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Research Paper

Comparative Evaluation of Ibuprofen/β-Cyclodextrin Complexes Obtained by Supercritical Carbon Dioxide and Other Conventional Methods

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Purpose. The preparation of drug/cyclodextrin complexes is a suitable method to improve the dissolution of poor soluble drugs. The efficacy of the Controlled Particle Deposition (CPD) as a new developed method to prepare these complexes in a single stage process using supercritical carbon dioxide is therefore compared with other conventional methods.
Materials and Methods. Ibuprofen/β-cyclodextrin complexes were prepared with different techniques and characterized using FTIR-ATR spectroscopy, powder X-ray diffractometry (PXRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). In addition, the influences of the processing technique on the drug content (HPLC) and the dissolution behavior were studied.
Results. Employing the CPD-process resulted in a drug content of 2.8 ± 0.22 wt.% in the carrier. The material obtained by CPD showed an improved dissolution rate of ibuprofen at pH 5 compared with the pure drug and its physical mixture with β-cyclodextrin. In addition CPD material displays the highest dissolution (93.5 ± 2.89% after 75 min) compared to material obtained by co-precipitation (61.3 ± 0.52%) or freeze-drying (90.6 ± 2.54%).
Conclusion. This study presents the CPD-technique as a well suitable method to prepare a drug/β-cyclodextrin complex with improved drug dissolution compared to the pure drug and materials obtained by other methods.

KEY WORDS: β-cyclodextrin; Controlled Particle Deposition; ibuprofen; poorly water-soluble; supercritical fluids.

INTRODUCTION

In pharmaceutical practice poor water solubility of drugs is a well-known problem. At present about 40% of the drugs in the development pipelines and up to 60% of the compounds coming directly from synthesis are categorized as poorly soluble (1). To act on target structures, the drugs must be dissolved in the physiological fluid and thereafter absorbed through entrance ports. Due to cost, convenience and compliance, the oral application of solid forms is the preferential way. The bioavailability of orally applied drugs, however, depends on the rate of dissolution and absorption. Thus poor water solubility leads to poor bioavailability and a slow onset of action, this causes the need to increase the dose of a poorly soluble drug to obtain the efficacy required (2,3). In the past, various methods have been used to increase the dissolution rate including micronization, modification of the physicochemical properties of the drug, the addition of water-soluble polymers and the complex formation with cyclodextrins (CDs).

Cyclodextrins (Fig. 1) are cyclic oligosaccharides that have a cone structure which contains a relatively hydrophobic central cavity and a hydrophilic outer surface. CDs are able to form inclusion complexes with many drugs by taking up the drug molecule or a hydrophobic moiety of the molecule into their cavity. This complexation has been applied as one of the most useful means to improve the dissolution of poorly water-soluble drugs in intravenous and oral formulations (4,5). Several methods have been used to prepare inclusion complexes including co-precipitation, kneading, freeze-drying and many more (4–11). The applications of these methods in the pharmaceutical industry, however, were limited due to the disadvantages of some of these conventional complex formation techniques, including the requirement of organic or toxic solvents. The latter may result in residues in the products, environmental pollution and requires a multi-stage processing including long drying steps that may affect the drug stability. To overcome these disadvantages, alternative methods for preparing drug/CD complexes using supercritical fluids (SCF) as a non-toxic solvent have been developed (12–18). In 1999, Van Hees *et al.* (13) prepared a piroxicam/β-cyclodextrin (1:2.5 molar ratio) inclusion complex using a static system with a multistage process by keeping a physical mixture of the drug with a native cyclodextrin 3 h in the supercritical carbon dioxide at 150°C and 45 MPa. The authors assumed the high inclusion yield was due to the high temperature and pressure of CO_2, which could promote

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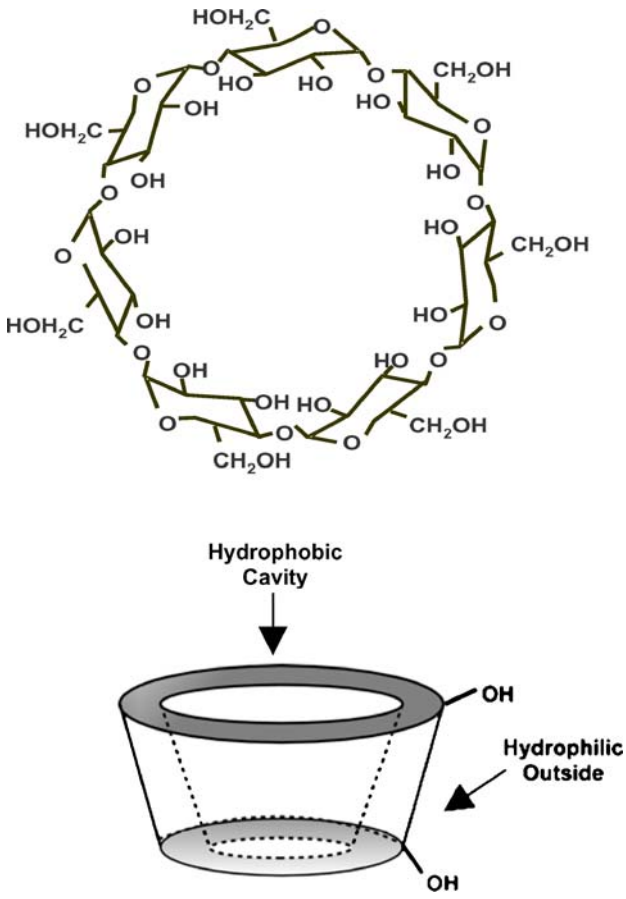

