(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
09 November 2017 (09.11.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/191651 A1

(51) International Patent Classification:
C07D 401/04 (2006.01) *C07D 235/14* (2006.01)
C07D 235/08 (2006.01) *C07D 211/62* (2006.01)

(21) International Application Number:
PCT/IN2017/000099

(22) International Filing Date:
02 May 2017 (02.05.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201641015655 05 May 2016 (05.05.2016) IN

(71) Applicant: **MSN LABORATORIES PRIVATE LIMITED, R & D CENTER** [IN/IN]; Plot No.12 Phase-IV, Survey No.119 to 140, 258,275 to 280,IDA Pashamylaram (Vill), Patancheru(Mdl), Sangareddy (dist), Telangana 502307 (IN).

(72) Inventors; and

(71) Applicants: **THIRUMALAI RAJAN, Srinivasan** [IN/IN]; Plot No.12 Phase-IV, Survey No.119 to 140, 258,275 to 280,IDA Pashamylaram (Vill), Patancheru(Mdl), Sangareddy (dist), Telangana 502307 (IN). **ESWARAIAH, Sajja** [IN/IN]; Plot No.12 Phase-IV, Survey No.119 to 140, 258,275 to 280,IDA Pashamylaram (Vill), Patancheru(Mdl), Sangareddy (dist), Telangana 502307 (IN). **VENKAT REDDY, Ghojala** [IN/IN]; Plot No.12 Phase-IV, Survey No.119 to 140, 258,275 to 280,IDA Pashamylaram (Vill), Patancheru(Mdl), Sangareddy (dist), Telangana 502307 (IN). **RAJESHWAR REDDY, Sagyam** [IN/IN]; Plot No.12 Phase-IV, Survey No.119 to 140, 258,275 to 280,IDA Pashamylaram (Vill), Patancheru(Mdl), Sangareddy (dist), Telangana 502307 (IN). **ADILAKSHMI, Singavarapu** [IN/IN]; Plot No.12 Phase-IV, Survey No.119 to 140, 258,275 to 280,IDA Pashamylaram (Vill), Patancheru(Mdl), Sangareddy (dist), Telangana 502307 (IN). **RAJESHAM, Boge** [IN/IN]; Plot No.12 Phase-IV, Survey No.119 to 140, 258,275 to 280,IDA Pashamylaram (Vill), Patancheru(Mdl), Sangareddy (dist), Telangana 502307 (IN).

(74) Common Representative: **THIRUMALAI RAJAN, Srinivasan**; Plot No.12 Phase-IV, Survey No.119 to 140, 258,275 to 280,IDA Pashamylaram (Vill), Patancheru(Mdl), Sangareddy (dist), Telangana 502307 (IN).

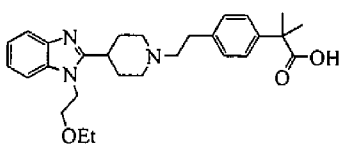
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

(54) Title: SOLID STATE FORMS OF 2-[4-(2-{4-[1-(2-ETHOXYETHYL)-1H-BENZIMIDAZOL-2-YL]-1-PIPERIDINYL}ETHYL)PHENYL]-2-METHYLPROPANOIC ACID AND PROCESS FOR PREPARATION THEREOF



Formula-1

(57) Abstract: The present invention relates to solid state forms of 2-[4-(2-{4-[1 -(2-ethoxyethyl)- 1H-benzimidazol-2-yl] - 1 -piperidinyl } ethyl)phenyl]-2-methylpropanoic acid compound represented by the following structural formula- 1 and process for preparation thereof.

WO 2017/191651 A1

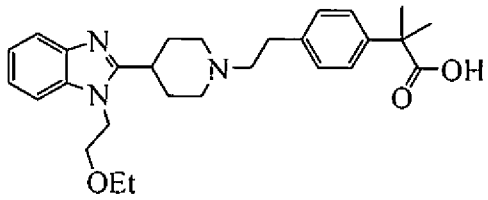
Solid state forms of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid and process for preparation thereof

Related Application:

This application claims the benefit of priority of our Indian patent application 201641015655 filed on May 05, 2016 which is incorporated herein as reference.

Field of the Invention:

The present invention provides solid state forms of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid represented by the following structural formula-1 and process for preparation thereof.



Formula-1

Background of the Invention:

US5877187A patent has first described 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid, its analogous compounds and also disclosed their process for preparation.

US7612095B2 patent has described three crystalline polymorphic forms of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methyl propanoic acid, namely crystalline form-1, form-2 and form-3.

The present inventors were able to prepare new solid state forms of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid, which are useful for the preparation of various pharmaceutical compositions.

The present inventors have also developed process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid.

Brief description of the invention:

The first aspect of the present invention is to provide pure amorphous form of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methyl propanoic acid compound of formula-1.

The second aspect of the present invention is to provide a process for the preparation of pure amorphous form of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methyl propanoic acid compound of formula-1.

The third aspect of the present invention is to provide amorphous solid dispersion comprising 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl) phenyl]-2-methylpropanoic acid compound of formula-1 and at least one pharmaceutically acceptable excipient.

The fourth aspect of the present invention is to a provide process for the preparation of amorphous solid dispersion comprising 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 and at least one pharmaceutically acceptable excipient.

The fifth aspect of the present invention is to provide a process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1.

The sixth aspect of the present invention is to provide another process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1.

Brief Description of the Drawings:

Figure-1: Illustrates the PXRD pattern of compound of formula-1 obtained according to example-1

Figure-2: Illustrates the PXRD pattern of crystalline form-M of compound of formula-1

Figure-3: Illustrates the PXRD pattern of pure amorphous form of compound of formula-1

Figure-4: Illustrates the PXRD pattern of amorphous solid dispersion comprising compound of formula-1 and Povidone K-30

Figure-5: Illustrates the PXRD pattern of amorphous solid dispersion comprising compound of formula-1 and hydroxypropyl cellulose (HPC)

Figure-6: Illustrates the PXRD pattern of amorphous solid dispersion comprising compound of formula-1 and hydroxypropyl methyl cellulose (HPMC)

Figure-7: Illustrates the PXRD pattern of amorphous solid dispersion comprising compound of formula-1 and hydroxypropyl methyl cellulose acetate succinate (HPMCAS)

Figure-8: Illustrates the PXRD pattern of amorphous solid dispersion comprising compound of formula-1 and Eudragit.

Detailed description of the Invention:

The term "suitable solvent" used in the present invention refers to "hydrocarbon solvents" such as n-pentane, n-hexane, n-heptane, cyclohexane, pet ether, benzene, toluene, xylene and the like; "ether solvents" such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane and the like; "ester solvents" such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and the like; "polar-aprotic solvents" such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone (NMP) and the like; "chloro solvents" such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; "nitrile solvents" such as acetonitrile, propionitrile, isobutyronitrile and the like; "alcohol solvents" such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol and the like; "polar solvents" such as water; formic acid, acetic acid, propanoic acid or mixture of any of the aforementioned solvents.

The first aspect of the present invention provides pure amorphous form of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1. The pure amorphous form of compound of formula-1 of the present invention is characterized by its PXRD pattern as illustrated in figure-3.

An embodiment of the present invention provides a process for the preparation of pure amorphous form of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methyl propanoic acid compound of formula-1, comprising of;

a) Dissolving the compound of formula-1 in a suitable solvent at a suitable temperature,
b) removing the solvent from the solution to provide pure amorphous form of compound of formula-1.

Wherein, the suitable solvent is selected from alcohol solvents, chloro solvents, polar-aprotic solvents or their mixtures; and the suitable temperature ranges from 25°C to reflux temperature of the solvent used.

The second aspect of the present invention provides a process for the preparation of pure amorphous form of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methyl propanoic acid compound of formula-1, comprising of;

a) Dissolving the compound of formula-1 in a mixture of dichloromethane and methanol,
b) removing the solvent from the solution to provide pure amorphous form of compound of formula-1.

In the above processes, the suitable techniques which may be used for the removal of solvent from the reaction mixture includes but not limited to evaporation, evaporation under reduced pressure, flash evaporation, vacuum drying, concentrating the reaction mixture, atmospheric distillation, agitated thin film drying (ATFD), melt extrusion, spray drying, freeze drying (lyophilization), spray-freeze drying, cooling the clear solution to lower temperatures to precipitate the solid followed by filtration of the reaction or by any other suitable techniques known in the art.

After dissolving the compound of formula-1 in the said solvent system, the solution may optionally be treated with charcoal or any other suitable material to remove color and/or to clarify the solution and the solution may optionally be filtered to make it particle free.

The solvent may be removed optionally under reduced pressures, at temperatures less than about 130°C, less than about 60°C, less than about 40°C, less than about 20°C, less than about 0°C, less than about -20°C, less than about -40°C or less than about -60°C.

A preferred embodiment of the present invention provides a process for the preparation of pure amorphous form of compound of formula-1, comprising of;

a) Dissolving the compound of formula-1 in a mixture of dichloromethane and methanol,
b) optionally filtering the solution to make it particle free,
c) spray drying the solution to provide pure amorphous form of compound of formula-1.

