Inclusion complex formation of salicylic acid in triacetyl-b-cyclodextrins in supercritical carbon dioxide

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The aim of this study was to test the feasibility of using supercritical carbon dioxide to prepare salicylic acid/triacetyl-β-cyclodextrins inclusion complexes. These acetylated cyclodextrins exhibit high solubility in $scCO_2$. Completely homogeneous solutions of triacetyl-β-cyclodextrin + salicylic acid (1:1 ratio)+CO_2 were obtained between 313.15 and 333.15 K, at pressures up to 30MPa. Samples were obtained by rapid depressurisation and were analysed by differential scanning calorimetry and ultraviolet absorption spectroscopy, showing evidence of inclusion complexation.

INTRODUCTION

Supercritical carbon dioxide is a very attractive medium for pharmaceutical processing as an alternative to aqueous and organic solvents. Many drug formulations use cyclodextrins since its lipophilic cavity provides a microenvironment where the drug molecule can enter and form an inclusion complex. The complexation of a drug into cyclodextrins could reduce unpleasant side effects of the drug by improving the rate and extent of dissolution of the drug and increasing its rate of absorption. In our previous work we were able to obtain partial inclusion complexation of naproxen, a non-steroidal anti-inflammatory drug, into β-cyclodextrins. [1,2]
Although β-cyclodextrins were found to be insoluble in $scCO_2$, [1] very recently Potluri et al.[3] showed that per-acetylated α-, β- and γ-cyclodextrins exhibit melting point reduction and high solubility in dense carbon dioxide, since the acyl group of the acetylated cyclodextrins are accessible to acid:base Lewis interactions.
Salicylic acid is a drug with keratolytic properties being usually applied topically in concentrations between 2 and 20%(w/w) for the treatment of hyperkeratotic and scaling skin conditions such as dandruff and seborrhoeic dermatitis, psoriasis and acne. The solubility of salicylic acid in supercritical carbon dioxide was measured by Ke et al.[4]
The complexation of salicylic acid with triacetyl-β-cyclodextrin has the potential to modify the release rate of the drug from the complex and to decrease the local irritation. The high solubility of triacetyl-β-cyclodextrins led us to investigate the inclusion complexes formation in $scCO_2$.

MATERIALS AND METHODS

Materials

Triacetyl-β-cyclodextrins (CAVASOL W7 TA) were obtained from Wacker-Chemie GmbH, with an average molecular weight ~2018 and an average degree of substitution per anhydroglucose unit of 2.9-3.0, which corresponds to ~20.3-21.0 of acetyl substituents per macrocycle. The salicylic acid (2-hydroxybenzoic acid) was purchased to Rhodia. Both

components were used as received. Carbon dioxide was supplied by Air Liquid, with purity better than 99.998%. All other chemicals were reagent grade and used without further purification.

Thermal analysis

Differential scanning calorimetry (DSC), between 30ºC and 300ºC, was performed by a Mettler TA4000 apparatus equipped with a DSC 25 cell. Known mass samples were heated in perforated aluminium pans. The heating rate was 10 $Kmin^{-1}$.

Ultraviolet Absorption Spectroscopy

The UV spectra were carried out with a Hitachi U-200 spectrophotometer between 200 and 360 nm in order to analyse the drug content accurately. Weighed samples were dissolved in a known amount of NaOH 0.1 M solution. The amount of salicylic acid was determined by measuring the UV absorbance at 296 nm with a pre-calibrated curve. The presence of the cyclodextrins does not interfere with the spectrophotometric assay of the drug.

Phase behaviour studies

Cloud-point measurements for the system CO_2+triacetyl-β-cyclodextrin were performed in a 33 mL variable-volume view cell between 313.15 and 333.15 K. In a typical experiment a known amount of the cyclodextrin was placed in the cell and CO_2 was added to the required pressure by means of a high-pressure compressor (New Ways of Analytics PM101). The cell is internally stirred with a magnetic *teflon* bar induced by a stir plate immersed in a water bath (±0.01K). The internal volume of the cell is changed by a *teflon* piston moved by a water driven manual compressor (HIP). The amount of CO_2 was quantified using the density of pure carbon dioxide [4], at the initial pressure and temperature conditions, assuming that changes in density due to the presence of the compound were negligible. Starting from a homogeneous phase, the volume was expanded till the separation of phases, which corresponds to a cloudy appearance. This procedure was repeated several times with good reproducibility (± 1.1 bar). Figure 1 presents the phase behaviour of triacetyl-β-cyclodextrin in carbon dioxide.

