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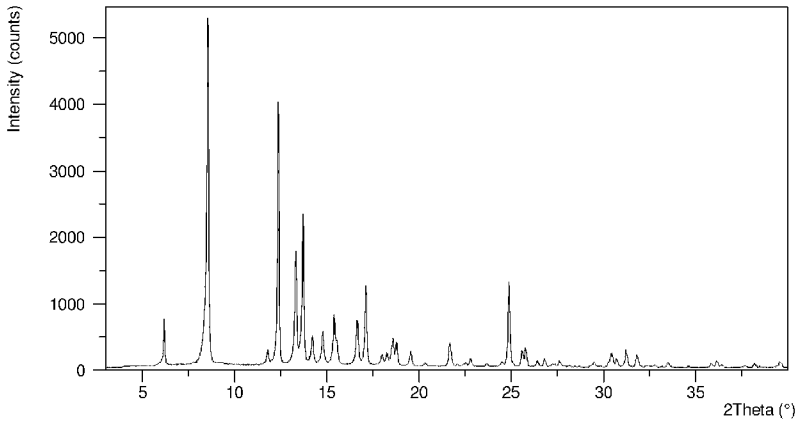
(54) Title: NEW CRYSTALLINE POLYMORPHS OF BARDOXOLONE METHYL

Figure 1. XRPD of Bardoxolone methyl Form C (obtained according to Example 1).



(57) Abstract: Disclosed are crystalline polymorphs of Bardoxolone methyl, and pharmaceutical compositions thereof.

[Continued on next page]

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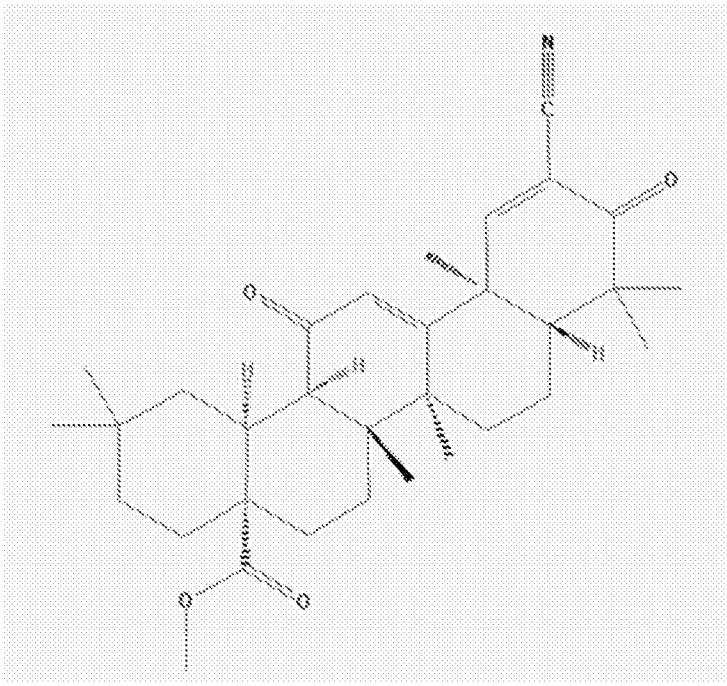
NEW CRYSTALLINE POLYMORPHS OF BARDOXOLONE METHYL

FIELD OF THE DISCLOSURE

[0001] The present disclosure encompasses crystalline polymorphs of Bardoxolone methyl, and pharmaceutical compositions thereof.

BACKGROUND OF THE DISCLOSURE

[0002] Bardoxolone methyl chemical name is Methyl-2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid, having the following chemical structure:



[0003] Bardoxolone methyl is an oral synthetic triterpenoid, under development for the treatment of certain pathologies, e.g.: connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH)pulmonary arterial hypertension, hereditary nephritis, diabetic kidney disease, chronic kidney disease, and Alport syndrome.

[0004] The compound is described in European Patent No. EP 1089724. A process for its preparation is described in US Patent No. 6326507, as well as in WO 2013-169553 (US 8981144). European Patent No. EP 2187741 and EP 2450057 (US 8088824, US 8309601 and US 8633243) described crystalline forms of Bardoxolone methyl. CN 102887936 (A) and CN 102875634 (B) relate to polymorphic forms. CN-106560473 (A) relates to a process. WO2010093944 relates to dosage compositions.

[0005] Polymorphism, the occurrence of different crystalline forms, is a property of some molecules and molecular complexes. A single molecule may give rise to a variety of

polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviors (e.g., measured by thermogravimetric analysis – "TGA", or differential scanning calorimetry – "DSC"), X-ray diffraction (XRD) pattern, infrared absorption fingerprint, and solid state (13C) NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0006] Different salts and solid state forms (including solvated forms) of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts and solid state forms and solvates may provide a basis for improving formulation, for example, by facilitating better processing or handling characteristics, changing the dissolution profile in a favorable direction, or improving stability (polymorph as well as chemical stability) and shelf-life. These variations in the properties of different salts and solid state forms may also offer improvements to the final dosage form, for instance, if they serve to improve bioavailability. Different salts and solid state forms and solvates of an active pharmaceutical ingredient may also give rise to a variety of polymorphs or crystalline forms, which may in turn provide additional opportunities to assess variations in the properties and characteristics of a solid active pharmaceutical ingredient.

[0007] Discovering new solid state forms and solvates of a pharmaceutical product may yield materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New solid state forms of a pharmaceutically useful compound can also provide an opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., a different crystal habit, higher crystallinity, or polymorphic stability, which may offer better processing or handling characteristics, improved dissolution profile, or improved shelf-life (chemical/physical stability). For at least these reasons, there is a need for additional solid state forms (including solvated forms) of Bardoxolone methyl which are both stable and soluble.

SUMMARY OF THE DISCLOSURE

[0008] The present disclosure provides crystalline polymorphs of Bardoxolone methyl, processes for preparation thereof, and pharmaceutical compositions thereof. These crystalline polymorphs can be used to prepare other forms of Bardoxolone methyl.

[0010] The present disclosure provides crystalline polymorphs of Bardoxolone

methyl and for use in the preparation of pharmaceutical compositions and/or formulations for use in medicine, preferably for the treatment of conditions associated with chronic inflammation such as pulmonary hypertension, diabetic kidney disease, Alport syndrome, chronic kidney disease, connective tissue disease-associated pulmonary arterial hypertension or hereditary nephritis.

[0011] The present disclosure also encompasses the use of crystalline polymorph of Bardoxolone methyl of the present disclosure for the preparation of pharmaceutical compositions and/or formulations.

[0012] In another aspect, the present disclosure provides pharmaceutical compositions comprising crystalline polymorph of Bardoxolone methyl according to the present disclosure.

[0013] In yet another embodiment, the present disclosure encompasses pharmaceutical formulations comprising the described crystalline polymorph of Bardoxolone methyl, or pharmaceutical compositions comprising the described crystalline polymorph of Bardoxolone methyl and at least one pharmaceutically acceptable excipient.

[0014] The present disclosure comprises processes for preparing the above mentioned pharmaceutical compositions. The processes comprise combining crystalline polymorph of Bardoxolone methyl with at least one pharmaceutically acceptable excipient.