The third aspect of the present invention provides amorphous solid dispersion comprising 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl) phenyl]-2-methylpropanoic acid compound of formula-1 and at least one pharmaceutically acceptable excipient.

As used herein, the term "solid dispersion" means any solid composition having at least two components. In certain embodiments, a solid dispersion as disclosed herein includes an active ingredient (compound of formula-1) dispersed among at least one other component, for example an excipient.

In general, the excipient is selected from but not limited to polyvinylpyrrolidone (povidone or PVP; PVP of different grades like K-15, K-30, K-60, K-90 and K-120 may be used), polyvinylpolypyrrolidone, polysorbate, cross linked polyvinyl pyrrolidone (crospovidone), Eudragit, polyethylene glycol (macrogol or PEG), polyvinyl alcohol, polyvinyl chloride, polyvinyl acetate, propylene glycol, cellulose, cellulose acetate phthalate (CAP), methyl cellulose, carboxymethyl cellulose (CMC, its sodium and calcium salts), carboxymethylethyl cellulose (CMEC), ethyl cellulose, hydroxymethyl cellulose, ethyl hydroxyethyl cellulose, hydroxyethylcellulose, hydroxypropyl cellulose (HPC), hydroxypropyl cellulose acetate succinate, hydroxypropyl methyl cellulose (hypromellose or HPMC), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), hydroxyethyl methyl cellulose succinate (HEMCS), hydroxypropyl cellulose acetate succinate (HPCAS), hydroxypropyl methylcellulose phthalate (HPMC-P), hydroxypropyl methylcellulose acetate phthalate, microcrystalline cellulose (MCC), cross linked sodium carboxymethyl cellulose (croscarmellose sodium), cross linked calcium carboxymethyl cellulose, magnesium stearate, aluminium stearate, calcium stearate, magnesium carbonate, talc, iron oxide (red, yellow, black), stearic acid, dextrates, dextrin, dextrose, sucrose, glucose, xylitol, lactitol, sorbitol,

mannitol, maltitol, maltose, raffinose, fructose, maltodextrin, anhydrous lactose, lactose monohydrate, starches such as maize starch or com starch, sodium starch glycolate, sodium carboxymethyl starch, pregelatinized starch, gelatin, sodium dodecyl sulfate, edetate disodium, sodium phosphate, sodium lauryl sulfate, triacetin, sucralose, calcium phosphate, polydextrose, α-, β-, γ-cyclodextrins, sulfobutylether beta-cyclodextrin, sodium stearyl fumarate, fumaric acid, alginic acid, sodium alginate, propylene glycol alginate, citric acid, succinic acid, carbomer, docusate sodium, glyceryl behenate, glyceryl stearate, meglumine, arginine, polyethylene oxide, polyvinyl acetate phthalates and the like.

In one preferred embodiment, the excipient s selected from povidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, Eudragit.

The pure amorphous form as well as amorphous solid dispersion of compound of formula-I of the present invention are having purity of greater than 98%, preferably greater than 99% by HPLC and is useful for the preparation of various pharmaceutical compositions formulated in a manner suitable for the route of administration to be used where at least a portion of compound of formula-I is present in the composition in particular polymorphic form mentioned. Such pharmaceutical compositions may comprise compound of formula-I present in the composition in a range of between 0.005% and 100% (wt/wt), with the balance of the pharmaceutical composition comprising additional substances such as excipients, diluents, lubricants, binders, wetting agents, disintegrating agents, glidants, sweetening agents, flavoring agents, emulsifying agents, solubilizing agents, pH buffering agents, perfuming agents, surface stabilizing agents, suspending agents and other conventional pharmaceutically inactive agents.

The amorphous solid dispersion of the present invention is stable at room temperature under normal stability conditions and does not convert to any other solid state form.

An embodiment of the present invention provides a process for the preparation of amorphous solid dispersion comprising compound of formula-1 and at least one pharmaceutically acceptable excipient, comprising of;

a) Dissolving the compound of formula-1 and at least one excipient in a suitable solvent at a suitable temperature,
b) removing the solvent from the reaction mixture and drying the material to provide amorphous solid dispersion comprising compound of formula-1 and excipient.

Wherein, the suitable solvent is selected from but not limited to alcohol solvents, chloro solvents, polar-aprotic solvents or their mixtures; and the suitable temperature ranges from 25°C to reflux temperature of the solvent used.

The fourth aspect of the present invention provides a process for the preparation of amorphous solid dispersion comprising 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 and at least one pharmaceutically acceptable excipient, comprising of;

a) Dissolving the compound of formula-1 and at least one excipient in a mixture of dichloromethane and methanol,
b) removing the solvent from the reaction mixture and drying the material to provide amorphous solid dispersion comprising compound of formula-1 and excipient.

Wherein, in step-a) the excipient is same as defined above in the third aspect;

After dissolving the compound of formula-1 and excipient in the solvent system, the solution may optionally be treated with charcoal or any other suitable material to remove color and/or to clarify the solution and the solution may optionally be filtered to make it particle free.

In step-b) of the above processes the suitable technique which may be used for the removal of the solvent from the reaction mixture and the conditions under which the solvent can be removed are same as defined in the second aspect of the present invention. The suitable techniques may also include vacuum distillation, distillation by using a rotational distillation device such as a Buchi Rotavapor.

In the present invention, filtering the reaction mixture/solution to make it particle free can be carried out by passing through paper, cloth, glass fiber or other membrane material or a bed of a clarifying agent such as Celite® or hyflow. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization.

In the present invention, the ratio of the amount by weight of compound of formula-1 within the solid dispersion to the amount by weight of the excipient therein ranges from but not limited to about 1:0.05 to about 1:5.

A preferred embodiment of the present invention provides a process for the preparation of amorphous solid dispersion comprising compound of formula-1 and at least one excipient, comprising of;

a) Dissolving the compound of formula-1 and at least one excipient in a mixture of dichloromethane and methanol,
b) optionally filtering the solution,
c) distilling off the solvent from the solution and drying the material to provide amorphous solid dispersion comprising compound of formula-1 and excipient.

An embodiment of the present invention provides a process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1, comprising of;

a) Dissolving the compound of formula-1 in a suitable solvent or mixture of solvents,
b) distilling off the solvent completely from the solution under reduced pressure,
c) optionally slurrying the obtained compound in a suitable second solvent at a suitable temperature and filtering the material,
d) drying the obtained compound to provide crystalline form-2 of compound of formula-1.

Wherein, in step-a) the suitable solvent is selected from alcohol solvents, chloro solvents, polar-aprotic solvents or their mixtures;

In step-c) the suitable second solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, ketone solvents, nitrile solvents, polar solvents or their mixtures; and the suitable temperature ranges from -40°C to 40°C.

The fifth aspect of the present invention provides a process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1, comprising of;

a) Dissolving the compound of formula-1 in a mixture of dichloromethane and methanol,
b) distilling off the solvent completely from the solution under reduced pressure,
c) optionally slurrying the obtained compound in cyclohexane and filtering the material,
d) drying the obtained compound to provide crystalline form-2 of compound of formula-1.

Wherein, in step-a) the dissolution can be carried out at 20-35°C;

In step-c) the compound can be slurried in cyclohexane at a suitable temperature ranges from -30°C to 40°C.

An embodiment of the present invention provides a process for the preparation of crystalline form-2 of compound of formula-1, comprising of;

a) Dissolving the compound of formula-1 in a suitable solvent or mixture of solvents at a suitable temperature,
b) optionally filtering the solution,
c) combining the solution with a suitable anti-solvent at a suitable temperature,
d) filtering the solid,
e) optionally slurrying the solid in a suitable solvent at a suitable temperature,
f) drying the material to provide crystalline form-2 of compound of formula-1.

Wherein, in step-a) the suitable solvent is selected from but not limited to alcohol solvents, chloro solvents, polar-aprotic solvents or their mixtures; and the suitable temperature ranges from 25°C to reflux temperature of the solvent used;

In step-c) the suitable anti-solvent is selected from but not limited to polar solvents, hydrocarbon solvents, ether solvents, ketone solvents, ester solvents, nitrile solvents or their mixtures; and the suitable temperature ranges from -70°C to 40°C;

In step-e) the suitable solvent is selected from but not limited to polar solvents, hydrocarbon solvents, ether solvents, ketone solvents, ester solvents, nitrile solvents or their mixtures; and the suitable temperature ranges from -70°C to 40°C.

In the above process, before combining the solution of step-a) or step-b) with anti-solvent, a small amount of crystalline form-2 can be added as seeding material either to the solution of step-a) or step-b) or to the anti-solvent in order to facilitate the formation of crystalline form-2 as product.

The sixth aspect of the present invention provides a process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1, comprising of;

a) Dissolving the compound of formula-1 in a mixture of dichloromethane and methanol,
b) combining the solution with methyl tert.butyl ether or a mixture of methyl tert.butyl ether and cyclohexane containing a small amount of form-2 seeding material at a suitable temperature,
c) filtering the precipitated solid,
d) optionally slurrying the obtained compound in cyclohexane at a suitable temperature,
e) drying the material to provide crystalline form-2 of compound of formula-1.

