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Ibuprofen-Cyclodextrin Inclusion Complex Formation Using Supercritical Carbon Dioxide

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Abstract

Supercritical carbon dioxide (SC-CO_2) processing was performed with mixtures of cyclodextrins (CDs) and ibuprofen (IBP) to create inclusion complexes of ibuprofen and CD. Mixtures of IBP and trimethyl-β-CD showed new powder X-ray diffraction peaks after SC-CO_2 processing, although samples after processing with β-CD showed identical X-ray diffraction patterns with the physical mixture. The differential scanning calorimetry curves of samples after processing with trimethyl-β-CD showed no fusion peak of IBP and a new melting peak at around 185 °C. The physicochemical properties are similar to the co-precipitated samples of IBP and trimethyl-β-CD. Therefore, inclusion complex between IBP and trimethyl-β-CD was successfully prepared using SC-CO_2 technique. No inclusion formation was found when nitrogen was used as the supercritical fluid. Complexation of IBP and CD would not occur only on a high-pressure condition. The solubility of cyclodextrin into SC-CO_2 might play an important role in the formation of the inclusion complex.

Introduction

It is well known that cyclodextrins (CDs), cyclic oligosaccharides consisting of glucopyranose units, have an ability to form inclusion complexes with a variety of organic compounds due to its peculiar structure [1–2]. To improve the solubility and stability of drugs, several techniques have been used to prepare inclusion complexes with CDs, including kneading, sealed-heating, grinding, and coprecipitation [3–5].

Recently, technologies based on supercritical fluids have been widely employed in the food industry [6], and analytical chemistry [7]. Supercritical fluids have several advantageous properties including high densities, low viscosities, and high diffusion rates. Since supercritical carbon dioxide has a relatively low critical temperature and pressure and is non-toxic, several trials of pharmaceutical applications have been reported [8–10]. However, most of the reports concern the extraction of active ingredients [8], size reduction of drug particles [9], and preparation of polymorphs [10]. The preparation of solid dispersions or inclusion complexes of a drug and an additive under the supercritical fluid condition is still one of the most challenging targets on the area of functional solid dispersions.

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We have reported several articles regarding the inclusion complex formation and peculiar interactions of drug and cyclodextrins [11–12], and we are interested in whether complexes of medicines and cyclodextrins can be formed in supercritical carbon dioxide. Ibuprofen, a cyclo-oxygenase enzyme inhibitor, was used for the model active pharmaceutical ingredients, since the solubility of the ibuprofen in supercritical carbon dioxide has reported to be relatively high compared to the other medicines [13]. The aim of this work was to investigate the effect of supercritical fluid condition on the inclusion complex formation of ibuprofen and cyclodextrins.

Experimental

Materials

Racemic ibuprofen (IBP) was purchased from Tokyo Kasei Kogyo Co., Ltd. Japan and was used without further purification. Cyclodextrins (CDs) were obtained from sources as follows: β-CD from Nihon Shokuhin Kako Co. Ltd., Japan. Heptakis(2,6-di-*O*-methyl)-β-CD (DM-β-CD) from Junsei Chemical Co. Ltd., Japan, and heptakis(2,3,6-tri-*O*-methyl)-β-CD (TM-β-CD) from Tohshin Chemical Co. Ltd., Japan.

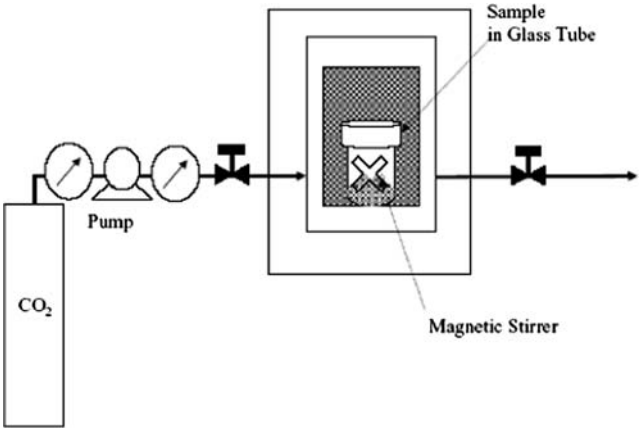

Figure 1. Schematic diagram of apparatus for complex formation of ibuprofen (IBP) and cyclodextrins (CDs) using supercritical carbon dioxide.

