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(54) Title: A PROCESS FOR PREPARATION OF AMORPHOUS APREMILAST

(57) Abstract: The present invention relates to processes for the preparation of an active pharmaceutical ingredient consisting essentially of amorphous apremilast.

A PROCESS FOR PREPARATION OF AMORPHOUS APREMILAST

RELATED APPLICATIONS

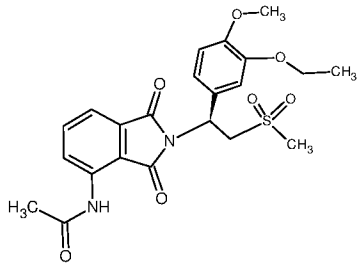
This application claims the benefit of Indian Patent Application no. 2617/MUM/2015 filed on July 09, 2015 which is hereby incorporated by reference.

FIELD OF INVENTION

The present invention relates to an active pharmaceutical ingredient consisting essentially of amorphous apremilast and process for its preparation.

BACKGROUND OF INVENTION

Apremilast or *N*-[2-[(1*S*)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1*H*-isoindol-4-yl]acetamide having following structure



Apremilast

was approved by the USFDA in March 2014 for treatment of adults with active psoriatic arthritis. The compound was first disclosed in U.S. Patent No.7,427,638. Apremilast is first oral phosphodiesterase-4 (PDE-4) inhibitor which inhibits spontaneous production of TNF-alpha from human rheumatoid synovial cells.

Apremilast is reported to be present in various polymorphic forms in the literature. US patent number 7893101 (the '101 patent) discloses polymorphic forms A to F. The '101 patent discloses that when Form D is subjected to stability studies at 40 °C temperature and about 75 % RH for four weeks the intensity of the peaks of Form D X-ray powder diffraction (XRPD) pattern is reduced. This reduction in XRPD peak intensity results from the formation of amorphous material.

WIPO application 2014072259 discloses a process for preparing a composition of apremilast with at least one excipient by hot melt extrusion technique. The excipients are selected from a polymer, a copolymer, a saccharide, an oligosaccharide, a polysaccharide, a sugar alcohol, a lipid, and a wax. The composition is amorphous in nature.

SUMMARY OF THE INVENTION

The present invention provides an active pharmaceutical ingredient consisting essentially of amorphous apremilast.

The present invention also provides a process for preparation of active pharmaceutical ingredient consisting essentially of amorphous apremilast comprising dissolving apremilast in a solvent and freeze drying the solution.

The present invention further provides a process for preparation of active pharmaceutical ingredient consisting essentially of amorphous apremilast comprising dissolving apremilast in a solvent and subjecting the solution to evaporation under reduced pressure.

Amorphous apremilast prepared by the invention of the present invention is substantially free of crystalline apremilast. Such amorphous form provides predictable behavior during manufacture dosage form containing them.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: XRPD pattern of amorphous apremilast.
Figure 2: Differential Scanning Calorimetry (DSC) plot of amorphous apremilast.

DEFINITIONS

The phrase "Active pharmaceutical ingredient consisting essentially of amorphous apremilast" as referred herein means amorphous apremilast which is free from pharmaceutical excipients.

Amorphous apremilast as referred herein means apremilast is either free of crystalline apremilast or is substantially free of crystalline apremilast.

DESCRIPTION OF THE INVENTION

The present invention provides an active pharmaceutical ingredient consisting essentially of amorphous apremilast. The amorphous apremilast of present invention is free of pharmaceutical excipients.

Present invention also provides processes for preparation of active pharmaceutical ingredient consisting essentially of amorphous apremilast. The active pharmaceutical ingredient consisting essentially of amorphous apremilast can be prepared by a process comprising dissolving apremilast in a solvent and freeze drying the solution. Dissolution of apremilast in the solvent may be facilitated by heating the mixture to a temperature of about 40 °C to about 120 °C. The preferred solvent for the purpose is selected from acetic acid, formic acid or mixtures thereof. The quantity of the solvent required for preparing the solution may vary depending upon the solubility of apremilast. Preferably, the solvent is at least 5 times by weight of apremilast. More preferably, the quantity of the solvent is 5 to 10 times of the apremilast. For instance, the solvent used for dissolving 1 g apremilast is about 5 mL to 10 mL. Preferably the solution thus formed is a saturated solution of apremilast in the solvent.

The active pharmaceutical ingredient consisting essentially of amorphous apremilast can also be prepared by a process comprising dissolving apremilast in a solvent and subjecting the solution to evaporation under reduced pressure. A preferred solvent for the purpose is selected from acetic acid, formic acid or mixtures thereof. Dissolution of apremilast in the solvent may be facilitated by heating the mixture to a temperature of about 40 °C to about 120 °C. The evaporation of solvent under reduced pressure can be carried out by techniques able to accomplish rapid evaporation such as ATFD (agitated thin film drying), flash evaporation and the like. Preferably, the evaporation is completed within 30 minutes, more preferably, within 15 minutes and most preferably, within 10 minutes. Preferably, the evaporation of solvent under reduced pressure is carried out by using flash evaporation. The evaporation of the solvent under reduced pressure may be carried out at temperature of about 40 °C to 80 °C under reduced pressure of about 1 mmHg to about 50 mmHg. The quantity of solvent required to form the solution of apremilast is as described earlier in the specification.

