyl Methacrylate Copolymer (1:1) dispersion and Methacrylic Acid - Methyl Methacrylate Copolymer (1:2) dispersion to form Enteric coated pellets II.

4. Enteric coated pellets I and II obtained in step (2) and (3) respectively were blended with F – Melt® Type C, microcrystalline cellulose, crospovidone, mannitol, aspartame, strawberry flavor and colloidal silicon dioxide and this blend was lubricated with magnesium stearate and compressed into tablets.

Example 21 – Film coated tablet MUPS

Sr. No	Ingredients	Mg/Capsule
	Dry Mix	
1	(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate	74.94
2	Light Magnesium Carbonate	16.00
3	Pulverised Sugar	13.06
4	Low substituted Hydroxypropyl cellulose	12.00
5	Sugar spheres	60.00
	TOTAL	**176.00**
	Binder	
6	Hydroxypropyl Cellulose	1.80
7	Purified Water	q.s
	TOTAL	**177.80**
	Seal Coating	
8	Hydroxypropylmethyl Cellulose	11.50
9	Purified Talc	5.20
10	Titanium dioxide	6.30
11	Purified Water	q.s
	TOTAL	**200.80**
	Enteric Coating I	
12	Seal coated pellets	50.20
13	Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion	15.00
14	Triethyl Citrate	1.50
15	Polysorbate 80	0.55
16	Purified Talc	1.95

17	Titanium dioxide	1.50
18	Purified Water	q.s
	TOTAL	**70.70**
	Enteric Coating II	
19	Seal coated pellets	150.60
20	Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)	7.52
21	Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)	22.60
22	Triethyl citrate	3.01
23	Purified talc	7.52
24	Isopropyl alcohol	q.s
25	Purified Water	q.s
	TOTAL	**191.25**
	Compression	
26	Microcrystalline cellulose	168.17
27	Crospovidone	36
28	Colloidal Silicon Dioxide	17
29	Sodium Stearyl Fumarte	4.88
	Coating	
30	Opadry	12
31	Purified Water	q.s
	TOTAL	**500**

Process:

1. (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate, light magnesium carbonate, pulverised sugar and low substituted hydroxypropyl cellulose were blended together to produce a dry mix which was loaded on sugar spheres in a coating machine using a binder to form drug loaded pellets.

2. The drug loaded pellets obtained in step (1) were seal coated using HPMC, talc and titanium dioxide and part of the seal coated pellets were enteric coated Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) dispersion to form Enteric coated pellets I.

3. Remaining part of seal coated pellets were then enteric coated using Methacrylic Acid - Methyl Methacrylate Copolymer (1:1) dispersion and Methacrylic Acid - Methyl Methacrylate Copolymer (1:2) dispersion to form Enteric coated pellets II.

4. Enteric coated pellets I and II obtained in step (2) and (3) respectively were blended with F – Melt® Type C, microcrystalline cellulose Crospovidone and Colloidal anhydrous silica and this blend was lubricated with sodium stearyl fumatrate and compressed into tablets followed by coating with Opadry.

Example 22 – Sachets for oral suspension

Sr. No	Ingredients	Mg/Capsule
	Dry Mix	
1	(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate	74.94
2	Light Magnesium Carbonate	16.00
3	Pulverised Sugar	13.06
4	Low substituted Hydroxypropyl cellulose	12.00
5	Sugar spheres	60.00
	TOTAL	**176.00**
	Binder	
6	Hydroxypropyl Cellulose	1.80
7	Purified Water	q.s
	TOTAL	**177.80**
	Seal Coating	
8	Hydroxypropylmethyl Cellulose	11.50
9	Purified Talc	5.20
10	Titanium dioxide	6.30
11	Purified Water	q.s
	TOTAL	**200.80**
	Enteric Coating I	
12	Seal coated pellets	50.20
13	Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion	15.00

14	Triethyl Citrate	1.50
15	Polysorbate 80	0.55
16	Purified Talc	1.95
17	Titanium dioxide	1.50
18	Purified Water	q.s
	TOTAL	**70.70**
	Enteric Coating II	
19	Seal coated pellets	150.60
20	Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)	7.52
21	Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)	22.60
22	Triethyl citrate	3.01
23	Purified talc	7.52
24	Isopropyl alcohol	q.s
25	Purified Water	q.s
	TOTAL	**191.25**
26	Sucrose	4352.05
27	Mannitol	500.00
28	Xanthan Gum	300.00
29	Crospovidone	40.00
30	Colloidal silicon dioxide	15.00
31	Citric Acid	100.00
32	Sodium Citrate	10.00
33	Red Oxide of Iron	2.00
34	Strawberry Flavour	5.50
35	Magnesium Stearate	13.50
	TOTAL	**5600.00**

Process:

1. (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H benzimidazole glycerol solvate, light magnesium carbonate, pulverised sugar and low substituted hydroxypropyl cellulose were blended together to produce a dry mix was loaded on sugar spheres in a coating machine using a binder to form drug loaded pellets.