Sample preparation using supercritical fluid

The experimental apparatus (SC sprayer®, Nikkiso, Co. Ltd., Japan) for preparing the inclusion complex is illustrated in Figure 1. The physical mixture of IBP and CD was placed in a glass container (30 ml) with a magnetic stirrer. The glass container was covered with a polytetrafluoroethylene (PTFE) membrane filter (0.45 μm), and then put in an extraction unit. CO_2 or N_2 was introduced into the temperature-controlled reaction vessel (internal volume: 90 ml) in the extraction unit by a pump NP-AX-403 (Nihon Seimitsu Kagaku Co., Ltd., Japan) up to the desired pressure (upper limit: 29 MPa).

Powder X-ray diffraction (PXRD) measurement

Powder X-ray diffraction was carried out on a Rigaku Miniflex diffractometer (Rigaku Corporation, Japan). Measurements were performed at 30 kV voltage, 15 mA current, a scanning speed of 4 min^{-1}, a Ni filter and a radiation source of CuKα.

Differential scanning calorimetry (DSC)

Differential scanning calorimetric studies were performed on an EXSTAR6000 DSC6200 (Seiko Instruments, Japan) using a crimp-aluminum pan. The measurement was carried out from 50 to 200 °C at a heating rate of 5°C/min under nitrogen gas flow of 60 ml/min.

Fourier-transformed infrared (FT-IR) spectroscopy

Fourier-transformed infrared spectra were measured by the KBr disc method at a resolution of 4 cm^{-1} for 32 scans using a JASCO FT/IR-230 spectrophotometer (Japan Spectroscopy Co., Ltd., Japan).

