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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 May 2017 (11.05.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/077551 A2

(51) International Patent Classification:
C07D 209/34 (2006.01)

(21) International Application Number:
PCT/IN2016/050378

(22) International Filing Date:
2 November 2016 (02.11.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
5942/CHE/2015 3 November 2015 (03.11.2015) IN

(71) Applicant: **MYLAN LABORATORIES LIMITED** [IN/IN]; Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(72) Inventors: **JETTI, Ramakoteswara Rao;** Mylan Laboratories Ltd, Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **INDUKURI, Anjaneyaraju;** Mylan Laboratories Ltd, Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **BOMMAREDDY, Aggi Ramireddy;** Mylan Laboratories Ltd, Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **SINGH, Amith;** Mylan Laboratories Limited, Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **GHOSH, Soumyajit;** Mylan Laboratories Ltd, Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **JOSHI, Rajesh;** Mylan Laboratories Ltd, Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **SHINDE, Dattatraya;** Mylan Laboratories Limited, Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **HUBLIKAR, Mahesh;** Mylan Laboratories Limited, Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **BHOITE, Shivaji;** Mylan Laboratories Limited, Plot No 564/**A**/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(74) Agents: **HASAN, Afzal** et al; Hasan and Singh, Flat No. 04, Sree Nilayam Apartment Plot No. 12, Camelot Layout (Near Chirec Public School), Kondapur, Hyderabad 500084 (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, 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:

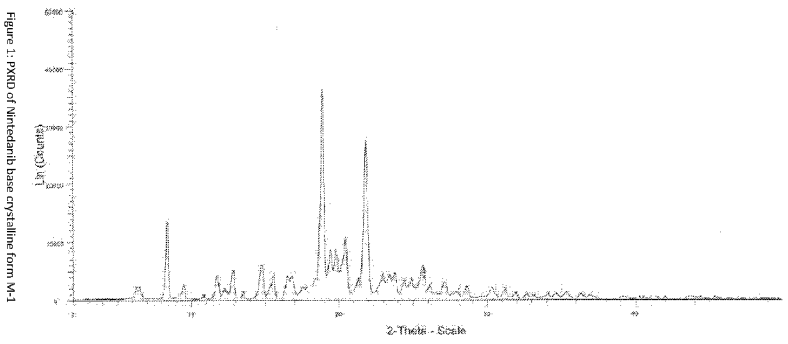
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

[Continued on next page]

(54) Title: AN AMORPHOUS NINTEDANIB ESYLATE AND SOLID DISPERSION THEREOF



(57) Abstract: Nintedanib base polymorphic forms and processes for preparing the same. A process for the purification of nintedanib base is disclosed. An amorphous form of nintedanib and process for the preparation of the same are also disclosed. A solid dispersion of amorphous nintedanib with pharmaceutically acceptable excipients and processes for the preparation of the same are also disclosed.

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

AN AMORPHOUS NINTEDANIB ESYLATE AND SOLID DISPERSION THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of Indian provisional patent application no. 5942/CHE/2015 filed on November 03, 2015, which is hereby incorporated by reference in its entirety.

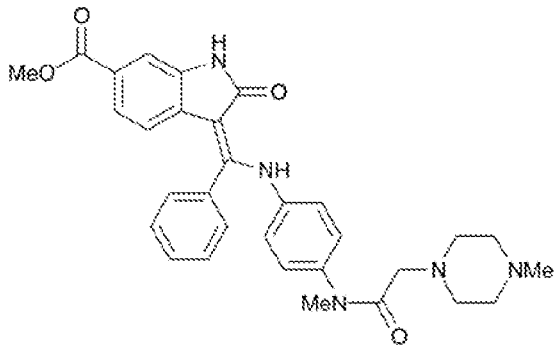
BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present disclosure generally relates to the pharmaceutical arts and more specifically to novel nintedanib polymorphic forms of nintedanib base. The present disclosure provides crystalline nintedanib form-Mi, nintedanib form-M2, as well as processes for preparing each form. The present disclosure also provides a process for the purification of nintedanib base. The present disclosure further provides amorphous forms of nintedanib esylate and processes for preparing the same. The present disclosure further also provides solid dispersions of amorphous nintedanib esylate and processes for the preparation of the same.

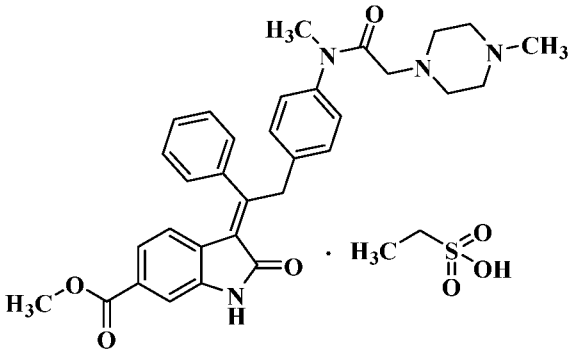
DESCRIPTION OF RELATED ART

Nintedanib is chemically known as methyl (3Z)-3-{[(4-{methyl[(4-methylpiperazin-l-yl)acetyl]amino}phenyl)amino](phenyl)methylidene}-2-oxo-2,3-dihydro- 1H-indole-6-carboxylate and is shown below in Formula-II:



Formula-II

Nintedanib esylate, the esylate salt of nintedanib, is chemically known as methyl (3Z)-3-{[(4-{methyl[(4-methylpiperazin- 1-yl)acetyl]amino }phenyl)amino](phenyl)methylidene }-2-oxo-2,3-dihydro-lH-indole-6-carboxylate ethanesulfonate and has the structure shown below in Formula-I.



Formula-I

Nintedanib is a kinase inhibitor and as such, nintedanib esylate is approved for the treatment of idiopathic pulmonary fibrosis (IPF) and is marketed under the brand name OFEV®.

United States Patent No. 6,762,180 discloses the nintedanib base and a process for its preparation.

United States Patent Nos. 8,304,541 and 8,067,617 also disclose processes for the preparation of nintedanib base and process for the purification of nintedanib base.

Impurities arising during the preparation of nintedanib are a concern. For example, dimer and desmethyl impurities are common. Purification of nintedanib may often be procedurally complex, for example, purification often employs column chromatography. Furthermore, many purification processes disclosed in the prior art may not reduce or eliminate dimer and/or desmethyl impurities from the prepared nintedanib. The presently disclosed invention overcomes such limitations of the prior by providing processes whereby nintedanib may be prepared on an industrial scale with high purity without the use of complex purification procedures.

United States Patent No. 7,119,093 discloses crystalline nintedanib esylate hemihydrate and processes for its preparation.

Different polymorphs may provide different advantages in a variety of capacities, for example, in ease of formulation, stability of the polymorphic form, stability of the formulation, and in pharmacokinetic profiles. These advantages may arise from the different properties present in each polymorph. The present invention provides amorphous nintedanib esylate and a process for the preparation thereof.

Furthermore, preparation of pharmaceutical dosage forms is often procedurally complex, particularly when combining the active ingredient with excipients. For example, workability or stability issues may arise when different components of the pharmaceutical dosage form come into intimate contact with one another. It may, thus, be advantageous to supply the manufacturer of pharmaceutical dosage forms with a pre-combined mixture (pre-mix) of excipients and active pharmaceutical ingredient (API) to facilitate and simplify the final processing of dosages forms. The present invention provides a solid dispersion of nintedanib esylate and processes for the preparation thereof.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides amorphous nintedanib esylate.

Within the context of the present invention, the amorphous nintedanib esylate may be characterized by the powder X-ray diffraction pattern shown in Figure 7.

In another aspect, the present invention provides a process for preparing amorphous nintedanib esylate.

In one embodiment, amorphous nintedanib esylate may be prepared by a process that includes the following steps:

a) dissolving nintedanib esylate in a solvent or mixture of solvents; and
b) removing the solvent to isolate amorphous nintedanib esylate.

Within the context of the present invention the solvent may be, for example, an alcohol solvent, a ketone solvent, a chlorinated solvent, water, or miscible mixtures thereof.

Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-

butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl-l-propanol, 1,1-dimethyl-1-propanol, and mixtures thereof. Examples of suitable ketone solvents include acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, and mixtures thereof. Examples of suitable chlorinated solvents include dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, and mixtures thereof.

Within the context of this embodiment, the solvent may be removed by evaporation, distillation, spray drying, lyophilization, agitated thin film drying, or any combination thereof.

In another aspect, the present invention provides a process for preparing a solid dispersion of amorphous nintedanib esylate.

In one embodiment, a solid dispersion of amorphous nintedanib esylate may be prepared by a process that includes the following steps:

a) dissolving nintedanib esylate and one or more pharmaceutically acceptable excipients in a solvent to form a solution; and
b) removing the solvent to isolate the solid dispersion of amorphous nintedanib esylate.

Within the context of the present invention the solvent may be, for example, an alcohol solvent, a ketone solvent, a chlorinated solvent, water, or miscible mixtures thereof.

Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl-l-propanol, 1,1-dimethyl-1-propanol, and mixtures thereof. Examples of suitable ketone solvents include acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, and mixtures thereof. Examples of suitable chlorinated solvents include dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, and mixtures thereof.

Within the context of this embodiment, examples of suitable pharmaceutically acceptable excipient include polysaccharides, polyvinylpyrrolidone, polyvinyl acetate, polyvinyl alcohol, polymers of acrylic acid and salts thereof, polyacrylamide, polymethacrylates, vinylpyrrolidone-vinyl acetate copolymers, Ci-C_6 polyalkylene glycols, and mixtures thereof. Examples of suitable polysaccharides include hydroxypropyl methyl cellulose,

croscarmellose, carboxymethyl cellulose, a sodium salt of carboxymethyl cellulose, a calcium salt of carboxymethyl cellulose, methyl cellulose, hydroxyethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, microcrystalline cellulose, optionally substituted a-cyclodextrins, optionally substituted β-cyclodextrins, optionally substituted γ-cyclodextrins, and mixtures thereof. Examples of suitable Ci-C_6 polyalkylene glycols include polyethylene glycol, polypropylene glycol, and mixtures thereof. Examples of optionally substituted cyclodextrin include β-cyclodextrin, hydroxypropyl -P-cyclodextrin, and mixtures thereof.

In some embodiments, the vinylpyrrolidone-vinyl acetate copolymer is a polymer containing N-vinyl-2-pyrrolidone and vinyl acetate in a 60:40 ratio, by mass.

Within the context of this embodiment, the solvent may be removed by evaporation, distillation, spray drying, lyophilization, agitated thin film drying, or any combination thereof.

In another embodiment, a solid dispersion of amorphous nintedanib esylate may be prepared by a process that includes the following steps:

a) dissolving nintedanib esylate in a first solvent to form a first solution;
b) preparing a second solution containing one or more pharmaceutically acceptable excipients in a second solvent; and
c) combining the first solution and the second solution;
d) removing the first solvent and the second solvent to isolate a solid dispersion of amorphous nintedanib esylate.

Within the context of the present invention the first solvent and the second solvent may be, for example, independently an alcohol solvent, a ketone solvent, a chlorinated solvent, water, or miscible mixtures thereof.

Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl- 1-propanol, 1,1-dimethyl- 1-propanol, and mixtures thereof. Examples of suitable ketone solvents include acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, and mixtures thereof. Examples of

suitable chlorinated solvents include dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, and mixtures thereof.

Within the context of this embodiment, the first and second solvents may be the same or different.

Within the context of this embodiment, examples of suitable pharmaceutically acceptable excipient include polysaccharides, polyvinylpyrrolidone, polyvinyl acetate, polyvinyl alcohol, polymers of acrylic acid and salts thereof, polyacrylamide, polymethacrylates, vinylpyrrolidone-vinyl acetate copolymers, Ci-C_6 polyalkylene glycols, and mixtures thereof. Examples of suitable polysaccharides include hydroxypropyl methyl cellulose, croscarmellose, carboxymethyl cellulose, a sodium salt of carboxymethyl cellulose, a calcium salt of carboxymethyl cellulose, methyl cellulose, hydroxyethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, microcrystalline cellulose, optionally substituted a-cyclodextrins, optionally substituted β-cyclodextrins, optionally substituted γ-cyclodextrins, and mixtures thereof. Examples of suitable Ci-C_6 polyalkylene glycols include polyethylene glycol, polypropylene glycol, and mixtures thereof. Examples of optionally substituted cyclodextrin include β-cyclodextrin, hydroxypropyl -P-cyclodextrin, and mixtures thereof.

In some embodiments, the vinylpyrrolidone-vinyl acetate copolymer is a polymer containing N-vinyl-2-pyrrolidone and vinyl acetate in a 60:40 ratio, by mass.

Within the context of this embodiment, the solvent may be removed by evaporation, distillation, spray drying, lyophilization, agitated thin film drying, or any combination thereof.

In some particularly useful embodiments, pharmaceutically acceptable excipient is PLASDONE S-630.

In other particularly useful embodiments, pharmaceutically acceptable excipient is β-cyclodextrin.

Within the context of the present invention, solid dispersions of amorphous nintedanib esylate prepared by processes disclosed herein, including those containing PLASDONE S-630 and β-cyclodextrin may degrade less than about 1% when the solid dispersion is stored for three months at 5 ± 3 °C.

Within the context of the present invention, solid dispersions of amorphous nintedanib esylate prepared by processes disclosed herein, including those containing PLASDONE S-630 and β-cyclodextrin may degrade less than about 1% when the solid dispersion is stored for three months at 25 °C and at 60% relative humidity.

Within the context of the present invention, amorphous nintedanib esylate or solid dispersions thereof may be formulated into an oral pharmaceutical dosage form.

In another aspect, the present invention provides nintedanib crystalline form-Ml.

Within the context of the present invention the nintedanib crystalline form-Ml prepared by process disclosed herein may be characterized by a powder X-ray diffraction pattern having peaks at 8.3, 11.7, 12.7, 14.7, 15.5, 18.8, 19.4, 20.4, and 21.7 (+) 0.2 °2Θ.

In another aspect, the present invention provides a process for preparing nintedanib crystalline form-Ml.

In one embodiment, nintedanib crystalline form-Ml may be prepared by a process that includes the following steps:

a) providing nintedanib in a solvent;
b) adding tetrahydrofuran; and
c) isolating nintedanib crystalline form-Ml.

