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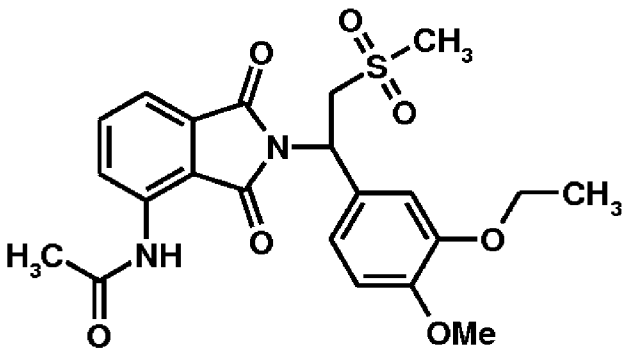
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(54) Title: COMPOSITION COMPRISING APREMILAST IN AMORPHOUS FORM



(I)

(57) Abstract: The present invention relates to solid solutions or solid dispersions comprising compound (I) and processes for the preparation thereof.

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COMPOSITION COMPRISING APREMILAST IN AMORPHOUS FORM

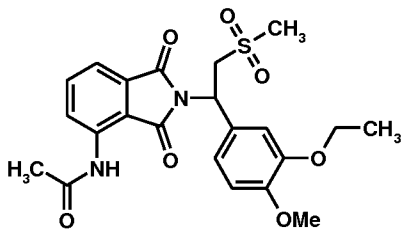
Field of the Invention

The present invention relates to N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide (also referred to as compound (I)). In particular, the invention relates to compositions comprising compound (I) or a pharmaceutically acceptable salt thereof and processes for the preparation thereof.

Background of the Invention

N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide is an experimental inhibitor of phosphodiesterase (PDE) 4, interferon gamma antagonist; IL-2 gene inhibitor; leukotriene synthesis inhibitor; TNF alpha synthesis inhibitor; IL-6 antagonist; IL-17 gene inhibitor; angiogenesis inhibitor; NO-synthase inhibitor; and IL-23 gene inhibitor.

The structure of N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide is shown below:



Compound (I)

Enantiomerically pure compound (I) has low solubility in aqueous solution. In aqueous buffer pH 7.4 the solubility measured at room temperature is about 0.01mg/ml. Poor solubility typically leads to poor oral bioavailability, fed/fasted variations in bioavailability, cumbersome and inconvenient dosage forms, and may necessitate the use of harsh solubilising agents that are associated with adverse side effects.

WO2011/059931 describes a method for preparing a nanosuspension of a poorly soluble drug in order to improve bioavailability. Said method comprises stirring the drug, which has been micronized, in an aqueous polymeric excipient solution in the absence of surfactants

and passing the concentrate through a high-shear microfluidizer processor to obtain the nanosuspension.

WO2009/120167 describes solid forms of (+)-N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide (also known as apremilast). However, there is no enabling disclosure of an amorphous form.

US 2015/0283249 relates to amorphous apremilast and a process for the preparation thereof.

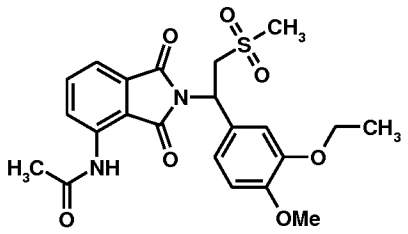
There remains a need in the art for solid forms of compound (I) with improved properties. In particular, a solid form of compound (I) should exhibit at least one of the following properties: adequate dissolution properties; storage stability at ambient conditions, preferably avoiding the requirement of desiccants in the packages; and be easily preparable with good content uniformity.

It has now surprisingly been found that at least one of the above properties can be achieved by the solid forms of the present invention.

In particular, it has been found that the compositions of the invention have advantageous properties over compositions comprising crystalline forms of compound (I). For instance, dissolution studies have shown that a composition comprising a solid solution or solid dispersion or melt of compound (I) according to the present invention exhibits at least a similar rate of dissolution to a composition comprising crystalline compound (I). Furthermore, compositions comprising a solid solution or dispersion or melt of compound (I) according to the invention have been shown to retain at least 80% dissolution within 30 minutes in dissolution tests after being subjected to accelerated storage conditions.

Summary of the Invention

In a first aspect, the present invention relates to a solid solution or solid dispersion comprising compound (I)



Compound (I)

In a second aspect, the present invention relates to a process for preparing a solid solution or solid dispersion comprising compound (I) comprising spray drying compound (I), together with at least one pharmaceutically acceptable excipient.

In third aspect, the present invention relates to a process for preparing a solid solution or solid dispersion of compound (I) comprising freeze drying compound (I), together with at least one pharmaceutically acceptable excipient.

In a fourth aspect, the present invention relates to a solid solution or solid dispersion comprising compound (I) obtainable by a process according to the second and third aspects of the invention.

In a fifth aspect, the present invention relates to a melt consisting essentially of compound (I).

In an embodiment of the fifth aspect, the present invention relates to a melt consisting of compound (I).

In a sixth aspect, the present invention relates to a process for preparing a melt consisting essentially of compound (I) comprising melting compound (I).

In an embodiment of the sixth aspect the present invention relates a process for preparing a melt consisting of compound (I) comprising melting compound (I).

In a seventh aspect, the present invention relates to a melt obtainable by a process according to the sixth aspect of the invention.

In an eight aspect, the present invention relates to a pharmaceutical composition comprising a solid solution or solid dispersion according to the above aspects of the invention, or a melt according to the above aspects of the invention, and a pharmaceutically acceptable excipient.

In a ninth aspect, the present invention relates to a method of treating or preventing a disease or disorder ameliorated by the inhibition of TNF-[alpha] production, wherein the method comprises administering a therapeutically or prophylactically effective amount of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention.

In an embodiment of the ninth aspect, the present invention also relates to the solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention for use in the treatment of a disease or disorder ameliorated by the inhibition of TNF-[alpha] production.

In an embodiment of the ninth aspect, the present invention also relates to the use of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention in the manufacture of a medicament for the treatment of a disease or disorder ameliorated by the inhibition of TNF-[alpha] production.

In a tenth aspect, the present invention relates to a method of treating or preventing a disease or disorder ameliorated by the inhibition of PDE4, wherein the method comprises administering a therapeutically or prophylactically effective amount of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention.

In an embodiment of the tenth aspect, the present invention also relates to the solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention for use in the treatment of a disease or disorder ameliorated by the inhibition of PDE4.

In an embodiment of the tenth aspect, the present invention also relates to the use of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention in the manufacture of a medicament for the treatment of a disease or disorder ameliorated by the inhibition of PDE4.

In an eleventh aspect, the present invention relates to a method of treating or preventing a cancer, wherein the method comprises administering a therapeutically or prophylactically effective amount of an amorphous form of a solid solution or solid dispersion according to the

invention, a melt according to the invention, or a pharmaceutical composition according to the invention.

In an embodiment of the eleventh aspect, the present invention also relates to the solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention for use in the treatment or prevention of cancer.

In an embodiment of the eleventh aspect, the present invention also relates to the use of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention in the manufacture of a medicament for the treatment or prevention of cancer.

Brief Description of the Figures

Figure 1 shows the XRPD pattern of the product of preparative example 1. The diffraction pattern of reference standard corundum (ASTM standard ref) is superimposed.

Figure 2 shows the HPLC chromatogram for the product of preparative example 1.

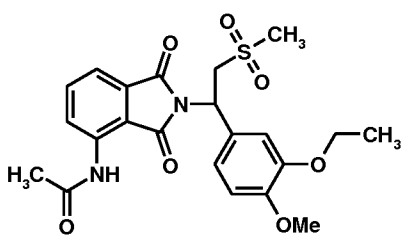
Figure 3 shows the DSC and TGA pattern for the product of preparative example 1.

Figure 4 shows the XRPD pattern of crystalline Form B of apremilast.

Detailed Description of the Invention

Definitions

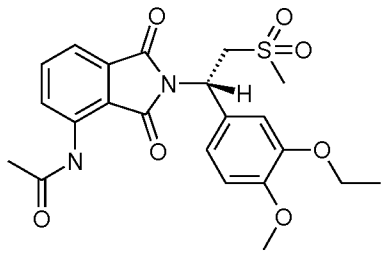
As used herein compound (I) refers to N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide, which has the following structure:



Compound (I);

or a pharmaceutically acceptable salt thereof.

As used herein the term “apremilast” refers to (+)-N-[2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl]acetamide (compound (Ia))



(Ia)

As used herein the term “a solid solution or solid dispersion” as used in reference to compound (I) or (Ia) refers to dissolution or molecular dispersion of compound (I) or (Ia) within an excipient matrix which is in the solid state at ambient temperature and pressure (e.g. at 20°C and a pressure of 101 kPa).

As used herein the term “a melt” as used in reference to compound (I) or (Ia) refers to the material which results when pure, or essentially pure, compound (I) or (Ia) is heated at least to about its melting point and optionally allowed to cool, preferably to ambient temperature.

As used herein “pure” refers to compound (I) or (Ia) which has a purity of 99% or more, as determined by UV-HPLC for instance. “Essentially pure” refers to compound (I) or (Ia) which has a purity of 95% or more, as determined by UV-HPLC for instance.

Compound (I)

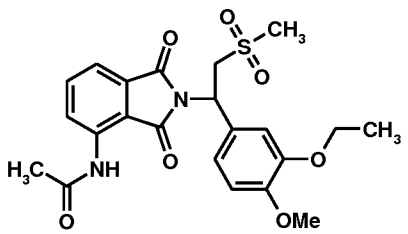
In all aspects of the present invention previously discussed, the invention includes, where appropriate all enantiomers of compound (I). The person skilled in the art will recognise compounds that possess optical properties (one or more chiral carbon atoms). The corresponding enantiomers may be isolated/prepared by methods known in the art. Thus, where reference is made to compound (I), both the (+) and (-)-enantiomers of compound (I) separately, or mixtures thereof in any ratio, including a racemic mixture of enantiomers for example, are encompassed.

In one embodiment compound (I) is substantially all in the (+)-enantiomeric form and is also known as apremilast; preferably compound (I) is 80% or more in the (+)-enantiomeric form, more preferably compound (I) is 90% or more in the (+)-enantiomeric form, more preferably compound (I) is 95% or more in the (+)-enantiomeric form, more preferably compound (I) is 99% or more in the (+)-enantiomeric form.

Pharmaceutically acceptable salts of compound (I) may include, without limitation, non-toxic acid addition salts such as those derived from organic and inorganic acids, e.g. without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embonic acid, enanthic acid, and the like.

Solid Solution or Solid Dispersion of Compound (I)

In a first aspect, the present invention relates to a solid solution or solid dispersion comprising compound (I)



Compound (I)

Preferably, the solid solution or solid dispersion comprises amorphous compound (I).

In one embodiment, the solid solution or solid dispersion compound (I) is substantially free of any crystalline forms. In another embodiment, the solid solution or solid dispersion of compound (I) contains 20% or less of any crystalline form, preferably 10% or less, more preferably 5% or less, more preferably 2% or less, more preferably 1% or less. The crystalline proportion can be determined by means of quantitative X-ray diffractometry according to the method of Hermans and Weidinger.

In one embodiment, the solid solution or solid dispersion of compound (I) comprises at least one pharmaceutically acceptable excipient.

In another embodiment, the solid solution or solid dispersion consists essentially of compound (I) and at least one pharmaceutically acceptable excipient.

In another embodiment, the solid solution or solid dispersion consists of compound (I) and at least one pharmaceutically acceptable excipient.

In one embodiment, the pharmaceutically acceptable excipient has a softening point (Ts) or a glass transition temperature (Tg) of about 20°C or higher, preferably about 20°C to about 220°C, more preferably about 20°C to about 200°C, even more preferably about 40°C to about 180°C, most preferably about 60°C to about 140°C.

The softening point and the glass transition temperature can be determined by any known means. For example, the softening point and glass transition temperature can be determined by means of differential scanning calorimetry (DSC). Suitable methods of determining softening points and glass transition temperatures are as described in the European Pharmacopoeia 7 (Ph. Eur., chapter 2.2.34) and the United States Pharmacopoeia (USP, chapter 891), the content of which is incorporated herein by reference.