[0010] The crystalline polymorph of Bardoxolone methyl as defined herein and the pharmaceutical compositions or formulations of the crystalline polymorph Bardoxolone methyl may be used as medicaments, particularly for the treatment of conditions associated with chronic inflammation such as pulmonary hypertension, diabetic kidney disease, Alport syndrome, chronic kidney disease, connective tissue disease-associated pulmonary arterial hypertension or hereditary nephritis.

[0011] The present disclosure also provides methods of treating Pulmonary arterial hypertension or hereditary nephritis, comprising administering a therapeutically effective amount of crystalline polymorph Bardoxolone methyl of the present disclosure, or at least one of the above pharmaceutical compositions or formulations, to a subject suffering from Pulmonary arterial hypertension or hereditary nephritis , or otherwise in need of the treatment.

[0012] The present disclosure also provides the uses of crystalline polymorph of Bardoxolone methyl of the present disclosure, or at least one of the above pharmaceutical compositions or formulations, for the manufacture of medicaments for treating Pulmonary arterial hypertension or hereditary nephritis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] Figure 1 shows a characteristic X-ray powder diffraction pattern (XRPD) of Bardoxolone methyl Form C.

[0014] Figure 2 shows a characteristic X-ray powder diffraction pattern (XRPD) of Bardoxolone methyl Form D.

[0015] Figure 3 shows a characteristic X-ray powder diffraction pattern (XRPD) of Bardoxolone methyl Form E.

[0016] Figure 4 shows a Raman spectrum of Bardoxolone methyl Form D.

[0017] Figure 5 shows a Raman spectrum of Bardoxolone methyl Form D at a range of 3300 to 1400 cm^{-1}.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0018] The present disclosure encompasses crystalline polymorphs of Bardoxolone methyl. Solid state properties of Bardoxolone methyl and crystalline polymorphs thereof can be influenced by controlling the conditions under which Bardoxolone methyl and crystalline polymorphs thereof are obtained in solid form.

[0019] A solid state form (or polymorph) may be referred to herein as polymorphically pure or as substantially free of any other solid state (or polymorphic) forms. As used herein in this context, the expression "substantially free of any other forms" will be understood to mean that the solid state form contains about 20% (w/w) or less, about 10% (w/w) or less, about 5% (w/w) or less, about 2% (w/w) or less, about 1% (w/w) or less, or about 0% of any other forms of the subject compound as measured, for example, by XRPD. Thus, a crystalline polymorph of Bardoxolone methyl described herein as substantially free of any other solid state forms would be understood to contain greater than about 80% (w/w), greater than about 90% (w/w), greater than about 95% (w/w), greater than about 98% (w/w), greater than about 99% (w/w), or about 100% of the subject crystalline polymorph of Bardoxolone methyl. In some embodiments of the disclosure, the described crystalline polymorph of Bardoxolone methyl may contain from about 1% to about 20% (w/w), from about 5% to about 20% (w/w), or from about 5% to about 10% (w/w) of one or more other crystalline polymorph of the same Bardoxolone methyl.

[0020] Depending on which other crystalline polymorphs a comparison is made, the crystalline polymorphs of Bardoxolone methyl of the present disclosure has advantageous properties selected from at least one of the following: chemical purity, flowability, solubility,

dissolution rate, morphology or crystal habit, stability- such as chemical stability as well as thermal and mechanical stability with respect to polymorphic conversion, stability towards dehydration and/or storage stability, low content of residual solvent, a lower degree of hygroscopicity, flowability, and advantageous processing and handling characteristics such as compressibility, and bulk density.

[0021] A solid state form, such as a crystal form or an amorphous form, may be referred to herein as being characterized by graphical data "as depicted in" or "as substantially depicted in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. As is well-known in the art, the graphical data potentially provides additional technical information to further define the respective solid state form (a so-called "fingerprint") which cannot necessarily be described by reference to numerical values or peak positions alone. In any event, the skilled person will understand that such graphical representations of data may be subject to small variations, *e.g.*, in peak relative intensities and peak positions due to certain factors such as, but not limited to, variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms. A crystal form of Bardoxolone methyl referred to herein as being characterized by graphical data "as depicted in" or "as substantially depicted in" a Figure will thus be understood to include any crystal forms of Bardoxolone methyl characterized with the graphical data having such small variations, as are well known to the skilled person, in comparison with the Figure.

[0022] As used herein, and unless stated otherwise, the term "anhydrous" in relation to crystalline forms of Bardoxolone methyl, relates to a crystalline form of Bardoxolone methyl which does not include any crystalline water (or other solvents) in a defined, stoichiometric amount within the crystal. Moreover, an "anhydrous" form would typically not contain more than 1% (w/w), of either water or organic solvents as measured for example by TGA.

[0023] The term "solvate," as used herein and unless indicated otherwise, refers to a crystal form that incorporates a solvent in the crystal structure. When the solvent is water, the solvate is often referred to as a "hydrate." The solvent in a solvate may be present in either a stoichiometric or in a non-stoichiometric amount.

[0024] As used herein, and unless indicated otherwise, the term "wet crystalline

form" refers to a polymorph that was not dried using any conventional techniques to remove residual solvent. Examples for such conventional techniques can be, but not limited to, evaporation, vacuum drying, oven drying, drying under nitrogen flow etc.

[0025] As used herein, and unless indicated otherwise, the term "dry crystalline form" refers to a polymorph that was dried using any conventional techniques to remove residual solvent. Examples for such conventional techniques can be, but not limited to, evaporation, vacuum drying, oven drying, drying under nitrogen flow etc.

[0026] As used herein, the term "isolated" in reference to crystalline polymorph of Bardoxolone methyl of the present disclosure corresponds to a crystalline polymorph of Bardoxolone methyl that is physically separated from the reaction mixture in which it is formed.

[0027] As used herein, unless stated otherwise, the XRPD measurements are taken using copper Kα radiation wavelength 1.54184 Å. XRPD peaks reported herein are measured using CuK α radiation, λ = 1.5418 Å, at a temperature of 25 ± 3°C.

[0028] A thing, *e.g.*, a reaction mixture, may be characterized herein as being at, or allowed to come to "room temperature" or "ambient temperature", often abbreviated as "RT." This means that the temperature of the thing is close to, or the same as, that of the space, *e.g.*, the room or fume hood, in which the thing is located. Typically, room temperature is from about 20°C to about 30°C, or about 22°C to about 27°C, or about 25°C.

[0029] The amount of solvent employed in a chemical process, e.g., a reaction or crystallization, may be referred to herein as a number of "volumes" or "vol" or "V." For example, a material may be referred to as being suspended in 10 volumes (or 10 vol or 10V) of a solvent. In this context, this expression would be understood to mean milliliters of the solvent per gram of the material being suspended, such that suspending a 5 grams of a material in 10 volumes of a solvent means that the solvent is used in an amount of 10 milliliters of the solvent per gram of the material that is being suspended or, in this example, 50 mL of the solvent. In another context, the term "v/v" may be used to indicate the number of volumes of a solvent that are added to a liquid mixture based on the volume of that mixture. For example, adding solvent X (1.5 v/v) to a 100 ml reaction mixture would indicate that 150 mL of solvent X was added.

