

Therapeutic agents used for treating pulmonary disorders are typically administered directly into the respiratory tract using an inhalation device, such as a dry powder inhaler (DPI), a metered-dose inhaler (MDI) or a nebulizer inhaler. When formulating a therapeutic agent for use in such devices, it is advantageous to have a stable crystalline form of the therapeutic agent that can be micronized or otherwise formulated and stored without significant decomposition or loss of crystallinity. In particular, the crystalline form should not be excessively hygroscopic or deliquescent. Additionally, the crystalline form should have a relatively high melting point (i.e. greater than about 130 °C) to minimize thermal degradation during processing and storage.

However, the formation of crystalline forms of organic compounds is highly unpredictable. No reliable methods exist for predicting which, if any, form of an organic compound will be crystalline. Moreover, no methods exist for predicting which, if any, crystalline form will have the physically properties desired for use in, e.g., pharmaceutical inhalation devices.

At present, no crystalline form of biphenyl-2-ylcarbamic acid 1-(2-{{4-(4-{{(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino}methyl}-phenylcarbamoyl)butyl}methylcarbamoyl}ethyl)piperidin-4-yl ester has been disclosed. Accordingly, a need exists for a stable crystalline form of this compound. In particular, a need exists for a stable, non-deliquescent crystalline form which has an acceptable level of hygroscopicity and a relatively high melting point.

~~SUMMARY OF THE INVENTION~~

The present ~~invention~~disclosure relates to oxalic acid addition salts of biphenyl-2-ylcarbamic acid 1-(2-{{4-(4-{{(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino}methyl}-phenylcarbamoyl)butyl}methylcarbamoyl}ethyl)piperidin-4-yl ester in crystalline solid state form. Such crystalline oxalate salts include crystalline oxalate isopropanol solvate salts and crystalline oxalate hydrate salts.

Certain crystalline oxalate salts of the ~~invention~~present disclosure have been discovered to be non-deliquescent and to have acceptable hygroscopicity properties when exposed to atmospheric moisture. Moreover, the crystalline oxalate salts of the present ~~invention~~disclosure have a relatively high melting point of at least about 160 °C.

Accordingly, in one ~~aspect~~embodiment, the present ~~invention~~disclosure provides a crystalline oxalate salt of biphenyl-2-ylcarbamic acid 1-(2-{{4-(4-{{(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-

dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)butyl]methylcarbamoyl}-ethyl)piperidin-4-yl ester.

In one aspect, there is provided a crystalline oxalate salt of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-phenylcarbamoyl)butyl]methylcarbamoyl}ethyl)piperidin-4-yl ester; wherein the crystalline oxalate salt is selected from:

(a) an isopropanol solvate characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 11.66 ± 0.20 , 15.75 ± 0.20 , 19.55 ± 0.20 , 23.00 ± 0.20 and 23.45 ± 0.20 ; and

(b) a hydrate characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 15.32 ± 0.20 , 16.90 ± 0.20 , 19.25 ± 0.20 and 23.73 ± 0.20 .

In one embodiment, the crystalline oxalate salt of the ~~invention~~present disclosure is an isopropanol solvate characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 11.66 ± 0.20 , 15.75 ± 0.20 , 19.55 ± 0.20 , 23.00 ± 0.20 and 23.45 ± 0.20 . This crystalline form or polymorph has been designated as Form 1.

In another embodiment, the crystalline oxalate salt of the ~~invention~~present disclosure is a hydrate characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 15.32 ± 0.20 , 16.90 ± 0.20 , 19.25 ± 0.20 and 23.73 ± 0.20 . This crystalline form or polymorph has been designated as Form 2.

In one embodiment, the crystalline oxalate salt of the ~~invention~~present disclosure is a hydrate prepared by exposing a crystalline oxalate salt of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-phenylcarbamoyl)butyl]methylcarbamoyl}ethyl)piperidin-4-yl ester to about 80 % to about 100 % relative humidity for a period of about 1 to about 5 days.

