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ORIGINAL ARTICLE

Preparation of borneol–methyl-β-cyclodextrin inclusion complex by supercritical carbon dioxide processing

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Abstract In this work, the complex of borneol–methyl-β-cyclodextrin was prepared both by supercritical carbon dioxide processing and by the sealed heating treatment at mild pressure and temperature. An amorphous complex was obtained by the sealed heating treatment. A crystalline inclusion complex was obtained by the supercritical carbon dioxide processing. The crystalline complex is more stable than the amorphous complex. The apparent aqueous solubility of borneol could be enhanced about 70 times by complexation with methyl-β-cyclodextrin.

Keywords Supercritical carbon dioxide · Borneol · Methyl-β-cyclodextrin · Complex · Crystalline inclusion complex · Solubility

Introduction

Borneol, a component of traditional Chinese medicine, is an efficacious officinal compound [1]; its melting point is 205–210 °C; its boiling point is 212 °C; it is easy to sublimate into gaseous phase and its solubility in water is limited [2, 3]. Thus it is easy to be lost during the preparation and storage of the medicine. A promising way to improve its properties is to complex it with hydrophilic cyclodextrins. Cyclodextrins (CDs), from the enzymatic degradation of starch, have cone like structures with a hydrophobic internal cavity and a hydrophilic outside. They have been widely used to include many hydrophobic drugs in pharmacy, thus enhance the water solubility/dissolution rate/stability/bioavailability and reduce the side effect/toxicity of these hydrophobic drugs [4]. Several methods were already used to prepare the inclusion complex between cyclodextrin and borneol, such as kneading, grinding, freeze-drying and co-precipitation from saturated aqueous solution [5–7]. In these approaches organic solvents were needed, they might remain in the products and be difficult to be removed. In recent years a "green chemistry" method based on supercritical carbon dioxide ($scCO_2$) was introduced due to its favorable characteristics; such as its relatively low cost, lack of toxicity and easily obtainable supercritical conditions [8–25]. In most of these works, medicine β-cyclodextrin complexes were prepared [8, 10–12, 14–23, 25]. Ryu et al. [24] prepared itraconazole 2-hydroxypropyl-β-cyclodextrin (HPBCD) complex using a supercritical aerosol solvent extraction system. Bandia et al. [13] prepared the complexes of budesonide or indomethacin with HPBCD in supercritical carbon dioxide in a static way. Foster and co-workers [9] obtained ibuprofen methyl-β-cyclodextrin (MBCD) complex by passing ibuprofen/CO_2 solution through a MBCD bed. They found that the glass transition temperature of MBCD was depressed from 180 to 45 °C when MBCD was exposed to compressed carbon dioxide at 94 bar. Due to the high solubility of HPBCD and MBCD in water, multi-step processing was needed to get their solid complexes by the conventional method. From the $scCO_2$ processing, the solid complex could be directly obtained from one step processing.

In this work, borneol with a rigid 3D molecular structure was used as the guest. The complex between borneol and MBCD (Tg = 182 °C) was prepared in $scCO_2$ at mild pressure and temperature quite lower than the melting point of borneol. The product was compared with that obtained by the sealed heating treatment. For better understanding

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the formation of borneol complexes, the complex between borneol and HPBCD (Tg = 278 °C) in $scCO_2$ was also studied.

Materials and methods

Materials

Borneol with purity of 98% was purchased from Sigma-Aldrich Co. MBCD with 1.7–1.9 mol CH_3 per unit anhydroglucose was obtained from the Sigma-Aldrich Co. HPBCD with purity of 97% was provided by Acros Organics. Carbon dioxide with purity of 99.95% was supplied by Beijing Analytical Instrument Factory. Cyclohexane with purity above 99.5% was produced by Beijing Chemical Company.

Physical state and solubility of borneol and CDs in $scCO_2$

To estimate the solubility in CO_2, 15 mg borneol powder was put in a glass tube ($\phi = 6.0$ mm, $l = 10$ mm, with one end sealed). The tube containing borneol was accurately weighted (±0.1 mg) and put vertically in the stainless-steel vessel used for the complex reaction. The vessel was sealed and heated to desired temperature; then carbon dioxide was pumped in to the desired pressure. The content was left in static condition for 20 h, and then the vessel was slowly depressed to atmospheric pressure in 4 h. The tube was weighted again after equilibrated in air for 10 min. The solubility of borneol in $scCO_2$ was estimated from the weight loss of the tube and the volume of the vessel.