[0030] A process or step may be referred to herein as being carried out "overnight." This refers to a time interval, e.g., for the process or step, that spans the time during the night, when that process or step may not be actively observed. This time interval is from about 8 to

about 20 hours, or about 10-18 hours, typically about 16 hours.

[0031] As used herein, the term “reduced pressure” refers to a pressure that is less than atmospheric pressure. For example, reduced pressure is about 10 mbar to about 50 mbar.

[0032] As used herein and unless indicated otherwise, the term "ambient conditions" refer to atmospheric pressure and a temperature of 18-25°C, or preferably 22-24°C.

[0033] The present disclosure comprises a crystalline polymorph of Bardoxolone methyl, designated Form C. The crystalline Form C of Bardoxolone methyl may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in Figure 1; an X-ray powder diffraction pattern having peaks at 6.2, 12.4, 15.4, 18.6 and 24.9 degrees 2-theta ± 0.2 degrees 2-theta; and combinations of these data.

[0034] Crystalline Form C of Bardoxolone methyl may be further characterized by an X-ray powder diffraction pattern having peaks at 6.2, 12.4, 15.4, 18.6 and 24.9 degrees 2-theta ± 0.2 degrees 2-theta, and also having any one, two, three, four or five additional peaks selected from the group consisting of 8.6, 13.3, 13.7, 17.1 and 21.7 degrees 2-theta ± 0.2 degrees 2-theta.

[0035] Crystalline Form C of Bardoxolone methyl may be characterized by an X-ray powder diffraction pattern having peaks at 6.2, 8.6, 12.4, 13.3, 13.7, 15.4, 17.1, 18.6, 21.7 and 24.9 degrees 2-theta ± 0.2 degrees 2-theta.

[0036] Crystalline Form C of Bardoxolone methyl may be characterized by each of the above characteristics alone/or by all possible combinations, e.g., an XRPD pattern having peaks at 6.2, 12.4, 15.4, 18.6 and 24.9 degrees 2-theta ± 0.2 degrees 2-theta; an XRPD pattern as depicted in Figure 1, and combinations thereof.

[0037] In one embodiment of the present disclosure, crystalline Form C of Bardoxolone methyl is isolated.

[0038] The present disclosure further comprises a crystalline polymorph of Bardoxolone methyl, designated Form D. The crystalline Form D of Bardoxolone methyl may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in Figure **2**; an X-ray powder diffraction pattern having peaks at 3.6, 7.1, 10.8, 12.4 and 16.5 degrees 2-theta ± 0.2 degrees 2-theta; and combinations of these data.

[0039] Crystalline Form D of Bardoxolone methyl may be further characterized by an X-ray powder diffraction pattern having peaks at 3.6, 7.1, 10.8, 12.4 and 16.5 degrees 2-theta

± 0.2 degrees 2-theta, and also having any one, two, three, four or five additional peaks selected from the group consisting of 12.9, 13.9, 14.8, 18.6 and 20.6 degrees 2-theta ± 0.2 degrees 2-theta.

[0040] Crystalline Form D of Bardoxolone methyl may also be characterized by an X-ray powder diffraction pattern having peaks at 14.2, 15.6, 17.2, 17.6, 22.9, 23.8, 24.2, 25.8, 26.7 and 27.9.

[0041] Crystalline form D of Bardoxolone methyl as defined in any of the embodiments described herein may alternatively or additionally be characterized by data selected from: a Raman spectrum having peaks at 2949, 1671, 1618 and 1464 ± 4 cm^{-1}; Raman spectrum as depicted in Figure 4 and/or Figure 5; and combinations of these data.

[0042] Crystalline Form D of Bardoxolone methyl may also be characterized by an X-ray powder diffraction pattern having peaks at 3.6, 7.1, 10.8, 12.4, 12.9, 13.9, 14.8, 16.5, 18.6, and 20.6 degrees 2-theta ± 0.2 degrees 2-theta.

[0043] Crystalline Form D of Bardoxolone methyl may alternatively or additionally be characterized by a PXRD pattern having peaks at: 3.6, 7.1, 10.8, 12.4, 12.9, 13.9, 14.2, 14.8, 15.5, 15.6, 16.5, 17.2, 17.6, 17.8, 18.6, 20.6, 21.7, 22.9, 23.8, 24.2, 24.9, 25.8, 26.7, 27.3, 27.9, 28.7, 29.1, 29.7, 31.5, 33.3, 33.9, 34.8, 36.0, 37.9 and 39.0 degrees 2-theta ± 0.2 degrees 2-theta.

[0044] Crystalline Form D of Bardoxolone methyl as defined in any embodiment described herein may be characterized by each of the above characteristics alone/or by all possible combinations, e.g., an XRPD pattern having peaks at 3.6, 7.1, 10.8, 12.4 and 16.5 degrees 2-theta ± 0.2 degrees 2-theta; an XRPD pattern as depicted in Figure 2, and combinations thereof.

[0045] In one embodiment of the present disclosure, crystalline Form D of Bardoxolone methyl as defined in any embodiment described herein is isolated. Crystalline Form D of Bardoxolone methyl according to any of the embodiments described herein may be an anhydrous, non-solvated form.

[0046] Crystalline Form D of Bardoxolone methyl is stable at various conditions and is resistant to conversion to any other forms, for example under pressure of 1t (75 KN/m^2) or 2t (150 KN/m^2) for 1 minute, after heating for 5 min to 100^0C and after exposure to water sauna condition (wherein "water sauna condition" refers to room temperature and a relative humidity (RH) of about 90% - 100% for 24 hours in a closed flask). Crystalline Form D of Bardoxolone is also stable to conversion after exposure to an atmosphere containing organic solvents, for example ethylene glycol, in a closed vessel at room temperature for 24 hours).

Such stability may enable the use of form D in variety of preparation methods including preparation of solid dispersion by spray drying, wet granulation etc.

[0047] As indicated in WO2010093944 crystalline Form A has relatively low oral bioavailability, while a non-crystalline form of Bardoxolone methyl ("Form B") shows markedly superior oral bioavailability compared to Form A. Crystalline Form D of the present invention surprisingly showed an improved solubility compared to the crystalline form A and comparable solubility to the non-crystalline form B. This may allow the use of Form D in preparation of different kind of pharmaceutical compositions/formulations.

[0048] The present disclosure further comprises a crystalline polymorph of Bardoxolone methyl, designated Form **E**. The crystalline Form **E** of Bardoxolone methyl may be characterized by data selected from one or more of the following: an X-ray powder diffraction pattern substantially as depicted in Figure **3**; an X-ray powder diffraction pattern having peaks at 7.0, 13.2, 13.9, 15.1 and 16.8 degrees 2-theta ± 0.2 degrees 2-theta; and combinations of these data.

[0049] Crystalline Form **E** of Bardoxolone methyl may be further characterized by an X-ray powder diffraction pattern having peaks at 7.0, 13.2, 13.9, 15.1 and 16.8 degrees 2-theta ± 0.2 degrees 2-theta, and also having any one, two, three, four or five additional peaks selected from the group consisting of 10.0, 10.5, 11.2, 18.6 and 22.1 degrees 2-theta ± 0.2 degrees 2-theta.