In one embodiment, the pharmaceutically acceptable excipient is selected from the group consisting of a polymer, a saccharide, an oligosaccharide, a polysaccharide, a sugar alcohol, a lipid, and a wax.

In one embodiment, the pharmaceutically acceptable excipient is selected from the group consisting of a saccharide, an oligosaccharide, a polysaccharide, a sugar alcohol, a lipid, and a wax.

In one embodiment, the pharmaceutically acceptable excipient is a polymer.

In one embodiment, the polymer has a number-average molecular weight of 1,000 to 4,000,000 g/mol, more preferably from 1,000 to 3,500,000 g/mol, even more preferably from 1,500 to 3,000,000 g/mol, and particularly preferably from 3,500 to 2,500,000 g/mol.

In another embodiment, the polymer has a viscosity of 150,000 mPa•s or less, more preferably 100,000 mPa•s or less, and especially 75,000 mPa•s or less when dissolved in (distilled) water (if the polymer is insoluble in water any other suitable solvent as described in “Handbook of Pharmaceutical Excipients“ Sixth Edition, Edited by Raymond C Rowe, Paul J

Sheskey and Marianne E Quinn, Pharmaceutical Press and American Pharmacists Association 2009 is to be used) in an amount of 2 % by weight, and measured at 25°C in accordance with the European Pharmacopoeia (Ph. Eur.), 6th edition, section 2.2.10.

Hydrophilic and amphiphilic polymers may be used. "Hydrophilic" refers to polymers which possess hydrophilic groups. Examples of suitable hydrophilic groups are hydroxy, alkoxy, acrylate, methacrylate, sulphonate, carboxylate and quaternary ammonium groups. Hydroxy groups are preferable.

Suitable polymers are, for example, cellulosic polymers and non-cellulosic polymers, such as methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxyethyl methyl cellulose (HEMC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate (HPMCA), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl cellulose acetate succinate (HPCAS), hydroxyethyl cellulose acetate succinate (HECAS), hydroxyethyl methyl cellulose succinate (HEMCS), hydroxyethyl methyl cellulose acetate succinate (HEMCAS) ,carboxymethyl cellulose (CMC), carboxyethyl cellulose (CEC), carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methyl cellulose acetate phthalate (HPMCAP), hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), polyvinyl acetate (PVAc), vinylpyrrolidon vinylacetat copolymer (VP/VAc copolymer, such as Copovidon Kollidon VA 64), polyvinylacetat polyvinylpyrrolidon copolymer (PVAc/PVP copolymer, Povidon), polyvinyl polypyrrolidon (PVPP copolymer, Crospovidon), polyvinyl alcohol polyethylene glycol copolymer (PVA/PEG copolymer), poly propylen glycols (PPGs), poly ethylen glycols (PEGs 1500, 3000, 3350, 4000, 6000, 8000, 10000, 12000, 20000), polyoxyethylene polyoxypropylene copolymers (Poloxamers), polymethacrylates (such as the EUDRAGITS®), carboxylic acid functionalized polyacrylates (such as the EUDRAGITS®), amine-functionalized polyacrylates and polymethacrylates, acrylate and methacrylate copolymers (such as the EUDRAGITS®), and polyoxyethylene-polyoxypropylene copolymers (such as the PLURONICS®), or mixture thereof.

In one embodiment, the polymer may be selected from one or more of methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxyethyl methyl cellulose (HEMC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate (HPMCA), hydroxypropyl cellulose acetate succinate (HPCAS), hydroxyethyl cellulose acetate succinate (HECAS), hydroxyethyl methyl cellulose

succinate (HEMCS), hydroxyethyl methyl cellulose acetate succinate (HEMCAS) ,carboxymethyl cellulose (CMC), carboxyethyl cellulose (CEC), carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methyl cellulose acetate phthalate (HPMCAP), hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), polyvinyl alcohol (PVA), polyvinyl acetate (PVAc), vinylpyrrolidon vinylacetat copolymer (VP/VAc copolymer, such as Copovidon Kollidon VA 64), polyvinyl alcohol polyethylene glycol copolymer (PVA/PEG copolymer), poly propylen glycols (PPGs), poly ethylen glycols (PEGs 1500, 3000, 3350, 4000, 6000, 8000, 10000, 12000, 20000), polyoxyethylene polyoxypropylene copolymers (Poloxamers), amine-functionalized polyacrylates and polymethacrylates, acrylate, and polyoxyethylene-polyoxypropylene copolymers (such as the PLURONICS®), or mixture thereof.

In one embodiment, the polymer may be selected from one or more of methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxyethyl methyl cellulose (HEMC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate (HPMCA), hydroxypropyl cellulose acetate succinate (HPCAS), hydroxyethyl cellulose acetate succinate (HECAS), hydroxyethyl methyl cellulose succinate (HEMCS), hydroxyethyl methyl cellulose acetate succinate (HEMCAS) ,carboxymethyl cellulose (CMC), carboxyethyl cellulose (CEC), carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methyl cellulose acetate phthalate (HPMCAP), hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), polyvinyl alcohol (PVA), polyvinyl acetate (PVAc), polyvinyl alcohol polyethylene glycol copolymer (PVA/PEG copolymer), poly propylen glycols (PPGs), poly ethylen glycols (PEGs 1500, 3000, 3350, 4000, 6000, 8000, 10000, 12000, 20000), polyoxyethylene polyoxypropylene copolymers (Poloxamers), amine-functionalized polyacrylates and polymethacrylates, acrylate, and polyoxyethylene-polyoxypropylene copolymers (such as the PLURONICS®), or mixture thereof.

The pharmaceutical composition of the invention may in particular comprise the following polymers: polyvinyl pyrrolidone, polyvinyl acetate (PVAC), polyvinyl alcohol (PVA), polymers of acrylic acid and their salts, polyacrylamide, polymethacrylates, vinyl pyrrolidone/vinyl acetate copolymers (such as Kollidon® VA64, BASF), polyalkylene glycols, such as polypropylene glycol or preferably polyethylene glycol, co-block polymers of polyethylene glycol, especially co-block polymers of polyethylene glycol and polypropylene glycol (Pluronic®, BASF), polyethylene oxide hydroxylpropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), polyvinylcaprolactam-polyvinylacetat-polytethylene glycol graft copolymer (Soluplus®) and mixtures thereof.

The pharmaceutical composition of the invention may in particular comprise the following polymers: polyvinyl acetate (PVAC), polyvinyl alcohol (PVA), polyacrylamide, polymethacrylates, vinyl pyrrolidone/vinyl acetate copolymers (such as Kollidon® VA64, BASF), polyalkylene glycols, such as polypropylene glycol or preferably polyethylene glycol, co-block polymers of polyethylene glycol, especially co-block polymers of polyethylene glycol and polypropylene glycol (Pluronic®, BASF), polyethylene oxide, polyvinylcaprolactam-polyvinylacetat-polytethylene glycol graft copolymer (Soluplus®) and mixtures thereof.

In another embodiment, the pharmaceutical composition of the invention may in particular comprise the following polymers: polyvinyl acetate (PVAC), polyvinyl alcohol (PVA), polyacrylamide, polymethacrylates, polyalkylene glycols, such as polypropylene glycol or preferably polyethylene glycol, co-block polymers of polyethylene glycol, especially co-block polymers of polyethylene glycol and polypropylene glycol (Pluronic®, BASF), polyethylene oxide, polyvinylcaprolactam-polyvinylacetat-polytethylene glycol graft copolymer (Soluplus®) and mixtures thereof.

In one embodiment the polymer is a cellulosic polymer.

In another embodiment, the polymer is a non-ionizable cellulosic polymer. For example, methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxyethyl methyl cellulose (HEMC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC).

In another embodiment, the polymer is selected from methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxyethyl methyl cellulose (HEMC) and hydroxypropyl cellulose (HPC.

In another embodiment, the polymer is an ionizable cellulosic polymer. For example, hydroxypropyl methyl cellulose phtalate (HPMCP), hydroxypropyl methyl cellulose acetate (HPMCA), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl cellulose acetate succinate (HPCAS), hydroxyethyl cellulose acetate succinate (HECAS) hydroxyethyl methyl cellulose succinate (HEMCS), hydroxyethyl methyl cellulose acetate succinate (HEMCAS), carboxymethyl cellulose (CMC), carboxyethyl cellulose (CEC) and carboxymethyl ethyl cellulose (CMEC).

In another embodiment, the polymer is selected from hydroxypropyl methyl cellulose phtalate (HPMCP), hydroxypropyl methyl cellulose acetate (HPMCA), hydroxypropyl cellulose acetate succinate (HPCAS), hydroxyethyl cellulose acetate succinate (HECAS) hydroxyethyl methyl cellulose succinate (HEMCS), hydroxyethyl methyl cellulose acetate succinate (HEMCAS), carboxymethyl cellulose (CMC), carboxyethyl cellulose (CEC) and carboxymethyl ethyl cellulose (CMEC).

In another embodiment, the polymer is an amphiphilic cellulosic polymer. For example, cellulose acetate phtalate (CAP) and cellulose acetate trimellitate (CAT) where the cellulosic repeat units that have one or more acetate substituents are hydrophobic relative to those that have no acetate substituents, or hydroxypropyl methyl cellulose acetate phthalate (HPMCAP) and hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT) which have one or more ionized phtalate or trimellitate substituents.

In one embodiment the polymer is a non-cellulosic polymer.

In another embodiment, the polymer is a non-ionizable, non-cellulosic polymer. For example, vinyl polymers and copolymers having hydroxyl, alkylacyloxy, or cyclicamido substituents; and polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), polyvinyl acetate (PVAc), vinylpyrrolidon vinylacetat copolymer (VP/VAc copolymer), polyvinylacetat polyvinylpyrollidon copolymer (PVAc/PVP copolymer, Povidon), polyvinyl polypyrrolidon (PVPP copolymer, Crospovidon), polyvinyl alcohol polyethylene glycol copolymer (PVA/PEG copolymer), poly propylen glycols (PPGs), poly ethylen glycols (PEGs 1500, 3000, 3350, 4000, 6000, 8000, 10000, 12000, 20000) and polyoxyethylene polyoxypropylene copolymers (Poloxamers).

In another embodiment, the polymer is selected from vinyl polymers and copolymers having hydroxyl, alkylacyloxy, or cyclicamido substituents; and polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinyl alcohol (PVA), polyvinyl acetate (PVAc), vinylpyrrolidon vinylacetat copolymer (VP/VAc copolymer), polyvinyl alcohol polyethylene glycol copolymer (PVA/PEG copolymer), poly propylen glycols (PPGs), poly ethylen glycols (PEGs 1500, 3000, 3350, 4000, 6000, 8000, 10000, 12000, 20000) and polyoxyethylene polyoxypropylene copolymers (Poloxamers).

In another embodiment, the polymer is selected from vinyl polymers and copolymers having hydroxyl, alkylacyloxy, or cyclicamido substituents; and polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form, polyvinyl alcohol (PVA), polyvinyl acetate (PVAc), polyvinyl alcohol polyethylene glycol copolymer (PVA/PEG copolymer), poly propylen glycols (PPGs), poly ethylen glycols (PEGs 1500, 3000, 3350, 4000, 6000, 8000, 10000, 12000, 20000) and polyoxyethylene polyoxypropylene copolymers (Poloxamers).

In another embodiment, the polymer is an ionizable, non-cellulosic polymer. For example, carboxylic acid-functionalized vinyl polymers, polymethacrylates (such as the EUDRAGITS®), carboxylic acid functionalized polyacrylates (such as the EUDRAGITS®), amine-functionalized polyacrylates and/or polymethacrylates.

In another embodiment the polymer is an amine-functionalized polyacrylate and/or polymethacrylates.

In another embodiment, the polymer is an amphiphilic non-cellulosic polymer. For example, copolymers of a relatively hydrophilic and a relatively hydrophobic monomer, acrylate and methacrylate copolymers (such as the EUDRAGITS®), polyoxyethylene-polyoxypropylene copolymers (such as the PLURONICS®), Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (such as the Soluplus).

In another embodiment, the polymer is selected from polyoxyethylene-polyoxypropylene copolymers (such as the PLURONICS®) and Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (such as the Soluplus).

