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Preparation and Characterization of Two Polymorphs of (3aRS,4RS,7RS,7aSR)-2-(Tricyclo[3.3.1.1^{3,7}]decan-1-yl)-4,5,6,7-tetrahydro-4,7-eposyisoindoline-1,3-dione (SU2162) with PXRD and DSC

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Abstract

Objective: To develop the characterization of the polymorphs and the best preparation method of two forms of the title compound (SU2162). After SU2162 was prepared in accordance with the patent process, the crystal form I was recrystallized by ethyl acetate and the crystal form II was obtained by the recrystal in acetone. And the two crystal forms were characterized with differential scanning calorimetry (DSC) and X-ray powder diffraction (PXRD). The melting point of crystal form I (triclinic) is at 158˚C, and the melting point of crystal form II (monoclinic) is at 163˚C. The PXRD studies of the two crystalline samples indicate that they have the distinct diffraction patterns. The method herein can be stably prepared for the two crystal forms of the title compound.

Keywords

SU2162, Crystal Form, DSC, PXRD

1. Introduction

Cancer is a threat to human health and its incidence is increasing worldwide. The American Cancer Society re-

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port provides that Cancer remains the second most common cause of death in the US, accounting for nearly 1 of every 4 deaths [1]. According to the report, the United States issues new cancer cases are about 165,540 people and the deaths are about 585,720 people. The latest World Health Organization research shows that over the next 20 years, new cases of cancer worldwide will rise to 22 million/year. In the same time, the cancer deaths are predicted to increase from 8.2 million/year to 13 million/year [2]. Not only does cancer cause illness, multiple organ failure and death, it also contributes to social economic losses, and cancer is reported to cause the greatest economic loss than any other disease ($895.2 billion per year), followed by cardiovascular and cerebrovascular diseases, HIV/ AIDS, lower respiratory infections (including pneumonia), hepatocirrhosis, and malaria [3]. Anticancer drugs research has become a hot field.

(3aRS,4SR,7RS,7aSR)-2-(tricyclo-[3.3.1.1^{3,7}]decan-1-yl)-4,5,6,7-tetrahydro-4,7-epoxyisoindoline-1,3-dione (SU2162) is a novel anticancer agent (**Figure 1**: structure). Pharmacodynamic studies of SU2162 suggest that it has remarkable, dose-response inhibitory effects on glioma growth (IC50 = 0.721 mmol/l) [4]. The chemical synthesis of SU2162 from norcantharidin and amantadine has been established [4] (**Figure 2**) and its single crystal structures are known [5] [6]. Also, the pharmacokinetics study of SU2162 has been performed [7] [8].

Our research shows that there are at least two crystalline forms of the title compound polymorph [5] [6]. Their melting points are close and the transformation is easy between two crystalline forms [9]. This instability makes the preparation designated crystalline form difficult. Polymorphism has achieved significance in last decade due to the fact that different polymorphs exhibit different solubilities. In the case of slights soluble drugs, this may affect the rate of dissolution. As a result, one polymorph may be more therapeutically active than another polymorph of the same drug. Polymorphism is very important in pharmaceutical processes, including dissolution and formulation, explaining the primary reason why we are interested in polymorphs [10] [11]. In order to get a stable crystalline form, to meet the needs and requirements of clinical trials and the production process, we made a series of further experiments. The stable crystalline forms of the title compound were prepared and polymorphs were characterized. The main process and the results are reported in this article.

2. Experimental

2.1. Preparation of Polymorphs

SU2162 samples were prepared by the patent process [4]. 0.9 g of adamantine and 1.0 g of norcanthardin were dissolved in 10 ml of DMF and the mixture was refluxed continuously for 18 hours. Then, the solution was transferred into a petri dish and evaporated off. The crude product obtained was dissolved in 20 ml of ethyl acetate by adequate stirring. After filtration, pure SU2162 samples were achieved by slow evaporation from the filtrate to dryness at room temperature covering the beaker with plastic film that was perforated with several small holes. Finally, the samples were washed with boiling 20 ml of ethanol water (ethanol:water = 1:4) and dried in an oven to obtain the light yellow solid of SU2162.

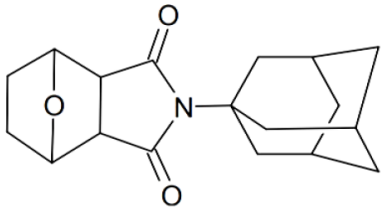

Figure 1. The structure of SU2162.