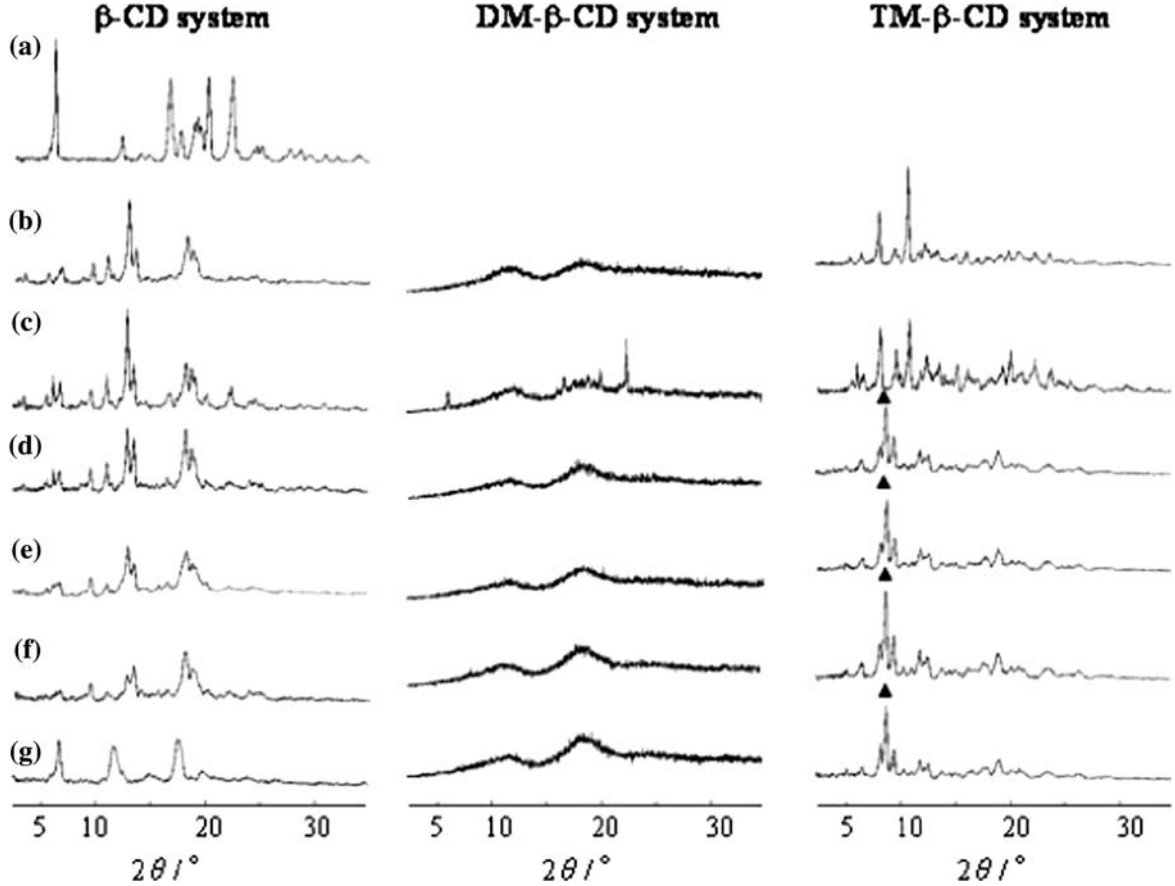

Figure 2. Powder X-ray diffraction (PXRD) patterns in the IBP-CD systems: (a) ibuprofen, (b) cyclodextrins, (c) physical mixtures (molar ratio of 1:1), (d) supercritical carbon dioxide processing (SCP) for 1 h, (e) SCP for 3 h, (f) SCP for 6 h, (g) co-precipitates.

Results and discussion

Changes in the powder X-ray diffraction (PXRD) patterns of the physical mixture of ibuprofen and CDs after the supercritical carbon dioxide (SC-CO_2) processing are shown in Figure 2. The sample after SC-CO_2 processing of the mixture of IBP and β-CD showed same PXRD patterns as the physical mixture, indicating that no inclusion formation was observed between IBP and β-CD. The physical mixture of IBP and DM-β-CD showed a halo pattern with the disappearance of the IBP diffraction peaks on SC-CO_2 processing. Although it is difficult to identify the inclusion complex formation of IBP and DM-β-CD, IBP crystals in the physical mixture changed to an amorphous state during SC-CO_2 processing. Mixtures of IBP and TM-β-CD behaved differently to those with β-CD or DM-β-CD with respect to the SC-CO_2 processing. The diffraction peaks arising from IBP and TM-β-CD crystals disappeared and new diffraction peaks appeared. The PXRD patterns were quite similar to the coprecipitate from aqueous solution, showing that the sample, after SC-CO_2 processing, could form inclusion complexes with TM-β-CD.

FT-IR spectra also supported the observation of inclusion complex formation between IBP and TM-β-CD as shown in Figure 3. The carbonyl stretching vibration band of IBP crystals observed at 1719 cm^{-1} in the crystals remained unchanged in the physical mixture but shifted to a higher frequency of 1738 cm^{-1} after SC-CO_2 processing with TM-β-CD. This peak shift of the carbonyl stretching vibration band of IBP was also observed after SC-CO_2 processing with DM-β-CD, but it was not observed after SC-CO_2 processing with β-CD. IBP has been reported as having a crystal structure with four molecules in a monoclinic unit cell and these four molecules form two dimers, each composing a chiral molecule hydrogen bonded to its mirror image across a center of inversion [14]. The observed IR peak shift was attributed to the breakdown of the intermolecular hydrogen bonds of IBP crystals, followed by the formation of a monomeric dispersion of IBP as a consequence of its interaction with TM-β-CD as reported by Mura *et al.* [15]. Since the spectral pattern was quite similar to that in the co-precipitated samples, these IR peak shifts resulted from the inclusion of the drug into the hydrophobic cavity of TM-β-CD. The effect of the processing time on the thermal properties of the mixture is shown in Figure 4. The physical mixture still shows endothermic peaks at around 75 and 150 °C arising from the fusion of IBP crystals and TM-β-CD, respectively. In the SC-CO_2 processed sample, the melting peak of IBP disappeared and a new melting peak at around 185 °C appeared. An increase in processing time induced a decrease of the enthalpy of fusion of TM-β-CD at around 150°C, accompanied by an increase of the enthalpy of the new endotherm peak. This new endothermic peak was attributed to the heat of fusion of the new inclusion complex induced by the SC-CO_2 processing. The appearance of the new melting peak at around 185 °C on heating the physical mixture indicates the possibility of forming the inclusion complex in this manner. However heating is not an appropriate manufacturing method as thermal decomposition of drugs often occurs at high temperature. Therefore SC-CO_2 processing is considered to be a unique preparation method for inclusion complexes.