Fig. 1. Chemical and functional structure scheme of β-cyclodextrin.

exchange of the water molecules with piroxicam inside the cyclodextrin. The use of high temperature processing, however, isn't attractive for heat-sensitive pharmaceutical substances.

Charoenchaitrakool *et al.* (14) prepared the complex of ibuprofen with methyl-β-cyclodextrin (MBCD) as a solid dispersion using a multi-stage dynamic system by passing a supercritical CO_2/ibuprofen mixture through a MBCD packed bed. The authors showed that the maximum of the drug loading was 10.8 wt.% at 19 MPa, 35°C and 24 h static contacting time in CO_2. In this procedure, it should be considered that under these conditions MBCD was melted since MBCD starts to transform into a liquid at 14.7 MPa and 35°C when contacted with supercritical CO_2.

Recently, Bandi *et al.* (15) prepared the complex of budesonide and indomethacin with amorphous cyclodextrin (hydroxypropyl-β-cyclodextrin) (HPBCD) by exposing physical mixtures of budesonide–HPβCD (0.31:1 molar ratio) and indomethacin–HPβCD (0.85:1 and 0.35:1 molar ratio) 20 h to supercritical CO_2 at 40°C and 21.1 MPa.

In our study we used the Controlled Particle Deposition (CPD), originally developed for the generation of particles with improved dissolution behavior, to form an ibuprofen/β-cyclodextrin complex in a single step process using $scCO_2$ (16–18). The CPD process is intended for a controlled deposition of drug particles in porous carriers. The key idea behind CPD is to dissolve the solute of interest in supercritical CO_2, followed by permeation of the supercritical solution into the pores of the insoluble carrier and precipitation of the drug inside the pores, caused by a fast pressure drop. By control of the working conditions (pressure, temperature and drug concentration) the size, amount and modification of the particles obtained can be modulated.

In order to evaluate the usefulness of this new technique, the physiochemical characteristics of the ibuprofen/β-cyclodextrin complex produced by CPD are compared to materials obtained by different conventional methods (co-precipitation and freeze-drying). In addition, the dissolution properties of the products have been investigated.

MATERIALS AND METHODS

Materials

Ibuprofen 50 was generously supplied from Knoll Pharmaceuticals (Nottingham, UK), β-cyclodextrin was purchased from Wacker–Chemie GmbH (München, Germany). CO_2 (MW 44.01 g/mol, Air Liquide; Germany) was chosen as supercritical solvent since it is a non-flammable, inexpensive, and non-toxic solvent. All other materials and solvents were from Merck (Darmstadt, Germany). A MES-buffer System pH 5 (containing g/l: $CaCl_2$ 0.14, KCl 0.40, KH_2PO_4 0.06, $MgCl_2 \times 6\ H_2O$ 0.10, $MgSO_4 \times 7\ H_2O$ 0.10, NaCl 8.00, $Na_2HPO_4 \times 2\ H_2O$ 0.06, D-glucose 1.00, MES 2.13, 0.1 N NaOH-solution q. s.) was used to determine the drug release.

Preparation of Binary Systems

The solid complexes of ibuprofen (MW 206.3 g/mol) and β-cyclodextrin (MW 1,135.0 g/mol) were prepared by different processing: by CPD as the new-developed technique using $scCO_2$ and by freeze-drying and co-precipitation, according to Kurozumi *et al.* (20), as well known standard methods for comparison. A physical mixture of the drug and β-cyclodextrin was prepared as a control.

CPD Method Using $scCO_2$

The CPD experimental set-up (Fig. 2) for preparing the inclusion complexes consists of a high-pressure vessel ($V = 0.5\ dm^3$) containing separate cartridges which have a sieve form to carry the drug and the carrier, respectively. The pressure inside the high-pressure vessel was monitored with a pressure gauge, and the vessel itself was maintained in a temperature-controlled bath. This apparatus allows investigations in a temperature range of 5 to 80°C and a pressure up to 30 MPa (16–19). The experiments for loading the $scCO_2$ soluble drug (ibuprofen) into the solid carrier (β-cyclodextrin) for complex formation were carried out at 39.7°C and a pressure of 24.7 MPa. These conditions were optimized in pilot experiments to ensure that only a solid-fluid two-phase equilibrium ($S_2 = G$) exists for each pressure, due to the fact that ibuprofen exhibits melting point depression when contacted with $scCO_2$ (16). Loading was repeated in six separate experiments.

