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Ibuprofen Cocrystal Preparation and Structure Study Using Fluorescence Spectrometry

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Abstract

Ibuprofen (IBU) was cocrystallized with nicotinamide (NIC), saccharin (SAC) and succinic acid (SUC) using solvent evaporation method and grinding method. Ibuprofen cocrystals were characterized by FTIR, XRD to analyze crystalline structure. Fluorescence spectrometer (FS) was also applied to verify the formation of ibuprofen cocrystals. The formation of IBU-NIC cocrystal, IBU-SAC cocrystal and IBU-SUC cocrystal were demonstrated by IR character peaks shift and new XRD character peaks. Solution method can produce IBU cocrystal with higher purity. The change of maximal fluorescence emission wavelength and strength can be used to verify the formation of cocrystal.

Keywords

Ibuprofen; Nicotinamide; Saccharin; Succinic Acid; Cocrystal.

1. Introduction

Ibuprofen (IBU) is a common anti-inflammatory, antipyretic and analgesic drug. The dissolution rate and the bioavailability of common ibuprofen tablets after oral administration are low. With the development of crystal engineering, it has been found that pharmaceutical cocrystal has the ability to improve the physical and chemical properties of ibuprofen [1-2]. Pharmaceutical cocrystal is a crystalline material with two components present in definite stoichimetric amounts. The two components are an active pharmaceutical ingredient (API), and cocrystal coformer (CCF) [3-4]. A pharmaceutical cocrystal can improve solubility behavior of an API [5-7]. During past years, the research of ibuprofen cocrystal focused on the preparation method and the selection of pharmaceutical cocrystal coformer, while the research of ibuprofen cocrystal structure was neglected. The modern analytical methods used for cocrystal characterization are usually FTIR, XRD, DSC and so on. In this study, IBU was selected as active pharmaceutical ingredient, nicotinamide (NIC), saccharin (SAC), and succinic acid (SUC) as cocrystal coformer, IBU cocrystal were prepared through solution method and grinding method[8-10]. The IBU cocrystals were characterized by FTIR and XRD. Besides, Fluorescence spectrometer (FS) analysis method was also applied, with the aim to explore a new convenient method to identify the formation of pharmaceutical cocrystal.

2. Materials and Methods

2.1. Materials

Ibuprofen (IBU, ≥98% purity), nicotinamide (NIC, ≥99% purity), saccharin (SAC, ≥98% purity) and succinic acid(SUC) were obtained from Aladdin Industrial Co. (Shanghai, China). Ethanol

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from Yongda Chemical Reagent Co., Ltd. (Tianjin, China) was of analytical grade and used as received.

2.2. Methods

(1)IBU cocrystal prepared by solution methods

2.06g IBU and 1.22g NIC (with 1:1 molar ratio), and 5mL of ethanol-water mixture with an ethanol-to-water ratio of 4:1 (v/v) were added in a crystallizer flask of 50 mL. After stirring for about 15min, the mixture of IBU and NIC dissolved completely; a transparent solution was obtained. After incubation for 7~10 days at RT, a solid sample precipitated at the bottom of the flask, which was collected by filtration and dried. The cocrystal sample was named as IBU-NIC solution. IBU-SAC solution and IBU-SUC solution were prepared using same method.

(2)IBU cocrystal prepared by grinding methods

2.06g IBU, 1.22g NIC (with 1:1 molar ratio), and two drops of ethanol were added in an agate mortar. The mixture was grinded for more than two hours to obtain the cocrystal samples, which was marked as IBU-NIC grinding. IBU-SAC grinding and IBU-SUC grinding were prepared using same method.

(3) IBU cocrystal characterized by FTIR

A NETZSCH QMS403C FTIR spectrometer was used for collecting the IR spectra of the samples. The settings used to record the data were as follows: resolution = 0.4 cm^{-1}, data range = 4000–6400 cm^{-1}, and the number of runs per spectrum = 16.

(4) IBU cocrystal characterized by XRD

The XRD patterns were recorded using OptiPlex 7050 Tower diffractometer. Data collection was performed at room temperature using monochromatic Cu/Kα radiation (λ= 1.54180 Å), 40 kV/100 mA, in the 2θ region between 3°and 40°, a step of 0.1°.

(5) IBU cocrystal characterized by FS

Fluorescence spectrums of samples were tested by PerkinElmer LS55 fluorescence spectrophotometer. The settings used to record the data were as follows: emission wavelength 300~650nm, excitation wavelength 280nm, and scanning voltage 650V.