In another ~~aspect~~embodiment, the present ~~invention~~disclosure provides a composition comprising a crystalline oxalate salt of the ~~invention~~present disclosure.

In one ~~embodiment~~aspect, the composition is a pharmaceutical composition comprising (a) a crystalline oxalate salt as disclosed hereinof the ~~invention~~ and (b) a pharmaceutically-acceptable carrier.

In another ~~embodiment~~aspect, the composition is a pharmaceutical composition comprising (a) a crystalline oxalate salt ~~as disclosed herein of the invention~~; (b) a steroidal anti-inflammatory agent or a pharmaceutically acceptable salt or solvate thereof; and (c) a pharmaceutically-acceptable carrier.

5 | In another aspect, the present ~~invention~~disclosure provides a crystalline oxalate salt of the ~~invention~~present disclosure for use in therapy.

In one embodiment, a crystalline oxalate salt of the ~~invention~~present disclosure is used in the treatment of a pulmonary disorder. In a particular embodiment, the pulmonary disorder is chronic obstructive pulmonary disease. In another particular embodiment, the
10 | pulmonary disorder is asthma.

In one embodiment, the present ~~invention~~disclosure provides a method of treating a pulmonary disorder, the method comprising administering to a patient a crystalline oxalate salt of the ~~invention~~present disclosure.

In another embodiment, the present ~~invention~~disclosure provides a method of treating a pulmonary disorder, the method comprising administering to a patient (a) a crystalline oxalate salt of the ~~invention~~present disclosure; and (b) a steroidal anti-inflammatory agent or a pharmaceutically acceptable salt or solvate thereof.

5 In yet another embodiment, the present ~~invention~~disclosure provides a method of producing bronchodilation in a mammal, the method comprising administering a crystalline oxalate salt of the ~~invention~~present disclosure to the mammal by inhalation.

In another embodiment, the present ~~invention~~disclosure provides a crystalline oxalate salt of the ~~invention~~present disclosure for use in the manufacture of a
10 medicament.

In another aspect, there is provided the use of a crystalline oxalate salt as defined above in the manufacture of a medicament for treating a pulmonary disorder.

In another aspect, there is provided the use of (a) a crystalline oxalate salt as defined above; and (b) a steroidal anti-inflammatory agent or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for treating a
15 pulmonary disorder.

In another aspect, there is provided the use of a crystalline oxalate salt as defined above in the manufacture of a medicament to produce bronchodilation in a mammal, wherein the medicament is to be administered to the mammal by inhalation.

20 Other aspects and embodiments of this invention are disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Various aspects of the present invention are illustrated by reference to the accompanying drawings.

25 FIG. 1 shows a powder x-ray diffraction (PXRD) pattern for a crystalline oxalate isopropanol solvate salt of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)butyl]-methylcarbamoyl}ethyl)piperidin-4-yl ester (Form 1).

FIG. 2 shows a differential scanning calorimetry (DSC) trace for a crystalline
30 oxalate isopropanol solvate salt of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-{[(R)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}-phenylcarbamoyl)butyl]methylcarbamoyl}ethyl)piperidin-4-yl ester (Form 1).

FIG. 3 shows a thermal gravimetric analysis (TGA) trace for a crystalline oxalate isopropanol solvate salt of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)butyl]-methylcarbamoyl}ethyl)piperidin-4-yl ester (Form 1).

5 FIG. 4 shows a powder x-ray diffraction (PXRD) pattern for a crystalline oxalate hydrate salt of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-{[(*R*)-2-hydroxy-2-(8-hydroxy-2-oxo-1,2-dihydroquinolin-5-yl)ethylamino]methyl}phenylcarbamoyl)butyl]-methylcarbamoyl}ethyl)piperidin-4-yl ester (Form 2).

10 FIG. 5 shows a differential scanning calorimetry (DSC) trace for a crystalline oxalate hydrate salt of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-{[(*R*)-2-hydroxy-2-(8-