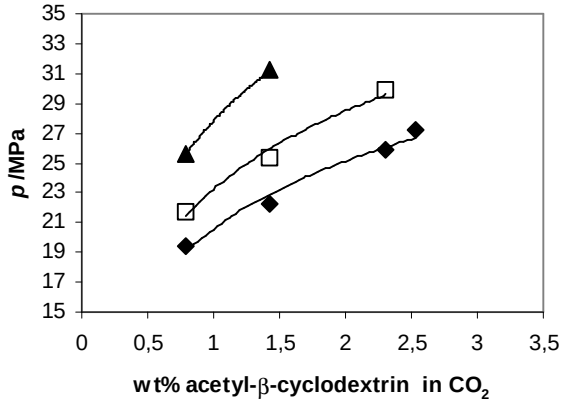

Figure 1: Solubility of triacetyl-β-cyclodextrin in carbon dioxide at 313.15 (?), 323.15 (?) and 333.15K (?).

Inclusion experiments

The inclusion experimental apparatus was described elsewhere.[1,2] Two visual stainless-steel cells (10 and 33mL) equipped with two sapphire windows were used. Experiments were carried out between 313.15 and 333.15K and at 28 MPa. At these conditions completely

homogeneous solutions of triacetyl β-cyclodextrin + salicylic acid (1:1 ratio) in CO_2 were obtained. Salicylic acid shows enough solubility in $scCO_2$ to be tested without using ethanol as co-solvent. Blends of 1:1 triacetyl-β-cyclodextrins:salicylic acid molar ratios were tested. At the end of the experiments the inclusion complexes were obtained in the cell since they precipitate upon a rapid depressurisation.

RESULTS

Samples were analysed by differential scanning calorimetry for thermal analysis and by ultraviolet absorption spectroscopy for drug content. Figure 2 shows DSC data.
Thermal analysis of salicylic acid (figure 2 a) indicates its crystalline anhydrous state, with melting peak at 158-161ºC. For triacetyl-ß-cyclodextrin (figure 2b) an extended peak before 100ºC was obtained due to water loss, as well as a melting range between 185-200ºC accompanied by thermal degradation at above temperatures. The DSC curve for the physical mixture (figure 2c) consisted of three endothermic peaks: first up to 100ºC due to dehydration, second shows lower drug melting point and heat of fusion than native salicylic acid and another between 180-220ºC corresponding to the cyclodextrin melting decomposition range.

