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Short communication

Thermal analysis of β-cyclodextrin/Berberine chloride inclusion compounds

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ABSTRACT

Solid inclusion compounds of Berberine chloride (Berb) and β-cyclodextrin (β-CD) were prepared by grinding method and co-evaporation method. The formation and thermal characterization of solid inclusion compounds were investigated by Fourier transform-infrared (FT-IR) and differential scanning calorimetry (DSC). The results showed that the inclusion compounds of Berb and β-CD could be prepared by the grinding method and co-evaporation method. DSC analysis afforded the quantitative evaluations of inclusion efficiency and showed that grinding method offered higher inclusion efficiency compared with co-evaporation method. Influence of grinding time on inclusion ratio of Berb with β-CD was further studied by DSC measurement. DSC analysis could be considered as a rapid qualitative and quantitative analytical method in the preparation of cyclodextrins inclusion compounds.

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1. Introduction

β-Cyclodextrin (β-CD) is a cyclic (α-1,4)-linked oligosaccharide, containing a relatively hydrophobic central cavity and a hydrophilic outer surface. The most notable feature of β-CD is its ability to form solid inclusion compounds (host–guest complexes) with a very wide range of solid, liquid and gaseous compounds by molecular complexation [1]. Several methods are often used to form cyclodextrin complexes, such as co-evaporation [2], grinding [3] and spray-drying [4]. As the results of complex formation the characteristic properties of the included compounds, such as solubility, chemical reactivity and thermal property, will be changed. Thus, β-CD is extensively studied by various experimental methods [5,6] and in the pharmaceutical industry β-CD has been used to enhance the solubility, stability and bioavailability of drugs [1,7,8]. It is well known that thermal methods (mainly differential scanning calorimetry, DSC; or thermogravimetic analysis, TGA) have been used as powerful tools in the characterization of both β-CD and its inclusion compounds. The purpose is to provide evidence for the differences between the physical mixtures and the putative inclusion compounds. However, little or no speculation is dedicated to quantitative considerations [9].

In this study, Berberine chloride (Berb, Fig. 1) was selected as the model drug in order to quantitatively investigate the thermal behaviors of inclusion compounds by DSC. The main reasons of Berb as the model drug were: (a) Berb was typical of crystalline drug and was appropriate for quantitative analysis by DSC; (b) Berb and its β-CD inclusion compounds had some application value. Berb is the main effective component in many Chinese drugs such as coptis and barberry. Berb has an effective function of antibiosis and antihypertension [10]. It also has high effect on resisting digestive system infections, but a big dosage is required and side effects (e.g., lead to intestinal pH value changes) are very strong because Berb is poorly absorbed by body [11]. It is very valuable to study the inclusion compounds of Berb with β-CD, for it may decrease the bitter taste, enhance the absorption of Berb and can provide better understanding of drug complex process.

The aim of this work is: (a) to study the formation and thermal characterization of the Berb/β-CD inclusion compounds employing FT-IR and DSC; (b) to characterize the influences of the different preparation methods and different preparation times on the inclusion efficiency of Berb/β-CD by DSC; (c) to afford, in detail, the quantitative evaluation methods of inclusion compounds using the DSC profiles.

2. Experimental

2.1. Materials

Berb (pharmaceutical grade, purity >97 wt%) was obtained from Chengdu Di'ao chemistry of plant Co., Ltd.; β-cyclodextrin was purchased from Sigma. All other materials were of analytical grade.

2.2. Method

2.2.1. Preparation of solid samples

2.2.1.1. Physical mixtures. Physical mixtures were prepared by homogeneous blending of previously sieved and weighed Berb and

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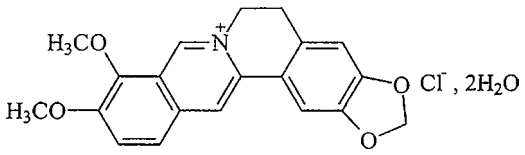

Fig. 1. Chemical structures of Berb.

β-CD in a mortar with a pestle for 15 min at room temperature.

2.2.1.2. Grinding method. β-CD (2.270 g) and distilled water (6 ml) were mixed together in a mortar so as to obtain a homogeneous paste. Berb (0.815 g) was added slowly to the above mixture. The mixture was then ground individually for 4, 8, 12 and 20 h at room temperature. During this process, an appropriate quantity of water was added to the mixture in order to maintain a suitable consistency. The paste was dried in oven at 40 °C for 24 h and then was ground into powder. With the same method, the powder of 2:1 and 3:1 (the molar ratio of β-CD to Berb) was obtained.