In this study, equimolar amounts of the drug (ibuprofen, 8.04 ± 0.05 g) and the carrier (β-CD, 13.00 ± 0.03 g) were placed each into a separate cartridge inside the high-pressure cell. After closing the system was purged with low CO_2 pressure to remove moisture and air. Thereafter, the required

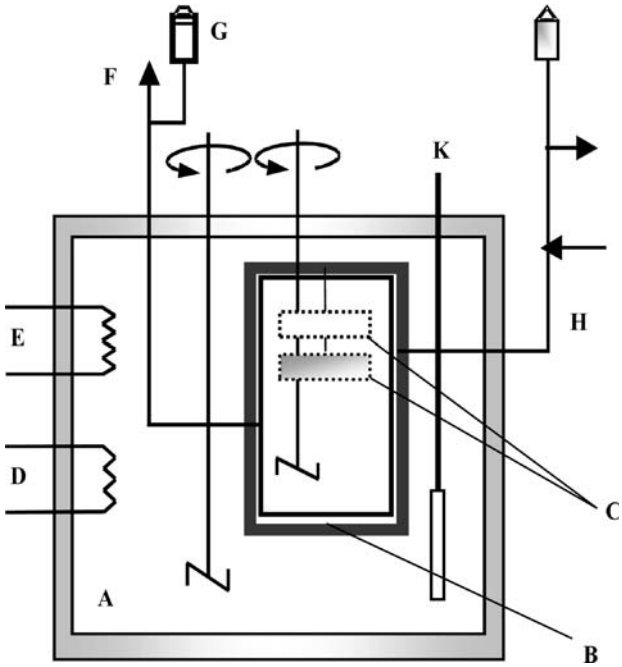

Fig. 2. The CPD experimental set-up for preparing the inclusion complexes in supercritical fluids. (*A*) liquid thermostat, (*B*) high pressure cell, (*C*) drug and carrier chamber, (*D*) heating, (*E*) cooling, (*F*) pressure-relief valve, (*G*) pressure sensor, (*H*) inlet and outlet, (*K*) Pt-100 thermometer.

amount of liquid CO_2 was condensed into the high-pressure cell. The system was then immersed in a water bath and heated to the desired temperature to reach the supercritical state. The temperature of the water bath was measured with a calibrated Pt-100 thermometer; a piezo-resistive pressure gauge was used to determine the system pressure. The total accuracy of the temperature and pressure measurements was ±0.07°C and ±0.06 MPa, respectively.

As soon as the selected pressure in the high pressure cell was reached, the exposure time was fixed to 15.5 h. At the end of the experiments, depressurization was performed within 4 min. Samples were taken from the β-cyclodextrin cartridge. More details about the experimental procedure have been published earlier (16).

Co-precipitation Method

The inclusion complexes ($n = 3$) were prepared with a molar ratio of 1:3 ibuprofen:β-cyclodextrin. Ibuprofen and β-cyclodextrin were dissolved in diethyl ether and water, respectively, and mixed together. The mixture was stirred at room temperature for 24 h. After that, the suspension was kept at 0°C and finally the microcrystalline precipitate was filtered, washed with a small amount of water and dried at 50°C.

Freeze-drying Method

The complex formation ($n = 3$) was prepared by dissolving ibuprofen and β-cyclodextrin (1:3 molar ratio) in 2.34% aqueous ammonium solution. After 15 min of agitation at room temperature, the resulting solution was frozen and lyophilised for 24 h (Lyovac GT 2 freeze-dryer, Finn Aqua Santasalo-Sohlberg Co., Tuusula, Finland).

Preparation of the Physical Mixture

A physical mixture was prepared as a reference by mixing of previously sieved ibuprofen and β-cyclodextrin with 1:3 molar ratio in a Turbula T2C mixer for 15 min at 42 rpm.

Characterization of the Complexes

Determination of Drug Content

The "*n*-hexane wash" method was used to detect the true complex formation and to determine the free drug content in the solid state (4,22,23). This method is based on the fact that the β-cyclodextrin and its complexes are insoluble but the free drug is soluble in *n*-hexane. To determine the free drug content in the complex, a sample (10 mg) of each product was shaken with *n*-hexane (1 ml). The *n*-hexane supernatant was separated and dried. The residue from the *n*-hexane layer was dissolved in acetonitrile (10 ml) and analyzed by HPLC.

The drug content in the complex was determined by dissolving the previously washed complex with a small amount of dimethylsulfoxide (400 µl) and diluted with acetonitrile. After 12 h, the β-cyclodextrin had sedimented, and the supernatant was centrifuged (Megafuge 1.0 R, Heraeus, Hanau, Germany) for 15 min at 1,300 rpm, removed and analyzed by HPLC.