Wherein, in step-a) the dissolution can be carried out at 20-35°C;
In step-b) the suitable temperature ranges from -30°C to 30°C, preferably 0-5°C;
In step-d) the suitable temperature ranges from -30°C to 30°C.

An embodiment of the present invention provides a process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1, comprising of adding a small amount of crystalline form-2 to the reaction mixture as seed material.

The processes for the preparation of crystalline form-2 of compound of formula-1 developed by the present inventors is efficient and produces the product with high yield and polymorphic purity as well as with greater stability.

An embodiment of the present invention provides crystalline polymorph of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methyl propanoic acid compound of formula-1, herein after designated as crystalline form-M. The crystalline form-M of compound of formula-1 of the present invention is characterized by its PXRD pattern having peaks at 2.8, 5.7, 9.1 ± 0.2° of 2-theta and is further characterized by its PXRD pattern as illustrated in figure-2.

The another embodiment of the present invention provides a process for the preparation of crystalline form-M of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methyl propanoic acid compound of formula-1, comprising of;

a) Dissolving the compound of formula-1 in a mixture of dichloromethane and methanol,
b) combining the solution with n-heptane at a suitable temperature,
c) filtering the precipitated solid and drying to provide form-M of compound of formula-1.

Wherein, in step-a) the dissolution can be carried out at suitable temperature ranges from 20-35°C;

In step-b) the suitable temperature ranges from -30°C to 30°C; preferably 0-5°C.

In the above process, small amount of form-M seeding material can optionally be added to n-heptane before combining it with step-a) solution to facilitate the formation of crystalline form-M.

In the above processes, any physical form of compound of formula-1 can be utilized as input for the preparation of crystalline form-M, crystalline form-2, pure amorphous form as well as amorphous solid dispersion of compound of formula-1.

The crystalline form-M, crystalline form-2, pure amorphous form as well as amorphous solid dispersion of compound of formula-1 of the present invention can be further micronized to achieve desired particle size distribution in order to make suitable formulation.

The crystalline form-M, crystalline form-2 and pure amorphous form of compound of formula-1 of the present invention can be utilized as input for the preparation of any known polymorphic form of compound of formula-1 and they can also be used in the preparation of other novel polymorphic forms of compound of formula-1.

An embodiment of the present invention provides crystalline form-2 of compound of formula-1 having particle size distribution of D_{90} less than 400 μm, preferably less than 200 μm, more preferably less than 100 μm, most preferably less than 20 μm.

The PXRD analysis of compound of formula-1 of the present invention was carried out using BRUKER/D8 ADVANCE X-Ray diffractometer using CuKα radiation of wavelength 1.5406 A° and at a continuous scan speed of 0.03°/min.

The compound of formula-1 of the present invention was analyzed by HPLC under the following conditions;

Apparatus: A liquid chromatographic system equipped with variable wavelength UV detector; Column: Xbridge shield RP18 150 × 4.6 mm, 3.5 μm or equivalent; Column temperature: 20°C; Wave length: 215 nm; Injection volume: 5 μL; Elution: Gradient; Diluent: Acetonitrile: Water (20:80 v/v); Buffer: Weigh accurately about 6.8 gm of potassium dihydrogen phosphate and add 2.5 gm of 1-octane sulfonic acid sodium salt anhydrous into 1000 mL of milli-Q-water, mix well. Filter this solution through 0.22 μm Nylon membrane filter paper; Mobile phase-A: Buffer:Acetonitrile (90:10 v/v); Mobile phase-B: Acetonitrile: Buffer (70:30 v/v).

The best mode of carrying out the present invention is illustrated by the below mentioned examples. These examples have been provided as illustration only and hence should not be construed as limitation to the scope of the invention.

Examples:

Example-1: Preparation of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl[-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid (Formula-1)

1-(2-ethoxyethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole (100 gm), 2-(4-(2-chloroethyl)phenyl)-N-methoxy-N,2-dimethylpropanamide (98.68 gm), tetrabutylammonium bromide (5.89 gm) and methyl isobutyl ketone (500 ml) were added to a mixture of sodium carbonate (77.55 gm) and water (50 ml) at 25-30°C. Heated the reaction mixture to 95-100°C and stirred for 28 hrs at the same temperature. Cooled the reaction mixture to 25-30°C, water was added and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated. Hydrochloric acid and water were added to the organic layer at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the aqueous layer with methyl isobutyl ketone. Basified the aqueous layer using aqueous sodium carbonate solution and extracted the product into dichloromethane. Both the organic and aqueous layers were separated and washed the organic layer with water. Distilled off the solvent completely from the organic layer and cooled the obtained compound to 25-30°C. n-Butanol (500 ml) and sodium hydroxide (73.16 gm) were added to the obtained compound at 25-30°C and stirred the reaction mixture for 5 min at the same temperature. Heated the reaction mixture to 105-110°C and stirred for 8 hrs at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure and co-distilled with water. Water (1000 ml) was added to the obtained compound, acidified the reaction mixture using acetic acid at 25-30°C and stirred for 40 min at the same temperature. Filtered the solid and washed with water. Dimethyl sulfoxide (300 ml) and n-butanol (300 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 105-110°C and stirred for 15 min at the same temperature. Reduced the temperature of the reaction mixture to 75-80°C and stirred for 2 hrs at the same temperature. Further cooled the reaction mixture to 25-30°C and stirred for 40

min at the same temperature. Filtered the solid and washed with a mixture of dimethylsulfoxide and n-butanol. Water followed by aqueous sodium hydroxide solution were added to the obtained compound at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Acidified the reaction mixture using acetic acid at 25-30°C and stirred the reaction mixture for 40 min at the same temperature. Filtered the solid, washed with water and dried the material to provide the title compound.

The PXRD pattern of the obtained compound is shown in figure-1.

Yield: 98.0 gm.

Example-2: Preparation of crystalline form-2 of compound of formula-1

A mixture of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 (120 gm) and dichloromethane (1200 ml) were stirred for 5 min at 25-30°C. Distilled off the solvent completely from the reaction mixture. Methanol (180 ml) and dichloromethane (360 ml) were added to the obtained compound at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Filtered the reaction mixture and washed with dichloromethane. Transfer the filtrate to Buchi RBF and distilled off the solvent completely under reduced pressure. Cyclohexane (600 ml) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 45 min at the same temperature. Filtered the solid, washed with cyclohexane and dried the material to provide the title compound.

Yield: 102.0 gm; M.R: 205.3°C.

Particle size distribution:

Before micronization: D(0.1) is 1.42 µm; D(0.5) is 13.73 µm; D(0.9) is 101.81 µm.

After micronization: D(0.1) is µm; D(0.5) is µm; D(0.9) is µm.

Example-3: Preparation of crystalline form-2 of compound of formula-1

A mixture of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 (50 gm), methanol (100 ml) and dichloromethane (400 ml) was stirred for 15 min at 25-30°C and kept the reaction mixture aside. Crystalline form-2 of compound of formula-1 as seeding material (5 gm) was added to pre-cooled methyl tert.butyl ether (2500 ml) at 0-5°C in another RBF and stirred the

reaction mixture for 20 min at the same temperature. The above prepared solution of compound of formula-1 in methanol and dichloromethane was slowly added to the reaction mixture at 0-5°C and stirred the reaction mixture for 45 min at the same temperature. Filtered the precipitated solid, washed with methyl tert.butyl ether and dried to provide title compound.

Yield: 48.0 gm; M.R: 204-205.3°C.

Particle size distribution:

Before micronization: D(0.1) is 1.00 µm; D(0.5) is 7.79 µm; D(0.9) is 56.49 µm.

After micronization: D(0.1) is 0.41 µm; D(0.5) is 2.05 µm; D(0.9) is 6.68 µm.

Example-4: Preparation of crystalline form-M of compound of formula-1

A mixture of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 (1 gm), dichloromethane (9 ml) and methanol (1 ml) was stirred for 5 min at 25-30°C and kept the reaction mixture aside. Crystalline form-M of compound of formula-1 as seeding material (0.02 gm) was added to pre-cooled n-heptane (40 ml) at 0-5°C in another RBF and stirred the reaction mixture for 10 min at the same temperature. The above prepared solution of compound of formula-1 in dichloromethane and methanol was slowly added to the reaction mixture at 0-5°C and stirred the reaction mixture for 45 min at the same temperature. Filtered the precipitated solid, washed with n-heptane and then dried the material to provide the title compound. The PXRD pattern of the obtained compound is shown in figure-2.

Yield: 0.8 gm.

Example-5: Preparation of crystalline form-M of compound of formula-1

A 1:1 mixture of dichloromethane and methanol (40 ml) was added to 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 (5 gm) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. The obtained solution was slowly added to pre-cooled n-heptane (80 ml) at 0-5°C and stirred the reaction mixture for 30 min at the same temperature. Filtered the precipitated solid and then dried the material to provide the title compound.