2.2.1.3. Co-evaporation method. After dissolution of 0.01 mol β-CD in 150 ml water, equimolar Berb was added into the solution. This solution was kept stirring for 72 h at 60 °C and then was evaporated at 45 °C in a rotary evaporator. The solid residue was further dried completely at 40 °C for 24 h. The dried complex was ground into powder. With the same method, the powder of 2:1 and 3:1 was obtained.

Pure Berb, β-CD, the physical mixtures and the complexes were desiccated over phosphorous pentoxide for 2 days prior to assay.

2.2.2. Fourier transform-infrared spectroscopy

Infrared spectra of the inclusion compounds were obtained by PerkinElmer Model 1600 spectrophotometer (PerkinElmer, Inc., USA), according to potassium bromide disk method. The above samples (i.e. physical mixtures, complexes, pure Berb and β-CD) were investigated by IR analysis. The scans were executed at a resolution of 8 cm^{-1}, from 4000 to 400 cm^{-1}.

2.2.3. Differential scanning calorimetry

DSC was used as a quantitative measure of crystallinity of Berb and was developed to characterize the formation of true inclusion compounds. DSC measurements were performed by DSC 204 F_1 Phoenix® (Netzsch Instruments, Inc., Germany), and the data were analyzed by thermal analysis software Proteus®. All accurately weighed samples (about 1.5 mg of Berb or its equivalent) were separately placed in pierced aluminum pans with perforated lids, under nitrogen flow (sweep gas: 20 ml min^{-1}, protecting gas: 60 ml min^{-1}) at a scanning rate of 10 K min^{-1}, and the temperature range of 50–300 °C. An empty aluminum pan was used as the reference.

3. Results and discussion

3.1. IR characterization

The IR spectra are shown in Fig. 2. Since there are seven repeating units in the β-CD molecule, the spectra of both the inclusion complex and the physical mixture were largely dominated by the vibrational bands of the cyclodextrin molecule. There were some differences in the spectra of the complex and the corresponding physical mixture. Berb (Fig. 2b) had a C–O–C antisymmetric stretching vibration absorption band of 1232–1273 cm^{-1}. The vibration of cycloether group (–O–C–O–) appeared in the 1002–1042 cm^{-1} region. A sharp and intense band in 1496–1522 cm^{-1} could be assigned to the skeleton vibrations of the benzene groups. It was clear from Fig. 2 that pattern *d* was the superposition of the pattern *a* (Berb) and pattern *b* (β-CD), and the typical vibration absorption band of Berb could be clearly detected in the spectrum of physical mixture. However, in the corresponding complex (Fig. 2c), the absorption band of C–O–C group of Berb completely disappeared, the vibration absorption intensity of benzene group weakened, which indicated the involvement of interactions between the C–O–C group and β-CD cavity. This was in agreement with the results of Yu et al. [12], indicating the formation of a true inclusion complex. Infrared spectra of the samples of other molar ratio were similar. Differences could be found in the intensity of absorption peaks (figures were omitted).

3.2. Differential scanning calorimetry analysis

DSC has been shown to be a very powerful analytical tool in the characterization of solid-state interactions between drugs and cyclodextrins. When guest molecules were embedded into β-CD cavities, their melting, boiling or sublimating points generally shifted to different temperatures or disappeared [7,9]. Thermograms were analyzed qualitatively by examination of both the peak temperatures and the endothermic transition contours. The relative crystallinity of drug ($drug_{RDC}$) in physical mixture and complex was estimated by the ratio between the melting enthalpy of the drug calculated in the sample (ΔH_{sam}) and that of the pure drug (ΔH_d), according to Eq. (1):

$$drug_{RDC} = \frac{\Delta H_{sam}}{\Delta H_d} \quad (1)$$

where ΔH_{sam} is the melting enthalpy of drug calculated in the physical mixture or complex, and ΔH_d is the melting enthalpy of the pure drug sample [2,13,14]. The inclusion efficiency (IE) of Berb was also estimated directly by Eq. (2):

$$IE(\%) = \frac{\Delta H_d - \Delta H_{sam}}{\Delta H_d} \times 100\% = (1 - drug_{RDC}) \times 100\% \quad (2)$$

