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CO-AMORPHOUS FORM OF (3S,4R)-3-ETHYL-4-(3H-IMIDAZO[1,2-A] PYRROLO[2,3-E] PYRAZIN-8-YL)-N-(2,2,2-TRIFLUOROETHYL) PYRROLIDINE-1-CARBOXAMIDE AND PROCESS FOR ITS PREPARATION THEREOF

MSN Laboratories Private Limited, R & D Center, Srinivasan Thirumalai Rajan, Sajja Eswaraiah, Vijayavitthal T. Mathad, Saladi Venkata Narasayya, Kammari Balraju, Dodle Beerappa

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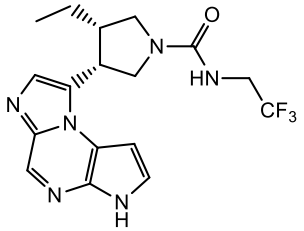
Abstract

The present invention pertains to co-amorphous form of (3*S*,4*R*)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of formula (I) and process for its preparation thereof. The chemical structure of compound of formula (I) is shown below:



Formula (1)

Introduction

(3*S*,4*R*)-3-Ethyl-4-(3*H*-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoro ethyl)pyrrolidine-1-carboxamide of formula (I) is commonly known as 'Upadacitinib'. Upadacitinib is a Janus kinase (JAK) inhibitor & indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate, and it is approved by USFDA under brand name of RINVOQ™.

US patent 8426411 B2 assigned to Abbott discloses Upadacitinib and its process for preparation thereof.

PCT application, WO 2017066775 A1 assigned to Abbvie Inc., discloses Upadacitinib crystalline (solvate) form A, crystalline (hydrate) form B, crystalline (hemihydrate) form C, crystalline (anhydrous) form D and amorphous form thereof. The patent document discloses that the crystallinity of Form A and Form B are poor and unstable, and it is easy to dehydrate and converted to amorphous; Form D can only be obtained at lower water activity, and the crystallization is slow. Further, under water activity, Form D is converted to Form C; Form C is not ready to crystallize from a

solution.

Hence, there is a significant need in the pharmaceutical industry to develop an alternative forms such as co-amorphous form of Upadacitinib of formula (I) which improves the performance characteristics of a pharmaceutical product.

Above cited references does not discloses co-amorphous form of Upadacitinib and process for its preparation thereof.

Brief description of the invention

In first embodiment, the present invention provides co-amorphous form of Upadacitinib.

In second embodiment, the present invention provides a process for the preparation of co-amorphous form of Upadacitinib.

In third embodiment, the present invention provides a pharmaceutical composition comprising co-amorphous form of Upadacitinib and one or more pharmaceutically acceptable excipients.

In fourth embodiment, the present invention provides a process for the preparation of pharmaceutical composition comprising co-amorphous form of Upadacitinib and one or more pharmaceutically acceptable excipients.

Detailed description of the invention

The term “co-amorphous” as defined as miscible system containing amorphous API and amorphous small molecular co-former, (or) co-amorphous solid is an amorphous homogeneous solid form containing two or more molecular components at ambient conditions present in a definite stoichiometric ratio with a single glass transition temperature in DSC/MDSC and/or with an evidence of non-covalent or non-ionic interaction between participant molecular components (No-salt formation or chemical reaction between or among participants). The participant components may or may not be crystalline or amorphous before forming co-amorphous solid. The molecular components participating in the formation of co-amorphous solid in pharmaceutical industry is an active pharmaceutical ingredient (API) and one or more co-formers/excipients/any GRAS listed/safe molecules for human consumption.

In first embodiment, the present invention provides co-amorphous form of Upadacitinib.

In first aspect of first embodiment, the present invention provides co-amorphous form of Upadacitinib characterized by PXRD pattern as illustrated in figure 1 and figure 3.

In second aspect of first embodiment, the present invention provides co-amorphous form of Upadacitinib characterized by differential scanning calorimetry thermogram as illustrated in figure 2 and figure 4.

In second embodiment, the present invention provides a process for the preparation of co-amorphous form of Upadacitinib, comprising:

a) providing a solution of Upadacitinib and one or more co-formers in a solvent,

b) removing the solvent to get co-amorphous form of Upadacitinib of formula (I),

wherein, the co-former used in step a) is selected from vanillin, methylparaben, L-proline, pyroglutamic acid, ascorbic acid, urea, citric acid, malic acid, benzoic acid, glutamic acid, meglumine, pyrogallol, tryptophan and thereof. Preferably, vanillin or methylparaben.

