POLYMORPHIC FORMS OF (R)-OXYBUTYNIN HYDROCHLORIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

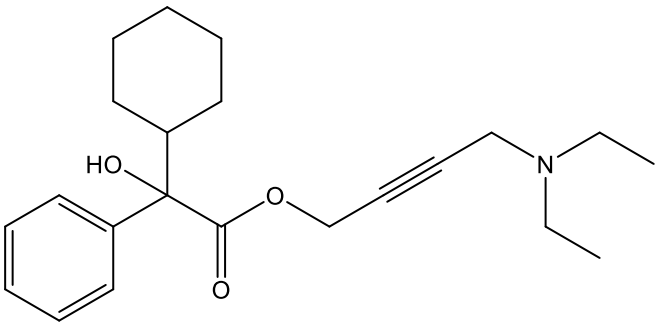
[0001] This application claims priority to United States provisional application 63/020,301, filed May 5, 2020, and United States provisional application 63/136,691, filed January 13, 2021, the entire contents of each of which are incorporated herein by reference.

TECHNICAL FIELD

[0002] The present invention provides various polymorphic forms of (R)-oxybutynin, along with pharmaceutical compositions thereof, preparation methods thereof, and uses thereof.

BACKGROUND

[0003] Oxybutynin and its derivatives are typically taken by mouth or applied to the skin and are applicable as bronchodilators or a remedy for overactive bladder. In addition, oxybutynin exerts a direct antispasmodic effect on various forms of smooth muscle, mainly by inhibiting the action of acetylcholine on smooth muscle as an anti-cholinergic drug and the like. Oxybutynin is marketed in the hydrochloride form. The chemical name for oxybutynin is 4-(diethylamino)but-2-yn-1-yl 2-cyclohexyl-2-hydroxy-2-phenylacetate for which the chemical structure is provided below as **I**:



I

Oxybutynin

SUMMARY

[0003a] In a first aspect of the present disclosure, there is provided a solid crystalline form of (R)-oxybutynin HCl, designated as Form C.

[0003b] In another aspect of the present disclosure, there is provided a solid crystalline form of (R)-oxybutynin HCl, having a combination of the Form B and Form C polymorphs as shown in Figure 9.

[0003c] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the solid crystalline form as disclosed herein and one or more pharmaceutically acceptable excipients.

[0003d] In a further aspect of the present disclosure, there is provided a process for preparing the solid crystalline form as disclosed herein, comprising precipitating the solid crystalline form from a solution comprising (R)-oxybutynin HCl and a solvent, or slurrying (R)-oxybutynin HCl in a solvent, wherein the solvent comprises an organic solvent excluding methanol, and the content of water is at or below 5% v/v.

[0003e] In another aspect of the present disclosure, there is provided a use of a solid crystalline form as disclosed herein, in the manufacture of a medicament for treating a condition associated with pharyngeal airway collapse.

[0003f] In another aspect of the present disclosure, there is provided a solid crystalline form of (R)-oxybutynin HCl.

[0003g] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a solid crystalline form of (R)-oxybutynin HCl as disclosed herein and optionally one or more pharmaceutically acceptable excipients.

[0003h] In another aspect of the present disclosure, there is provided a solid crystalline form of (R)-oxybutynin citrate.

[0003i] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a solid crystalline form of (R)-oxybutynin citrate as disclosed herein and optionally one or more pharmaceutically acceptable excipients.

[0003j] In a further aspect of the present disclosure, there is provided a process for producing crystalline R-oxybutynin HCl of Form C, the process comprising:

isolating (R)-oxybutynin from racemic oxybutynin via chiral resolution with D-malic acid; and

adding HCl to the isolated (R)-oxybutynin to produce crystalline (R)-oxybutynin HCl of Form C.

[0003k] In another aspect of the present disclosure, there is provided a solid crystalline form as disclosed herein, for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] The following figures are provided by way of example and are not intended to limit the scope of the claimed invention.

[0005] FIG. 1: Overlay of XRPD patterns obtained from the crystalline Form A, B, and C polymorphs of (R)-oxybutynin HCl.

[0006] FIG. 2: XRPD pattern of the (R)-oxybutynin HCl Form A polymorph at ambient RH (e.g., 40-65% RH).

CLAIMS

1. A solid crystalline form of (R)-oxybutynin HCl, designated as Form C.

2. The solid crystalline form of claim 1, having an X-ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 6.9 degrees 2θ ± 0.2 degree 2θ, 18.3 degrees 2θ ± 0.2 degree 2θ, 11.7 degrees 2θ ± 0.2 degree 2θ, 16.8 degrees 2θ ± 0.2 degree 2θ and 14.2 degrees 2θ ± 0.2 degree 2θ, at about ambient relative humidity.

3. The solid crystalline form of claim 1, having an X-ray powder diffraction pattern comprising at least four peaks, in terms of 2-theta, selected from the group consisting of 6.9 degrees 2θ ± 0.2 degree 2θ, 18.3 degrees 2θ ± 0.2 degree 2θ, 11.7 degrees 2θ ± 0.2 degree 2θ, 16.8 degrees 2θ ± 0.2 degree 2θ, 14.2 degrees 2θ ± 0.2 degree 2θ, 7.6 degrees 2θ ± 0.2 degree 2θ, and 14.8 degrees 2θ ± 0.2 degree 2θ, at about ambient relative humidity.

4. The solid crystalline form of claim 1, having an X-ray powder diffraction pattern comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 6.9 degrees 2θ ± 0.2 degree 2θ, 18.3 degrees 2θ ± 0.2 degree 2θ, 11.7 degrees 2θ ± 0.2 degree 2θ, 16.8 degrees 2θ ± 0.2 degree 2θ, 14.2 degrees 2θ ± 0.2 degree 2θ, 7.6 degrees 2θ ± 0.2 degree 2θ, and 14.8 degrees 2θ ± 0.2 degree 2θ, 24.2 degrees 2θ ± 0.2 degree 2θ, 13.9 degrees 2θ ± 0.2 degree 2θ, and 8.7 degrees 2θ ± 0.2 degree 2θ, at about ambient relative humidity.