3. Results and Discussions

3.1. IBU Cocrystal Characterized by FTIR

(1)FTIR spectra for IBU-NIC samples

The FTIR spectra for IBU, NIC, and the IBU-NIC grinding and IBU-NIC solution are shown in Figure 1.

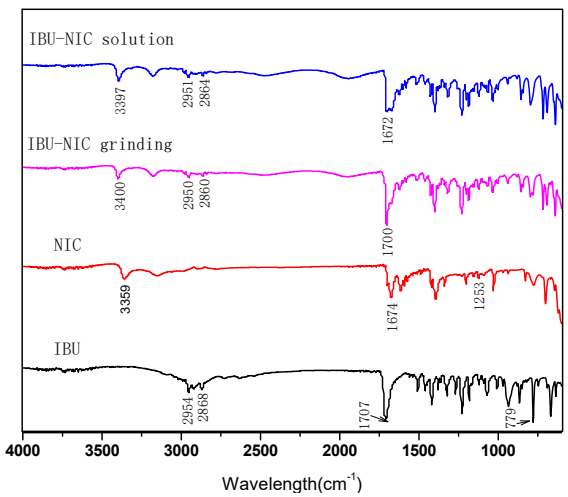

Figure 1. IR spectra for IBU, NIC, IBU-NIC grinding and IBU-NIC solution.

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The IR spectra of IBU-NIC grinding and IBU-NIC solution were different from those of IBU and NIC, suggesting the formation of IBU-NIC cocrystal. The stretching frequencies of the hydroxyl group O-H and the carbonyl group C =O of IBU were shifted to 2950~2951, 2860~2864, and 1700cm^{-1}, respectively. The characteristic peaks of NIC were shifted to 3397~3400 corresponding to the amino group (NH_2); the peaks for the carbonyl group (C =O) shifted to 1672 cm^{-1}.

(2)FTIR spectra for IBU-SAC samples

The FTIR spectra for IBU, SAC, and the IBU-SAC grinding and IBU-SAC solution are shown in Figure 2.

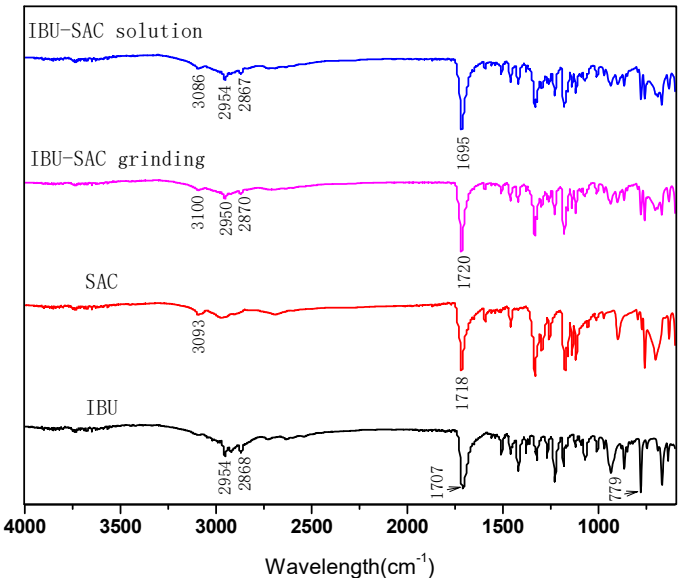

Figure 2. IR spectra for IBU, SAC, IBU-SAC grinding and IBU-SAC solution.

In the IR spectra of IBU-SAC grinding and IBU-NIC solution, the stretching frequencies of the hydroxyl group O-H and the carbonyl group C =O of IBU were shifted to 2950~2954, 2867~2870, and 1695~1720cm^{-1}, respectively. The characteristic peaks of SAC were shifted to 3086~3100 corresponding to the amino group (NH); the peaks for the carbonyl group (C =O) shifted from 1718 to 1695~1720cm^{-1}. IR results preliminary indentify the formation of IBU-SAC cocrystal.

(3)FTIR spectra for IBU-SUC samples

The FTIR spectra for IBU, SUC, and the IBU-SUC grinding and IBU-SUC solution are shown in Figure 3.