Wherein, the solvent used in step a) is selected from “alcohol solvents” such as methanol, ethanol, n- propanol, isopropanol, n-butanol, isobutanol, t-butanol, n-pentanol, isopentanol, 2-nitroethanol, ethylene glycol, 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monoethyl ether, benzyl alcohol, phenol, or glycerol and the like; "ether solvents" such as dimethyl ether, diisopropyl ether, diethyl ether, methyl tert-butyl ether, 1,2-dimethoxy ethane, tetrahydrofuran, trifluoroacetic anhydride, 1,4-dioxane and the like; "ester solvents" such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate 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; "polar solvents" such as water or mixtures thereof. Preferably, the solvent used in step a) is methanol.

Wherein, the term "removing the solvent" in step-b) can be carried out by suitable techniques but not limited to distillation or filtration or decantation, drying from the mixture or any other suitable techniques in the art. Preferably, distillation.

Wherein distillation can be carried out by under reduced pressure or under atmospheric pressure or buchi rotavapor or agitated thin film dryer (ATFD) or spray drying or any other suitable techniques known in the art.

In first aspect of second embodiment, the present invention provides a process for the preparation of co-amorphous form of Upadacitinib, comprising:

a) providing a solution of Upadacitinib and vanillin in a methanol,
b) removing the solvent to get co-amorphous form of Upadacitinib of formula (I).

In second aspect of second embodiment, the present invention provides a process for the preparation of co-amorphous form of Upadacitinib, comprising:

a) providing a solution of Upadacitinib and methylparaben in a methanol,
b) removing the solvent to get co-amorphous form of Upadacitinib of formula (I).

In third embodiment, the present invention provides a pharmaceutical composition comprising co-amorphous form of Upadacitinib and one or more pharmaceutically acceptable excipients. The pharmaceutically acceptable excipient is selected from but not limited to polyvinylpyrrolidone (povidone or PVP), Povidone K-30, copovidone, polyvinylpolypyrrolidone, polysorbate, cross linked polyvinyl pyrrolidone (crospovidone), 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 (HPCAS), hydroxypropyl methyl cellulose (hypromellose or HPMC), hydroxypropyl methylcellulose E5 grade (HPMC-E5), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), hydroxyethyl methyl cellulose succinate (HEMCS), hydroxypropyl methylcellulose phthalate (HPMC-P), hydroxypropyl methylcellulose acetate phthalate, microcrystalline cellulose (MCC),

plasdone s630, 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-, y-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 thereof.

In fourth embodiment, the present invention provides a process for the preparation of pharmaceutical composition comprising co-amorphous form of Upadacitinib and pharmaceutically acceptable excipients, comprising:

a) providing a solution of co-amorphous form of Upadacitinib and one or more pharmaceutically acceptable excipients in solvent or mixture of solvents,
b) removing the solvent from the mixture to provide pharmaceutical composition comprising co-amorphous form of Upadacitinib and one or more pharmaceutically acceptable excipients.

The starting material Upadacitinib of formula (I) can be prepared by to the methods known from the art.

The PXRD analysis of the compounds produced by the present invention were carried out using BRUKER/AXS X-Ray diffractometer using Cu-Ka radiation of wavelength 1.5406 A° and at continuous scan speed of 0.02 °/min.

Differential scanning calorimetric (DSC) analysis was performed on a DSC 25 with closed aluminum pans, by heating, cooling and reheating the samples from - 40-350°C at a rate of 10°C/min.

The process described in the present invention was demonstrated in examples illustrated below. These examples are prodvided as illustration only and therefore should not be construed as limitation of the scope of the invention:

Examples

Example 1: Preparation of co-amorphous form of Upadacitinib

Dissolving Upadacitinib (200 mg) and vanillin (80 mg) in methanol (10 ml) at 25-30°C. Filtered the mixture for particle free solution. Distilled off the solvent completely from the filtrate under reduced pressure and then dried to provide the title compound (Yield: 215 mg).

The obtained compound is characterized by PXRD pattern as illustrated in Figure 1.

The obtained compound is characterized by DSC as illustrated in Figure 2.

Example 2: Process for the preparation of co-amorphous form of Upadacitinib

Dissolving Upadacitinib (1 g) and vanillin (400 mg) in methanol (50 ml) at 25-30°C. Filtered the mixture for particle free solution. Distilled off the solvent completely from the filtrate under reduced pressure and then dried to get the title compound (Yield: 1.2 g).

The PXRD of obtained compound is similar to the PXRD pattern as illustrated in Figure 1.

The DSC of obtained compound is similar to the DSC as illustrated in Figure 2.