Amorphous apremilast obtained by the process may be isolated by stirring the solid obtained after evaporation with another solvent which does not dissolve apremilast, filtering the mixture and drying the solid obtained therefrom. Alternatively, the solid obtained after evaporation is as such dried to obtain amorphous apremilast.

The apremilast of present invention is amorphous as determined by the X-ray powder diffraction (XRPD) analyses for example XRPD scan of an embodiment is provided in Figure 1 as illustrative example. The illustrated figure shows that the apremilast is amorphous and lacks any peaks which are characteristic crystalline apremilast.

The present invention is further illustrated in detail with reference to the following examples. It is desired that the examples be considered in all respect as illustrative and are not intended to limit the scope of the claimed invention.

EXAMPLES

Instrument details:

XRPD: X-ray powder diffraction analyses were carried out on a PANalytical Empyrean X-ray powder diffractometer using Cu K alpha radiation. The instrument was equipped with a line focus X-ray tube, and the voltage and amperage were set to 45 kV and 40 mA respectively. The scanning rate was set as 10 second per step and step size is set as 0.01°. The diffractometer was equipped with Pixcel^{1D} solid state detector and rotating sample stage. X-ray diffractometer was used to record diffractogram from 4° to 40° (2-theta).

DSC: Differential Scanning Calorimetry (DSC) analysis were performed on a TA Instruments Q2000™. Approximately 2 mg of sample was placed into a tared DSC Aluminium pan and sealed hermetically. Typically, the sample was heated under nitrogen at a rate of about 10 °C/min from about 35 °C up to a final temperature of about 250 °C.

Example 1: Apremilast (1.0 g) was dissolved in acetic acid (7.0 mL) and resulting clear solution was subjected to lyophilization for 24 hours. Yield: 0.95 g.

Example 2: Apremilast (1.0 g) was dissolved in acetic acid (7.0 mL) and resulting clear solution was subjected to flash distillation or evaporation at 65 °C under reduced pressure. Yield: 0.95 g.

Example 3: Apremilast (2.0 g) was dissolved in glacial acetic acid (14 mL) and the resultant solution was filtered through 0.45 micron filter paper. Acetic acid was distilled out at 60 °C to 65 °C under reduced pressure. The resultant mass was degased at 60 °C to 65 °C for 2.0 hours and then cooled to room temperature. Water (20 mL) was added into the above degased mass and stirred for 2.0 hours. The solid was filtered, washed with water (10 mL) and dried in vacuum oven at 60 °C to 65 °C for 15.0 hours to get 1.86 g of amorphous apremilast.

Example 4: Apremilast (2.0 g) was dissolved in formic acid (10 mL) and the resultant solution was filtered through 0.45 micron filter paper. Formic acid was distilled out at 50 °C to 55 °C under vacuum. The resultant mass was degased at 50 °C to 55 °C for 2.0 hours and then cooled to room temperature. Water (20 mL) was added into the above degased mass and stirred for 2.0 hours. The solid was filtered, washed with water (10 mL) and dried in vacuum oven at 60 °C to 65 °C for 15.0 hours to get 1.83 g of amorphous apremilast.

Example 5: Apremilast (10.0 g) was dissolved in acetone (100 mL) and the resultant solution was filtered through 0.45 micron filter paper. Acetone was distilled out at 40 °C to 45 °C under reduced pressure. The resultant mass was degased at 40 °C to 45 °C for 30 min and then cooled to room temperature. Water (200 mL) was added into the above degased mass and stirred for 2.0 hours. The solid was filtered, washed with water (10 mL) and dried in vacuum oven at 40 °C to 45 °C for 15.0 hours to get 9.3 g of amorphous apremilast.

Example 6: Apremilast (10.0 g) was dissolved in acetone (100 mL) and the resultant solution was filtered through 0.45 micron filter paper. Acetone was distilled out at 40 °C to 45 °C under reduced pressure. The resultant mass was degased at 40 °C to 45 °C for 30 min and then cooled to room temperature. Diisopropylether (200 mL) was added into the above degased mass and stirred for 2.0 hours. The solid was filtered, washed with diisopropylether (50 mL) and dried in vacuum oven at 50 °C to 55 °C for 15.0 hours to get 9.4 g of amorphous apremilast.

CLAIMS:

1. A process for preparation of amorphous apremilast comprising dissolving apremilast in a solvent selected from acetic acid, formic acid or mixtures thereof and freeze drying the solution.