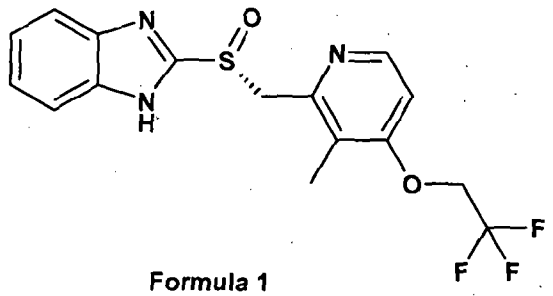
2. The drug loaded pellets obtained in step (1) were seal coated using HPMC, talc and titanium dioxide andpart of the seal coated pellets were enteric coated Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) dispersion to form Enteric coated pellets I.

3. Remaining part of seal coated pellets were then enteric coated using Methacrylic Acid - Methyl Methacrylate Copolymer (1:1) dispersion and Methacrylic Acid - Methyl Methacrylate Copolymer (1:2) dispersion to form Enteric coated pellets II.

4. Enteric coated pellets I and II obtained in step (2) and (3) respectively were blended with sucrose, mannitol, xanthan gum, crospovidone, colloidal silicon dioxide, citric acid, sodium citrate, red oxide of iron and strawberry flavor and this blend was lubricated with magnesium stearate and filled into sachets.

Claims

1. A triol solvate of (R)- 2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl] sulphinyl]-1H-benzimidazole (Formula I)



Formula 1

2. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H benzimidazole glycerol solvate.

3. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to claim 2, in crystalline form.

4. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A.

5. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to claim 4, characterized by having an XRD pattern comprising peaks at 9.48, 12.9 and 16.4 ± 0.2°2θ.

6. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to claim 5, characterized by having an XRD pattern comprising further peaks at 6.2, 19.94, 21.82 and 24.63 ± 0.2°2θ.

7. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to claim 6, characterized by having an XRD pattern

comprising further peaks at 3.64, 7.18, 10.74, 15.58, 18.52, 18.96, 20.30, 21.21, 22.99, 23.54, 25.17 and 29.02 ± 0.2°2θ.

8. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to any one of claims 4 to 7, characterized by having an XRD pattern as shown in Figure 1.

9. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to any one of claims 4 to 8, characterized by having an intrinsic dissolution profile as shown in Figure 4.

10. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to any one of claims 4 to 9, characterized by a glycerol content of about 20% by weight.

11. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C.

12. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to claim 11, characterized by having an XRD pattern comprising peaks at 18.21 , 18.88 , 20.68 , 22.38 , 22.90 and 26.79 ± 0.2°2θ.

13. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to claim 12, characterized by having an XRD pattern comprising further peaks at 5.63, 13.78, 14.88, 19.74, 20.32 and 26.36 ± 0.2°2θ.

14. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to claim 13, characterized by having an XRD pattern comprising further peaks at 7.48, 10.10, 13.22, 16.76, 21.33, 21.83, 23.71 and 28.42 ± 0.2 °2θ.

15. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to any one of claims 11 to 14, characterized by having an XRD pattern as shown in Figure 3.

16. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to any one of claims 11 to 15, characterized by having an intrinsic dissolution profile as shown in Figure 5.

17. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate according to any one of claims 11 to 16, characterized by a glycerol content of about 20% by weight.

18. A process for preparing a triol solvate of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole according to claim 1, comprising (i) dissolving or suspending (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole or a salt or solvate thereof in a first suitable solvent; (ii) optionally adding an organic base to the solution or suspension so formed; (iii) contacting (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole with a triol; and optionally thereafter (iii) isolating the compound so formed by addition of a second solvent.

19. A process according to claim 18, wherein the triol is glycerol.

20. A process according to claim 19, wherein the glycerol solvate is (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole Form A according to any one of claims 4 to 10.

21. A process according to claim 19, wherein the glycerol solvate is (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole Form C according to any one of claims 11 to 17.