Yield: 4.0 gm.

Example-6: Preparation of pure amorphous form of compound of formula-1

A 1:1 mixture of methanol and dichloromethane (50 ml) was added to 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 (5 gm) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature to get a clear solution. Filtered the reaction mixture to make it particle free and spray dried the filtrate to provide the title compound.

The PXRD pattern of the obtained compound is shown in figure-3.

Yield: 1.6 gm.

Example-7: Alternate process for the preparation of pure amorphous form of compound of formula-1

2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 (100 gm) was added to a mixture of methanol (200 ml) and dichloromethane (800 ml) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature to get a clear solution. Filtered the reaction mixture to make it particle free and spray dried the filtrate to provide the title compound.

Yield: 59.0 gm.

Example-8: Preparation of amorphous solid dispersion comprising compound of formula-1 and Povidone K-30

A 1:1 mixture of methanol and dichloromethane (30 ml) was added to a mixture of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methyl propanoic acid compound of formula-1 (500 mg) and Povidone K-30 (500 mg) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Slowly heated the reaction mixture to 55-60°C and transferred the solution into a Buchi flask. Distilled off the solvent completely from the reaction mixture under reduced pressure and dried the material to provide the title compound.

The PXRD pattern of the obtained compound is shown in figure-4.

Yield: 800.0 mg.

Example-9: Preparation of amorphous solid dispersion comprising compound of formula-1 and hydroxypropyl cellulose (HPC)

A 1:1 mixture of methanol and dichloromethane (30 ml) was added to a mixture of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methyl propanoic acid compound of formula-1 (500 mg) and hydroxypropyl cellulose (500 mg) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Slowly heated the reaction mixture to 55-60°C and transferred the solution into a Buchi flask. Distilled off the solvent completely from the reaction mixture under reduced pressure and then dried the material to provide the title compound.

The PXRD pattern of the obtained compound is shown in figure-5.

Yield: 450.0 mg.

Example-10: Preparation of amorphous solid dispersion comprising compound of formula-1 and hydroxypropyl methyl cellulose (HPMC)

A 1:1 mixture of methanol and dichloromethane (30 ml) was added to a mixture of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methyl propanoic acid compound of formula-1 (500 mg) and hydroxypropyl methyl cellulose (500 mg) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Slowly heated the reaction mixture to 55-60°C and transferred the solution into a Buchi flask. Distilled off the solvent completely from the reaction mixture under reduced pressure and then dried the material to provide the title compound.

The PXRD pattern of the obtained compound is shown in figure-6.

Yield: 490.0 mg.

Example-11: Preparation of amorphous solid dispersion comprising compound of formula-1 and hydroxypropyl methyl cellulose acetate succinate (HPMCAS)

A 1:1 mixture of methanol and dichloromethane (30 ml) was added to a mixture of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methyl propanoic acid compound of formula-1 (500 mg) and hydroxypropyl methyl cellulose acetate succinate (500 mg) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Slowly heated the reaction mixture to 55-60°C and transferred the solution into

a Buchi flask. Distilled off the solvent completely from the reaction mixture under reduced pressure and then dried the material to provide the title compound.

The PXRD pattern of the obtained compound is shown in figure-7.

Yield: 500.0 mg.

Example-12: Preparation of amorphous solid dispersion comprising compound of formula-1 and Eudragit

A 1:1 mixture of methanol and dichloromethane (30 ml) was added to a mixture of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methyl propanoic acid compound of formula-1 (500 mg) and Eudragit (500 mg) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Slowly heated the reaction mixture to 55-60°C and transferred the solution into a Buchi flask. Distilled off the solvent completely from the reaction mixture under reduced pressure and then dried the material to provide the title compound.

The PXRD pattern of the obtained compound is shown in figure-8.

Yield: 480.0 mg.

Example-13: Preparation of 2-(4-(2-chloroacetyl)phenyl)-N-methoxy-N,2-dimethyl propanamide

Step-1:

A mixture of 2-methyl-2-phenylpropanoic acid (50 Kg) and dichloromethane (250 Lt) was stirred for 15 min at 25-30°C. N,N-dimethylformamide (2.5 Lt) was added to the obtained solution at 25-30°C. Thionyl chloride (54.5 Kg) was slowly added to the reaction mixture at 25-30°C under nitrogen atmosphere and stirred the reaction mixture for 2 hrs at the same temperature. Distilled off the solvent completely from the reaction mixture and co-distilled with dichloromethane.

Step-2:

Dichloromethane (250 Lt) was added to the compound obtained in step-1 at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. The obtained solution was slowly added to a pre-cooled mixture of sodium carbonate (39 Kg), water (250 Lt) and N,O-dimethylhydroxylamine hydrochloride (33.5 Kg) at 0-5°C under nitrogen atmosphere and

stirred the reaction mixture for 30 min at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 1 hr at the same temperature. Filtered the reaction mixture through hyflow bed and washed the hyflow bed with dichloromethane. Both the organic and aqueous layers were separated from the filtrate and washed the organic layer with water. Distilled off the solvent completely from the organic layer. Dichloromethane (188 Lt) was added to the obtained compound at 25-30°C and stirred the reaction mixture for 10 min at the same temperature and kept the reaction mixture aside.

Step-3:

Aluminium trichloride (81 Kg) and dichloromethane (313 Lt) were charged into a reactor at 25-30°C under nitrogen atmosphere and cooled the reaction mixture to 0-5°C. Chloroacetyl chloride (41.5 Kg) was slowly added to the reaction mixture at 0-5°C and stirred the reaction mixture for 1 hr at the same temperature. The reaction mixture obtained in step-2 was slowly added to the resulting reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 3 hr at the same temperature. The obtained reaction mixture was slowly added to pre-cooled water at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 30 min at the same temperature. Both the organic and aqueous layers were separated and washed the organic layer with aqueous sodium carbonate solution followed by with water. Distilled off the solvent completely from the organic layer and co-distilled with cyclohexane. Ethyl acetate (25 Lt) and cyclohexane (250 Lt) were added to the obtained compound at 25-30°C and stirred the reaction mixture for 20 min at the same temperature. Cooled the reaction mixture to 5-10°C and stirred for 90 min at the same temperature. Filtered the solid, washed with chilled cyclohexane and dried the material to provide the title compound.

Yield: 51.6 Kg.

Example-14: Preparation of 2-(4-(2-chloroethyl)phenyl)-N-methoxy-N,2-dimethyl propanamide

A solution of 2-(4-(2-chloroacetyl)phenyl)-N-methoxy-N,2-dimethyl propanamide (35 Kg) in dichloromethane (35 Lt) was slowly added to a pre-cooled mixture of aluminium trichloride (49.35 Kg) and dichloromethane (350 Lt) at 0-5°C and stirred the reaction mixture for 30 min at the same temperature. 1,1,3,3-tetramethyldisiloxane (22.75 Kg) was dried on

sodium sulfate and added to the above reaction mixture at 0-5°C and stirred the reaction mixture for 4 hrs at the same temperature. The resulting reaction mixture was added to pre-cooled water at 0-5°C and raised the temperature of the reaction mixture to 25-30°C. Both the organic and aqueous layers were separated and washed the organic layer with aqueous sodium bicarbonate solution followed by with aqueous sodium chloride solution. Distilled off the solvent completely from the organic layer. The obtained compound was purified by silica gel column chromatography using ethyl acetate/cyclohexane mixture as eluent and collected the pure fractions. Distilled off the solvent completely from the pure fractions under reduced pressure. Petroleum ether (25 Lt) was added to the obtained compound at 25-30°C. Cooled the reaction mixture to -20°C to -25°C and stirred for 40 min at the same temperature. Filtered the solid, washed with chilled petroleum ether and dried the material to provide the title compound. Yield: 23.8 Kg.

Example-15: Preparation of compound of formula-1

1-(2-ethoxyethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole (17.5 kg), 2-(4-(2-chloroethyl)phenyl)-N-methoxy-N,2-dimethylpropanamide (17.3 Kg) and methyl isobutyl ketone (87.5 Lt) were added to a mixture of sodium carbonate (13.7 Kg) and water (8.75 Lt) at 25-30°C and stirred the reaction mixture for 10 min at the same temperature. Tetrabutyl ammonium bromide (1 Kg) was added to the reaction mixture at 25-30°C. Heated the reaction mixture to 100-105°C and stirred for 25 hrs at the same temperature. Cooled the reaction mixture to 25-30°C, water was added and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated. Water and hydrochloric acid were added to the organic layer at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Both the organic and aqueous layers were separated and washed the aqueous layer with methyl isobutyl ketone. Basified the aqueous layer using aqueous sodium carbonate solution at 25-30°C. Extracted the product into dichloromethane and washed the organic layer with water. Distilled off the solvent completely from the organic layer. n-Butanol (87.5 Lt) and sodium hydroxide (12.8 Kg) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 105-110°C and stirred for 7 hrs at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure and co-distilled with water. Water (175 Lt) was added to the obtained compound at

25-30°C. Heated the reaction mixture to 65-70°C, acidified the reaction mixture using acetic acid and stirred for 20 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 40 min at the same temperature. Filtered the precipitated solid and washed with water. The obtained solid was added to a mixture of dimethyl sulfoxide (35 Lt) and n-butanol (35 Lt) at 25-30°C. Heated the reaction mixture to 105-110°C and stirred for 15 min at the same temperature. Reduced the temperature of the reaction mixture to 80-85°C and stirred for 2 hrs at the same temperature. Further cooled the reaction mixture to 25-30°C and stirred for 40 min at the same temperature. Filtered the precipitated solid and washed with n-butanol. The obtained solid was added to water (175 Lt) at 25-30°C. Heated the reaction mixture to 65-70°C and stirred for 40 min at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 40 min at the same temperature. Filtered the solid, washed with water and dried the material to provide the title compound.
Yield: 18.74 Kg.