Example 3: Process for the preparation of co-amorphous form of Upadacitinib

Dissolving Upadacitinib (200 mg) and methylparaben (80 mg) in methanol (10 ml) at 25-30°C. Filtered the mixture for particle free solution. Distilled off the solvent completely from the filtrate under reduced pressure and then dried to get the title compound (Yield: 120 mg).

The obtained compound is characterized by PXRD pattern as illustrated in Figure 3.

The obtained compound is characterized by DSC as illustrated in Figure 4.

Brief description of the drawings

Figure 1: Illustrates characteristic Powdered X-Ray Diffraction (PXRD) pattern of co-amorphous form of Upadacitinib obtained according to Example-1 & 2.

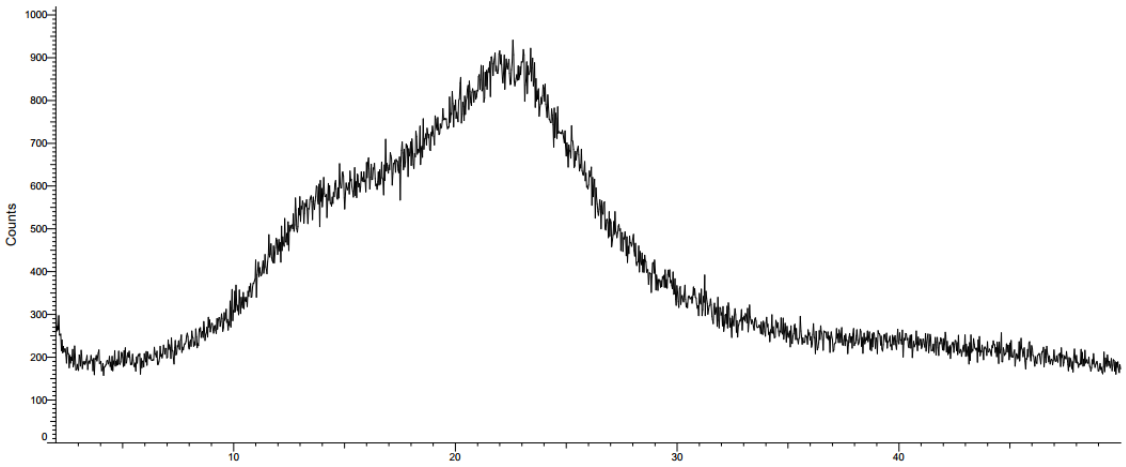


Figure-1

Figure 2: Illustrates Differential Scanning Calorimetry (DSC) thermogram corresponding to co-amorphous form of Upadacitinib obtained according to Example-1 & 2.

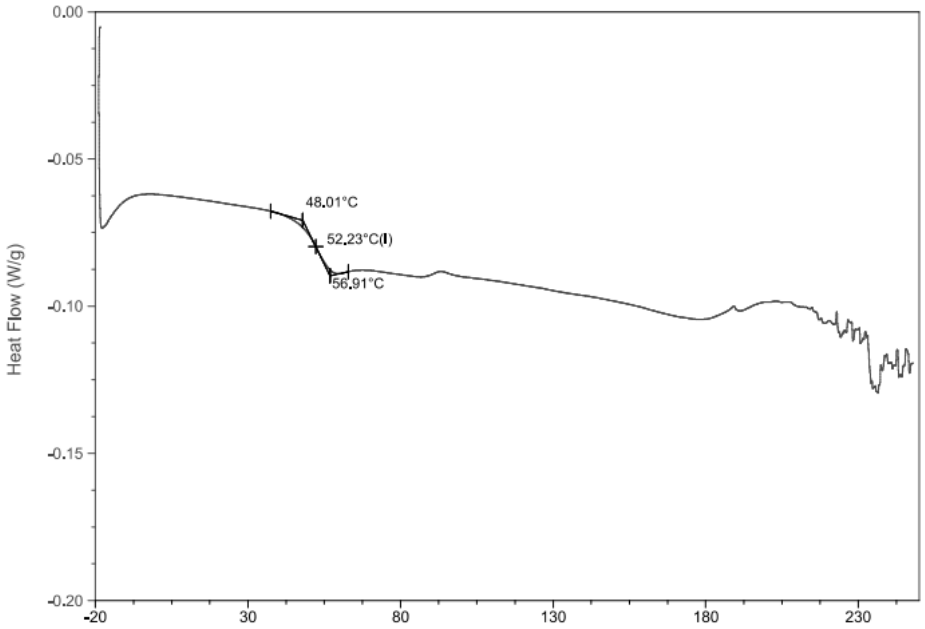


Figure-2

Figure 3: Illustrates characteristic Powdered X-Ray Diffraction (PXRD) pattern of co-amorphous form of Upadacitinib obtained according to Example-3.

