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Utilization of supercritical carbon dioxide for complex formation of ibuprofen and methyl-β-cyclodextrin

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Abstract

The dissolution rate of a drug into the biological environment can be enhanced by forming complexes with cyclodextrins and their derivatives. In this study, ibuprofen–methyl-β-cyclodextrin complexes were prepared successfully by passing ibuprofen-laden CO_2 through a methyl-β-cyclodextrin packed bed. The maximum drug loading obtained in this work was 10.8 wt.%, which was comparable to that of a 1:1 complex (13.6 wt.% of ibuprofen). The complex exhibited instantaneous dissolution profiles in water solution. The enhanced dissolution rate was attributed to the amorphous character and improved wettability of the product.

Keywords: Ibuprofen; Methyl-β-cyclodextrin; Supercritical CO_2

1. Introduction

In the pharmaceutical industry, many drugs exhibit poor solubility in water, and their absorptions in the gastrointestinal tract are limited by their dissolution rates. Various methods have been used to increase the dissolution rate; these include micronisation, modification of the physicochemical properties of the drug, and complexation with cyclodextrins and derivatives.

Cyclodextrins (CDs) are cyclic oligosaccharides, consisting of glucopyranose units, which are linked by α-1,4 glycosidic bonds. Due to the lack of free rotation about the bonds linking the glucopyranose units, the cyclodextrins are not perfectly cylindrical but are toroidal or a truncated cone shape. Cyclodextrins are water-soluble since all the hydroxyl groups of the glucopyranose units are located on the outside surface of the rings. However, the internal cavity of the doughnut-shaped molecule is relatively non-polar. This unique characteristic of cyclodextrins allows a guest molecule with an appropriate size to be included fully or partially in the hydrophobic cavity. During the guest-cyclodextrin complex formation no covalent bonds are established or broken. The formation of inclusion complexes has been used to improve the solubility, stability and bioavailability of a wide variety of pharmaceuticals, such as poorly water-soluble drugs (Szejtli,

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1988; Loftsson and Brewster, 1996; Loftsson, 1999). Side effects of the drug and local irritation can also be reduced upon forming the inclusion complexes.

The most common cyclodextrins are α-, β- and γ-cyclodextrins, which consist of six, seven and eight glucopyranose units, respectively. Among these natural cyclodextrins, β-cyclodextrin is widely used in the pharmaceutical industry due to its cavity size, availability in pure form, efficiency of drug complexation and relatively low cost (Loftsson, 1999). The chemical structure and the toroidal shape of β-cyclodextrin are given in Fig. 1.

Several techniques have been used to prepare a complex such as an inclusion complex, including kneading, freeze drying, grinding, coprecipitation and melting. However, the disadvantages of using these methods are that they are time-consuming, necessitate multistage processing and often result in residual solvent in the product.

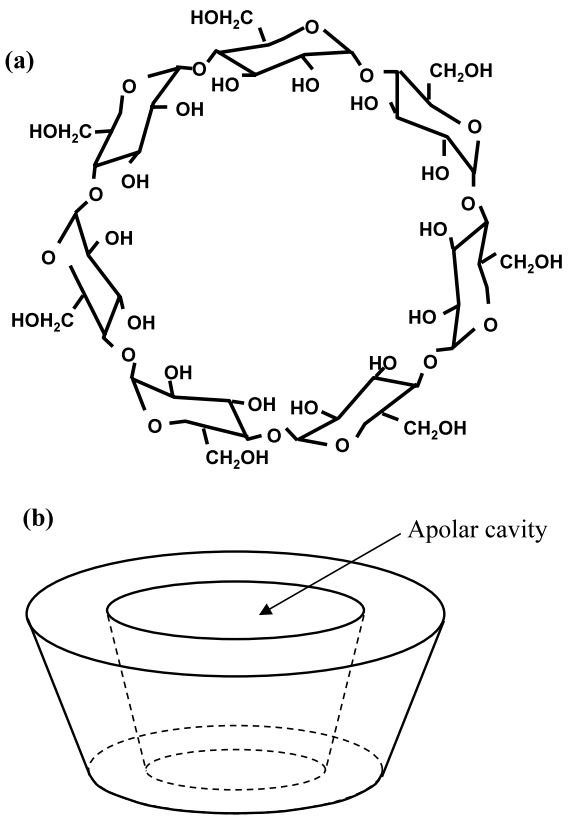

Fig. 1. (a) The chemical structure and (b) the toroidal shape of β-cyclodextrin.

