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Application of Supercritical Carbon Dioxide for the Preparation of Drug-Cyclodextrin Inclusion Compounds

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Abstract

Inclusion complexes of drugs into cyclodextrins (CDs) can be obtained at the solid state by means of supercritical dioxide ($SCCO_2$). A successful inclusion with a yield >98.5% has been achieved with piroxicam and β-CD. The temperature and the time of exposure to $SCCO_2$ have a significant effect on the inclusion yield while the pressure has a negative effect. However, there is a strong interaction between temperature and pressure and this interaction has a positive influence. The molar ratio piroxicam-β-CD and the addition of ternary alkaline agents were also found to be significant factors. The dissolution rate of the complexes formed using $SCCO_2$ was found to be significantly higher than that of the physical mixture. Inclusion complexes have also been obtained with miconazole treating mixtures of miconazole, CDs and citric acid by $SCCO_2$. This new technique of inclusion of poorly soluble drugs into CDs allows the preparation of solid complexes without using organic solvents and thus without residues.

Introduction

In a previous study [1], we investigated the feasibility of preparing a piroxicam-β-CD complex using $SCCO_2$. More recently, Charoenchaitrakool *et al.* [2] prepared ibuprofen-methyl-β-CD complexes by passing ibuprofen-laden CO_2 through a methyl-β-CD packed bed. In this study, we go deeper into the experimental conditions of preparing piroxicam-β-CD complexes using $SCCO_2$ and another drug, miconazole whose aqueous solubility is very poor, is chosen as a model substance to demonstrate that a supercritical fluid process can be an efficient method to prepare inclusion complexes of drugs into CDs at the solid state.

Experimental

Materials

Piroxicam (99.5%, E.P.), miconazole (99.7%, E.P.) and miconazole nitrate (99.2%, E.P.) were used as model drugs. Carbon dioxide (Air liquide, 99.998%, N48 quality) was used as the solvent. β-CD (E.P., 13.74% of water) was purchased from CNI (Neuilly-sur-Seine, France). HP-β-CD was kindly donated by ROQUETTE, France while γ-CD and HP-γ-CD were kindly donated by Wacker-Chemie GmbH, Germany. Trometamol (E.P.), L-lysine (Fluka) were used as the ternary alkaline compounds whereas citric acid anhydrous (E.P.) was used as the ternary acidic compound. Acetonitrile was of HPLC grade and all other reagents and solvents were of analytical grade.

Equipment for preparing the inclusion complexes

Inclusion experiments with $SCCO_2$ were performed in a SUPREX SF Extractor Autoprep 44 (Pittsburgh, PA, USA) using the same technique previously described [1]. A schematic diagram of the apparatus for complex formation using $SCCO_2$ is illustrated in Figure 1.

Preparation of complexes using $SCCO_2$

A physical mixture of piroxicam-β-CD 1 : 2.5 (mol-mol) was mainly used for the first experiments because this molar ratio was already described in previous studies [3, 4]. An experimental design 2×3^2 was used to investigate the influence of temperature, pressure and time on the inclusion yield of piroxicam at 3 levels of temperature (125–137 and 150 °C), 3 levels of pressure (15–30 and 45 MPa) and 2 different contact times (60 and 180 min).

The kinetics of the complex formation in function of temperature, the influence of different molar ratios from 1 : 0.5 to 1 : 2.5 and the effect of the addition of ternary alkaline compounds were also studied.

Characterization of the complexes

DSC thermograms were obtained using a Mettler TC 11 TA Processor DSC apparatus between 30 °C and 230 °C at a heating rate of 10 °C/min under a nitrogen gas stream.

