POLYMORPHIC FORMS OF RAD1901-2HCL

PRIORITY CLAIM

[0001] This application claims priority under 35 U.S.C. § 119(e) to United States Provisional Patent Application No. 62/694,003, filed July 4, 2018, the contents of which are incorporated by reference herein in its entirety, including drawings.

BACKGROUND

[0002] RAD1901 is a selective estrogen receptor down-regulator/degrader, or SERD, that crosses the blood-brain barrier and is particularly useful for the treatment of metastatic breast cancer. RAD1901 has been shown to bind with good selectivity to the estrogen receptor (ER) and to have both estrogen-like and estrogen-antagonistic effect in different tissues. In many cancers, hormones, like estrogen, stimulate tumor growth, and thus a desired therapeutic goal is to block this estrogen-dependent growth while inducing apoptosis of the cancer cells. SERDs have the potential to be an emerging class of endocrine therapies that could directly induce ER degradation, thus potentially enabling them to remove the estrogen growth signal in ER-dependent tumors without allowing ligand-independent resistance to develop.

SUMMARY

[0003] Various polymorphic forms of RAD1901-2HCl are disclosed herein, along with pharmaceutical compositions thereof, preparation methods thereof, and uses thereof.

[0003a] In one aspect, the present disclosure provides a solid form of RAD1901-2HCl having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees 2θ ± 0.2 degree 2θ, and at least four peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees 2θ ± 0.2 degree 2θ, 14.04 degrees 2θ ± 0.2 degree 2θ, 19.23 degrees 2θ ± 0.2 degree 2θ, 26.84 degrees 2θ ± 0.2 degree 2θ, 8.94 degrees 2θ ± 0.2 degree 2θ, and 22.39 degrees 2θ ± 0.2 degree 2θ, at about relative humidity 0%.

[0003b] In another aspect, the present disclosure provides a pharmaceutical composition comprising the solid form as described herein and one or more pharmaceutically acceptable excipients.

[0003c] In another aspect, the present disclosure provides a process for preparing the solid form of claim 1 comprising precipitating from a solution comprising RAD1901-2HCl and a solvent, or slurring RAD1901-2HCl in a solvent, wherein the solvent comprises an organic

solvent selected from the group consisting of 2-ethoxyethanol, 1,2-dichloroethane, and ethyl acetate, and the content of water is at or below 5% v/v.

[0003d] In yet another aspect, the present disclosure provides a use of the solid form of RAD1901-2HCl as described herein in the manufacture of a pharmaceutical composition for treating breast cancer or ovarian cancer.

[0003e] In yet another aspect, the present disclosure provides the solid form of RAD1901-2HCl as described herein for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] Figure 1: Conversion among Forms 1, 2, and 3 of RAD1901-2HCl.

[0005] Figure 2A: RP-HPLC Chromatogram of Sample 1 collected at 255 nm.

[0006] Figure 2B: ^{1}H NMR of Sample 1 collected in d_6-DMSO.

[0007] Figure 3A: RP-HPLC Chromatogram of Sample 2 collected at 255 nm.

[0008] Figure 3B: ^{1}H NMR of Sample 2 collected in d_6-DMSO.

[0009] Figure 4A: XRPD diffraction pattern of Sample 1 at ambient RH (e.g., 40-65% RH).

[0010] Figure 4B: Overlay of XRPD patterns obtained for Sample 1 pre- (bottom) and post-storage (top) at elevated condition analysis.

[0011] Figure 4C: Overlay of VH-XRPD patterns of Sample 1 collected at varied RH.

[0012] Figure 4D: Overlay of XRPD patterns obtained for Sample 1 pre- (bottom) and post- (top) GVS (uptake 0-90% RH) analysis.

Claims

1. A solid form of RAD1901-2HCl having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees 2θ ± 0.2 degree 2θ, and at least four peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees 2θ ± 0.2 degree 2θ, 14.04 degrees 2θ ± 0.2 degree 2θ, 19.23 degrees 2θ ± 0.2 degree 2θ, 26.84 degrees 2θ ± 0.2 degree 2θ, 8.94 degrees 2θ ± 0.2 degree 2θ, and 22.39 degrees 2θ ± 0.2 degree 2θ, at about relative humidity 0%.

2. The solid form of claim 1, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees 2θ ± 0.2 degree 2θ, and further comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees 2θ ± 0.2 degree 2θ, 14.04 degrees 2θ ± 0.2 degree 2θ, 19.23 degrees 2θ ± 0.2 degree 2θ, 26.84 degrees 2θ ± 0.2 degree 2θ, 8.94 degrees 2θ ± 0.2 degree 2θ, 22.39 degrees 2θ ± 0.2 degree 2θ, and 24.80 degrees 2θ ± 0.2 degree 2θ, at about relative humidity 0%.