[0050] Crystalline Form **E** of Bardoxolone methyl may be characterized by an X-ray powder diffraction pattern having peaks at 7.0, 10.0, 10.5, 11.2, 13.2, 13.9, 15.1, 16.8, 18.6 and 22.1 degrees 2-theta ± 0.2degrees 2-theta, and optionally, additionally by the absence of a peak at 12.0 degrees 2-theta ± 0.2 degrees two-theta. Crystalline Form **E** of Bardoxolone methyl may be characterized by each of the above characteristics alone/or by all possible combinations, e.g., an XRPD pattern having peaks at 7.0, 13.2, 13.9, 15.1 and 16.8 degrees 2-theta ± 0.2 degrees 2-theta; an XRPD pattern as depicted in Figure **3**, and combinations thereof.

[0051] Crystalline Form **E** of Bardoxolone methyl may be further characterized by an X-ray powder diffraction pattern having peaks at 7.0, 13.2, 13.9, 15.1 and 16.8 degrees 2-theta ± 0.2 degrees 2-theta, and also by the absence of a peak at 12.0 degrees 2-theta ± 0.2 degrees two-theta.

[0052] In one embodiment of the present disclosure, crystalline Form E of Bardoxolone methyl is isolated.

[0053] The step of isolating Bardoxolone methyl or crystalline polymorph of

Bardoxolone methyl may be performed by crystallization.

[0054] The present disclosure provides pharmaceutical composition or formulation comprising any of the above crystalline forms of Bardoxolone methyl or combinations thereof, optionally in combination with any other solid state forms of Bardoxolone methyl such as amorphous or crystalline form. The pharmaceutical composition or formulation is preferably for oral treatment, and more preferably wherein the pharmaceutical composition is in a form of capsules.

[0055] The above crystalline polymorphs can be used to prepare other crystalline polymorphs of Bardoxolone methyl.

[0056] The present disclosure provides crystalline polymorphs of Bardoxolone methyl for use in the preparation of pharmaceutical compositions comprising Bardoxolone methyl and/or crystalline polymorphs thereof.

[0057] The present disclosure also encompasses the use of crystalline polymorph of Bardoxolone methyl of the present disclosure for the preparation of pharmaceutical compositions of crystalline polymorph Bardoxolone methyl and/or crystalline polymorphs thereof.

[0058] The present disclosure comprises processes for preparing the above mentioned pharmaceutical compositions/formulations. The processes comprise combining the crystalline polymorphs of Bardoxolone methyl of the present disclosure with at least one pharmaceutically acceptable excipient.

[0059] The present invention further encompasses a pharmaceutical composition or formulation which is obtainable by a process selected from the group consisting of:

(A) combining one or a combination of the solid state forms of Bardoxolone methyl of the present invention, preferably crystalline Form D or crystalline Form C, and more preferably crystalline Form D, with a solvent and at least one pharmaceutically acceptable excipient, and removing the solvent to form a solid solution, and optionally further combining the solid solution with one or more pharmaceutically acceptable excipients;

(B) combining one or a combination of the solid state forms of Bardoxolone methyl of the present invention, preferably crystalline Form D or crystalline Form C, and more preferably crystalline Form D and at least one pharmaceutically acceptable excipient and optionally a solvent to form a mixture, and thermally extruding the mixture, and optionally combining the extruded mixture with one or more pharmaceutically acceptable excipients; or

(C) combining one or a combination of the solid state forms of Bardoxolone methyl of the present invention, preferably crystalline Form D or crystalline Form C, and

more preferably crystalline Form D and at least one pharmaceutically acceptable excipient and a solvent to form a mixture, and spray drying the mixture, and optionally combining the spray-dried mixture with one or more pharmaceutically acceptable excipients.

[0060] Pharmaceutical formulations of the present invention contain any one or a combination of the solid state forms of Bardoxolone methyl of the present invention. In addition to the active ingredient, the pharmaceutical formulations of the present invention can contain one or more excipients. Excipients are added to the formulation for a variety of purposes.

[0061] Diluents increase the bulk of a solid pharmaceutical composition, and can make a pharmaceutical dosage form containing the composition easier for the patient and caregiver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized 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.

[0062] Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, can 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.

[0063] The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach can 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.

[0064] Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that can function as glidants

include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, and tribasic calcium phosphate.

[0065] 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 dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, 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 dye. 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.

[0066] Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that can be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

[0067] Solid and liquid compositions can also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

[0068] In liquid pharmaceutical compositions of the present invention, the active ingredient and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol, or glycerin.

[0069] Liquid pharmaceutical compositions can 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 can 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.

[0070] Liquid pharmaceutical compositions of the present invention can 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.

[0071] Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol, and invert sugar can be added to improve the taste.

[0072] Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxyl toluene, butylated hydroxyanisole, and ethylenediamine tetraacetic acid can be added at levels safe for ingestion to improve storage stability.

[0073] According to the present invention, a liquid composition can 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 can be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

[0074] 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 can be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

[0075] Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches, and lozenges, as well as liquid syrups, suspensions, and elixirs.

[0076] The dosage form of the present invention can 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 can be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

[0077] The active ingredient and excipients can be formulated into compositions and dosage forms according to methods known in the art.

[0078] 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 can then be tableted, or other excipients can be added prior to tableting, such as a glidant and/or a lubricant.

[0079] A tableting composition can be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients can be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules can subsequently be compressed into a tablet.

[0080] As an alternative to dry granulation, a blended composition can 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.

[0081] A capsule filling of the present invention can comprise any of the aforementioned blends and granulates that were described with reference to tableting, but they are not subjected to a final tableting step.

[0082] A pharmaceutical formulation of Bardoxolone methyl is preferably formulated for administration to a mammal, preferably a human. Bardoxolone methyl can be formulated, for example, as a viscous liquid solution or suspension, preferably a clear solution, for injection. The formulation can contain one or more solvents. A suitable solvent can be selected by considering the solvent's physical and chemical stability at various pH levels, viscosity (which would allow for syringeability), fluidity, boiling point, miscibility, and purity. Suitable solvents include alcohol USP, benzyl alcohol NF, benzyl benzoate USP, and Castor oil USP. Additional substances can be added to the formulation such as buffers, solubilizers, and antioxidants, among others. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th ed.

[0083]

[0084] The crystalline polymorphs of Bardoxolone methyl and the pharmaceutical compositions/formulation of Bardoxolone methyl of the present disclosure can be used as medicaments, particularly in the treatment of: conditions associated with chronic inflammation such as pulmonary arterial hypertension, diabetic kidney disease, Alport syndrome, chronic kidney disease, connective tissue disease-associated pulmonary arterial hypertension or hereditary nephritis.

[0085] The present disclosure also provides methods of treating conditions associated with chronic inflammation such as pulmonary arterial hypertension, diabetic kidney disease, Alport syndrome, chronic kidney disease, connective tissue disease-associated pulmonary

arterial hypertension or hereditary nephritis comprising administering a therapeutically effective amount of crystalline polymorph of Bardoxolone methyl of the present disclosure, or at least one of the above pharmaceutical compositions/formulations, to a subject in need of the treatment.