3.2.1. Comparative researches on the different preparation methods

Fig. 3 illustrates the DSC profiles of β-CD, Berb, the physical mixtures and corresponding complexes. Quantitative data for Berb crystallinity and inclusion efficiency were extracted from DSC curves in Fig. 3 and are summarized in Table 1. The Berb thermal curve (Fig. 3a) was typical of crystalline substance and was characterized by a sharp endothermic peak (temperature at 187.90 °C), assigned to its melting point. A wide and strong endothermic effect in the 95–130 °C range could be ascribed to dehydration of Berb. The curve of β-CD (Fig. 3b) displayed a wide and strong endothermic effect in the 100–130 °C range (peak T_{max} = 117.6 °C), which

Table 1
DSC data, $drug_{RDC}$ and IE for the inclusion compounds by different preparation methods.

Sample	Preparation methods	β-CD/Berb (mol:mol) ratio	Peak temperature (°C)	$Drug_{RDC}$	IE (%)
Berb (a)	–	0:1	187.90	1.00	–
β-CD (b)	–	1:0	0	0	–
Berb/β-CD					
(c)	PM	1:1	185.42	0.98	–
(d)	CE	1:1	183.24	0.71	28.6
(e)	GR	1:1	177.91	0.44	56
(f)	PM	2:1	183.11	0.97	–
(g)	CE	2:1	181.39	0.38	62
(h)	GR	2:1	175.16	0.34	66
(i)	PM	3:1	185.9	0.97	–
(j)	CE	3:1	183.31	0.36	64
(k)	GR	3:1	0	0	100

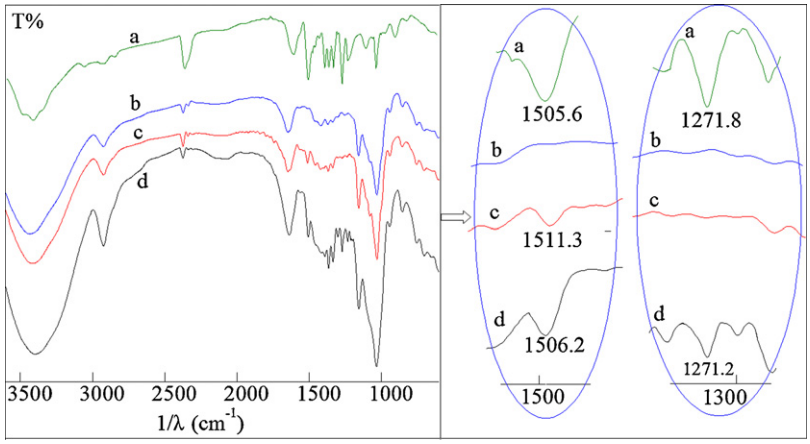

Fig. 2. FT-IR spectra: (a) β-CD; (b) Berb; (c) 3:1 β-CD/Berb inclusion complex (ground method); (d) 3:1 β-CD/Berb physical mixture.