The HPLC system consisted of a Shimadzu LC-6A pump (Shimadzu Europe, Duisburg, Germany), an AS-200A injector (Merck/Hitachi, Darmstadt, Germany), a Nucleosil 100-5 C18 125 × 4 mm column (Macherey–Nagel, Düren, Germany), a Shimadzu SPD-6A UV-detector (Shimadzu Europe, Duisburg, Germany) at 230 nm, and a Shimadzu C-R6A integrator (Shimadzu Europe, Duisburg, Germany). The mobile phase was 50:50 (v/v) acetonitrile/20 mM K_2HPO_4 pH 2.5 at a flow rate of 1.5 ml/min. The injection volume was adjusted to 20 µl.

The inclusion yield (wt.%) of the ibuprofen/β-cyclodextrin binary system prepared with various methods was evaluated according to the following equation:

$$\text{Percentage of included ibuprofen} = \left[\frac{\text{complexed amount of ibuprofen}}{\text{free amount} + \text{complexed amount}}\right] \times 100$$

Table I. Inclusion Data of Ibuprofen/β-cyclodextrin Systems Prepared by CPD ($n = 6$) and Other Methods ($n = 3$) (values are mean ± SD)

Product	Total Ibuprofen Content wt.%	Inclusion Yield (%)
CPD	2.8 ± 0.22	49.83 ± 3.65
Co-precipitation	5.39 ± 0.07	51.91 ± 1.73
Freeze-drying	5.34 ± 0.22	97.01 ± 1.70
Physical mixture	5.37 ± 0.28	3.25 ± 1.89

Infrared Spectroscopy

Fourier Transformed Infrared-Attenuated Total Reflectance (FTIR-ATR) from dried samples of pure ibuprofen and β-cyclodextrin, as well as their binary products, were obtained with a Spectrum One FTIR-spectrometer with diffuse reflectance, horizontal ATR (HATR) and universal ATR (UATR) systems (Perkin–Elmer Co, USA). The frequency range of the analysis was from 650 to 4,000 cm^{-1} and the resolution was 0.5 cm^{-1}.

Thermal Analysis

Differential Scanning Calorimetry (DSC) measurements were performed using a Mettler DSC system (TA 8000, DSC 820, Mettler Toledo, Giessen: Germany). The samples (4–8 mg per run) were placed in perforated 40 µl aluminum standard pans and covered with punched lids. The heating sequences were carried out within a temperature range from 25 to 200°C, at a heating rate of 10 K/min, purged continuously with nitrogen gas (20 ml/min).

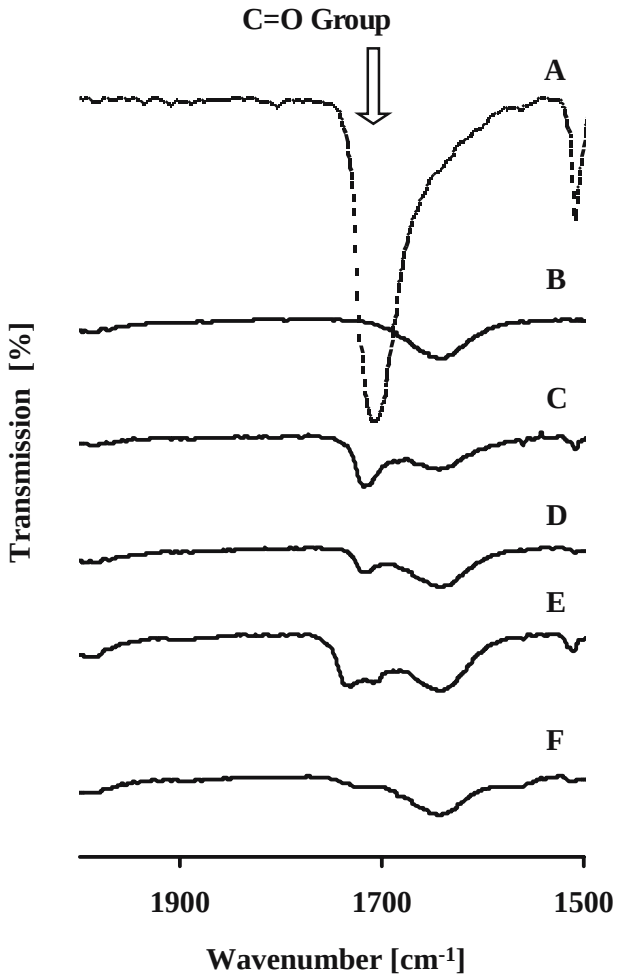

Fig. 3. FTIR-ATR spectrums of pure ibuprofen (*A*), β-cyclodextrin (*B*), ibuprofen/β-cyclodextrin physical mixture (*C*), CPD (*D*), co-precipitation (*E*), and freeze-drying (*F*) products.

