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INTERACTION OF PHARMACEUTICAL HYDRATES WITH SUPERCRITICAL CO_2
Solubility, solid-state and chemical modifications

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Abstract

The aim of this work was to study the solubility in supercritical CO_2 of the hydrated phase of three model drugs, namely theophylline, carbamazepine, and diclofenac sodium, in comparison with the respective anhydrous form. Possible solid-state modifications, stemming from the interaction with supercritical CO_2, were investigated by differential scanning calorimetry, thermogravimetric analysis, hot stage microscopy, Fourier transform infrared spectroscopy and Karl–Fischer titrimetry.

It was found that all three pharmaceutical hydrates exhibited higher solubility in supercritical CO_2 than the relevant anhydrous phases.

In the case of theophylline monohydrate, the instability of the crystal phase at the experimental temperature adopted has been evidenced.

Diclofenac sodium tetrahydrate represents a peculiar case of chemical interaction with the acid supercritical fluid, mediated by crystal water.

Keywords: carbamazepine, diclofenac sodium, hydrates, pseudopolymorphism, solid-state chemistry, solubility, supercritical CO_2, theophylline

Introduction

Although the interest in pharmaceutical polymorphs can be dated back to late 60 s [1], there has been recently a huge increase of interest in solid-state chemistry [2–4] due to its large impact on the pharmaceutical development process [5].

Polymorphism is defined as the ability of a substance to exist in the solid-state in different molecular arrangements or conformations, giving rise to more than one crystalline form.

Pseudopolymorphism is also an important issue occurring when solvent molecules are incorporated in the crystal structure, usually in stoichiometric proportion. These crystalline solid adducts are therefore called solvates. Pharmaceutical solvates are generally hydrates in which the incorporated solvent is water.

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The presence of water molecules within the crystal lattice alters a number of properties, among which thermodynamic activity is probably the most important since it can strongly affect physico-chemical properties such as stability, solubility, dissolution rate, and, hence, bioavailability [6].

Concerning the solubility in water, the anhydrous form of a substance is more soluble in water than the corresponding hydrate, which separates from aqueous media at the same temperature. This is a consequence of the lower amount of free energy released by the hydrate on dissolution and on further interaction with the solvent, having already interacted with water in the solid-state [7].

With increasing scrutiny of solvent residues in pharmaceuticals, medical products, and nutraceuticals, and with stricter regulations on volatile organic compounds and ozone depleting chemical emissions, the use of supercritical fluids SCF is rapidly proliferating in these industrial sectors. This interest is well documented by the overwhelming number of scientific reports dealing with the use of SCF for the preparation of drugs or dosage forms, having peculiar characteristics [8]. Being chemically inert, non-flammable, inexpensive and environmentally clean, and possessing easily reachable critical temperature and pressure (T_c 31.1°C; P_c 7.38 MPa), carbon dioxide is presently the most used gas in this field.

The determination of the relevant solubility of a drug or an excipient in SC CO_2 represents the unavoidable first step for the development of industrial scale operations. In fact, it is necessary for driving the selection of a technique implying the use of SC CO_2 as a solvent rather than an anti-solvent. Furthermore, it has been reported that the interaction of a crystalline compound with a fluid in the supercritical state often leads to the formation of a different solid phase [9–11]. To our best knowledge, no data are presently available on the behaviour of crystalline hydrates in SC CO_2.

This work was therefore aimed at studying the solubility in SC CO_2 and possible solid-state modifications of three pharmaceutical hydrates in comparison with the corresponding anhydrates. This goal was pursued by measuring the solubility in supercritical CO_2 of three model drugs showing different physico-chemical properties (i.e. solubility in water), namely theophylline (THP, slightly soluble), carbamazepine (CRB, practically insoluble), and diclofenac sodium (DCLNa, sparingly soluble), as hydrates ($THP{\cdot}H_2O$, $CRB{\cdot}2H_2O$, and $DCLNa{\cdot}4H_2O$) or as anhydrates. Solid-state properties, before and after interaction with SC CO_2, were investigated by differential scanning calorimetry (DSC), thermogravimetric analysis (TG), hot stage microscopy (HSM), Fourier transform infrared spectroscopy (FT-IR), and Karl–Fischer titrimetry (KF).