A relatively new technique that has been developed for the preparation of complexes involves the use of dense gases (a fluid in the vicinity of its critical point). One advantage of using dense gas processing to prepare inclusion complexes is the lack of toxicity in the product since there is no residual solvent after depressurisation. The unique properties of dense gases, such as excellent mass transfer properties and high solvating power, render this technique suitable for the complexation of thermally labile compounds with cyclodextrins. In 1990, Kamihira et al. utilised various cyclodextrins for the entrapment of volatile aromatic compounds after extraction with CO_2 at 20 °C and 100 bar. The formation of the inclusion complexes was achieved by passing a stream of CO_2 containing the aromatic compounds through the inclusion vessel packed with CDs. More recently, in 1999, Van Hees et al. prepared a piroxicam-β-cyclodextrin inclusion compound by pressurising a physical mixture of the drug and β-cyclodextrin with supercritical (SC) CO_2 up to 150 bar at 150 °C. The mixture was kept in a static mode for 6 h to obtain a nearly complete inclusion (inclusion yield > 98.5%).

In this study the chiral non-steroidal anti-inflammatory drug, racemic ibuprofen, was used as an example of a drug whose dissolution rate is limited by its poor solubility in water. Ibuprofen is most often prescribed to treat arthritis, menstrual symptoms, fever and pains. The side effects and required intakes of this drug can be minimised by improving its effectiveness in terms of increasing the dissolution rate in the biological environment.

Previous studies have reported the possibility of preparing complexes of ibuprofen with β-cyclodextrin and its derivatives (Chow and Karara, 1986; Zecchi et al., 1988; Orienti et al., 1989; Mura et al., 1998; Khan and Zhu, 1998). Various techniques have been used to prepare the ibuprofen–cyclodextrin complexes, including freeze-drying an aqueous ammonia solution containing the physical mixture (Mura et al., 1998), and coprecipitating the complex from aqueous/ethanol solu-

tion (Khan and Zhu, 1998). However, these techniques possess disadvantages such as long processing time and residual organic solvent in the product.

In this study the feasibility of using SC CO_2 to prepare complexes of ibuprofen and cyclodextrin was investigated. Methyl-β-cyclodextrin (MBCD) was chosen as a host molecule since its solubility in aqueous solution (>2000 mg/mL) at room temperature is significantly higher than that of the unsubstituted-β-cyclodextrin (18.5 mg/mL). It was expected that the higher solubility of MBCD in aqueous solution would lead to higher solubility of the ibuprofen–cyclodextrin complexes. Moreover, Mura et al. (1996, 1998) also reported that MBCD was the most effective carrier for ibuprofen compared to unmodified BCD and other cyclodextrin derivatives. The complex of ibuprofen and MBCD had a stoichiometric ratio of 1:1 (Mura et al. 1998).

Prior to complex formation, the phase behaviour of MBCD in the presence of CO_2 was investigated. A procedure to prepare the complex of ibuprofen and MBCD using SC CO_2 was developed. The dissolution kinetic studies were then carried out to assess the performance of the complex. Finally, the effect of pressure, static contacting time and mixing on the complex formation was examined.

2. Experimental

2.1. Materials

Racemic ibuprofen (Sigma, 99.8% purity) was used as received. Carbon dioxide (BOC Gases, 99.95%) was used as the solvent. Methyl-β-cyclodextrin (MW = 1310, pharmaceutical grade, with an average substitution degree per anhydroglucose unit of 1.8) was kindly donated by Wacker-Chemie GmbH. Potassium phosphate monobasic (Sigma, 99% purity) and sodium hydroxide (Sigma, min. 98% purity) were used to prepare phosphate buffer solution for analysing the drug content.