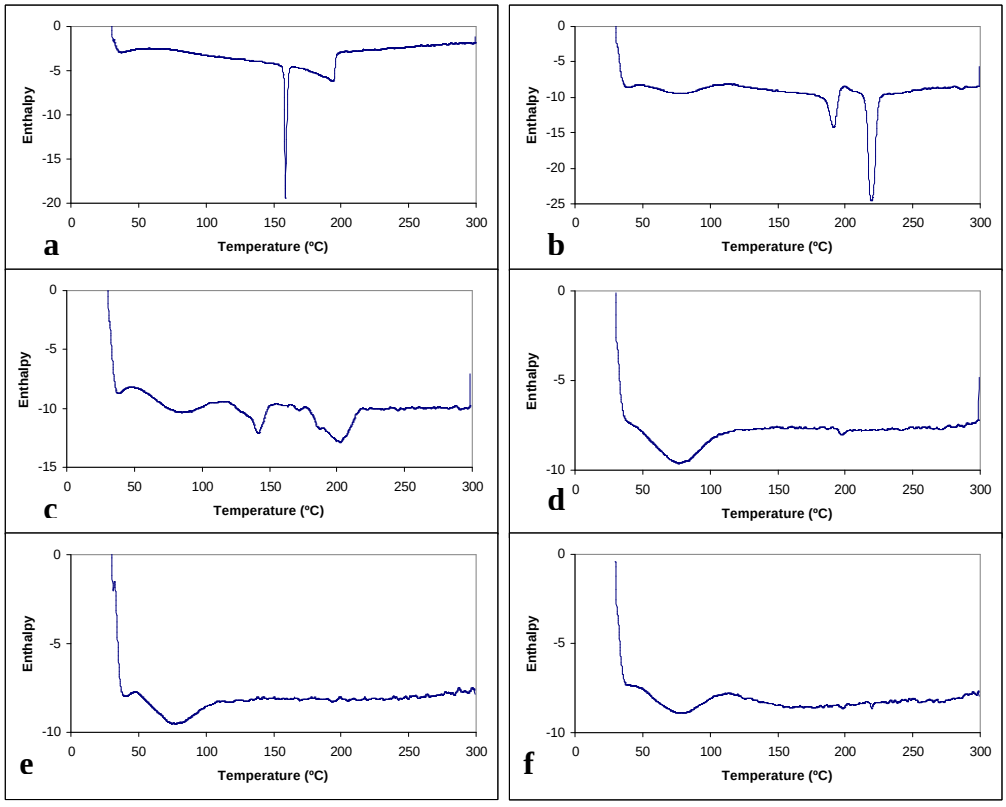

Figure 2: a) Salicylic acid pure component; b) Triacetylated beta-cyclodextrin pure component c) Salicylic acid:triacetylated-β-cyclodextrin 1:1 physical mixture d) sample obtained at 28 MPa, 323.15K, 3 hours; e) sample obtained at 28 MPa, 313.15K, 3 hours; f) sample obtained at 28 MPa, 313.15K, 6 hours.

In the DSC curves of samples obtained by the $scCO_2$ process (figure 2 d,e,f), the endothermic peak of salicylic acid disappeared, which may be attributed to the formation of inclusion

complexes. The former peak between 50ºC and 100ºC corresponds to the water loss upon heating the sample.
The UV spectra of the samples confirmed the presence of the salicylic acid, showing its characteristics absorption bands (figure 3). For the conditions tested all the UV spectra were very similar. The complexes formed in $scCO_2$ at 313.15K and 323.15 K, 28 MPa for 3 hours contained approximately 4wt% of salicylic, almost 47% of the total initial drug content.

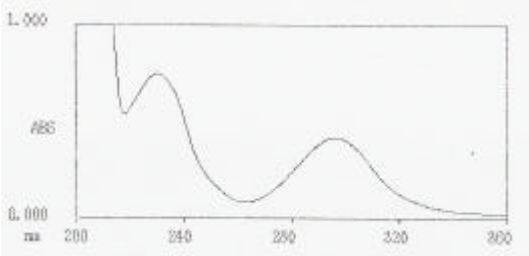

Figure 3: UV spectra of sample obtained at 28 MPa, 313.15K and 3 hours.

CONCLUSIONS

The UV and DSC analysis strongly suggest the formation of salicylic acid:triacetyl-ß-cyclodextrins inclusion complexes in supercritical carbon dioxide.
Conventional methods of complexation using these acetylated cyclodextrins are obtained in ethyl acetate or acetone solutions, leaving undesirable residues. As triacetyl-ß-cyclodextrins show high solubility in $scCO_2$, supercritical carbon dioxide could be a clean alternative medium to prepare this kind of complexes.

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REFERENCES

[1] JUNCO, S., CASIMIRO, T., RIBEIRO, N., NUNES DA PONTE, M., MARQUES, H. M. C., Journal of Inclusion Phenomena and Macrocyclic Chemistry, 44, **2002**, 69-73.
[2] JUNCO, S., CASIMIRO, T., RIBEIRO, N., NUNES DA PONTE, M., MARQUES, H. M. C., Journal of Inclusion Phenomena and Macrocyclic Chemistry, 44, **2002**, 117-121.
[3] POTLURI, V. K., HAMILTON, A. D., KARANIKAS, C.F., BANE, S. E., XU, J., BECKMAN, E. J., ENICK, R.M., Fluid Phase Equilibria, 211, **2003**, 211-217.
[4] KE, J., MAO, C., ZHONG, M., HAN, B., YAN, H., Journal of Supercritical Fluids, 9, **1996**, 82-87.
[5] ANGUS, S.; ARMSTRONG, B.; DE REUCK, K.M. - International Thermodynamic Tables of the Fluid State Carbon Dioxide 3; IUPAC, Pergamon Press, Oxford, **1976**.