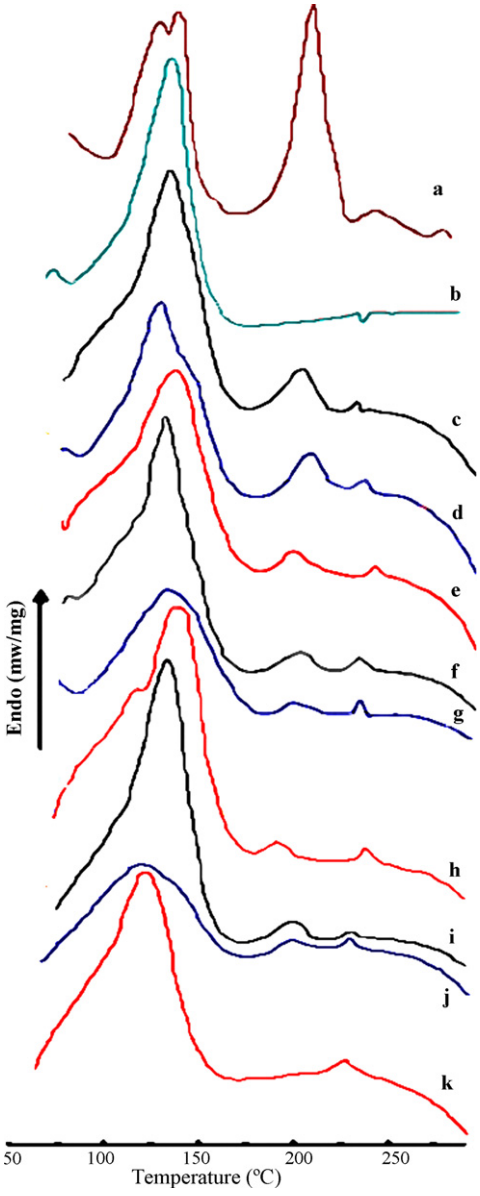

Fig. 3. DSC curves of single components, physical mixtures (PM), ground systems (GR, grinding time 4 h) and co-evaporation systems (CE) of Berb with β-CD at different feed molar ratios: (a) pure Berb; (b) β-CD; (c) 1:1 PM; (d) 1:1 CE; (e) 1:1 GR; (f) 2:1 PM; (g) 2:1 CE; (h) 2:1 GR; (i) 3:1 PM; (j) 3:1 CE; (k) 3:1 GR.

could be ascribed to dehydration. The thermograms of the physical mixtures (Fig. 3c, f, i) showed the broad endothermic effects due to the β-CD dehydration process. The Berb melting peaks slightly shifted to lower temperatures and the relative crystallinities of Berb slightly decreased in the physical mixtures, which could be explained by the weak molecular interactions between the Berb and β-CD at high temperature. But these were not evidences of the formation of true inclusion compounds. Similar behaviors were observed in the omeprazole-β-CD system by Figueiras et al. [15]. The thermal curves of the complexes (Fig. 3d, e, g, h, j and k) were similar to the corresponding physical mixtures, but endothermic areas and intensities were significantly smaller than those of corresponding physical mixtures. Furthermore, the characteristic endothermic effects of complexes slightly shifted to lower temperatures for the ground systems and co-evaporated systems. These observations indicated the partial formation of amorphous solids, i.e., the Berb molecules inside the β-CD cavities and formation of true inclusion compounds. In fact, even though not unambiguously attributable to inclusion complexation, these phenomena were indicative of stronger interactions between Berb and β-CD in the solid state. The curves of Berb, complexes and physical mixtures (Fig. 3) with short endothermic peaks at about 225 °C, could be ascribed to melting point of the impurities of Berb. The endothermic areas and intensities of the impurities in the complexes and the corresponding physical mixtures were almost same, indicating that there were no unambiguous interactions between the impurities and β-CD in the complexes as well as in the physical mixtures.

Based on thermodynamics, the process of the inclusion of Berb with β-CD was spontaneous (change in Gibbs free energy, $\Delta G = -13.45$ kJ mol^{-1} at 278 K and -10.8 kJ mol^{-1} at 313 K) and the formation of a 1:1 complex, as described earlier [12]. However, if molar ratio of Berb to β-CD was 1:1 in the preparation, the Berb could not be complexed completely because the inclusion reaction was reversible (Eq. (3)):

$$\text{Berb(L)} + CD \cdot m\text{H}_2\text{O(L)} \overset{K_{1:1}}{\rightleftharpoons} \text{Berb} \cdot \text{CD} \cdot (m-n)\text{H}_2\text{O(L)} + n\text{H}_2\text{O(L)} \quad (3)$$

where m is stoichiometric coefficient of water in the cavity of β-CD, n the stoichiometric coefficient of water released from the cavity of β-CD. L indicates liquid states. It was also clear from above research that grinding method had higher inclusion efficiency than co-evaporation method. The result could be explained mainly from two aspects. On the one hand, based on thermodynamics, low inclusion temperature was beneficial to the formation of inclusion compounds. Grinding method had lower preparation temperature than co-evaporation method, which indicated