To estimate the solubility of cyclodextrin (CDs) in CO_2, 3 mg CD was put in a glass tube. And the procedure was the same as above. For observing the physical format of CD, 100 mg CD powder was put in the same stainless-steel vessel, and treated with $scCO_2$ in the same way as that for the complexation reaction. Then the vessel was depressed to 0.1 MPa in 2 min. The physical format of CD in the vessel was observed. If the product was transparent or semi-transparent granules or blocks, the CD was considered to be melted in $scCO_2$ media at the corresponding experimental condition.

The observation was done for the two CDs at 90 and 110 °C up to 15.0 MPa with a pressure interval of 1.0 MPa.

The preparation of the physical mixture

The borneol and MBCD or HPBCD were weighted and homogeneously blended with a molar ratio of 1.00:1.00, ground in a mortar with a pestle.

The preparation of the complexes by $scCO_2$ processing

A total of 100 mg physical mixture was put into a 10.0 mL high pressure stainless-steel vessel; the vessel was sealed and heated to the desired temperature. Then carbon dioxide was pumped into the vessel to the desired pressure. The content was left in static condition for 20 h. At the end, the vessel was depressed to atmospheric pressure in 2 min and the solid products in the vessel were collected.

In the sealed heating treatment, the complex was prepared in similar way in 0.1 MPa air.

The analysis for the content of borneol in the product

At first, the solubility of MBCD, HPBCD, borneol in water or cyclohexane was measured. The total and the uncomplexed content (free) of borneol in the products were analyzed by a gas chromatographic (GC) method. The instrument was Agilent Technologies 6820 (Agilent Technologies Co. Ltd. USA), the capillary column was SUPEL COWAX^{TM} 10, the temperature of the column-oven was 180 °C, the temperature of the injector was 210 °C and the temperature of FID detector was 215 °C. The amount was 0.30 μL for each injection with a 0.50 μL micro-injector. The area of borneol peak was calibrated with borneol/cyclohexane solutions of known concentration.

To determine the total content of borneol in the product, about 10 mg product was accurately weighted (±0.1 mg) and dissolved in 4.00 mL deionized water in a 10 mL glass centrifugal tube. The tube was sealed with glass stopple, heated to 40 °C, and then 1.00 mL cyclohexane was added in. The content was ultrasounded for 5 min and centrifuged for 10 min at 3,200 rpm. The organic layer was taken out for analysis. From the area of borneol peak in the GC analysis and the calibration curve, the concentration of borneol in the cyclohexane layer was derived. The total amount of borneol in the sample was the product of the borneol concentration in the cyclohexane layer and the volume of cyclohexane added. The amount of CD was the mass of the product added in the deionized water minus the total mass of borneol in the sample. Then the molar ratio of total borneol to total CD (total ratio) in this product could be calculated.

To measure the content of the free borneol in the product, the product was crushed. About 20 mg product was accurately weighted (±0.1 mg), dispersed in 1.00 mL cyclohexane and stirred thoroughly for 10 min. Then the content was also centrifuged and the clear supernatant solution was taken out for analysis. Thus the amount of free borneol in the sample was measured; then the molar ratio of free borneol to total CD (free ratio) in this product was calculated.

The molar ratio of complex borneol to total CD was obtained from the difference between the total ratio and the free ratio of borneol in this product.

The powder X-ray diffraction analysis

The XRD pattern of borneol, MBCD, the physical mixture and the products were collected using a RIGAKU D/MAX 2500 X-ray diffractometer (Rigaku International Corp. Japan), the 2θ scan range was 3–60°, the scan rate was 8°/min, with Cu kα radiation (40 kv, 200 mA).

The differential scanning calorimetric analysis

The thermal analysis of various samples was performed using a PERKIN ELMER diamond DSC (Perkin Elmer, USA) from 25 to 250 °C at 10 °C/min, with a nitrogen flow rate of 20 mL/min.

The thermogravimetric analysis

The thermal stability of the crushed products was analyzed with a PERKIN-ELMER-S II Diamond TG-DTA (Perkin Elmer, USA) from 25 to 250 °C at 5 °C/min with a nitrogen flow rate of 20 mL/min.

