Preparation and Characterization of Amorphous Nateglinide

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Abstract Amorphous nateglinide was prepared by a solvent removal process, using pure H-form nateglinide that is a kind of poorly water-soluble antidiabetic drug as the raw material. The amorphous nateglinide was characterized by high-performance liquid chromatography (HPLC), X-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier-transform infrared spectrometry (FT-IR), and solution test. Results obtained from the analysis revealed that the produced nateglinide was in amorphous state, and there was neither other chemical reaction nor raw material decomposed in the solvent removal process, and the result of the solution test showed that solution rate of the amorphous nateglinide was significantly enhanced when compared with the crystalline nateglinide. The results demonstrate that the solvent removal process is a direct and feasible method which could be utilized for improvement of the solution property of the poorly water-soluble crystalline nateglinide.

Key words: nateglinide; amorphous; solution rate

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无定型那格列奈的制备与表征

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[摘要] 本文以水难溶的抗糖尿病药物 H 型那格列奈为原料, 通过溶剂去除法制备出无定型那格列奈. 用高效液相色谱(HPLC)、X-射线粉末衍射(XRD)、差示扫描量热分析(DSC)、红外光谱(FT-IR)以及溶解速率实验等分析手段对所制备的无定型那格列奈进行了表征.

分析结果表明, 制得的那格列奈样品呈无定型状态, 而且在制备过程中既没有化学反应发生, 也没有原料分解. 溶解速率实验结果表明, 制得的无定型那格列奈的溶解速率相对于结晶型那格列奈有明显提高. 这说明, 使用溶剂去除法制备无定型那格列奈是个直接有效的方法, 可以改善水难溶晶型那格列奈的溶解特性.

[关键词] 那格列奈, 无定型, 溶解速率

Nateglinide is a pancreatic, beta-cell-selective, K-ATP potassium channel blocker which improves overall glycemic control of form 2 diabetes[1]. Across stimulating insulin release, nateglinide could induce insulin more readily available during and just after the meal. This leads to a significant reduction in postprandial hyperglycaemia without the danger of hypoglycaemia between meals[2]. The commercial nateglinide is mainly using H-form as the technical material[3], but the solubility of H-form is low[4]. As a poorly water-soluble drug, nateglinide features a low solubility and solution rate in the gastrointestinal tract, which limits its effective absorption and bio-

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availability.

If the solution rate of nateglinide can be enhanced, bioavailability following oral administration of it could be significantly improved. Amorphous substances lack three-dimensional long range order, which exists in crystalline materials. The amorphous state is a high-energy state that exhibits enhanced solubility and solution rate, and thus increased bioavailability[5]. Recently, many researches have revealed that there were various crystal structures of nateglinide in existence[6-8]. However, a direct and feasible method for producing amorphous nateglinide as the technical material has not been reported.

The objective of this study was to directly produce amorphous nateglinide by the solvent removal process. In this method, the amorphous nateglinide was successfully obtained in pure water as solvent at room temperature. The process of production avoided chemical reaction, byproduct and any other impurity without using the organic solvents. Furthermore, it could be expected to have more economic advantages compared with other processes. The amorphous nateglinide by the solvent removal process was characterized by high-performance liquid chromatography (HPLC), X-ray diffraction (XRD), differential scanning calorimetry (DSC), Fourier-transform infrared spectrometry (FT-IR), and solution test. The data of commercial H-form nateglinide was also shown for comparison.

1 Materials and Methods

1.1 Materials

The H-form nateglinide (purity 99.84%) was supplied by Jiangsu Provincial Institute of Materla Medica. All other chemicals and solvents were of analytical grade.

1.2 Preparation of amorphous nateglinide

The molecular structure of nateglinide is N-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine.

Pure H-form nateglinide was used as the raw material. Amorphous nateglinide was prepared by a solvent removal process. H-form nateglinide was dissolved in sufficient amount of water to obtain saturation solution at room temperature and filtrated by a 0.22 μm filter to obtain clear solution. The solution was placed in an oven at 30℃ to remove the solvent and reach dryness. The dried solid was analyzed by HPLC, XRD, DSC, FT-IR and solution test. After preparation, all samples were stored at -20℃ until further use.