3. The solid form of claim 1, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees 2θ ± 0.2 degree 2θ, and further comprising at least five peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees 2θ ± 0.2 degree 2θ, 14.04 degrees 2θ ± 0.2 degree 2θ, 19.23 degrees 2θ ± 0.2 degree 2θ, 26.84 degrees 2θ ± 0.2 degree 2θ, 8.94 degrees 2θ ± 0.2 degree 2θ, 22.39 degrees 2θ ± 0.2 degree 2θ, 24.80 degrees 2θ ± 0.2 degree 2θ, and 25.58 degrees 2θ ± 0.2 degree 2θ, at about relative humidity 0%.

4. The solid form of claim 1, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees 2θ ± 0.2 degree 2θ, and further comprising at least six peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees 2θ ± 0.2 degree 2θ, 14.04 degrees 2θ ± 0.2 degree 2θ, 19.23 degrees 2θ ± 0.2 degree 2θ, 26.84 degrees 2θ ± 0.2 degree 2θ, 8.94 degrees 2θ ± 0.2 degree 2θ, 22.39 degrees 2θ ± 0.2 degree 2θ, 24.80 degrees 2θ ± 0.2 degree 2θ, 25.58 degrees 2θ ± 0.2 degree 2θ, and 21.66 degrees 2θ ± 0.2 degree 2θ, at about relative humidity 0%.

5. The solid form of claim 1, having an X-ray powder diffraction pattern comprising a peak, in terms of 2-theta, at 11.53 degrees 2θ ± 0.2 degree 2θ, and further comprising at least seven

peaks, in terms of 2-theta, selected from the group consisting of 22.63 degrees 2θ ± 0.2 degree 2θ, 14.04 degrees 2θ ± 0.2 degree 2θ, 19.23 degrees 2θ ± 0.2 degree 2θ, 26.84 degrees 2θ ± 0.2 degree 2θ, 8.94 degrees 2θ ± 0.2 degree 2θ, 22.39 degrees 2θ ± 0.2 degree 2θ, 24.80 degrees 2θ ± 0.2 degree 2θ, 25.58 degrees 2θ ± 0.2 degree 2θ, 21.66 degrees 2θ ± 0.2 degree 2θ, and 28.76 degrees 2θ ± 0.2 degree 2θ, at about relative humidity 0%.

6. The solid form of claim 1, having an X-ray powder diffraction pattern comprising the peaks, in terms of 2-theta, of 8.94 degrees 2θ ± 0.2 degree 2θ, 11.53 degrees 2θ ± 0.2 degree 2θ, 14.04 degrees 2θ ± 0.2 degree 2θ, 19.23 degrees 2θ ± 0.2 degree 2θ, 21.66 degrees 2θ ± 0.2 degree 2θ, 22.39 degrees 2θ ± 0.2 degree 2θ, 22.63 degrees 2θ ± 0.2 degree 2θ, 24.80 degrees 2θ ± 0.2 degree 2θ, 25.58 degrees 2θ ± 0.2 degree 2θ, 26.84 degrees 2θ ± 0.2 degree 2θ, and 28.76 degrees 2θ ± 0.2 degree 2θ, at about relative humidity 0%.

7. The solid form of claim 1, having an X-ray powder diffraction pattern as shown in Figure 22C at about relative humidity 0%.

8. The solid form of claim 1, having a differential scanning calorimetry (DSC) thermogram comprising a melting onset at 210.3 °C and an endothermic peak at 233.8 °C.

9. The solid form of claim 1, having a thermogravimetric analysis (TGA) thermogram as shown in the top of Figure 21A.

10. A pharmaceutical composition comprising the solid form of claim 1 and one or more pharmaceutically acceptable excipients.

11. A process for preparing the solid form of claim 1 comprising precipitating from a solution comprising RAD1901-2HCl and a solvent, or slurring RAD1901-2HCl in a solvent, wherein the solvent comprises an organic solvent selected from the group consisting of 2-ethoxyethanol, 1,2-dichloroethane, and ethyl acetate, and the content of water is at or below 5% v/v.

12. The solid form of claim 1, having a ^{13}C solid-state CPMAS NMR pattern as shown for Pattern B in Figure 23, a ^{1}H solid-state MAS NMR pattern as shown for Pattern B in Figure 24, an FT-IR pattern as shown in Figure 25C, and a Raman Spectroscopy pattern as shown for Pattern B in Figure 26.

13. Use of the solid form of RAD1901-2HCl as described in claim 1 in the manufacture of a pharmaceutical composition for treating breast cancer or ovarian cancer.

14. The use of claim 13 wherein said breast cancer is positive for the estrogen receptor.

15. The solid form of RAD1901-2HCl as described in claim 1 for use in therapy.