22. A process for preparing (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A according to any one of claims 4 to 10, comprising (i) dissolving (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in a first suitable solvent; (ii) distilling the reaction mass optionally in the presence of a base; (iii) adding glycerol; (iv) heating the resulting solution to a temperature in the range of about 25°C to about reflux temperature of the solvent used; (v) adding a suitable second solvent; (vi) isolating (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A.

23. A process for the preparation of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H- benzimidazole glycerol solvate Form C according to any one of claims 11 to 17, which process comprises: (i) dissolving (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole in a suitable first solvent; (ii) adding glycerol to the mixture so formed and optionally a suitable aqueous base; (iii) heating the resulting solution to a temperature in the range from about 25°C to about the reflux temperature of the solvent used; (iv) adding a suitable second solvent; and (v) isolating (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]-methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C.

24. A process according to any one of claims 18 to 23, wherein the first solvent used is selected from the group comprising methanol, ethanol, isopropanol, acetone, methyl ethyl ketone, dichloromethane (MDC), methyl acetate, ethyl acetate, butyl acetate and mixtures thereof.

25. A process according to any one of claims 18 to 24, wherein the base used is selected from the group comprising trimethylamine, triethylamine, tripropylamine, tributylamine, dimethylamine, diethylamine, dipropylamine, dibutylamine, monomethylamine, monoethylamine, monopropylamine, monobutylamine, diisopropylethylamine, pyridine, pyrrolidine, piperidine, morpholine, N-methyl morpholine, N-methyl piperidine, piperazine or mixtures thereof.

26. A process according to any one of claims 18 to 25, wherein the second solvent used is selected from the group comprising diisopropyl ether, methyl t-butylether, toluene, xylene,

chlorobenzene, 1,2-dichlorobenzene, n-pentane, n-hexane, n-heptane, cyclopentane, cyclohexane and mixtures thereof.

27. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A prepared by a process according to any one of claims 20, 22 or 24 to 26.

28. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole Form C prepared by a process according to any one of claims 21 or 23 to 26.

29. A process according to any one of claims 18 to 26, wherein the (R)- 2-[[[3-methyl-4(2, 2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole used to prepare a triol solvate of (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole is in any polymorphic form or in a mixture of any polymorphic forms.

30. A process according to claim 29, wherein the (R)- 2-[[[3-methyl-4(2, 2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole used to prepare a triol solvate of (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole is (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole sesquihydrate.

31. A pharmaceutical composition comprising a triol solvate of (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole optionally in combination with one or more pharmaceutically acceptable excipients.

32. A pharmaceutical composition comprising (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy) pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate optionally in combination with one or more pharmaceutically acceptable excipients.

33. A pharmaceutical composition according to claim 32, comprising (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy) pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate in crystalline form.

34. A pharmaceutical composition according to claim 33, comprising (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy) pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A according to any one of claims 4 to 10.

35. A pharmaceutical composition according to claim 33, comprising (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy) pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form C according to any one of claims 11 to 17.

36. A pharmaceutical composition according to claim 31 to 35, in the form of tablets (single layer, bilayer, multilayer, tablet in tablet and the like) which may be coated or uncoated, capsule, (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, film coated tablets, MUPS, film coated tablets MUPS, orally disintegrating MUPS, disintegrating tablets, dispersible tablets, granules, and microspheres, multiparticulates and the like), a soft gelatin capsule, a sachet (filled with powders, pellets, beads, mini-tablets, pills, micro-pellets, small tablet units, film coated tablets, MUPS, film coated tablets MUPS, orally disintegrating MUPS, disintegrating tablets, dispersible tablets, granules, and microspheres, multiparticulates and the like), sprinkle, liquid dosage forms (liquids, liquid dispersion, suspension, solution, emulsion, microemulsions, spray, syrup, spot-on formulation, injection preparation, gel, aerosol, ointment, creams and the like).

37. A pharmaceutical composition according to claim 36, in the form of controlled release formulations, modified release formulations, lyophilized formulations, delayed release formulations, extended release formulations, pulsatile release formulations or dual release formulations.

38. A pharmaceutical composition according to any one of claims 31 to 37, wherein the drug particles are present in nanosize form, preferably the drug particles have D_{50} less than 2000 nm.

39. A pharmaceutical composition according to any one of claims 31 to 38, comprising one or more active(s) selected from NSAIDS, antacids, anti-emetic agents, antibiotics, HMG-CoA reductase inhibitors, ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, and any other vasodilatory or anti-hypertensive agents or platelet aggregation inhibitors and oral anticoagulants.