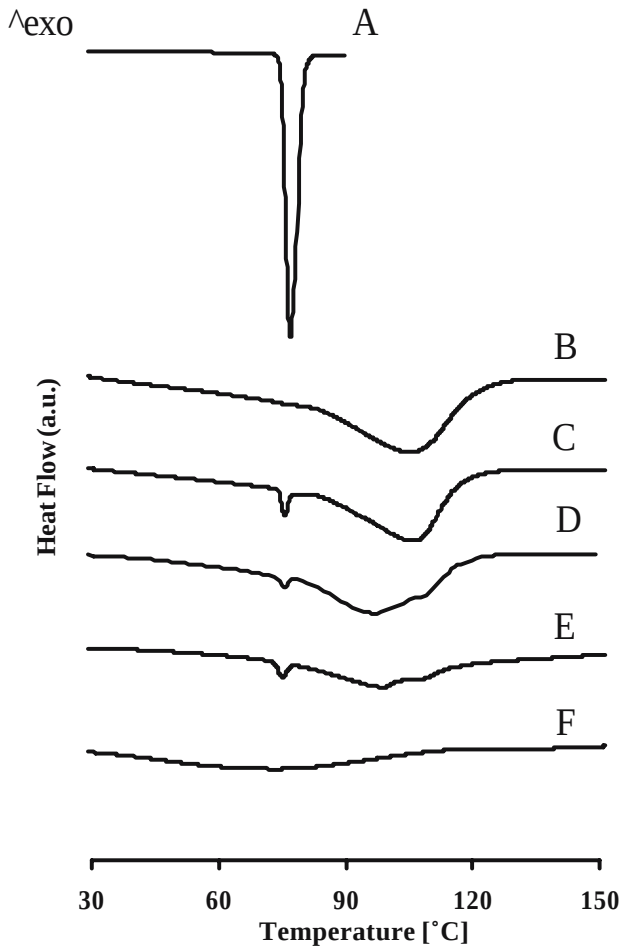

Fig. 4. DSC thermograms of pure ibuprofen (*A*), β-cyclodextrin (*B*), ibuprofen/β-cyclodextrin physical mixture (*C*), CPD (*D*), co-precipitation (*E*), and freeze-drying (*F*) materials.

Powder X-ray Diffractometry

The Powder X-ray diffraction (PXRD) patterns were carried out using a Guinier step scan diffractometer (G600, Huber Diffraktionstechnik, Rimsting, Germany) with monochromatic CuKα_1 radiation ($\lambda = 1.54056$ Å). The voltage and current were at 40 kV and 30 mA. The diffraction patterns were recorded in the rang of $5° \leq 2\theta \leq 60°$, with a step size of 0.025°, and a 5 s time per step.

Scanning Electron Microscopy

The surface morphology of the raw material and the obtained products were examined by the use of a scanning electron microscope (DSM 940 A, Carl Zeiss, Oberkochen, Germany). The samples were coated with gold, by employing a Sputter Coater (E 5100, Bio-Rad, München, Germany).

Determination of Drug Release

The drug release was investigated using a flow through cell system according to Stricker (24) (Sartorius AG, Göttingen, Germany) to keep sink conditions.

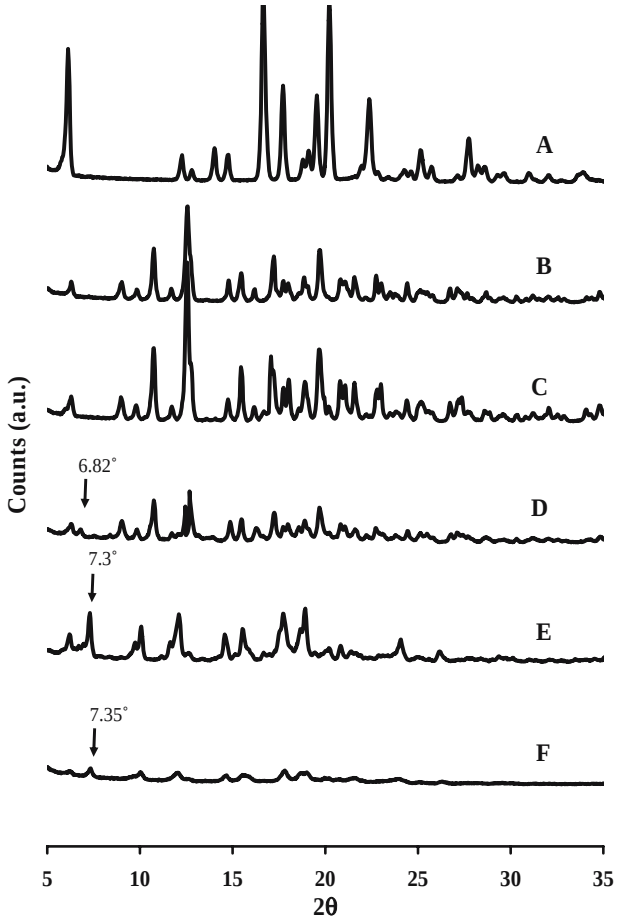

Fig. 5. PXRD patterns of pure ibuprofen (*A*), β-cyclodextrin (*B*), ibuprofen/β-cyclodextrin physical mixture (*C*), CPD (*D*), co-precipitation (*E*), and freeze-drying (*F*) products.