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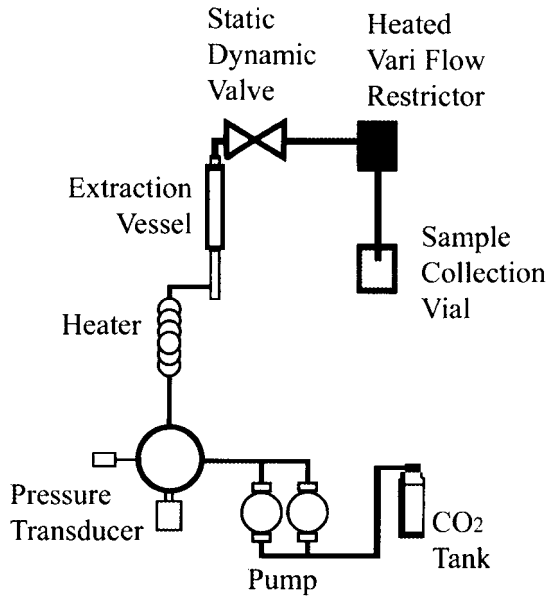

Figure 1. Schematic diagram of the apparatus for preparing the inclusion complexes.

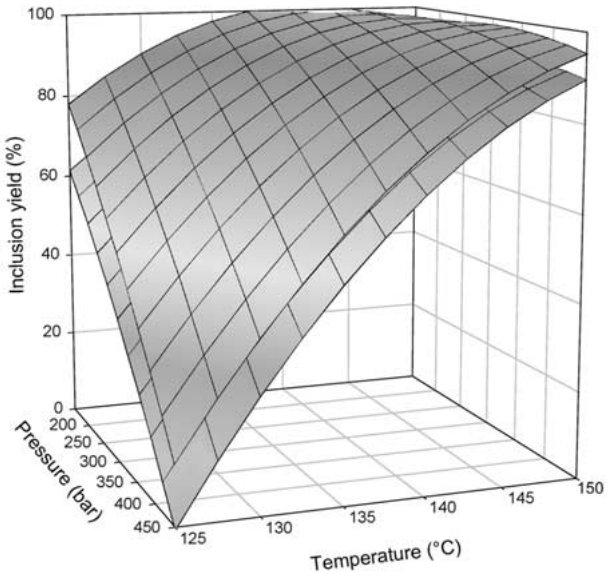

Figure 2. Inclusion yield (%) of piroxicam into β-CD in function of temperature, pressure and contact time in $SCCO_2$ (upper leaf: 180 min; lower leaf: 60 min).

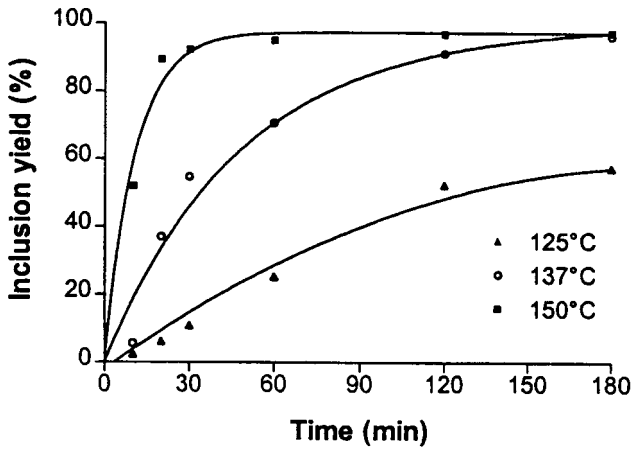

Figure 3. Kinetics of the complex formation by $SCCO_2$ in function of temperature at a constant pressure of 30 MPa.

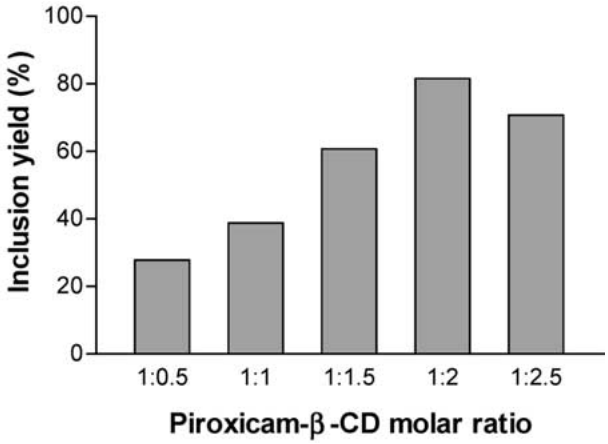

Figure 4. Inclusion yield (%) of piroxicam into β-CD in function of the piroxicam-β-CD molar ratio (137 °C, 30 MPa, 60 min in $SCCO_2$).

