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# Optimisation of Supercritical Carbon Dioxide Systems for Complexation of Naproxen : Beta-Cyclodextrin

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**Abstract**

Supercritical carbon dioxide ($scCO_2$) offers several attractive scenarios for the pharmaceutical processing as an alternative to aqueous and organic solvents. In this work naproxen, a widely used non steroidal anti-inflammatory drug with analgesic and anti-inflammatory properties, was chosen as a model drug. Its complexation with cyclodextrins improves the rate and extent of dissolution of the drug, increase its rate of absorption and may reduce the unpleasant side-effects of the drug. The interest in using this supercritical technology led us to develop an experimental unit for the use of supercritical $CO_2$ as a processing medium for the complexation of naproxen with beta cyclodextrin (CD).

## Introduction

In recent years, the use of supercritical fluids is becoming more important in the pharmaceutical field. Besides their applications in preparative or analytical chromatography of drug compounds and for extraction of pharmaceutical compounds, supercritical fluids are receiving increased attention in pharmaceutical processing, specially in reaction and particle formation processes [1] and to avoid the final steps of removing solvents at the end of the process. The interest in using this technology leads us to develop an experimental unit for the use of supercritical fluid $CO_2$ as a processing medium for the complexation of naproxen with beta cyclodextrin (CD).

For every solvent there exists a critical temperature ($T_c$) and a critical pressure ($P_c$). A substance is stated to be supercritical when its pressure and temperature are higher than its $P_c$ and $T_c$. The pressure-temperature diagram of a pure substance is shown in Figure 1.

The three lines divide the diagram into three regions: solid, liquid and gas. Along the lines, two phases are in equilibrium and the three stages of aggregation coexist at the triple point. The discontinuous transition from liquid to gas ends at the critical point ($T_c$, $P_c$). Beyond this point, a low-density gas can be compressed into a dense fluid continuously. In this region, the compressed gas is called supercritical fluid, having characteristics of both, gases and liquids, and the thermophysical properties exhibit very high rates of change with respect to temperature and pressure [3]. The supercritical fluid has a density similar to that of a liquid and behaves like a liquid solvent, but it diffuses easily like a gas since its viscosity is low.

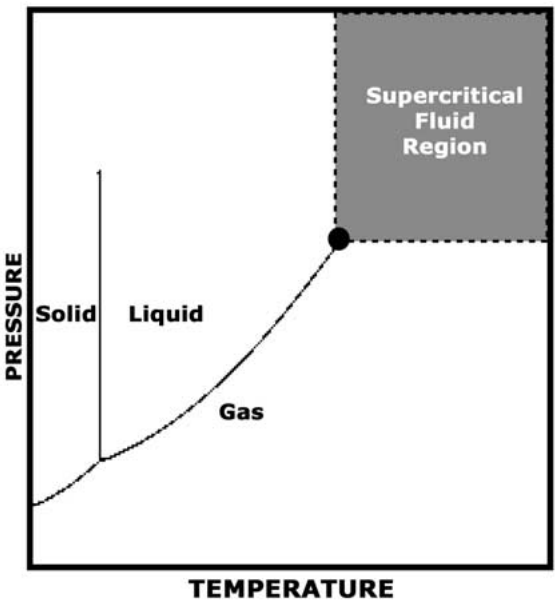


*Figure 1.* Pressure-temperature projection of the phase diagram for a pure component (adapted from [2]).

Carbon dioxide is the solvent of choice for many reasons. It is (a) inert and non-corrosive; (b) non-flammable and non-explosive; (c) abundant and inexpensive; (d) non-toxic; (e) has desirable physical properties such as low $T_c$ (31 °C) and low $P_c$ (73.8 bar), low viscosity, low surface tension, and high diffusivity. Although $CO_2$ is the most common supercritical fluid being used, it does have limitations in dissolving many active ingredients because

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it is a non-polar solvent. The solubilities of three inhibitors of anti-inflammatory activity, ketoprofen, piroxicam and nimesulide, in supercritical $CO_2$ were measured by Macnaughton *et al.* [4]. The addition of a small amount of co-solvent, also known as entrainers, to a supercritical fluid can have dramatic effects on its solvent power. Ting and coworkers [5] studied the influence of six polar co-solvents, ethyl acetate, acetone, methanol, ethanol, 1-propanol and 2-propanol, on the solubility of naproxen in supercritical $CO_2$. The solubility enhancement with these co-solvents is considerable.