[0086] Having thus described the disclosure with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the disclosure as described and illustrated that do not depart from the spirit and scope of the disclosure as disclosed in the specification. The Examples are set forth to aid in understanding the disclosure but are not intended to, and should not be construed to limit its scope in any way.

XRPD method

[0087] Sample after being powdered in a mortar and pestle is applied directly on a silicon plate holder. The X-ray powder diffraction pattern was measured with Philips X'Pert PRO X-ray powder diffractometer, equipped with Cu irradiation source =1.54184 Å (Ångström), X'Celerator (2.022° 2θ) detector.

[0088] Scanning parameters: angle range: 3-40 deg., step size 0.0167, time per step 37 s, continuous scan.

Thermogravimetric analysis ("TGA")

TGA analysis was performed on instruments Mettler Toledo TG-DSC 1 with a heating rate of 10°C/min and under nitrogen flow of 30 mL/min. Standard aluminum open pan was used, sample mass was 3-5 mg.

FT-Raman spectroscopy ("Raman")

Raman analysis was performed on a Nicolet 6700 interferometer, equipped with NXR FT-Raman modul, CaF2 beamsplitter and a liquid nitrogen cooled Ge detector. Spectra were recorded at a resolution of 4 cm-1. Nd-YAG laser (1064 nm, 500 mW) was used to excite the sample.

Ultra-high performance liquid chromatography ("UHPLC")

UHPLC analyses was performed on Agilent 1290 Infinity LC system with a DAD. UV spectra were recorded at 190-400 nm, with the working wavelength of 240 nm. The column used was Waters Acquity UPLC BEH Phenyl (100 mm × 2.1 mm i.d., particle size 1.7 μm),

at the column temperature of 50°C. Mobile phases employed for gradient elution were water with 0.1% of formic acid as mobile phase A and acetonitrile with 0.1% of formic acid as mobile phase B. Gradient conditions for the analysis were: isocratic flow from 0.0 to 0.5 min with 40% of mobile phase B; linear gradient from 40 % of mobile phase B up to 90% of mobile phase B from 0.5 to 4.0 min; isocratic flow at 90% of mobile phase B from 4.0 to 4.5 min; linear gradient down to 40% of mobile phase B from 4.5 to 5.0 min and finally, reconditioning the column for 0.5 min on starting conditions. 1 μL to 10 μL of sample solution was injected at a flow rate of 0.7 mL min^{-1}.

Preparation of starting materials

[0089] Bardoxolone methyl can be prepared for example as described in US 6326507. Bardoxolone methyl (form A) can be prepared for example as described in US 8309601. Bardoxolone methyl (form B; glassy) can be prepared for example as described in US 8088824. Alternatively Bardoxolone methyl form A may be prepared according to reference example A and Bardoxolone methyl form B may be prepared according to reference example B.

Reference example A. Preparation of Bardoxolone methyl form A

Bardoxolone methyl (0.2 g) was dissolved in THF (2.4 mL) at r.t. (room temperature). Solution was added drop wise in heptane (40 mL) at r.t. The obtained suspension was stirred for 24 hours and the solid was filtered.

Reference example B. Preparation of Bardoxolone methyl form B

Bardoxolone methyl form A (2.0 g) was milled for 3 h at 800 rpm in a stainless steel jar with 4 stainless steel balls.

Example 1. Preparation of Bardoxolone methyl form C

[0090] Bardoxolone methyl (50 ± 5 mg) was dissolved in 1-methylpyrrolidin-2-one (1 mL) at room temperature (r.t.). The solution was left in an open flask at r.t. for 5 weeks to evaporate. Obtained solid was analyzed by XRPD.

Example 2. Preparation of Bardoxolone methyl form D

[0091] Bardoxolone methyl form A (500 mg) was slurried in methanol (1 mL) at r.t. in a closed flask for 48 days. The solid was filtered, dried in a vacuum oven at 50°C for 30

min and analyzed by XRPD.

Example 3. Preparation of Bardoxolone methyl form E

[0092] Bardoxolone methyl form A (2.3 g) was dissolved in methanol/water (95:5) mixture (126 mL) by heating to reflux. The solution was cooled down to 0°C and the formed suspension was filtered. The filtrate was left to evaporate in an open flask at r.t. for 5 days. The obtained precipitate was analyzed by XRPD.

Example 4. Preparation of Bardoxolone methyl form D

Bardoxolone methyl form B (1.0 g) was slurried in methanol (2 mL) at 10°C for 2 days. Solid was filtered and analyzed by XRPD.

Example 5. Preparation of Bardoxolone methyl form D

Bardoxolone methyl form B (1.0 g) was slurried in methanol/MTBE (methyl tert-butyl ether) 1:2 (10 mL) at 10°C for 4 days. Solid (640 mg) was filtered and analyzed by XRPD.

Example 6. Preparation of Bardoxolone methyl form D

Bardoxolone methyl form B (4.35 g) was slurried in methanol/MTBE 1:3 (43 mL) at 10°C for 5 days. Solid (3.0 g) was filtered, dried in a vacuum oven at 70°C for 4 hours (2.7 g) and analyzed by XRPD.

Example 7. Preparation of Bardoxolone methyl form D

Bardoxolone methyl form A (2.54 g) was dissolved in methanol/water 5% (220 mL) at about 67°C. The solution was cooled to 0-5°C. Crystallization occurred at about 10°C. The obtained suspension was stirred at 0-5°C for 2 days. Solid (2.2 g) was filtered, dried in a vacuum oven at 70°C for 4 hours (1.9 g) and analyzed by XRPD.

Example 8. Evaluation of solubility of form D and patent forms in US8309601 and US8088824

Solubility of Bardoxolone methyl form D and the patent forms in US8309601and US8088824 were determined in aqueous buffers and water. Suspension of tested substance (150 mg/8 mL) was stirred on a shaker (200 rpm) in a closed vial at 37°C. Suspension was filtered and concentration of Bardoxolone methyl in filtrate was determined by UHPLC. Undissolved residue was analyzed by XRPD.

pH	Buffer
1.2	0.063 M HCl + 2.0 g/L NaCl
4.5	0.05 M acetate buffer (PhEur)

Results

Bardoxolone methyl starting form	**Buffer**	**Time** at 37°C	**Concentration** mg/mL (UHPLC)
Form A disclosed in US8088824	pH 1.2	2 h	LTQL
Form B disclosed in US8309601			0.00008
form D			0.00004
Form A disclosed in US8088824		4 h	LTQL
Form B disclosed in US8309601			
form D			
Form A disclosed in US8088824	pH 4.5	2 h	LTQL
Form B disclosed in US8309601			0.00004
form D			0.00002

Conclusion

Surprisingly, the solubility of Bardoxolone methyl form D was found to be comparable with the amorphous form B disclosed in US8309601. The solubility of form D was found to be higher than the solubility of the crystalline form A disclosed in US8088824.