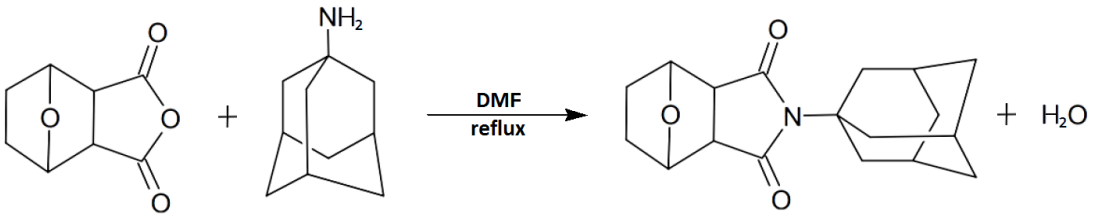

Figure 2. The compounds synthesis route.

To identify SU2162, the infrared (IR) spectra was measured by a PerkinElmer spectrum 100 IR spectrometers, the sample was prepared by pressing a mixture of about 2 mg of SU2162 powder and 100 mg of anhydrous KBr powder. IR spectrum (KBr, cm^{-1}): 2909 cm^{-1} (saturate C-H), 1767 cm^{-1} and 1692 cm^{-1} (five membered ring lactam), 1452 cm^{-1} (C-N), 1199 cm^{-1} and 1164 cm^{-1} (C-O-C) (see **Figure 3** in supporting information). The above data are consistent with the reference document [4].

For the preparation of crystal form I (triclinic), 0.5 g of SU2162 samples were heated to 80˚C in 5 ml of ethyl acetate. Recrystallization was accomplished by slow cooling of a saturated solution to room temperature and stationary for several days. Crystal form I was filtered and dried at 30˚C.

For the preparation of crystal form II (monoclinic), 0.2 g of SU2162 samples were heated to 80˚C in 2 ml of acetone. Recrystallization was accomplished by rapidly down to −18˚C and stationary for a few days at −18˚C. Crystal form II was filtered and dried at 30˚C.

2.2. Analysis of DSC

The thermal behavior of crystal forms samples was determined on a PerkinElmer DSC 4000 Differential Scanning Calorimetry (DSC). 6 - 7 mg powder for each sample was putted in sealed aluminum pans and its temperature was raised from 30˚C to 200˚C with a rate of 10˚C/min under dry nitrogen flow at 20 ml/min. The run proceeded with quench cooling at a rate of −10˚C/min to return to 30˚C. DSC data were analyzed using the Origin 8.0 software.

2.3. Determination of PXRD

X-ray powder diffraction patterns were recorded and used to determine the physical form of the individual crystal. The X-ray powder diffraction (PXRD) spectra was collected on a Rigaku D/max 2200 vpc X-ray diffractometer, using CuKα radiation at 40 kV and 30 mA. The scans were run from 3.0˚ to 60.0˚ 2θ with steps of 0.02˚ and scan rate of 2˚/min. Data were processed using the Origin 8.0 software.

3. Result and Discussion

3.1. Analysis of DSC

Figure 4 shows the thermograms for SU2162 crystal (I) recrystallized from ethyl acetate. Curve I in **Figure 4** represents the thermogram obtained by heating a sample to 200˚C. There is a sharp peak with temperature 158˚C, the other is an asymmetrical peak in the range of 130˚C - 150˚C. **Figure 5** shows the thermograms for SU2162 crystal (II) recrystallized from acetone. Curve II in **Figure 5** represents the thermogram obtained by heating a sample to 200˚C. This curve indicates there is a sharp peak at 163˚C and an asymmetrical peak in the range of 130˚C - 150˚C.

From Curve I and Curve II, the thermal study demonstrates that the melting points of crystal form I (triclinic) is at 158˚C and the melting points of crystal form II (monoclinic) is at 163˚C. The similar endothermic peaks below the melting temperature in each curve might be a desolvation. Additionally, the melting point of the two crystal forms have been measured by capillary method, the melting point of crystal (I) is 157˚C - 158˚C and that of crystal (II) is 164˚C - 165˚C. The results of DSC and capillary tube are both in agreement with the literature [2] [9].

