metered-dose inhalers (MDI) and nebulizer inhalers. When preparing pharmaceutical compositions and formulations for use in such devices, it is highly desirable to have a crystalline form of the therapeutic agent that is neither hygroscopic nor deliquescent and which has a relatively high melting point thereby allowing the material to be micronized without significant decomposition. Although crystalline freebase forms of the compound of formula I have been reported in U.S. Patent Publication No. 2007/0112027 to Axt et al. as Form I and Form II, the crystalline freebase forms of the present invention have different and particularly useful properties, including higher melting points.

SUMMARY OF THE DISCLSOURE

One embodiment of the disclosure relates to crystalline freebase forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl) piperidin-4-yl ester characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1.

One aspect of the disclosure relates to a crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl) piperidin-4-yl ester, designated as form III, which is characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1; and further characterized by having five or more additional diffraction peaks at 2θ values selected from 8.8±0.1, 10.1±0.1, 11.4±0.1, 11.6±0.1, 14.8±0.1, 15.2±0.1, 16.1±0.1, 16.4±0.1, 16.9±0.1, 17.5±0.1, 18.2±0.1, 19.3±0.1, 19.9±0.1, 20.8±0.1, 21.1±0.1, 21.7±0.1, and 22.3±0.1.

Another aspect of the disclosure relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and form III.

Another aspect of the disclosure relates to form III in micronized form.

Another aspect of the disclosure relates to a process for purifying biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl) piperidin-4-yl ester, comprising forming form III.

Another aspect of the disclosure relates to form III for use in therapy.

Another aspect of the disclosure relates to form III for use in the treatment of chronic obstructive pulmonary disease or asthma, or for producing bronchodilation.

Another aspect of the disclosure relates to the use of form III for the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease or asthma, or for producing bronchodilation.

Another embodiment of the disclosure relates to a crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl) piperidin-4-yl ester, designated as form IV, which is characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 6.6±0.1, 13.1±0.1, 18.6±0.1, 19.7±0.1, and 20.2±0.1; and further characterized by having five or more additional diffraction peaks at 2θ values selected from 10.6±0.1, 15.0±0.1, 16.0±0.1, 17.3±0.1, 17.7±0.1, 20.9±0.1, 21.4±0.1, 22.6±0.1, 24.6±0.1, and 27.8±0.1.

Another embodiment of the disclosure relates to pharmaceutical composition comprising a crystalline freebase described herein and a pharmaceutically acceptable carrier. Yet another embodiment of the disclosure relates to pharmaceutical compositions comprising a crystalline freebase of the disclosure in combination with one or more other therapeutic

agents. Accordingly, in one embodiment, the disclosure relates to a pharmaceutical composition comprising (a) a pharmaceutically acceptable carrier and a therapeutically effective amount of a crystalline freebase of the disclosure; and (b) a therapeutically effective amount of an agent selected from a steroidal anti-inflammatory agent such as a corticosteroid; a β_2 adrenergic receptor agonist; a phosphodiesterase-4 inhibitor; or a combination thereof; wherein the crystalline freebase and the agent are formulated together or separately. When the agent is formulated separately, a pharmaceutically acceptable carrier may be included. Typically, the crystalline freebase of the disclosure and the agent will be present in therapeutically effective amounts.

Another embodiment of the disclosure relates to a pharmaceutical composition comprising an aqueous isotonic saline solution comprising a crystalline freebase of the disclosure, wherein the solution has a pH in the range of from about 4 to 6. In a particular embodiment, an aqueous nebulizer formulation is buffered with citrate buffer to a pH of about 5.

In one embodiment, this disclosure relates to a drug delivery device comprising a dry powder inhaler containing a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a crystalline freebase of the disclosure.

The compound of formula I has muscarinic receptor antagonist activity. Accordingly, a crystalline freebase of the compound of formula I is expected to have the same activity, and thus find utility in treating pulmonary disorders such as asthma and chronic obstructive pulmonary disease. Thus, another embodiment of the disclosure relates to a method for treating a pulmonary disorder comprising administering to a patient a therapeutically effective amount of a crystalline freebase of the disclosure. Still another embodiment of the disclosure relates to a method of producing bronchodilation in a patient comprising administering to the patient a bronchodilation-producing amount of a crystalline freebase of the disclosure. In one embodiment, the compound is administered by inhalation. The disclosure also provides a method of treating chronic obstructive pulmonary disease or asthma comprising administering to a patient a therapeutically effective amount of a crystalline freebase of the invention. Another embodiment of the disclosure relates to a method for antagonizing a muscarinic receptor in a mammal comprising administering to the mammal a therapeutically effective amount of a crystalline freebase of the disclosure.

The disclosure also relates to processes for preparing crystalline freebase forms of the compound of formula I. The disclosure also provides a process for purifying the compound of formula I comprising forming a crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl) piperidin-4-yl ester. The disclosure further relates to products prepared by the processes described herein.

The disclosure also relates to a crystalline freebase of the compound of formula I in a micronized form; and to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a micronized crystalline freebase disclosure.

The disclosure also relates to crystalline freebase forms of the compound of formula I for use in therapy or as a medicament. Additionally, the disclosure relates to use of a crystalline freebase disclosure for the manufacture of a medicament; especially for the manufacture of a medicament for the treatment of a pulmonary disorder or for antagonizing a muscarinic receptor in a mammal.

BRIEF DESCRIPTION OF THE DRAWINGS

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

FIG. 1 shows a powder x-ray diffraction (PXRD) pattern of Form III of the crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester (the compound of formula I). Other characteristics of Form III are presented in FIG. 4, which shows a differential scanning calorimetry (DSC) thermogram and FIG. 6, which shows a thermal gravimetric analysis (TGA) trace.

FIG. 2 shows a PXRD pattern of Form IV of the crystalline freebase of the compound of formula I. FIG. 3 shows an overlay of the PXRD patterns of Form III and Form IV. Other characteristics of Form IV are presented in FIG. 5, which shows a DSC thermogram, and FIG. 7, which shows a TGA trace.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides crystalline freebase forms of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester (formula I). Surprisingly, the crystalline freebase forms of the invention have been found not to be deliquescent, even when exposed to atmospheric moisture. Additionally,