Example-16: Preparation of crystalline form-1 of compound of formula-1

A mixture of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 (15 Kg), dichloromethane (45 Lt) and methanol (45 Lt) was stirred for 15 min at 25-30°C. Filtered the reaction mixture and washed with a mixture of dichloromethane and methanol. Distilled off the solvent completely from the filtrate under reduced pressure and co-distilled with n-butanol. n-Butanol (120 Lt) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 105-110°C and stirred for 20 min at the same temperature. Reduced the temperature of the reaction mixture to 85-90°C and stirred the reaction mixture for 2 hrs at the same temperature. Cooled the reaction mixture to 25-30°C and stirred for 40 min at the same temperature. Filtered the precipitated solid, washed with n-butanol and dried the material to provide the title compound. Yield: 14.4 Kg; Purity by HPLC: 99.82%.

Example-17: Preparation of compound of formula-1

A mixture of 1-(2-ethoxyethyl)-2-(piperidin-4-yl)-1H-benzo[d]imidazole (100 gm), 2-(4-(2-chloroethyl)phenyl)-N-methoxy-N,2-dimethylpropanamide (98.68 gm), sodium carbonate (77.55 gm), tetrabutyl ammonium bromide (5.89 gm), water (50 ml) and methyl

isobutyl ketone (500 ml) was heated to 95-100°C and stirred the reaction mixture for 28 hrs at the same temperature. Cooled the reaction mixture to 25-30°C, water was added and stirred for 15 min at the same temperature. Both the organic and aqueous layers were separated. HCl and water were added to the organic layer at 25-30°C and stirred for 10 min. Both the organic and aqueous layers were separated and washed the aqueous layer with methyl isobutyl ketone. Basified the aqueous layer using aqueous sodium carbonate solution. Extracted the aqueous layer with dichloromethane and washed the organic layer with water. Distilled off the solvent completely from the organic layer and cooled the obtained compound to 25-30°C. n-Butanol (500 ml) and sodium hydroxide (73.16 gm) were added to the obtained compound at 25-30°C and stirred for 5 min at the same temperature. Heated the reaction mixture to 110-115°C and stirred for 8 hrs at the same temperature. Distilled off the solvent from the reaction mixture under reduced pressure and co-distilled with water. Water was added to the obtained compound at 25-30°C, acidified the reaction mixture by using acetic acid and stirred the reaction mixture for 40 min at the same temperature. Filtered the solid and washed with water. Dimethyl sulfoxide (300 ml) and n-butanol (300 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 105-110°C and stirred for 15 min at the same temperature. Reduced the temperature of the reaction mixture to 80-85°C and stirred for 2 hrs at the same temperature. Further cooled the reaction mixture to 25-30°C and stirred for 40 min at the same temperature. Filtered the solid and washed with a mixture of dimethyl sulfoxide and n-butanol. Water and aqueous sodium hydroxide solution were added to the obtained compound at 25-30°C and stirred for 15 min at the same temperature. Acidified the reaction mixture with acetic acid at 25-30°C and stirred for 40 min at the same temperature. Filtered the solid, washed with water and dried the material to get the title compound. Yield: 98.0 gm; M.R: 205-210°C.

Example-18: Preparation of crystalline form-2 of compound of formula-1

Dichloromethane (500 ml) was added to compound of formula-1 (50 gm) at 25-30°C. Distilled off the solvent completely from the reaction mixture. Methanol (100 ml) and dichloromethane (350 ml) were added to the obtained compound at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. Filtered the reaction mixture and washed with dichloromethane. Distilled off the solvent completely from the filtrate.

Dichloromethane (400 ml) and methanol (100 ml) were added to the obtained compound at 25-30°C and stirred the reaction mixture for 15 min at the same temperature. The obtained solution was slowly added to pre-cooled methyl tert.butyl ether (2500 ml) containing crystalline form-2 seeding material (5 gm) at -5°C to -10°C and stirred the reaction mixture for 45 min at the same temperature. Filtered the solid and washed with methyl tert.butyl ether. The obtained material was added to pre-cooled cyclohexane (250 ml) at 10-15°C and stirred the reaction mixture for 45 min at the same temperature. Filtered the solid, washed with chilled cyclohexane and dried the material to get the title compound.

Yield: 48.52 gm; M.P. 205.3°C.

Particle size distribution: D(0.1) is 0.76 µm; D(0.5) is 5.41 µm; D(0.9) is 50.40 µm.

Example-19: Preparation of crystalline form-2 of compound of formula-1

Compound of formula-1 (50 gm) was added to a mixture of methanol (100 ml) and dichloromethane (400 ml) at 25-30°C and stirred the reaction mixture for 20 min at the same temperature. The obtained solution was slowly added to a pre-cooled mixture of methyl tert.butyl ether (2000 ml) and cyclohexane (500 ml) containing crystalline form-2 seeding material (5 gm) at -5°C to -10°C and stirred the reaction mixture for 45 min at the same temperature. Filtered the solid and dried the material to get the title compound.

Yield: 50.0 gm; M.P. 205.3°C.

Example-20: Preparation of crystalline form-3 of compound of formula-1

A mixture of compound of formula-1 (25 gm), toluene (400 ml) and methanol (50 ml) was heated to 80-85°C and stirred the reaction mixture for 1 hr at the same temperature. Slowly cooled the reaction mixture to 10-15°C and stirred for 1 hr at the same temperature. Filtered the solid, washed with a mixture of toluene and methanol and dried the material to get the title compound.

The PXRD pattern of the obtained compound is similar to figure-7 of WO2017017301A1.

Yield: 20.0 gm.

We Claim:

1. A process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1, comprising of;
   a) Dissolving the compound of formula-1 in a suitable solvent or mixture of solvents,
   b) distilling off the solvent completely from the solution under reduced pressure,
   c) optionally slurrying the obtained compound in a suitable second solvent at a suitable temperature and filtering the material,
   d) drying the compound to provide crystalline form-2 of compound of formula-1.

2. The process according to claim 1, wherein,

   in step-a) the suitable solvent is selected from alcohol solvents, chloro solvents, polar-aprotic solvents or their mixtures;

   in step-c) the suitable second solvent is selected from hydrocarbon solvents, ether solvents, ester solvents, ketone solvents, nitrile solvents, polar solvents or their mixtures; and the suitable temperature ranges from -40°C to 40°C.

3. A process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1, comprising of;
   a) Dissolving the compound of formula-1 in a mixture of dichloromethane and methanol,
   b) distilling off the solvent completely from the solution under reduced pressure,
   c) optionally slurrying the obtained compound in cyclohexane and filtering the material,
   d) drying the compound to provide crystalline form-2 of compound of formula-1.

4. The process according to claim 3, wherein,

   in step-a) the dissolution is carried out at 20-35°C;

   in step-c) the compound is slurried in cyclohexane at a suitable temperature ranges from -30°C to 40°C.

5. A process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1, comprising of;
   a) Dissolving the compound of formula-1 in a suitable solvent or mixture of solvents at a suitable temperature,
   b) optionally filtering the solution,
   c) combining the solution with a suitable anti-solvent at a suitable temperature,
   d) filtering the solid,
   e) optionally slurrying the solid in a suitable solvent at a suitable temperature,
   f) drying the material to provide crystalline form-2 of compound of formula-1.

6. The process according to claim 5, wherein,

   in step-a) the suitable solvent is selected from alcohol solvents, chloro solvents, polar-aprotic solvents or their mixtures; and the suitable temperature ranges from 25°C to reflux temperature of the solvent used;

   in step-c) the suitable anti-solvent is selected from polar solvents, hydrocarbon solvents, ether solvents, ketone solvents, ester solvents, nitrile solvents or their mixtures; and the suitable temperature ranges from -70°C to 40°C;

   in step-e) the suitable solvent is selected from polar solvents, hydrocarbon solvents, ether solvents, ketone solvents, ester solvents, nitrile solvents or their mixtures; and the suitable temperature ranges from -70°C to 40°C.

7. The process according to claims 5 & 6 further optionally comprises before combining the solution of step-a) or step-b) with anti-solvent, a small amount of crystalline form-2 as seeding material is added either to the solution of step-a) or step-b) or to the anti-solvent in order to facilitate the formation of crystalline form-2.