In this work we chose naproxen as a model drug, a widely used non steroidal anti-inflammatory drug with analgesic and anti-inflammatory properties. Ethanol was the co-solvent elected to improve the solubility of naproxen in supercritical $CO_2$, as a processing medium for the inclusion of naproxen with $\beta$-cyclodextrin.

Complexation of naproxen with cyclodextrins improves the rate and extent of dissolution of the drug and increase its rate of absorption. Reducing the contact time between the drug and the tissue mucosa the acute local gastrointestinal irritation produced by the complex is smaller than by the drug alone. The parent cyclodextrin ($\beta$-CD) used contain 7 glucopyranose units linked by 1,4-glycosidic bonds with a cone shape. The molecular encapsulation, i.e., the complex formation with CD is probably stabilised by various intermolecular forces such as hydrophobic interaction, van der Walls forces, hydrogen bonding and others.

Microencapsulation of naproxen in polymer coating of poly(L-lactic acid) using rapid expansion of supercritical solutions was described in 1996 [6]. Two studies have looked the preparation of guest-$\beta$-CD inclusion compounds with other type of supercritical apparatus, for piroxicam [7] and for the flavours, citral, carvacrol and thymal [8].

## Experimental

### *Materials*

Cyclodextrins were obtained from Wacker-Chemie and naproxen was kindly donated by Janssen Cilag, both were used as received. Carbon dioxide was supplied by Carburos Metalicos with a purity of 99.999% (SCF grade). All other chemicals were reagent grade and used without further purification.

### *Experimental apparatus*

The high-pressure apparatus were built using 1/16″ stainless steel material from HIP and Swagelok. The systems are relatively simple but safety precautions must be taken when working at high-pressures.

As naproxen is poorly soluble in supercritical carbon dioxide, ethanol was used as co-solvent. Ting *et al.* (1993) [5] reported the solubility of naproxen in supercritical $CO_2$ by the addition of co-solvents, such as ethanol. However no similar data was found in literature for cyclodextrins. Preliminary solubility measurements in supercritical carbon dioxide at 65 °C and at pressures up to 270 bar were undertaken on the different cyclodextrins ($\alpha$-, $\beta$-, $\gamma$-, Hydroxypropyl-$\beta$- and Dimethyl-$\beta$-CD). A small amount of each cyclodextrin was placed in a 10 mL visual stainless steel cell with two aligned sapphires which allow full observation of the inside. Visually no perceptible amount of cyclodextrin was dissolved which means that at the experiment conditions the system is heterogeneous.

Three different systems were tested. The first one consisted in a continuous system and the two others in batch mode, the second in a 140 mL cell and the third in a 33 mL visual cell.

*Test 1*

A mixture of $CO_2$ and ethanol (4%) was previously prepared in a stainless steel cylinder. Naproxen was introduced in a $\frac{1}{4}''$ high-pressure tube, which was connected to a high-pressure tubular cell charged with the cyclodextrins mixed with glass spheres. In the proportion of 1 : 2 (115 mg of naproxen and 1136 mg of beta-cyclodextrin). A thermostated oven was used (65 °C). The mixture of $CO_2$ with ethanol in the cylinder was pumped into the system by means of a liquid pump up to the desired pressure (125 bar). When the experiment pressure was reached the back-pressure regulator controls the flow in order to maintain the pressure constant in the continuous process. All the naproxen was dissolved and forced to pass through the cyclodextrins. At the end fresh-high pressure $CO_2$ was used to clean the naproxen presumably not included. A schematic diagram of the apparatus of test 1 is shown in Figure 2.