5. The solid crystalline form of claim 1, having an X-ray powder diffraction pattern comprising at least seven peaks, in terms of 2-theta, selected from the group consisting of 6.9 degrees 2θ ± 0.2 degree 2θ, 18.3 degrees 2θ ± 0.2 degree 2θ, 11.7 degrees 2θ ± 0.2 degree 2θ, 16.8 degrees 2θ ± 0.2 degree 2θ, 14.2 degrees 2θ ± 0.2 degree 2θ, 7.6 degrees 2θ ± 0.2 degree 2θ, and 14.8 degrees 2θ ± 0.2 degree 2θ, 24.2 degrees 2θ ± 0.2 degree 2θ, 13.9 degrees 2θ ± 0.2 degree 2θ, and 8.7 degrees 2θ± 0.2 degree 2θ, at about ambient relative humidity.

6. The solid crystalline form of claim 1, having an X-ray powder diffraction pattern comprising the peaks, in terms of 2-theta, of 6.9 degrees 2θ ± 0.2 degree 2θ, 18.3 degrees 2θ ± 0.2 degree 2θ, 11.7 degrees 2θ ± 0.2 degree 2θ, 16.8 degrees 2θ ± 0.2 degree 2θ, 14.2

degrees 2θ ± 0.2 degree 2θ, 7.6 degrees 2θ ± 0.2 degree 2θ, and 14.8 degrees 2θ ± 0.2 degree 2θ, 24.2 degrees 2θ ± 0.2 degree 2θ, 13.9 degrees 2θ ± 0.2 degree 2θ, and 8.7 degrees 2θ ± 0.2 degree 2θ, at about ambient relative humidity.

7. The solid crystalline form of claim 1, having an X-ray powder diffraction pattern substantially as shown in Figure 4 at about ambient relative humidity.

8. The solid crystalline form of any one of claims 1-7, having a differential scanning calorimetry (DSC) thermogram comprising a melting onset at 109.6 °C and an endothermic peak at 119.1 °C.

9. The solid crystalline form of claim 8, having a differential scanning calorimetry (DSC) thermogram substantially as shown in Figure 7.

10. A solid crystalline form of (R)-oxybutynin HCl, having a combination of the Form B and Form C polymorphs as shown in Figure 9.

11. A pharmaceutical composition comprising the solid crystalline form of any one of claims 1-9 and one or more pharmaceutically acceptable excipients.

12. A process for preparing the solid crystalline form of any one of claims 1-9, comprising precipitating the solid crystalline form from a solution comprising (R)-oxybutynin HCl and a solvent, or slurrying (R)-oxybutynin HCl in a solvent, wherein the solvent comprises an organic solvent excluding methanol, and the content of water is at or below 5% v/v.

13. The process according to claim 12, wherein the organic solvent is selected from the group consisting of n-heptane, propyl acetate, ethyl acetate, isopropyl acetate, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), 1-propanol, ethanol, methyl t-butyl ether (MTBE), 1,4-dioxane, toluene, 1,2-dimethoxyethane, tetrahydrofuran, dichloromethane, acetonitrile, nitromethane, and mixtures thereof.

14. The process of claim 13, wherein the organic solvent is MTBE.

15. Use of a solid crystalline form of any one of claims 1-9, in the manufacture of a medicament for ~~A method of~~ treating a condition associated with pharyngeal airway collapse

~~comprising administering to a subject in need thereof the solid crystalline form of any one of claims 1-9~~.

16. The ~~method~~ use of claim 15, wherein the condition associated with pharyngeal airway collapse is sleep apnea or snoring.

17. The ~~method~~ use of claim 15, wherein the condition associated with pharyngeal airway collapse is Obstructive Sleep Apnea (OSA).

18. A solid crystalline form of (R)-oxybutynin HCl.

19. The solid crystalline form of claim 18, which is Form A.

20. The solid crystalline form of claim 19, having an X-ray powder diffraction pattern substantially as shown in Figure 2 at about ambient relative humidity.

21. The solid crystalline form of claim 18, which is Form B.

22. The solid crystalline form of claim 21, having an X-ray powder diffraction pattern substantially as shown in Figure 3 at about ambient relative humidity.

23. A pharmaceutical composition comprising a solid crystalline form of (R)-oxybutynin HCl according to any one of claims 18-22 and optionally one or more pharmaceutically acceptable excipients.

24. A solid crystalline form of (R)-oxybutynin citrate.

25. A pharmaceutical composition comprising a solid crystalline form of (R)-oxybutynin citrate according to claim 24 and optionally one or more pharmaceutically acceptable excipients.

26. A process for producing crystalline R-oxybutynin HCl of Form C, the process comprising:

isolating (R)-oxybutynin from racemic oxybutynin via chiral resolution with D-malic acid; and

adding HCl to the isolated (R)-oxybutynin to produce crystalline (R)-oxybutynin HCl of Form C.

27. The process of claim 26, wherein isolating (R)-oxybutynin from racemic oxybutynin comprises adding D-malic acid to racemic oxybutynin free base.

28. The process of claim 27, wherein D-malic acid is added to racemic oxybutynin free base in the presence of 2-propanol.

29. The process of claim 26, wherein the HCl is added in the presence of ethyl acetate.

30. The process of claim 26, further comprising adding MTBE to the isolated (R)-oxybutynin after addition of HCl.

31. A solid crystalline form of any one of claims 1-9, for use in therapy.