40. A pharmaceutical composition according to any one of claims 31 to 39, administered simultaneously, separately or sequentially.

41. A pharmaceutical composition according to any one of claims 31 to 40, provided in the form of a kit.

42. A triol solvate of (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole for use in the prevention or treatment of gastrointestinal disorders.

43. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate for use in the prevention or treatment of gastrointestinal disorders.

44. (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate Form A and/or Form C for use in the prevention or treatment of gastrointestinal disorders.

45. A pharmaceutical composition according to any one of claims 31 to 41, for use in the prevention or treatment of gastrointestinal disorders.

46. A method of treatment and/or prophylaxis of gastrointestinal disorders by administering a therapeutically effective amount of a pharmaceutical composition according to any one of claims 31 to 41, to a patient in need thereof.

47. Use of (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate in the preparation of (R)- 2-[[[3-methyl-4(2, 2,2-trifluoroethoxy) pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole sesquihydrate.

48. Use of (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole glycerol solvate in the preparation of anhydrous (R)- 2-[[[3-methyl-4(2, 2,2-trifluoroethoxy) pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole.

49. Use according to claim 47 or claim 48, wherein the glycerol solvate of (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole is in crystalline form.

50. Use according to claim 49, wherein the crystalline form is of (R)-2-[[[3-methyl-4(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulphinyl]-1H-benzimidazole Form A or Form C according to any one of claims 4 to 17.