2. The process as in claim 2, wherein the solvent is acetic acid.

3. A process for preparation of amorphous apremilast comprising dissolving apremilast in a solvent selected from acetic acid, formic acid or mixtures thereof and subjecting the solution to evaporation under reduced pressure.

4. The process as in claim 3, wherein the reduced pressure is 1 mmHg to 50 mmHg.

5. The process as in claim 4, wherein the solvent is acetic acid.

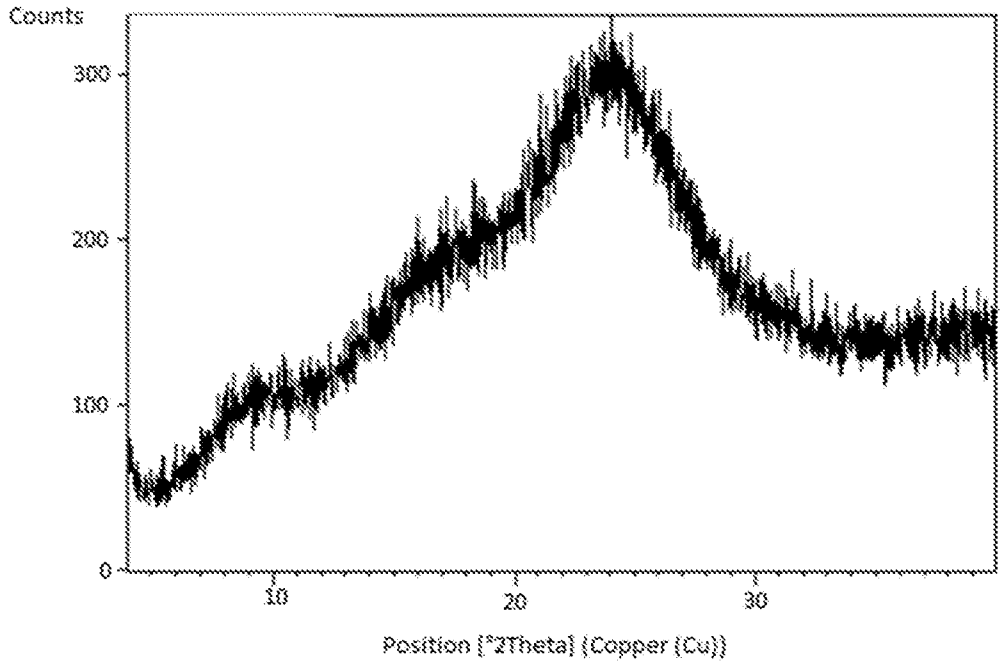


Figure 1: XRPD pattern of amorphous apremilast

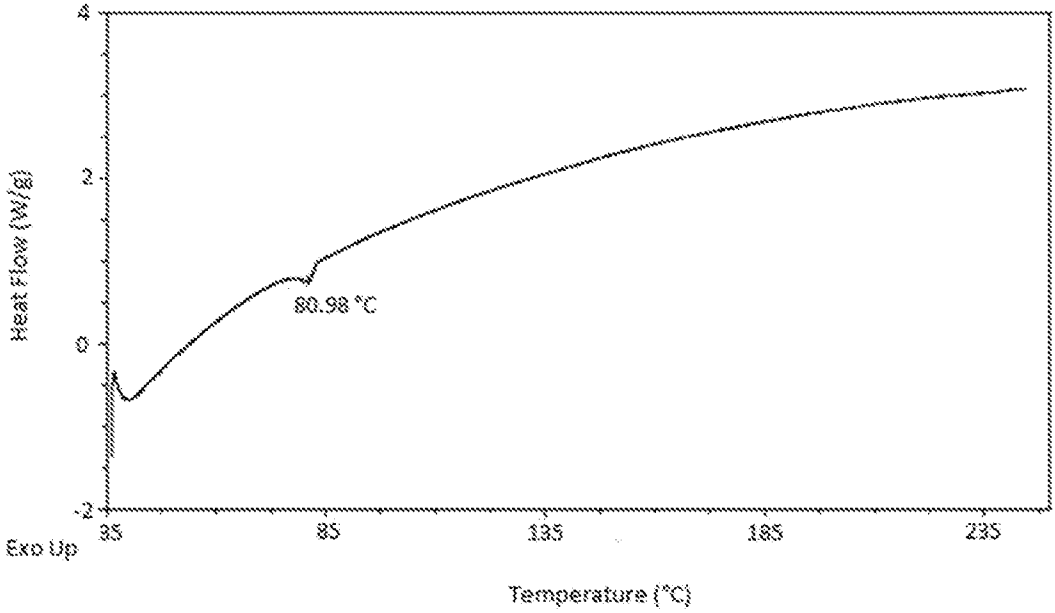


Figure 2: Differential Scanning Calorimetry (DSC) plot of amorphous apremilast