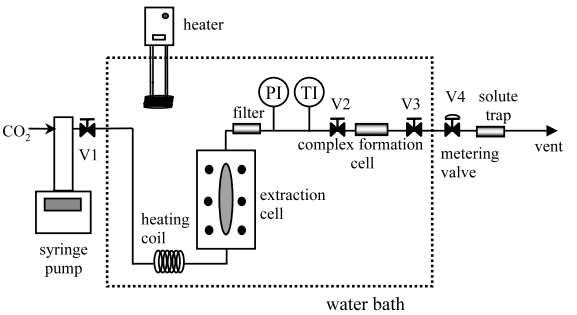

Fig. 2. Schematic diagram of the apparatus for complex formation using supercritical CO_2.

2.2. Phase behavior studies

A phase observation study of the MBCD–CO_2 system was carried out using a static technique. A glass tube (i.d. = 5.8 mm) loaded with solid MBCD was placed inside the view cell (Jerguson sight gauge series No. 32). The system was then immersed in the constant temperature water bath. Prior to commencing experiments, the system was purged with low pressure CO_2 in order to remove moisture and air. Since MBCD is an amorphous macromolecular compound, the compound does not have a melting point. Thus, it was expected that no droplets of the liquid MBCD would be observed under high pressure. In this study, carbon dioxide was gradually fed into the view cell at 3 bar increments. The system was isolated and equilibrated for at least 10 min after each pressurisation in order to observe any phase transition of the MBCD.

2.3. Preparation of a complex using supercritical fluid

The experimental apparatus for preparing the complexes is illustrated in Fig. 2. The equipment can be divided into two main units: the extraction and the complex formation sections. The extraction cell consisted of a high pressure Jerguson sight gauge (model 13-R-32) which was packed with alternative layers of glass wool and racemic ibuprofen. The complex formation unit was loaded with 0.6 g of methyl-β-cyclodextrin. The temperature of the system was controlled to

within ± 0.1 °C by a heater circulator (Thermoline Unistat) that was placed in the water bath. The system pressure was controlled by a syringe pump (ISCO model 260D). The pressure of the system was monitored using a Druck pressure transducer (model PDCR 911) coupled to a Druck pressure indicator, while the system temperature was measured with a pt 100 RTD with an accuracy of ± 0.1 °C.

2.4. Procedure

Liquid CO_2 from a cylinder was fed into a syringe pump, and delivered to the pre-heating coil. The extraction cell was pressurised to the required pressure with valve V_2 closed. The extraction vessel was equilibrated at the desired extraction pressure and temperature for at least 1 h prior to commencing the complex formation. The complex was formed by gradually opening a ball valve V_2 to pressurise the cell (V_3 was opened, and V_4 was shut), while the pump was operating at a constant pressure mode. Once the pressure in the complex formation cell was the same as the extraction cell, a metering valve V_4 was opened slightly to allow the ibuprofen laden SC CO_2 to pass through the cyclodextrin. This procedure was used to remove moisture and air in the cell, and also allow the drug–MBCD complex formation. As a basis for this study, the SC solution was passed through the MBCD loaded cell for 45 min with a typical flow rate of 0.1 ml of liquid CO_2/min. The complex formation cell was then isolated and left in a static mode with ibuprofen laden CO_2 (V_4, V_3 and V_2 were shut, respectively). The system was then depressurised to atmospheric pressure by opening V_3 fully and V_4 slightly. The depressurisation step was usually completed within 10 min.

In this study, the effects of operating pressure and exposure time in a static mode on the complex formation were studied. All the experiments were repeated at least 3 times.

2.5. Characterization of the complex

2.5.1. Drug content

Accurately weighed samples were dissolved in a known amount of phosphate buffer solution (pH 6.3). The amount of ibuprofen in the solution was determined by measuring the UV absorbance at 221 nm with a precalibrated curve. Note that the presence of MBCD did not interfere with the spectrophotometric assay of the drug.

2.5.2. Thermal analysis

Differential Scanning Calorimetry (DSC) thermograms were obtained using DSC (2010), TA Instruments). A known mass of sample (≈ 10 mg) was heated in an aluminum pan under a nitrogen gas flow of 6 mL/min. A heating rate of 10 °C/min was used up to a maximum temperature of 230 °C.

2.5.3. X-ray powder diffractometry

The powder X-ray diffraction patterns of unprocessed MBCD, the physical mixture (10 wt.% ibuprofen, 90 wt.% MBCD) and the mixture processed by supercritical CO_2 were determined by X-ray diffraction (XRD) (Rigaku).