The aqueous solubility measurement

Solubility of borneol and some complexes in water were determined by the above gas chromatographic method in duplicates.

Borneol in an excess amount was put in water, ultrasounded for 5 min and stirred thoroughly for 1 day at 20 ± 1 °C, the mixture was centrifuged at 5,000 rpm for 10 min and the clear supernatant solution was used for analysis.

A total of 50 mg borneol–MBCD complex with molar ratio about 1.0:1.0 was put in 1.00 mL water, the dissolution of the complex was observed. Under stirring, some borneol–MBCD complexes were gradually put in water until obvious indissoluble solid was observed in solution. The content was also centrifuged and the clear supernatant solution was accurately diluted for analysis.

Results and discussion

Physical state and solubility of borneol or CDs in $scCO_2$

Solubility data of borneol in $scCO_2$ is presented in Fig. 1; the uncertainty was ±10% of the determined value. In 90–110 °C 0.1 MPa air, the borneol sublimated in the reaction vessel was already 7–13% of the total borneol used for the complex reaction. At 110 °C, when carbon dioxide was added in to 10.0 MPa, borneol used for the complexation should all be dissolved in $scCO_2$ if there was no CD in the vessel. The weight loss of tube containing CDs was less than 0.1 mg after $scCO_2$ processing, thus the solubility of CD in $scCO_2$ was lower than 2×10^{-5} mol/L, and the CD dissolved in $scCO_2$ was less than 0.2% of the total CD used for the complexation reaction.

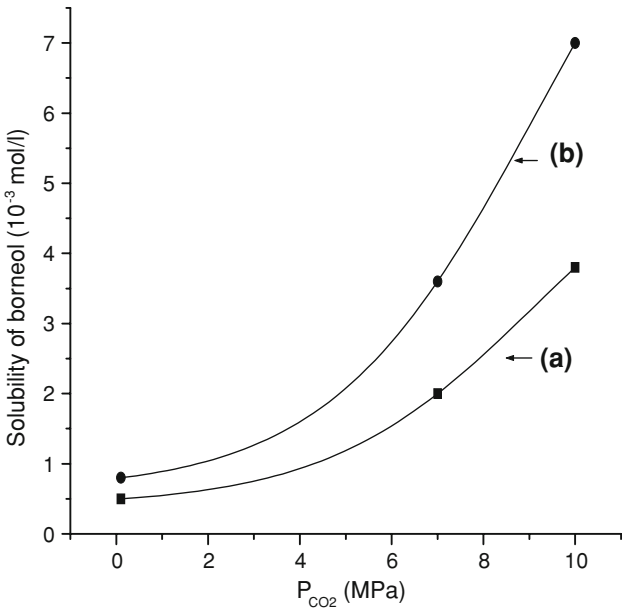

Fig. 1 Solubility of borneol in $scCO_2$: (a) 90 °C, (b) 110 °C

After $scCO_2$ was slowly depressed to atmospheric pressure, some thin sheets of crystal borneol were found attached vertically on the inner wall of the reaction vessel and the borneol left in the glass tube was still in powder state. In 4.0 and 5.0 MPa $scCO_2$, the liquefying temperature of MBCD was reduced to 110 and 90 °C respectively. In 0.1 MPa air, melting of MBCD was not found up to 150 °C. And HPBCD could not be liquefied in all our experimental condition. Thus MBCD is in liquid state and HPBCD is in solid state under our experimental conditions for the complexation reaction in $scCO_2$.

Contents of borneol in the products

MBCD is easy to be dissolved in water (>0.22 mol/L) and hard to be dissolved in cyclohexane ($<1 \times 10^{-6}$ mol/L). HPBCD is easy to be dissolved in water (>0.15 mol/L) and also insoluble in cyclohexane ($<1 \times 10^{-6}$ mol/L). The solubility of borneol in cyclohexane is (1.1 ± 0.1) mol/L.

The contents of borneol in products and the physical format of products are showed in Tables 1 and 2. There was a distinctive difference between borneol–MBCD products and borneol–HPBCD products.