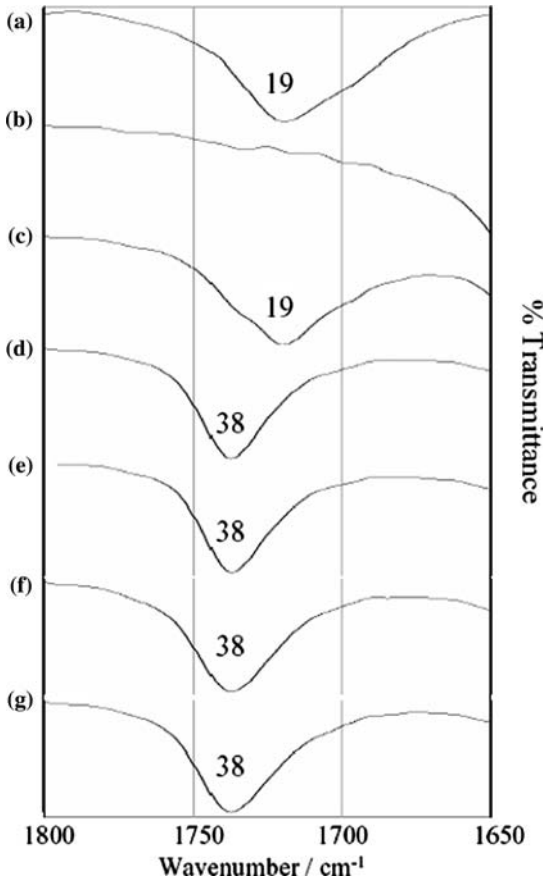

Figure 3. Change in FT-IR spectra of IBP and TM-β-CD mixture: (a) IBP, (b) TM-β-CD, (c) physical mixture, (d) SCP for 1 h, (e) SCP for 3 h, (f) SCP for 6 h, and (g) co-precipitate.

The effect of pressure on the formation of inclusion complexes is described in Figure 5. When the supercritical nitrogen (at 35 °C, 10 MPa for 3 h) was used as the supercritical media, the sample showed identical powder X-ray diffraction patterns to the physical mixture. It was found that weight losses of IBP and TM-β-CD, before and after processing with SC-N_2, were negligible. Since SC-N_2 had no specific interactions with solutes compared to SC-CO_2 [16], both IBP and TM-β-CD were almost insoluble in SC-N_2. When the physical mixture was kept at 860 MPa for 3 h in the compression cell, the sample also showed the same X-ray diffraction patterns as the physical mixture. These results suggest that complexation of IBP and CD does not only occur at high pressure.