8. A process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1, comprising of;

a) Dissolving the compound of formula-1 in a mixture of dichloromethane and methanol,
b) combining the solution with methyl tert.butyl ether or a mixture of methyl tert.butyl ether and cyclohexane containing a small amount of form-2 seeding material at a suitable temperature,
c) filtering the precipitated solid,
d) optionally slurrying the obtained compound in cyclohexane at a suitable temperature,
e) drying the material to provide crystalline form-2 of compound of formula-1.

9. The process according to claim 8, wherein,
in step-a) the dissolution is carried out at 20-35°C;
in step-b) the suitable temperature ranges from -30°C to 30°C, preferably 0-5°C;
in step-d) the suitable temperature ranges from -30°C to 30°C.

10. A process for the preparation of crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methylpropanoic acid compound of formula-1, comprising of adding a small amount of crystalline form-2 to the reaction mixture as seed material.

11. Amorphous 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl) phenyl]-2-methylpropanoic acid compound of formula-1.

12. Amorphous form of compound of formula-1 according to claim 11, which is characterized by its PXRD pattern as shown in figure-3.

13. A process for the preparation of amorphous form of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl} ethyl)phenyl]-2-methyl propanoic acid compound of formula-1, comprising of;
a) Dissolving the compound of formula-1 in a mixture of dichloromethane and methanol,

b) removing the solvent from the solution to provide pure amorphous form of compound of formula-1.

14. The process according to claim 13, wherein the solvent is removed from the solution by suitable techniques which include evaporation, evaporation under reduced pressure, flash evaporation, vacuum drying, concentrating the reaction mixture, atmospheric distillation, agitated thin film drying (ATFD), melt extrusion, spray drying, freeze drying (lyophilization), spray-freeze drying, cooling the clear solution to lower temperatures to precipitate the solid followed by filtration of the reaction.

15. The process according to claims 13 & 14, wherein the solvent is removed optionally under reduced pressures, at temperatures less than about 130°C, less than about 60°C, less than about 40°C, less than about 20°C, less than about 0°C, less than about -20°C, less than about -40°C or less than about -60°C.

16. A process for the preparation of amorphous form of compound of formula-1 according to claim 11, comprising of;
    a) Dissolving the compound of formula-1 in a mixture of dichloromethane and methanol,
    b) optionally filtering the solution to make it particle free,
    c) spray drying the solution to provide amorphous form of compound of formula-1.

17. Amorphous solid dispersion comprising 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 and at least one pharmaceutically acceptable excipient.

18. Amorphous solid dispersion according to claim 17, wherein the excipient is preferably selected from polyvinylpyrrolidone (povidone or PVP), Eudragit, hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (hypromellose or HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMC-AS).

19. A process for the preparation of amorphous solid dispersion comprising 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 and at least one pharmaceutically acceptable excipient, comprising of;
    a) Dissolving the compound of formula-1 and at least one excipient in a mixture of dichloromethane and methanol,
    b) removing the solvent from the reaction mixture and drying the material to provide amorphous solid dispersion comprising compound of formula-1 and excipient.

20. The process according to claim 19, wherein

    in step-a) the suitable excipient is selected from polyvinylpyrrolidone (povidone or PVP), Eudragit, hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (hypromellose or HPMC) and hydroxypropyl methylcellulose acetate succinate (HPMCAS).

    in step-b) the suitable technique which is used for the removal of the solvent from the reaction mixture include evaporation, evaporation under reduced pressure, flash evaporation, vacuum drying, concentrating the reaction mixture, atmospheric distillation, agitated thin film drying (ATFD), melt extrusion, spray drying, freeze drying (lyophilization), spray-freeze drying, cooling the clear solution to lower temperatures to precipitate the solid followed by filtration of the reaction, vacuum distillation, distillation by using a rotational distillation device such as a Buchi Rotavapor.

21. A process for the preparation of amorphous solid dispersion comprising compound of formula-1 and at least one excipient according to claim 17, comprising of;
    a) Dissolving the compound of formula-1 and at least one excipient in a mixture of dichloromethane and methanol,
    b) optionally filtering the solution,
    c) distilling off the solvent from the solution and drying the material to provide amorphous solid dispersion comprising compound of formula-1 and excipient.

22. Crystalline form-2 of 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid compound of formula-1 having particle size distribution of D_{90} less than 200 µm.

23. Crystalline form-2 of compound of formula-1 according to claim 22, having particle size distribution of D_{90} less than 100 µm.

24. Crystalline form-2 of compound of formula-1 according to claims 22 & 23, having particle size distribution of D_{90} less than 20 µm.