Example 9. Evaluation of stability of form D

The physical stability of Form D was investigated at different conditions: in heating, under pressure and by sauna. Results are listed in the tables below:

PRESSURE			
Initial sample/form	**Pressure**	**Time**	**XRD**
form D	1 t	1 min	Form D
	2 t	1 min	Form D

HEATING (open vessel)			
Initial sample/form	**Temperature**	**Time**	**XRD**
form D	100 °C	5 min	Form D

TRANSFORMATION BY SAUNA (Closed flask, RT)			
Initial sample/form	**Days**	**Solvent**	**XRD**
Form D	1	water	Form D
	1	ethylene glycol	Form D

All samples were analyzed by XRPD, Form D was maintained.

Claims:

1. A crystalline form D of Bardoxolone methyl, which is characterized by data selected from one or more of the following:
   (i) a PXRD pattern having peaks at 3.6, 7.1, 10.8, 12.4 and 16.5 degrees 2-theta ± 0.2 degrees 2-theta;
   (ii) a PXRD pattern as depicted in Figure 2;
   and combinations of (i) and (ii).
2. The crystalline form D of Bardoxolone methyl according to claim 1, which is characterized by data selected from one or more of the following:
   (i) one, two, three, four or five additional peaks selected from the group consisting of 12.9, 13.9, 14.8, 18.6 and 20.6 degrees 2-theta ± 0.2 degrees 2-theta;
   (ii) a Raman spectrum having peaks at 2949, 1671, 1618 and 1464 ± 4 cm^{-1};
   (iii) a Raman spectrum as depicted in Figure 4; or
   (iv) a Raman spectrum as depicted in Figure 5;
   and combinations of any of (i)-(iv).
3. A crystalline form C of Bardoxolone methyl, which is characterized by data selected from one or more of the following:
   (i) a PXRD pattern having peaks at 6.2, 12.4, 15.4, 18.6 and 24.9 degrees 2-theta ± 0.2 degrees 2-theta;
   (ii) a PXRD pattern as depicted in figure 1;
   and combinations of (i) and (ii).
4. The crystalline form C of Bardoxolone methyl according to claim 3, which is characterized by one, two, three, four or five additional peaks selected from the group consisting of 8.6, 13.3, 13.7, 17.1 and 21.7 degrees 2-theta ± 0.2 degrees 2-theta.
5. The crystalline form of Bardoxolone methyl according to any one of Claims 1-4, wherein the crystalline form is isolated.
6. The crystalline form D of Bardoxolone methyl according to any one of Claims 1-2 or according to claim 5, which is non-solvated form.
7. The crystalline form D of Bardoxolone methyl according to any one of Claims 1-2 or according to claim 5, which is an anhydrous form.
8. The crystalline form of Bardoxolone methyl according to any one of Claims 1-7, which is polymorphically pure, preferably wherein the solid state form contains: about

20% or less, about 10% or less, about 5% or less, about 2% or less, about 1% or less, or about 0% of any other solid state forms of Bardoxolone methyl.

9. Use of crystalline form of Bardoxolone methyl according to any one of Claims 1-8, for preparing other solid state forms of Bardoxolone methyl.
10. Use of crystalline form of Bardoxolone methyl according to any one of Claims 1-8 for the preparation of a pharmaceutical composition or formulation, preferably wherein the pharmaceutical composition or formulation is for treating: conditions associated with chronic inflammation such as pulmonary arterial hypertension, diabetic kidney disease, Alport syndrome, chronic kidney disease, connective tissue disease-associated pulmonary arterial hypertension or hereditary nephritis.
11. The crystalline form of Bardoxolone methyl according to any one of Claims 1-8 for use as a medicament, preferably for the treatment of: conditions associated with chronic inflammation such as pulmonary arterial hypertension, diabetic kidney disease, Alport syndrome, chronic kidney disease, connective tissue disease-associated pulmonary arterial hypertension or hereditary nephritis.
12. The crystalline form of Bardoxolone methyl according to any one of Claims 1-8 for use in the preparation of a pharmaceutical composition or formulation, preferably for the treatment of: conditions associated with chronic inflammation such as pulmonary arterial hypertension, diabetic kidney disease, Alport syndrome, chronic kidney disease, connective tissue disease-associated pulmonary arterial hypertension or hereditary nephritis.
13. The crystalline form of Bardoxolone methyl according to any one of Claims 1-8 for use in the preparation of other solid state forms of Bardoxolone methyl.
14. A pharmaceutical composition or formulation comprising a solid state form of Bardoxolone methyl or combinations thereof according to any one of Claims 1-8.
15. A pharmaceutical composition or formulation according to Claim 14 comprising at least one pharmaceutically acceptable excipient, preferably wherein the pharmaceutical composition or formulation is for oral treatment, and more preferably wherein the pharmaceutical composition is in a form of capsules.
16. A process for preparing a pharmaceutical composition or formulation according to Claim 14 or Claim 15 comprising combining a solid state form of Bardoxolone methyl according to any one of Claims 1-8, and at least one pharmaceutically acceptable excipient.

17. A process for preparing other solid state forms of Bardoxolone methyl comprising preparing a solid state form of Bardoxolone methyl according to any one of claims 1-8 and converting it to other crystalline form of Bardoxolone methyl.
18. A method of treating: conditions associated with chronic inflammation such as pulmonary arterial hypertension, diabetic kidney disease, Alport syndrome, chronic kidney disease, connective tissue disease-associated pulmonary arterial hypertension or hereditary nephritis, comprising administering a therapeutically effective amount of the solid state form of Bardoxolone methyl according to any one of Claims 1-8, or a pharmaceutical composition or formulation according to any one of Claims 14-15 to a subject suffering from: conditions associated with chronic inflammation such as pulmonary arterial hypertension, diabetic kidney disease, Alport syndrome, chronic kidney disease, connective tissue disease-associated pulmonary arterial hypertension or hereditary nephritis, or otherwise in need of the treatment.

Figure 1. XRPD of Bardoxolone methyl Form C (obtained according to Example 1).