*Test 2*

As the contact time between the naproxen and the cyclodextrins was very short in Test 1, batch experiments were planned. The system is similar but a 140 ml high-pressure cell was used. The cell was charged with a 1 : 2 mixture of naproxen and beta-cyclodextrin (115 mg of naproxen and 1136 mg of beta-cyclodextrin). The cell was immersed in a thermostated paraffin bath (62 °C) and was internally stirred with a Teflon magnetic bar, which is an efficient stirring device. The mixture in the cylinder was pumped into the system by means of a liquid pump up to the desired pressure (160 bar). The naproxen + cyclodextrin mixture were 43 hours in contact with the supercritical carbon dioxide + 2.5% ethanol mixture. At the end of the experiment, the system was slowly vented in a continuous mode. The powder obtained was washed with fresh high-pressure $CO_2$ to remove the ethanol before depressurising. In Figure 3 a schematic diagram of the system is represented.

*Test 3*

In this experiment two visual cells were used. The first one (10 mL) was charged with ethanol and the other (33 mL) with a mixture of naproxen and cyclodextrin. The idea was to solubilise all the ethanol and then transferring the solution

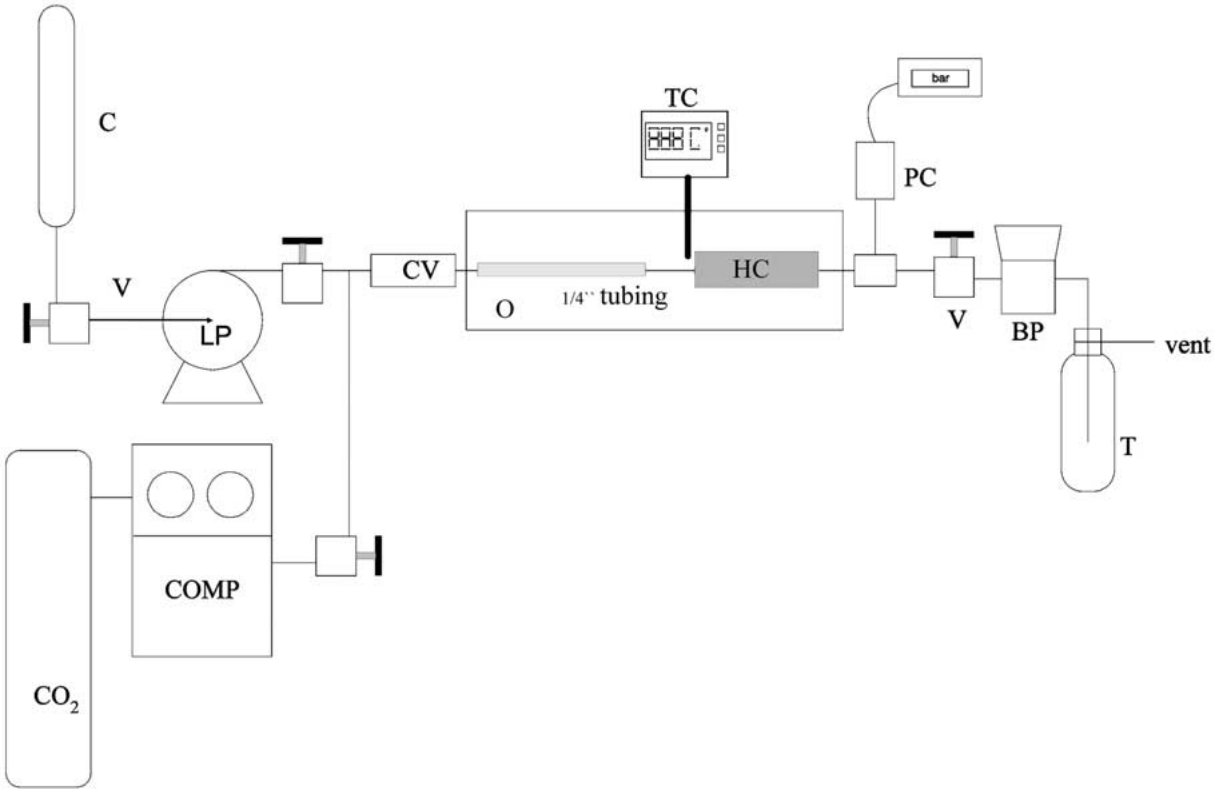


*Figure 2.* Schematic diagram of the apparatus of test 1. COMP – high-pressure compressor; C – gas cylinder; V – valves; LP – liquid pump; CV – check-valve; HC – high-pressure tubular cell; O – thermostated oven; PC – pressure transducer; BP – back-pressure regulator; T – cold trap, TC – temperature controller.