Table 1 Molar ratio of borneol in borneol–MBCD products

T (°C)	*P* (MPa)	Total ratio	Free ratio	Complex ratio	Phy. format
Mix	0.1	1.00:1.00	0.98:1.00	0.02:1.00	Powder
90	0.1	0.94:1.00	0.11:1.00	0.83:1.00	Aggregate powder
90	7.0	0.88:1.00	<0.01:1.00	0.88:1.00	Aggregate powder
100	0.1	1.00:1.00	0.08:1.00	0.92:1.00	Aggregated powder
100	7.0	0.94:1.00	<0.01:1.00	0.94:1.00	Aggregated powder
100	10.0	1.02:1.00	<0.01:1.00	1.02:1.00	Block
100	15.0	0.88:1.00	<0.01:1.00	0.88:1.00	Granule
100	20.0	0.68:1.00	<0.01:1.00	0.68:1.00	Granule
110	0.1	1.05:1.00	0.04:1.00	1.01:1.00	Aggregate powder
110	7.0	1.06:1.00	0.01:1.00	1.05:1.00	Block
110	10.0	1.05:1.00	<0.01:1.00	1.05:1.00	Block
140	0.1	0.94:1.00	<0.01:1.00	0.94:1.00	Wax block

The uncertainty was ±5% of the determined values except for the lower free content ±0.004:1.00

Table 2 Molar ratio of borneol in borneol–HPBCD products

T (°C)	*P* (MPa)	Total ratio	Free ratio	Complex ratio	Phy. format
100	0.1	0.90:1.00	0.90:1.00	0.00:1.00	Powder
100	7.0	0.77:1.00	0.77:1.00	0.00:1.00	Powder
100	10.0	0.15:1.00	0.12:1.00	0.03:1.00	Powder
100	15.0	0.15:1.00	0.12:1.00	0.03:1.00	Powder

The uncertainty was ±5% of the determined values

For borneol–MBCD, most borneol used for the reaction was left in the solid product and the complex yield was shown by the complex ratio of borneol in the products. With the sealed heating method, the complex yield and the aggregation of the products were enhanced with the temperature rise. When carbon dioxide was introduced, the content of free borneol was obviously reduced; the complex yield first increased with the pressure of carbon dioxide and then decreased at higher pressure; the products aggregated at comparative low temperature/pressure and formed transparent hard blocks/granules at higher temperature or carbon dioxide pressure. Thus in air, the gaseous borneol was interacted with the solid matrix of MBCD; in $scCO_2$ at appropriate pressure, the gaseous borneol was complexed with the melted MBCD.

For borneol–HPBCD (showed in Table 2), part of the borneol used was sublimated into gaseous state, especially at pressure above 10.0 MPa (seen from the total ratio); there was almost no complex formation between the host and the guest. No difference in physical format was found between the products and the physical mixture.

Powder X-ray diffraction patterns

The diffraction patterns of borneol in Fig. 2 indicated the influence of carbon dioxide on the borneol structure. The

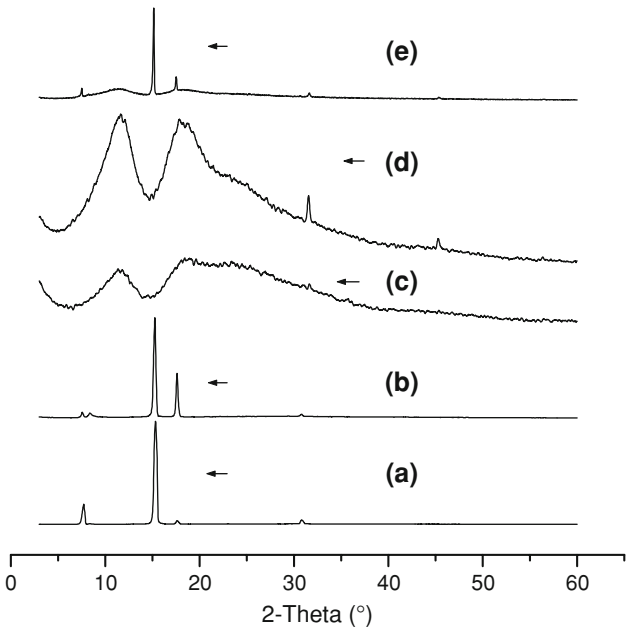

Fig. 2 X-ray diffraction pattern of: (a) borneol untreated, (b) borneol treated with carbon dioxide at 100 °C 15.0 MPa, (c) MBCD untreated, (d) MBCD treated with carbon dioxide at 90 °C 15.0 MPa, (e) physical mixture of borneol and MBCD

borneol treated with $scCO_2$ showed a distinctive XRD pattern (7.6°, 8.4°, 15.3°, 17.6°, 30.8°) different from that of the untreated borneol (7.7°, 15.3°, 30.8°). The diffraction pattern of amorphous MBCD was also changed by $scCO_2$ processing. The comparative intensity at 11° and 18° was obviously increased after MBCD was liquefied. The diffraction pattern of the physical mixture was a simply superposition of those for the untreated borneol and MBCD; thus there was no interaction between borneol and MBCD in the physical mixture, which was in accord with the quantitative analysis result.