Preferably, the polymer is selected from copovidone, PEG 6000, Polyoxyethylene-polyoxypropylene block copolymer (e.g. Pluronic F68), Isomalt and Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (Soluplus). Even more preferably the polymer is copovidone.

Preferably, the polymer is selected from PEG 6000, Polyoxyethylene-polyoxypropylene block copolymer (e.g. Pluronic F68), Isomalt and Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (Soluplus).

Preferably the polymer is selected from HPMCAS, Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (Soluplus), HPMC or copovidone. Even more preferably the polymer is copovidone.

Preferably the polymer is selected from Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (Soluplus) or copovidone.

In another embodiment, the polymer comprises copovidone and the weight ratio of compound (I) to copovidone may be in the range of 1:1 to 1:10. Preferred ranges are for example 1:2 to 1:8, 1:3 to 1:6 and 1:3 to 1:5. A preferred ratio is about 1:5.

In another embodiment, the polymer consists essentially of copovidone and the weight ratio of compound (I) to copovidone may be in the range of 1:1 to 1:10. Preferred ranges are for example 1:2 to 1:8, 1:3 to 1:6 and 1:3 to 1:5. A preferred ratio is about 1:5.

In another embodiment, the polymer consists of copovidone and the weight ratio of compound (I) to copovidone may be in the range of 1:1 to 1:10. Preferred ranges are for example 1:2 to 1:8, 1:3 to 1:6 and 1:3 to 1:5. A preferred ratio is about 1:5.

In another embodiment, the polymer is copovidone and the weight ratio of compound (I) to copovidone may be in the range of 1:1 to 1:10. Preferred ranges are for example 1:2 to 1:8, 1:3 to 1:6 and 1:3 to 1:5. A preferred ratio is about 1:5.

In another embodiment, the solid dispersion or solid solution comprises compound (I) and copovidone and the weight ratio of compound (I) to copovidone may be in the range of 1:1 to 1:10. Preferred ranges are for example 1:2 to 1:8, 1:3 to 1:6 and 1:3 to 1:5. A preferred ratio is about 1:5.

In another embodiment, the solid dispersion or solid solution consists essentially of compound (I) and copovidone and the weight ratio of compound (I) to copovidone may be in the range of 1:1 to 1:10. Preferred ranges are for example 1:2 to 1:8, 1:3 to 1:6 and 1:3 to 1:5. A preferred ratio is about 1:5.

In another embodiment, the solid dispersion or solid solution consists of compound (I) and copovidone and the weight ratio of compound (I) to copovidone may be in the range of 1:1 to

1:10. Preferred ranges are for example 1:2 to 1:8, 1:3 to 1:6 and 1:3 to 1:5. A preferred ratio is about 1:5.

Further examples of possible polymers include HPMCAS, carboxymethyl cellulose (CMC, especially sodium and calcium salts), ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose (HPC); microcrystalline cellulose, and mixtures of the polymers mentioned; or mixtures of the polymers mentioned with polymers listed above.

In another embodiment, the polymers may be selected from carboxymethyl cellulose (CMC, especially sodium and calcium salts), ethyl cellulose, methyl cellulose, hydroxyethyl cellulose, ethyl hydroxyethyl cellulose, hydroxypropyl cellulose (HPC); microcrystalline cellulose, and mixtures of the polymers mentioned; or mixtures of the polymers mentioned with polymers listed above.

In another embodiment natural gum can be used as the polymer, e.g. gum traganth, alginates, gum Arabic and gum guar.

In one embodiment, the pharmaceutically acceptable excipient is a non-polymeric compound which preferably contains polar side groups. Examples include sugar alcohols and sugars. Examples of sugar alcohols are glycerol, xylitol, sorbitol, mannitol, isomalt and maltitol. Examples of sugars are aldoses, such as glucose and galactose, ketoses such as fructose, acetales, such as saccarose and trehalose, and hemiacetales, such as maltose and lactose.

In another embodiment, the pharmaceutically acceptable excipients include substances which behave like polymers, in particular semisolid excipients. Examples of these are fats and waxes.

Waxes suitable for use in the present invention include cetyl palmitate, carnauba wax or bees' wax. It is likewise possible to use fats, such as glycerol fatty acid esters (e.g. glycerol palmitate, glycerol behenate, glycerollaurate, glycerol stearate), PEG glycerol fatty acid esters or vegetable oils or hydrogenated vegetable oils. Further examples are glycerol, stearyl alcohol, salts of fatty acids (e.g. aluminium monostearate). Further specific examples of semisolid excipients are PEG 400, poly(oxy-1,2-ethanediyl) (Solutol HS 15), poloxamer 407 (Pluronic F127), macrogolglycerolhydroxystearat 40 (Cremophor RH 40), ceteareth - 6 and stearyl alcohol (Cremophor A6), lauroyl macrogol-32 glycerides (Gelucire 44/14),

stearoyl macrogol-32 glycerides (Gelucire 50/13) and macrogol-20-glycerolmono-stearat (Tagat S2).

It is preferable that the type and quantity of the excipient should be selected such that the resulting matrix or solid solution has a glass transition temperature (Tg) of 20°C or higher, preferably of 25°C or higher.

The ratio of compound (I) to pharmaceutically acceptable excipient is not particularly limited. The ratio can be adjusted to obtain the desired dilution effect or to allow for the solubility of the active substance in the suitable excipient. For example, the weight ratio of compound (I) to excipient may be in the range of 1:1 to 1:1,000. Preferred ranges are for example 1:1 to 1:500, 1:1 to 1:150, 1:1 to 1:100, 1:10 to 1:50, and in particular about 1:50. In one embodiment, the ratio is about 1:1. All of the above-mentioned upper and lower limits can also be combined with each other in order to form additional preferred ranges.

In another embodiment, the weight ratio of compound (I) to excipient may be in the range of 1:1 to 1:10. Preferred ranges are for example 1:2 to 1:8, 1:3 to 1:6 and 1:3 to 1:5. A preferred ratio is about 1:5.

In one embodiment the solid solution or solid dispersion is comminuted, for example by crushing, milling, grinding etc. Comminuting can be carried out by any known method in the art.

In one embodiment, the solid solution or solid dispersion contains 15% by weight or less of particles of compound (I) with a particle size of more than 1 µm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 1 µm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 1 µm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 1 µm.

In one embodiment, the solid solution or solid dispersion contains 15% by weight or less of particles of compound (I) with a particle size of more than 800 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 800 nm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 800 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 800 nm.

In one embodiment, the solid solution or solid dispersion contains 15% by weight or less of particles of compound (I) with a particle size of more than 500 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 500 nm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 500 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 500 nm.

In one embodiment, the solid solution or solid dispersion contains 15% by weight or less of particles of compound (I) with a particle size of more than 300 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 300 nm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 300 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 300 nm.

More preferably, the solid solution or solid dispersion contains substantially no particles, in particular no particles of compound (I), having a particle size of more than 300 nm, based on the total weight of the active ingredient present in the solid solution or solid dispersion.

In one embodiment, the solid solution or solid dispersion contains 15% by weight or less of particles of compound (I) with a particle size of more than 200 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 200 nm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 200 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 200 nm.

In one embodiment, the solid solution or solid dispersion contains 15% by weight or less of particles of compound (I) with a particle size of more than 100 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 100 nm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 100 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 100 nm.

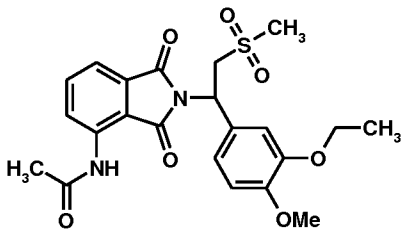
As used herein, particle size may refer to particle diameter.

The particle size may be determined by means of confocal Raman spectroscopy. For example, pressed disks can be made of the samples, and a mapping measurement can be performed on the surface of the samples along a quadratic raster of 15 x 15 points, spaced by 2 µm in both directions. The measurements can be performed with a INTEGRA-Spectra Nanofinder of the company NT-MDT or a Senterra Raman microscope (Bruker Optics) at 785 nm (100 mW) using a 50x objective (laser beam diameter approx. 2 µm).

In a preferred embodiment, the solid solution is a "single-phase" solid solution. As a monophase system, the solid solution is defined by reference to a common glass transition point of the excipient and the active ingredient. This can be determined by means of DSC.

Processes for preparing a Solid Solution or Solid Dispersion

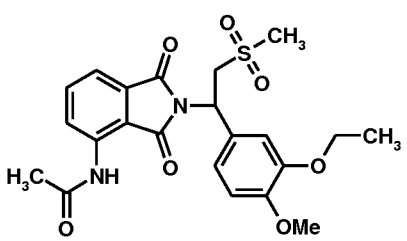
In a second aspect, the present invention relates to a process for preparing a solid solution or solid dispersion comprising compound (I) comprising spray drying compound (I), together with at least one pharmaceutically acceptable excipient.



Compound (I)

In one embodiment, the pharmaceutically acceptable excipients may be selected from any of the embodiments described above.

In third aspect, the present invention relates to a process for preparing a solid solution or solid dispersion of compound (I) comprising freeze drying compound (I), together with at least one pharmaceutically acceptable excipient.



Compound (I)

In one embodiment, the process comprises the steps of:

i. dissolving compound (I) and at least one pharmaceutically acceptable excipient, preferably a polymer as described above, in a solvent; and
ii. freeze drying the solution provided in step (i).

In one embodiment, the process comprises the steps of:

i. dissolving compound (I) and at least one pharmaceutically acceptable excipient, preferably a polymer as described above, in a solvent; and
ii. spray drying the solution provided in step (i).

The starting form of compound (I) which is dissolved with excipient can be any form of compound (I). In one embodiment the starting form of compound (I) is crystalline Form B. Preferably, the starting form of compound (I) is Form B with a purity of 90% or more; more preferably 95% or more; most preferably 99% or more. Form B may be characterised by XRPD peaks located at 10.1, 13.5, 20.7, 22.5, 24.7 and 26.9 degrees 2theta. Form B may be further characterised by XRPD peaks located at 10.1, 12.4, 13.5, 15.7, 16.3, 18.1, 20.7, 22.5, 24.7, 26.2, 26.9, and 29.1 degrees 2theta. The XRPD of Form B is provided in Figure 4. Form B can be prepared according to the procedure of WO2000/025777, which is incorporated herein by reference.

In one embodiment, the solvent is selected from water, alcohol (e.g. methanol, ethanol, isopropanol, butanol, pentanol), dimethyl sulphoxide (DMSO), acetone, ethyl acetate, heptane, dichloromethane or mixtures thereof.

In one embodiment, the solvent is selected from water, dimethyl sulphoxide (DMSO), acetone, ethyl acetate, heptane, dichloromethane or mixtures thereof.

In one embodiment, the solvent is selected from water, dimethyl sulphoxide (DMSO), acetone, ethyl acetate, heptane or mixtures thereof.

In one embodiment, the solvent is selected from water, dimethyl sulphoxide (DMSO), and heptane or mixtures thereof.

In another embodiment, the solvent comprises a hydrocarbon solvent, such as hexane or heptane. Preferably the solvent comprises heptane.

In another embodiment, the solvent is selected from a methanol/dichloromethane mixture. Preferably, the volume ratio of methanol:dichloromethane is 1:1 to 1:99 (v/v), more preferably the ratio is in the range of 1:50 (v/v), more preferably the ratio is in the range of 1:10 (v/v), more preferably the ratio is in the range of 1:5 (v/v).

In one embodiment, the inlet temperature in spray drying step (ii) is between about 60°C to about 200°C, preferably between about 60°C to about 160°C.

In one embodiment, the inlet temperature in spray drying step (ii) is between about 101°C to about 200°C, preferably between about 121°C to about 160°C, more preferably between about 130°C to about 160°C.

In one embodiment, the spray rate in spray drying step (ii) is about 7% to about 20%, preferably the spray rate is about 16%.

In one embodiment, the aspirator in spray drying step (ii) runs at about 80% to about 100%.

The spray-drying may be carried out in a spray tower. As an example, a Büchi B-290 is suitable (Büchi Labortechnik GmbH, Germany). Spray-drying has the advantage of being a continuous method, which enhances the reproducibility and hence also the homogeneity and uniformity of content of active agent.

