

Study on Stability of Nateglinide Polymorphism

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Abstract: The stability of three forms of nateglinide, especially S-form and H-form, was determined. S-form was a new crystal structure of nateglinide. Three forms of nateglinide were treated in different conditions, such as in various temperatures, humidity, light and so on. Analysis of their crystal structures was performed by X-ray powder diffraction (XRD) and their particle shapes were observed with scanning electron microscope (SEM). The results indicated that the stability of S-form of nateglinide is the best among the three forms and their particle shapes are quite different. S-form is the sheet structure of layer upon layer, H-form looks like a hank of silk lines and B-form is the clubbed shape.

Keywords: Diabetes, nateglinide, polymorphism, X-ray powder diffraction, stability.

Nateglinide, also called Starlix in Brand Names, proved effective in both blunting blood-sugar spikes associated with meals and in lowering overall blood sugar as measured by the hemoglobin A1C test. Because of its short action, it does not linger in the body where it might cause overproduction of insulin and lead to dangerously low blood-sugar levels. The B-form and H-form were reported² and it was considered that H-form crystal is more stable and more suitable for use in medicines than the B-form. Nateglinide is a derivative of the amino acid, D-phenylalanine. Nateglinide is internationally marketed by Novartis Pharmaceutical Corporation. In August 1999, nateglinide received first approval for use in type II diabetics in Japan, where it is marketed under the names Starsis and Fastic. In December 2000, the United States Food and Drug Administration (FDA) approved nateglinide for use as monotherapy or in combination with metformin in type II diabetic patients whose blood sugar is not controlled with diet and exercise. It is currently available in 24 countries throughout Europe, Asia, and North and South America.

In last article¹, we first reported that a new crystal form of nateglinide was found and named S-form. Recently its stability in various conditions such as temperature, humidity and intensity of light were studied, its medicine efficacy was also tested in first model and the results are exciting.

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Materials and Methods

Three crystal forms of nateglinide were obtained from Jiangsu Institute of Materia Medica, China. And they were divided into three groups to be performed the test of their stability. The first group was treated in various temperature holding on 15 min. (S-form: 20, 60, 100, 140 and 170°C, H-form: 20, 60, 100, 136°C and B-form: 20, 60, 100, 130°C), the second group was in high humidity (relative humidity 92.5%) holding on 10 day, and the third group was in light (3500LX) for 10 day, respectively.

The X-ray powder diffraction patterns of three crystal forms of nateglinide treated in various conditions, humidity and light were obtained with a Rigaku Corporation D/max-rC rotating anode X-ray powder diffractometer using a copper target, equipped with a scintillation counter, a graphite crystal monochrometer. The aperture of the divergence, scattering and receiving slits were 1°, 1° and 0.30mm respectively. The scan speed was 3°/min. over the range from 3° to 40° (2θ), in step scan mode increasing at a step size of 0.02°, operating at 40 kV and 100 mA. Powder samples were contained in a glass dish after being smoothed with a glass slide.

Treated in various temperature

Three forms of nateglinide was treated in various temperatures (from room temperature to their own melts¹) and held on 15 min. respectively. Their intensities, positions and shapes of peaks had proved that the thermal stability of S-form was the best (from room temperature to 170°C), next was H-form (from room temperature to 136°C), and B-form is varying with temperature. The Bragg angles (2θ) and relative intensities (I/I_0) were calculated and listed below. **S-form** (At 20°C): 3.86 (100), 7.64 (15), 8.40 (5), 11.18 (6), 15.70 (7), 16.84 (6), 18.78 (6), 19.48 (5); (At 60°C): 3.86 (100), 7.66 (14), 8.40 (4), 11.16 (6), 15.68 (8), 16.90 (6), 18.80 (6), 19.46 (4); (At 100°C): 3.86 (100), 7.66 (14), 8.40 (4), 11.18 (5), 15.72 (6), 16.88 (7), 18.78 (6), 19.54 (3); (At 140°C): 3.86 (100), 7.64 (14), 8.38 (4), 11.16 (6), 15.62 (7), 16.82 (6), 18.76 (6), 19.52 (4); (At 170°C): 3.86 (100), 7.64 (13), 8.38 (5), 11.14 (5), 15.64 (8), 16.88 (6), 18.76 (7), 19.50 (4); **H-form** (At 20°C): 5.50 (91), 8.14 (72), 11.52 (63), 13.16 (59), 15.18 (87), 15.96 (90), 19.58 (85), 19.90 (100); (At 60°C): 5.50 (100), 8.16 (69), 11.50 (62), 13.16 (54), 15.18 (87), 15.96 (78), 19.58 (79), 19.88 (83); (At 100°C): 5.50 (100), 8.18 (79), 11.52 (68), 13.16 (56), 15.20 (95), 15.98 (92), 19.60 (94), 19.88 (87); (At 136°C): 5.50 (100), 8.14 (69), 11.52 (58), 13.14 (57), 15.18 (81), 15.98 (91), 19.58 (79), 19.88 (84); **B-form** (At 20°C): 3.90 (33), 4.72 (100), 5.22 (63), 7.56 (29), 13.48 (26), 14.08 (43), 15.08 (31), 18.60 (28); (At 60°C): 3.92 (30), 4.46 (43), 4.96 (100), 5.18 (86), 5.48 (27), 6.16 (21), 14.10 (30), 15.50 (19), (At 100°C): 3.90 (28), 4.42 (38), 4.90 (100), 5.22 (100), 5.54 (25), 6.16 (27), 14.06 (45), 20.32 (23); (At 130°C): 3.94 (38), 4.94 (100), 5.22 (53), 6.18 (27), 6.60 (18), 13.86 (31), 14.12 (48), 20.36 (18); and their patterns are shown in **Figure 1**.

