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CERTIFICATE

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Application No.:	201710648135.2
Application Type:	Patent for Invention
Title of Invention:	A Crystal Form of Orexin Receptor Antagonist, Its Preparation Method and Use
Application Date:	August 1, 2017
Applicant:	Crystal Pharmaceutical (Suzhou) Co., Ltd.
Inventors/Designers:	Chen Minhua, Zhang Yanfeng, Huang Chunxiang, Zhang Xiaoyu

Bureau Director

Shen Changyu [signature]

March 5, 2020

Claims

1. A crystal form of CS2 of E-2006, is characterized in that its X-ray powder diffraction (XRPD) presents a characteristic peak at the places whose diffraction angle 2θ value is 7.8°±0.2°, 15.6°±0.2° or 11.4°±0.2°.

2. The crystal form of CS2 as stated in Claim 1, is also characterized in that its XRPD presents a characteristic peak at one or several places whose diffraction angle 2θ value is 12.5°±0.2°, 21.3°±0.2° or 27.3°±0.2°.

3. The crystal form of CS2 as stated in Claim 1, is also characterized in that its XRPD presents a characteristic peak at one or several places whose diffraction angle 2θ value is 24.0°±0.2°, 19.4°±0.2° or 22.3°±0.2°.

4. Preparation methods for the crystal form of CS2 of E2006, are characterized in and comprise:

(1) Dissolve E-2006 into ketone, haloalkane or amide solvents, and evaporate slowly to get the crystal form of CS2; or

(2) Dissolve E-2006 into nitrile solvent, add ionic liquid for induction, and evaporate slowly to get the crystal form of CS2; or

(3) Dissolve E-2006 into the positive solvent to make an E-2006-containing solution, then drip anti-solvent slowly into the positive solvent solution or drip the positive solvent solution into anti-solvent, and stir and crystallize to get the crystal form of CS2; or

(4) Dissolve E-2006 into ketone solvent, ketone and water mixed solvent, ketone and normal heptane mixed solvent, cyclic ether and water mixed solvent or haloalkane solvent, and heat to accelerate evaporation to get the crystal form of CS2.

5. According to the preparation methods as stated in Claim 4, as stated in Method (1), the ketone solvent is acetone, the haloalkane solvent is chloroform and the amide solvent is dimethylformamide or dimethylacetamide; as stated in Method (2), the nitrile solvent is acetonitrile, the ionic liquid is 1-ethyl-3-methylimidazolium methylsulfate, 1-ethyl-3-methylimidazolium hexafluorophosphate or 1,3-dimethyl-methylimidazole phosphate salt; as stated in Method (3), if anti-solvent is normal heptane, the positive solvent can be haloalkane or arene solvent, and if anti-solvent is water, the positive solvent can be alcohol or amide solvent; as stated in Method (4), the ketone solvent is butanone, the ketone and water mixed solvent refers to acetone and water mixed, the ketone and normal heptane mixed solvent refers to acetone and normal heptane mixed, the cyclic ether and water mixed solvent refers to tetrahydrofuran and water mixed, the haloalkane solvent is dichloromethane, and the heating temperature is 40□~100□.

Claims

6. According to the preparation methods as stated in Claim 5, as stated in Method (3), the haloalkane solvent is dichloromethane, the arene solvent is methylbenzene, the alcohol solvent is methanol and the amide solvent is dimethylformamide; as stated in Method (4), the volume ratio of acetone to water, acetone to normal heptane and tetrahydrofuran to water are 1:1, and the heating temperature is 100□.

7. A pharmaceutical composition, comprising the crystal form of CS2 of curative dose as stated in Claim 1 and a pharmaceutically acceptable carrier, diluents or excipient.

8. Use of the crystal form of CS2 as stated in Claim 1 in producing the agents adopted to prepare orexin receptor antagonist.

9. Use of the crystal form of CS2 as stated in Claim 1 in producing the agents adopted to prepare the drugs for prevention and treatment of insomnia and/or sleep disorder and/or irregular sleep-wake rhythm disorder (ISWRD).

Specification

A Crystal Form of Orexin Receptor Antagonist, Its Preparation Method and Use

Technical Field

This invention refers to the field of crystal technology of drugs, specifically, involving a crystal form of orexin receptor antagonist, its preparation method and use.

Background Art

Polymorphism or heteromorphism is an exclusive characteristic of certain molecules and molecular compounds. Even the same molecule may have different crystal forms due to different spread spectrums, and these crystal forms may have different crystal structures and physical properties, such as solubility, stability, mobility, thermal property, mechanical nature, purifying ability, X-ray diffraction spectrum, infrared absorption spectrum, Raman spectrum and solid-state NMR (referring to *P. Di Martino et al, J. Thermal Anal., 48:447-458(1997)*). One or some analysis and detection methods can be adapted to distinguish different crystal forms of the same molecule or molecular compound.

Different crystal forms of a solid chemical may bring differences in solubility, stability, mobility, compressibility and some other properties to affect the safety and efficacy of such chemical-contained drug products (referring to *K. Knapman, Modern Drug Discovery, 3,53-54,57,2000.*), resulting in different clinical drug efficacies. Finding of new crystal forms (including anhydride, hydrate, solvate, etc.) of APIs (Active Pharmaceutical Ingredients) may bring the substances owning more processing advantages or providing better physicochemical properties, such as better bioavailability, storage stability, easy processing, easy purification or acting as the intermediate crystal form for the transformation of other crystal forms. New crystal forms of pharmaceutical compounds can help to improve the performance of drugs and to expand the forms of APIs that can be chosen from pharmaceutically.

Researched by EISAI, E-2006 (Lemborexant) is used for the clinical treatment of insomnia. Insomnia is a commonly seen sleep disorder featured on difficult to fall asleep and maintain sleep. Research shows that orexin is the key regulator of the sleep-wake cycle, and orexin receptor antagonist owns the potential of avoiding improperly timed night waking and boosting normal sleep-wake cycle. E-2006 is an orexin receptor antagonist. In the clinical trial, E-2006 can obviously improve insomniacs' sleep efficiency, including faster asleep and shorter night waking. Besides, E-2006 also presents a huge potential in curing ISWRD of patients with Alzheimer's disease. Different from common insomnia symptoms, some medical demands of ISWRB are not satisfied in this field until now.

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