2.5.4. Scanning electron microscopy (SEM)

The morphologies of unprocessed MBCD, MBCD treated with CO_2, the physical mixture (10 wt.% ibuprofen, 90 wt.% MBCD) and the complex formed by supercritical CO_2 were determined by scanning electron microscopy (SEM) (Hitachi S4500). Samples were coated with gold using a sputter coater (Edwards) prior to analysis.

2.5.5. Dissolution kinetics studies

In vitro dissolution studies were performed for unprocessed ibuprofen, its physical mixture with MBCD, and the complex formed by supercritical CO_2 using the USP paddle method. Distilled water (pH 5.5, 500 ml) was used as dissolution medium in this study. The determinations were conducted at a rotational speed of 50 rpm, and at a constant temperature of 37 °C. Samples containing the same amount of ibuprofen were introduced into the dissolution medium simultaneously. Aliquots ($\approx$ 4 mL) were withdrawn over certain time intervals and passed through a 0.45 μm filter. The amounts of ibupro-

fen in the withdrawn samples were determined by measuring the absorbance at $\lambda = 221$ nm using spectrophotometry (Hewlett Packard 8453).

3. Results and discussion

3.1. Phase behavior studies

It is well known that compressed fluids such as CO_2 can lower the melting point of some organic compounds. The melting point of a solute decreases due to CO_2 sorption into the solute matrix and solute–solvent intermolecular interactions, thus resulting in weaker attractions between the solute segments within the matrix (Sze Tu, 2000). As was reported by Charoenchaitrakool et al. (2000), ibuprofen exhibits melting point depression when contacted with SC CO_2. The melting point depression was also observed for MBCD when exposed to SC CO_2. The melting point of MBCD decreased to 25, 35, 40, 45 °C when contacted with CO_2 at 190, 147, 143 and 94 bar, respectively.

3.2. Preparation and characterization of ibuprofen–MBCD complex

As was mentioned earlier MBCD was melted under high pressure CO_2, hence it is most likely possible to prepare a complex by impregnating the MBCD with ibuprofen. In this study, ibuprofen–MBCD complexes were prepared using a similar technique to that described previously by Kamihira et al. (1990). The ibuprofen–MBCD complexes was formed upon passing ibuprofen-laden CO_2 at 190 bar, 35 °C through the bed of MBCD for 45 min, and left in a static mode for 3 h. At the end of the process, the system was depressurised in order to collect the solid complex. The ibuprofen content in the product was found to be 9 ± 2 wt.%.

Typical DSC thermograms of both the physical mixture and the complex are depicted in Fig. 3. The DSC curve of the physical mixture consisted of two endothermic peaks: a broad peak between 30 and 60 °C, and a peak around 75 °C. The former peak corresponded to the water loss upon heating the sample, the latter represented the melting of ibuprofen. It should be noted that the intensity of the second peak was proportional to the amount of ibuprofen in the physical mixture.

Despite the fact that the complex formed by the SCF process contained approximately 9 wt.% of ibuprofen, the endothermic peak of ibuprofen disappeared (Fig. 3b). This evidence may be attributed to the transformation of ibuprofen into an amorphous state, or the formation of a complex such as an inclusion complex or a combination of both phenomena. The results of the previous studies (Charoenchaitrakool et al., 2000) demonstrate that ibuprofen precipitated as a crystalline material upon the rapid expansion of ibuprofen-laden SC solution. The presence of MBCD in the system may obstruct ibuprofen molecules to precipitate in a crystal form. Ibuprofen was therefore precipitated as an amorphous compound after the depressurisation of the system. The disappearance of the ibuprofen peak may also be attributed to the formation of a complex. Since concentrations of free ibuprofen as low as 1 wt.% in the physical mixture could be