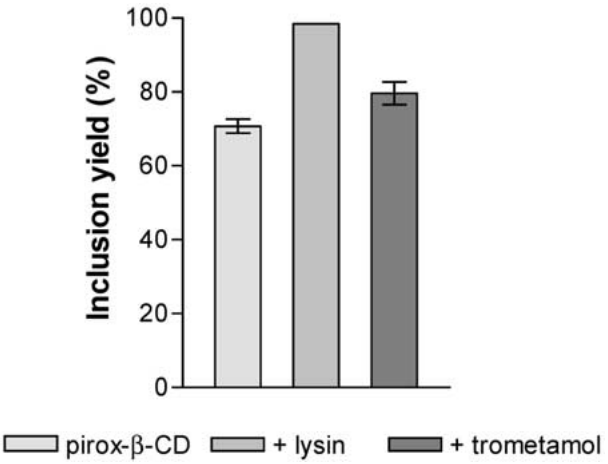

Figure 5. Inclusion yield (%)of piroxicam into β-CD in function of the addition of a ternary alkaline compound (137 °C, 30 MPa, 60 min in $SCCO_2$).

The determination of the free/complexed drug ratio was performed using a new method based on the differential solubility of the drug-CD complexes in water-acetonitrile or in anhydrous acetonitrile [5].

Dissolution kinetics studies

Intrinsic dissolution rate studies were performed for unprocessed piroxicam, its physical mixture with β-CD and different complexes formed by $SCCO_2$ according to a method described by Amighi *et al.* [6]. The tablet with one face in contact with the dissolution medium was immersed in vessels containing 500 mL of media at pH 1.2 or at pH 6.8. The determinations were conducted at a rotational speed of 50 rpm using the EP paddle method and at a constant temperature of 37 °C. Aliquots were withdrawn every 2 min and passed through a 0.45 μm filter. The amounts of dissolved piroxicam in the withdrawn samples were determined by measuring the absorbance at $\lambda = 334$ nm or at $\lambda = 354$ nm depending on the pH of the medium using UV spectrophotometry (HITACHI U-3000).