51. A pharmaceutical composition substantially as described herein with reference to the examples.

Fig.1

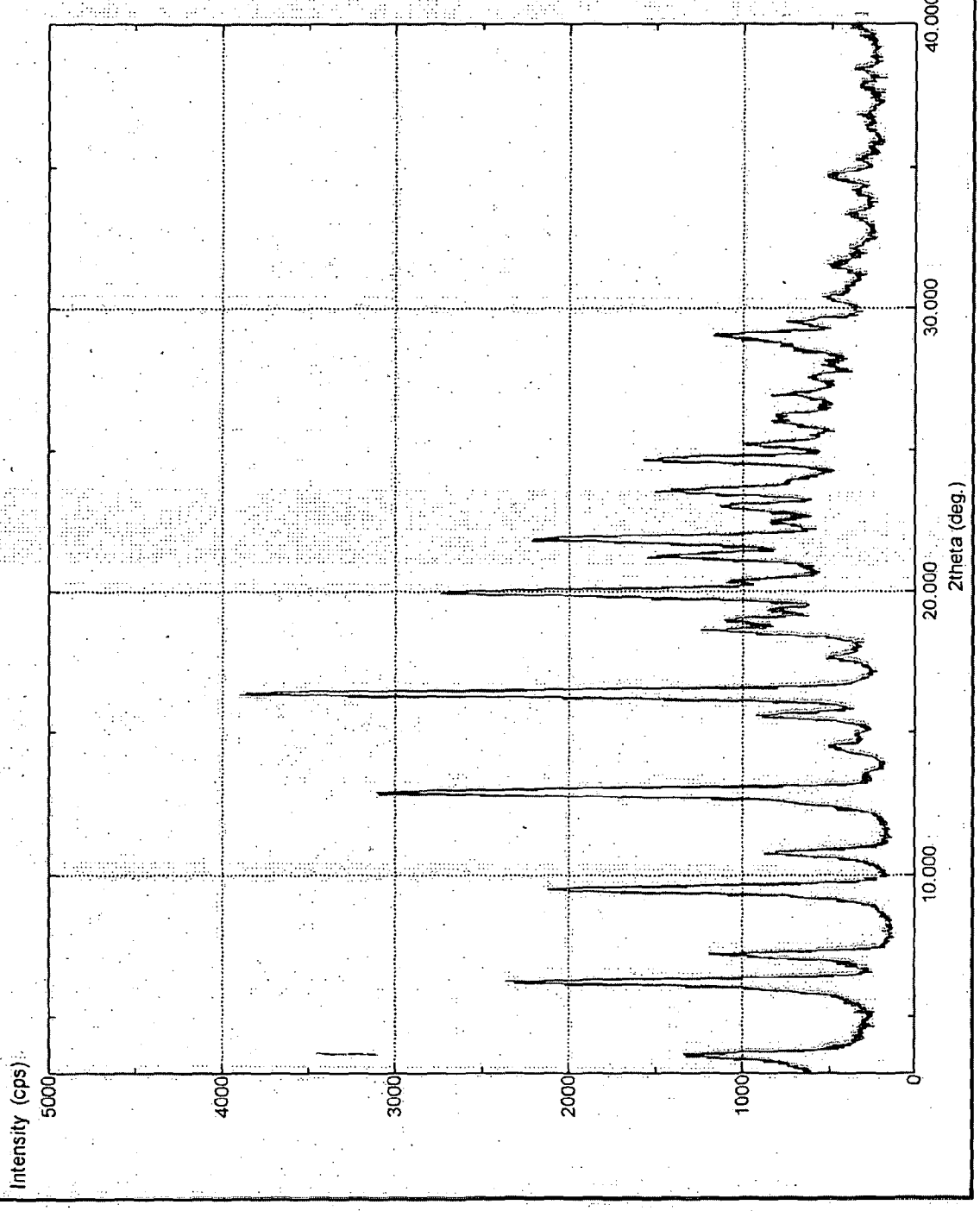

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1000
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10.000
20.000
30.000
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2theta (deg.)

Fig. 2

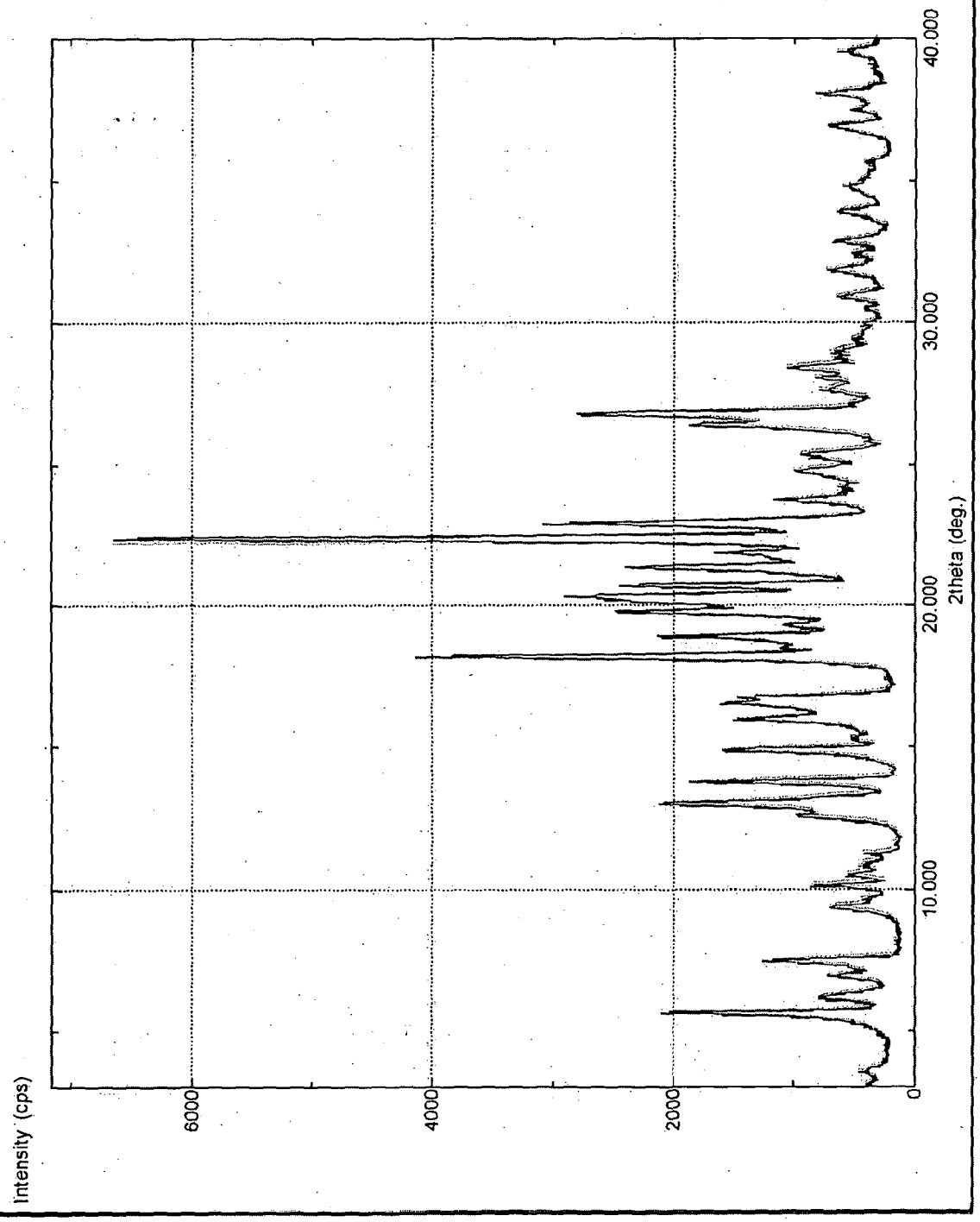

Intensity (cps)
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4000
2000
0
10.000
20.000
30.000
40.000
2theta (deg.)