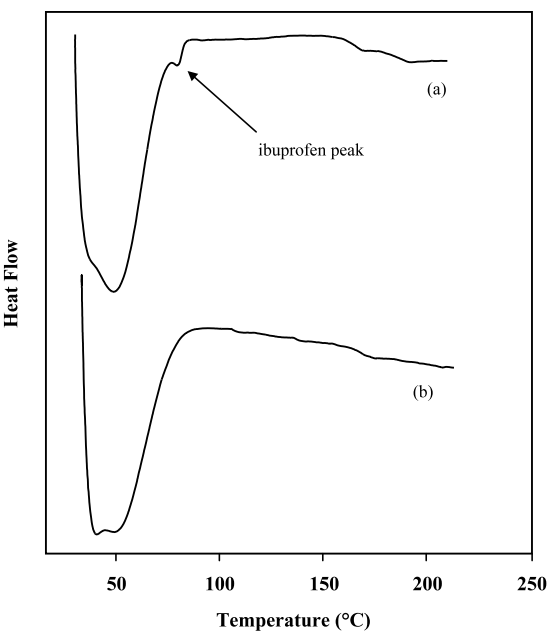

Fig. 3. DSC thermograms of (a) the physical mixture (1 wt.% ibuprofen); (b) complex formed by SC CO_2.

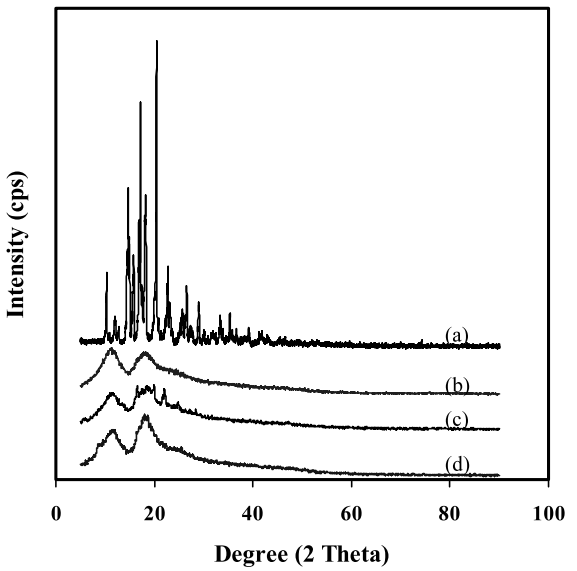

Fig. 4. XRD patterns of (a) ibuprofen; (b) MBCD; (c) the physical mixture of ibuprofen and MBCD (10 wt.% ibuprofen); (d) the complex.

detected by the DSC analysis, the disappearance of the second peak in the complex may indicate that there was no free ibuprofen on the surface of the complex.

The X-ray diffraction patterns of the unprocessed ibuprofen illustrated in Fig. 4a confirm that ibuprofen is a crystalline material. As shown in Fig. 4b, the X-ray diffraction patterns of the MBCD reveals two broad peaks, confirming the amorphous character of the compound. In the case of the physical mixture, the XRD patterns depicted in Fig. 4c were simply the superposition of those of the single components. The sharp peaks indicate the retention of crystalline structure of the drug in the physical mixture. On the other hand, the XRD patterns of the complex formed with SC CO_2 (Fig. 4d) consisted of two broad peaks similar to those of the MBCD. The disappearance of ibuprofen diffraction patterns may be credited to the formation of inclusion complex in which ibuprofen was entrapped in the MBCD cavity.

Prior to performing the dissolution kinetics studies, the morphology and particle size of unprocessed MBCD, MBCD treated with SC CO_2, the physical mixture of ibuprofen–MBCD and ibuprofen–MBCD complex formed by SC CO_2 were analysed by scanning electron microscope (SEM). As is illustrated in Fig. 5a, the unprocessed MBCD consisted of hollow spherical particles (ca. 22 μm in diameter) with a narrow size distribution. Methyl-β-cyclodextrin particles obtained after treating with SC CO_2 at 190 bar, 35 °C were irregular in shape with a broad particle size distribution between 2 and 260 μm. The increase in particle size of the MBCD resulted from the melting and phase transition of MBCD powders under high pressure CO_2. It was also found that the product was brittle and could be ground easily.

The SEM images of the Ibuprofen–MBCD physical mixture and the complex formed by SC CO_2 are illustrated in Fig. 5c and d, respectively. The particle size of the physical mixture was found to be in the range of 1 to 75 μm, which was smaller than that of the complex (10–480 μm).

As a basis for comparison, the dissolution rate coefficient (K_w) is defined as the reciprocal of the time after which 63.2% of the original amount of material has dissolved (Loth and Hemgesberg, 1986). The dissolution rate coefficients for all samples were determined and were listed in Table 1. It was clearly shown that the physical mixture and the complex produced in this study exhibited higher dissolution rate than the unprocessed drug.