Within the context of this embodiment, the solvent may be an alcohol solvent, a chlorinated solvent, an aprotic polar solvent, ketone, water, or miscible mixtures thereof. Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl- 1-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl- 1-propanol, 1,1-dimethyl- 1-propanol, and mixtures thereof. Examples of suitable chlorinated solvents include dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, and mixtures thereof. Examples of suitable aprotic polar solvent include N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), and mixtures thereof. Examples of suitable ketone solvent include acetone, methyl ethyl ketone, methyl isobutyl ketone, and mixtures thereof.

In another embodiment, nintedanib crystalline form-Ml may be prepared by a process that includes the following steps:

a) deprotecting protected nintedanib;
b) adding tetrahydrofuran; and
c) isolating nintedanib crystalline form-Ml.

Within the context of this embodiment, the nintedanib may be protected at the amine moiety on the indole ring with a suitable amine protecting group.

Within the context of this embodiment, the deprotecting step may be carried out with a base. The base may be, for example, an inorganic base or an organic base. Examples of suitable inorganic bases include alkali metal hydroxides, alkali metal hydrides, alkali metal bicarbonates, alkali metal carbonates, and alkali alkoxides. Examples of suitable organic bases include piperidine, pyridine, triethylamine, and N,N-diisopropylethylamine.

The solvent may be an alcohol solvent, a chlorinated solvent, water, or miscible mixtures thereof.

Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl- 1-propanol, 1,1-dimethyl- 1-propanol, and mixtures thereof. Examples of suitable chlorinated solvents include dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, and mixtures thereof.

In another aspect, the present invention provides nintedanib crystalline form-M2.

Within the context of the present invention the nintedanib crystalline form-M2 prepared by processes disclosed herein may be characterized by a powder X-ray diffraction pattern having peaks at 6.2, 6.9, 11.3, 16.8, 17.3, 18.9, 21.5, and 22.5 (+) 0.2 °2Θ.

In another aspect, the present invention provides a process for preparing nintedanib crystalline form-M2.

In one embodiment, nintedanib crystalline form-M2 may be prepared by a process that includes the following steps:

a) dissolving nintedanib base in a solvent;
b) adding anisole; and
c) isolating nintedanib crystalline form-M2.

Within the context of this embodiment, the solvent may be an alcohol solvent, a chlorinated solvent, an aprotic polar solvent, a ketone solvent, an ether solvent, water, or miscible mixtures thereof. Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl- 1-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl-l -propanol, 1,1-dimethyl-1 -propanol, and mixtures thereof. Examples of suitable chlorinated solvents include dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, and mixtures thereof. Examples of suitable aprotic polar solvent include N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), and mixtures thereof. Examples of suitable ketone solvent include acetone, methyl ethyl ketone, methyl isobutyl ketone, and mixtures thereof. Examples of suitable ether solvents include tetrahydrofuran, dimethyl ether, diethyl ether, dioxane, and mixtures thereof.

In another embodiment, nintedanib crystalline form-M2 may be prepared by a process that includes the following steps:

a) deprotecting protected nintedanib;
b) adding anisole; and
c) isolating nintedanib crystalline form-M2.

Within the context of this embodiment, the nintedanib may be protected at the amine moiety on the indole ring with a suitable amine protecting group.

Within the context of this embodiment, the deprotecting step may be carried out with a base. The base may be, for example, an inorganic base or an organic base. Examples of suitable inorganic bases include alkali metal hydroxides, alkali metal hydrides, alkali metal bicarbonates, alkali metal carbonates, and alkali alkoxides. Examples of suitable organic bases include piperidine, pyridine, triethylamine, and N,N-diisopropylethylamine.

The solvent may be an alcohol solvent, a chlorinated solvent, water, or miscible mixtures thereof.

Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl- 1-propanol, 1,1 -dimethyl- 1-propanol, and mixtures thereof. Examples of suitable chlorinated solvents include dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, and mixtures thereof.

In another aspect the present invention provides a process for the purification of nintedanib base. Within the context of the invention, the purification of nintedanib base by methods disclosed herein may be substantially free from dimer and des-methyl impunity of nintedanib.

In one aspect, nintedanib base may be prepared by a process that includes the following steps:

a) desolvating a nintedanib solvate; and
b) isolating nintedanib base which is substantially free from dimer and des-methyl impurity.

Within the context of this embodiment, the desolvating step may be carried out in a solvent.

The solvent may be, for example, an alcohol solvent, a chlorinated solvent, water, or miscible mixtures thereof. Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l -butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl- 1-propanol, 1,1-dimethyl-1 -propanol, and mixtures thereof. Examples of suitable chlorinated solvents include dichloromethane, 1,2-dichloroethane, and mixtures thereof.

Within the context of the present invention, nintedanib crystalline form-Mi, nintedanib crystalline form-M2, amorphous nintedanib esylate, and solid dispersion of amorphous nintedanib may be formulated into a pharmaceutical dosage form that optionally contain one or more further pharmaceutically acceptable excipients.

BRIEF DESCRIPTION OF THE DRAWINGS

Further aspects of the present disclosure together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of embodiments of the disclosure which are shown in the accompanying drawing figures wherein:

Figure 1 is a powder X-ray diffraction (PXRD) pattern of nintedanib crystalline form-Ml;

Figure 2 is a differential scanning calorimetry (DSC) curve of nintedanib crystalline form-Ml;

Figure 3 is a thermogravimetric analysis (TGA) thermogram of nintedanib crystalline form-Ml;

Figure 4 shows a PXRD pattern of nintedanib crystalline form-M2;

Figure 5 is a DSC curve of nintedanib crystalline form-M2;

Figure 6 is a TGA thermogram of nintedanib crystalline form-M2;

Figure 7 is a PXRD pattern of the amorphous nintedanib esylate;

Figure 8 is a PXRD pattern of a solid dispersion of amorphous nintedanib esylate with 10% w/w PLASDONE S-630;

Figure 9 is a PXRD pattern of a solid dispersion of amorphous nintedanib esylate with 50% w/w PLASDONE S-630; and

Figure 10 is a PXRD pattern of a solid dispersion of amorphous nintedanib esylate with 10% w/w β-cyclodextrin.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure provides crystalline polymorphic forms of nintedanib base designated as nintedanib crystalline form-Ml and nintedanib crystalline form-M2. The present invention also provides processes for preparing each.

The present disclosure also provides a process for the purification of nintedanib base.

The present disclosure further provides amorphous forms of nintedanib esylate and processes for preparing the same.

The present disclosure further also provides solid dispersions of amorphous nintedanib esylate and processes for the preparation of the same.

Within the context of the present invention, the polymorphic forms of nintedanib, including nintedanib crystalline form-Ml and nintedanib form-M2 may be characterized by powder x-ray diffraction (PXRD). Therefore, samples of each were analyzed with a BRUKER D-8 Discover powder diffractometer equipped with a goniometer of Θ/2Θ configuration and Lynx Eye detector. The Cu-anode X-ray tube was operated at 40 kV and 30 mA. The experiments were conducted over the 2Θ range of 2.0°-50.0°, 0.030° step size, and 0.4 seconds step time.

The crystalline polymorphic forms of nintedanib, including nintedanib crystalline form-Ml and nintedanib form-M2 may be further characterized by differential scanning calorimetry (DSC). Therefore, samples of each were analyzed by DSC on a DSC Q 1000 V9.9 Build 303 differential scanning calorimeter instrument. The experiments were performed at a heating rate of 10.0 °C/min over a temperature range of 30 °C - 330 °C, purging with nitrogen at a flow rate of 50 mL/min.

The crystalline polymorphic forms of nintedanib, including nintedanib crystalline form-Ml and nintedanib form-M2 may also be further be characterized by thermal gravimetric analysis (TGA). Therefore, samples of each were analyzed by TGA using a TA Q5000 SA (TA Instruments). The experiments were performed at a heating rate of 10.0 °C/min over a temperature range of ambient - 300 °C, purging with nitrogen at a flow rate of 25 mL/min.

In one aspect, the present invention provides nintedanib crystalline form-Ml.

According to some aspects of the present invention, nintedanib crystalline form-Ml may be characterized by a PXRD pattern with characteristic peaks at angles of 8.3, 11.7, 12.7, 14.7, 15.5, 18.8, 19.4, 20.4, and 21.7 ± 0.2 ^{0} 2Θ.

Nintedanib crystalline form-Ml may be further characterized by a PXRD pattern having characteristic peaks at angles of 6.2, 6.4, 8.3, 9.4, 10.7, 11.7, 12.2, 12.7, 13.4, 14.7, 15.5,

16.4, 16.7, 17.5, 18.3, 18.8, 19.4, 19.7, 20.4, 21.2, 21.7, 22.9, 23.3, 23.7, 24.3, 24.8, 25.6, 26.0, 27.1, 27.9, 28.6, and 30.3 ± 0.2 ^{0} 2Θ. Nintedanib crystalline form-Ml may be further characterized by the PXRD pattern in Figure 1.

According to some aspects of the present invention, nintedanib crystalline form-Ml may be further characterized by a DSC thermogram with peaks at about 129.53 °C and 247.87 °C. Nintedanib crystalline form-Ml may be further characterized by the DSC thermogram shown in Figure 2. As used herein, the term "about" means 10% above or below the value recited.

According to the present invention, nintedanib crystalline form-Ml may further be characterized by the TGA curve in Figure 3. It is believed that the weight loss of 11.80% in Figure 3 corresponds to the loss of solvent. It is thus believed that nintedanib crystalline form-Ml is a tetrahydrofuran solvate of nintedanib. It is further believed that the ratio of nintedanib to tetrahydrofuran in nintedanib crystalline form-Ml is 1:1.

In another aspect, the present invention provides a process for the preparation of nintedanib base crystalline form-Ml.

In one embodiment, nintedanib base crystalline form-Ml may be prepared by a process that includes the following steps:

a) preparing a solution of nintedanib;
b) adding tetrahydrofuran; and
c) isolating nintedanib base crystalline form-Ml.

As a first step in practicing of the present embodiment, a solution of nintedanib may be prepared. In some embodiments, the solution of nintedanib may be prepared by dissolving nintedanib in a solvent.

Examples of suitable solvents include aprotic polar solvents, alcohol solvents, ketone solvents, chlorinated solvents, water, and mixtures thereof. Within the context of this embodiment, examples of suitable alcohol solvents include, but are not limited to, methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, t-butanol, 1-pentanol, 2-pentanol, 3-pentanol, and mixtures thereof. Examples of suitable ketone solvents include, but are not limited to, acetone, methyl ethyl ketone, methyl isobutyl ketone, and mixtures thereof. Examples of suitable chlorinated solvents include, but are not limited to, dichloromethane,

1,1-dichloroethane, 1,2-dichloroethane, and chloroform. Examples of suitable aprotic polar solvent include, but are not limited to, N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), and mixtures thereof.

In particularly useful embodiments, nintedanib is dissolved in dichloromethane. In other particularly useful embodiments, nintedanib is dissolved in dichloromethane at a temperature of about 20 °C to about 25 °C.

In some embodiments, the solution of nintedanib may be prepared *in situ* during the synthesis of nintedanib. Thus, according to this embodiment, the starting nintedanib material may be crude or unpurified. For example, the synthetic route for nintedanib often results in the formation of a protected nintedanib. In some embodiments, the nintedanib is protected on the amine moiety on the indole group of nintedanib. By deprotecting the nintedanib by methods well known in the art, one may prepare a solution of nintedanib suitable for use in the first step of the above disclosed process for preparing nintedanib base crystalline form-Mi.

Within the context of these embodiments, the protected nintedanib may be protected at the amine group on the indole moiety. Suitable amine protecting groups are well known in the art. Examples of suitable amine protecting groups, as well as suitable conditions for protecting and deprotecting, can be found in prior art, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973; T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999; "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981; in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Vol. 15/1, Georg Thieme Verlag, Stuttgart 1974; H.-D. Jakubke and H. Jescheit, "Aminosauren, Peptide, Proteine", Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982; and Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate", Georg Thieme Verlag, Stuttgart 1974.

In some embodiments, nintedanib protected with an acetyl or propionyl is used. In some embodiments, deprotection is carried out with a base. For example, the base may be an inorganic base or an organic base. Examples of suitable inorganic bases include, but are not limited to, alkali metal hydroxides, alkali metal hydrides, alkali metal bicarbonates, alkali metal carbonates, and alkali alkoxides. Examples of suitable organic bases include, but are not limited to, piperidine, pyridine, triethylamine, and N,N-diisopropylethylamine. In some

embodiments, piperidine base is used. Deprotection may be carried out in a solvent, for example, in an alcohol solvent, a chlorinated solvent, water, or miscible mixtures thereof.

In some particularly useful embodiments, once prepared, the nintedanib solution is stirred for about 2 hours to about 4 hours maintaining a temperature of about 20 °C to about 23 °C.

Next, tetrahydrofuran may be added to the nintedanib solution. In some embodiments, it is found that stirring the solution for about 14 hours to about 20 hours while maintaining the temperature at about 20 °C to about 23 °C may result in precipitation of nintedanib base crystalline form-Mi.

Next, nintedanib base crystalline form-Mi may be isolated, for example, by methods well known in the art. For example, the precipitate may be isolated by filtration. The obtained solid may be further treated, for example, by drying, to result in a final product with desired properties suitable for pharmaceutical use.

In another aspect, the present invention provides nintedanib crystalline form-M2.

According to the present invention, nintedanib crystalline form-M2 may be characterized by a PXRD pattern with characteristic peaks at angles of 6.2, 6.9, 11.3, 16.8, 17.3, 18.9, 21.5, and 22.5 ± 0.2 °2Θ. Nintedanib crystalline form-M2 may be further characterized by a PXRD pattern having characteristic peaks at angles of 6.2, 6.9, 11.3, 12.4, 13.0, 13.7, 14.7, 16.0, 16.8, 17.3, 18.9, 19.5, 20.6, 21.1, 21.9, 22.5, 23.4, 24.0, 26.1, 27.5, 28.5, 29.6, and 31.4 ± 0.2 °2Θ. Nintedanib crystalline form-M2 may be further characterized by the PXRD pattern in Figure 4.

According to the present invention, nintedanib crystalline form-M2 may be further characterized by a DSC thermogram with an endotherm peaks at about 150.04 °C and 250.91 °C. Nintedanib crystalline form-M2 may be further characterized by the DSC thermogram shown in Figure 5.