****

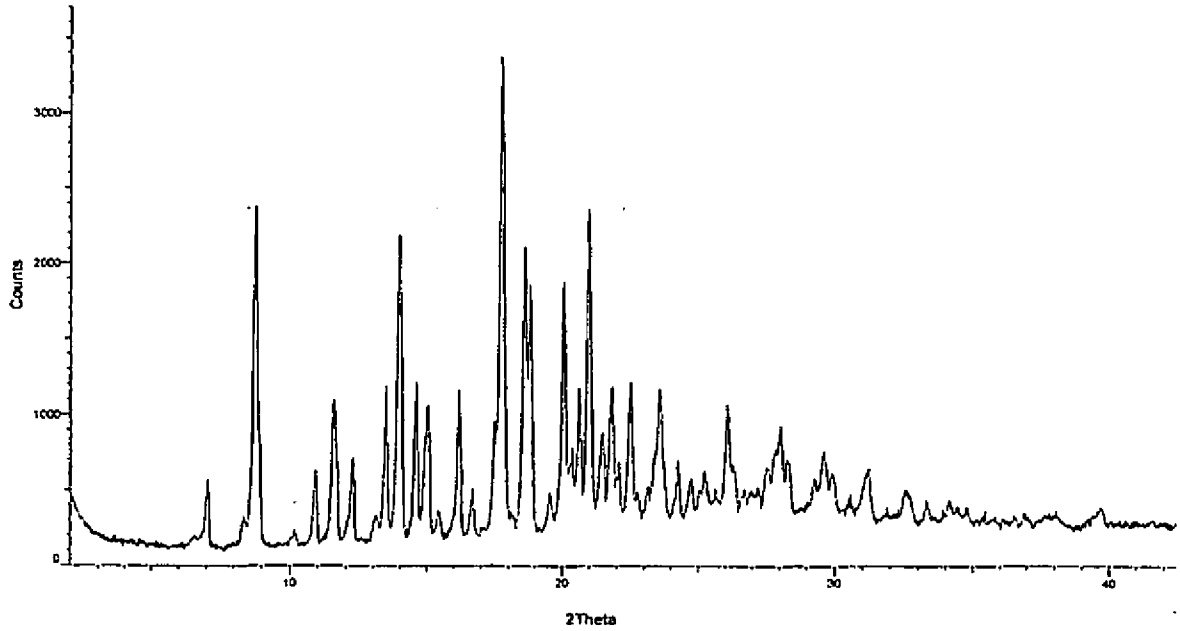


Figure-1

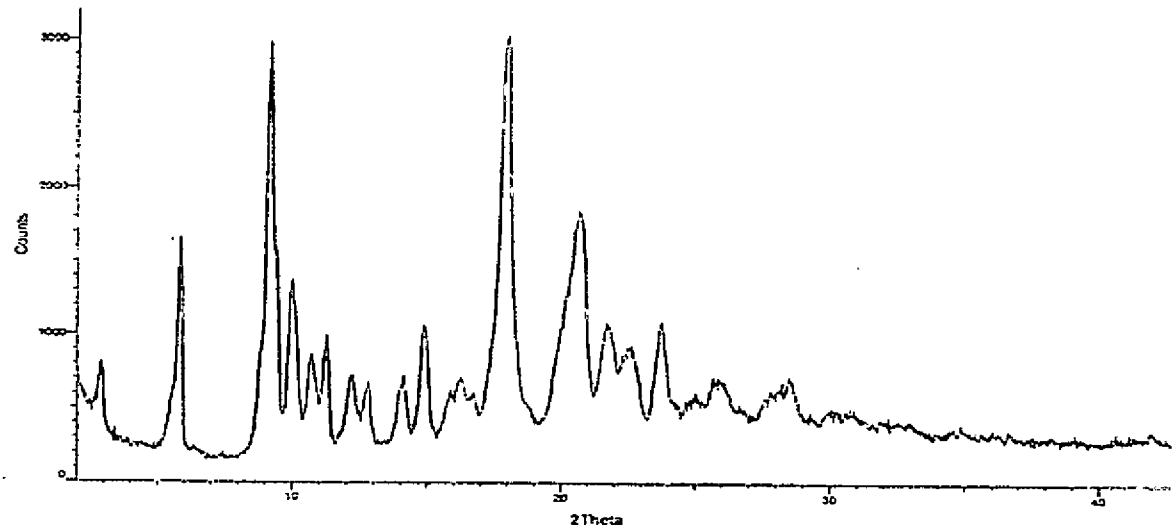


Figure-2

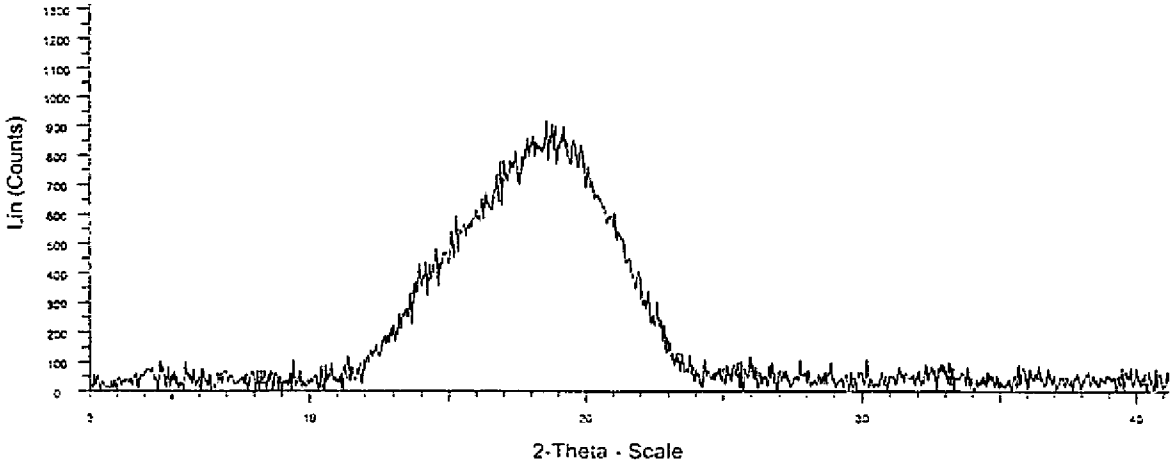


Figure-3

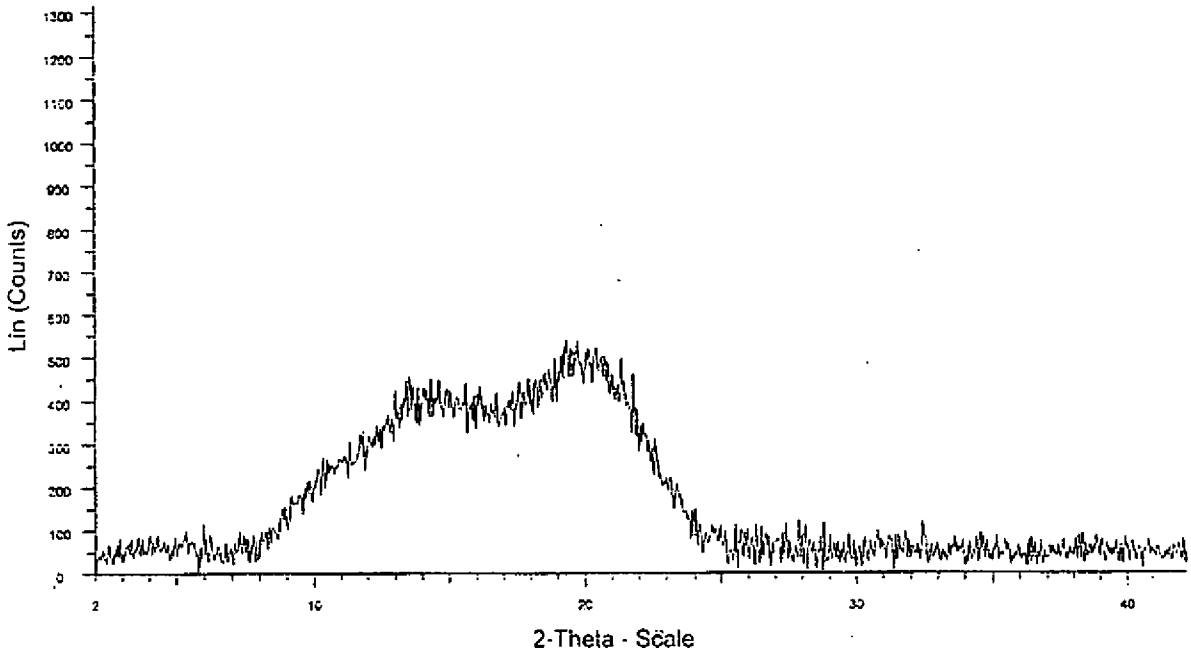


Figure-4

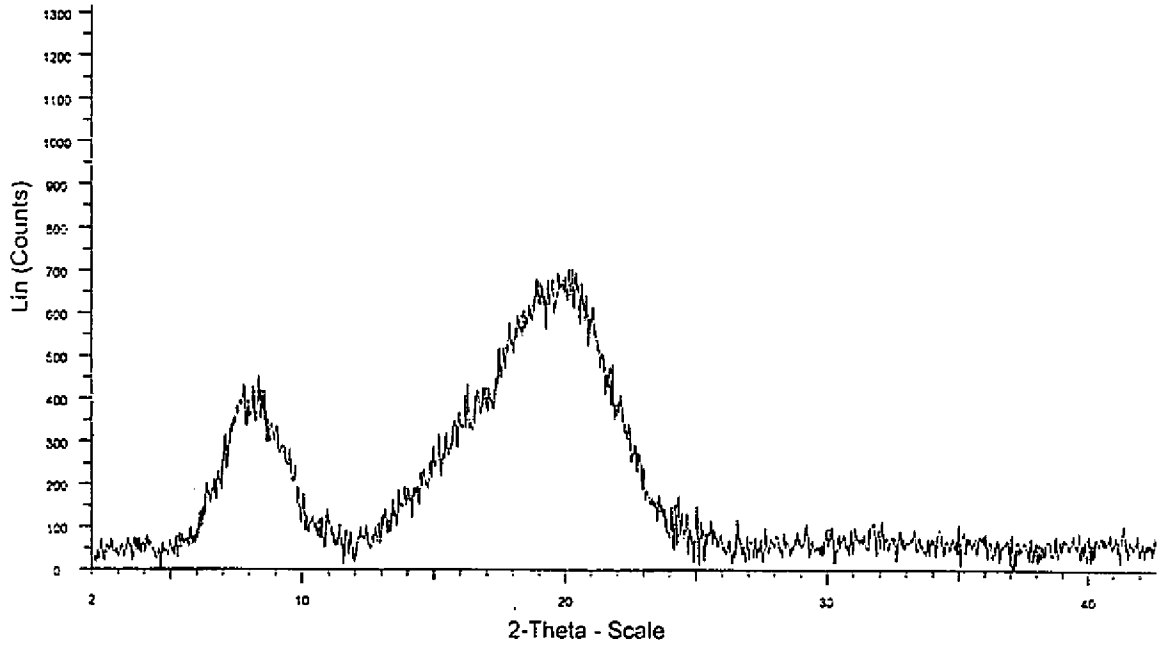


Figure-5

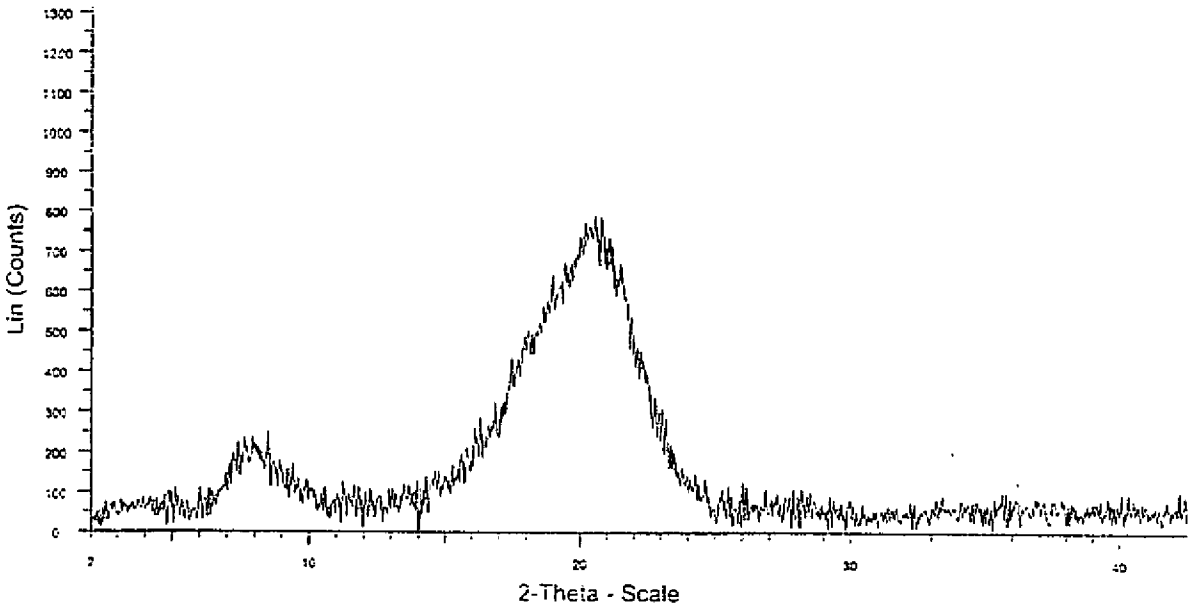


Figure-6

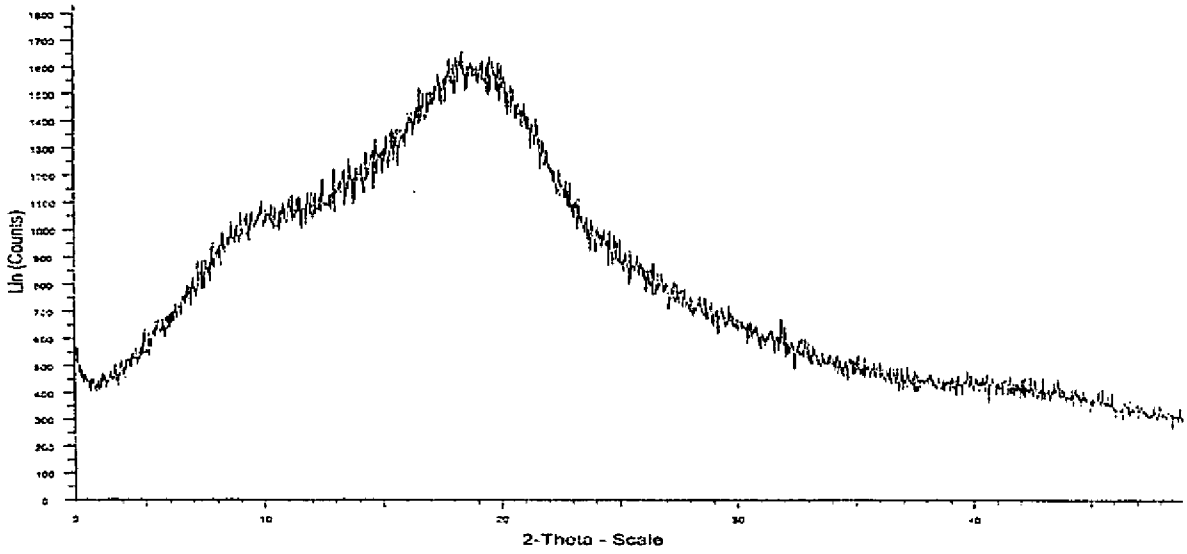


Figure-7

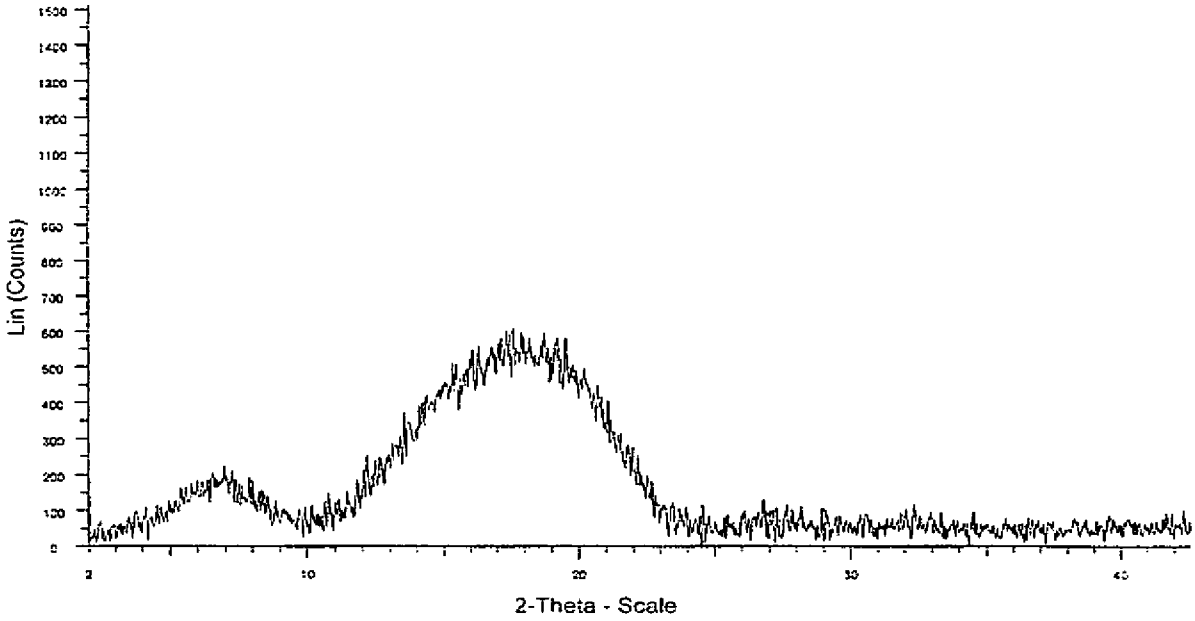


Figure-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/000099

A. CLASSIFICATION OF SUBJECT MATTER
C07D401/04,C07D235/08,C07D235/14,C07D211/62 Version=2017.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Patseer, STN, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2017017301 A1 (URQUIMA S.A) 2 February 2017 (02.02.2017) Examples 1,8 and claims 19-21;	22-24
Y	US 2010/0004285 A1 (FAES FARMA, S.A.) 7 January 2010(07.01.2010) Abstract, Para 12,13, Examples 1-5;	1-4
Y	WO 2014/026657 A2 (ZENTIVA, K.S) 20 February 2014 (20.02.2014) Page 10 lines 5-7, Examples 1,11,12;	1-4
Y	US 2011/0009636 A1 (CHUN-HO LEE) 13 January 2011 (13.01.2011) Abstract, Examples 16-19;	1-4
Y	IN-CHE-2013-0539 A (MSN LABORATORIES PVT. LTD.) 29 may 2015 (29.05.2015) (family none) Abstract, page 8 lower para, Example 3,7;	1-4
Y	US 5877187 A (FAES) 2 March 1999 (02.03.1999) Example 2;	1-4
Y	"Crystalline Polymorphism of Organic Compounds" by Mino R. Caira, pages 163-203, Topic in Current	

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18-08-2017	18-08-2017
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Veera R Kattula Telephone No. +91-1125300200

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Chemistry, vol. 198 published by Springer Verlag Berlin Heidelberg(1998). Page 177,178;	1-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2017/000099

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

Group-I: Claims 1-4, 22-24(part);

The subject matter of Group-I invention relates to a process for the preparation of crystalline Form-2 of a compound having formula-1 by dissolving in a first solvent, then distilling of it, then forming a slurry with the second solvent followed by drying.
Group-II: Claims 5-7, 22-24(part);

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Group-I: Claims 1-4, 22-24(part);

