Influence of the Preparation Method on Dissolution Behaviour of Drug/β-Cyclodxtrin Complexes Prepared Using scCO$_2$ and Other Conventional Methods

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The aim of this study was to compare the influence of preparation methodology on the dissolution behavior of the drug/β-cyclodextrin complexes prepared with our previously developed technique "Controlled Particle Deposition (CPD)" using scCO2 in a single step process with materials obtained with other conventional methods.
In this study, the CPD was optimized and employed to load a model drug (ibuprofen) in a porous carrier (β-cyclodextrin). We assayed the reproducibility of this method and the solid – state of CPD materials was compared to the classical methods co-precipitation and freeze-drying. The obtained materials were characterized using fourier transform infrared spectroscopy (FT-IR), powder x-ray diffraction (PXRD), differential scanning calorimetry (DSC) and scanning electron microscopy (SEM). In addition, the influence of the processing methods on drug content (HPLC) and the effect of the preparation method on the dissolution behavior were studied.
In the CPD, loading of 2.9 ± 0.13 wt. % (n = 3) of ibuprofen in β-cyclodextrin, respectively a 1:3 (mol/mol) complex, was obtained. The investigation of the CPD material showed an absence of C = O stretching (FT-IR), a reduction of the diffraction patterns of the drug (PXRD), and in parallel a disappearance of the typical melting peak of ibuprofen (DSC). The SEM micrographs indicate a morphological change of the β-cyclodextrin crystal, confirming the inclusion. The CPD product significantly improved the dissolution 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 rate (97.94 % after 75 min) compared to material obtained by co-precipitation (61.37 %) or freeze-drying (90.67 %). Taking together, an effective improvement of the drug dissolution was achieved by producing drug/β-cyclodextrin complexes using CPD compared to other conventional methods.

INTRODUCTION

In the pharmaceutical practice poor water solubility is a well-known problem. At present about 40 % of the drugs being in the development pipelines are poorly soluble, and up to 60 % of compounds coming directly from synthesis are poorly soluble [1]. The bioavailability of orally applied drugs depends on the velocity of dissolution rate and absorption. Thus a poor water solubility can lead to poor bioavailability, a slow onset of action and cause the need to increase the dose to obtain the efficacy required [2]. Appropriate methods to improve the dissolution rate of poor water-soluble drugs are therefore required.

The complex formation with cyclodextrins (CDs) is one of the most useful means to improve the dissolution of poorly water-soluble drugs [3]. Several methods have been used to prepare this inclusion complex; including co-precipitation, kneading, freeze-drying and recently by supercritical fluids (SCF) using a different technique [4-8] as an alternative to avoid the use of toxic and organic solvents and multi stage processes including long lasting drying steps, that may affect the drugs stability.
In this study the physiochemical properties of the ibuprofen/β-cyclodextrin complex prepared with our previously developed CPD technique using scCO2 in a single step process, were compared with materials obtained with conventional methods (co-precipitation and freeze-drying). The influence of the preparation methodology on the dissolution behavior was investigated too.

I- MATERIALS AND METHODS

1. Materials:

Ibuprofen 50 was generously supplied from Knoll Pharmaceuticals (Nottingham, UK). The β-cyclodextrin was supplied by Wacker-Chemie GmbH (München, Germany) and CO_2 (M = 44.01 g/mol, Air Liquid; 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), and MES-buffer System pH 5 was used to determine the drug release.

2. Methods

2.1. Preparation of the Solid Complexes

2.1.1. CPD Method Using SCF

Ibuprofen/β-cyclodextrin complexes (n=3) were formed using a static incubation SCF set-up (Figure 1).

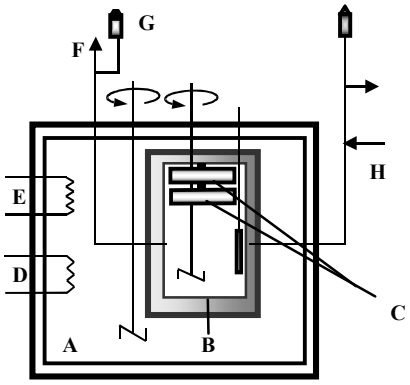

Figure 1: Schematic diagram of the CPD experimental apparatus A) Liquid Thermostat, B) Pressure Cell, C) Drug and Carrier Chamber, D) Heating, E) Cooling, F) Pressure-Relief Valve, G) Pressure sensor, H) Inlet.

Defined amounts of ibuprofen and the carrier β-cyclodextrin were placed into separate cartridges inside the high-pressure cell. The ibuprofen concentration in the CO_2-fluid phase was adjusted at 3.0 wt%. Prior to the inclusion experiments, the system was purged with low pressure CO_2 to remove moisture and air. Thereafter, the required amount of liquid CO_2 was condensed into the high-pressure cell and heated to the desired temperature. 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 occurred and samples were taken from the β-cyclodextrin cartridge.