According to the present invention, nintedanib crystalline form-M2 may further be characterized by the TGA curve in Figure 6. It is believed that the weight loss of 8.22% in Figure 6 corresponds to the loss of solvent. It is thus believed that nintedanib crystalline form-M2 is an anisole solvate of nintedanib. It is further believed that nintedanib crystalline form-M2 is a hemianisole solvent of nintedanib (i.e., the ratio of nintedanib to anisole is 2:1).

In another aspect, the present invention provides a process for the preparation of nintedanib base crystalline form-M2.

In one embodiment, nintedanib base crystalline form-M2 may be prepared by a process that includes the following steps:

a) preparing a solution of nintedanib base;
b) adding anisole; and
c) isolating nintedanib base crystalline form-M2

According to this embodiment, a solution of nintedanib base may be prepared. This may be carried out by dissolving nintedanib base in a solvent.

The solvent may be, for example, a polar solvent, a chlorinated solvent, or miscible mixtures thereof. Examples of suitable polar solvents include, for example, alcohol solvents, ketone solvents, aprotic polar solvents, and mixtures thereof. Examples of suitable alcohol solvents include, but are not limited to, methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, pentanol, and mixtures thereof. Examples of suitable ketone solvents include, but are not limited to, acetone, methyl ethyl ketone, methyl isobutyl ketone, and mixtures thereof. Examples of suitable chlorinated solvents include, but are not limited to, dichloromethane, dichloroethane, chloroform, and mixtures thereof. Examples of suitable aprotic polar solvent include, but are not limited to N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), and mixtures thereof.

Within the context of this embodiment, the starting nintedanib material may be a nintedanib solvate or nintedanib base. In some embodiments, starting material is a nintedanib tetrahydrofuran solvate. For example, the starting material may be nintedanib base crystalline form-Mi as described herein. In some embodiments, the nintedanib solvate starting material may be dissolved in a mixture of dichloromethane and methanol. In yet other embodiments, dissolving the nintedanib solvate starting material in dichloromethane/methanol is carried out at a temperature of about 25°C to about 27 °C.

In some embodiments, the solution of nintedanib may be prepared *in situ* during the synthesis of nintedanib. According to this embodiment, the starting material may be a nintedanib solvate. Within the context of this embodiment, a nintedanib solvate is may be any solvent

capable of forming a solvate with nintedanib base such as THF solvate. In some embodiments, the starting nintedanib material may be crude or unpurified. For example, the synthetic route for nintedanib often results in the formation of a protected nintedanib. In some embodiments, the nintedanib is protected on the amine moiety on the indole group of nintedanib. By deprotecting the nintedanib by methods well known in the art, one may prepare a solution of nintedanib suitable for use in the first step of the above-disclosed process for preparing nintedanib base crystalline form-M2.

Within the context of these embodiments, the nintedanib may be protected at the amine group on the indole moiety. Suitable amine protecting groups are well known in the art. Examples of suitable amine protecting groups, as well as suitable conditions for protecting and deprotecting, can be found in prior art, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973; T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999; "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981; in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Vol. 15/1, Georg Thieme Verlag, Stuttgart 1974; H.-D. Jakubke and H. Jescheit, "Aminosauren, Peptide, Proteine", Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982; and Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate", Georg Thieme Verlag, Stuttgart 1974.

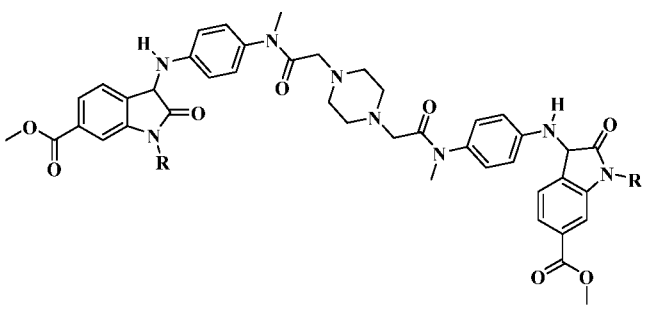
In some embodiments, nintedanib protected with an acetyl or propionyl is used. In some embodiments, deprotection is carried out with a base. For example, the base may be an inorganic base or an organic base. Examples of suitable inorganic bases include, but are not limited to, alkali metal hydroxides, alkali metal hydrides, alkali metal bicarbonates, alkali metal carbonates, and alkali alkoxides. Examples of suitable organic bases include, but are not limited to, piperidine, pyridine, triethylamine, and N,N-diisopropylethylamine. In some embodiments, piperidine base is used. Deprotection may be carried out in a solvent, for example, in an alcohol solvent, a chlorinated solvent, water, or miscible mixtures thereof.

Next, after a solution of nintedanib is prepared, anisole may be added. In some embodiments, the mixture is stirred for about 14 hours to about 20 hours maintaining the temperature at about 25 °C to about 27 °C. In some embodiments, these conditions may lead to precipitation of nintedanib base crystalline form-M2.

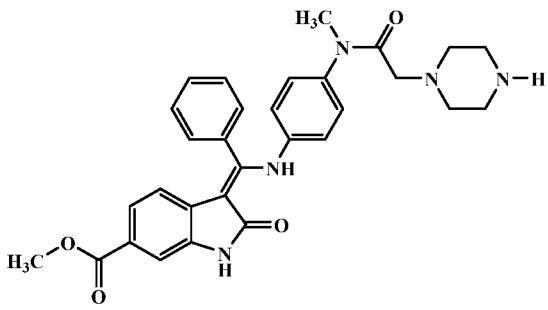
The isolation of nintedanib base crystalline form-M2 may then be carried out by methods well known in the art, for example, by filtering the mixture to isolate a solid. The solid may be further treated, for example, by drying, to result in a final nintedanib product with desired pharmaceutical properties.

Within the context of this invention, the nintedanib starting material used to prepare nintedanib base crystalline form-Mi and nintedanib base crystalline form-M2 may be obtained through the processes disclosed in U.S. Patent Nos. 6,762,180 and US 8,304,541.

It has been found that the process disclosed in U.S. Patent Nos. 6,762,180 and US 8,304,541 may result in the formation of dimer and des-methyl impurities. The structures of the dimer impurity and the des-methyl impurity are shown below:



Dimer impurity
(R is H, acetyl, or propionyl group)



Des-methyl impurity

Therefore, in another aspect, the present invention provides a process for the purification of nintedanib base.

Within the context of this embodiment, the disclosed methods of purification may result in a final product that is substantially free of the dimer impurity and the des-methyl impurity. Within this context, the nintedanib obtained by this purification process may reduce des-methyl and dimer impurities to 0-0.15%.

Within the context of this invention, substantially pure refers to a product where nintedanib is present at 99% or greater and desmethyl and dimer impurities are less than 0.15%.

In one embodiment, nintedanib base may be purified by a process that includes the following steps:

a) desolvating a nintedanib solvate to form a solution; and
b) isolating nintedanib base free from dimer impurity.

According to this embodiment, a nintedanib solvate may be desolvated. Within the context of this embodiment, the solvent in the nintedanib solvate may be any solvent capable of forming a solvate with nintedanib base. For example, in some embodiments, the nintedanib solvate is a tetrahydrofuran solvate, an anisole solvate, or a hemianisole solvate. This desolvation may be carried by first dissolving the nintedanib solvate in a polar solvent such as, for example, an alcohol solvent, a chlorinated solvent, water, or mixture thereof.

Within the context of this embodiment, examples of suitable alcohol solvents include, but are not limited to methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl- 1-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl- 1-propanol, 1,1 -dimethyl- 1-propanol, and mixtures thereof.

Within the context of this embodiment, examples of suitable chlorinated solvents include dichloromethane, 1,2-dichloroethane, and mixtures thereof.

In some embodiments, the nintedanib solvate is dissolved in methanol solvent. In some embodiments, the nintedanib solvate is dissolved in methanol at a temperature of about 25 °C to about 27 °C.

In some embodiments, the solution of nintedanib solvate is stirred for about 14 hours to about 20 hours maintaining the temperature at about 25°C to about 27°C. In some embodiments using these conditions, substantially pure nintedanib base may be prepared.

Within this context, the nintedanib obtained by this purification process may reduce dimer and des-methyl impurities to less than 0.1%

In another aspect, the present disclosure provides an amorphous form of nintedanib esylate and processes for the preparation of the same.

The amorphous form of nintedanib esylate of the present disclosure may be characterized by its PXRD pattern. Thus, the PXRD patterns of the amorphous form of nintedanib esylate were obtained on BRUKER D-8 Discover powder diffractometer equipped with goniometer of Θ/2Θ configuration and Lynx Eye detector. The Cu-anode X-ray tube was operated at 40 kV and 30 niA. The experiments were conducted over the 2Θ range of 2.0°-50.0°, 0.030° step size, and 0.4 seconds step time.

Within the context of the present invention, the amorphous form of nintedanib esylate as prepared by methods disclosed herein may be characterized as amorphous by the PXRD pattern in Figure 7.

Another aspect of the present disclosure provides a process for the preparation of amorphous nintedanib esylate.

In one embodiment, amorphous nintedanib esylate may be prepared by a process that includes the following steps:

a) dissolving nintedanib esylate in a solvent;
b) removing the solvent to isolate the amorphous nintedanib esylate.

According to the present disclosure, nintedanib esylate may be dissolved in a solvent to form a solution. Within the context of the present disclosure, the nintedanib esylate starting material may be any polymorphic form.

Within the context of the present disclosure, the solvent may be, for example, an alcohol solvent, a ketone solvent, a nitrile solvent, a chlorinated solvent, water, or miscible mixtures thereof.

Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 2-2-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl-l -propanol, 1,1,dimethyl- 1-propanol, and mixtures thereof. Examples of suitable ketone solvents include acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, and mixtures thereof. Examples of suitable nitrile solvents include acetonitrile, propionitrile, and mixtures thereof. Examples of suitable chlorinated solvents include dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, and mixtures thereof.

In some embodiments of the present disclosure, dissolving nintedanib esylate in an alcohol solvent is useful. In some embodiments of the present disclosure, dissolving nintedanib esylate in methanol is particularly useful.

According to the present disclosure, the solvent may then be removed from the solution to isolate amorphous nintedanib esylate. This may be carried out by well-known techniques such as, for example, evaporation, distillation, spray drying, lyophilization, agitated thin film drying, or combinations thereof. In certain embodiments of the present disclosure, spray drying is used when removing the solvent.

The amorphous nintedanib esylate when prepared by methods disclosed herein may possess a purity of more than 99% when measured by HPLC.

In another aspect, the present disclosure provides solid dispersions containing amorphous nintedanib esylate and process for the preparation of the same. In certain embodiments, the solid dispersion of amorphous nintedanib esylate may include, for example, amorphous nintedanib esylate and one or more pharmaceutically acceptable excipients. In certain other embodiments, the solid dispersion of amorphous nintedanib esylate consist essentially of, or consist of, amorphous nintedanib esylate and one or more pharmaceutically acceptable excipients.

Another aspect of the present disclosure provides a method for preparing a solid dispersion of amorphous nintedanib esylate.

In one embodiment, a solid dispersion of amorphous nintedanib esylate may be prepared by a process that includes the following steps:

a) preparing a solution of nintedanib esylate and one or more pharmaceutically acceptable excipients in a solvent; and
b) removing the solvent to isolate a solid dispersion of amorphous nintedanib esylate.

According this embodiment, a solution of nintedanib esylate and one or more pharmaceutically acceptable excipients is prepared. Within the context of this embodiment, this may be carried out by adding nintedanib esylate and the one or more excipients to a solvent at the same time or sequentially in any order. The pharmaceutically acceptable excipients may be added to the solvent as a solid or as a solution in which the

pharmaceutically acceptable excipients are dissolved. Similarly, the nintedanib esylate may be added to the solvent as a solid or as a solution in which the nintedanib esylate is dissolved. The solvent used to dissolve the pharmaceutically acceptable excipient and nintedanib esylate may be different from or the same as the solvent used for the generation of amorphous nintedanib esylate described above.

The nintedanib esylate starting material may be any polymorphic form or amorphous. Within the context of the present disclosure, the solvent may be, for example, the same or different as those listed above for use in the preparation of amorphous nintedanib esylate. Suitable examples of solvents include alcohol solvents, a ketone solvents, nitrile solvents, chlorinated solvents, water, and mixtures thereof.

Examples of suitable alcohol solvents include methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl- 1-propanol, 1,1 -dimethyl- 1-propanol, and mixtures thereof. Examples of suitable ketone solvents include acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, and mixtures thereof. Examples of suitable nitrile solvents include acetonitrile, propionitrile, and mixtures thereof. Examples of suitable chlorinated solvents include dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, carbon tetrachloride, and mixtures thereof.

In some embodiments of the present disclosure, an alcohol solvent is used. In some embodiments of the present disclosure, methanol is used.

Examples of suitable pharmaceutically acceptable excipients include, but are not limited to, polysaccharides, polyvinylpyrrolidone, polyvinyl acetate (PVAC), polyvinyl alcohol (PVA), polymers of acrylic acid and their salts, polyacrylamide, polymethacrylates, vinylpyrrolidone-vinyl acetate copolymers, Ci-C_6 polyalkylene glycols (e.g., polypropylene glycol, polyethylene glycol), copolymers of polyethylene glycol and polypropylene glycol (e.g., the families of block copolymers based on ethylene oxide and propylene oxide sold under the PLURONIC® tradename), and mixtures thereof. Suitable polysaccharides include, for example, microcrystalline cellulose, hydroxypropyl methylcellulose (HPMC), croscarmellose, carboxymethyl cellulose (CMC) and salts thereof, methyl cellulose, hydroxyethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose (HPC), optionally substituted a-cyclodextrins, optionally substituted β-cyclodextrins (e.g.,

hydroxypropyl β-cyclodextrin), optionally substituted γ-cyclodextrins (e.g., hydroxypropyl γ-cyclodextrin)and mixtures thereof. As used herein, the term "substituted" with respect to cyclodextrin means the addition of side chain groups such as hydroxyl, hydroxypropyl, and other CrC $_6$ alkyl and Ci-C$_6$ hydroxyalkyl.

According to the present disclosure, the solvent may then be removed from the solution to isolate a solid dispersion of amorphous nintedanib esylate. This may be carried out by well-known techniques, for example, evaporation, distillation, spray drying, lyophilization, agitated thin film drying, or combinations thereof. In certain embodiments of the present disclosure, the technique of spray drying is particularly useful for removing the solvent.