Material and methods

Preparation of hydrates

$DCLNa{\cdot}4H_2O$ was prepared by suspending DCLNa (Lisapharma, Erba, Italy) in boiling distilled water. The hot saturated solution was then filtered and kept at room tem-

perature for 24 h. The solid phase recovered by suction filtration was air dried. The obtained crystals were polygonal flat chips.

THP·H_2O was prepared in a similar way by suspending THP (SIMS, Florence, Italy) in distilled water at 37°C. The crystals, isolated by paper filtration and air dried, were needle shaped.

CRB·$2H_2O$ was prepared according to Han *et al*. and Li *et al*. [12, 13] by suspending commercial CRB (low melting polymorph, Recordati, Milan, Italy) in water at ambient temperature for 30 h. The suspension was then filtered under vacuum and kept in air stream up to constant mass.

Solubility in SC-CO_2

The solubility in SC-CO_2 of both the anhydrous and the hydrate form of each drug was determined under dynamic conditions at low CO_2 flux according to the method previously described [9, 14]. Briefly, a saturation cell (internal volume 3 mL) was loaded with about 500 mg of each single drug mixed with glass beads (1 mm diameter) in order to allow a thorough diffusion of the fluid and placed in a thermostatic chamber at 40°C. A pump operating at constant-pressure mode imposed the pressure in a range between 10 and 35 MPa, while a micrometric expansion valve allowed a manual tuning of the flow rate, normally set approximately at 100 μL of liquid CO_2 min^{-1} (~0.1 g min^{-1}). In a typical determination, the pressure of the saturation cell was raised up to the desired value, the outlet valve being closed. Then, the outlet valve was opened in order to allow CO_2 to flow through the saturation cell. The run was stopped when 20–25 g of CO_2 had passed through the cell. The dissolved drug, conveyed by the SC CO_2 stream, was collected in a 50 mL flask containing anhydrous methanol (in the case of theophylline and diclofenac sodium) or chloroform (in the case of carbamazepine) positioned after the micrometric valve. To avoid the risk of missing portions of the solute, at the end of each measurement all valves and connection tubings were carefully washed with portion of methanol or chloroform. The total amount of drug dissolved was determined by high performance liquid chromatography (HPLC, below).

At the end of each experiment, the column content was recovered and the glass beads manually separated from the drug powder. Each measurement was performed at least in triplicate.

HPCL analysis

THP was analysed according to the method reported in USP 25 [15]. 20 μL of a THP solution in methanol were manually injected (Rheodyne, USA) in a liquid chromatographer (Pump LC-10AS ; detector UV set at 280 nm, SPD 10A, Integrator C-R6A Chromatopac, Shimadzu, Japan). The column was a μBondapak™ C_{18} 3.9×300 mm (Waters, Milford, USA). The flow rate of the mobile phase (64:35:1 water:methanol:acetic acid) was 1 mL min^{-1}.

Linearity of response was verified in the 0.004–0.4 mg mL^{-1}concentration range ($r = 0.999$).

CRB was analysed according to the method reported by Behme and Brooke [16]. The equipment was the same used for THP. The UV detector was set at 220 nm. Solutions of CRB in chloroform were vacuum dried and re-dissolved in the mobile phase (45:55 acetonitrile:water). Linearity of response was assessed in the 5.2×10^{-5}–1.02×10^{-3} mg mL^{-1} concentration range ($r = 0.990$).

DCLNa was analysed at 280 nm with the same equipment using a Licasorb® RP–8 column (5 μm, Hibar®, Merck, Darmstadt, Germany) at a flow of 0.6 mL min^{-1}. The mobile phase was a 50:50 water:acetonitrile solution adjusted to pH 3.3 with acetic acid.

FT-IR spectroscopy

FT-IR spectra were recorded by means of a 200 MicroSampling FT-IR (Jasco, Tokyo, Japan) in the 4000–400 cm^{-1} wavenumber interval. Powder samples were simply placed on a KBr disc under the objective of the microscope and directly scanned.