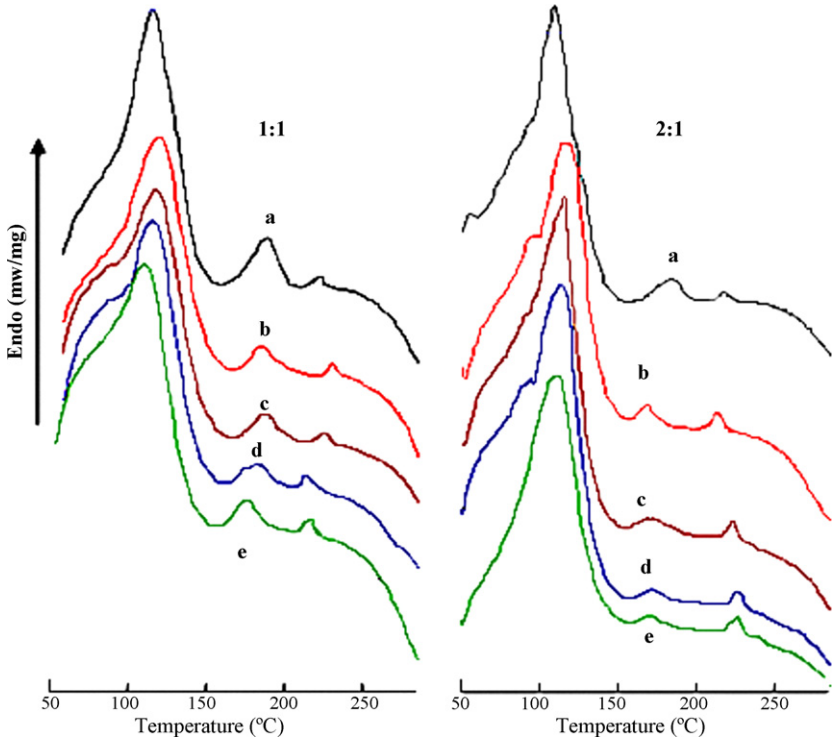

Fig. 4. DSC curves of ground systems (feed molar ratios: 1:1and 2:1) of Berb with β-CD at different grinding time: (a) 0 h; (b) 4 h; (c) 8 h; (d) 12 h; (e) 20 h.

that grinding method had higher inclusion efficiency than co-evaporation method. On the other hand, it could be seen from Eq. (3), when the inclusion compounds were prepared in aqueous solution, low reactant concentrations did not favor the formation of inclusion compounds. However, when grinding method was applied to preparation of inclusion compounds, only a little of water was required, high reactant concentrations were more beneficial to the rightward reaction and could form more inclusion compounds.

The inclusion compounds prepared by grinding method offer a higher inclusion efficiency, which could be of particular interest to industrial scale preparations because of the low cost and the simple process, which involved less energy, time and equipment.

3.2.2. *Influence of grinding time*

Fig. 4 shows the influence of grinding time on Berb inclusion ratio. The inclusion ratio increased with increasing grinding time and the increase extent was more obvious at higher feed ratio. Quantitative data for Berb crystallinity were extracted from DSC curves in Fig. 4 and are resumed in Table 2. It is clear from Table 2 that 3:1 reaction system took only 4 h to obtain 100% inclusion ratio, but 1:1 reaction system took 20 h to obtain only 60% inclusion ratio. The results indicated that both the feed ratio of drug/CD and the grinding time should be considered when β-CD/Berb inclusion compounds were prepared.

Table 2
Effect of grinding time on the DSC fusion endotherm (β-CD/Berb, ground systems).

β-CD/Berb (mol:mol) ratio	Grinding time (h)	Peak temperature (°C)	$Drug_{RDC}$	Inclusion ratio (%)
1:1	0	185.42	0.98	–
	4	177.91	0.44	56
	8	177.93	0.43	57
	12	177.58	0.41	59
	20	177.62	0.40	60
2:1	0	183.11	0.97	–
	4	175.16	0.34	66
	8	173.23	0.25	75
	12	171.80	0.21	79
	20	171.93	0.16	84
3:1	0	185.90	0.97	–
	4	0	0	100

4. Conclusions

The results obtained by FT-IR and DSC analysis clearly indicated that both the grinding method and co-evaporation method could form solid inclusion compounds of Berb and β-CD. DSC analysis afforded the quantitative evaluations of inclusion efficiency and showed that grinding method offered higher inclusion efficiency compared with co-evaporation method. The solid β-CD/Berb compounds prepared by grinding method involved relatively simple preparation steps and could be utilized to formulate pharmaceutical dosage forms. DSC analysis could be considered as a rapid qualitative and quantitative analytical method in the preparation of cyclodextrins inclusion compounds. It could also be our future interested studies on extensive applications of DSC in the pharmaceutical preparations.

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