Within the context of this embodiment of the present disclosure, the pharmaceutically acceptable excipient may be combined with the solution of nintedanib esylate from about 5 % w/w (pharmaceutically acceptable excipient/total composition mass) to about 90 % w/w, which may be about 10% w/w, 15% w/w, 20% w/w, 25% w/w, 30% w/w, 35% w/w, 40% w/w, 45% w/w, 50% w/w, or between any of the aforementioned w/w percentages, including the ranges of about 10%-40%, 10%-30%, 10%-20%, 20%-50%, 20%-40%, 20%-30%, 30%-50%, 30%-40%, and 40%-50% w/w.

In some embodiments, it was found that using vinylpyrrolidone-vinyl acetate copolymer, polyvinylpyrrolidone, or a cyclodextrin (e.g., an optionally substituted a-cyclodextrin, an optionally substituted β-cyclodextrin, or an optionally substituted γ-cyclodextrin) permitted the generation of useful nintedanib esylate solid dispersions. Within the context of the present invention, povidone with K-values ranging from about 12 to about 103 may be useful, including povidone K-12, povidone K-15, povidone K-17, povidone K-25, povidone K-30, povidone K-90, and mixtures thereof. One of skill in the art would readily recognize different forms of povidone that would be useful and how each form may confer desired properties to the final dosage form.

In particularly useful embodiments of the present disclosure, a copolymer of N-vinyl-2-pyrrolidone and vinyl acetate may be utilized as the pharmaceutically acceptable excipients added to the nintedanib esylate solution. Suitable examples of copolymers include a copolymer of N-vinyl-2-pyrrolidone and vinyl acetate with a mass ratio of 60:40 (e.g., PLASDONE S-630 or KOLLIDON® VA 64).

Therefore, another aspect of the present disclosure provides a solid dispersion of amorphous nintedanib esylate with PLASDONE-630. In certain embodiments, nintedanib esylate is combined with PLASDONE-630 at a ratio of 10% w/w, 25% w/w, or 50% w/w. For example, PXRD patterns of a solid dispersion of amorphous nintedanib esylate combined with 10% w/w and 50% w/w PLASDONE S-630 are shown in Figures 8 and 9, respectively.

In other embodiments, polyvinylpyrrolidone is used as the pharmaceutically acceptable excipient. In further embodiments, polyvinylpyrrolidone with a K-value of about 30 and an average molecular weight of 40 kDa (i.e., povidone K-30) is used as the pharmaceutically acceptable excipient. In other embodiments of the present disclosure, combining polyvinylpyrrolidone (e.g., a polyvinylpyrrolidone with a K-value of 30) with nintedanib esylate at concentrations recited above, including from about 10% to 50% w/w, is used.

As used herein, the term "molecular weight" means the weight-averaged molecular weight (M_w).

In yet other particularly useful embodiments of the present disclosure, β-cyclodextrin or hydroxypropyl -P-cyclodextrin may be employed as the pharmaceutically acceptable excipient. Therefore, another aspect of the present disclosure provides a solid dispersion of amorphous nintedanib esylate with β-cyclodextrin. In yet other embodiments of the present disclosure, combining β-cyclodextrin with nintedanib esylate at concentrations recited above, including from about 10% to 50% w/w, is used.

Therefore, another embodiment of the present disclosure provides a solid dispersion of amorphous nintedanib esylate with 50% w/w β-cyclodextrin. As an example, Figure 10 shows a PXRD pattern of a solid dispersion of amorphous nintedanib esylate combined with 50% w/w β-cyclodextrin.

The amorphous nintedanib esylate solid dispersions of the present disclosure possess several benefits useful in formulations of nintedanib esylate. For example, the amorphous nintedanib esylate solid dispersions are particularly stable and may possess superior pharmaceutical workability (e.g., tackiness, flowability) and may permit the use of formulation techniques, such as dry and/or wet granulation. As such, the amorphous nintedanib esylate solid dispersions are easily utilized in the generation of pharmaceutical formulations. In using the amorphous nintedanib esylate solid dispersions described herein, one of ordinary skill in the

art is now able to generate stable formulations containing amorphous nintedanib esylate solid dispersions efficiently and effectively.

With all of the reactions and processes disclosed above, one of skill in the art will recognize that the reaction conditions (e.g., reaction time, temperature) may be adjusted to achieve appropriate yield without undertaking undue experimentation and without departing from the scope of the present disclosure.

According to the present disclosure, a solid dispersion of amorphous nintedanib esylate disclosed herein prepared according to the present disclosure may have HPLC purity of more than 99% (i.e., the solid dispersion contains 1% or less of impurities or components other than amorphous nintedanib esylate or excipients).

In some embodiments, solid dispersions of amorphous nintedanib esylate with PLASDONE-630 prepared according to the present disclosure may have HPLC purity of more than 99% (i.e., the solid dispersion contains 1% or less of impurities or components other than amorphous nintedanib esylate or PLASDONE-630).

Within the context of the present disclosure, the solid dispersion of amorphous nintedanib esylate with PLASDONE S-630 may exhibit long-term physical and chemical stability. As an example, Table 1 below shows data collected on solid dispersions of amorphous nintedanib esylate with 10% w/w PLASDONE S-630 and 50% w/w PLASDONE S-630, each prepared according to the processes disclosed herein. The data demonstrate that the solid dispersions of amorphous nintedanib esylate that include PLASDONE S-630 show no significant degradation or change in PXRD pattern (e.g., is stable at 1, 3 and 6 months storage) when stored for 6 months at 5 ± 3 °C or at 25 °C/60% relative humidity (RH). In certain particularly effective embodiments, the solid dispersion of amorphous nintedanib esylate and PLASDONE S-630 displayed less than 1% degradation over six months under those conditions.

The purity of solid dispersions of amorphous nintedanib esylate, prepared by methods disclosed herein may be analyzed by HPLC. Therefore, samples of solid dispersions of amorphous nintedanib esylate were analyzed by HPLC. HPLC purity analyses were carried out on an X-bridge BEH C18 column (100 x 4.6 mm, 2.5μιη) (but may be carried out in some embodiments using any equivalent) using a UV detector set at 210 nm with a column oven

temperature of about 30 °C. A flow rate of 1.0 mL/min with an injection volume of 10 µL was used, with a run time of approximately 25 minutes.

TABLE 1

Storage Time	10% w/w PLASDONE S-630		50% w/w PLASDONE S-630	
	HPLC purity (%)	PXRD	HPLC purity (%)	PXRD
at 25 °C/60% RH				
Initial	99.86	Amorphous	99.86	Amorphous
1 month	99.71	Stable	99.72	Stable
3 months	99.77	Stable	99.68	Stable
6 months	99.79	Stable	99.72	Stable
at 5 ± 3 °C				
Initial	99.86	Amorphous	99.86	Amorphous
1 month	99.70	Stable	99.71	Stable
3 months	99.77	Stable	99.70	Stable
6 months	99.78	Stable	99.75	Stable

Solid dispersions of amorphous nintedanib esylate that include β-cyclodextrin prepared according to the present disclosure may have HPLC purity of more than 99% (i.e., the solid dispersion contains 1% or less of impurities or components other than amorphous nintedanib esylate or β-cyclodextrin).

Within the context of the present disclosure, the solid dispersion of amorphous nintedanib with β-cyclodextrin may exhibit long-term physical and chemical stability. As an example, Table 2 below shows data collected on the solid dispersion of amorphous nintedanib esylate with 50% w/w β-cyclodextrin prepared according to the processes disclosed in the present disclosure. The data demonstrate that the solid dispersions of amorphous nintedanib esylate that include 50% w/w β-cyclodextrin tested show no significant degradation or change in PXRD pattern (e.g., is stable at 1, 3 and 6 months storage) when stored for up to 6 months at 5 ± 3 °C or at 25 °C/60% relative humidity (RH). In certain particularly effective embodiments, the solid dispersion of amorphous nintedanib esylate and a β-cyclodextrin displayed less than 1% degradation over six months under those conditions.

TABLE 2

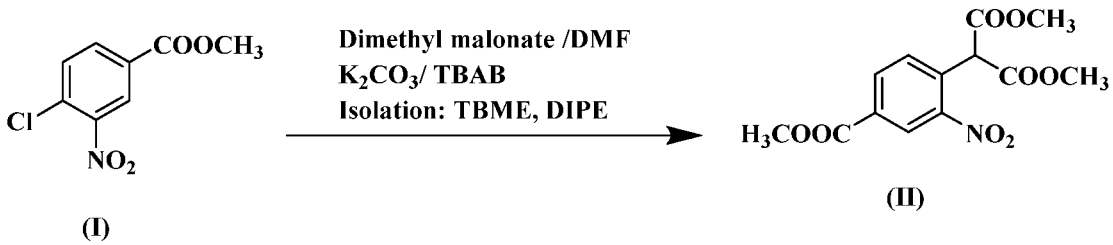
Storage time	50% w/w β-cyclodextrin	
	HPLC purity (%)	PXRD
at 25 °C/60% RH		
Initial	99.79	Amorphous
1 months	99.53	Stable
3 months	99.53	Stable
6 months	99.62	Stable
at 5 ± 3°C		
Initial	99.79	Amorphous
2 months	99.58	Stable
3 months	99.50	Stable
6 months	99.71	Stable

The crystalline forms of nintedanib, including form-Ml and form-M2, amorphous nintedanib esylate and solid dispersions of amorphous nintedanib disclosed herein may be may be useful in the treatment of idiopathic pulmonary fibrosis (IPF). The crystalline forms of nintedanib, including form-Ml and form-M2, amorphous nintedanib esylate and solid dispersions of amorphous nintedanib may be formulated as a capsule or a tablet for consumption by patients. Tablets or capsules may contain one or more inactive ingredients, including, for example, triglycerides, hard fat, lecithin, and mixtures thereof. That tablet or capsule, in some embodiments, may be coated with a film that includes gelatin, glycerol, titanium dioxide, and artificial colorings such as red ferric oxide, yellow ferric oxide, and inks, such as black ink.

In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of molecules according to the present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive, but merely illustrative of only a few of the many aspects and embodiments contemplated by the present disclosure.

EXAMPLES

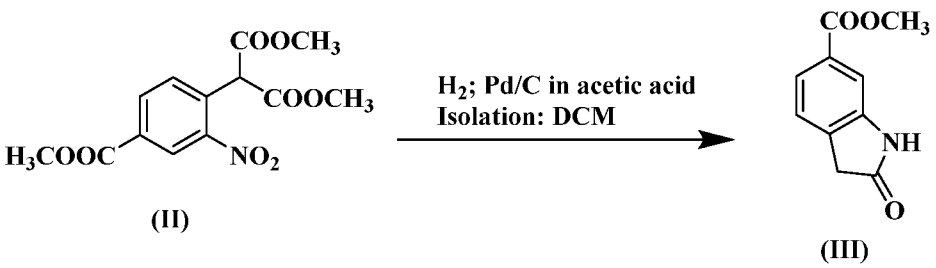
Example 1: Preparation of methyl-4-methoxycarbonylmethyl-3-nitro benzoate of formula (II)



(I) (II)

4-chloro-3-nitro methyl benzoate (formula I, 100 g) was dissolved in dimethylformamide (250 mL). Potassium carbonate (128 g) in dimethylformamide (300 mL) was added to the reaction mass and the reaction mass was stirred for 10-15 minutes. Dimethyl malonate (91.96 g) and tetrabutylammonium bromide (1 g) were added to the reaction mass and the temperature was raised to about 62 °C to 65 °C. The reaction mass was stirred for about 10-12 hours. Next, the reaction mass was cooled to 30 °C to 35 °C and filtered. Concentered hydrochloric acid (75 mL) was added to the filtrate which was then stirred for about 1 hour. Tert-butyl methyl ether (1 L) was added and the mixture was stirred for about 1 hour. The organic layer was separated from the aqueous layer and concentrated. Tert-butyl methyl ether (400 mL) was added and the reaction mass was stirred to form a clear solution. Diisopropyl ether (300 mL) was added to the clear solution and the mixture was cooled to 5 °C, resulting in the precipitation of the product. The mixture was filtered to obtain a solid which was dried at 40-43 °C.

Example 2: Preparation of methyl-2-indolinone-6-carboxylate (III)

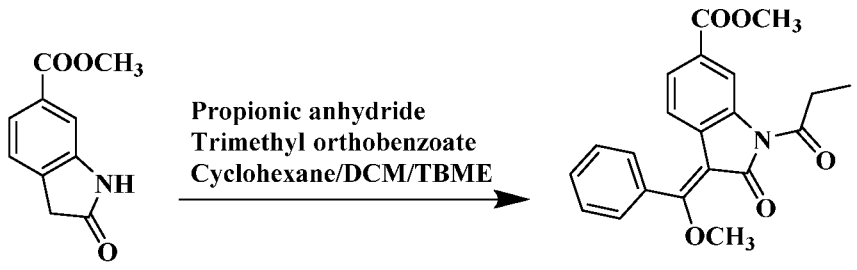


(II) (III)

Compound (II) (100 g) in acetic acid (IM, 1 L) was autoclaved. The solution was stirred for about 15-20 minutes to obtain a clear solution. 10 % Pd/C (10 g in 1 M 100 mL acetic acid) was added and pressure was applied using hydrogen (5 kg/cm^2). The temperature was further

raised to about 45 °C to 48 °C. The reaction mass was stirred maintaining pressure of under 4-5 kg/cm^2 for about 9-10 hours. After the reaction was completed, the reaction mass was cooled and filtered through a Hyflo bed. The filtrated was concentrated under vacuum distillation to obtain a thick slurry mass. Dichloromethane (200 mL) was added to the slurry mass, and the mixture was stirred for about 1 hour, resulting in the titled product. The mixture was filtered to obtain a solid which was dried at 50-53 °C.