Thermal analysis

Differential scanning calorimetry was performed on an Indium calibrated Mettler DSC 821e (Mettler Toledo, USA) driven by STARe software (Mettler Toledo). DSC traces were recorded by placing precisely weighed quantities (3–10 mg) in a 40 μL aluminium pan sealed and pierced. Scans of both hydrated and anhydrous forms were performed under a flux of dry nitrogen (200 mL min^{-1}) between 25 and 300°C at 20 K min^{-1} for THP; between 30 and 300°C at 10 K min^{-1} for DCLNa and between 25 and 240°C at 40 K min^{-1} for CRB.

Each sample was analysed at least in triplicate. All data are expressed as mean value and standard deviation in parenthesis.

Thermogravimetric analysis (TG 50, Mettler Toledo, USA) was carried out on samples placed in 70 μL alumina pans with a pierced cover. Hydrate and anhydrous samples were heated under a flux of dry nitrogen (200 mL min^{-1}) at 20 K min^{-1} in the 25–300°C temperature range for THP, at 10 K min^{-1} between 35–180°C for DCLNa and between 25–240°C at different scanning rates (5–20 K min^{-1}) for CRB.

Hot Stage Microscopy observations were carried out with a HSF 91 apparatus (Linkam Scientific Instruments, Tadworth, U.K.) equipped with a polarising microscope (Labophot II Nikon, Tokyo, Japan) and a colour video camera (XC-003P Sony, Tokyo, Japan), supported by Image-Pro® Plus 4.0 software (Media Cybernetics, MD, USA). Samples, placed between two glass cover slides, were heated at 10 K min^{-1} from ambient temperature up to 300°C.

Water titration

The water content of DCLNa samples was determined by Karl–Fischer titrimetry. 100 mg of each sample were placed in a methanol-containing titration chamber of an automatic titrator (633 Karl–Fischer Automat, and 645 Multi-Dosimat automatic burette, Metrohm, Herisau, Switzerland) and titrated with Karl–Fischer reagent (Hydranal®-Composite5, Sigma Aldrich GmbH, Seeize, Germany).

The percentage of water in the sample was calculated as follows:

$$\%\text{water} = \frac{W \cdot \text{mL KF} \cdot 100}{sm} \quad (1)$$

where W, mg of water titrated with 1 mL of Karl-Fischer reagent; mL KF, mL of Karl–Fischer reagent used; sm, sample mass (in mg). The value of W was previously determined by calibrating the apparatus with Karl–Fischer standard sodium tartrate dihydrate (Fluka Chemika, Switzerland).

Results

Theophylline

The solubility of THP was measured at 40°C in the 10–30 MPa range. The obtained data for both the hydrated and anhydrous forms are reported in Fig. 1, as mole of drug dissolved per mole of CO_2 *vs.* the relevant pressure values.

Data of the anhydrous form are in agreement with those reported by Saldana *et al*. [17]. For both species the solubility increases linearly with pressure. At all pres-

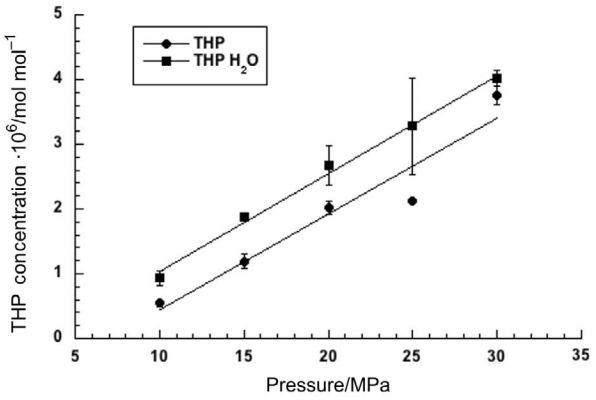

Fig. 1 Solubility in CO_2 of anhydrous (circles) and hydrate (squares) THP as a function of pressure at 40°C. The bars represent the standard deviation (n=3)

sure values the hydrate shows higher solubility with respect to the anhydrous form. Although the difference between the solubility of the two forms at each single pressure value is at the lower limit of statistical significance (P value between 0.3 and 0.05), it remains constant with increasing pressure. In fact, the straight lines obtained by linear regression of the experimental points are parallel, showing the same slope (0.15 mol mol^{-1} MPa) and differing only for the intercept value.