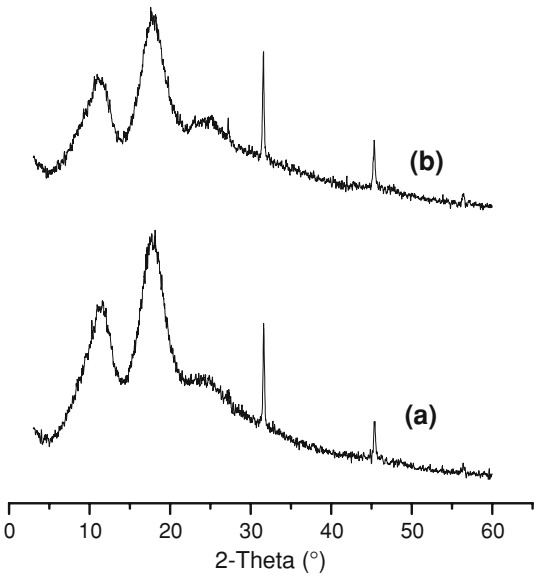

Fig. 3 X-ray diffraction pattern of borneol–MBCD products produced by the sealed heating method: (a) 100 °C, (b) 140 °C

The diffraction patterns of borneol–MBCD products obtained by the sealed heating method was shown in Fig. 3, the characteristic peaks of borneol were no longer existed. The absence of the crystalline peaks of both untreated and treated borneol was attributed to the amorphous or complex of borneol dispersed in MBCD matrix. The diffraction patterns of products processed by $scCO_2$ were illustrated in Figs. 4 and 5, indicating the formation of a new solid phase for borneol–MBCD complex. In these patterns, the characteristic peaks of the crystalline borneol

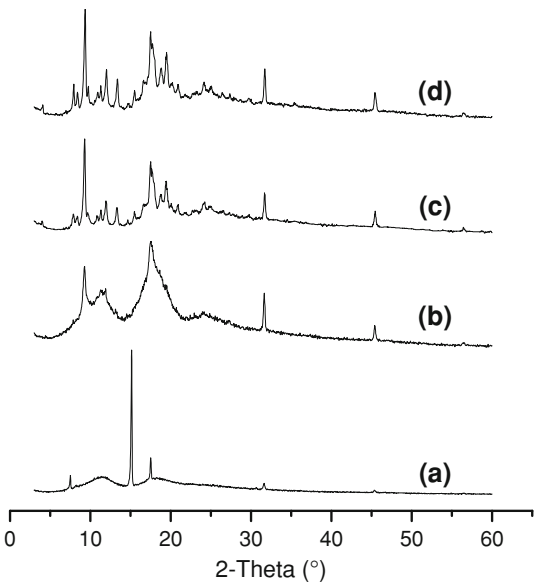

Fig. 4 X-ray diffraction pattern of borneol–MBCD products obtained by $scCO_2$ processing: (a) physical mixture, (b) 100 °C 7.0 MPa, (c) 100 °C 10.0 MPa, (d) 100 °C 15.0 MPa

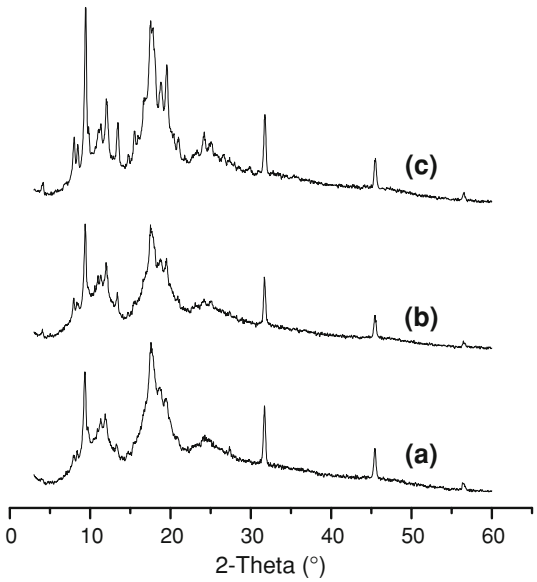

Fig. 5 X-ray diffraction pattern of borneol–MBCD processed in $scCO_2$ media: (a) 90 °C 10.0 MPa, (b) 90 °C 15.0 MPa, (c) 110 °C 10.0 MPa