2.1.2. Co-precipitation Method

For preparing the ibuprofen/β-cyclodextrin complex with a molar ratio of 1:3, the required quantity of ibuprofen and β-cyclodextrin were dissolved in diethyl ether and water, respectively, and mixed together. The mixture was stirred at room temperature for 24 hours. 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 [8, 9].

2.1.3. Freeze-Drying Method

Ibuprofen and β-cyclodextrin in 1:3 molar ratios were dissolved in aqueous ammonium solution. After 15 min of agitation at room temperature, the resulting solution was frozen and was lyophilised in a Lyovac GT 2 freeze-dryer (Finn Aqua Santasalo-Sohlberg Co., Tuusula, Finland) for 24 hours [8, 9].

2.1.4. 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 ratios in a Turbula T2C mixer for 15 min.

2.2 Characterization of the Solid Complexes

2.2.1. Determination of the Drug Content

Samples of each powder were washed with n-Hexane to determine the free drug amount in the complex. Afterwards the n-Hexane layer was removed and dried. The residue was dissolved in a cetonitrile and was analysed by HPLC. The remaining drug was then dissolved in dimethylsulfoxide and filed up with acetonitrile After 12 hours, the β-cyclodextrin had sedimented, and the supernatant was centrifuged (Megafuge 1.0 R, Heraeus, Hanau, Germany) for 15 min at 1300 rpm and analysed by HPLC.
Shimadzu HPLC system (Shimadzu Europe, Duisburg, Germany) was employed to determine the free and in the complex ibuprofen content. [8]

2.2.2. FT-IR

Fourier transform Infrared spectra (FT-IR) of samples were obtained in the range of 400 to 4000 cm^{-1}using a spectrum one FT-IR spectrometer (Perkin-Elmer Co, USA).

2.2.3. The Thermal Analysis

The differential Scanning calorimetry (DSC) measurements were performed using a Mettler DSC system (TA 8000, DSC 820, Mettler Toledo, Giessen Germany). 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 (20 ml/min) nitrogen gas.

2.2.4. Powder X-ray Diffractometery:

Powder X-ray diffraction patterns were measured using a Guinier step scan diffractometer (G600, Huber Diffraktionstechnik, Rimsting, Germany) with monochromatic CuKα1 radiation (λ = 1.54056 Å).

2.2.5. Scanning Electron Microscopy

The surface morphology of raw materials 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).

5.2.3. Determination of Drug Release

The dissolution of ibuprofen was tested using a dissolution model according to Stricker (Sartorius AG, Göttingen, Germany). The dissolution vessel, containing 100 ml MES-buffer (pH 5, 37 °C), was rotating at 1.2 rpm to simulate a gastrointestinal motility. A weighed quantity of ibuprofen (3 mg), or a sample of the product after removing the free ibuprofen by washing with n-hexane, equivalent to 3 mg ibuprofen, was added to the vessel. Samples of 4 ml were taken from the dissolution fluid after 5, 10, 15, 30, 45, 60 and 75 minutes, 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 evaluated according to Weibull [10].

II RESULTS AND DISCUSSION

1. Determination of Drug Content

The HPLC determination of the stoichiometric composition of the CPD products shows that the true content of drug in the complex at a pressure of 25 MPa, temperature 39.5 °C and a time of exposure of 15.5 h, was 2.9 ± 0.13 wt % (n = 3), which is comparable to 1:3 (mol:mol) ibuprofen/β-cyclodextrin ratio. The physical mixture and the complexes prepared were adjusted to the same ratio of ibuprofen/β-cyclodextrin.

2. Characterization of the Complexes

The FT-IR spectrum (Figure 2) of ibuprofen shows a characteristic band at 1730 cm^{-1} due to the carbonyl stretching. A slight shift and a reduction of the intensity of this band were seen in the CPD materials compared to the physical mixture and co-precipitation material. This band was completely absent in the freeze dried material. The spectroscopic change may indicate the interaction and the formation of intermolecular bond between the guest and the host molecule.

