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Supercritical Solution Impregnation of naproxen into mesoporous SiO_2 SBA-15

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ABSTRACT

Naproxen was impregnated into mesoporous SiO_2 SBA-15 using the Supercritical Solution Impregnation (SSI) technique. Experiments were performed at 50–70ºC and 15–25 MPa in pure CO_2 and CO_2 modified with ethanol, ethyl acetate and menthol. Materials were also impregnated from liquid solutions in ethanol and chloroform. In the SSI experiments, naproxen was deposited on the internal surface of the mesopores as shown by N_2-adsorption experiments. The percentage of naproxen impregnated decreased from 11.1% to 7.4% mass as the CO_2 density increased. Likewise, adding ethanol, ethyl acetate or menthol to CO_2 decreased the percentage of naproxen adsorbed on the support. Thermal analysis showed that naproxen impregnated on SiO_2 by SSI became amorphous. FTIR and XRD confirmed the loss of crystallinity of naproxen and its interaction with the SiO_2 support. Samples impregnated in liquid medium however kept partially their crystallinity. Release tests of naproxen on SiO_2 SBA-15 prepared by SSI followed an almost zero-order release profile; the drug is released at a constant rate into a PBS pH= 7.4 medium. The release rate slowed down in comparison to that of pure naproxen, due to the interaction of the drug with the support and the diffusion of the drug outside the support mesopores. Thus, a sustained release system was achieved, which may help to attain a longer therapeutic effect with a lower naproxen dose.

1. Introduction

The need to improve the bioavailability of orally applied drugs has been a challenge during the last decades [1]. Since the bioavailability of poorly water-soluble compounds depends strongly on the particle size distribution, morphology and crystallinity of the particles, most efforts have been directed to control these variables.

Most of the new Active Pharmaceutical Ingredients (API) brought to the market belong to class II in the Biopharmaceutics Classification System (BCS); they have high permeability but low solubility. Many solutions have been proposed to improve the bioavailability of drugs: (i) size reduction by micronization to improve the intracellular uptake and enable the use of different administration routes [2], (ii) encapsulation with different polymers/excipients to permit a controlled delivery, prevent the degradation of the active ingredients or mask unpleasant properties as taste or odour, [3] or (iii) impregnation into polymeric or mesoporous supports to develop controlled drug-delivery systems [4]. Interaction of the drug with the excipient may increase the solubility of the drug by decreasing its crystallinity [5].

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) class II BCS which has anti-inflammatory, analgesic and antipyretic properties. It is used to treat arthritis, musculoskeletal pain, headache and fever [6]. When the drug is administered, plasma drug levels are maximized after two hours, at which point the concentration of naproxen begins to gradually decline [7].

Naproxen has various side effects, such as heartburn, digestive problems, ulcers and stomach bleeding[8]. The concentration and presence of naproxen in the body can be controlled through the use of controlled drug delivery systems. By developing a system in which the drug is interacting with the carrier/excipient and is not introduced directly into the body, adverse effects can be avoided or minimized.

The use of mesoporous SiO_2 materials as non-toxic excipients in the preparation of drug formulations has been proposed [9,10]. Mesoporous silica materials offer excellent properties as they are stable mesoporous structures with large surface areas, which imply high adsorption power, they have tunable pore sizes and pore volumes to allow sufficient drug loading and well-defined surface properties as their silanol surface can be functionalized in different ways.

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The loading of the drug into mesoporous drug-delivery systems and its controlled release may help to prolong and more effectively deliver the drug, reducing many undesired side effects [11]. High dosing frequency of drugs and their absorption at unrelated sites leads to restriction of therapeutic effect and is a cause of adverse drug reactions. This can be avoided if the delivery of the drug can be controlled.

There are numerous reviews on the use of mesoporous silica materials in drug delivery and biomedical applications [10,12–15]. Drugs of all kinds have been impregnated into SiO_2 SBA-15. Examples include antihypertensives, antibiotics, antifungal, psychoactive, anticancer and anti-inflammatory drugs among others [16]. These composite systems can be used to produce intravenous, oral and topical formulations and in the preparation of implants. In some cases, the functionalization of the support was studied to test its effect on drug release. In particular, naproxen has been impregnated into SiO_2 SBA-15 [11] and MCM-41 functionalized mesoporous SiO_2 supports [17].