1.3 High-performance liquid chromatography (HPLC)

HPLC (Agilent 1100, USA) was used to measure the H-form and amorphous nateglinide samples with a 150 mm × 4.6 mm C-18 column. The mobile phase consisted of 30% water and 70% methanol, and the detection wavelength was 210 nm. The flow rate was about 1 mL/min. The injection volume was 10 μL for each testing sample.

1.4 X-ray diffraction (XRD)

The XRD patterns were recorded on X-ray diffractometer (Rigaku D/max-2500VL/PC type X-ray powder diffractometer). Samples were irradiated with monochromatized Cu Kα radiation (0.154 06 nm) and a divergence slit of 1°. The X-ray generator was set to an acceleration voltage of 40 kV and a filament emission of 200 mA. The 2θ scan range was 3-40° with a step size of 0.02° and the scan speed was 5°/min.

1.5 Differential scanning calorimetry (DSC)

DSC measurements were performed using a Analysis Diamond DSC (USA). 3-5 mg of H-form and amorphous nateglinide samples were hermetically sealed in aluminum pans respectively and heated at a constant rate of 10℃/min over a temperature range of 70-200℃. A dry nitrogen purge of 25 mL/min was employed in the process.

1.6 Fourier transform infrared spectrometry (FT-IR)

FT-IR spectra were recorded with a NEXUS-670 spectrometer in the range 450-4 000 cm^{-1}. Samples were diluted with KBr and pressed to obtain the test piece.

1.7 Solution test

Solution test for the nateglinide samples was carried out using a dissolution apparatus (D-800LS, Tianjin, CN) following the USP apparatus II (paddle) method. Paddle speed and bath temperature were set at 100 rpm and 37.0℃, respectively. 20mg amount of nateglinide samples were placed into vessels containing 900mL water. 3mL sample was withdrawn at specific intervals. These samples were filtered using a 0.22μm filter. The concentration of samples was analyzed in an ultraviolet spectrophotometer (Cary 5000, VARIAN, USA) at 258 nm.

2 Results and Discussion

2.1 High-performance liquid chromatography (HPLC)

H-form and amorphous nateglinide samples were measured by HPLC. The result showed that the purity of H-form samples was 99.84%, and the retention time was 8.666 min(Fig 1). In comparison with it, the purity of the amorphous nateglinide samples was 99.86%, and the retention time was 8.690min(Fig 2). This showed that there was neither other reaction nor raw material decomposed in the solvent removal process.