Powders recovered from the saturation cell after solubility measurements were analysed by DSC and TG.

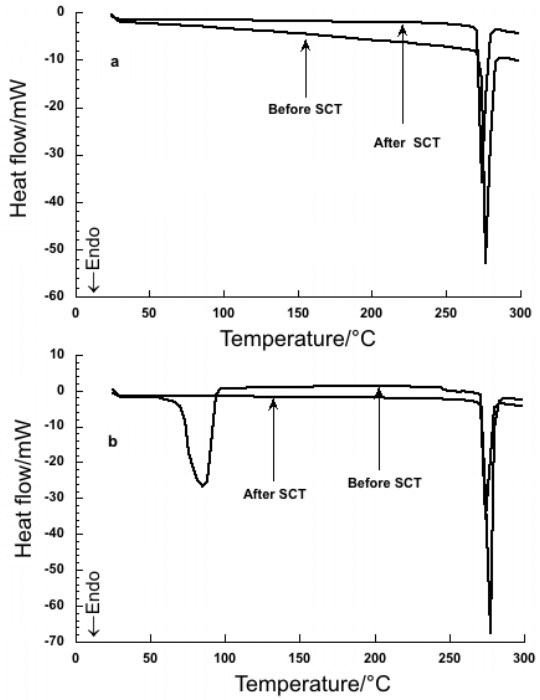

Fig. 2 DSC traces of anhydrous (panel a) and hydrate (panel b) THP before and after supercritical treatment (SCT) at 40°C and 20 MPa

As an example, Fig. 2 reports the DSC traces of THP (panel a) and THP·H_2O (panel b) before and after SC treatment at 20 MPa. In the case of the anhydrous form, the two curves are practically superimposable showing only a sharp endothermic peak at 272.7 (0.7)°C (T_m) associated with an enthalpy variation of –160.2 (0.5) J g^{-1} (ΔH_m), corresponding to the final melting of the drug, in agreement with the USP 25 that reports a melting point for THP between 270 and 274°C [15].

On the contrary, the two curves obtained before and after SC treatment of the hydrate form were different. The thermal trace of the sample before SC treatment

presented a broad endothermic peak between 60 and 100°C, likely due to water removal, followed by the final melting endotherm at 273°C: The trace of the treated sample was similar to that of the anhydrous ones. This observation suggests that THP·H_2O undergoes dehydration during the SC treatment.

Both SC treated and untreated samples showed ΔH_m values slightly lower than the anhydrous form (–151.7 and –150.2 J g^{-1}, respectively) indicating a possible lower crystallinity of the anhydrous THP obtained by dehydration [18].

TG measurements indicated for THP·H_2O a 9.09% mass loss between 40 and 80°C. The calculated value (% *w*/*w*) for the removal of one water molecule is 9.08. The sample obtained after SC treatment undergoes negligible mass loss in the same temperature interval, thus confirming that heating the sample in the saturation cell at 40°C was sufficient to effect dehydration.

Isothermal TG measurements at 40°C for 2 h lead to a mass loss of 7% within 8 min, as confirmed by HSM which showed that the needle shaped birefringent THP·H_2O crystals darkened after heating at 40°C for 10 min or after SC treatment. THP· H_2O therefore undergoes a similar dehydration pattern upon heating in dry atmosphere or under SC CO_2 stream.

These results can explain the constant difference between solubility values of anhydrate and hydrate (approximately 0.56×10^{-6} mole of theophylline per mole of CO_2) shown in Fig. 1. In fact, the values recorded for THP hydrate do not represent the solubility of this form in SC CO_2 because of its instability in the experimental conditions (40°C), but they should be considered as a mean between the solubility of the anhydrous and hydrate form, 'weighted' with respect to the relevant existence time.