Fig.3

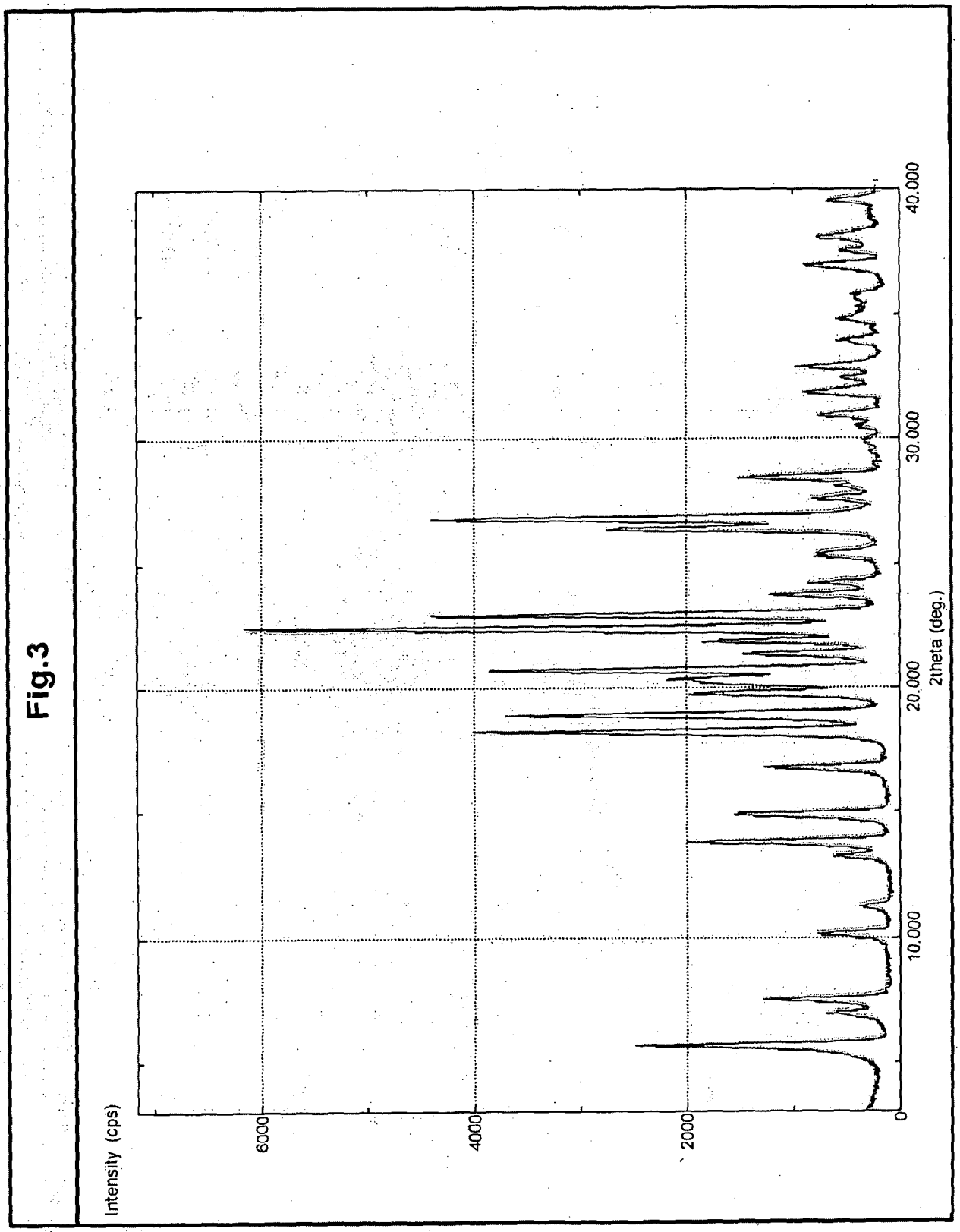

Intensity (cps)
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4000
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20.000
30.000
40.000
2theta (deg.)