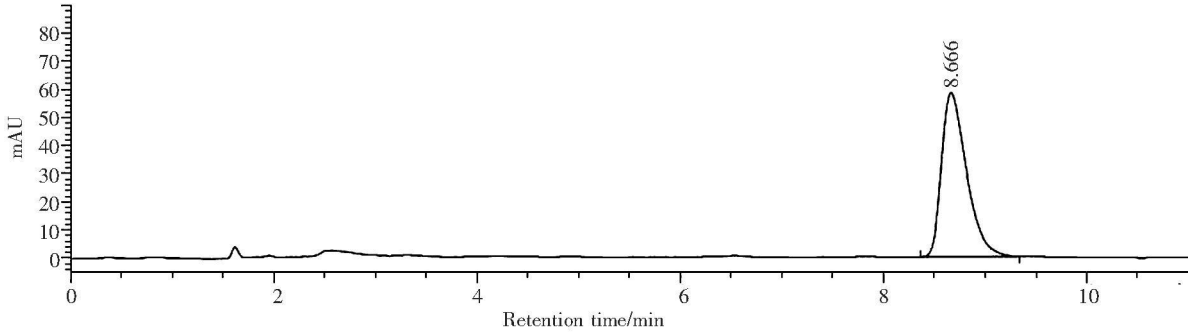

Fig.1 HPLC of H-form nateglinide

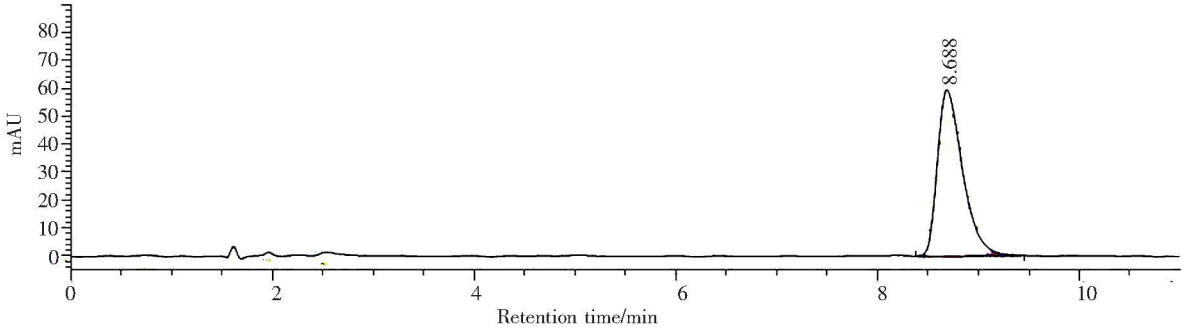

Fig.2 HPLC of amorphous nateglinide

2.2 X-ray diffraction (XRD)

The XRD pattern of H-form nateglinide samples showed characteristic diffraction peaks at 2θ values of 5.5, 8.1, 11.5, 13.1, 15.2, 15.9, 16.2, 19.6, and 19.9°(Fig 3). However, instead of intense crystalline peaks, the samples that prepared by a solvent removal process was in amorphous state, showing a halo-pattern in powder X-ray diffractogram (Fig 4).

2.3 Differential scanning calorimetry (DSC)

The DSC scan of H-form nateglinide samples showed one endothermic band around 141℃ ascribed to melting of drug(Fig 5). However, the amorphous nateglinide samples did not show any endothermic band from 70℃ to 200℃ (Fig 6). It proved that the samples were in substantially amorphous form.

2.4 Fourier-transform infrared spectrometry (FT-IR)

The molecular structures of the nateglinide were studied by means of FT-IR. The spectra of the nateglinide was characterized by the 1714 cm^{-1} (-COOH), 1649 cm^{-1}, 1542 cm^{-1} (-CO-NH), 1214 cm^{-1} (C-N).

The identical FT-IR spectra curves between the H-form (Fig. 7) and the amorphous nateglinide (Fig. 8) samples suggested that there was no chemical structure change in the samples.