were eliminated, the broad peaks of MBCD were remarkably reduced and new sharp peaks appeared at 7.9°, 9.3°, 12.0°, 13.4°, 17.5°, 17.7°, 18.8°, 19.5°. At 100 °C, the crystallization extent of the products increased with carbon dioxide pressure from 6.0 to 15.0 MPa, indicating the formation of a crystalline complex between borneol and MBCD in $scCO_2$ media at suitable pressure.

From the diffraction patterns in Fig. 5, no obvious crystallization was existed in the products treated in $scCO_2$ at 90 °C and the crystallization of the product was clear seen when temperature was raised to 110 °C in the processing.

Differential scanning calorimetric results

DSC curves for pure borneol, MBCD, the physical mixture and the product were displayed in Fig. 6.

Our DSC thermograms for borneol–MBCD were similar to those for borneol β-cyclodextrin inclusion complex prepared by Yuan et al. using co-precipitation method [6]. Pure borneol showed two endothermic peaks at 71 and 160 °C; pure MBCD exhibited a broad endothermic peak from 30 to 110 °C resulting from its dehydration and a small change around 180 °C due to its glass transition. The DSC thermogram of the physical mixture of borneol and MBCD was the sum of that for the two individual components, confirming no interaction in the physical mixture. For the products obtained by the sealed heating method, the characteristic peak of crystalline borneol at 71 °C was no longer observable and peak of borneol at 144 °C was broaden, approving the dispersion of borneol in the MBCD media. For the product processed by $scCO_2$, the two

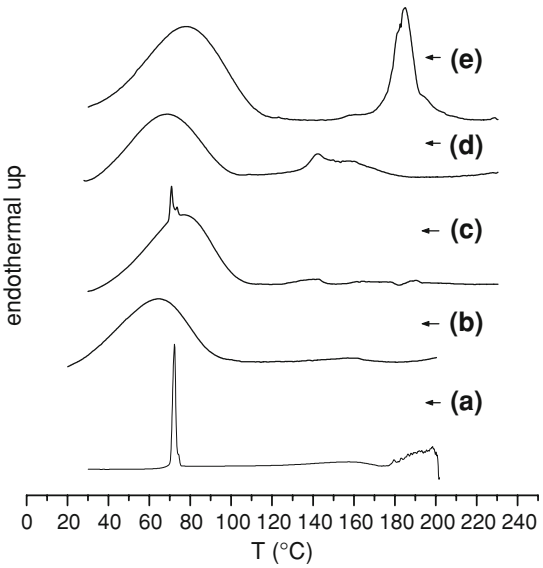

Fig. 6 DSC diagram of borneol–MBCD: (a) borneol, (b) MBCD, (c) physical mixture, (d) 100 °C 0.1 MPa, (e) 100 °C 10.0 MPa

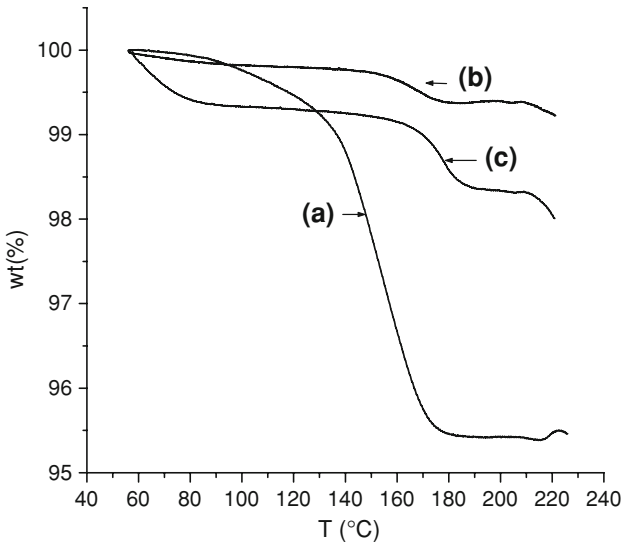

Fig. 7 TG diagram of borneol–MBCD products: (a) 100 °C 0.1 MPa, (b) 140 °C 0.1 MPa, (c) 100 °C 10.0 MPa