Treated in high humidity and intensity of light

Weight some S-form and H-form of nateglinide and put them in high humidity (RH 92.5%) and intensity of light (3500LX), respectively. After 10 days, remove them from the test system and weight again. And then they were analyzed by X-ray powder diffraction. The patterns are shown in **Figure 2**.

Figure 1 XRD patterns of B,H,S-form of nateglinide various temperature

Figure 2 XRD patterns of H,S-form of nateglinide in light and high humidity

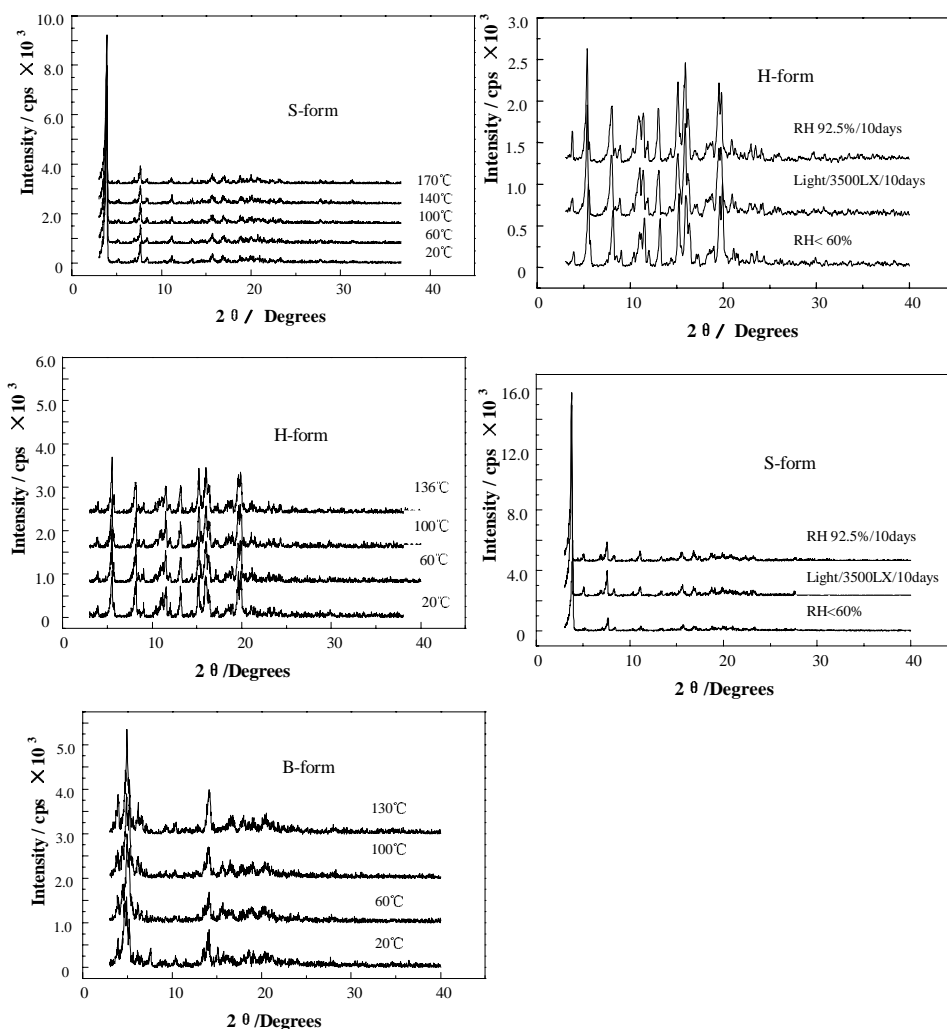
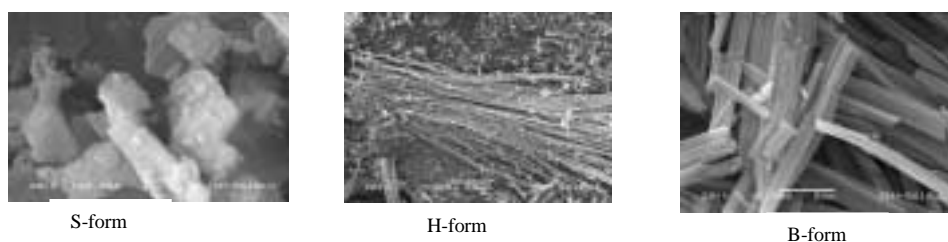


Figure 3 SEM images of three forms of nateglinide

Results and Discussion

X-ray powder diffraction analysis indicates three form crystals of nateglinide have different thermal stability. S-form is the most stable form, and B-form is the lowest. In the heating process, we can see that S-form became a melt state at about 170°C, H-form at about 136°C, and B-form at about 130°C, respectively. X-ray powder diffraction patterns also shown that S-form crystal structure of nateglinide are stable from 20°C to 170°C and H-form from 20°C to 136°C. But the crystal structure of B-form varies with temperature. In high humidity (RH92.5%) and intensity of light (3500LX) after 10 days, the weight of S-form and H-form have no changed (<5%), X-ray patterns had also shown that like H-form, S-form was stability in high humidity and light. From the image of SEM (in **Figure 3**), we can see that's three forms have different forms. S-form has the sheet structure of layer upon layer, H-form looks like a hank of silk lines and B-form is the clubbed shape to accumulate together.

Conclusion

The thermal stability of S-form of Nateglinide is the best among the three forms. As H-form, S-form is also stability in mulling, high humidity and light.

Acknowledgments

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References and Notes

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