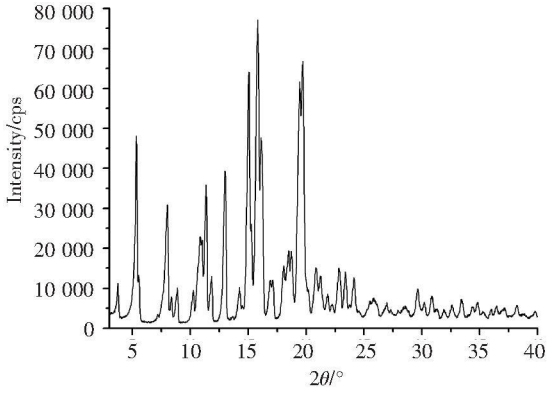

Fig.3 XRD pattern of H-form nateglinide

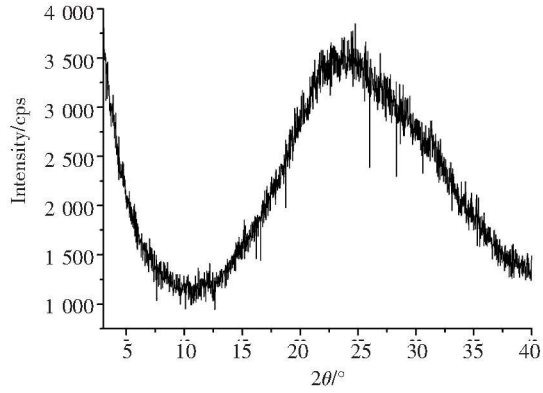

Fig.4 XRD pattern of amorphous nateglinide

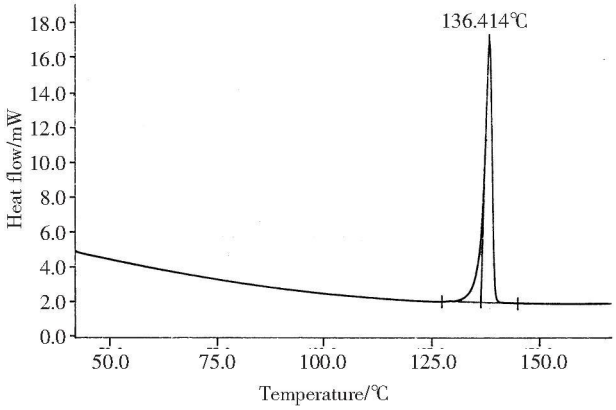

Fig.5 DSC pattern of H-form nateglinide

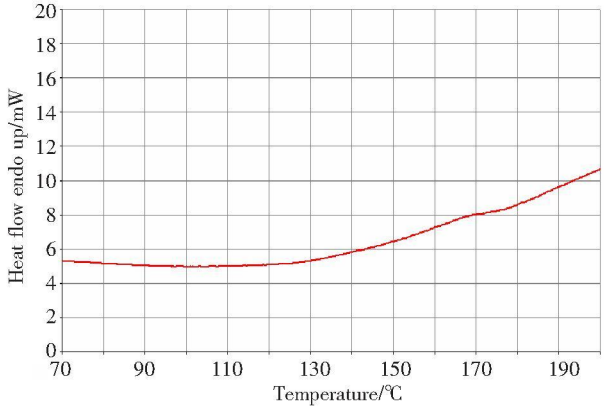

Fig.6 DSC pattern of amorphous nateglinide

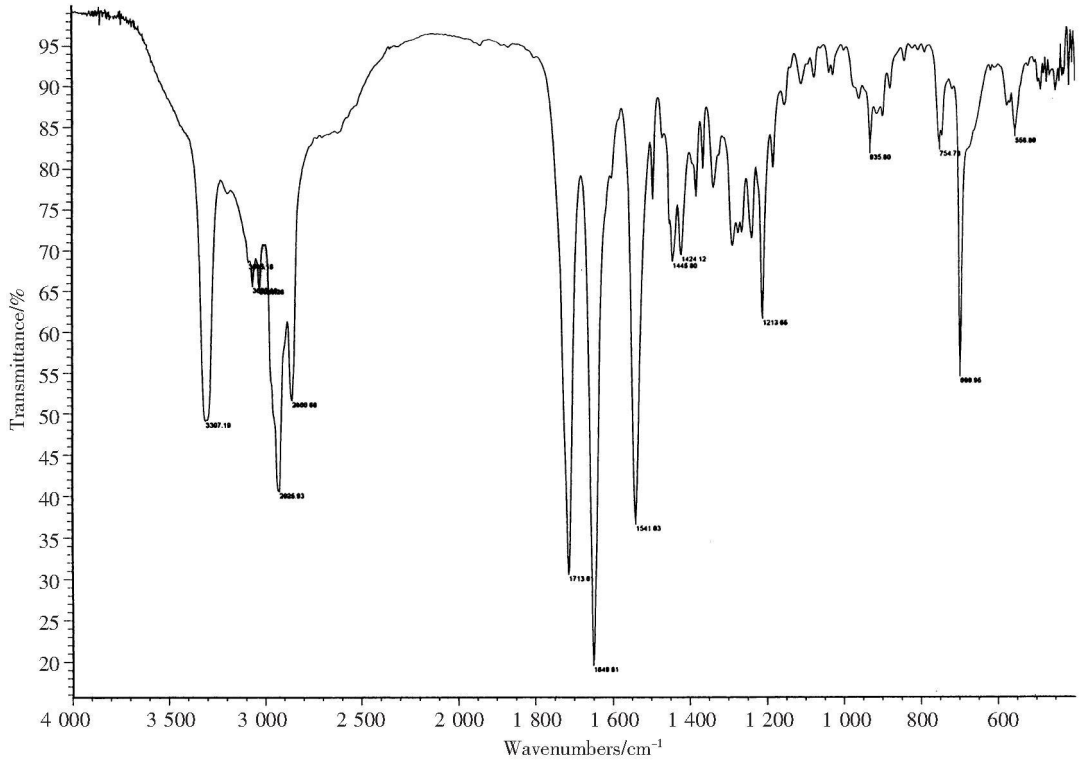

Fig.7 IR pattern of H-form nateglinide

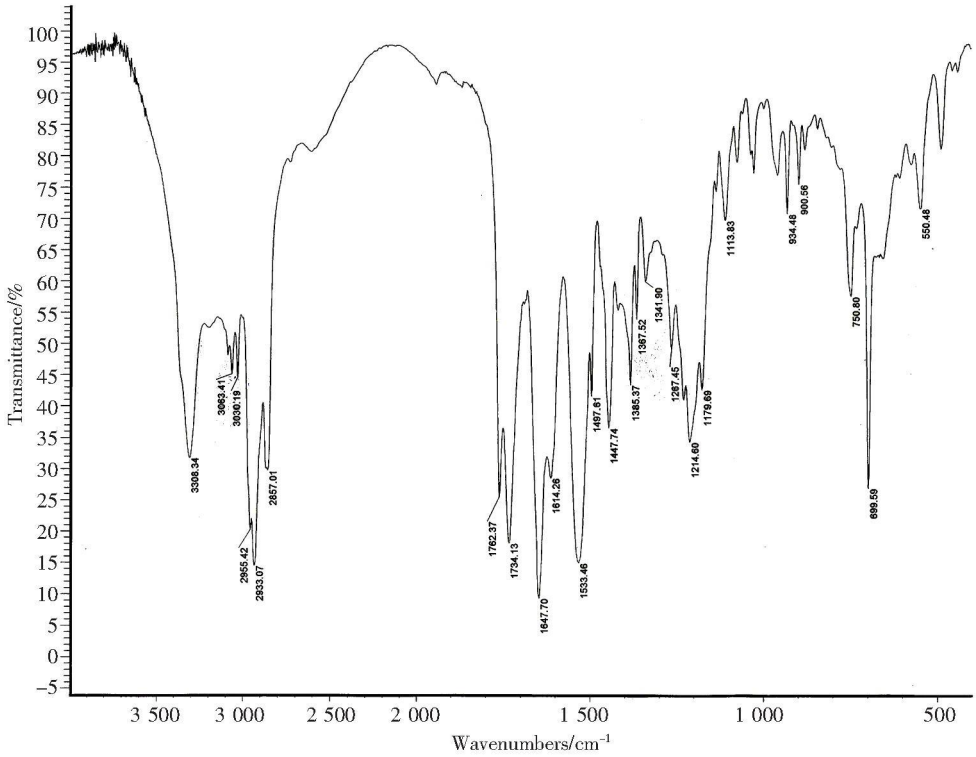

Fig.8　IR pattern of amorphous nateglinide

2.5　Solution test

The solution test profile of the H-form nateglinide samples and the amorphous nateglinide samples were shown in Fig 9. At 37℃, the amorphous nateglinide samples showed 89% drug were dissolved in 15 min, while 71% of the H-form at that time. And at 1 hour, 96% of the amorphous nateglinide samples had been dissolved, but only 81% of H-form. The amorphous nateglinide samples showed improvement in solution rate compared with that of the H-form, because of the amorphization decreased particle size and increased surface area. Thus, preparation of amorphous nateglinide is an effective approach for enhancing the solubility of nateglinide.