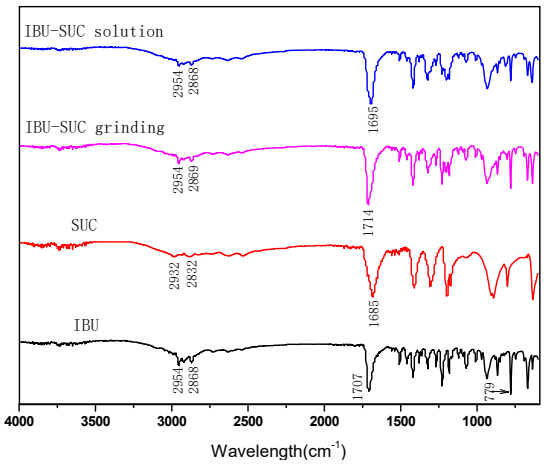

Figure 3. IR spectra for IBU, SUC, IBU-SUC grinding and IBU-SUC solution.

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Compared to the pure IBU and SUC, in the IR spectra of IBU-SUC grinding and IBU-SUC solution, the stretching frequencies of the hydroxyl group O-H was shifted from 2932 to 2954, the stretching frequencies of the carbonyl group C =O were shifted from 1685~1707 to 1695~1714cm^{-1}. IR results preliminary indentify the formation of IBU-SUC cocrystal.

3.2. IBU Cocrystal Characterized by XRD

(1) XRD spectra for IBU-NIC samples

The XRD spectra for IBU, NIC, and the IBU-NIC grinding and IBU-NIC solution are shown in Figure 4.

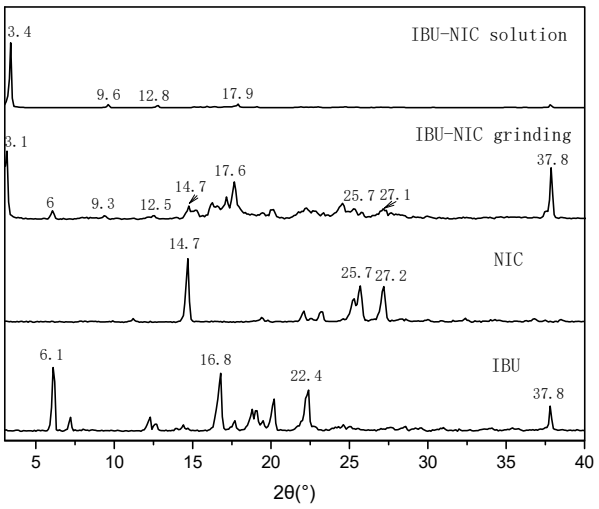

Figure 4. XRD spectra for IBU, NIC, IBU-NIC grinding and IBU-NIC solution.

Pure IBU showed characteristic peaks at 2θ 6.1°, 16.8°, and 22.4°. NIC showed characteristic peaks at 2θ 14.7°, 25.7° and 27.2°. Spectra of IBU-NIC grinding and IBU-NIC solution were different from those of IBU and NIC. IBU-NIC solution has new characteristic peaks at 3.4°, 9.6°, 12.8°and 17.9°. IBU-NIC grinding has new characteristic peaks at 3.1°, 9.3°, 12.5°and 17.6°. Additionally, the IBU-NIC grinding sample had some IBU and NIC characteristic peaks residue. The PXRD results indicated that both solution method and grinding method has successfully prepared IB-NIC cocrystal, and the IBU-NIC grinding sample was not pure IBU-NIC cocrystals.

(2) XRD spectra for IBU-SAC samples

The XRD spectra for IBU, SAC, and the IBU-SAC grinding and IBU-SAC solution are shown in Figure 5.

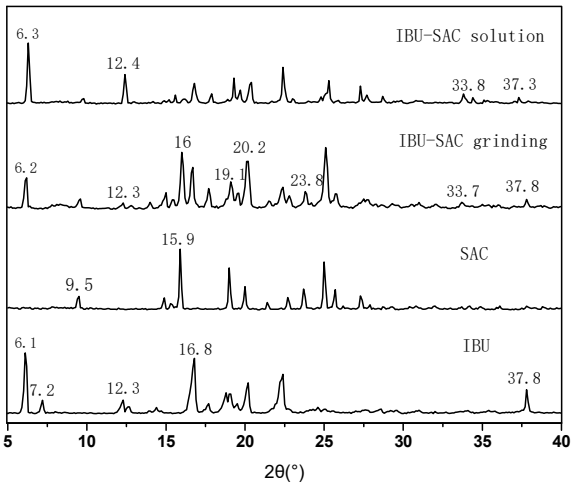

Figure 5. XRD spectra for IBU, SAC, IBU-SAC grinding and IBU-SAC solution.