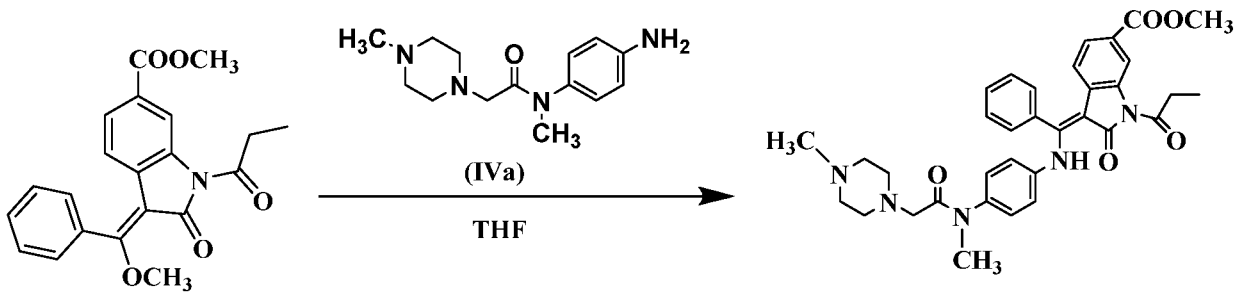
Example 3: Preparation of l-priopionyl-3-(l-ethoxy-l-phenylmethylene)-6-ethoxycarbonyl-2-indolinone-propionyl ether (IV)



(III) (IV)

Propionic anhydride (1.5 L) was added to compound (III) (100 g) under nitrogen atmosphere. The temperature of the reaction mixture was raised to 105 °C. Trimethyl orthobenzoate (800 mL) was added dropwise over about 2 hours maintaining the reaction under nitrogen atmosphere. The reaction mass was stirred for about 15 hours until the reaction was complete. The solution was concentrated under vacuum. Cyclohexane (1.3 L) was then added to the slurry. The reaction mixture was cooled to -3°C and stirred for about 1 hour before filtering. The obtained solid was dissolved in dichloromethane (700 mL) and tert-butyl methyl ether (1.4 L) was added. The reaction mixture was cooled to -3 °C and stirred for about 1 hour, resulting in the titled product. The mixture was filtered and the solid was dried at 40-45 °C.

Example 4: Preparation of propionyl protected nintedanib (V)

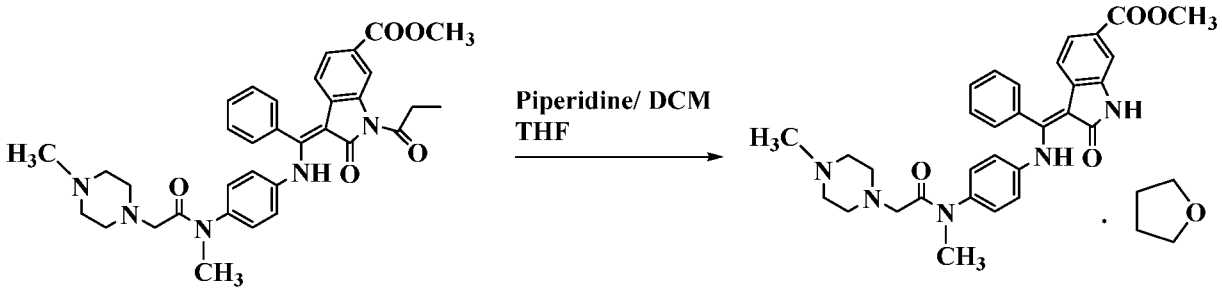


(IV)

Propionyl protected nintedanib (V)

Compound (IV) (100 g) was dissolved in tetrahydrofuran (2 L). N-(4-aminophenyl)-N-methyl-2-(4-methylpiperazin-l-yl)acetamide (IVa) (70.37 g) was added to the reaction mass. The temperature was to about 60°C to 63°C and the reaction mass was stirred for about 15 hours until the reaction was complete. The reaction mass was then cooled to 0°C then stirred for about 1 hour to result in the titled product. The solution was filtered and the obtained solid was dried at 40-45 °C.

Example 5: Preparation of nintedanib THF solvate

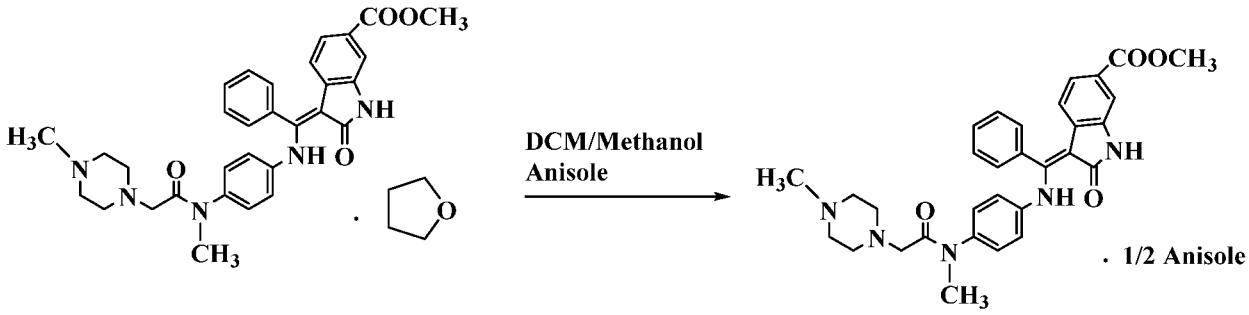


Propionyl protected nintedanib (V)

Nintedanib THF solvate

Propionyl protected nintedanib (100 g) was dissolved in dichloromethane (1 L) at 23 °C. Piperdine (75 mL) was slowly added to the solution and stirred the reaction mixture for about 2-3 hours. Tetrahydrofuran (THF, 500 mL) was added to the solution and the reaction mass was stirred for about 15-16 hours. The reaction mass was filtered and the obtained solid was dried at 40-43 °C.

Example 6: Preparation of nintedanib hemianisole solvate

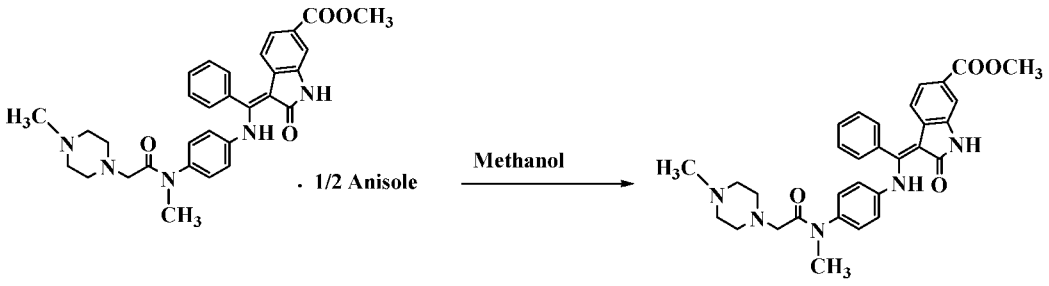


Nintedanib THF solvate

Nintedanib hemi anisole solvate

Nintedanib THF solvate (100 g) was dissolved in a mixture of dichloromethane (500 mL) and methanol (40 mL) at 27 °C. Anisole (1 L) was added to the solution and the reaction mass was stirred for about 15-16 hours. The solution was filtered and the resulting solid was dried to result in the titled compound.

Example 7: Purification of nintedanib base



Nintedanib hemi anisole solvate **Pure Nintedanib base**

Nintedanib anisole solvate (from example 2) was dissolved in methanol (700 mL). The reaction mass was stirred for about 15-16 hours. The solution was filtered and the obtained solid was washed with pre-cooled methanol (150 mL, 15 ± 5 °C) and dried to result in nintedanib base.

Desmethyl impurity is completely eliminated in final nintedanib base product and dimer impurity level in final nintedanib base product is less than 0.01%

Example 8: Preparation of amorphous nintedanib esylate

Nintedanib esylate (5.0 g) was dissolved in methanol (150 mL) at 60-65 °C. The solution was filtered through a Hyflo bed to remove any undissolved particulate. The clear filtrate was cooled to 25-30 °C and subjected to spray drying in a laboratory Spray Dryer (Model Buchi-290) with a feed rate of the solution 5 mL/min and inlet temperature at 75 °C with 100% aspiration to yield the amorphous form of nintedanib esylate.

Yield- 3.2g.

Example 9: Preparation of nintedanib esylate amorphous solid dispersion with PLASDONE S-630 (10%)

Nintedanib esylate (8.0 g) and PLASDONE S-630 (0.889 g) were dissolved in methanol (240 mL) at 60-65 °C. The solution was filtered through a Hyflo bed to remove any undissolved particulate. The clear filtrate was cooled to 25-30 °C and subjected to spray drying in a laboratory Spray Dryer (Model Buchi-290) with a feed rate of the solution 5 mL/min and inlet temperature at 75 °C with 100% aspiration to yield an amorphous solid dispersion of nintedanib esylate.

Yield- 5.3g.

Example 10: Preparation of nintedanib esylate amorphous solid dispersion with PLASDONE S-630 (50%)

Nintedanib esylate (8.0 g) and PLASDONE S-630 (8.0 g) were dissolved in methanol (240 mL) at 60-65 °C. The solution was filtered through a Hyflo bed to remove any undissolved particulate. The clear filtrate was cooled to 25-30 °C and subjected to spray drying in a laboratory Spray Dryer (Model Buchi-290) with a feed rate of the solution 5 mL/min and inlet temperature at 75 °C with 100% aspiration to yield an amorphous solid dispersion of nintedanib esylate.

Yield- 10.8g.

Example 11: Preparation of nintedanib esylate amorphous solid dispersion with β-cyclodextrin (10%)

Nintedanib esylate (5.0 g) was dissolved in methanol (180 mL) at 60-65 °C and cooled to 25-30°C. In another flask, β-cyclodextrin (0.55 g) was dissolved in water (20 mL) at 75-80 °C and cooled to 25-30 °C. Both the solutions were combined and filtered through a Hyflo bed to remove any undissolved particulate. The clear filtrate was cooled to 25-30 °C and subjected to spray drying in a laboratory Spray Dryer (Model Buchi-290) with a feed rate of the solution 5 mL/min and inlet temperature at 75 °C with 100% aspiration to yield an amorphous solid dispersion of nintedanib esylate.

Yield- 4.0g

We claim:

1. Amorphous nintedanib esylate.

2. The amorphous nintedanib esylate according to claim 1, characterized by the powder X-ray diffraction pattern shown in Figure 7.

3. A process for preparing amorphous nintedanib esylate, comprising the steps of:
    a. dissolving nintedanib esylate in a solvent or mixture of solvents; and
    b. removing the solvent to isolate amorphous nintedanib esylate.

4. The process according to claim 3, wherein the solvent is selected from the group consisting of an alcohol solvent, a ketone solvent, a nitrile solvent, a chlorinated solvent, water, and miscible mixtures thereof.

5. The process according to claim 4, wherein the alcohol solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, n-butanol, sec-butanol, 2-butanol, t-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 2-methyl-l-butanol, 2-2-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl-l-propanol, 1,1,dimethyl- 1-propanol, and mixtures thereof.

6. The process according to claim 4, wherein the ketone solvent is selected from the group consisting of acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, and mixtures thereof.

7. The process according to claim 4, wherein the nitrile solvent is selected from the group consisting of acetonitrile, propionitrile, and mixtures thereof.

8. The process according to claim 4, wherein the chlorinated solvent is selected from the group consisting of dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, and mixtures thereof.

9. A process for preparing a solid dispersion containing amorphous nintedanib esylate comprising:
   a. dissolving nintedanib esylate and a pharmaceutically acceptable excipient in a first solvent to form a solution; and
   b. removing the first solvent to isolate the solid dispersion containing amorphous nintedanib esylate.

10. A process for preparing a solid dispersion containing amorphous nintedanib esylate comprising:
   a. dissolving nintedanib esylate in a first solvent to form a first solution;
   b. dissolving a pharmaceutically acceptable excipient in a second solvent to form a second solution; and
   c. combining the first and second solutions to form a combined solution comprising the first and second solvents; and
   d. removing the first and second solvents from the combined solution to isolate the solid dispersion containing amorphous nintedanib esylate.

11. The process according to claims 9 or 10 wherein the first and second solvents are independently selected from the group consisting of an alcohol solvent, a ketone solvent, a chlorinated solvent, a nitrile solvent, water, and miscible mixtures thereof.

12. The process according to claim 11 wherein the alcohol solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, n-butanol, sec-butanol, 2-butanol, t-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-l-butanol, 2-methyl-l-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl-l-propanol, 1,1-dimethyl-1-propanol, and mixtures thereof.

13. The process according to claim 11, wherein the ketone solvent is selected from the group consisting of acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone, and mixtures thereof.

14. The process according to claim 11, wherein the chlorinated solvent is selected from the group consisting of dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, and mixtures thereof.

15. The process according to claim 11, wherein the nitrile solvent is selected from the group consisting of propionitrile, acetonitrile, and mixtures thereof.

16. The process according to any one of claims 3-15, wherein the solvent is removed by evaporation, distillation, spray drying, lyophilization, agitated thin film drying, or a combination thereof.

17. The process according to claim 9 or 10, wherein the pharmaceutically acceptable excipient is selected from the group consisting of polysaccharides, polyvinylpyrrolidone, polyvinyl acetate, polyvinyl alcohol, polymers of acrylic acid

and salts thereof, polyacrylamide, polymethacrylates, vinylpyrrolidone-vinyl acetate copolymers, Ci-C_6 polyalkylene glycols, and mixtures thereof.

18. The process according to claim 11, wherein the polysaccharide is selected from the group consisting of hydroxypropyl methyl cellulose, croscarmellose, carboxymethyl cellulose, a sodium salt of carboxymethyl cellulose, a calcium salt of carboxymethyl cellulose, methyl cellulose, hydroxyethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, microcrystalline cellulose, optionally substituted a-cyclodextrins, optionally substituted β-cyclodextrins, optionally substituted γ-cyclodextrins, and mixtures thereof.

19. The process according to claim 11, wherein the vinylpyrrolidone-vinyl acetate copolymer comprises N-vinyl-2-pyrrolidone and vinyl acetate in a 60:40 ratio, by mass.

20. The process according to claim 11, wherein the Ci-C_6 polyalkylene glycol is selected from the group consisting of polyethylene glycol, polypropylene glycol, and mixtures thereof.

21. The process according to claim 18, wherein said optionally substituted cyclodextrin is selected from the group consisting of β-cyclodextrin, hydroxypropyl -P-cyclodextrin, and mixtures thereof.