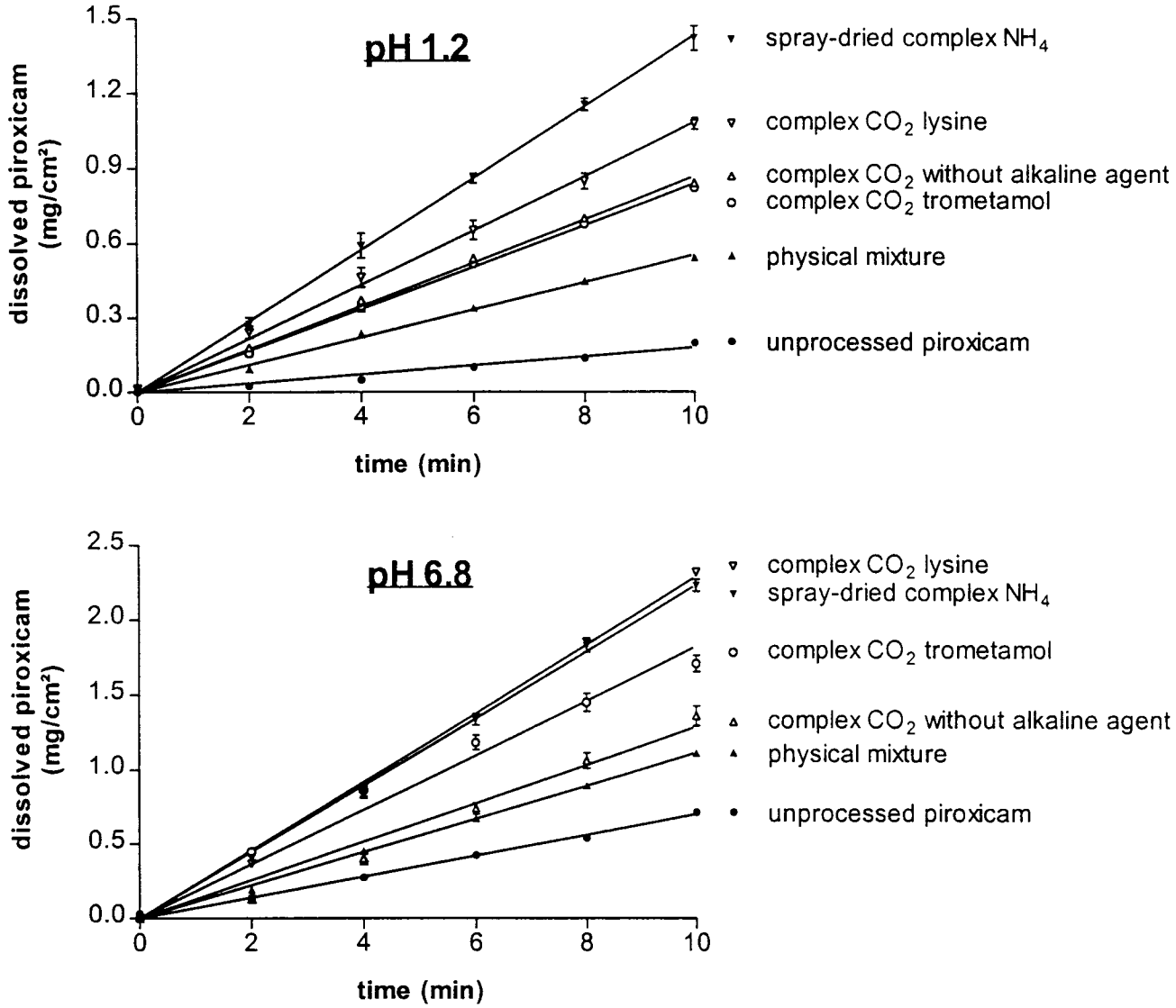

Figure 6. Intrinsic dissolution rate profiles at pH 1.2 (above) and at pH 6.8 (below) for unprocessed piroxicam, its physical mixture with β-CD (1 : 2.5 molar ratio) and different complexes formed by $SCCO_2$ or spray-drying (1 : 2.5 molar ratio).

Results and discussion

The influence of temperature, pressure and contact time in $SCCO_2$ on the inclusion yield (%) of piroxicam into β-CD is illustrated in Figure 2. As shown in this figure, there is practically no inclusion at 125 °C and 45 MPa; at 125 °C and at 30 MPa, the inclusion yield is 25.3% and 57.5% after 60 and 180 min, respectively. The maximum inclusion yield (97.1%) is obtained after 180 min at 150 °C and at 30 MPa. The temperature and the contact time have a positive influence on the inclusion while pressure has a negative influence. However, there is a significant interaction between the temperature and the pressure which has a positive influence. A quadratic effect of the temperature which has a significantly negative influence was also found and this effect is responsible for the convexity of the leafs. The other factors, i.e. the quadratic effect of the pressure and the interactions of temperature or pressure with the contact time are not significant.

As illustrated in Figure 3, increasing the temperature at a constant pressure of 30 MPa resulted in a higher included piroxicam content in the complex. At 125 °C, the inclusion percentage was 57.5% after 180 min while at 150 °C the inclusion was 51.9% after 10 min and reached a maximum of 97.1% after 120 min. A quadratic relationship between included piroxicam content in the complex was observed at 125 °C and 137 °C while an exponential relationship had to be used to depict the kinetics at 150 °C.

The effect of the piroxicam-β-CD molar ratio was investigated between 1 : 0.5 and 1 : 2.5. As shown in Figure 4, the highest inclusion yield was obtained with a 1 : 2 molar ratio and from 0.5 to 2.0 the inclusion yield increased steadily and then decreased when the molar ratio was higher than 1 : 2.