The process conditions of step (ii) are preferably selected such that the resulting particles have a volume-average particle diameter (D_{50}) of 1 to 250 µm, more preferably 2 to 150 µm, especially 3 to 100 µm.

In another embodiment, the process conditions of step (ii) are preferably selected such that the resulting particles have a volume-average particle diameter (D_{50}) of 51 to 250 µm, more preferably 51 to 150 µm, especially 51 to 100 µm.

The expression "volume-average particle diameter" relates in the context of this invention to the D_{50} value of the volume average particle diameter determined by means of laser diffractometry. For example, a Malvern Instruments Mastersizer 2000 may be used to determine the diameter (wet measurement with ultrasound for 5 min., 2,500 rpm, the

evaluation using the Fraunhofer method, and preferably using sun flower oil as dispersant). The average particle diameter, which is also referred to as the D_{50} value of the integral volume distribution, is defined in the context of this invention as the particle diameter at which 50 % by volume of the particles have a smaller diameter than the diameter which corresponds to the D_{50} value. Similarly, 50 % by volume of the particles then have a larger diameter than the D_{50} value.

In each of the above embodiments, the process may further comprise comminuting the solid solution or solid dispersion resulting from step (ii). Comminuting can be carried out by any suitable technique known in the art, for instance crushing, milling or grinding.

In one embodiment, the process comprises the following steps:

a) dissolving compound (I) and at least one pharmaceutically acceptable excipient, preferably a polymer as described above, in a solvent; and
b) freeze drying or spray drying the solution provided in step (a); and .
c) comminuting the product of (b).

In one embodiment, the process consists essentially of the following steps:

a) dissolving compound (I) and at least one pharmaceutically acceptable excipient, preferably a polymer as described above, in a solvent; and
b) freeze drying or spray drying the solution provided in step (a); and .
c) comminuting the product of (b).

In one embodiment, the process consists of the following steps:

a) dissolving compound (I) and at least one pharmaceutically acceptable excipient, preferably a polymer as described above, in a solvent; and
b) freeze drying or spray drying the solution provided in step (a); and .
c) comminuting the product of (b).

In a fourth aspect, the present invention relates to a solid solution or solid dispersion comprising compound (I) obtainable by any of the processes described above.

Melt of Compound (I)

In a fifth aspect, the present invention relates to a melt consisting essentially of compound (I).

Preferably, the melt consists essentially of amorphous compound (I).

In an embodiment of the fifth aspect, the present invention relates to a melt consisting of compound (I).

Preferably, the melt consists of amorphous compound (I).

In one embodiment, the melt of compound (I) is substantially free of any crystalline forms. In another embodiment, the melt of compound (I) contains 20% or less of any crystalline form, preferably 10% or less, more preferably 5% or less, more preferably 2% or less, more preferably 1% or less.

In one embodiment the melt is comminuted, for example by crushing, milling or grinding etc. Comminuting can be carried out by any known method in the art.

In one embodiment, the melt contains 15% by weight or less of particles of compound (I) with a particle size of more than 1 µm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 1 µm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 1 µm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 1 µm.

In one embodiment, the melt contains 15% by weight or less of particles of compound (I) with a particle size of more than 800 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 800 nm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 800 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 800 nm.

In one embodiment, the melt contains 15% by weight or less of particles of compound (I) with a particle size of more than 500 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 500 nm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 500 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 500 nm.

In one embodiment, the melt contains 15% by weight or less of particles of compound (I) with a particle size of more than 300 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 300 nm. More preferably, 5% by weight or

less of particles of compound (I) with a particle size of more than 300 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 300 nm.

More preferably, the melt contains substantially no particles, in particular no particles of compound (I), having a particle size of more than 300 nm, based on the total weight of the active ingredient present in the melt.

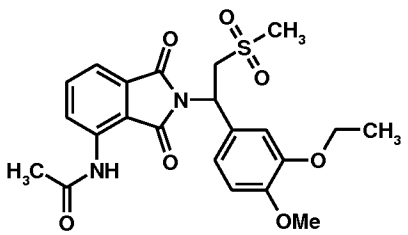
In one embodiment, the melt contains 15% by weight or less of particles of compound (I) with a particle size of more than 200 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 200 nm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 200 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 200 nm.

In one embodiment, the melt contains 15% by weight or less of particles of compound (I) with a particle size of more than 100 nm. Preferably, 10% by weight or less of particles of compound (I) with a particle size of more than 100 nm. More preferably, 5% by weight or less of particles of compound (I) with a particle size of more than 100 nm. More preferably, 2% by weight or less of particles of compound (I) with a particle size of more than 100 nm.

The particle size may be determined by means of confocal Raman spectroscopy using an INTEGRA-Spectra Nanofinder of the company NT-MDT.

Processes for preparing a Melt

In a sixth aspect, the present invention relates to a process for preparing a melt consisting essentially of compound (I) comprising melting compound (I).



Compound (I)

Preferably, the process of the sixth aspect is for preparing a melt consisting essentially of amorphous compound (I).

In an embodiment of the sixth aspect the present invention relates a process for preparing a melt consisting of compound (I) comprising melting compound (I).

Preferably, the process of the sixth aspect is for preparing a melt consisting of amorphous compound (I).

The starting form of compound (I) which is melted can be any form of compound (I). In one embodiment the starting form of compound (I) is crystalline Form B. Preferably, the starting form of compound (I) is Form B with a purity of 90% or more; more preferably 95% or more; most preferably 99% or more. Form B may be characterised by XRPD peaks located at 10.1, 13.5, 20.7, 22.5, 24.7 and 26.9 degrees 2theta. Form B may be further characterised by XRPD peaks located at 10.1, 12.4, 13.5, 15.7, 16.3, 18.1, 20.7, 22.5, 24.7, 26.2, 26.9, and 29.1 degrees 2theta. The XRPD of Form B is provided in Figure 4. Form B can be prepared according to the procedure of WO2000/025777, which is incorporated herein by reference.

In one embodiment, compound (I) is heated to a temperature of between about 150°C and about 200°C, preferably a temperature of between about 160°C and about 190°C, more preferably a temperature of between about 165°C and about 185°C, more preferably a temperature of between about 165°C and about 175°C, more preferably a temperature of about 170°C.

In one embodiment, the process further comprises cooling the melt of compound (I).

The melt may be cooled by allowing it to cool passively to room temperature. For example, the melt can be left to cool to room temperature by standing open to atmosphere. Alternatively, the melt may be left to cool to room temperature under an inert atmosphere, such as a nitrogen or argon blanket.

In another embodiment, the melt is cooled actively. For example, the melt may be quenched cooled. Quench cooling may take place by immersing the vessel that the melt is in a water bath. Alternatively, the melt may be cooled by exposing it to a stream of air or inert gas, such as nitrogen or argon.

In each of the above embodiments, the process may further comprise comminuting the melt. Comminuting can be carried out by any suitable technique known in the art, for instance crushing, milling or grinding.

In each of the above embodiments, the process may further comprise extrusion of the melt. Extrusion can be carried out using any technique known in the art. For example, suitable techniques include those described in "Pharmaceutical Extrusion Technology" by Isaac Ghebre-Sellassie, Charles Martin, ISBN 0824740505, Informa Healthcare Verlag, 2003, the content of which is incorporated herein by reference.

In one embodiment, the process comprises the following steps:

(a) melting pure or essentially pure compound (I)
(b) cooling compound (I) to room temperature; and
(c) comminuting the product of (b).

In one embodiment, the process consists essentially of the following steps:

(a) melting pure or essentially pure compound (I)
(b) cooling compound (I) to room temperature; and
(c) comminuting the product of (b).

In one embodiment, the process consists of the following steps:

(a) melting pure or essentially pure compound (I)
(b) cooling compound (I) to room temperature; and
(c) comminuting the product of (b).

As used herein “pure” refers to compound (I) which has a purity of 99% or more as determined by UV-HPLC. “Essentially pure” refers to compound (I) which has a purity of 95% or more as determined by UV-HPLC.

In a seventh aspect, the present invention relates to a melt obtainable by any of the processes described above.

Pharmaceutical Compositions

In an eight aspect, the present invention relates to a pharmaceutical composition comprising a solid solution or solid dispersion according to the invention, or a melt according to the invention, and a pharmaceutically acceptable excipient.

Pharmaceutical compositions may be prepared as medicaments to be administered orally, parenterally, rectally, transdermally, buccally, or nasally. Suitable forms for oral administration include tablets, compressed or coated pills, dragees, sachets, hard or gelatin capsules, sub-lingual tablets, syrups, and suspensions. Suitable forms of parenteral administration include an aqueous or non-aqueous solution or emulsion, while for rectal administration, suitable forms for administration include suppositories with hydrophilic or hydrophobic vehicle. For topical administration, the invention provides suitable transdermal delivery systems known in the art, and for nasal delivery, there are provided suitable aerosol delivery systems known in the art.

In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients or adjuvants. Selection of excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelitinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol, and talc.

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate, and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants

include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®), and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and die. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and die, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the die. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

Flavouring agents and flavour enhancers make the dosage form more palatable to the patient. Common flavouring agents and flavour enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

Solid and liquid compositions may also be dried using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, the active ingredient and any other solid excipients are suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the

liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol, and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth, and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol, and invert sugar may be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole, and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

According to the present invention, a liquid composition may also contain a buffer such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate, or sodium acetate.

Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates, and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant, and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches, and lozenges, as well as liquid syrups, suspensions, and elixirs.

The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin, and, optionally, contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling can be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended, and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried, and then screened and/or milled to the desired particle size. The granulate may then be tableted or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition can be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet, and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

Administration

Typically, a physician will determine the actual dosage which will be most suitable for an individual subject and it will vary with the age, weight and response of the particular patient and severity of the condition. The dosages below are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited.

The compositions (or component parts thereof) of the present invention may be administered orally. In addition or in the alternative the compositions (or component parts thereof) of the present invention may be administered by direct injection. In addition or in the alternative the compositions (or component parts thereof) of the present invention may be administered topically. In addition or in the alternative the compositions (or component parts thereof) of the present invention may be administered by inhalation. In addition or in the alternative the compositions (or component parts thereof) of the present invention may also be administered by one or more of: parenteral, mucosal, intramuscular, intravenous, subcutaneous, intraocular or transdermal administration means, and are formulated for such administration.

By way of further example, the pharmaceutical composition of the present invention may be administered in accordance with a regimen of 1 to 10 times per day, such as once or twice per day. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The term “administered” also includes but is not limited to delivery by a mucosal route, for example, as a nasal spray or aerosol for inhalation or as an ingestible solution; a parenteral route where delivery is by an injectable form, such as, for example, an intravenous, intramuscular or subcutaneous route.

Hence, the pharmaceutical composition of the present invention may be administered by one or more of the following routes: oral administration, injection (such as direct injection), topical, inhalation, parenteral administration, mucosal administration, intramuscular administration, intravenous administration, subcutaneous administration, intraocular administration or transdermal administration.

Medical uses

In a ninth aspect, the present invention relates to a method of treating or preventing a disease or disorder ameliorated by the inhibition of TNF-[alpha] production, wherein the method comprises administering a therapeutically or prophylactically effective amount of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention.

In one embodiment the disease or disorder ameliorated by the inhibition of TNF-[alpha] production is selected from psoriasis; psoriatic arthritis; rheumatoid arthritis; chronic cutaneous sarcoid; giant cell arteritis; Parkinson's Disease; prurigo nodularis; lichen planus; complex apthosis; Behcet's Disease; lupus; hepatitis; uveitis; Sjogren's Disease; depression; interstitial cystitis; vulvodynia; prostatitis; osteoarthritis; diffuse large B cell lymphoma; polymysoitis; dermatomyositis; inclusiuon body myositis; erosive osteoarthritis; interstitial cystitis; hepatitis; endometriosis; radiculopathy; and pyoderma gangrenosum.

Alternatively, the ninth aspect relates to a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention for use in the treatment of any of following: psoriasis; psoriatic arthritis; rheumatoid arthritis; chronic cutaneous sarcoid; giant cell arteritis; Parkinson's Disease; prurigo nodularis; lichen planus; complex apthosis; Behcet's Disease; lupus; hepatitis; uveitis; Sjogren's Disease; depression; interstitial cystitis; vulvodynia; prostatitis; osteoarthritis; diffuse large B cell lymphoma; polymysoitis; dermatomyositis; inclusiuon body myositis; erosive osteoarthritis; interstitial cystitis; hepatitis; endometriosis; radiculopathy; and pyoderma gangrenosum.