22. The process according to claim 10, wherein the first solvent and the second solvent are the same.

23. A solid dispersion, comprising amorphous nintedanib esylate and a pharmaceutically acceptable excipient.

24. The solid dispersion of claim 23, wherein the pharmaceutically acceptable excipient is a polyvinylpyrrolidone-vinyl acetate copolymer with a ratio of 60:40 polyvinylpyrrolidone to vinyl acetate by mass.

25. The solid dispersion of claim 23, wherein the pharmaceutically acceptable excipient is PLASDONE S-630.

26. The solid dispersion of claim 23, wherein the pharmaceutically acceptable excipient is β-cyclodextrin.

27. The solid dispersion of any of claims 23 - 26, wherein the solid dispersion degrades less than about 1% when the solid dispersion is stored for three months at 5 ± 3 °C.

28. The solid dispersion of any of claims 23 - 26, wherein the solid dispersion degrades less than about 1% when the solid dispersion is stored for three months at 25 °C and at 60% relative humidity.

29. An oral pharmaceutical dosage form comprising amorphous nintedanib esylate.

30. An oral pharmaceutical dosage form comprising a solid dispersion of amorphous solid dispersion and a pharmaceutically acceptable excipient.

31. Nintedanib crystalline form-Ml.

32. The nintedanib crystalline form-Ml according to claim 31, characterized by a powder X-ray diffraction pattern having peaks at 8.3, 11.7, 12.7, 14.7, 15.5, 18.8, 19.4, 20.4, and 21.7 (+) 0.2 °2Θ.

33. A process for preparing nintedanib crystalline form-Ml, comprising the steps of:

a. preparing nintedanib in a solvent;

b. adding tetrahydrofuran; and

c. isolating nintedanib crystalline form-Mi.

34. A process for preparing nintedanib crystalline form-Mi, comprising the steps of:

a. deprotecting a protected nintedanib in a solvent;

b. adding tetrahydrofuran; and

c. isolating nintedanib crystalline form-Mi.

35. The process according to claim 33, wherein the solvent is selected from the group consisting of an alcohol solvent, a chlorinated solvent, an aprotic polar solvent, a ketone solvent, water, and miscible mixtures thereof.

36. The process according to claim 34, wherein the solvent is selected from the group consisting of an alcohol solvent, a chlorinated solvent, water, and miscible mixtures thereof.

37. The process according to claim 35 or 36, wherein the alcohol solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, t-butanol, 1-butanol, 2-butanol, 1-pentanol, 2-pentanol, 3-pentanol, and mixtures thereof.

38. The process according to claim 35 or 36, wherein the chlorinated solvent is selected from the group consisting of dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform, and mixtures thereof.

39. The process according to claim 35, wherein the aprotic polar solvent is selected from the group consisting of N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), and mixtures thereof.

40. The process according to claim 35, wherein the ketone solvent is selected from the group consisting of acetone, methyl ethyl ketone, methyl isobutyl ketone, and mixtures thereof.

41. The process according to claim 34, wherein the protected nintedanib is protected at the amine group on the indole ring by an amine-protecting group.

42. Nintedanib crystalline form-M2.

43. The nintedanib crystalline form-M2 according to claim 41, characterized by a powder X-ray diffraction pattern having peaks at 6.2, 6.9, 11.3, 16.8, 17.3, 18.9, 21.5, and 22.5 (+) 0.2 ^{0} 2Θ.

44. A process for preparing nintedanib crystalline form-M2, comprising the steps of:

a. dissolving nintedanib base in a solvent;

b. adding anisole; and

c. isolating nintedanib crystalline form-M2.

45. A process for preparing nintedanib crystalline form-M2, comprising the steps of:

a. deprotecting a protecting nintedanib in a solvent;

b. adding anisole; and

c. isolating nintedanib crystalline form-M2.

46. The process according to claim 44, wherein the solvent is selected from the group consisting of an alcohol solvent, a chlorinated solvent, an aprotic polar solvent, a ketone solvent, an ether solvent, water, and mixtures thereof.

47. The process according to claim 45, wherein the solvent is selected from the group consisting of an alcohol solvent, a chlorinated solvent, water, and mixtures thereof.

48. The process according to claims 46 or 47, wherein the alcohol solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, pentanol, and mixtures thereof.

49. The process according to claim 46 or 47, wherein the chlorinated solvent is selected from the group consisting of dichloromethane, 1,1-dichloroethane, 1,2-dichloroethane, chloroform and mixtures thereof.

50. The process according to claim 46, wherein the aprotic polar solvent is selected from the group consisting of N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), and mixtures thereof.

51. The process according to claim 46, wherein the ketone solvent is selected from the group consisting of acetone, methyl ethyl ketone, methyl isobutyl ketone, and mixtures thereof.

52. The process according to claim 46, wherein the ether solvent is selected from the group consisting of tetrahydrofuran, dimethyl ether, diethyl ether, dioxane, and mixtures thereof.

53. The process according to claim 45, wherein the protected nintedanib is protected at the amine group on the indole ring by an amine-protecting group.

54. The process according to claim 45, wherein the deprotection of the protected nintedanib is carried out with a base.

55. The process according to claim 54, wherein the base is an inorganic base or an organic base.

56. The process according to claim 55, wherein the inorganic base is selected from the group consisting of alkali metal hydroxides, alkali metal hydrides, alkali metal bicarbonates, alkali metal carbonates, and alkali alkoxides.

57. The process according to claim 55, wherein the organic base is selected from the group consisting of piperidine, pyridine, triethylamine, and N,N-diisopropylethylamine.

58. A process for the purification of nintedanib base which is substantially free from dimer and des-methyl impunity of nintedanib, comprising the steps of:

a. desolvating a nintedanib solvate; and
b. isolating nintedanib base which is substantially free from dimer and des-methyl impurity.

59. The process according to claim 58, wherein the desolvating of the nintedanib solvate is carried out in a solvent.

60. The process according to claims 59, wherein the solvent is selected from the group consisting of an alcohol solvent, a chlorinated solvent, water, and mixtures thereof.

61. The process according to claims 60, wherein the alcohol solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, 1-butanol, 2-butanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl- 1-butanol, 3,3-methyl-2-butanol, 3-methyl-2-butanol, 2,2-dimethyl-l -propanol, 1,1 -dimethyl- 1-propanol, and mixtures thereof.

62. The process according to claim 60, wherein the chlorinated solvent is selected from the group consisting of dichloromethane, 1,2-dichloroethane, and mixtures thereof.

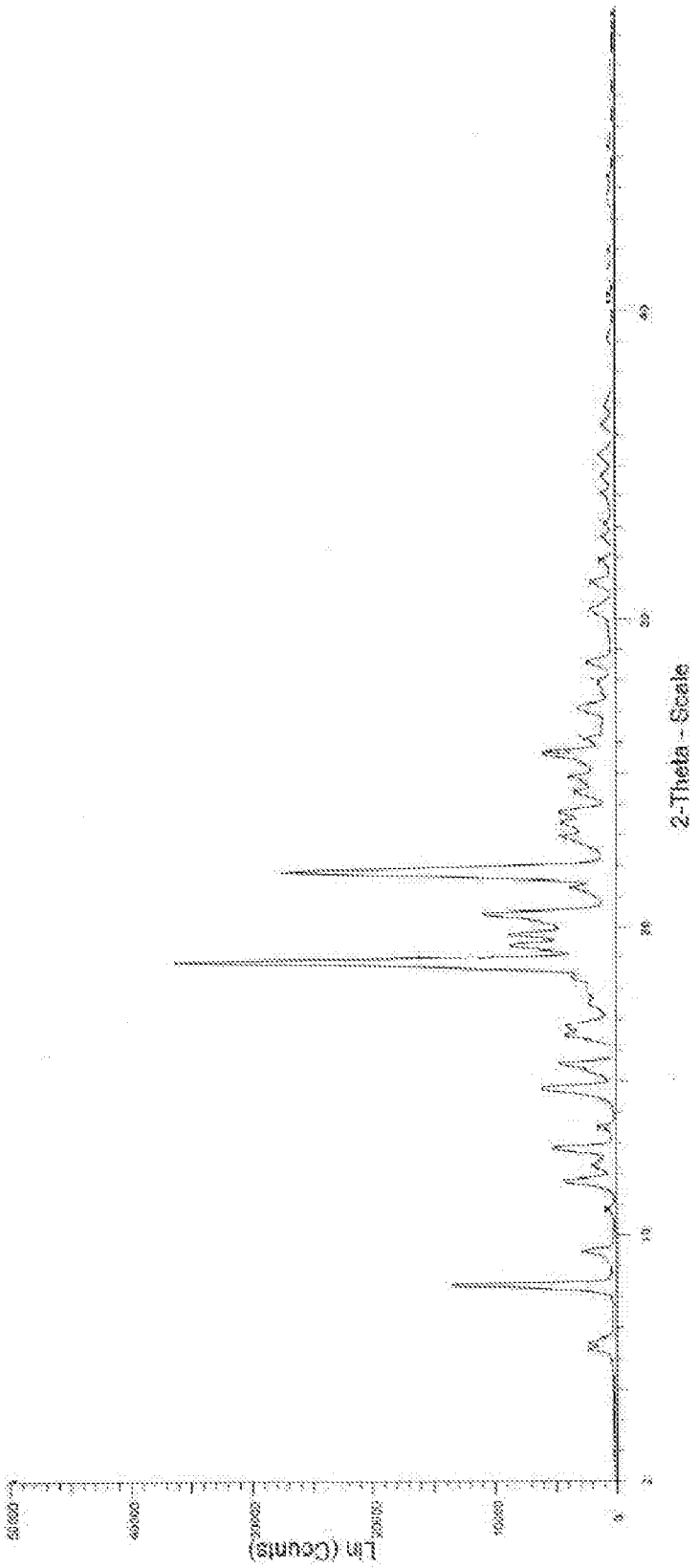


Figure 1: PXRD of Nintedanib base crystalline form M-1

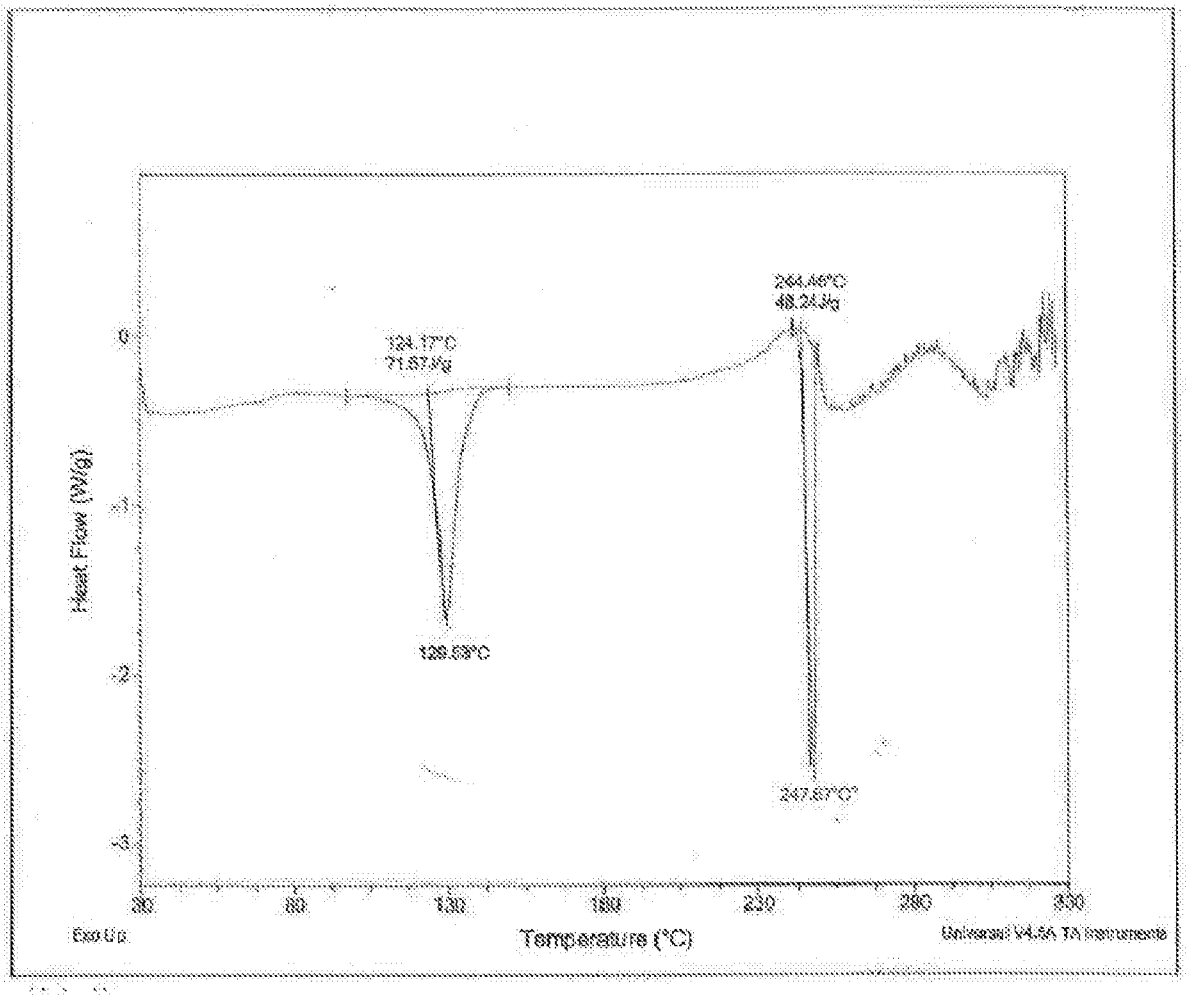
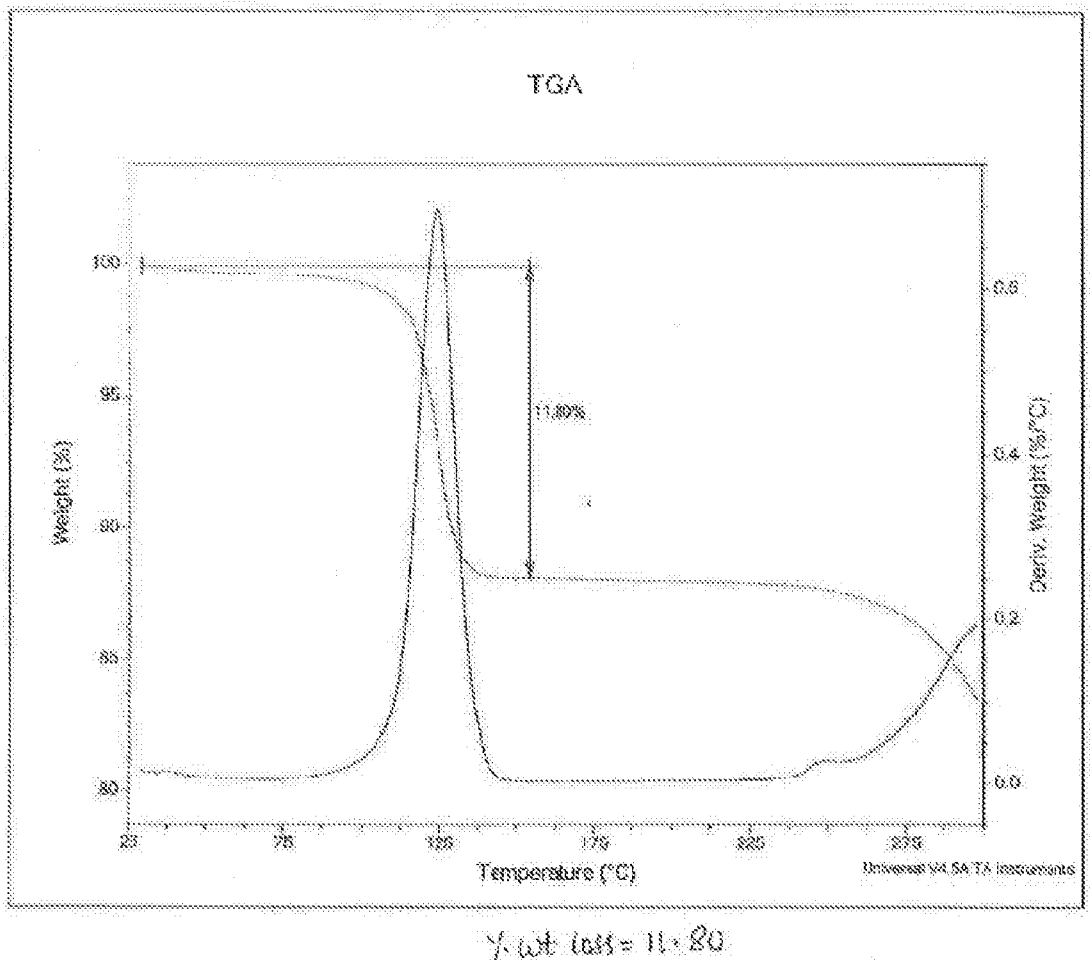