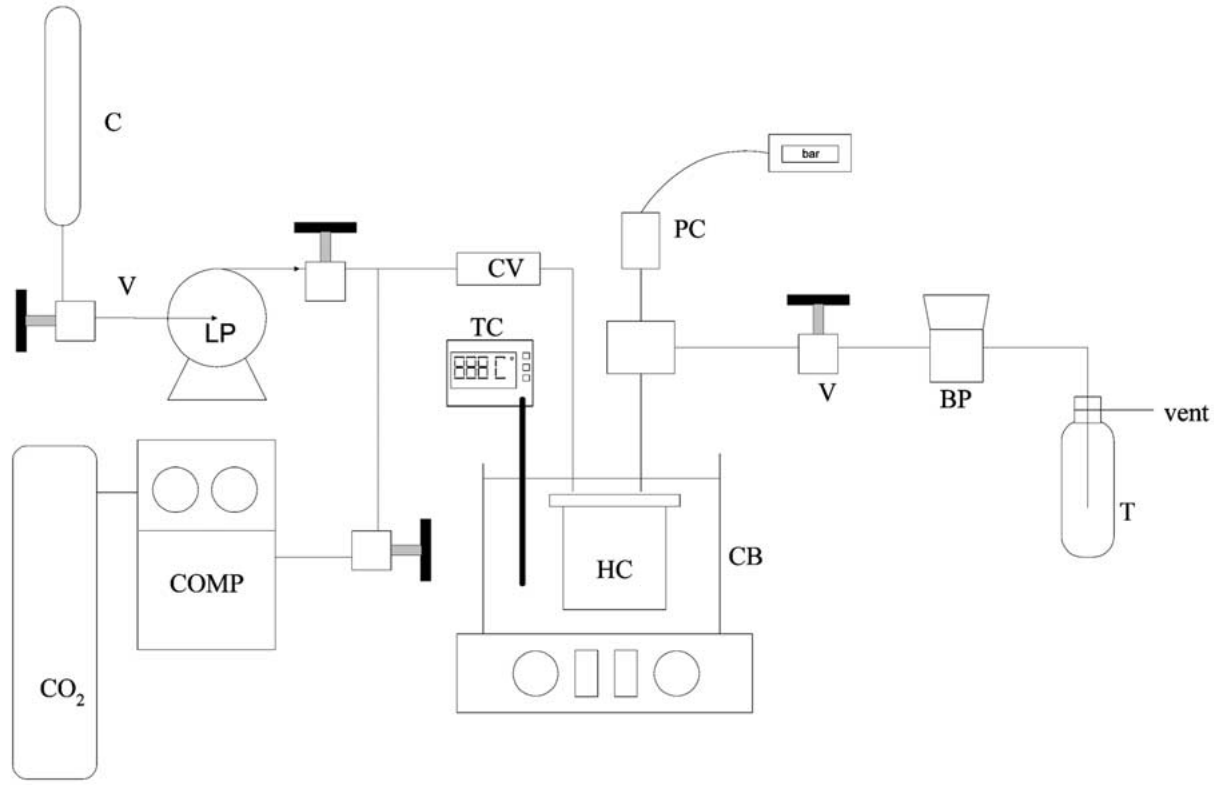


*Figure 3.* Schematic diagram of the apparatus of test 2. COMP – high-pressure compressor; C – gas cylinder; V – valves; LP – liquid pump; CV – check-valve; HC – high-pressure cell; CB – thermostated paraffin bath; PC – pressure transducer; BP – back-pressure regulator; T – trap, TC – temperature controller.