Alternatively, the ninth aspect relates to the use of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention in the manufacture of a medicament for the treatment of any of following: psoriasis; psoriatic arthritis; rheumatoid arthritis; chronic cutaneous sarcoid; giant cell arteritis; Parkinson's Disease; prurigo nodularis; lichen planus; complex apthosis; Behcet's Disease; lupus; hepatitis; uveitis; Sjogren's Disease; depression; interstitial cystitis; vulvodynia; prostatitis; osteoarthritis; diffuse large B cell lymphoma; polymysoitis; dermatomyositis; inclusiuon body myositis; erosive osteoarthritis; interstitial cystitis; hepatitis; endometriosis; radiculopathy; and pyoderma gangrenosum.

In a tenth aspect, the present invention relates to a method of treating or preventing a disease or disorder ameliorated by the inhibition of PDE4, wherein the method comprises administering a therapeutically or prophylactically effective amount of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention.

In one embodiment the disease or disorder ameliorated by the inhibition of PDE4 is selected from HIV; hepatitis; adult respiratory distress syndrome; bone resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; inflammatory skin disease, atopic dermatitis, cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory bowel disease; multiple sclerosis; systemic lupus erythrematosus; erythema nodosum leprosum in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

Alternatively, the tenth aspect relates to a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention for use in the treatment of any of following: HIV; hepatitis; adult respiratory distress syndrome; bone resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; inflammatory skin disease, atopic dermatitis, cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory bowel disease; multiple sclerosis; systemic lupus erythrematosus; erythema nodosum leprosum in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

Alternatively, the tenth aspect relates to the use of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention in the manufacture of a medicament for the treatment of any of following: HIV; hepatitis; adult respiratory distress syndrome; bone resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; inflammatory skin disease, atopic dermatitis, cystic fibrosis; septic shock; sepsis;

endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory bowel disease; multiple sclerosis; systemic lupus erythrematosus; erythema nodosum leprosum in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

In an eleventh aspect, the present invention relates to a method of treating or preventing a cancer, wherein the method comprises administering a therapeutically or prophylactically effective amount of an amorphous form of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention.

Alternatively, the eleventh aspect relates to a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention for use in the treatment of cancer.

Alternatively, the eleventh aspect relates to the use of a solid solution or solid dispersion according to the invention, a melt according to the invention, or a pharmaceutical composition according to the invention in the preparation of a medicament for the treatment of cancer.

In one embodiment the cancer is selected from multiple myeloma, malignant melanoma, malignant glioma, leukaemia and a solid tumour.

Although the foregoing compositions and methods have been described in some detail by way of illustration and examples for purposes of clarity of understanding, it will be apparent to those skilled in the art that certain changes and modifications may be made. Therefore, the description should not be construed as limiting the scope of the invention, which is delineated by the appended claims.

Examples

Materials and Methods

XPRD patterns were generated on a Bruker-AXS D8 Advance powder X-ray diffractometer (Bruker-AXS, Karlsruhe, Germany), equipped with a Vantec-1 detector (3° opening angle). The sample holder was rotated in a plane parallel to its surface at 20 rpm during measurement. The measurement conditions were as follows: Radiation: Cu K-alpha, Source 38 kV / 40 mA, divergence slit (variable V6, antiscattering slit 5.59 mm, detector slit 10.28 mm, start angle 2°, end angle 55°, Step 0.016° 2θ).

DSC measurements were performed using a Mettler Toledo DSC 1 apparatus. The work was performed at a heating rate of 1 to 20°C/min, preferably 5 to 15°C/min, and at a cooling rate of 5 to 25°C/min, preferably 10 to 20°C/min.

TGA measurements may be performed on a suitable instrument (e.g. a SEIKO Instrument) in a nitrogen atmosphere and platinum pans. The temperature range may be 30°C to 600°C at a rate of between 10°C/min.

Dissolution conditions were 900 mL buffer and 0.5% SDS, 37°C, 100 rpm paddle (USP app.II). The preparation of the buffers employed is provided below:

For pH of approximately 1.2 weigh 150 g of HCl 25% into a 10 litre vessel. Fill up with purified water to 10kg.

For sodium acetate trihydrate pH 4.5 (50 mM) buffer weigh about 29.9 g of CH_3COONa x $3H_2O$ into a 10 litre vessel. Fill up with purified water to 10kg. Adjust the pH with CH_3COOH to 4.5.

For potassium phosphate, pH 6.8 (50 mM) buffer weigh 68.05 g of KH_2PO_4 x H_2O and 9.6 g of NaOH pellets into a 10 litre vessel. Fill up with purified water to 10kg. Adjust the pH with NaOH or H_3PO_4 to 6.8.

Preparative Example 1 - Amorphous melt of Apremilast prepared by melting of Apremilast (crystal FormB):

An oil bath with silicon oil was heated to 170 - 175 °C 175°C, a PT100 temperature sensor was placed into the oil bath to regulate and control its temperature.

A 250 mL 3-necked round bottomed flask was tare weighed and Apremilast (10.03 g) was weighed into it. The flask was evaporated and vented with inert gas (Ar) three times and evacuated again (100 mbar). The flask was immersed into the thermo-regulated bath, while the bath was stirred slowly.

A temperature sensor in the inner of the flask reached 167°C, when the solid powder becomes coalescent. A greenish-lemon coloured melt had been formed at this temperature after 15 min, and little bubbles are expelled. When the bubbling had come to an end after 5-10 minutes a clear melt had been obtained.

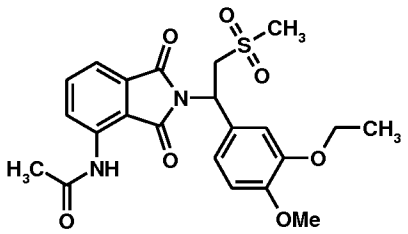
The flask was taken from heating bath, and immersed to cold water bath at 15°C. Immediately the melt becomes a solid and brittle glass. The flask with the residual glass had been weighed, a net weight of 9.9622 g was found. The brittle glass was broken from the inner walls of the flask by means of a spatula and transferred to a mortar of agate. The glass was finely ground to obtain a nearly white, light green shining powder (recovery 99.6%).
A weight loss of 0.71% (LOD) was calculated.

A sample of the solid was analysed by means of XRPD (see Figure 1) and TGA/DSC (see Figure 3), and the purity of the solid was analysed by HPLC (see Figure 2).

There was no residual crystalline solid visible in the diffraction pattern, and no endothermal or exothermal event was seen in the DSC profile. The purity of the amorphous solid was essentially retained through the melting process. The number and levels of impurities (i.e. rt=2.51 min., rt= 5.08 min, rt=7.88 min.), were found to be slightly raised (rt. 6.52 min.).

The invention will now be described by means of the following numbered paragraphs:

1. A solid solution or solid dispersion comprising compound (I)



Compound (I)

2. A solid solution or solid dispersion according to paragraph 1 wherein compound (I) is amorphous.

3. A solid solution or solid dispersion according to any preceding paragraph comprising/ essentially consisting of/ consisting of a pharmaceutically acceptable excipient selected from the group consisting of a polymer, a saccharide, an oligosaccharide, a polysaccharide, a sugar alcohol, a lipid, and a wax.

4. A solid solution or solid dispersion according to paragraph 3 wherein the pharmaceutically acceptable excipient has a softening point (Ts) or a glass transition temperature (Tg) of about 20°C or higher, preferably about 20°C to about 220°C, more preferably about 20°C to about 200°C, even more preferably about 40°C to about 180°C, most preferably about 60°C to about 140°C.

5. A solid solution or solid dispersion according to any preceding paragraph wherein the pharmaceutically acceptable excipient is a polymer.

6. A solid solution or solid dispersion according to paragraph 5 wherein the polymer has a number-average molecular weight of 1,000 to 4,000,000 g/mol, more preferably from 1,000 to 3,500,000 g/mol, even more preferably from 1,500 to 3,000,000 g/mol, and particularly preferably from 3,500 to 2,500,000 g/mol.

7. A solid solution or solid dispersion according to any one of paragraphs 3 to 6 wherein the polymer is a cellulosic polymer or a non-cellulosic polymer.

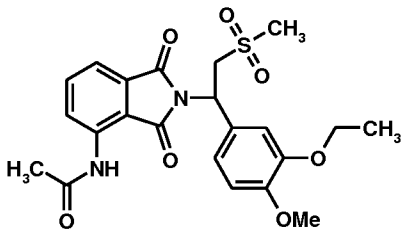
8. A solid solution or solid dispersion according to paragraph 7 wherein the polymer is a non-ionizable, non-cellulosic polymer

9. A solid solution or solid dispersion according to any one of paragraphs 3 to 8 wherein the polymer is selected from methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxyethyl methyl cellulose (HEMC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate (HPMCA), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl cellulose acetate succinate (HPCAS), hydroxyethyl cellulose acetate succinate (HECAS), hydroxyethyl methyl cellulose succinate (HEMCS), hydroxyethyl methyl cellulose acetate succinate (HEMCAS) ,carboxymethyl cellulose (CMC), carboxyethyl cellulose (CEC), carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methyl cellulose acetate phthalate (HPMCAP), hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), polyvinyl acetate (PVAc), vinylpyrrolidon vinylacetat copolymer (VP/VAc copolymer, such as Copovidon Kollidon VA 64), polyvinylacetat polyvinylpyrrolidon copolymer (PVAc/PVP copolymer, Povidon), polyvinyl polypyrrolidon (PVPP copolymer, Crospovidon), polyvinyl alcohol polyethylene glycol copolymer (PVA/PEG copolymer), poly propylen glycols (PPGs), poly ethylen glycols (PEGs 1500, 3000, 3350, 4000, 6000, 8000, 10000, 12000, 20000), polyoxyethylene polyoxypropylene copolymers (Poloxamers), polymethacrylates (such as the EUDRAGITS®), carboxylic acid functionalized polyacrylates (such as the EUDRAGITS®), amine-functionalized polyacrylates and polymethacrylates, acrylate and methacrylate copolymers (such as the EUDRAGITS®), and polyoxyethylene-polyoxypropylene copolymers (such as the PLURONICS®), or mixture thereof.

10. A solid solution or solid dispersion according to any preceding paragraph wherein the polymer is vinylpyrrolidone vinylacetate copolymer (VP/VAc copolymer, copovidone), PEG 6000, Polyoxyethylene-polyoxypropylene block copolymer (e.g. Pluronic F68), Isomalt and Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (Soluplus), preferably the polymer is copovidone.

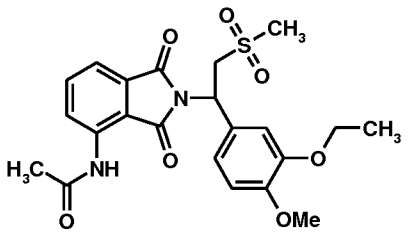
11. A solid solution or solid dispersion according to any preceding paragraph wherein compound (I) is 80% or more in the (+)-enantiomeric form.

12. A process for preparing a solid solution or solid dispersion comprising compound (I) comprising spray drying compound (I), together with at least one pharmaceutically acceptable excipient.



Compound (I)

13. A process for preparing a solid solution or solid dispersion comprising compound (I) comprising freeze drying compound (I), together with at least one pharmaceutically acceptable excipient.



Compound (I)

14. A process according to any one of paragraphs 12 and 13 wherein at least one of the pharmaceutically acceptable excipients is selected from a polymer, a copolymer, a saccharide, an oligosaccharide, polysaccharide, a sugar alcohol, a lipid and wax; preferably a polymer or a copolymer.

15. A process according to any one of paragraphs 12 to 14 wherein the pharmaceutically acceptable excipient has a softening point (Ts) or a glass transition temperature (Tg) of about 20℃ or higher, preferably about 20℃ to about 220℃, more preferably about 20℃ to about 200℃, even more preferably about 40℃ to about 180℃, most preferably about 60℃ to about 140℃.

16. A process according to any one of paragraphs 12 to 15 wherein the pharmaceutically acceptable excipient is a polymer.

