POLYMORPHIC FORMS OF (R)-OXYBUTYNIN HYDROCHLORIDE

CROSS-REFERENCE TO RELATED APPLICATIONS

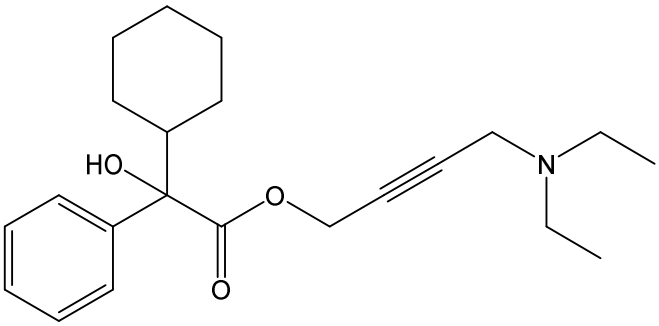
[0001] This application claims priority to United States provisional application 63/020,301, filed May 5, 2020, and United States provisional application 63/136,691, filed January 13, 2021, the entire contents of each of which are incorporated herein by reference.

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, 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.

[0003b] 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.

[0003c] 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.

[0003d] 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 obstructive sleep apnea (OSA).

[0003e] In another aspect of the present disclosure, there is provided a solid crystalline form of (R)-oxybutynin HCl, designated as Form A isopropanol solvate, having an X-ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 19.2 degrees 2θ ± 0.2 degree 2θ, 6.1 degrees 2θ ± 0.2 degree 2θ, 7.7 degrees 2θ ± 0.2 degree 2θ, 12.9 degrees 2θ ± 0.2 degree 2θ, and 21.6 degrees 2θ ± 0.2 degree 2θ, at about ambient relative humidity.

[0003f] In yet another aspect of the present disclosure, there is provided a solid crystalline form of (R)-oxybutynin HCl, designated as Form B, having an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at 7.5 degrees 2θ ± 0.2 degree 2θ, 17.2 degrees 2θ ± 0.2 degree 2θ, 14.1 degrees 2θ ± 0.2 degree 2θ, at ambient relative humidity.

[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 a further aspect of the present disclosure, there is provided a process for producing crystalline R-oxybutynin HCl of Form C as disclosed herein, 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.

[0003i] 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, 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.

2. 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.

3. 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, 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.

4. 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, 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 peaks, in terms of 2-theta, at 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 ambient relative humidity.

6. The solid crystalline form of claim 1, having an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at 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, 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 pharmaceutical composition comprising the solid crystalline form of any one of claims 1-9 and one or more pharmaceutically acceptable excipients.

11. 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.

12. The process according to claim 11, 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.

13. The process of claim 12, wherein the organic solvent is MTBE.

14. Use of a solid crystalline form of any one of claims 1-9, in the manufacture of a medicament for treating obstructive sleep apnea (OSA).

15. A solid crystalline form of (R)-oxybutynin HCl, designated as Form A isopropanol solvate, having an X-ray powder diffraction pattern comprising at least three peaks, in terms of 2-theta, selected from the group consisting of 19.2 degrees 2θ ± 0.2 degree 2θ, 6.1 degrees 2θ ± 0.2 degree 2θ, 7.7 degrees 2θ ± 0.2 degree 2θ, 12.9 degrees 2θ ± 0.2 degree 2θ, and 21.6 degrees 2θ ± 0.2 degree 2θ, at about ambient relative humidity.

16. The solid crystalline form of claim 15, having an X-ray powder diffraction pattern substantially as shown in Figure 2 at about ambient relative humidity.

17. A solid crystalline form of (R)-oxybutynin HCl, designated as Form B, having an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at 7.5 degrees 2θ ± 0.2 degree 2θ, 17.2 degrees 2θ ± 0.2 degree 2θ, 14.1 degrees 2θ ± 0.2 degree 2θ, at ambient relative humidity.

18. The solid crystalline form of claim 17, having an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at 7.5 degrees 2θ ± 0.2 degree 2θ, 17.2 degrees 2θ ± 0.2 degree 2θ, 14.1 degrees 2θ ± 0.2 degree 2θ, 21.1 degrees 2θ ± 0.2 degree 2θ, and 15.5 degrees 2θ ± 0.2 degree 2θ, at ambient relative humidity.

19. The solid crystalline form of claim 17, having an X-ray powder diffraction pattern comprising at least ten peaks, in terms of 2-theta, selected from the group consisting of 7.5 degrees 2θ ± 0.2 degree 2θ, 17.2 degrees 2θ ± 0.2 degree 2θ, 14.1 degrees 2θ ± 0.2 degree 2θ, 21.1 degrees 2θ ± 0.2 degree 2θ, 15.5 degrees 2θ ± 0.2 degree 2θ, 12.9 degrees 2θ ± 0.2 degree 2θ, 19.3 degrees 2θ ± 0.2 degree 2θ, 24.4 degrees 2θ ± 0.2 degree 2θ, 13.7 degrees 2θ ± 0.2 degree 2θ, 12.4 degrees 2θ ± 0.2 degree 2θ, 21.4 degrees 2θ ± 0.2 degree 2θ, 18.1 degrees 2θ ± 0.2 degree 2θ, 20.1 degrees 2θ ± 0.2 degree 2θ, 6.6 degrees 2θ ± 0.2 degree 2θ, 8.2 degrees 2θ ± 0.2 degree 2θ, and 20.4 degrees 2θ ± 0.2 degree 2θ, at ambient relative humidity.

20. The solid crystalline form of claim 17, having an X-ray powder diffraction pattern substantially as shown in Figure 3 at about ambient relative humidity.

21. A pharmaceutical composition comprising a solid crystalline form of (R)-oxybutynin HCl according to any one of claims 15-20 and optionally one or more pharmaceutically acceptable excipients.

22. A process for producing crystalline R-oxybutynin HCl of Form C according to claim 1, 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.

23. The process of claim 22, wherein isolating (R)-oxybutynin from racemic oxybutynin comprises adding D-malic acid to racemic oxybutynin free base.

24. The process of claim 23, wherein D-malic acid is added to racemic oxybutynin free base in the presence of 2-propanol.

25. The process of claim 22, wherein the HCl is added in the presence of ethyl acetate.

26. The process of claim 22, further comprising adding MTBE to the isolated (R)-oxybutynin after addition of HCl.

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