The dissolution kinetics of all samples was investigated using distilled water at 37 °C, pH 5.5 as a dissolution medium. The dissolution profiles of ibuprofen in water from unprocessed ibuprofen, the physical mixture and complex formed with SC CO_2 are shown in Fig. 6. It was clearly shown that the dissolution rate of the complex formed in this study was much higher than the physical mixture. The dissolution rate coefficient of the complex in water was found to be > 1 min^{-1}, which is at least 66 times higher than that of the physical mixture. Similarly, Mura et al. (1998) investigated the dissolution rate of ibuprofen–MBCD complex in water (pH 6) at 37 °C. The complex was prepared by freeze-drying an aqueous ammonia solution containing the physical mixture. An instantaneous dissolution profile of the complex was also observed.

The enhancement in dissolution rate of the complex could be attributed to the amorphous character of the complex and improved wettability. It should be noted that in this study the product was not sieved or ground prior to the dissolution tests. Based on the SEM analysis, the particle size of the complex was found to be larger than that of the physical mixture. As a result, the enhanced dissolution rate of the complex was not due to the reduction in particle size.

The dissolution rate coefficient of the physical mixture in water was found to be 0.015 min^{-1}, which is 3 times higher than the unprocessed drug. The enhanced dissolution rate of ibuprofen from the physical mixture could be accounted for by the improved wettability of hydrophobic ibuprofen. This result indicates that MBCD could be used as an additive in the solid ibuprofen formulations to enhance the dissolution rate of the drug.