17. A process according to any one of paragraphs 12 to 16 wherein the polymer has a number-average molecular weight of 1,000 to 4,000,000 g/mol, more preferably from 1,000 to 3,500,000 g/mol, even more preferably from 1,500 to 3,000,000 g/mol, and particularly preferably from 3,500 to 2,500,000 g/mol.

18. A process according to any one of paragraphs 12 to 17 wherein the polymer is a cellulosic polymer or a non-cellulosic polymer.

19. A process according to any one of paragraphs 12 to 18 wherein the polymer is a non-ionizable, non-cellulosic polymer

20. A process according to any one of paragraphs 12 to 19 wherein the polymer is selected from methyl cellulose (MC), ethyl cellulose (EC), hydroxyethyl cellulose (HEC), hydroxyethyl methyl cellulose (HEMC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose acetate (HPMCA), hydroxypropyl methyl cellulose acetate succinate (HPMCAS), hydroxypropyl cellulose acetate succinate (HPCAS), hydroxyethyl cellulose acetate succinate (HECAS), hydroxyethyl methyl cellulose succinate (HEMCS), hydroxyethyl methyl cellulose acetate succinate (HEMCAS) ,carboxymethyl cellulose (CMC), carboxyethyl cellulose (CEC), carboxymethyl ethyl cellulose (CMEC), hydroxypropyl methyl cellulose acetate phthalate (HPMCAP), hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), polyvinyl acetate (PVAc), vinylpyrrolidon vinylacetat copolymer (VP/VAc copolymer, such as Copovidon Kollidon VA 64), polyvinylacetat polyvinylpyrrolidon copolymer (PVAc/PVP copolymer, Povidon), polyvinyl polypyrrolidon (PVPP copolymer, Crospovidon), polyvinyl alcohol polyethylene glycol copolymer (PVA/PEG copolymer), poly propylen glycols (PPGs), poly ethylen glycols (PEGs 1500, 3000, 3350, 4000, 6000, 8000, 10000, 12000, 20000), polyoxyethylene polyoxypropylene copolymers (Poloxamers), polymethacrylates (such as the EUDRAGITS®), carboxylic acid functionalized polyacrylates (such as the EUDRAGITS®), amine-functionalized polyacrylates and polymethacrylates, acrylate and methacrylate copolymers (such as the EUDRAGITS®), and polyoxyethylene-polyoxypropylene copolymers (such as the PLURONICS®), or mixture thereof.

21. A process according to any one of paragraphs 12 to 20 wherein the polymer is vinylpyrrolidone vinylacetate copolymer (VP/VAc copolymer, copovidone), PEG 6000, Polyoxyethylene-polyoxypropylene block copolymer (e.g. Pluronic F68), Isomalt and Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (Soluplus), preferably the polymer is copovidone.

22. A process according to any one of paragraphs 12 to 21 wherein compound (I) is 80% or more in the (+)-enantiomeric form.

23. A process according to any one of paragraphs 12 to 22 wherein the compound (I) to polymer weight ratio is in the range of about 1:1 to about 1:150 (w/w), preferably in the range of about 1:1 to about 1:100 (w/w), preferably in the range of about 1:1 to about 1:50 (w/w), preferably in the range of about 1:1 to about 1:150 (w/w), preferably in the range of about 1:1 to about 1:10 (w/w), more preferably about 1:5 (w/w).

24. A process according to any preceding paragraph comprising the steps of:
    i. dissolving compound (I) and at least one pharmaceutically acceptable excipient, preferably a polymer, in a solvent; and
    ii. spray drying or freeze drying the solution provided in step (i).

25. A process according to paragraph 24 wherein the solvent is selected from water, alcohol (e.g. methanol, ethanol, isopropanol, butanol, pentanol), dimethyl sulphoxide (DMSO), acetone, ethyl acetate, heptane, dichloromethane or mixtures thereof.

26. A process according to paragraph 25 wherein the solvent is selected from a methanol/dichloromethane mixture.

27. A process according to paragraph 26 wherein the volume ratio of methanol:dichloromethane is about 1:1 to about 1:99 (v/v), more preferably the ratio is in the range of about 1:1 to about 1:50 (v/v), more preferably the ratio is in the range of about 1:1 to about 1:10 (v/v), more preferably the ratio is about 1:5 (v/v).

28. A process according to any preceding paragraph wherein the inlet temperature in step (ii) is between about 60°C to about 160°C.

29. A process according to any preceding paragraph wherein the spray rate in step (ii) is about 7% to about 20%, preferably the spray rate is about 16%.

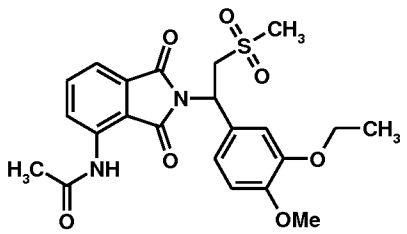
30. A solid solution or solid dispersion comprising compound (I) obtainable by a process according to any one of paragraphs 12 to 29.

31. A melt consisting essentially of compound (I).

32. A melt consisting of compound (I).

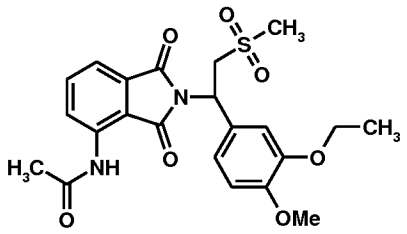
33. A melt according to any one of paragraphs 31 and 32 wherein compound (I) is amorphous.

34. A process for preparing a melt consisting essentially of compound (I) comprising melting compound (I).



Compound (I)

35. A process for preparing a melt consisting of compound (I) comprising melting compound (I).



Compound (I)

36. A process according to any one of paragraphs 34 and 35 wherein compound (I) is heated to a temperature of between about 150°C and about 200°C, preferably a temperature of between about 160°C and about 190°C, more preferably a temperature of between about 165°C and about 185°C, more preferably a temperature of between about 165°C and about 175°C, more preferably a temperature of about 170°C.

37. A process according to any one of paragraphs 34 to 36 further comprising cooling the melt of compound (I).

38. A process according to paragraph 37 wherein the melt is cooled by allowing the melt to cool passively to room temperature, or actively cooling the melt.

39. A process according to paragraph 38 wherein the melt is actively cooled by quench cooling, preferably by immersing the melt in a water bath.

40. A process according to paragraph 39 wherein the melt is passively cooled under an inert atmosphere.

41. A process according to paragraph 40 wherein the melt is passively cooled in air.

42. A process according to any one of paragraphs 34 to 41 further comprising comminuting the melt.

43. A process according to paragraph 42 wherein the melt is comminuted by grinding, milling or crushing.

44. A melt obtainable by a process according to any one of paragraphs 34 to 43.

45. A pharmaceutical composition comprising a solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 33 and 44, and a pharmaceutically acceptable excipient.

46. A method of treating or preventing a disease or disorder ameliorated by the inhibition of TNF-[alpha] production, wherein the method comprises administering a therapeutically or prophylactically effective amount of a solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45.

47. The method of paragraph 46 wherein the disease or disorder is selected from psoriasis; psoriatic arthritis; rheumatoid arthritis; chronic cutaneous sarcoid; giant cell arteritis; Parkinson's Disease; prurigo nodularis; lichen planus; complex apthosis; Behcet's Disease; lupus; hepatitis; uveitis; Sjogren's Disease; depression; interstitial

cystitis; vulvodynia; prostatitis; osteoarthritis; diffuse large B cell lymphoma; polymysoitis; dermatomyositis; inclusiuon body myositis; erosive osteoarthritis; interstitial cystitis; hepatitis; endometriosis; radiculopathy; and pyoderma gangrenosum.

48. A method of treating or preventing a disease or disorder ameliorated by the inhibition of PDE4, wherein the method comprises administering a therapeutically or prophylactically effective amount of a solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45.

49. The method of paragraph 48 wherein the disease or disorder is selected from HIV; hepatitis; adult respiratory distress syndrome; bone resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; inflammatory skin disease, atopic dermatitis, cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory bowel disease; multiple sclerosis; systemic lupus erythrematosus; erythema nodosum leprosum in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

50. A method of treating or preventing a cancer, wherein the method comprises administering a therapeutically or prophylactically effective amount of an amorphous form of a solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45.

51. The method of paragraph 50 wherein the cancer is selected from multiple myeloma, malignant melanoma, malignant glioma, leukemia and a solid tumor.

52. A solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45 for use in treating or preventing a disease or disorder ameliorated by the inhibition of TNF-[alpha] production.

53. A solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45 for use according to paragraph 43 wherein the disease or disorder is selected from psoriasis; psoriatic arthritis; rheumatoid arthritis; chronic cutaneous sarcoid; giant cell arteritis; Parkinson's Disease; prurigo nodularis; lichen planus; complex apthosis; Behcet's Disease; lupus; hepatitis; uveitis; Sjogren's Disease; depression; interstitial cystitis; vulvodynia; prostatitis; osteoarthritis; diffuse large B cell lymphoma; polymysoitis; dermatomyositis; inclusiuon body myositis; erosive osteoarthritis; interstitial cystitis; hepatitis; endometriosis; radiculopathy; and pyoderma gangrenosum.

54. A solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45 for use in treating or preventing a disease or disorder ameliorated by the inhibition of PDE4.

55. A solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45 for use according to paragraph 45 wherein the disease or disorder is selected from HIV; hepatitis; adult respiratory distress syndrome; bone resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; inflammatory skin disease, atopic dermatitis, cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory bowel disease; multiple sclerosis; systemic lupus erythrematosus; erythema nodosum leprosum in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

56. A solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45 for use in treating or preventing cancer.

57. A solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45 for use according to paragraph 47 wherein the cancer is selected from multiple myeloma, malignant melanoma, malignant glioma, leukemia and a solid tumor.

58. Use of a solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45 in the manufacture of a medicament for treating or preventing a disease or disorder ameliorated by the inhibition of TNF-[alpha] production.

59. Use according to paragraph 58 wherein the disease or disorder is selected from psoriasis; psoriatic arthritis; rheumatoid arthritis; chronic cutaneous sarcoid; giant cell arteritis; Parkinson's Disease; prurigo nodularis; lichen planus; complex apthosis; Behcet's Disease; lupus; hepatitis; uveitis; Sjogren's Disease; depression; interstitial cystitis; vulvodynia; prostatitis; osteoarthritis; diffuse large B cell lymphoma; polymysoitis; dermatomyositis; inclusiuon body myositis; erosive osteoarthritis; interstitial cystitis; hepatitis; endometriosis; radiculopathy; and pyoderma gangrenosum.

60. Use of a solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45 in the manufacture of a medicament for treating or preventing a disease or disorder ameliorated by the inhibition of PDE4.

61. Use according to paragraph 60 wherein the disease or disorder is selected from HIV; hepatitis; adult respiratory distress syndrome; bone resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; inflammatory skin disease, atopic dermatitis, cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis;

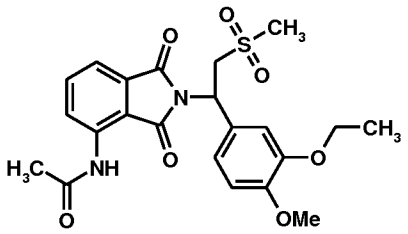
Crohn's disease; ulcerative colitis; inflammatory bowel disease; multiple sclerosis; systemic lupus erythrematosus; erythema nodosum leprosum in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

62. Use of a solid solution or solid dispersion according to any one of paragraphs 1 to 11 and 30, or a melt according to any one of paragraphs 31 to 34 and 44, or a pharmaceutical composition according to paragraph 45 in the manufacture of a medicament for treating or preventing cancer.

63. Use according to paragraph 62 wherein the cancer is selected from multiple myeloma, malignant melanoma, malignant glioma, leukemia and a solid tumor.

CLAIMS

1. A solid solution or solid dispersion comprising compound (I)



Compound (I)

2. A solid solution or solid dispersion according to claim 1 wherein compound (I) is amorphous.

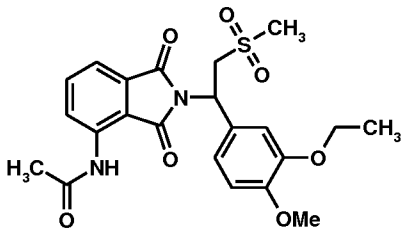
3. A solid solution or solid dispersion according to any preceding claim comprising a pharmaceutically acceptable excipient selected from the group consisting of a polymer, a saccharide, an oligosaccharide, a polysaccharide, a sugar alcohol, a lipid, and a wax.