In these examples, drugs were generally loaded into the mesoporous SiO_2 supports by liquid impregnation using an aqueous or organic solvent. Impregnation takes place thanks to the capillary forces. However, the poor wetting of the support surface with the liquid solvent may difficult filling the pores with the drug leading to non-homogenous materials, therefore the functionalization of the SiO_2 surface is oftentimes required. Then during the drying step, the support can also suffer from structural damage. If the impregnation is performed using liquid organic solvents, traces of toxic solvent residues may be left in the system. To overcome these limitations, impregnation using supercritical fluids has been proposed.

The process of impregnation using a supercritical fluid as a solvent is called Supercritical Solution Impregnation (SSI). The SSI method involves the dissolution of the drug in the supercritical fluid media, and its adsorption/precipitation onto the support. Of the different supercritical fluids, CO_2 is the compound most commonly used as it has very accessible critical parameters (31ºC and 7.38 MPa), and it is cheap, non-toxic, innocuous and non-flammable. CO_2 is a gas at room temperature, so it is easily removed by depressurization without leaving any kind of residue. The low surface tension of supercritical CO_2 favors the wetting of the support pores and enhances impregnation. The low temperatures avoid the thermal degradation of the drugs. In polymers, the supercritical fluid diffuses through the polymer chains, leading to the polymer's swelling/plasticization, and the drug is homogeneously impregnated and dispersed into the matrix [18,19]. Controlled pressurization and depressurization are required to avoid foaming. In porous matrixes, the solute dissolved in supercritical carbon dioxide diffuses into the porous network and impregnates the material not only via adsorption but via precipitation from the supercritical fluid solution during depressurizations in what has been called adsorptive precipitation [4]. Some authors also refer to this process as Controlled Particle Deposition (CPD) [20,21]. After depressurization, a homogeneous distribution of the active component through the solid matrix is obtained, without producing aqueous or organic liquid waste and eliminating the need for drying steps. SSI is considered a green technique for preparing drug formulations.

The SSI technique has been successfully applied to the preparation of pharmaceutical formulations for controlled drug-delivery systems [4,22–27] and the impregnation of nutraceuticals in polymers for the preparation of active packaging materials [28]. At the industrial scale is used in wood impregnation [29], leather tanning [30] and textile dyeing [31].

The impregnation of different NSAID in near-critical and supercritical CO_2 on mesoporous silica has been previously performed. For example, ibuprofen has been impregnated into SiO_2 SBA-15, MCM-41 and other large pore sizes spherical mesoporous silica supports [25,32–34]. Piroxicam was also loaded into mesoporous SiO_2 SBA-15 and Grace Syloid® [35]. Comparing the SSI process versus the conventional liquid impregnation [35,36], SSI led to higher drug loadings and modified the drug release profile. Gurikov and Smirnova have reviewed the impregnation of solid porous matrices with different drugs with an emphasis on drug amorphization [4].

Although naproxen has not been impregnated into mesoporous SiO_2 material by SSI, it has been impregnated into ethylcellulose/methylcellulose blends [37], polymer patches of ethylene vinyl acetate and Eudragit® E100 [38] and PLA suture materials [39] from $scCO_2$ solutions.

Cosolvents have been also used in an effort to increase the impregnation efficiency. The addition of cosolvents increases the solubility of the solute in $scCO_2$ and can favor adsorption in compounds with very low solubility in $scCO_2$, providing that there is a strong interaction with the support. However, if the interaction is not very strong, the cosolvent can change the partition coefficient of the solute between the surface and the fluid phase and induce desorption. Furthermore, the cosolvent can compete with the solute for the adsorption sites. Thus, depending on the interplay between these factors, the loading of a drug on a given support can increase or decrease with the use of cosolvents. For example, the use of small amounts of ethanol, methanol, acetone or cyclohexane dissolved in CO_2 had a negative impact when loading ibuprofen into mesostructured silica [32,33]. In contrast, the impregnation of nimesulide on hydrophilic mesoporous SiO_2 aerogels [40] or quercetin in silica mesoporous microparticles [41] increased when ethanol was used as a cosolvent.