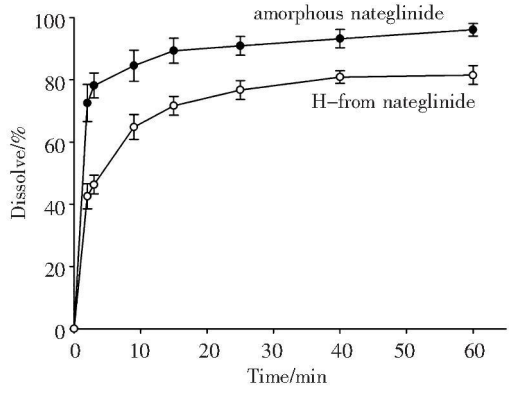

Fig.9　Solution test profile of H-form and amorphous nateglinide

3　Conclusion

The results obtained from the analysis revealed that application of removal process was a feasible method for preparing amorphous nateglinide without any reaction and interfused impurity. Solution test showed that the amorphous nateglinide samples dissolved significantly faster than that of the H-form. Reduced particle size of the amorphous nateglinide was induced to increase the surface area, which significantly enhanced the solution of the amorphous nateglinide. This demonstrates the potential enhancement of absorption and bioavailability of nateglinide. In conclusion, the solvent removal process offers a promising approach to obtain amorphous nateglinide, and improves the solution property of the poorly water-soluble nateglinide.

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