4. A solid solution or solid dispersion according to any preceding claim wherein the pharmaceutically acceptable excipient is a polymer.

5. A solid solution or solid dispersion according to claim 4 wherein the polymer is a non-ionizable, non-cellulosic polymer.

6. A solid solution or solid dispersion according to claim 5 wherein the polymer is vinylpyrrolidone vinylacetate copolymer (VP/VAc copolymer, copovidone), PEG 6000, Polyoxyethylene-polyoxypropylene block copolymer (e.g. Pluronic F68), Isomalt and Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (Soluplus), preferably the polymer is copovidone.

7. A process for preparing a solid solution or solid dispersion comprising compound (I) comprising spray drying or freeze drying compound (I), together with at least one pharmaceutically acceptable excipient.



Compound (I)

8. A process according to claim 7 wherein at least one of the pharmaceutically acceptable excipients is selected from a polymer, a copolymer, a saccharide, an oligosaccharide, polysaccharide, a sugar alcohol, a lipid and wax; preferably a polymer or a copolymer.

9. A process according to any one of claims 7 and 8 wherein the pharmaceutically acceptable excipient is a polymer; preferably vinylpyrrolidone vinylacetate copolymer (VP/VAc copolymer, copovidone), PEG 6000, Polyoxyethylene-polyoxypropylene block copolymer (e.g. Pluronic F68), Isomalt and Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft Co-polymer (Soluplus); more preferably the polymer is copovidone.

10. A process according to any one of claims 7 to 9 wherein the compound (I) to polymer weight ratio is in the range of about 1:1 to about 1:150 (w/w), preferably in the range of about 1:1 to about 1:100 (w/w), preferably in the range of about 1:1 to about 1:50 (w/w), preferably in the range of about 1:1 to about 1:150 (w/w), preferably in the range of about 1:1 to about 1:10 (w/w), more preferably about 1:5 (w/w).

11. A process according to any one of claims 7 to 10 comprising the steps of:
    i. dissolving compound (I) and at least one pharmaceutically acceptable excipient, preferably a polymer, in a solvent; and
    ii. spray drying or freeze drying the solution provided in step (i).

12. A process according to claim 11 wherein the solvent is selected from water, alcohol (e.g. methanol, ethanol, isopropanol, butanol, pentanol), dimethyl sulphoxide (DMSO), acetone, ethyl acetate, heptane, dichloromethane or mixtures thereof.

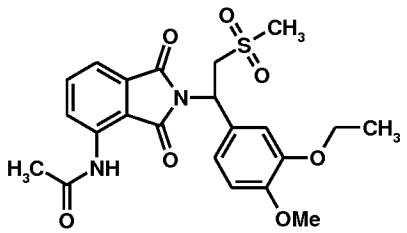
13. A solid solution or solid dispersion comprising compound (I) obtainable by a process according to any one of claims 7 to 12.

14. A melt consisting essentially of compound (I).

15. A melt consisting of compound (I).

16. A melt according to any one of claims 14 and 15 wherein compound (I) is amorphous.

17. A process for preparing a melt consisting essentially of compound (I) comprising melting compound (I).



Compound (I)

18. A process according to claim 17 wherein compound (I) is heated to a temperature of between about 150°C and about 200°C, preferably a temperature of between about 160°C and about 190°C, more preferably a temperature of between about 165°C and about 185°C, more preferably a temperature of between about 165°C and about 175°C, more preferably a temperature of about 170°C.

19. A process according to any one of claims 17 and 18 further comprising cooling the melt of compound (I).

20. A process according to any one of claims 17 to 19 further comprising comminuting the melt.

21. A melt obtainable by a process according to any one of claims 17 to 20.

22. A pharmaceutical composition comprising a solid solution or solid dispersion according to any one of claims 1 to 6 and 13, or a melt according to any one of claims 14 to 16 and 21, and a pharmaceutically acceptable excipient.

23. A method of treating or preventing a disease or disorder ameliorated by the inhibition of TNF-[alpha] production, wherein the method comprises administering a therapeutically or prophylactically effective amount of a solid solution or solid

dispersion according to any one of claims 1 to 6 and 13, or a melt according to any one of claims 14 to 16 and 21, or a pharmaceutical composition according to claim 22.

24. The method of claim 23 wherein the disease or disorder is selected from psoriasis; psoriatic arthritis; rheumatoid arthritis; chronic cutaneous sarcoid; giant cell arteritis; Parkinson's Disease; prurigo nodularis; lichen planus; complex apthosis; Behcet's Disease; lupus; hepatitis; uveitis; Sjogren's Disease; depression; interstitial cystitis; vulvodynia; prostatitis; osteoarthritis; diffuse large B cell lymphoma; polymysoitis; dermatomyositis; inclusiuon body myositis; erosive osteoarthritis; interstitial cystitis; hepatitis; endometriosis; radiculopathy; and pyoderma gangrenosum.

25. A method of treating or preventing a disease or disorder ameliorated by the inhibition of PDE4, wherein the method comprises administering a therapeutically or prophylactically effective amount of a solid solution or solid dispersion according to any one of claims 1 to 6 and 13, or a melt according to any one of claims 14 to 16 and 21, or a pharmaceutical composition according to claim 22.

26. The method of claim 25 wherein the disease or disorder is selected from HIV; hepatitis; adult respiratory distress syndrome; bone resorption diseases; chronic obstructive pulmonary diseases; chronic pulmonary inflammatory diseases; dermatitis; inflammatory skin disease, atopic dermatitis, cystic fibrosis; septic shock; sepsis; endotoxic shock; hemodynamic shock; sepsis syndrome; post ischemic reperfusion injury; meningitis; psoriasis; fibrotic disease; cachexia; graft rejection including graft versus host disease; auto immune disease; rheumatoid spondylitis; arthritic conditions, such as rheumatoid arthritis and osteoarthritis; osteoporosis; Crohn's disease; ulcerative colitis; inflammatory bowel disease; multiple sclerosis; systemic lupus erythrematosus; erythema nodosum leprosum in leprosy; radiation damage; asthma; and hyperoxic alveolar injury.

27. A method of treating or preventing a cancer, wherein the method comprises administering a therapeutically or prophylactically effective amount of an amorphous form of a solid solution or solid dispersion according to any one of claims 1 to 6 and 13, or a melt according to any one of claims 14 to 16 and 21, or a pharmaceutical composition according to claim 22.

28. The method of claim 27 wherein the cancer is selected from multiple myeloma, malignant melanoma, malignant glioma, leukemia and a solid tumor.

FIG. 1

XRPD of glass state of Apremilast, prepared from melt of solid Apremilast Form B. The diffraction pattern of reference standard corundum (ASTM standard ref) is superimposed.

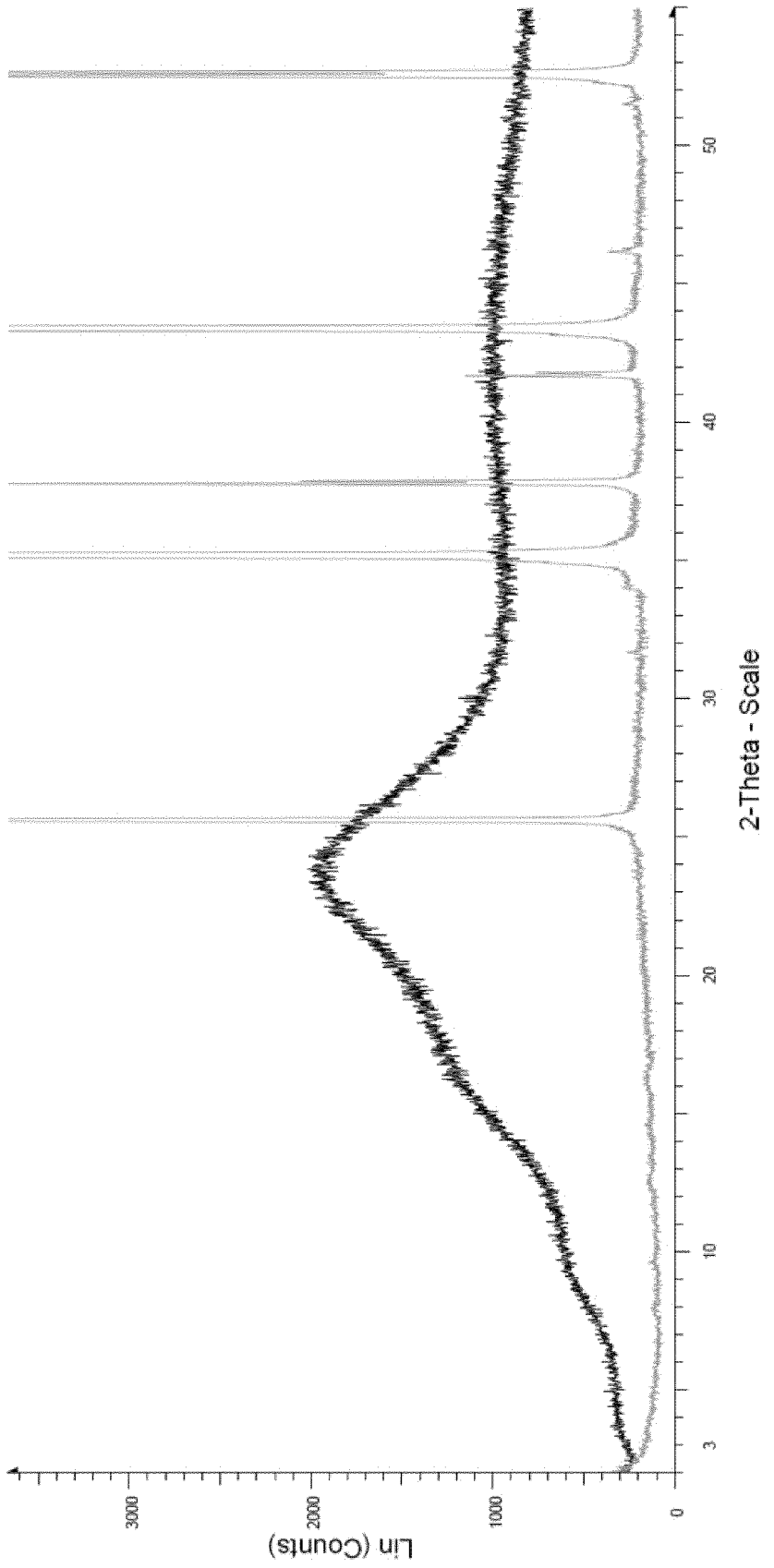


FIG. 2

Chromatogram (UV det. WL 254 nm) of Apremilast (crystal Form B) on top and of glass from Apremilast melt at 175°C (ext. temp.) on bottom.