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2017/000099

Citation	Pub.Date	Family	Pub.Date
WO 2017017301 A1	02-02-2017	ES 2600827 A1	10-02-2017
US 2010/0004285 A1	07-01-2010	CZ 20041122 A3	16-03-2005
		JP 2005529120 A	29-09-2005
		IL 164645 D0	18-12-2005
		CA 2484460 A1	30-10-2003
WO 2014/026657 A2	20-02-2014	CZ 20120551 A3	26-02-2014
US 2011/0009636 A1	13-01-2011	CN 104402773 A	11-03-2015
		EP 2240464 A2	20-10-2010
		WO 2009102155 A2	20-08-2009
		KR 20090087424 A	17-08-2009
US 5877187 A	02-03-1999	JP 4218991 B2	04-02-2009
		CA 2206754 A1	04-12-1997
		CN 1176964 A	25-03-1998
		DE 69728608 T2	21-04-2005
		TW 4387944 B	07-07-2001

International application No.
PCT/IN2017/000099

Continuation of Observations where unity of invention is lacking(Box III)

The subject matter of Group-II invention relates to a process for the preparation of crystalline Form-2 of a compound having formula-1 by dissolving in a first solvent, then obtaining a sold using anti-solvent then distilling of it, then forming a slurry with the third solvent followed by drying.
Group-III: Claims 8-10, 22-24(part);

The subject matter of Group-III invention relates to a process for the preparation of crystalline Form-2 of a compound having formula-1 by dissolving in a first solvent, then adding a small amount of form-2 as seeding material and anti-solvent then distilling of it, then forming a slurry with the third solvent followed by drying.
Group-IV: Claim 11-16;

The subject matter of Group-IV invention relates to a process for the preparation of amorphous form of a compound having formula-1.
Group-V: Claim 17-21;

The subject matter of Group-V invention relates to a process for the preparation of amorphous solid dispersion form of a compound having formula-1.
Multiple inventions listed above are not comes under single inventive concept because common technical feature/ special feature that connecting above described groups of inventions is "compound having formula-1", which is not a technical feature because solid form of compound having formula-1 is well known in the prior art US 7612095 B2 (cited by applicant). Hence the subject matter of Group I-V has been considered as a separate invention, and it does not meet the requirement of PCT Rule 13.1.