Fig.4

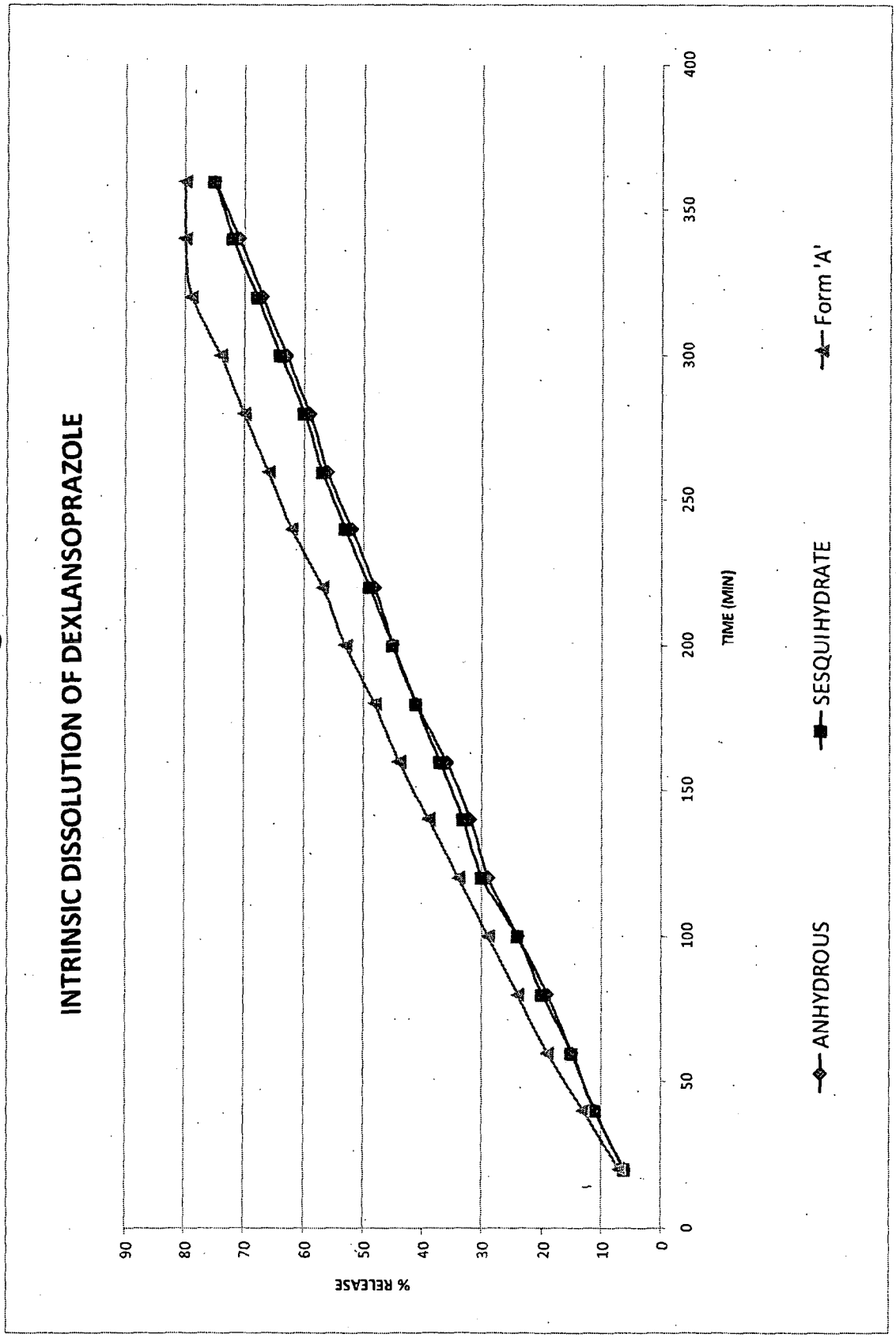
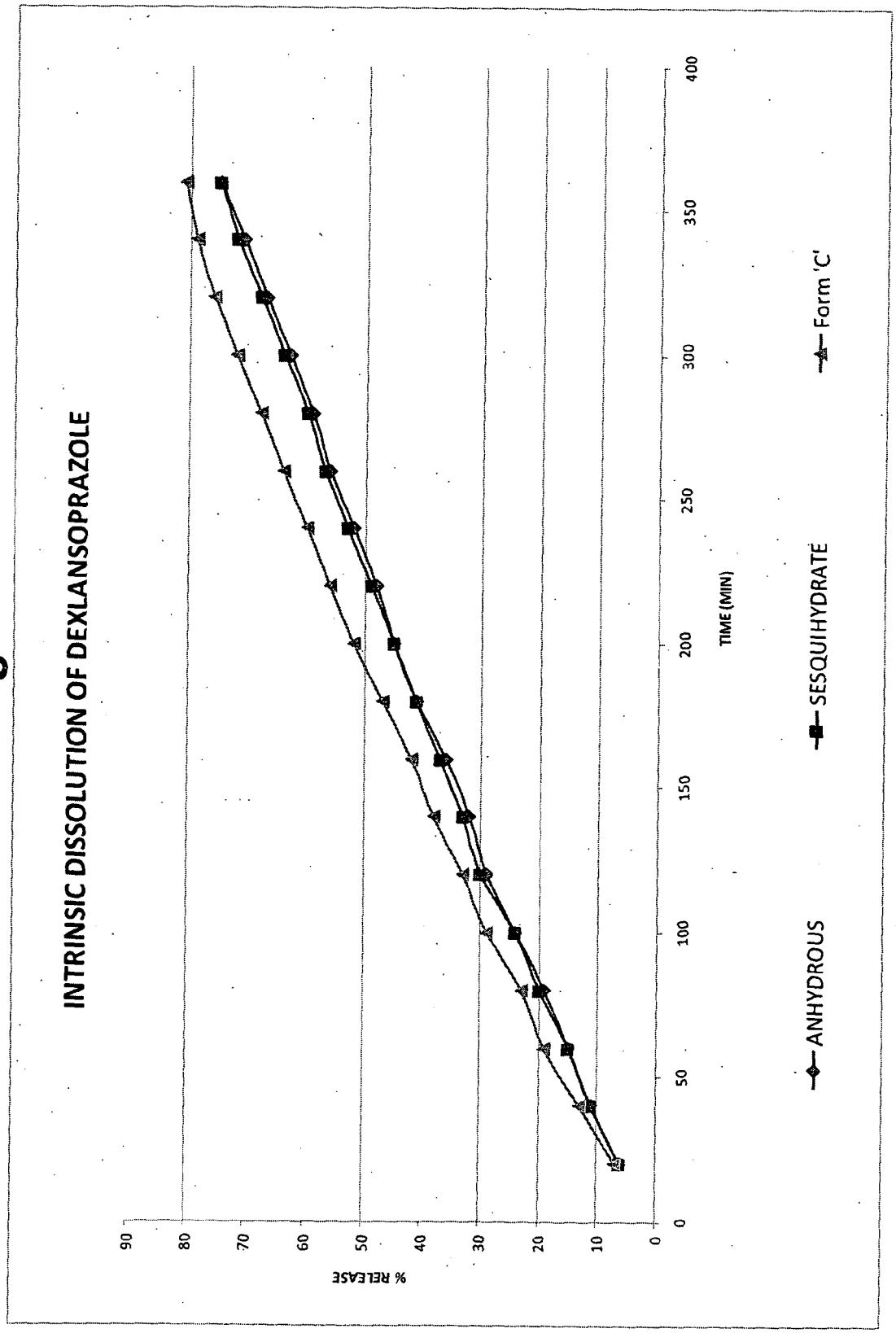

INTRINSIC DISSOLUTION OF DEXLANSOPRAZOLE
% RELEASE
0
10
20
30
40
50
60
70
80
90
TIME (MIN)
0
50
100
150
200
250
300
350
400
ANHYDROUS
SESQUIHYDRATE
Form 'A'

Fig. 5


INTRINSIC DISSOLUTION OF DEXLANSOPRAZOLE
% RELEASE
0
10
20
30
40
50
60
70
80
90
TIME (MIN)
0
50
100
150
200
250
300
350
400
ANHYDROUS
SESQUIHYDRATE
Form 'C'

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2013/000127

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 A61K31/4439 A61P1/04
ADD.

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)
EPO-Internal, WPI Data, CHEM ABS 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 2011/020189 A1 (APOTEX PHARMACHEM INC [CA]; WANG FAN [CA]; KELLS KEVIN W [CA]; MILNES) 24 February 2011 (2011-02-24) claims; examples	1-51
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2013	18/06/2013

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, Fax: (+31-70) 340-3016	Gavriliu, Daniela

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 0 219 471 A2 (FORBERG HALVOR) 22 April 1987 (1987-04-22) claims; examples	1-51
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Information on patent family members

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