Diclofenac Na

DCLNa and DCLNa·$4H_2O$ solubility measurements were carried out at 10, 20 and 30 MPa. Data obtained from these experiments are reported in Fig. 3 as a function of

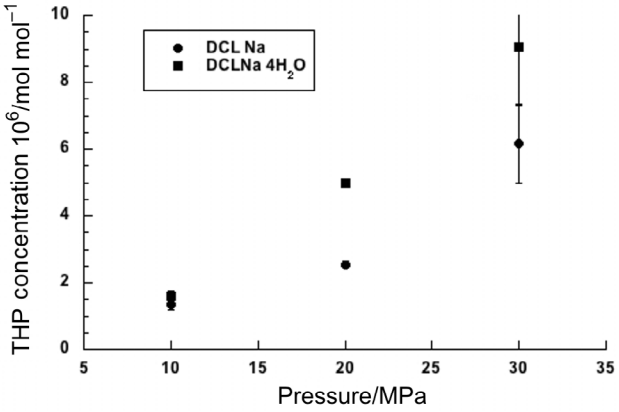

Fig. 3 Solubility in CO_2 of anhydrous (circles) and hydrate (squares) DCLNa as a function of pressure at 40°C. The bars represent the standard deviation (*n*=3)

the relevant pressure values. Once more, the solubility of the hydrate was higher than that of the anhydrate, although only at 20 MPa the difference was statistically highly significant (P = 0.002). The solubility of the hydrate form increased linearly with pressure, whereas, in the case of the anhydrate, a positive deviation from linearity was observed with pressure increase.

DCLNa·4H_2O, analysed before and after SC treatment, showed some intriguing differences that may make questionable the solubility values obtained for this compound. Attention was focused particularly on samples treated at 20 MPa since, for this pressure value, the statistical significance of the difference between solubility values of anhydrate and hydrate was maximal.

Figure 4 shows the morphological changes induced by SC treatment on DCLNa·4H_2O. While untreated DCLNa· 4H_2O (panel a) is characterized by homogeneous birefringent crystals, the SC treated specimen (panel b) is formed by dark and unhomogeneous aggregates.

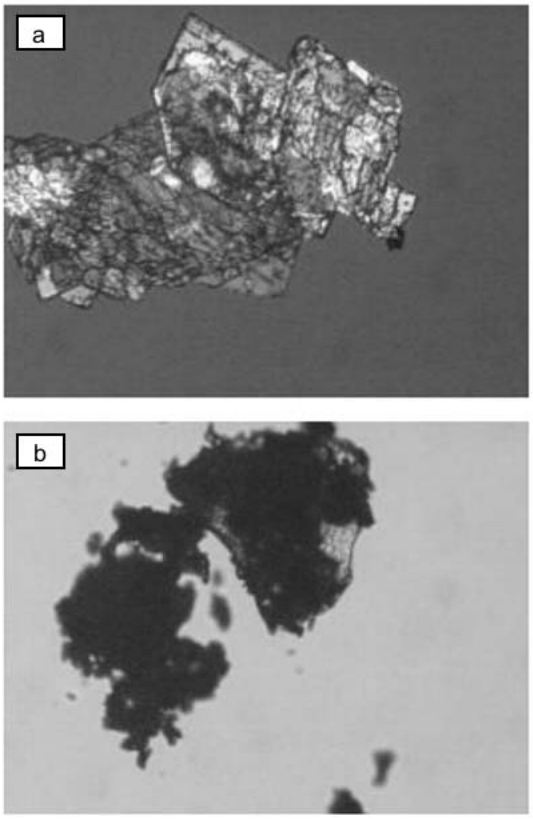

Fig. 4 Pictures taken under polarising microscope (40x) of DCLNa·4H_2O a – before or b – after supercritical treatment at 40°C and 20 MPa

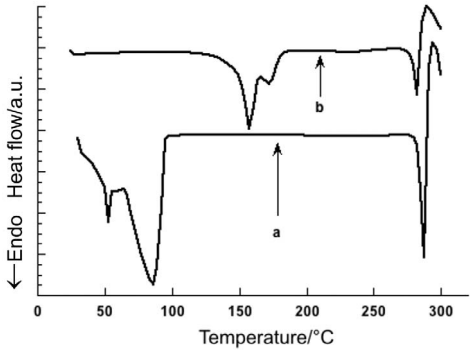

Fig. 5 DSC traces of DCLNa·4H_2O before (curve a) and after (curve b) supercritical treatment at 40°C and 20 MPa