Figure 2: DSC of Nintedanib base crystalline form M-1



% wt loss = 11.80

Figure 3: TGA of Nintedanib base crystalline form M-1

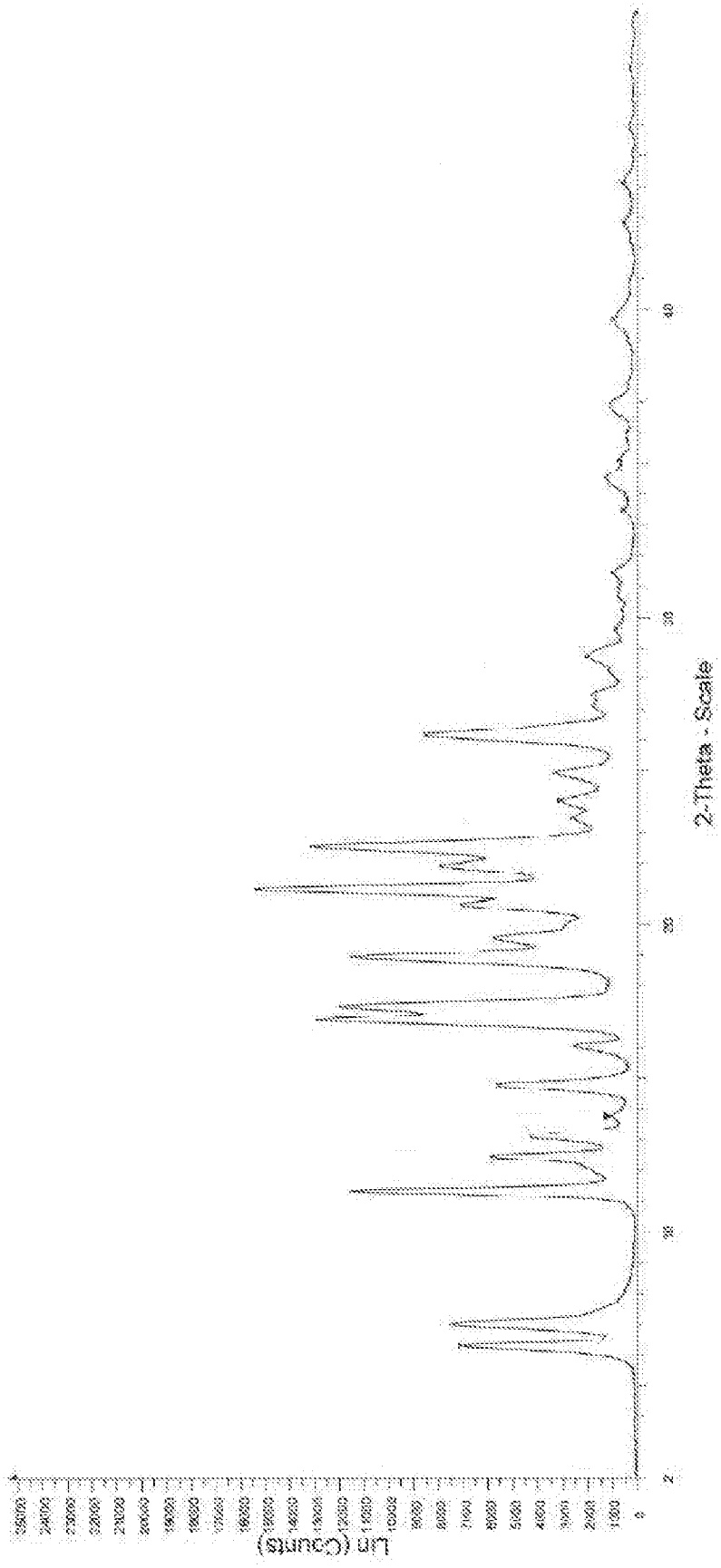


Figure 4: PXRD of Nintedanib base crystalline form M-2

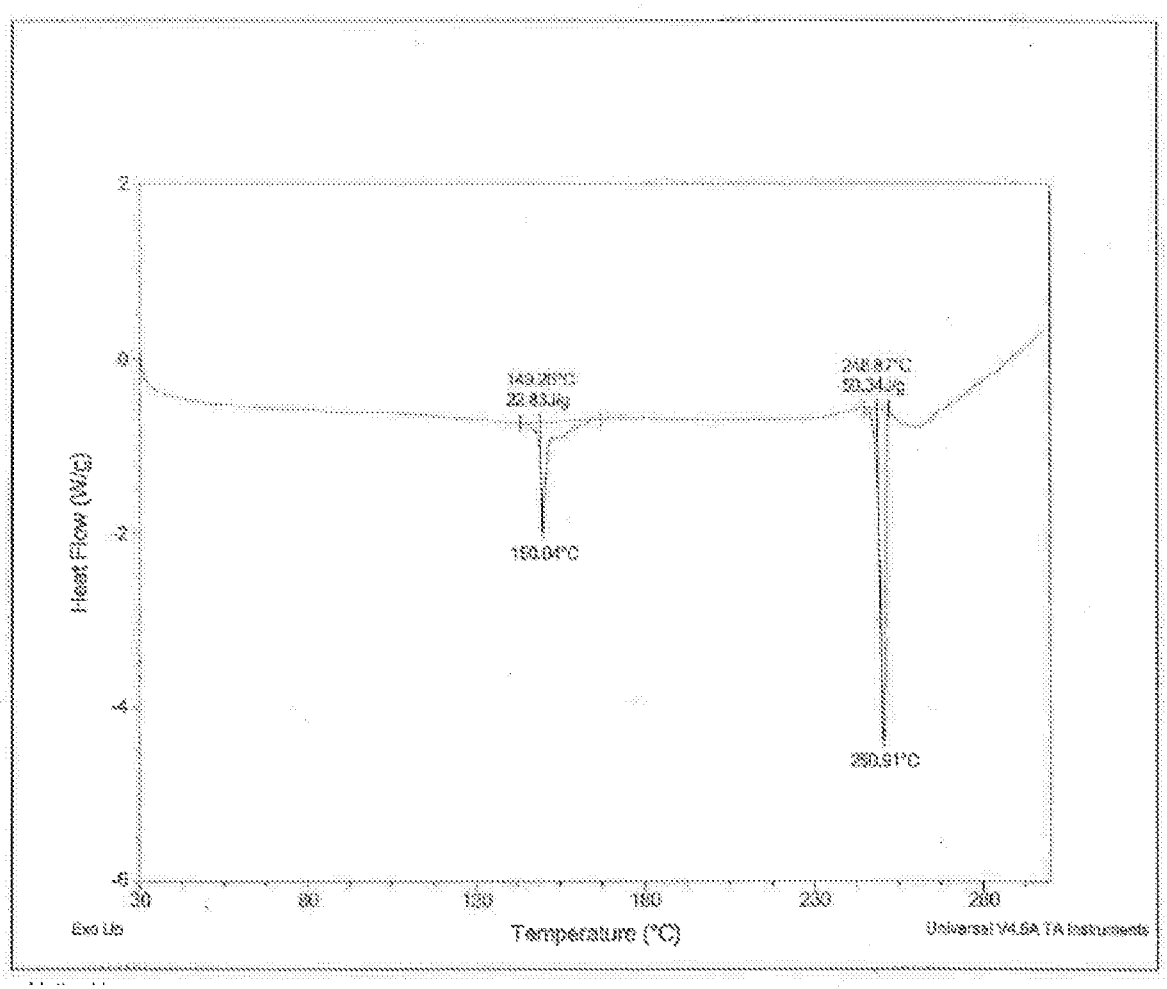
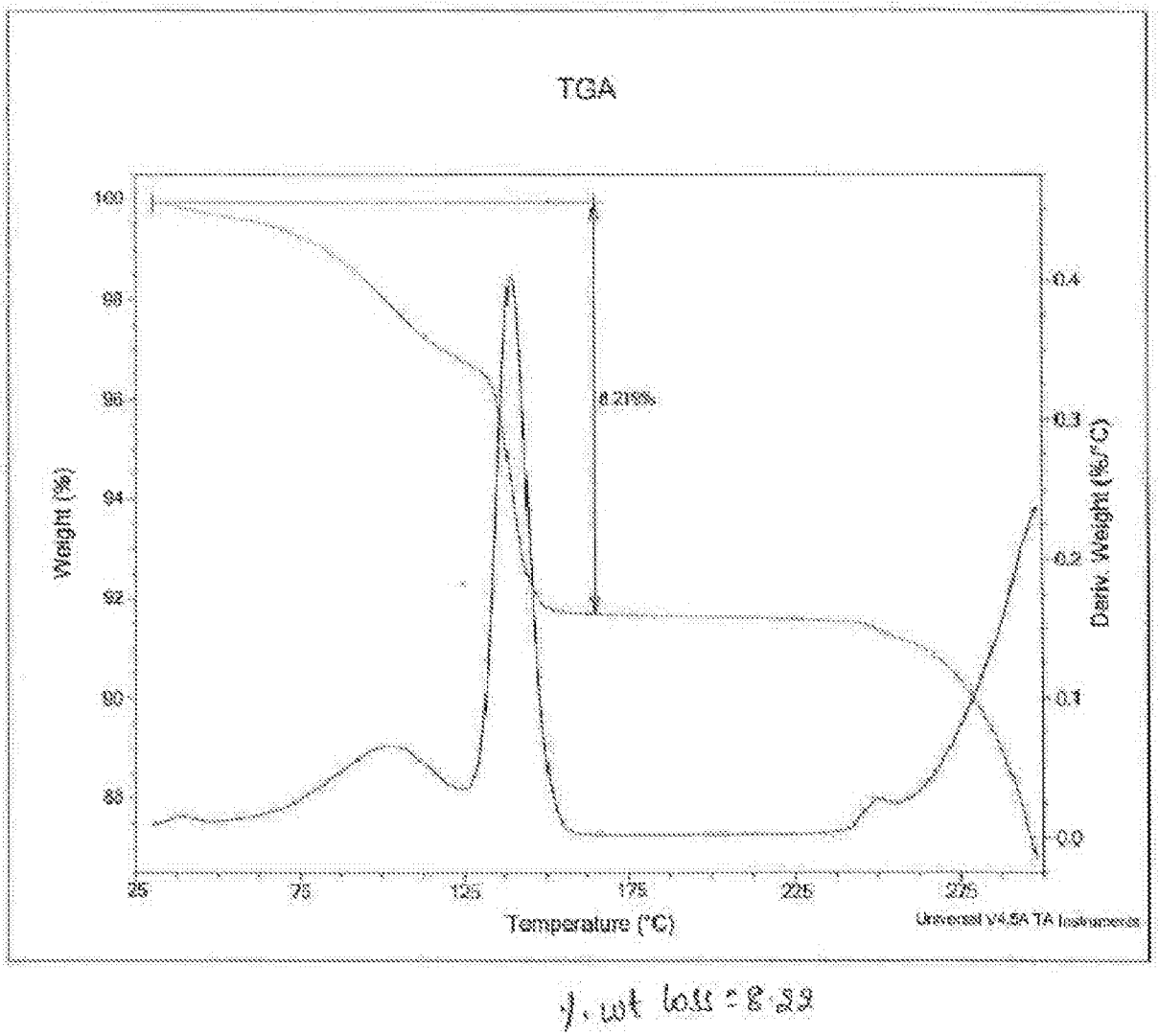


