POLYMORPHIC FORMS OF (R)-OXYBUTYNIN HYDROCHLORIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

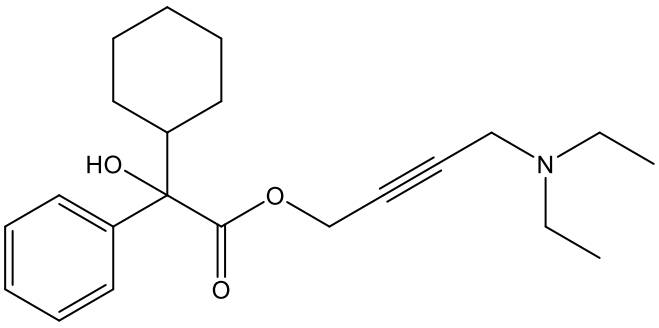
[0001] This application claims priority to United States provisional application 63/020,301, filed May 5, 2020, and United States provisional application 63/136,691, filed January 13, 2021, the entire contents of each of which are incorporated herein by reference.

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 treating a condition associated with pharyngeal airway collapse.

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

17. The 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.