characteristic peaks of borneol vanished and a new sharp endothermic peak appeared at 185 °C, which was a little bit higher than the glass transition temperature of MBCD and lower than the melting point of borneol. The difference in DSC curve confirmed again the formation of crystalline complex between borneol and MBCD in supercritical carbon dioxide processing. These results were coincident with those of the powder X-ray diffraction analysis.

TG analysis results

Thermal stabilities of some products produced by the sealed heating treatment or supercritical carbon dioxide processing are illustrated in Fig. 7.

The product of borneol–MBCD prepared at 100 °C 0.1 MPa began to loss weight at 80 °C and a rapid drop in weight of about 4% was found between 125 and 185 °C. The product treated at 140 °C 0.1 MPa showed a small drop about 0.4 wt% between 150 and 185 °C. The product processed by $scCO_2$ at 100 °C 10.0 MPa displayed a small loss of weight at low temperature and exhibited a drop of about 0.8% between 160 and 190 °C. The complex produced from $scCO_2$ processing was much more stable than the complex obtained from the sealed heating treatment at the same temperature.

The thermal stability of borneol and β-cyclodextrin was studied by Song et al. [5]. A rapid drop in weight above 138 °C was found for pure borneol and the dehydration of β-cyclodextrin was completed at a temperature lower then 125 °C. Thus the loss in weight above 125 °C could be associated with the loss of borneol in the products. In our study, the maximum total content of borneol in products of borneol–MBCD was 10%. About half of the borneol in product produced by the sealed heating treatment at 100 °C was lost in the TG analysis, suggesting that this part of the borneol molecules may be located between MBCD molecules. No more than 10% loss of borneol in the product obtained by $scCO_2$ processing was observed around the melting point of the complex, indicating the formation of the inclusion complex between borneol and MBCD in $scCO_2$ media.

Apparent solubility of borneol in water

The untreated borneol was difficulty to be dissolved in water, the aqueous solubility of pure borneol is about $(4.0 \pm 0.4) \times 10^{-3}$ mol/L. The dissolution of borneol in the physical mixture was quite slow. But the complexes obtained were quite easy to be dissolved under stirring. When 50 mg complex produced by the sealed heating method or by $scCO_2$ processing was put in 1.00 mL deionized water, it was soon all dissolved. The apparent solubility of borneol could be raised to $(3.0 \pm 0.3) \times 10^{-1}$ mol/L for the complex formed from $scCO_2$ processing at 100 °C 10 MPa, could be raised to $(2.4 \pm 0.3) \times 10^{-1}$ mol/L for the complex produced by the sealed heating treatment at 100 °C 0.1 MPa. Therefore, the solubility of borneol could be enhanced about 70 times by complexation with methyl-β-cyclodextrin.

Conclusions

Borneol has the 3D molecular structure showed in Fig. 8, can sublimate into gaseous phase and be easily dissolved in

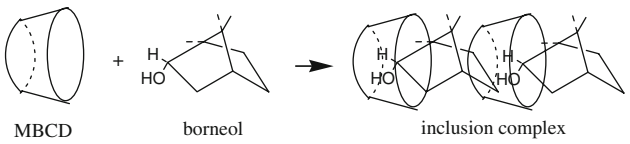

Fig. 8 Envisaged complex formation between borneol and MBCD in supercritical carbon dioxide media

$scCO_2$. MBCD exhibits a glass transition temperature around 180 °C and is liquefied in $scCO_2$ above 90 °C 5.0 MPa. In $scCO_2$ processing, borneol could be dissolved in MBCD melts and make contact with the cavities of two MBCD molecule. Thus, an inclusion complex with crystalline structure might be obtained as shown in Fig. 8. The crystalline complex is more stable than the amorphous complex prepared by the sealed heating treatment. The apparent aqueous solubility of borneol could be enhanced about 70 times by complexation with methyl-β-cyclodextrin. In contrast to this, HPBCD is a rigid solid in our experimental conditions, thus it is hard for the gaseous borneol molecules to diffuse into the HPBCD matrix to form a complex.

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