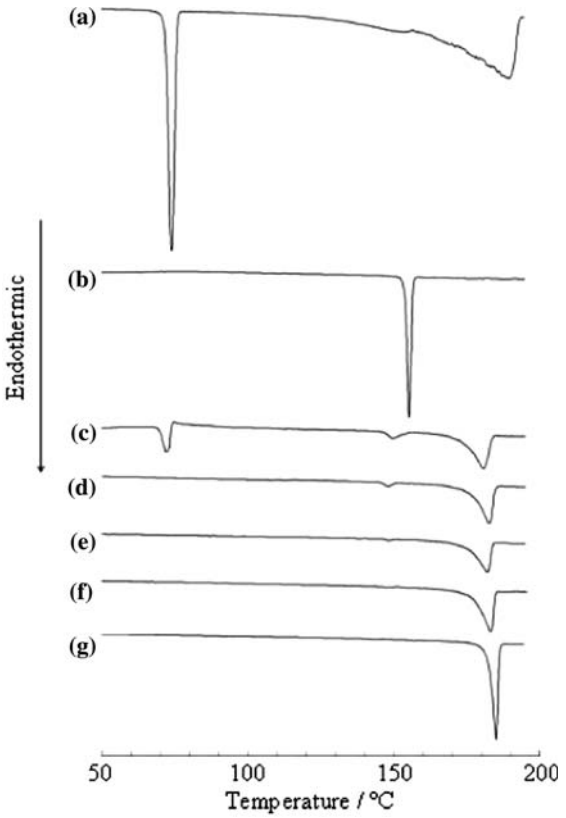

Figure 4. Change in DSC curves of IBP and TM-β-CD mixture: (a) IBP, (b) TM-β-CD, (c) physical mixture, (d) SCP for 1 h, (e) SCP for 3 h, (f) SCP for 6 h, and (g) co-precipitate.

The solubility of β-CDs into the SC-CO_2 was measured using the weight change of β-CDs before and after processing with SC-CO_2 for 3 h. The weight decrease of β-CD, DM-β-CD, and TM-β-CD was 0.4, 4.0, and 6.5%, respectively. The dissolution of TM-β-CD into SC-CO_2 is significantly higher than that of the β-CD. This finding suggests that solubility of CDs in SC-CO_2 might be related to the formation of inclusion complexes with IBP. If the solubility of the inclusion complex of IBP and TM-β-CD in SC-CO_2 is considerably lower than that of IBP or TM-β-CD itself, the inclusion complex would be precipitated from SC-CO_2 fluid. This effect might be a function of processing time.

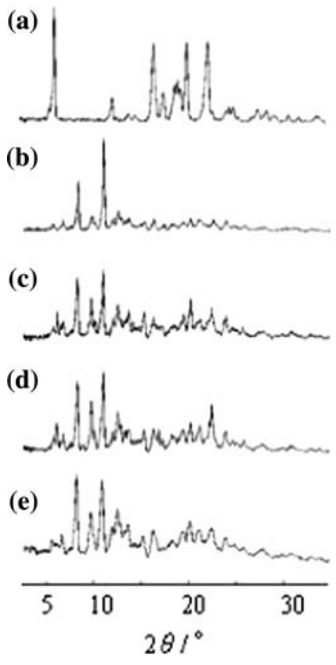

Figure 5. Effect of pressure on inclusion complex formation: (a) IBP, (b) TM-β-CD, (c) physical mixture, (d) supercritical-N_2 processing at 35 °C, 10 MPa for 3 h, and (e) compressed at 860 MPa for 3 h.

The differences in association constant between drug and CD might also affect the formation of an inclusion complex. After the dissolution of IBP and CD into aqueous solution, the association constants for the complexation were calculated by Benesi-Hildebrand plots [17]. In aqueous solution IBP formed the 1:1 complex with β-CDs, and the estimated association constant between IBP and CDs decreased in the order of DM-β-CD (13,560 M^{-1}) > β-CD (8,650 M^{-1}) > TM-β-CD (1,177 M^{-1}). The inclusion complex was clearly formed for the mixture with TM-β-CD, despite the fact that association constant of IBP and TM-β-CD is lower than that of IBP and β-CD. Although it is difficult to detect the molecular state of drugs and CDs in supercritical condition, association constants in supercritical fluids and the solubility of the inclusion complexes in the SC-CO_2 should be investigated further in order to clarifying the mechanism of inclusion complex formation.

Conclusions

The formation of inclusion complexes between IBP and TM-β-CD was clearly observed after processing with SC-CO_2. The observation of no inclusion formation between IBP and β-CD might arise from the low solubility of β-CD in supercritical CO_2. It is proposed that the solubilization of CDs into supercritical CO_2 is an important step for inclusion complex formation.

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