3.2. Determination of PXRD

X-ray powder diffraction patterns of crystal (I) and crystal (II) are shown respectively in **Figure 6** (crystal form I [triclinic]) and **Figure 7** (crystal form II [monoclinic]). The most intense line for 2θ in **Figure 6** occurred at 16.880˚, and the strong-to-weak sequence of XRD intensity in **Figure 6** is 16.880˚, 17.858˚, 16.402˚, 16.120˚, 11.821˚, 13.580˚, 9.481˚ (XRD line relative intensity I/I_0 > 10%). The most intense line for 2θ in **Figure 7** occurred at 44.621˚, and the strong-to-weak sequence of XRD intensity in **Figure 7** is 44.621˚, 36.161˚, 7.516˚, 25.160˚, 31.539˚, 22.999˚, 17.579˚, 19.540˚ (XRD line relative intensity I/I_0 > 10%). Compared to two sets of data, the figures indicate that there are different differences between two crystal forms, for example: 1) The most intense line for 2θ of crystal (I) occurred at 16.880˚, while that of crystal (II) occurred at 44.621˚. 2) The strong-to-weak sequence of XRD intensity between crystal (I) and crystal (II) is distinct. 3) PXRD pattern of

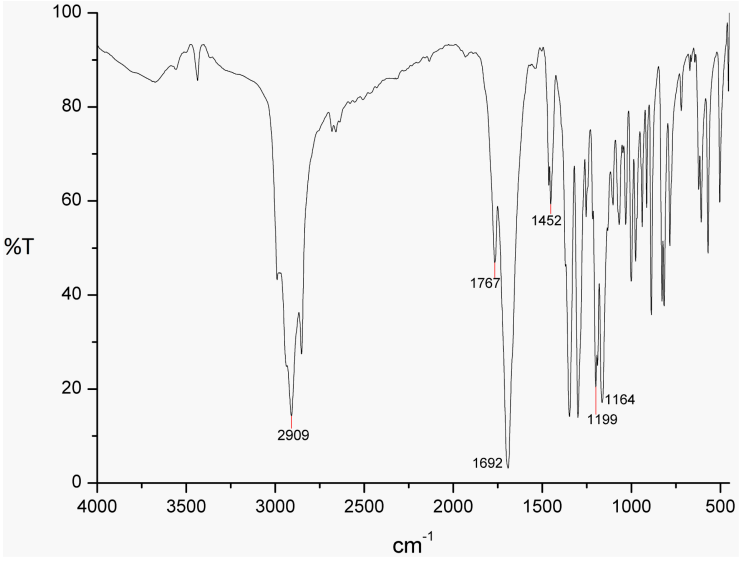

Figure 3. The IR spectra of SU2162.

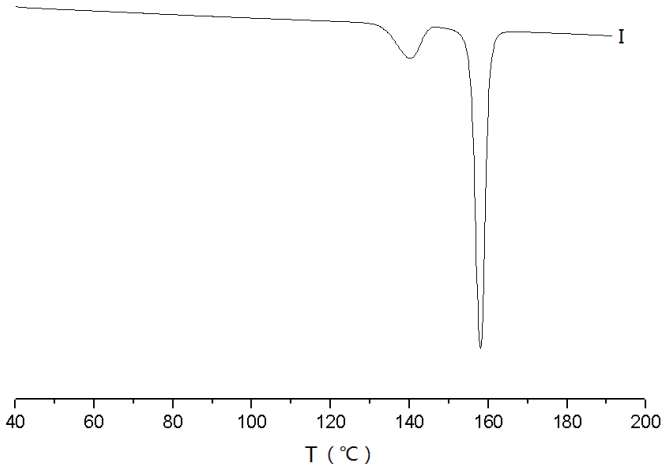

Figure 4. DSC thermogram for crystal form I of SU2162.

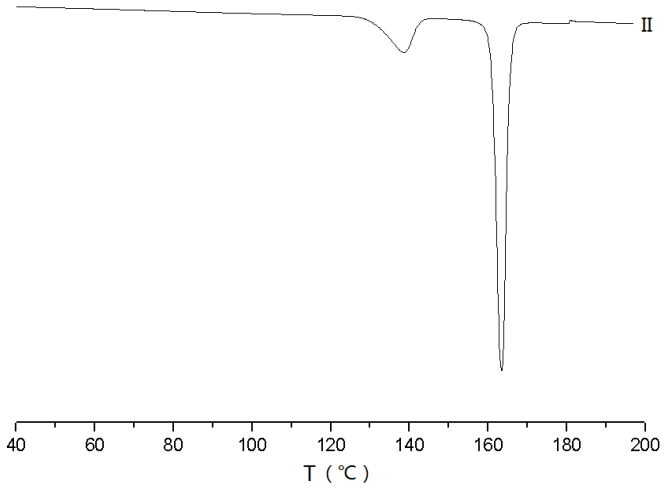

Figure 5. DSC thermogram for crystal forms II of SU2162.