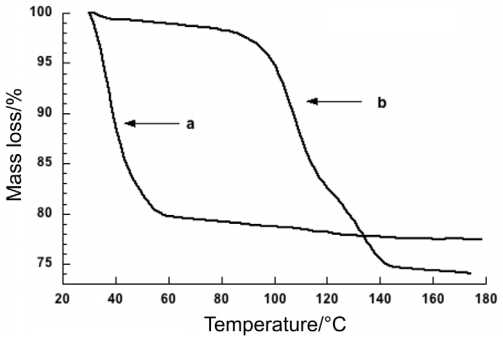

Fig. 6 TG traces of DCLNa·4H_2O before (curve a) and after (curve b) supercritical treatment at 40°C and 20 MPa

DSC and TG traces recorded before SC treatment (Figs 5, 6, curves a), in agreement with previously published results [19], showed endothermal effects between 40 and 100°C related to the elimination of 4 water molecules (measured and calculated mass loss 18.41 (1.7)% and 18.45%, respectively), followed by the melting endotherm around 286°C with decomposition.

Anhydrous DCLNa lost nearly 1% by mass in the 40–60°C interval (surface moisture) and melted with decomposition around 287°C, in agreement with Eur. Ph. [20].

DCLNa·4H_2O traces recorded after SC treatment (Figs 5 and 6, curves b) showed a 0.9% endothermal mass loss between 40 and 100°C. Surprisingly, a broad double peak was recorded at 158 and 175°C, associated with mass loss of 25.08 (1.3)% in the 90-200°C interval. Final melting with decomposition was recorded around 283°C.

HPLC analysis on this sample revealed a drug content of 80.5% *w*/*w*. It ought to underline that the HPLC method does not discriminate between dissociated or undissociated form of diclofenac, due to the acid nature of the mobile phase.

Anhydrous DCLNa after SC treatment presented a small endotherm ($\Delta H = -1.69$ J g^{-1}) at 156°C and no mass loss between 40 and 60°C (data not shown).

It is worthy to note that, curiously, the SC treated hydrate sample, re-tested after one week storage in closed vials, showed a thermal profile intermediate between that of the curves a and b of Fig. 5: both endothermal phenomena within 30–80 and 130–180°C intervals were present, the latter being nearly 70% lower than that observed in the freshly treated samples (calculated from the relevant ΔH values ratio). Furthermore, similar DSC traces were obtained by treating DCLNa·$4H_2O$ with a lower amount of SC CO_2 (10 g instead of 20).

To elucidate the nature of the endothermal phenomenon observed around 150°C, the water content of the SC treated samples was determined by KF titrimetry. A 1% *w/w* water content was found in agreement with what observed with TG in the 40–60°C interval. Thus, the endothermal mass loss recorded between 80 and 200°C could not be attributed to water removal.

The phenomenon was therefore explained by admitting that a reaction takes place between DCLNa·$4H_2O$ and CO_2 :

$$\text{DCLNa}\cdot 4H_2O + CO_2 \leftrightarrow \text{DCLH} + NaHCO_3 + 3H_2O$$

generating the free acid form of diclofenac (DCLH). Water can be either crystalline (as in the case of DCLNa·$4H_2O$) or residual moisture (as in the case of anhydrous DCLNa).

Volatile compounds (CO_2 and H_2O generated by thermal decomposition of $NaHCO_3$) represent approximately 27% by mass of the total mass of products, in agreement with TG and HPLC results.

Furthermore, upon heating the SC treated samples (DSC runs), DCLH interacts with $NaHCO_3$ shifting the reaction toward the formation of DCLNa. The broad endotherm between 140 and 160°C includes, therefore, different thermal events related to the presence of different chemical species. These events are substantially: *i*) decomposition of $NaHCO_3$ with *ii*) formation of Na_2CO_3, *iii*) reaction of Na_2CO_3 with DCLH, and *iv*) eutectic fusion of the binary DCLNa/DCLH (Fig. 7). The presence of so many different phenomena, all happening within the same limited temperature range, strongly hinders the possibility of a univocal interpretation of the thermal traces.