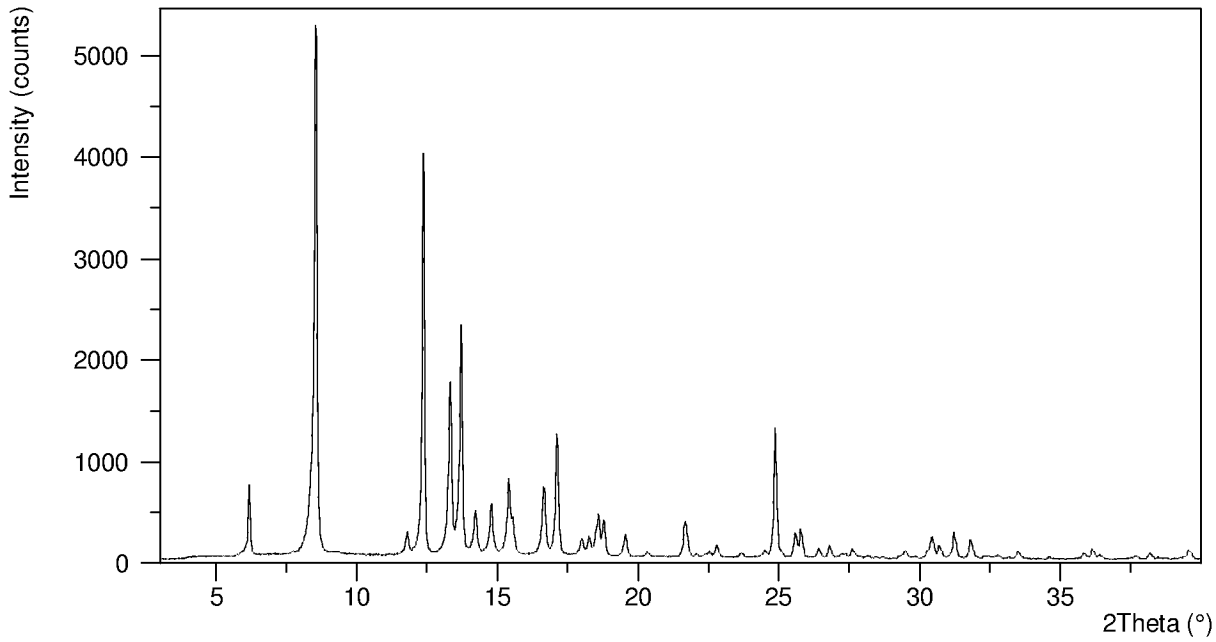


Figure 2. XRPD of Bardoxolone methyl Form D (obtained according to Example 2).

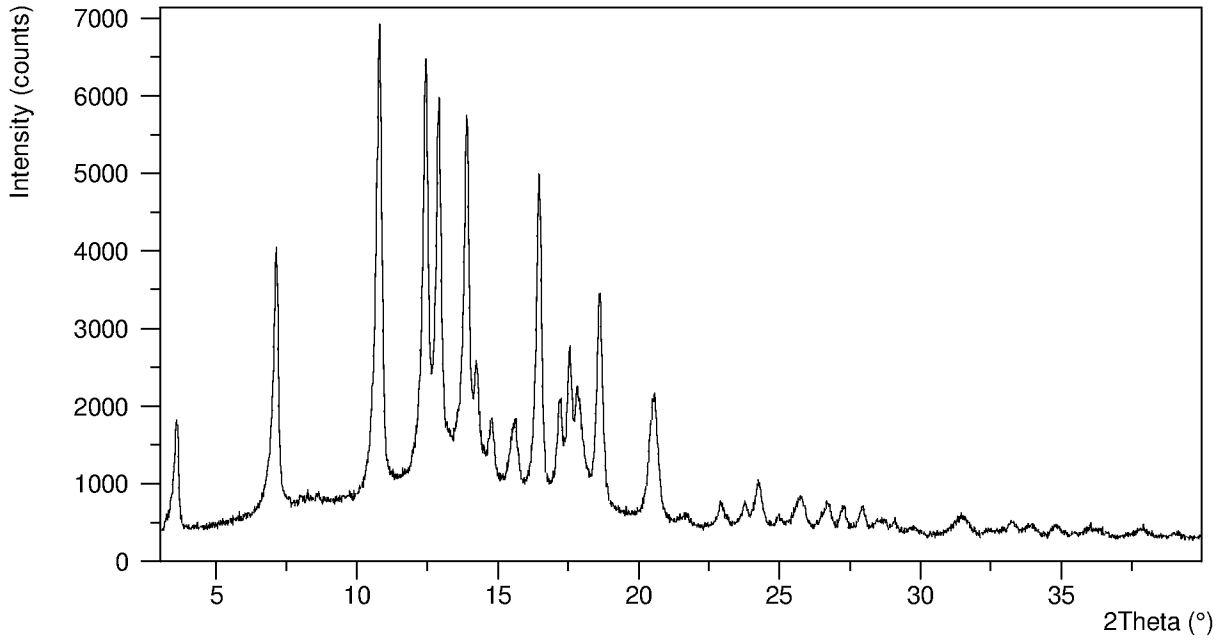


Figure 3. XRPD of Bardoxolone methyl Form E (obtained according to Example 3).