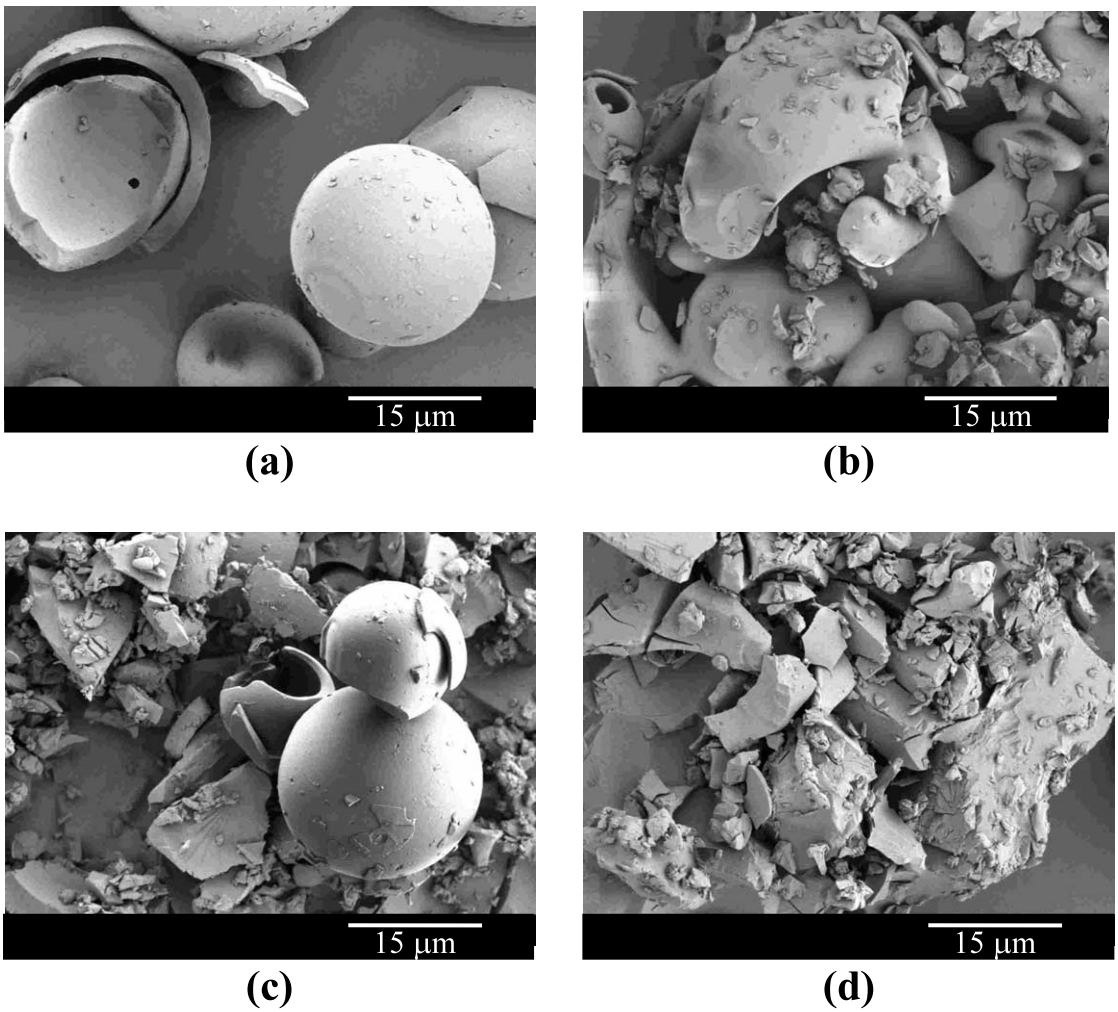

Fig. 5. SEM photographs of (a) MBCD; (b) MBCD treated with CO_2; (c) physical mixture (10 wt.% ibuprofen), (d) complex formed by SC CO_2.

Table 1
Dissolution rate coefficients (K_w) of ibuprofen at various conditions

Conditions	Dissolution rate coefficient, K_w (min^{-1})
Unprocessed	0.005
Physical mixture	0.015
Complex formed with SC CO_2	>1

Note: $K_w > 1$ means 63.2% of the drug dissolved within 1 min.

3.3. The effect of process parameters on the complex formation

Mura et al. (1998) reported that ibuprofen can form an inclusion complex with MBCD in the molar ratio of 1:1. The amount of ibuprofen in a 1:1 complex is equivalent to 13.6 wt.%. The complex formed in this study using SC process contained at least 9 wt.% ibuprofen. The effect of pressure, the static contacting time and mixing on improving the drug content was investigated. In order to establish a basis for comparison, the parameters that were kept constant include the amount of MBCD (0.6 g), temperature (35 °C), the flowrate (0.1 mL of liquid CO_2/min) and contact time of supercritical solution passing through the complex formation unit (45 min).

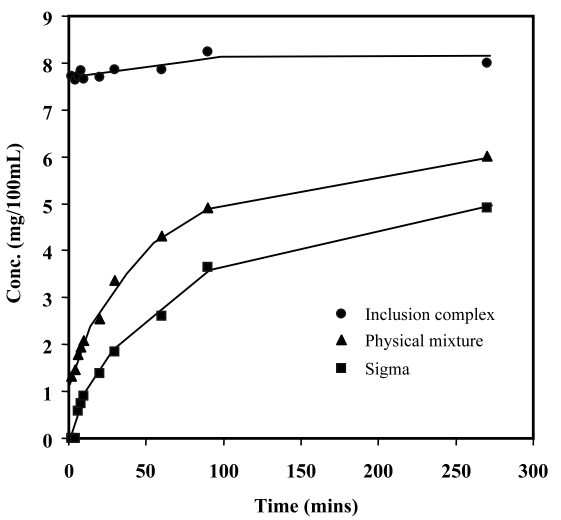

Fig. 6. Dissolution profiles of complex, physical mixture and unprocessed ibuprofen in distilled water at 37 °C, pH 5.5.

Table 2
Effect of static contacting time on the drug content

Static contacting time (h)	wt.% of ibuprofen in the complex
1	7.8 ± 1.1
3	8.9 ± 1.8
6	8.4 ± 0.5
12	7.9 ± 0.7
24	10.8 ± 1.5

3.4. Effect of static contacting time

Van Hees et al. (1999) reported that the contact time between SC CO_2 and the physical mixture of piroxicam and β-cyclodextrin in the static mode had a positive influence on the complex formation. The ibuprofen content in the complex increased when the contact time was increased. In this study, the effect of static contacting time on the drug content was investigated by varying contact time from 1 to 24 h. The extraction pressure of ibuprofen was maintained at 190 bar. Prior to determining the drug content, DSC analysis was performed for all samples. No free ibuprofen was observed in any of the complexes. The experimental conditions and the amount of ibuprofen in the complexes are listed in Table 2. No significant difference of the drug content was obtained as the static contacting time was varied from 1 to 24 h.

