

Another Novel Crystal Form of Nateglinide

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Abstract In this paper, another novel crystal form of nateglinide called X2- form was found. Its structure was characterized by X-ray powder diffraction, elemental analysis, high performance liquid chromatography and differential scan calorimetry. The patterns and data of the new form related were given.

Key words nateglinide, X-ray powder diffraction, differential scan calorimetry, high performance liquid chromatography, elemental analysis

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那格列奈的新晶型

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[摘要] 发现了那格列奈的一种新晶型 (命名为 X2), 并用 X 射线粉末衍射分析仪、元素分析仪、高效液相色谱仪、差示扫描量热仪对其进行了测定, 给出了相关的图谱与数据。

[关键词] 那格列奈, X 射线粉末衍射, 差示扫描量热分析, 高效液相色谱, 元素分析

0 Introduction

Nateglinide, a derivative of D-henylalanine, is a highly physiologic mealtime glucose regulator. It can rapidly increase insulin secretion when taken before meals, mimicking early-phase insulin release lost in patients with Type II diabetes^[1]. Nateglinide was first developed by Yamanouchi and marketed in Japan in 1999.

In recent years, the polymorphism of medicine has attracted scientists' great attention^[2]. The study of polymorphism of medicine is helpful to rebuild medicine, improve clinical effect and reduce side effect. The B-form, H-form and S-form of nateglinide have been reported^[3].

Recently, another novel crystal form of nateglinide was found and named X2-form. The new crystal phase was identified by X-ray powder diffractometer, HPLC, elemental analysis and the melting point was determined by differential scan calorimetry.

1 Experimental

1.1 Materials and methods

H-form nateglinide obtained by the process described in US Pat 5488150, 1996201230 is used to prepare the new X2-form. First put the H-form (2.5 g) into the solvent mixture (50 mL). The solvent mixture comprises ethanol and water in a ratio about 30:20 volume/volume and then stir at 40°C for complete dissolution (to

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obtain a transparent solution). The solution is cooled to 20~ 25℃ to form crystals. The product obtained is filtered under reduced pressure and dried at 15℃ for 17 h to give X2- form crystals.

1. 2 Elemental analysis(EA)

The calculated data of C, H and N contents are 71. 89%, 8. 57% and 4. 41%, respectively. The corresponding measured data (X2- form) are 71. 86%, 8. 66%, 4. 35%. The results of elemental analysis indicated that the X2 crystal forms and H crystal forms had the same chemical composition (C₁₉H₂₇NO₃).

1. 3 High performance liquid chromatography(HPLC)

HPLC was used to make sure that H- form and X2- form are the same compound. Chromatography was conducted on Agilent ODS Column (150mm × 4. 6 mm) at 30℃. The mobile phase was consisted of methanol and acetic acid (80: 20). The flow rate was 1 mL • min⁻¹. The detection wavelength was at 210 nm. The retention time of the two crystal forms (H- and X2- form) in HPLC was the same under the same condition, it indicated the H- form and X2- form of nateglinide were the same compound.

1. 4 Powder X-ray diffraction (PXRD)

The X-ray powder diffraction patterns of the four crystal forms of nateglinide were obtained with a D/ma_x-c rotating anode X-ray powder diffractometer equipped with a scintillation counter, a graphite crystal monochromator and Cu Kα 1 radiation source (wavelength, 0. 15406 nm). The aperture of the divergence, scattering and receiving slits were 1°, 1° and 0. 30mm, respectively. Data were collected from 3° to 40° (2θ), in continuous scan mode increasing at a step size of 0. 02°, operated at 40 kV and 100mA. Powder samples were examined in a glass holder after being smoothed with a glass slide. X-ray powder diffraction analysis indicated that X2- form crystal structure was different from the known B- form, H- form and S- form crystals.

1. 5 Differential scanning calorimetry (DSC)

The DSC of nateglinide samples were recorded on a Perkin-Elmer DSC7 connected to a Perkin-Elmer 7700 computer via a TAC7 microprocessor controller. Perkin-Elmer TAS7 software was used to calculate the extrapolated onset temperature, peak temperature, and enthalpy values for each thermal event. The temperature axis was calibrated with pure indium and confirmed with a zinc standard. Samples were examined in crimped aluminum pans with ventilated lids. The rate of heating was 10℃ • min⁻¹ over the temperature range from room temperature to 300℃. The melting point of X2- form crystals was measured. Its melting point was 124. 97℃, it was different from the melting points of B- form, H- form, and S- form.

2 Results and Discussion

X-ray powder diffraction analysis indicates that X2- form crystal structure is different from the known B- form, H- form and S- form crystals (see Fig. 1). The intensities of the reflections are expressed as percentage of most intense reflection. The novel crystal form has significant reflections expressed as 2θ values at about 4. 58, 7. 44, 13. 34, 14. 96, 15. 56, 18. 44, 19. 10, 20. 92 degree (see Table 1).