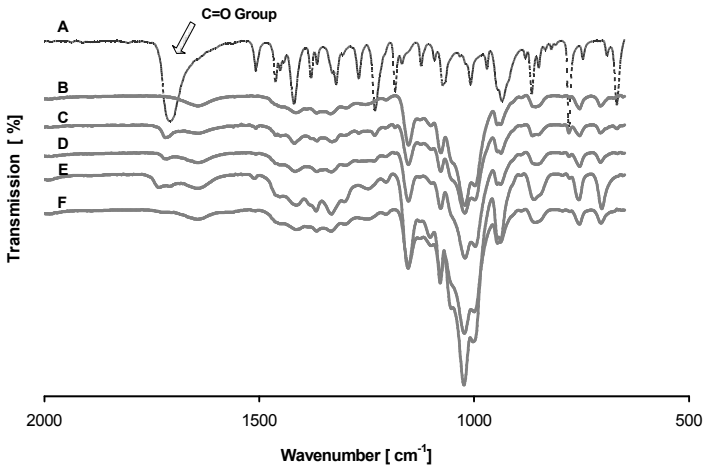

Figure 2: FT-IR spectrums of pure ibuprofen (A), β-cyclodextrin (B), ibuprofen/β-cyclodextrin physical mixture (C), CPD (D), co-precipitation (E), and freeze dried (F) products.

In the DSC a partial or complete disappearance of the typical melting peak of ibuprofen at 77 °C was observed in CPD and freeze dried product indicating the encapsulation of the drug in the β-cyclodextrin. In contrast, the co-precipitation material behaved like a physical mixture.

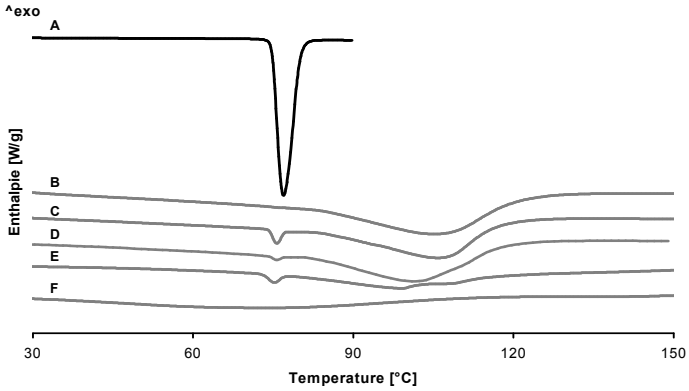

Figure 3: DSC thermograms of pure ibuprofen (A), β-cyclodextrin (B), ibuprofen/β-cyclodextrin physical mixture (C), CPD (D), co-precipitation (E), and freeze dried (F) products.

Significant reduction of the x-ray diffraction patterns of the drug (PXRD) was observed in all complex formation methods, especially in the freeze dried product. In addition a new peak was observed at 6.82°, 7.3° and 7.35° in all diffractograms of CPD, co-precipitation and freeze dried materials, respectively; this peak may suggest the formation of ibuprofen/β-cyclodextrin complexes (Figure 4), [3-5].

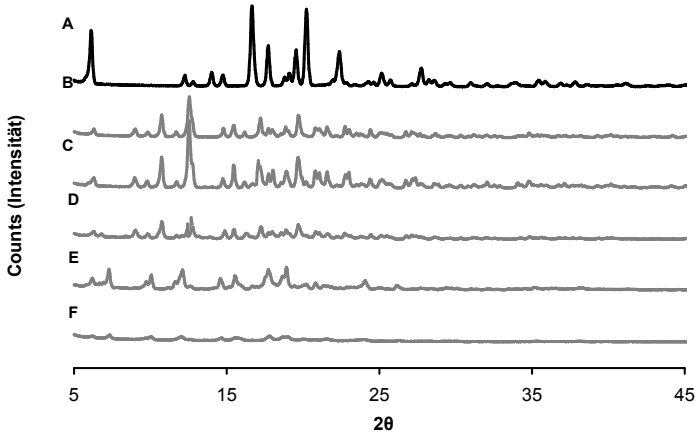

Figure 4: PXRD patterns of pure ibuprofen (A), β-cyclodextrin (B), ibuprofen/β-cyclodextrin physical mixture (C), CPD (D), co-precipitation (E), and freeze dried (F) products.

A new solid state (SEM) was indicated in the materials obtained by all complex preparation methods compared to the original morphology of ibuprofen and β-cyclodextrin and their physical mixture. This change in the particle shape may indicate the complex formation.

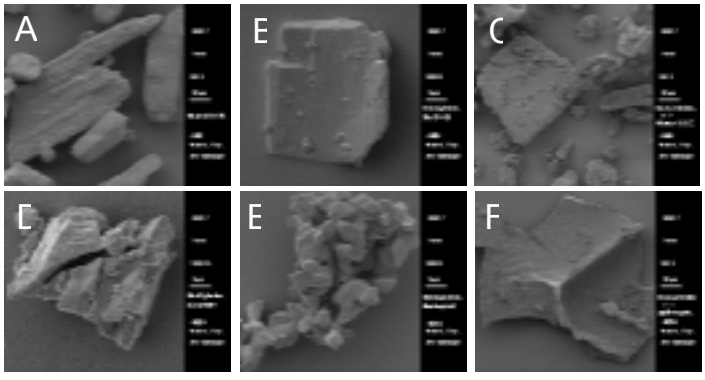

Figure 5: SEM micrograph of pure ibuprofen (A), β-cyclodextrin (B), ibuprofen/β-cyclodextrin physical mixture (C), CPD (D), co-precipitation (E), and freeze dried (F) products.