In order to improve the contact area between MBCD and ibuprofen, two complex formation cells in series, packed with glass beads, were used. Each cell was packed with 0.3 g MBCD. The pressure and the static contacting time were maintained at 190 bar and 3 h, respectively. The ibuprofen content in the complex prepared was found to be similar to that obtained without the use of glass beads. There was therefore sufficient contact between the ibuprofen-laden SC CO_2 phase and the MBCD melted phase at 190 bar without the need to use glass beads. This result indicates that the mass transfer was not a limiting factor for the amount of ibuprofen loaded in MBCD.

3.5. Effect of pressure

The effect of pressure on the complex formation was investigated between 130 and 220 bar. The static contacting time and temperature were kept constant at 3 h and 35 °C, respectively. Based on the previous phase behaviour study of the MBCD–CO_2 system, MBCD started to transform into a liquid when contacted with SC CO_2 at 147 bar and 35 °C. As a result, the physical state of MBCD changed from solid to liquid when the pressure was increased from 130 to 220 bar.

As is illustrated in Fig. 7, increasing the pressure resulted in a higher drug content in the complex. A linear relationship between ibuprofen content in the complex and the pressure was also observed within the range of operating conditions studied. As the pressure was increased from 130 bar to 220 bar, the concentration of ibuprofen in the supercritical solution increased by 1.8 times (Charoenchaitrakool et al., 2000), hence more ibuprofen was available for the complex formation. In addition, the viscosity of the MBCD liquid phase was decreased due to a higher amount of CO_2 dissolved into the MBCD matrix at higher pressures. The reduction in viscosity of the MBCD and the higher amount of ibuprofen available in the system accounted for the higher ibuprofen content in the complex.

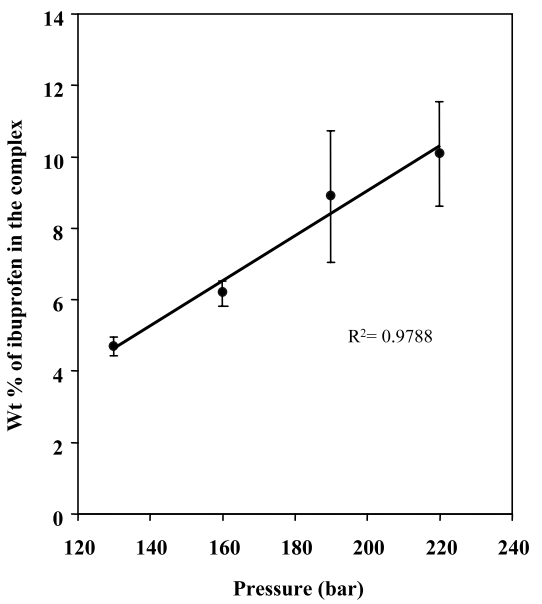

Fig. 7. Effect of extraction pressure on the ibuprofen content loaded in MBCD at 35 °C and 3 h static time.

4. Conclusion

The feasibility of preparing an ibuprofen–MBCD complex using SC CO_2 was investigated. The complex formed by the SC process is free of organic solvent. Under certain conditions, methyl-β-cyclodextrin was melted when the solute was present with SC CO_2. Upon passing ibuprofen-laden CO_2 through the MBCD bed, a complex was formed within a relatively short period (<2 h). The maximum drug content obtained in this work was approximately 10.8 wt.%, which was comparable to that of a 1:1 complex (13.6 wt.% of ibuprofen).

An increase in the pressure resulted in a higher drug content in the complex. However, no significant difference on the drug content was found when the static contacting time was varied from 1 to 24 h, or the contact surface area increased in the complex formation process.

The dissolution rate of the complex formed by SC CO_2 was found to be significantly higher than that of the physical mixture. The increase in dissolution rate of ibuprofen in the complex formed was attributed to the amorphous nature of the product, and improved wettability. The enhanced dissolution rate increases the bioavailability of the drug and minimizes the doses required and hence decreases the side effects. The results of this study demonstrate that a supercritical process can be an efficient method for inclusion complex formation.

Acknowledgements

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