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As shown in Figure 5, spectra of IBU-SAC grinding and IBU-SAC solution were different from those of IBU and SAC. IBU-SAC solution has new characteristic peaks at 6.8°, 12.4°, 33.8°and 37.3°. IBU-SAC grinding has new characteristic peaks at 6.2°, 12.3°, 33.7and 37.8°. Additionally, the IBU-SAC grinding sample also had some IBU and NIC characteristic peaks residue. The PXRD results indicated that both solution method and grinding method has successfully prepared IB-SAC cocrystal, and the purity of IBU-NIC solution sample was higher than that of IBU-SAC grinding.

(3) XRD spectra for IBU-SUC samples

The XRD spectra for IBU, SUC, and the IBU-SUC grinding and IBU-SUC solution are shown in Figure 6.

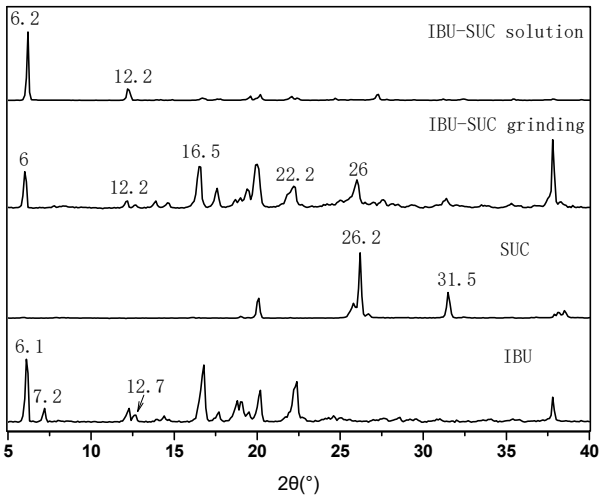

Figure 6. XRD spectra for IBU, SUC, IBU-SUC grinding and IBU-SUC solution.

Spectra of IBU-SUC grinding and IBU-SUC solution were different from those of IBU and SUC. IBU-SAC solution has new characteristic peaks at 6.2°, and 12.2°. IBU-SUC grinding has new characteristic peaks at 6°, and 12.2°. The IBU-SUC grinding sample also had some IBU and NIC characteristic peaks residue. The PXRD results indicated that both solution method and grinding method has successfully prepared IB-SUC cocrystal, and the purity of IBU-NUC solution sample was higher than that of IBU-SUC grinding.

3.3. IBU Cocrystal Structure Characterized by FS

(1) FS spectra for IBU-NIC samples

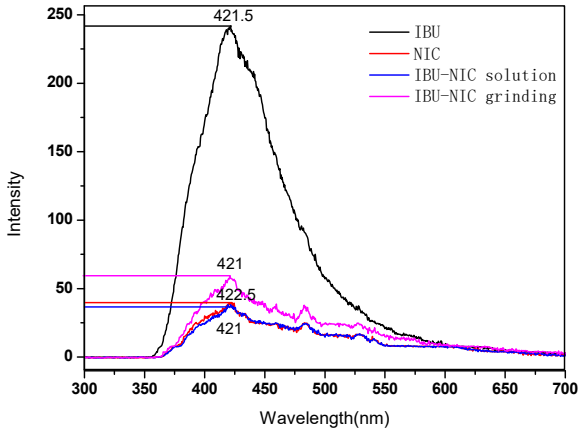

Figure 7. FS spectra for IBU, NIC, IBU-NIC grinding and IBU-NIC solution

In the fluorescence spectrum analysis, the maximum emission wavelength of IBU was 421.5nm and the fluorescence intensity was 242a.u. The maximum emission wavelength of NIC was

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422.5nm and the fluorescence intensity was 39.5a.u. The maximum emission wavelength of SAC was 423nm, and the fluorescence intensity was 76a. The maximum emission wavelength of SUC was 419.5nm.

The FS spectra for IBU, NIC, and the IBU-NIC grinding and IBU-NIC solution are shown in Figure 7.

The maximum emission wavelength of IBU-NIC solution sample fluorescence spectrum was 421nm, and the fluorescence intensity was 38a.u.The maximum excitation wavelength and fluorescence intensity of IBU-NIC grinding sample was 421nm and 59a.u. respectively.