The CPD product significantly improved the dissolution of ibuprofen in MES-Puffer pH 5 compared to the pure drug and its physical mixture with β-cyclodextrin (Figure 6). The CPD material displays the highest dissolution rate compared to materials obtained by co-precipitation or freeze-drying (Table 1).

For the physical mixture, however, the dissolution rate was enhanced too. This may be due to improved wettability.

Table1: Dissolution coefficient (Kw) according to Weibull and amount of ibuprofen (%) dissolved after 75 min.

Product	Dissolution rate coefficient (K_w) (min^{-1})	Release of ibuprofen (%) after 75 min
Ibuprofen	>0.038*	59.5
Physical Mixture	0.038	78.5
CPD	0.111	97.9
Co-Precipitation	>0.038*	61.3
Freeze-Drying	0.102	90.7

*Kw > 0.038 means that 63.2% of ibuprofen was not dissolved after 75 min

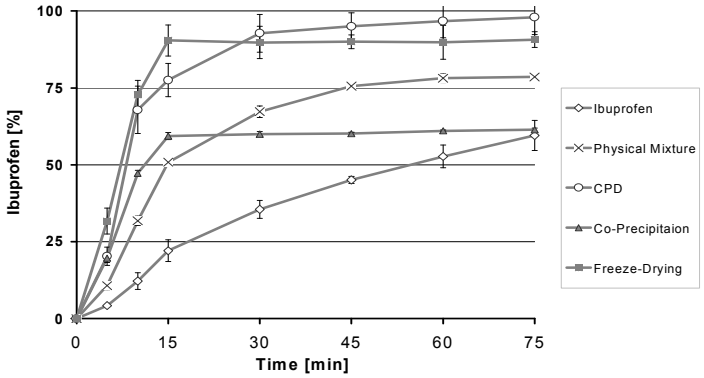

Figure 6: Dissolution profiles of ibuprofen, ibuprofen/β-cyclodextrin physical mixture, and the correspoinding ibuprofen/β-cyclodextrin complexes in MES-puffer solution at 37 °C pH 5 according to Stricker (± 95 % CI; n=3).

CONCLUSION

This study presents the Controlled Particle Deposition (CPD) as well suitable method to load a model drug (ibuprofen) in a porous carrier (β-cyclodextrin). This was achieved in a single step process using $scCO_2$ without the use of any organic or toxic solvents as required in the conventional method. The products obtained by the different preparation methods clearly indicate the influence of the complex formation method on the solid state and on their dissolution behavior. The CPD Products showed improved drug dissolution compared to the pure drug and materials obtained by co-precipitation or freeze-drying, proving the superiority of the CPD.

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REFERNECES:

[1] MERISKO-LIVERSIDGE, E., Abstract of the Conference Particles (Orlando/Florida, USA), **2002**, p. 20
[2] HORTER, D., DRESMAN, J. B., Adv. Drug Delivery Rev., Vol. 46, **2001**, p. 75
[3] FOERMMING, K-H., SZEJTLI, J., Cyclodextrins in Pharmacy, Vol. 5, **1994**, p. 1
[4] LOFTSSON, T., BREWESTER, M. E., J. Pharm. Sci., Vol. 85, **1996**, p. 1017
[5] HEDEGES, A. A., Chem. Rev., Vol. 98, **1998**, p. 2035
[6] VAN HEES, T., PIEL, G., EVRAD, B., OTTE, L., THUNUS, L., DELATTRE, L., Pharm. Res., Vol. 16, **1999**, p. 1864
[7] CHAROENCHAITRAKOOL, M., DEHGHANI, F., FOSTER, N, R., Iner. J. Pharm., Vol. 239, **2002**, p. 103
[8] HUSSEIN, Kh., TUERK. M., WAHL, M. A., 9th Meeting of Supercritical Fluids, (Trieste, Italy), **2004**
[9] KUROZUMI, M., NAMBU, N., NAGAI, T., Chem. Pharm. Bull., Vol. 23, **1975**, p. 3062
[10] HEINRICH, J., CHALABALA, m., RAK, J., Acta Pharm. Technol., Vol. 32, **1986**, p. 94