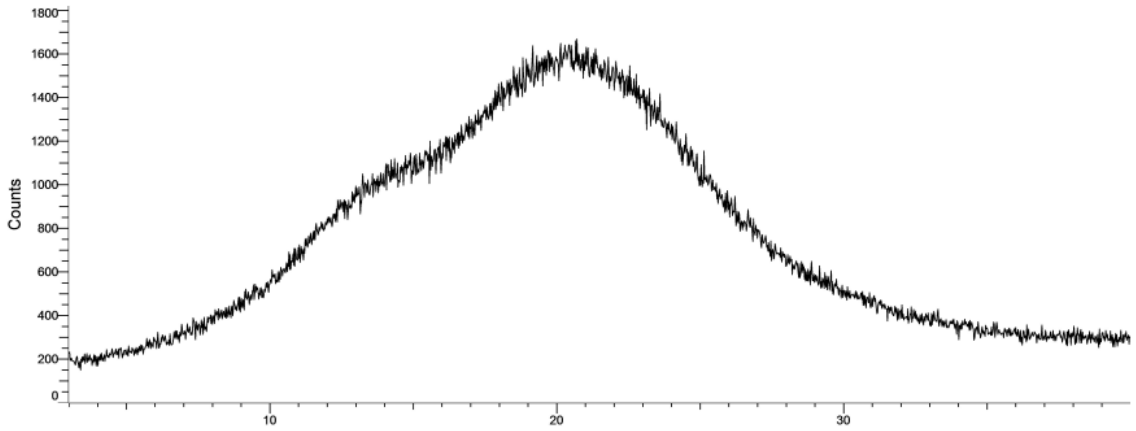


Figure-3

Figure 4: Illustrates Differential Scanning Calorimetry (DSC) thermogram corresponding to co-amorphous form of Upadacitinib obtained according to Example-3.

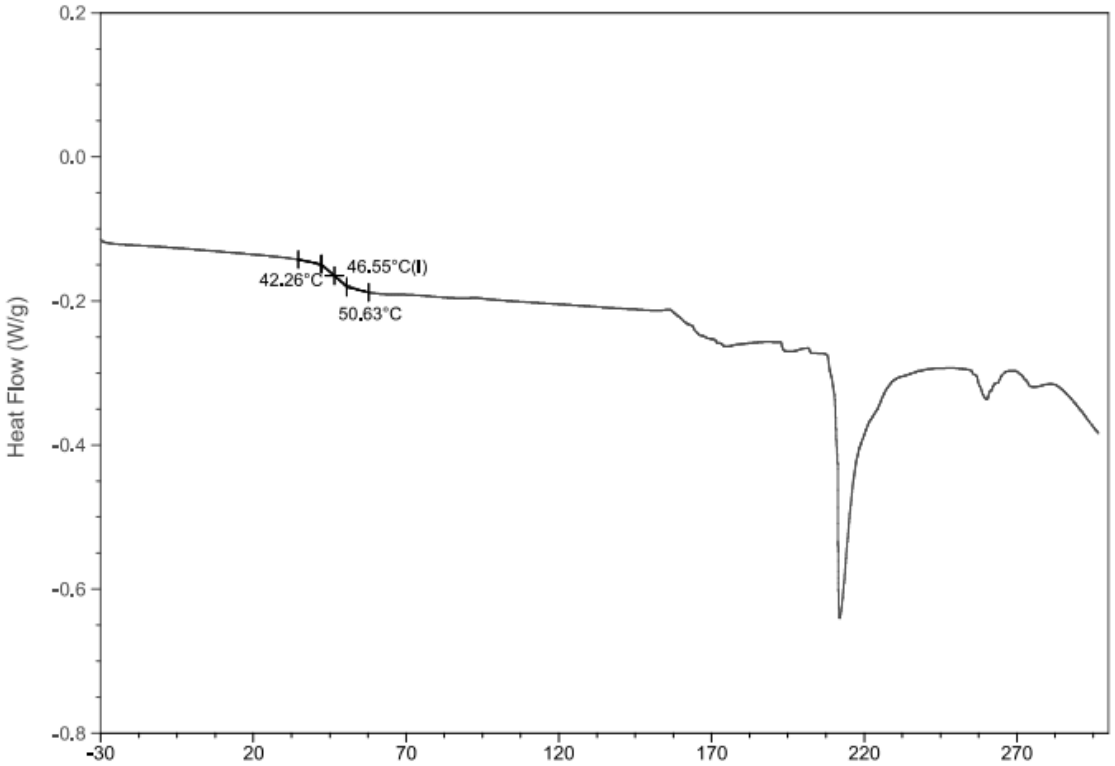


Figure-4