The dissolution vessel containing 100 ml MES-buffer (pH 5, 37°C) was rotating at 1.2 rpm. A weighed quantity of powdered samples (pure ibuprofen, physical mixture, or a sample of products previously washed with *n*-hexane to remove the uncomplexed drug), equivalent to 3 mg ibuprofen, was added to the chamber. Samples of 4 ml were taken from the dissolution fluid after 5, 10, 15, 30, 45, 60 and 75 min, filtered by a membrane filter (Sartorius Cellulose Nitrate Filter, 0.45 μm), and replaced with an equal volume of the dissolution fluid, giving a final dissolution volume of 128 ml during a 75 min experiment. The filtrates were assayed spectrophotometrically (UV-VIS spectrophotometer 550 S, Perkin Elmer, Überlingen, Germany) at 221 nm. The dissolution coefficient (K_w) was calculated according to the Weibull equation (25) in order to describe the kinetic parameter of the curve. The coefficient corresponds to the timepoint when 63.2% of the drug is dissolved:

$$K_W = \frac{1}{t_{63.2\%}}$$

The dissolution coefficient and the amount of drug (wt.%) released at 15 and 75 min were selected as parameters for evaluating the dissolution behavior of all systems. The dissolution data were statistically analyzed by one-way analysis of variance (ANOVA) followed by Tukey posterior test for multiple comparisons using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego California, USA, http://www.graphpad.com). A value of $p < 0.05$ was considered significant.

RESULTS

Determination of Drug Content

The HPLC determination of the ibuprofen content in the products shows the highest loading efficiency in the freeze dried, a medium efficiency in the CPD and co-precipitated and, as expected, almost no effect in the physical mixture. Significant amounts of the loaded drug were incorporated in the cyclodextrin (Table I) though a portion of physical mixture was present in all preparations except the freeze dried product.

Infrared Spectroscopy

The FTIR-ATR spectrum of pure ibuprofen shows all the characteristic bands of the drug, including the carbonyl stretching at 1,706 cm^{-1} (Fig. 3). A shift to higher frequency in the characteristic acid carbonyl stretching in the physical mixture to 1,714 cm^{-1}, CPD to 1,714 cm^{-1} and co-precipitated material to 1,731 cm^{-1} was seen. In addition the C=O stretching was very weak in the CPD and was completely absent in the freeze dried material, indicating the inclusion of this part of the drug molecule in the cyclodextrin. The disappearance or shift of the carbonyl stretching was

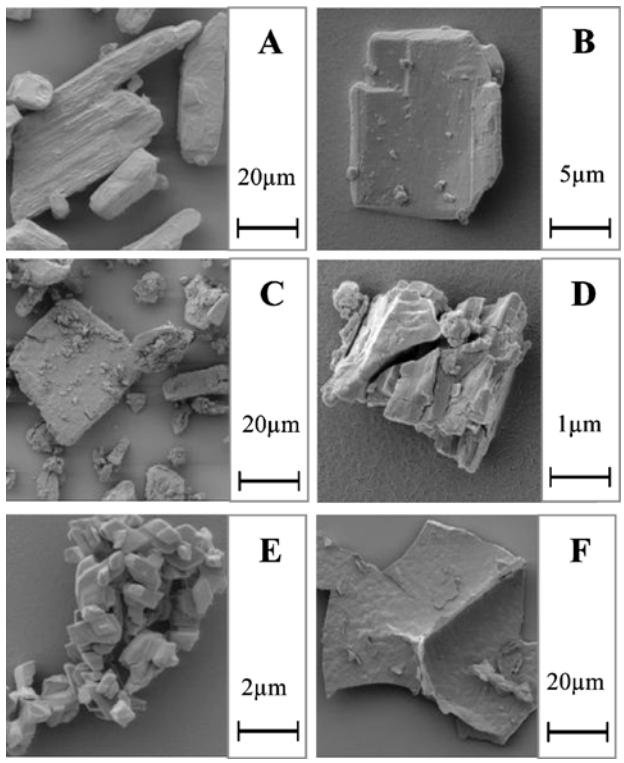

Fig. 6. SEM micrograph of pure ibuprofen (*A*), β-cyclodextrin (*B*), ibuprofen/β-cyclodextrin physical mixture (*C*), CPD (*D*), co-precipitation (*E*), and freeze-drying (*F*) products.