As an ammonium hydroxide solution is added for the preparation of a spray-dried inclusion complex, the influence of the addition of a ternary alkaline compound was also studied. As supercritical ammoniac is extremely corrosive for the extractor, two other alkaline agents, L-lysine and trometamol in a molar ratio 1 : 1 with piroxicam, were tested.

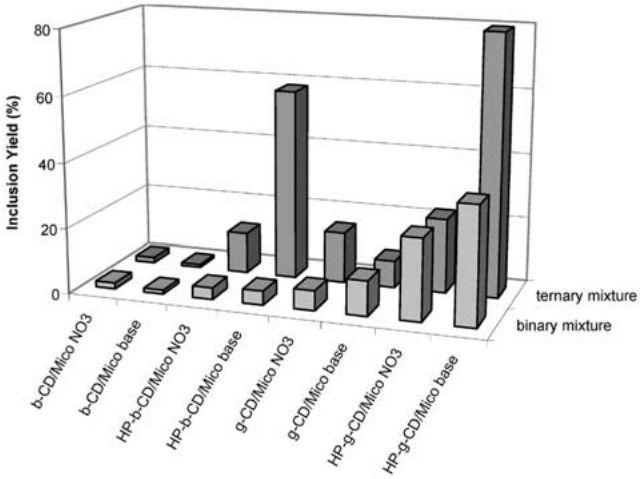

Figure 7. Influence of the type of CD, the type of miconazole and the addition of a ternary acidic agent on the inclusion yield using $SCCO_2$.

As is illustrated in Figure 5, the inclusion yield was found to be significantly higher when a ternary alkaline substance was added and the best results were obtained with L-lysine.

Figure 6 shows the results of dissolution tests at pH 1.2 and at pH 6.8. As piroxicam is poorly soluble in an acidic medium, the addition of β-CD has a positive influence since both the physical mixture and the complex produced with $SCCO_2$ exhibited higher dissolution rates than that of the unprocessed piroxicam. The addition of a ternary alkaline compound increases the dissolution rate and results similar to a reference spray-dried complex were obtained treating a mixture of piroxicam-L-lysine-β-CD 1 : 1 : 2.5 (mol/mol/mol) during 60 min in $SCCO_2$ at 137 °C and 30 Mpa.

Figure 7 shows the inclusion yield obtained for miconazole with binary and ternary compounds using $SCCO_2$ at 30 MPa and at 125 °C during 60 min.

Inclusion yields of miconazole and miconazole nitrate into β-CD are practically nil. There is an increase of the inclusion percentage using HP-β-CD, γ-CD and particularly HP-γ-CD. This higher inclusion yield could be attributed to the larger cavity of γ-CD and HP-γ-CD in comparison with that of β-CD. It can also be noticed that the inclusion of miconazole into both γ-CD and HP-γ-CD is significantly higher when using the miconazole base than with the nitrate salt.

With ternary mixtures 1 : 1 : 1 containing HP-β-CD or HP-γ-CD and citric acid, the inclusion yield was significantly improved. The addition of citric acid to mixtures containing miconazole and CDs has a similar positive influence on the inclusion yield as the addition of ternary alkaline substances to mixtures containing piroxicam.

Conclusion

The formation of inclusion complexes with CDs is an interesting approach to improve the aqueous solubility of poorly water-soluble drugs. However, the preparation of inclusion complexes at the solid state is problematic with those drugs and there is a limited number of techniques which are applicable at the production scale. Moreover, the use of organic solvents is progressively left owing to residual solvent in the finished product. Stricter environmental protection laws and the increasing cost of recycling organic solvents have motivated pharmaceutical research to develop alternative processes using supercritical fluids in all applications that used organic solvents. Inclusion complexes of drugs into CDs can be obtained at the solid state by $SCCO_2$ processing. A successful inclusion has been achieved with piroxicam and β-CD as well as with miconazole and γ-CD or HP-γ-CD by treating physical mixtures in $SCCO_2$. This new method might be attractive since the inclusion complex is at the solid state and it is free of organic solvent. Moreover, the inert character of CO_2 would limit degradation of unstable substances.

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