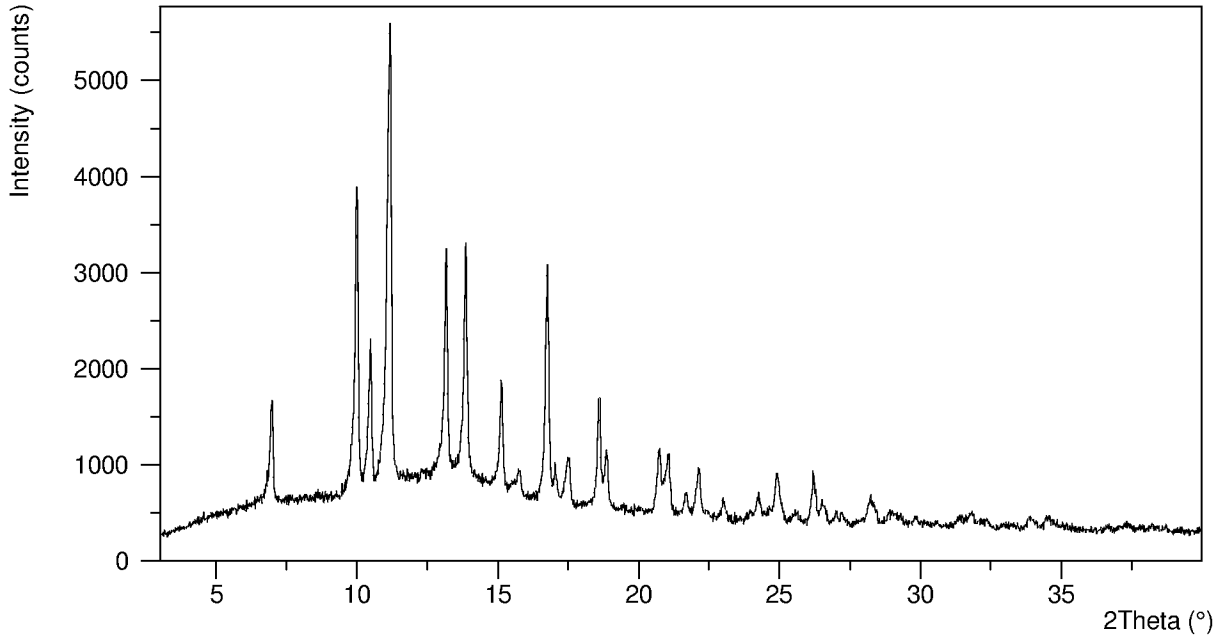


Figure 4. Raman spectrum of Bardoxolone methyl Form D

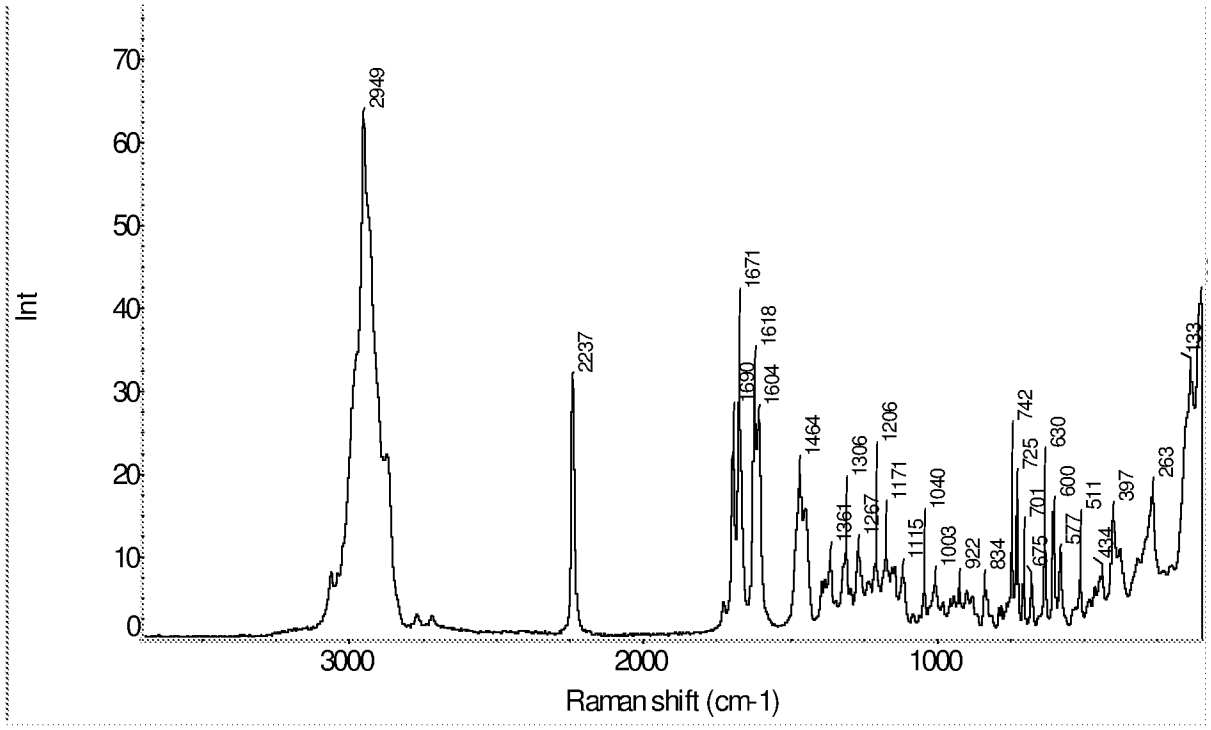
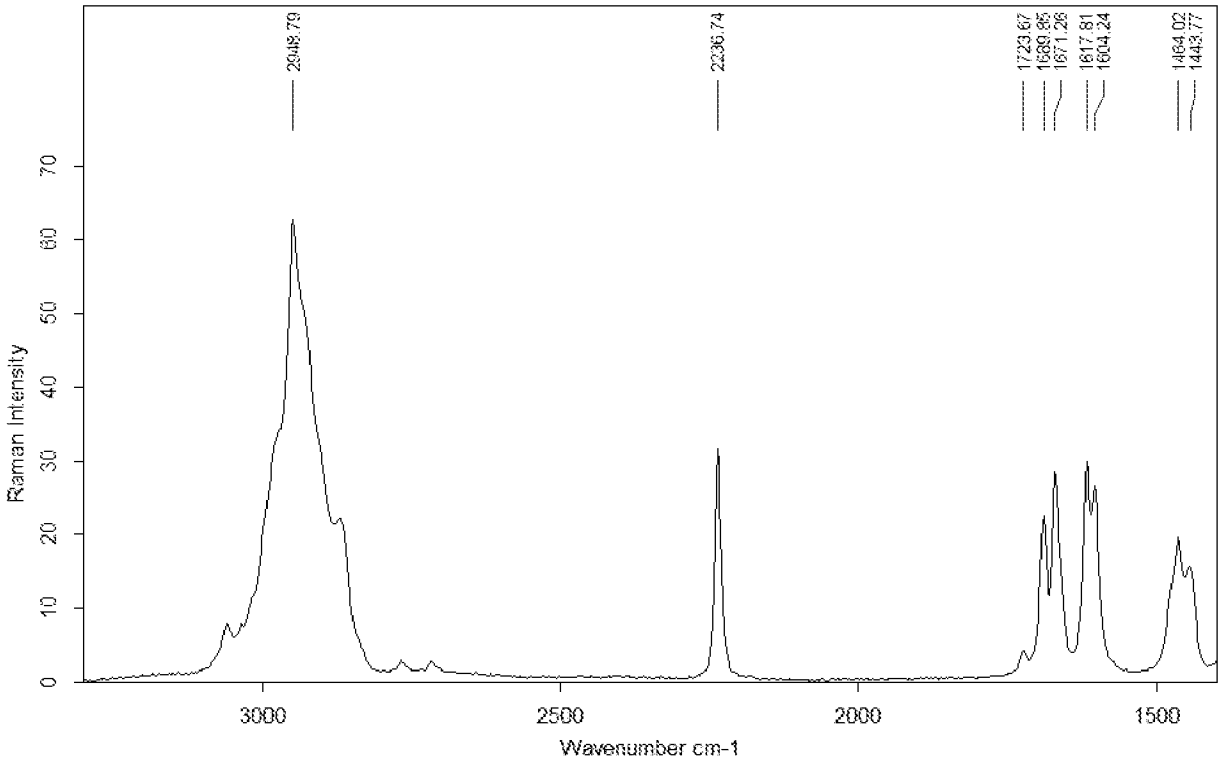


Figure 5. Raman spectrum of Bardoxolone methyl Form D at a range of 3300 to 1400 cm^{-1}



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/041752

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J63/00
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)
C07J C07B

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, 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.
A	WO 2009/023232 A1 (REATA PHARMACEUTICALS INC [US]; WALLING JOHN [US]; PARENT STEPHAN D [U) 19 February 2009 (2009-02-19) figures 18, 23, 24, 26; examples 3, 8, 9 page 9; tables 18, 19 page 45; tables 13, 14	1,2,5-18
A	WO 2009/023845 A2 (UNIV TEXAS [US]; REATA PHARMACEUTICLAS INC [US]; MEYER COLIN [US]; AND) 19 February 2009 (2009-02-19) page 2, paragraph 1 page 19, paragraph 3 page 20, paragraph 3 page 21, paragraph 5 figure 3	1,2,5-18

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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
12 September 2018	13/11/2018

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/041752

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CN 102 875 634 A (SUZHOU CRYSTAL PHARMACEUTICAL TECHNOLOGY CO LTD; SUZHOU PENGXU PHARMA) 16 January 2013 (2013-01-16) figures 1-5; examples 1-3 page 1, paragraphs 3, 5 -----	1,2,5-18
A	CN 102 887 936 A (SUZHOU CRYSTAL PHARMACEUTICAL TECHNOLOGY CO LTD; SUZHOU PENGXU PHARMA) 23 January 2013 (2013-01-23) figures 1,4,8; examples 1-3 page 1, paragraph 8 -----	1,2,5-18

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/041752

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, 2, 6, 7(completely); 5, 8-18(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, 2, 6, 7(completely); 5, 8-18(partially)

   CDDO-Me of crystalline form D, pharmaceutical compositions and medicinal indications and uses thereof.

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2. claims: 3, 4(completely); 5, 8-18(partially)

   CDDO-Me of crystalline form C, pharmaceutical compositions and medicinal indications and uses thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/041752

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