Figure 5: DSC of Nintedanib base crystalline form M-2



% wt loss = 8.33

Figure 6: TGA of Nintedanib base crystalline form M-2

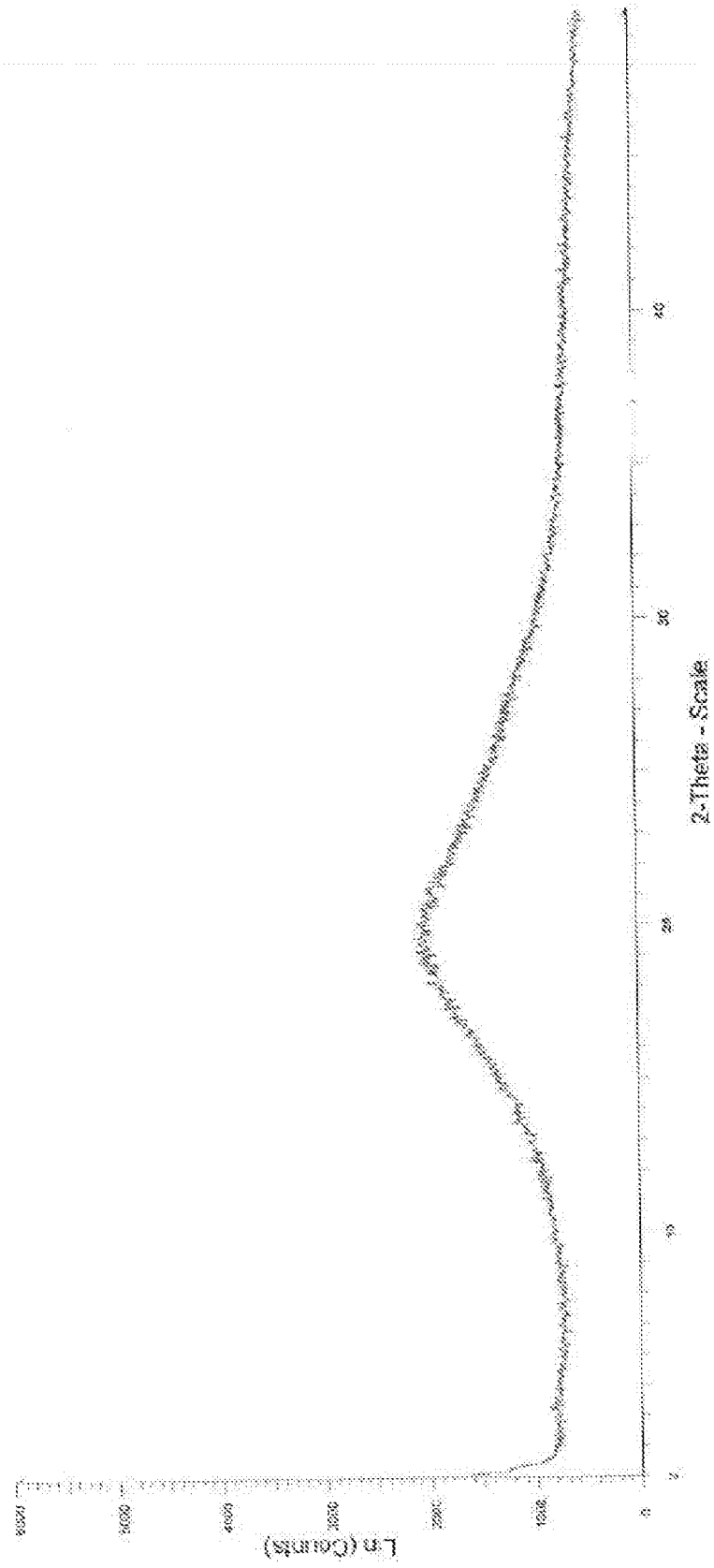


Figure 7: PXRD of amorphous Nintedanib esylate

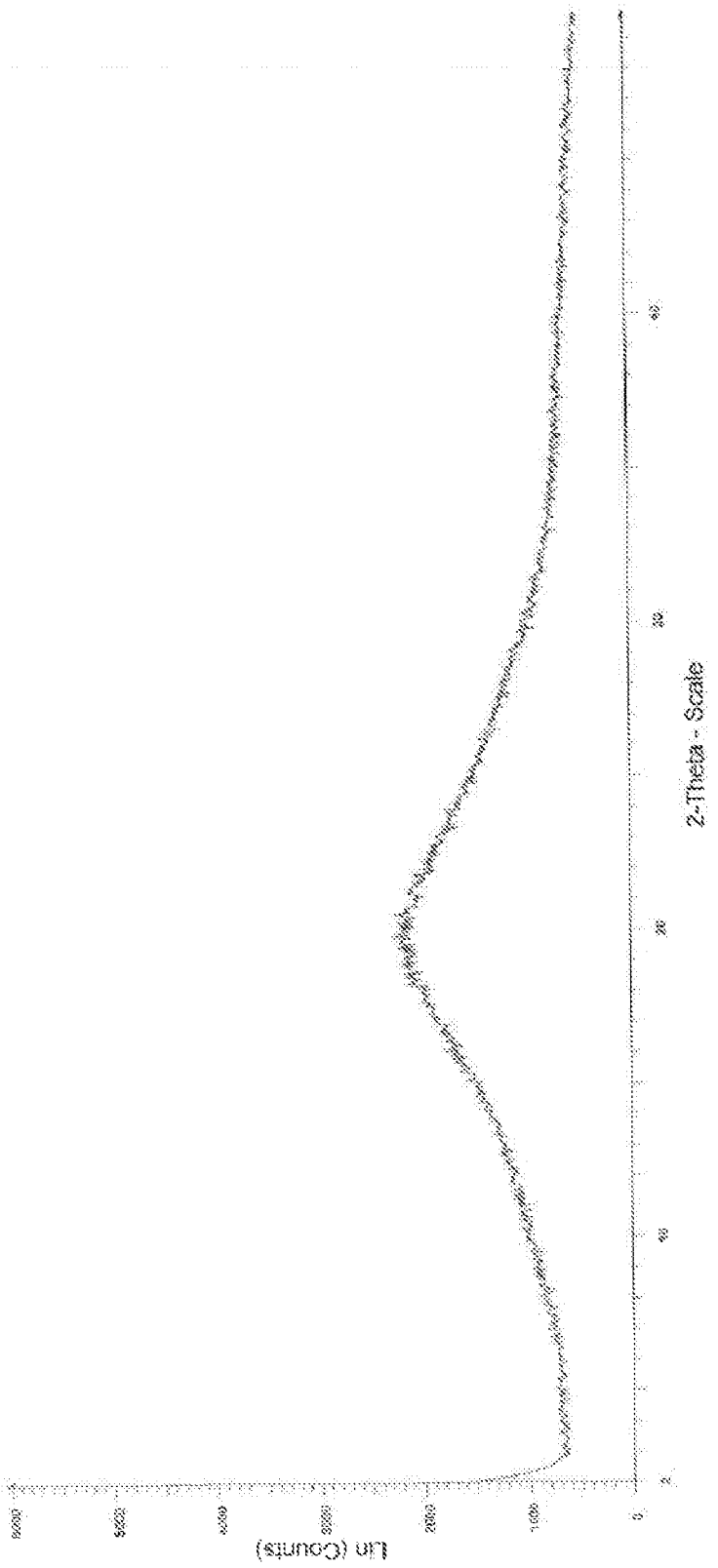


Figure 8: PXRD of solid dispersion of amorphous Nintedanib esylate with 10% w/w PLASDONE S-630

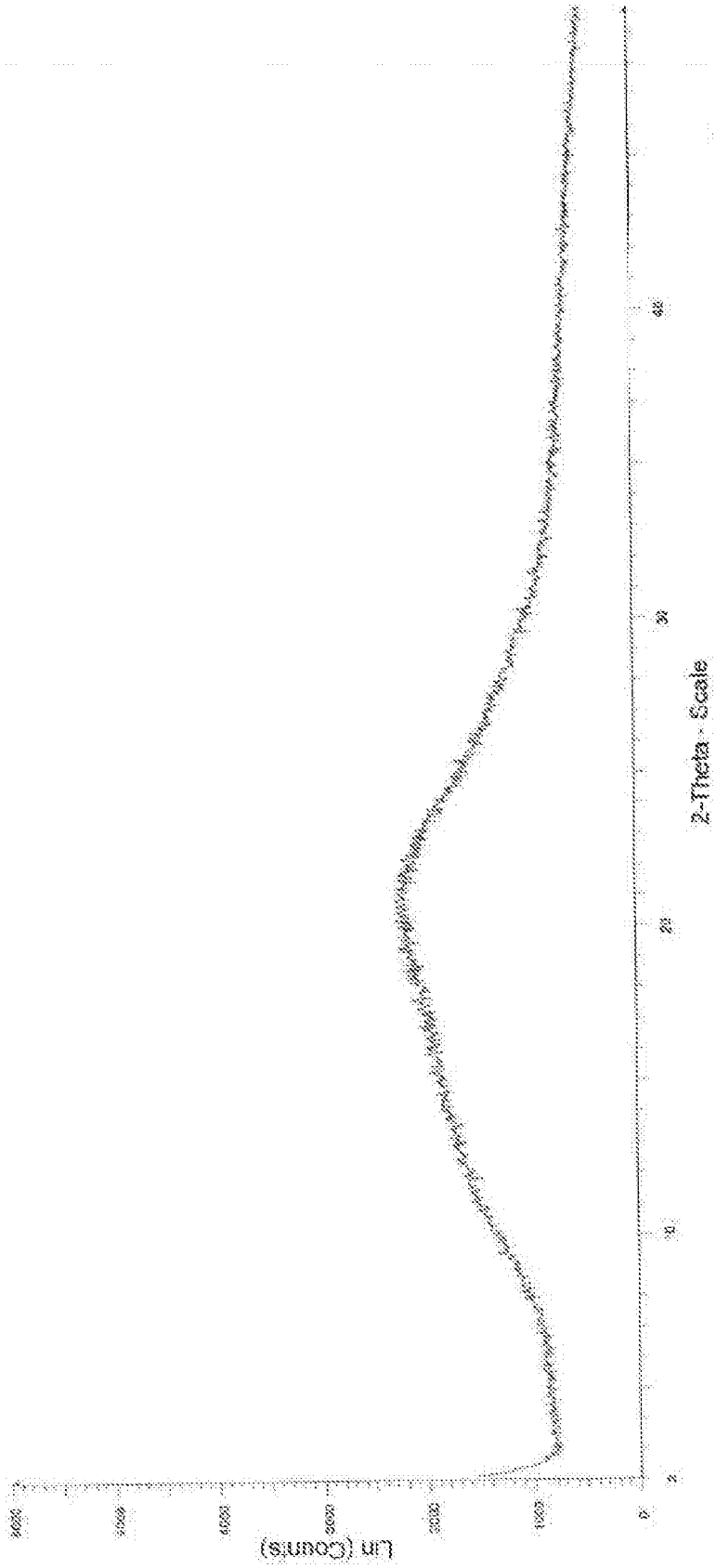


Figure 9: PXRD of solid dispersion of amorphous Nintedanib esylate with 50% w/w PLASDONE S-630

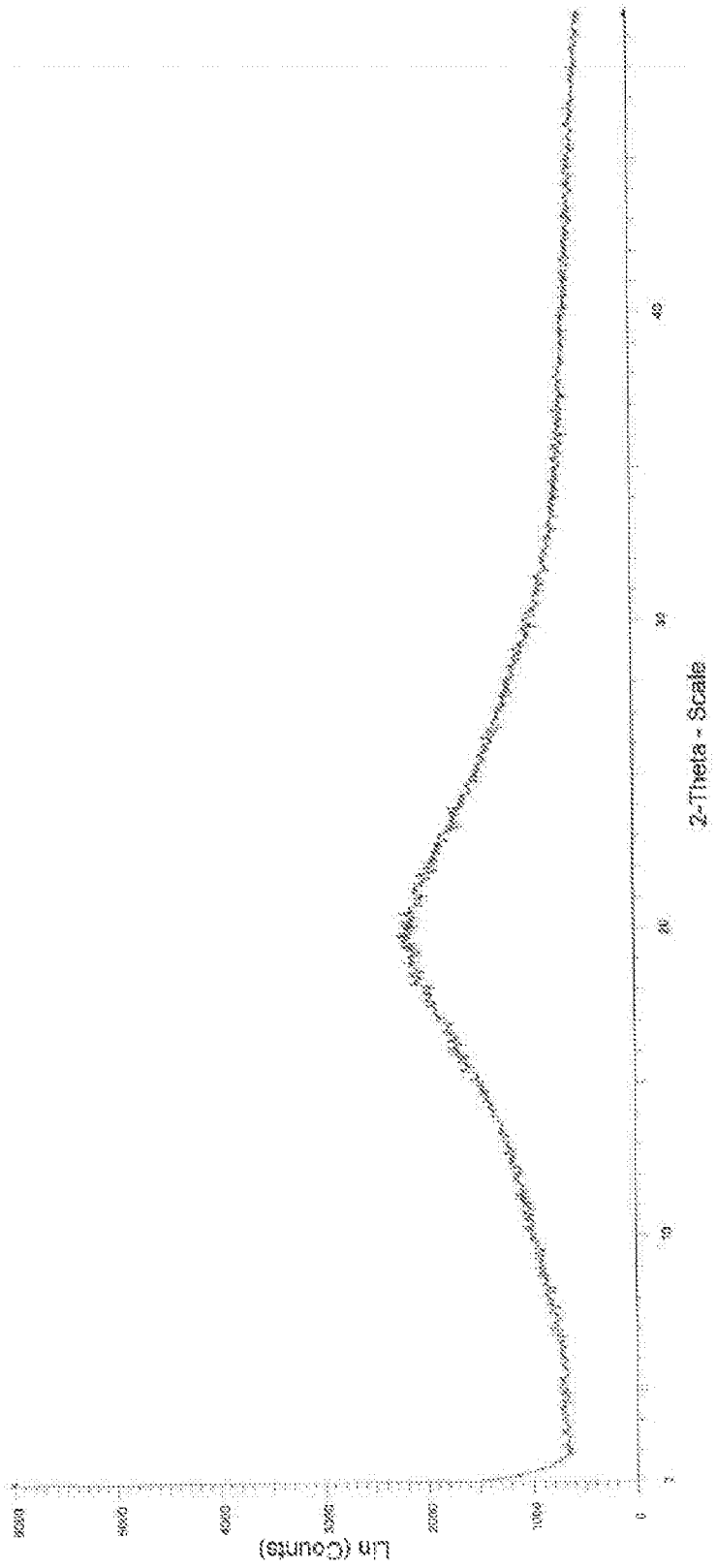


Figure 10: PXRD of solid dispersion of amorphous Nintedanib esylate with 10% w/w β-cyclodextrin.