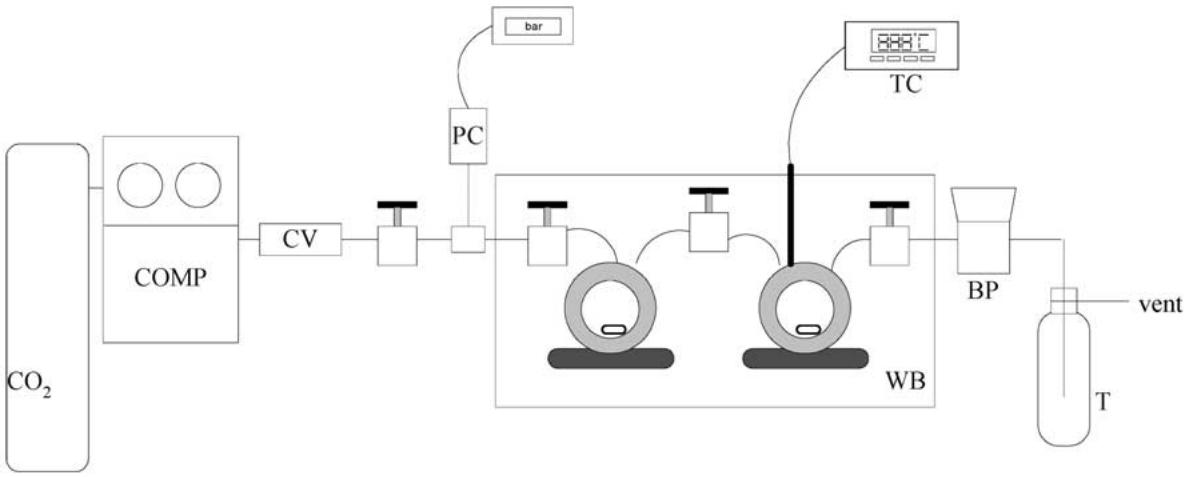


*Figure 4.* Schematic diagram of the experimental apparatus in test 3. COMP – high-pressure compressor; C – $CO_2$ cylinder; V – valves; CV – check-valve; PC – pressure transducer; TC – temperature controller; VC – visual high-pressure cell; WB – thermostated water bath; BP – back-pressure regulator; T – cold trap.

to the other cell by adding $CO_2$. When pumping into the system the mixture from the cylinder as in test 1 and 2 the homogeneity of the mixture may not be assured. The cell was immersed in a thermostated water bath (50 °C) and was internally stirred with a Teflon magnetic bar, which is an efficient stirring device. The system was allowed to stir for 24 hours at 234 bar. At the end of the experiment, the system was slowly vented in a continuous mode with fresh high-pressure $CO_2$.

*Thermal analysis*

Differential scanning calorimetry, between 30 °C and 270 °C, was performed by a Mettler TA4000 apparatus equipped with a DSC 25 cell.

*Ultraviolet absorption spectroscopy*

The UV spectra were carried out with a Hitachi U-200 spectrophotometer between 230 and 380 nm.

## Results and discussion

The results of the solubility measurements showed that all cyclodextrins tested are insoluble in pure supercritical $CO_2$ at the conditions of the experiments, 40–65 °C and at pressures up to 270 bar.

At the end of test 1, the naproxen was totally dissolved from the $\frac{1}{4}''$ high-pressure tube confirming its solubility on the supercritical mixture of $scCO_2$ and ethanol. The product obtained from the reactor was analysed by DSC which suggested inclusion complex formation with cyclodextrins. The DSC thermogram of Test 1 reactor at the end of the experiment is shown in Figure 5.

The melting peak (156 °C) of the drug was absent and showed the endotherm due to the cyclodextrins dehydration. However, the UV spectra presents a very slightly absorption spectra characteristic from naproxen which indicates that a small portion has been encapsulated.