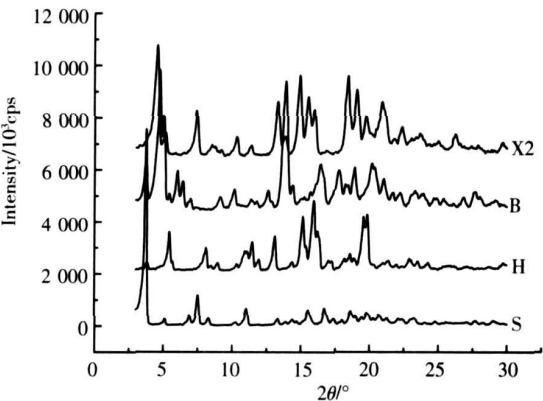


Fig.1 XRD patterns of X2,B,H,S forms of nateglinide

Table 1 The nine stronger reflection lines of B-, H-, S- and X2- forms of nateglinide

| Form | Brag angles (2θ/°) | | | | | | | | |
|------|--------------------|------|-------|-------|-------|-------|-------|-------|-------|
| B | 3.76 | 4.78 | 5.06 | 6.04 | 13.94 | 16.46 | 17.80 | 18.92 | 20.14 |
| H | 5.44 | 8.10 | 11.48 | 13.12 | 15.18 | 15.94 | 16.20 | 19.54 | 19.74 |
| S | 3.78 | 7.56 | 8.30 | 11.06 | 15.58 | 16.98 | 18.68 | 19.94 | 20.64 |
| X2 | 4.58 | 7.44 | 13.34 | 14.96 | 15.56 | 16.00 | 18.44 | 19.10 | 20.92 |

From the DSC pattern (see Fig. 2), we can see two peaks clearly. We think the first peak (at 101. 37℃)

is a phase change point of X2 form, and second peak (at 124.97°C) is the melting point. It was different from the melting points of B-form, H-form, and S-form. The melting points of the B, H and S-form crystals are 131.14°C, 139.17°C and 172.10°C, respectively.

The retention time of the H- and X2 crystal forms of nateglinide in HPLC is the same under the same condition (see Fig. 3) and their chemical composition are also the same ($C_{19}H_{27}NO_3$). So we can be sure they are the same compound with different crystal form.

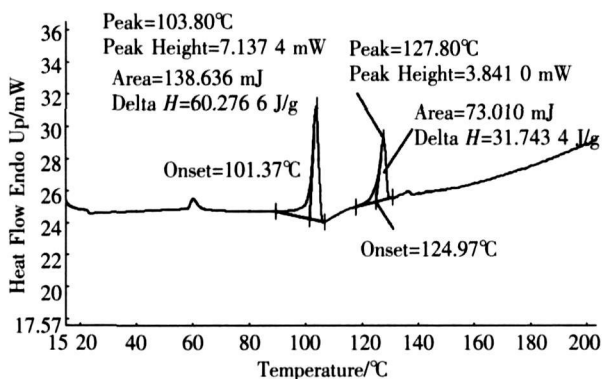


Fig.2 DSC patterns of X2-form of nateglinide

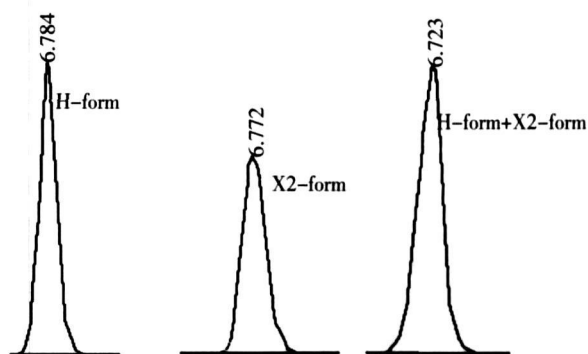


Fig.3 HPLC patterns of X2-form and H-form of nateglinide

From the results above, we can see clearly that nateglinide may have many kinds of crystal form. The B-form and H-form were reported and the H-form crystal is more stable and more suitable for use in medicines than the B-type because of B-form crystal suffering from the problem of instability, especially in the process of mechanical grinding. Recently, we also reported S-form, the stability^[4] of H-, B- and S-forms, the crystal structures of H-form and S-form and their medicine efficiency^[5]. We found S-form nateglinide also can significantly reduce the level of blood glucose in high glucosmia mice like the H-form, especially after 40 min.

The medicine efficacy of nateglinide is related with their crystal structure. Polymorphs are regarded as thermodynamically different phases, and different crystal forms possess different melting points, different heats of fusion, and different dissolution rates. Differences in properties can affect bioavailability and effective clinical use. So it is important to know which form is stable and effective and how to change them from an inefficient form to other efficient forms.

3 Conclusion

The X2-form is a new crystal structure of nateglinide. Its structure is different from that of known B-form, H-form and S-form and its melting point (124.97°C) is the lowest among the four forms of crystal structures.

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