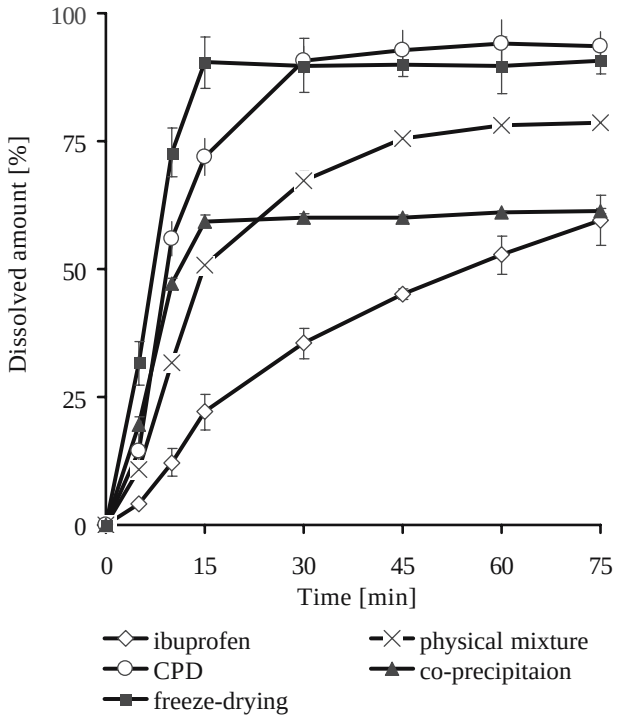

Fig. 7. Dissolution profiles of ibuprofen, ibuprofen/β-cyclodextrin physical mixture, and the corresponding ibuprofen/β-cyclodextrin complexes (±95% CI; $n = 3$) in MES-buffer at 37°C and pH 5.

reported earlier (8–10) as evidence for the inclusion of ibuprofen inside the β-cyclodextrin cavity.

Thermal Behavior

The thermal behavior of the β-cyclodextrin inclusion complexes was studied with DSC to confirm the formation of a solid complex by the disappearance of the endothermic melting peak of crystalline ibuprofen (Fig. 4). Pure ibuprofen exhibits an endothermic melting peak at about 77°C. The DSC thermograph of β-cyclodextrin shows a broad endothermic peak around 105°C, corresponding to the release of water. In the thermal curve of the physical mixture, the characteristic endothermic melting peak of ibuprofen was observed. The thermograph of the ibuprofen/β-cyclodextrin complex prepared by CPD and co-precipitation displayed a melting peak at 77°C, which still reflects the presence of drug crystals not incorporated in the carrier in this preparation. A complete disappearance of the endothermic peak of free ibuprofen was in contrast observed for the complex obtained by the freeze-drying method.

X-ray Powder Diffractometry

A change in the crystallinity of the drug (PXRD) indicates complex formation by appearance of a new or at least deviation from the original pattern (4,8,9). The PXRD of ibuprofen shows the characteristic pattern of the drug. A significant reduction of the X-ray diffraction pattern (Fig. 5) of the drug was observed in all complex formation methods, especially in the freeze dried product indicating a complete loss of crystallinity. In addition, new peaks were observed at 6.82, 7.3 and 7.35° in all diffractograms of CPD, co-precipitation and freeze dried material, respectively. These peaks may suggest the formation of ibuprofen/β-cyclodextrin complexes.

Scanning Electron Microscopy

Morphological changes were investigated by SEM (Fig. 6). Pure ibuprofen (a) appeared as needle-shaped crystals with a rough surface and β-cyclodextrin (b) with a parallelogram shape. The ibuprofen/β-cyclodextrin physical mixture (c) shows bulky particles (β-cyclodextrin) with small needles (ibuprofen) adhered to its surface. In all materials obtained by complex formation methods, a new population of particles with a typical shape occurred, which was not seen in the pure material and the physical mixture. The CPD material (d) showed crystals looking different from those of ibuprofen and β-cyclodextrin and having a smaller crystal size. Agglomerates of multiple crystals appeared in the co-precipitation material (e), and no crystals from the pure drug or pure β-cyclodextrin could de distinguished. The freeze dried material (f) appeared in a typical morphology with a soft and fluffy structure. The occurrence of the new form of crystals in all the produced materials gives evidence for the formation of the inclusion complex.

Determination of Drug Release

In vitro dissolution testing of pure ibuprofen at pH 5 (Fig. 7) shows poor dissolution of the drug, both after 15 or 75 min (Table II). The presence of β-cyclodextrin in the physical mixture improved the dissolution of ibuprofen significantly; this is likely to be due to the wettability-enhancing effect of β-cyclodextrin (26,27). Although the drug dissolution of the co-precipitation material after the first

Table II. Dissolution Rate Coefficient ($K_w \pm$ SD) and Amount of Ibuprofen (percent ± 95% CI) Dissolved After 15 and 75 min