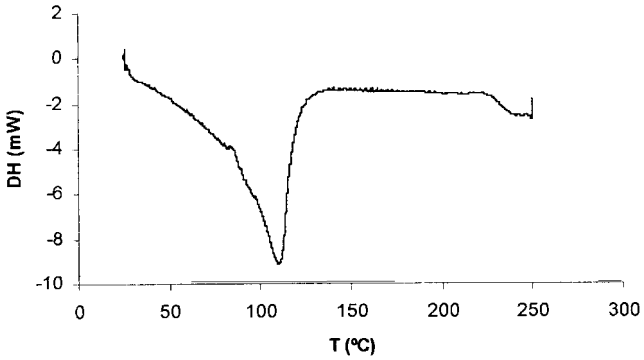


*Figure 5.* The DSC thermogram of Test 1 reactor at the end of the experiment.

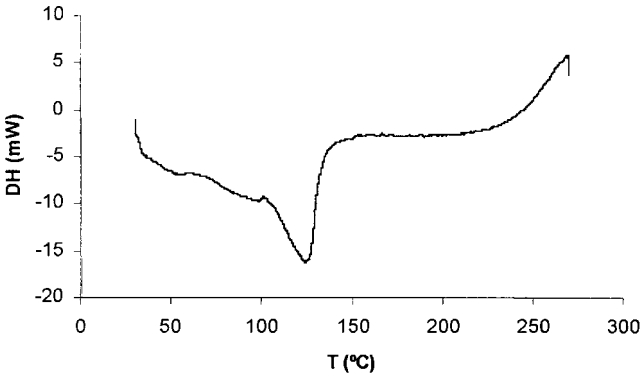


*Figure 6.* The DSC thermogram of the powder collected from the Test 2 final trap at the end of the experiment.

Test 2 proved to be more efficient for complexation since DSC thermogram from the powder collected from the trap (Figure 6) evidences loss of the endothermic peak of naproxen. UV spectroscopic method confirmed this latest finding because spectra of the drug was displayed. On the contrary, in the powder collected from the cell naproxen was not present as UV absorption spectra demonstrated.

The DSC curve of the product obtained from the test 3 experiment is shown in Figure 7. The thermogram reflected

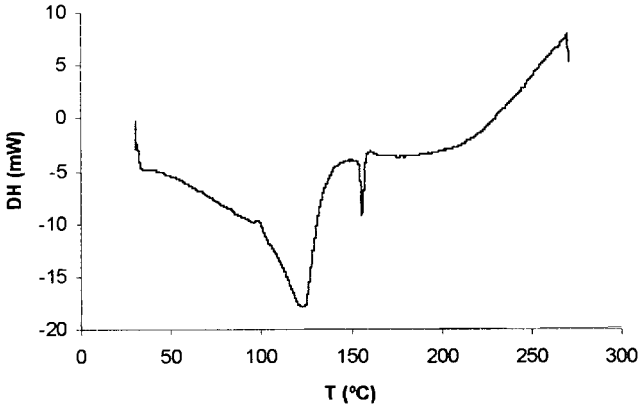


*Figure 7.* The DSC thermogram of the powder collected from the Test 3 cell at the end of the experiment.

that this supercritical unit constructed does not give complete encapsulation of naproxen. The UV spectra confirmed the partial inclusion complex formation. The naproxen concentration determined in the sample at $\lambda$ = 271 nm should give a more intense DSC melting peak if the naproxen was totally free in the powder collected.

Further work has to be done in the optimisation of this process, specially the study of the effect of the co-solvent. If the naproxen, which is soluble in the $CO_2$ + ethanol mixture is included in the cyclodextrin, what are the conditions to be extracted again? One way would be to find the correct conditions to depressurise the system by changing drastically the experiment conditions so the constant equilibrium inside the cyclodextrin structure would be enough to hold the naproxen during decompression. An optimum balance between the affinity of naproxen to the $CO_2$ with the help of the co-solvent and the equilibrium constant of its encapsulation in the cyclodextrin must be found.

In conclusion, these experiments showed that supercritical $CO_2$ with ethanol as a co-solvent could be an interesting production method for naproxen-CD complexes.

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