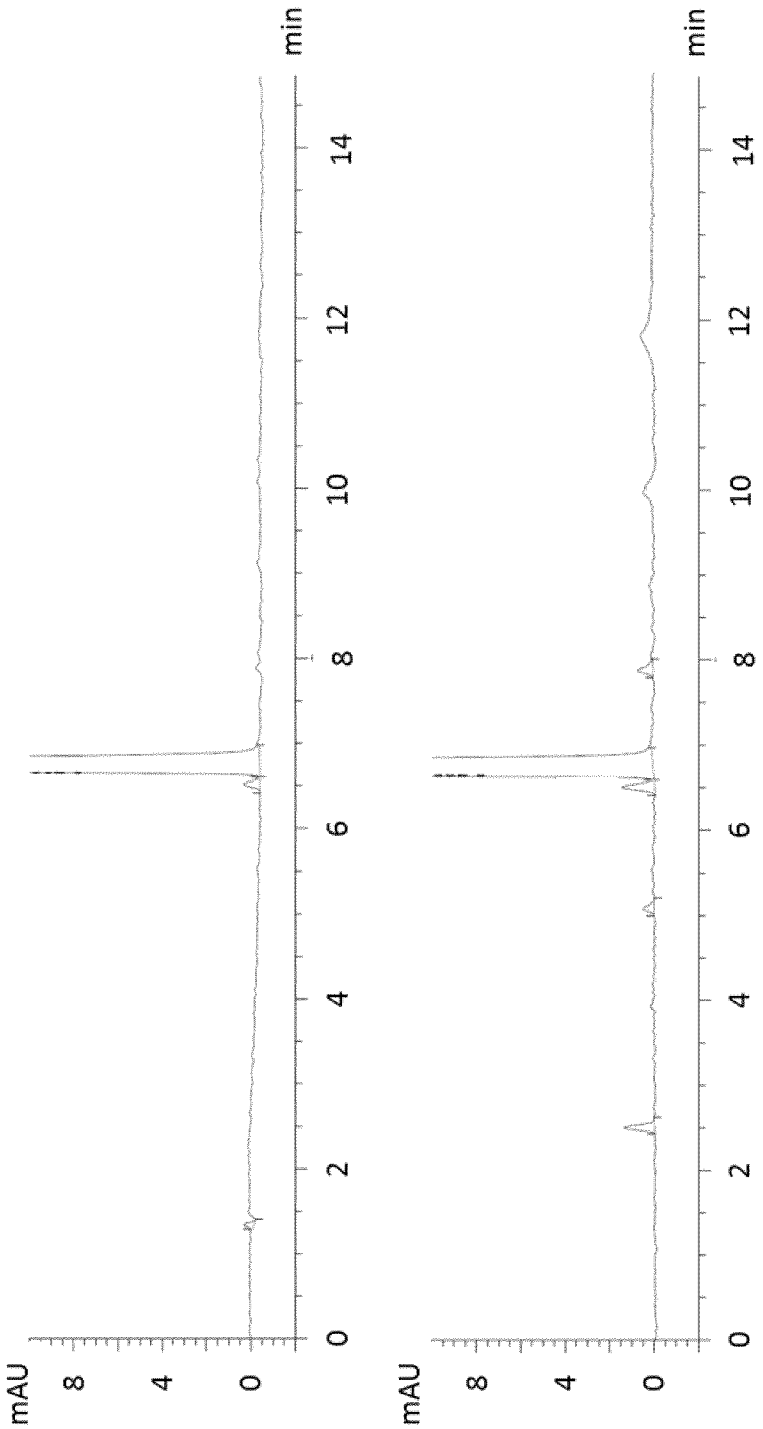
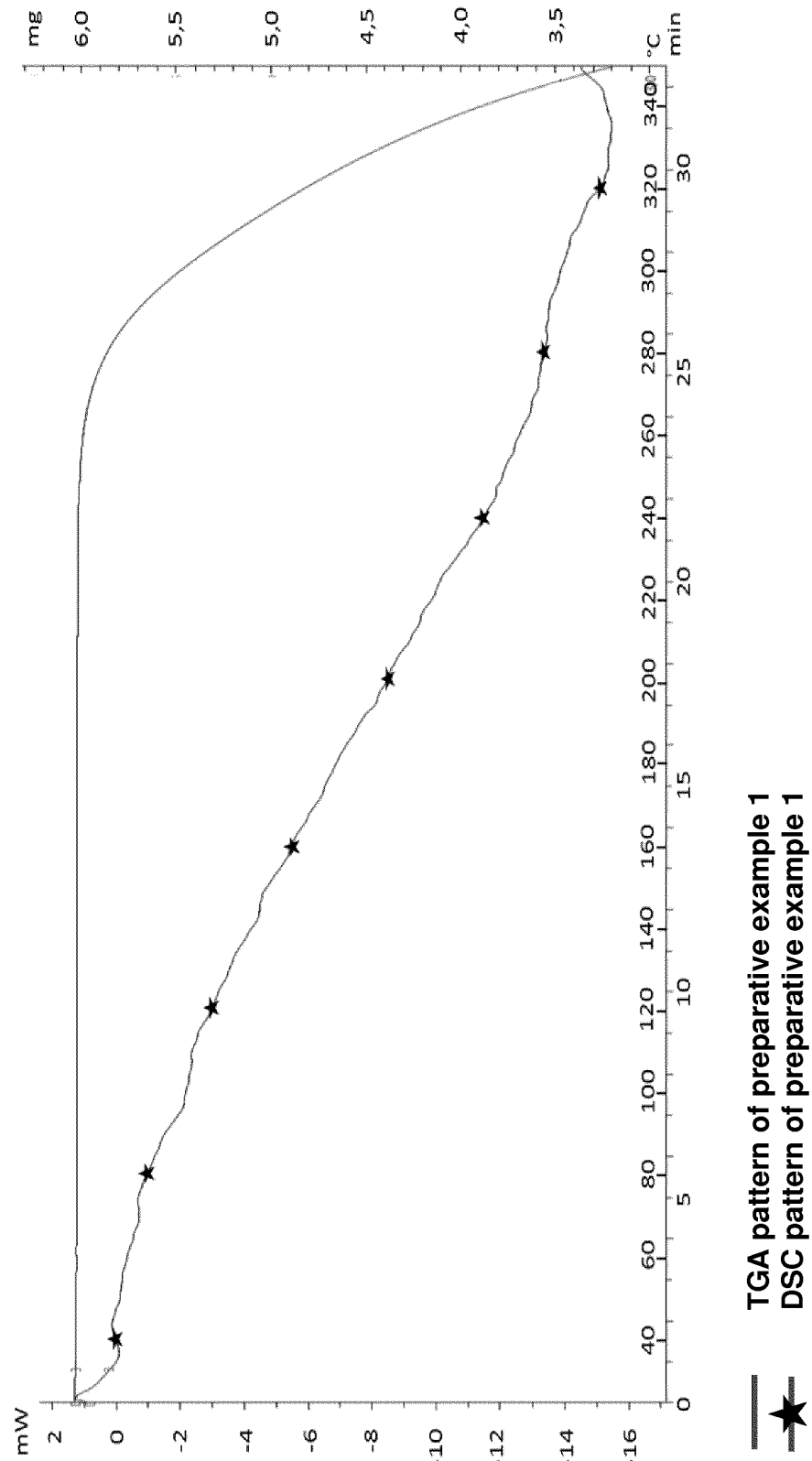


FIG. 3


DSC/ TGA of amorphous Apremilast (glass from melt)
mg
6,0
5,5
5,0
4,5
4,0
3,5
°C
min
mW
2
0
-2
-4
-6
-8
-10
-12
-14
-16
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
0
5
10
15
20
25
30
TGA pattern of preparative example 1
DSC pattern of preparative example 1

XRPD of Apremilast Form B

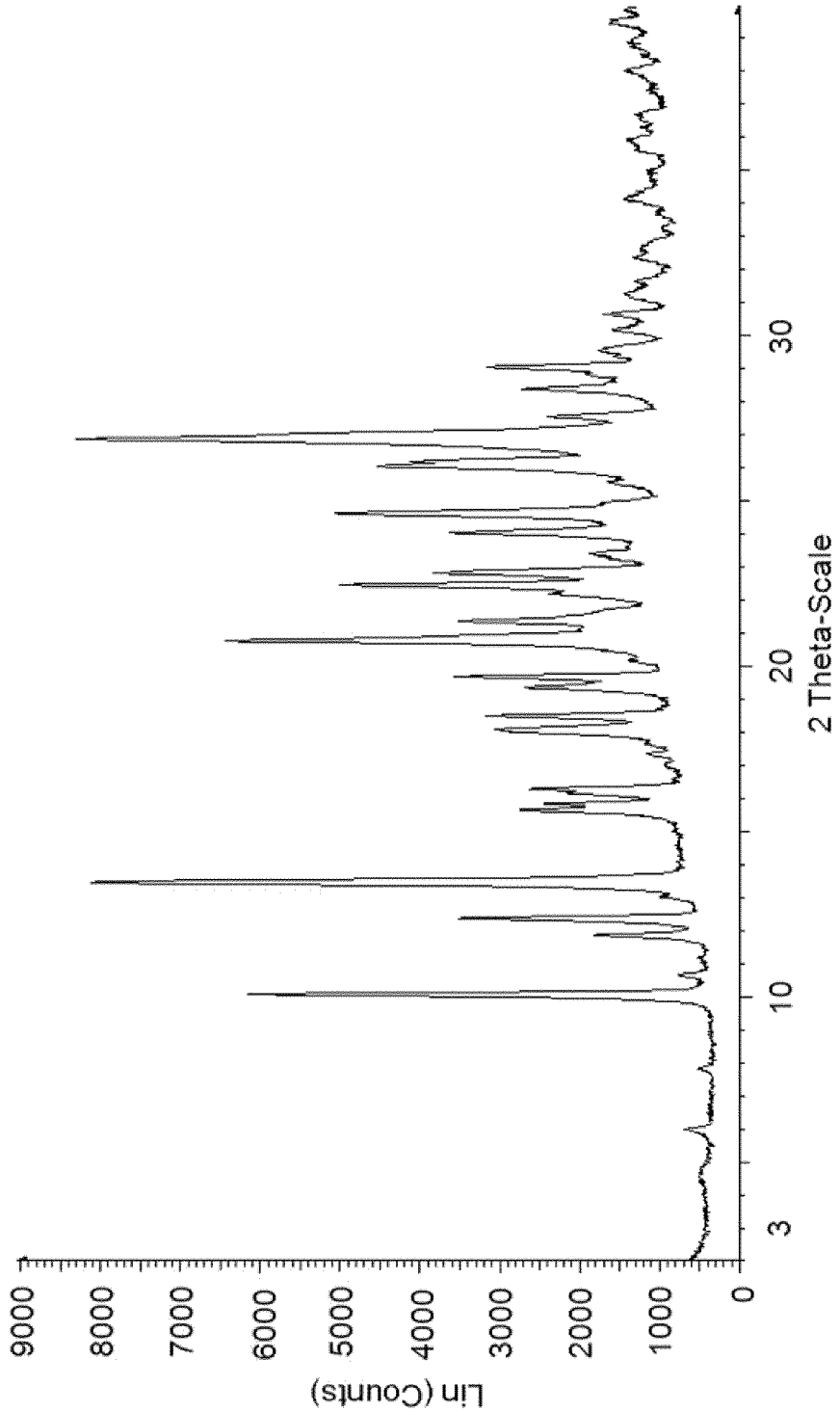


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/076589

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 A61K9/16 A61K31/4035 A61P19/02 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/283249 A1 (KHERA BRIJ [IN] ET AL) 8 October 2015 (2015-10-08) cited in the application paragraph [0063] - paragraph [0075]; claims; examples	1-13, 22-26
X	CN 104 523 574 A (CHANGSHA BAISHUN BIOTECHNOLOGY CO LTD) 22 April 2015 (2015-04-22) claims	1,3-6, 22-26
X	CN 104 546 831 A (HANGZHOU XINBOSI BIOLOG MEDICINE CO LTD) 29 April 2015 (2015-04-29) the whole document	1,3,7,8, 11-13,22

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2017	27/03/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Pacreu Largo, Marta

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/076589

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014/204825 A1 (CELGENE CORP [US]) 24 December 2014 (2014-12-24) page 65 - page 67	23-28
Y	WO 2009/120167 A1 (CELGENE CORP [US]; MULLER GEORGE W [US]; SCHAFER PETER H [US]; MAN HON) 1 October 2009 (2009-10-01) claims 27-31	23-28
X,P	WO 2016/135755 A1 (MYLAN LABORATORIES LTD [IN]) 1 September 2016 (2016-09-01) pages 10-11; claims 9-18,31; examples 1-14	1-6,22

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/076589

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

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

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

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

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

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

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

see additional sheet

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

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

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

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13(completely); 22-28(partially)

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-13(completely); 22-28(partially)

   A solid solution or solid dispersion comprising compound (I), process for preparing said solution/dispersion, pharmaceutical composition and medical uses thereof

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2. claims: 14-21(completely); 22-28(partially)

   A melt consisting of compound (I) , process for preparing said melt, a pharmaceutical composition and medical uses thereof

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/076589

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2015283249 A1	08-10-2015	NONE	
CN 104523574 A	22-04-2015	NONE	
CN 104546831 A	29-04-2015	NONE	
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		WO 2014204825 A1	24-12-2014
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		ZA 201006663 B	29-02-2012
WO 2016135755 A1	01-09-2016	NONE	