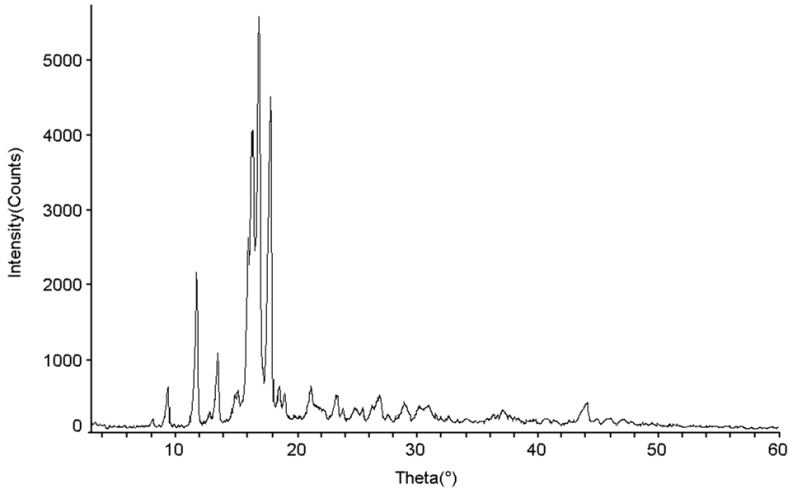

Figure 6. PXRD pattern for crystal form I of SU2162.

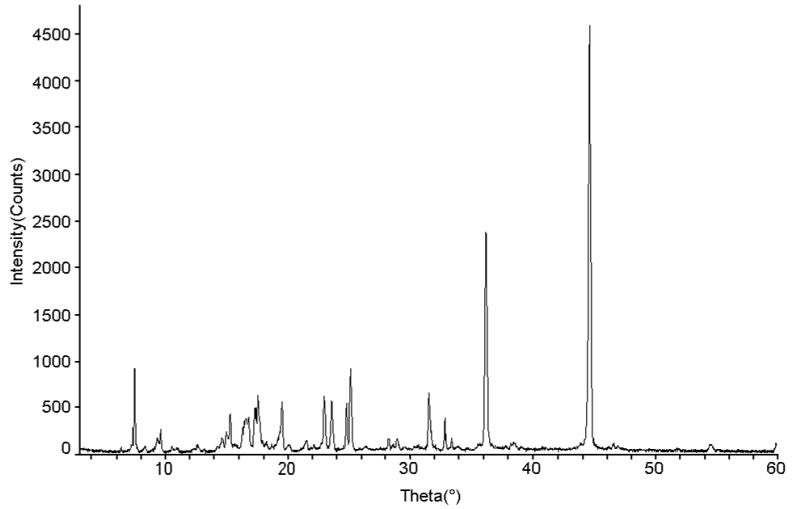

Figure 7. PXRD pattern for crystal form II of SU2162.

crystal (II) has the presence of a diffraction peak at $2\theta = 54.559^{\circ}$, which is absent on PXRD pattern of crystal (I). Comparing to the characteristic parameters (diffraction angle 2θ and XRD line relative intensity I/I_0) for PXRD of the two crystal forms, it certifies that crystal (I) and crystal (II) are two different crystal forms. The results of PXRD correspond to the literature [5] [6].

X-ray powder diffraction (PXRD) is one of the most credible methodology to characterize crystallographic compounds. Powder diffraction possesses their fingerprint type of unique diffraction patterns so that it can ordinarily be used for the verification with the equivalence of various crystalline samples. Because PXRD takes less time and money for structure detection than single crystal X-ray diffraction (SXRD), PXRD would be a better choose to characterize polymorphs. In this article, we want to develop this liable and accurate PXRD to identify the two crystal forms of SU2162.

4. Conclusion

In summary, from the view of the importance of crystal forms in the preparation of drugs and treatments, we optimized the preparation of two crystal forms of the title compound by screening experiments. We have determined the process to prepare a stable crystalline form. The stable polymorphs obtained were characterized available by DSC and PXRD. To ensure the clinical trials and drug development, the data from this article provide quality control standards and requirements.

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