Product	Dissolution Rate Coefficient (min^{-1})	Dissolved amount of drug after 15 min	Dissolved amount of drug after 75 min
CPD	0.086 ± 0.002 (a)	71.9 ± 3.62 (a)	93.5 ± 2.89 (a)
Co-precipitation	<0.038[a]	59.3 ± 1.17 (b)	61.3 ± 0.52 (b)
Freeze-drying	0.114 ± 0.007 (b)	90.4 ± 5.05 (c)	90.6 ± 2.54 (a)
Physical mixture	0.039 ± 0.002 (c)	50.8 ± 0.19 (d)	78.5 ± 0.85 (c)
Ibuprofen	<0.038[a]	22.0 ± 3.56 (e)	59.5 ± 4.86 (b)

Values marked with different letters differ significantly (ANOVA, $p < 0.05$; Tukey-test; $n = 3$).
[a] $K_w < 0.038$ means that of ibuprofen dissolution didn't reach 63.2% within 75 min. These values were excluded from statistical analysis.

15 min was well expressed, this improvement was rather limited but significant after 75 min (Table II). The highest enhancement of the drug dissolution was seen for the CPD product and the freeze dried material.

The calculated Weibull-coefficient (K_w) confirmed these results. Here the CPD and freeze dried materials show the highest dissolution rate compared to the pure drug, the physical mixture and the co-precipitation material. For pure ibuprofen and the co-precipitated material this coefficient couldn't be calculated because of their slow dissolution (less than 63.2% after 75 min).

DISCUSSION

Complexation of drugs with β-cyclodextrin is a common way to improve the dissolution and bioavailability. Employing ibuprofen as a model of a poor water-soluble drug and β-cyclodextrin as a carrier, an innovative way of complexation using supercritical fluid technology (the controlled particle deposition, CPD) was developed recently (16–18). A key element of the CPD-process is the use of separate cartridges to hold the drug and the carrier, which avoids the use of physical mixtures (13,15). The process requires solubility of the drug but insolubility of the carrier in the supercritical fluid. The drug is transported via the supercritical phase to the carrier and precipitates into the pores of the carrier after release of the pressure. Under these conditions, no melting of the drug is obtained, as it is in comparable methods of others (14,15), giving a better chance for stable, crystalline or molecular dispersed products (28).

In our hands, an inclusion complex with 2.8 ± 0.22 wt.% ($n = 6$) total content of ibuprofen was obtained by CPD. The determination of the inclusion yield showed that about 50% of ibuprofen found in the carrier was complexed, the rest remaining uncomplexed as a physical mixture with the carrier. This was comparable to the co-precipitation material. The freeze-drying method, however, showed a better inclusion rate. Partly complexation of ibuprofen in both, the co-precipitated and CPD material, was detected as well by a reduction of the C=O stretch at 1,714 and 1,731 cm^{-1}, respectively, in the IR spectra (Fig. 3). Absence of the C=O stretch can be observed in the freeze dried product, indicating again complete complexation obtained by this procedure. In parallel, the partial or complete disappearance of the typical melting peak of ibuprofen at 77°C in the DSC of CPD or the freeze dried product supports the view of partial formation of a complex in CPD. In contrast, the co-precipitation material here behaved like a physical mixture (Fig. 4).

Comparison of the X-ray pattern (Fig. 5) indicates loss of reflexions in the products manufactured by CPD, freeze drying and the coprecipitation. This again stands for the formation of inclusion complexes compared to the physical mixture and the raw material, but only to an incomplete extend for CPD and the coprecipitation method. The formation of the inclusion complexes, however, is seen by the appearance of a new reflection band. In the freeze dried product, a complete loss of crystallinity is likely due to the absence of reflection peaks, this may be due to amorphous structure of the complex caused by the use of ammonia during preparation (27). The SEM micrographs (Fig. 6) demonstrate the interaction of ibuprofen with β-cyclodextrin by indicating a morphological change of the crystals in all the obtained materials compare to the pure starting material due to the formation of an inclusion complex.

The drug dissolution (Fig. 7) at pH 5 was improved in the CPD, the freeze dried and the coprecipitated products as well as in the physical mixture. In the latter, even though no inclusion complexes are formed, wettability of the drug is thought to be improved by cyclodextrin (26,27) This improvement of dissolution, however, was quite limited in the coprecipitated material due to agglomeration after the drying step during the preparation, whereas the other products were obtained in fine powder form. The highest dissolution rate was found in the CPD and the freeze dried materials.

CONCLUSION

Our study presents the Controlled Particle Deposition (CPD) as a well suitable method to prepare a drug/cyclodextrin complex for the improvement of dissolution. The product is achieved in a single step process using $scCO_2$ without the use of any organic or toxic solvents, which were required in the conventional methods. The products, as obtained by the different preparation methods, clearly indicate the influence of the complex formation method on the solid state characteristics and on their dissolution behavior, which is in agreement with other studies (9,11,27). The CPD product shows improved drug dissolution compared to the pure drug and materials obtained by co-precipitation or freeze-drying, proving superiority of the CPD production method.

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