(2) FS spectra for IBU-SAC samples

The FS spectra for IBU, SAC, and the IBU-SAC grinding and IBU-SAC solution are shown in Figure 8.

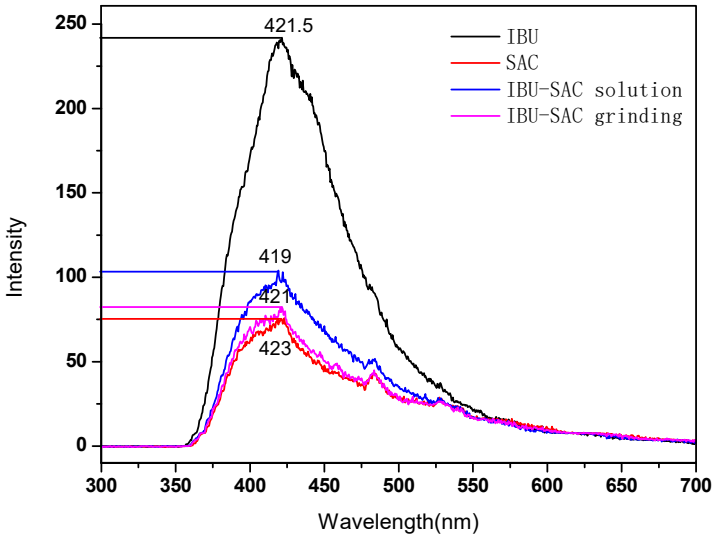

Figure 8. FS spectra for IBU, SAC, IBU-SAC grinding and IBU-SAC solution.

In the fluorescence spectrum of IBU-SAC solution sample, the maximum emission wavelength and fluorescence intensity of ibuprofen-saccharin eutectic prepared by solution method were 419nm and 1041.u. The maximum excitation wavelength and fluorescence intensity of IBU-SAC grinding sample were 421nm and 82a.u.

(3) FS spectra for IBU-SUC samples

The FS spectra for IBU, SUC, and the IBU-SUC grinding and IBU-SUC solution are shown in Figure 9.

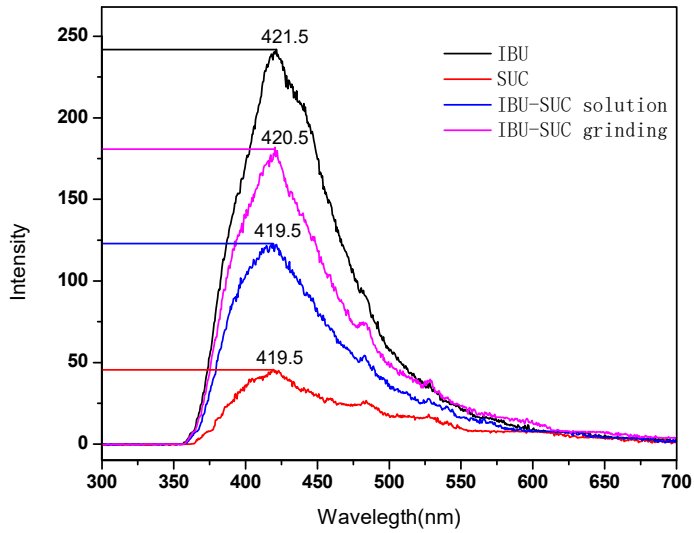

Figure 9. FS spectra for IBU, SUC, IBU-SUC grinding and IBU-SUC solution.

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In the fluorescence spectrum of IBU-SUC solution sample, the maximum emission wavelength was 419.5nm, and the fluorescence intensity was 123a.u. The maximum excitation wavelength and fluorescence intensity of IBU-SUC grinding method was 420.5nm and 181.7a.u. Because the lamellar structure in eutectic can affect the maximum excitation wavelength and fluorescence intensity.

4. Conclusion

In this study IBU-NIC cocrystal, IBU-SAC cocrystal and IBU-SUC cocrystal were prepared through solution method and grinding method. The formation of IBU cocrystal was demonstrated by its IR character peaks shift and new XRD character peaks. Solution method can produce IBU cocrystal with higher purity. The change of maximal fluorescence emission wavelength and strength can be used to verify the formation of cocrystal. The FTIR technique is a convenient method to preliminarily identify the formation of cocrystals, the fluorescence spectrometry can be a supplementary method to verify the cocrystal formation.

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