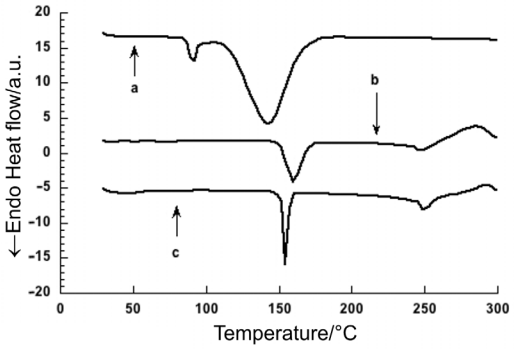

Fig. 7 DSC traces of $NaHCO_3$ (curve a), DCLH/Na_2CO_3 1:1 *w/w* mixture (curve b) and DCLNa/DCNH 1:1 *w/w* mixture (curve c)

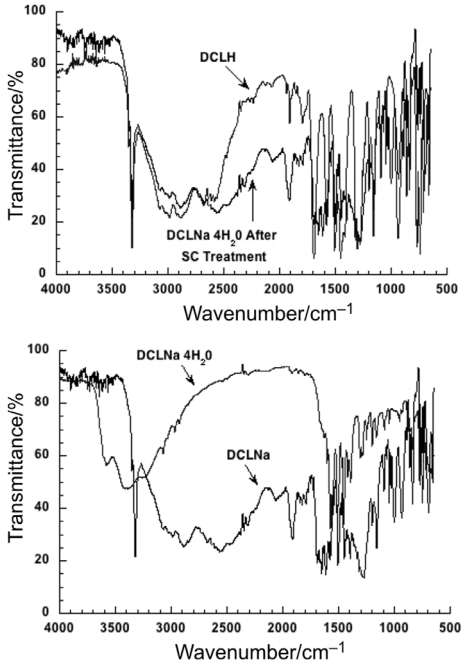

Fig. 8 FT-IR spectra of DCLNa, DCLH, DCLNa·4H_2O and DCLNa·4H_2O after supercritical treatment at 40°C and 20 MPa

The above reported hypothesis was further confirmed by comparing the FT-IR spectra of SC treated DCLNa·4H_2O with those of DCLNa, untreated DCLNa·4H_2O and DCLH reported in Fig. 8. Significantly different spectra were obtained with SC treated DCLNa·4H_2O and either DCLNa or untreated DCLNa·4H_2O. A good overlapping was observed with the spectra recorded with SC treated DCLNa·4H_2O and DCLH samples in the 4000–1900 cm^{-1} spectral region. However, at lower wavenumbers, DCLNa·4H_2O shows characteristic absorption bands absent in the DCLH spectrum. The presence of $NaHCO_3$ in the SC treated specimen was revealed by the CO_3^{2-} absorption band at 1400 cm^{-1} [21].

Carbamazepine

CRB·2H_2O solubility data determined at 40°C, 10, 20 and 35 MPa are reported in Fig. 9 along with those of the anhydrous form taken from a previously published report [9].

At all pressures tested, the hydrate presents a solubility significantly higher (P<0.05) than that of the anhydrate, although the two species give rise to qualitatively similar solubility *vs.* pressure profiles.

Figure 10 presents the DSC curves obtained from CRB·2H_2O samples before (curve a) and after SC treatment at 10 MPa (curve b). Curve a shows a broad endothermic event between 40 and 110°C corresponding to 14% mass loss as determined

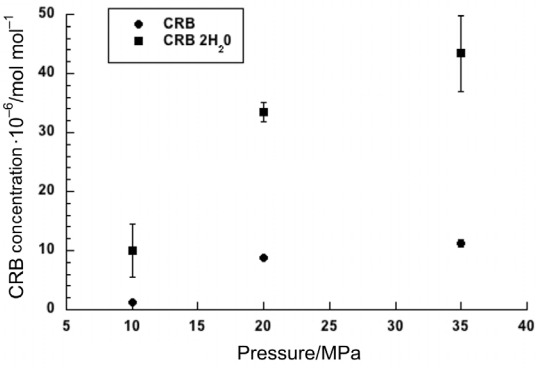

Fig. 9 Solubility in CO_2 of anhydrous (circles) and hydrate (squares) CRB as a function of pressure at 40°C. The bars represent the standard deviation (n=3)

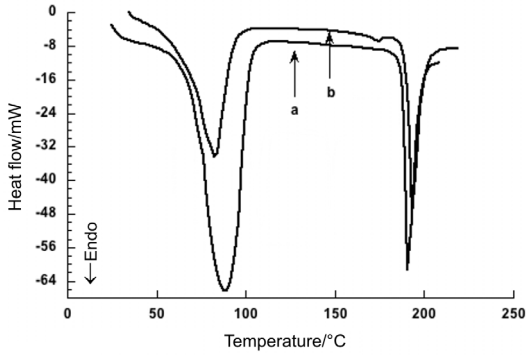

Fig. 10 DSC traces of $CRB{\cdot}2H_2O$ before (curve a) and after (curve b) supercritical treatment at 40°C and 35 MPa

by TG (calculated for two water molecules, 13.23%). Final melting of CRB Form I (high melting polymorph) occurs at 193°C, in agreement with previously published data [22]. It has been pointed out that CRB dehydration upon heating always yields CRB Form I, unless the process is carried out in a high relative humidity atmosphere, where Form III can be obtained [18].

In curve b the water loss endotherm is still present, though less pronounced (mass loss 8.38 (0.56)%) suggesting lower water content. A small endo-exo effect is observed between 160 and 180°C, which can be attributed to the melting of CRB Form III followed by recrystallization of Form I, with final melting at 191°C. Thus, during the SC treatment $CRB{\cdot}2H_2O$ undergoes partial dehydration and transforms into the low melting (177°C) polymorph. The endo-exo effect becomes more pronounced as the SC treatment is prolonged (6, 9 and 12 h instead of 3), namely by treating the same amount of $CRB{\cdot}2H_2O$ with 40, 60 or 80 g of CO_2 instead of 20.

To assess whether the observed dehydration could be attributed to heating, as in the case of THP·H_2O, CRB·$2H_2O$ was submitted to a subcritical (5.6 MPa) CO_2 stream for 12 h at 40°C. The DSC trace obtained from the recovered solid phase was practically superimposable to that of an untreated CRB·$2H_2O$ sample.

Therefore, the dehydration of CRB and its recrystallization as the low melting polymorph occurred as a consequence of its solubilisation in SC CO_2. Part of dissolved CRB was removed from the saturation cell by the CO_2 stream; the remaining portion recrystallized in the cell, upon pressure relief, as anhydrous Form III, the thermodynamically stable form at 40°C [16].

Similarly to the previously reported [9] CRB Form I → Form III conversion mediated by dissolution, this may imply a difference in the thermodynamic stability between anhydrous and hydrate CRB in the adopted experimental conditions, testified by the difference in solubility. The dihydrate should be considered the metastable form. In fact, thermodynamical stability of anhydrous phase relative to the hydrated phase does not depend only upon the transition temperature [23] but also on the water activity in the vapour phase, namely the relative humidity (or partial vapour pressure) of the system [24]. This, in turn, depends upon temperature and solubility of water in the solvent. The solubility behaviour of solvates in solvents different from that entrapped in the crystal structure depends obviously on the reciprocal miscibility of solvents. In the case of miscible solvents additional Gibbs free energy change of mixing is the major driving force, so that, for instance, caffeine hydrate is much more soluble in ethanol than anhydrous caffeine [25]. When solubility of hydrates in SC CO_2 is concerned, one should take into account the partial miscibility of water in SC CO_2 (2.55 mg of water per gram of CO_2 at 40°C and 20 MPa [26]). In this regard, further investigation, beyond the scope of this paper, is needed to evaluate the contribution of water–SC CO_2 mixing.

Conclusions

Three pharmaceutical hydrates under examination exhibited higher solubility in SC CO_2 than the anhydrous phases.

However, the solubility values obtained for THP monohydrate should be critically considered because of the instability of the crystal phase at the experimental temperature adopted.

DCLNa tetrahydrate represents a peculiar case of chemical interaction with the acidic supercritical fluid, mediated by crystal water.

In this regard, particular attention should be paid when conducting supercritical processes with a salt of a weak acid in the presence of crystal water or residual moisture, as the chemical inertness of SC CO_2 should be considered in relation to the specific experimental conditions.

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