In this paper, we propose the preparation of a controlled drug-delivery system using mesoporous silica SBA-15 as the excipient/support and naproxen as the drug by the SSI technique. This is the first time that this system has been addressed using this technique. Furthermore, we explore the use of ethanol, ethylacetate and menthol as cosolvents of the drug in CO_2. The use of menthol as a cosolvent in the impregnation processes has been never attempted before and it is interesting because menthol has pharmacological activity and can add beneficial properties to the composite system.

2. Experimental

2.1. Materials

Naproxen [$C_{14}H_{14}O_3$], tetraethyl orthosilicate (TEOS, purity>98%), poly(ethylene oxide)-co(propylene oxide)-co(ethylene oxide) block copolymer (Pluronics P123, non-ionic surfactant, $PEO_{20}PPO_{70}PEO_{20}$), hydrochloric acid (HCl, purity 37%) and Phosphate Buffered Solution (PBS) medium sachets were purchased from Sigma-Aldrich. Absolute ethanol (+99%) was obtained from Sharlab and ethyl acetate (+99%) from Fisher. L(-)-menthol (+99.5) was purchased from Across. The chemical structures of naproxen and L-menthol are shown in Fig. 1.

The dialysis bags (12,000 Da), 35 mm wide and variable length, used in the solubility tests were also purchased from Sigma-Aldrich.

Mesoporous SiO_2 SBA-15 was prepared using the PEO-PPO-PEO Pluronic surfactant as the structure-directing agent and TEOS as the precursor [42,43]. Briefly, 4.0 g of Pluronics P123 was dissolved in 30 mL of water and mixed with 120 mL of 2 M HCl in a round bottom flask with stirring at 35 ºC. When a completely transparent and colourless solution was observed, 8.5 g of TEOS was added to the solution and kept at a constant temperature for 24 h. Then, the temperature of the bath was increased to 100 ºC, and the mixture was aged without stirring at 100 °C for 12 h. After cooling, the white precipitate was

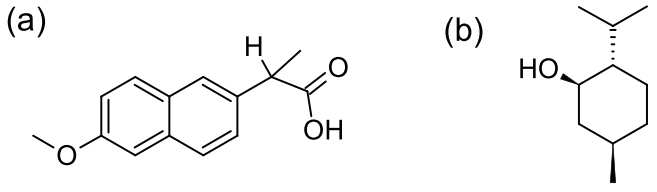


Fig. 1. Chemical structures of (a) naproxen and (b) L-menthol.

filtered and washed with ethanol several times and calcined in a furnace at 550 °C for 6 h with a temperature ramp of 1 °C/min.

2.2. Supercritical Solution Impregnation

Experiments were performed using a ca. 60 mL custom-made high-pressure vessel. A scheme of the SSI equipment is shown in Fig. 2. The vessel was provided with inlet and outlet lines which can be isolated by high-pressure valves (V1, V2). A relief valve (Swagelok) and a high-pressure transducer (Gems) were also connected. Heating was performed using an aluminium heating jacket with cartridge heaters and a Proportional-Integral-Derivative (PID) temperature controller (Micromega, model CN77322) connected to a J-type thermocouple located in a thermowell housed in the vessel. The system was mounted onto a stirring plate. Carbon dioxide was added using an ISCO 260D high-pressure syringe pump, thermostated at the temperature of the experiments.

For the supercritical CO_2 impregnation experiments, ca. 40 mg of naproxen was introduced directly into the vessel along with a magnet and, in some experiments, a small amount of cosolvent (1.5 mL ethanol or ethyl acetate or 100, 50 and 25 mg menthol) Then ca. 50 mg of mesoporous SiO_2 SBA − 15 were placed in a stainless steel basket covered with a perforated stainless steel plate. The basket was clamped in the thermocouple jacket in the upper part of the vessel to separate the drug and the support. Additional experiments were performed using ca. 60 mg of naproxen and 150 mg of SiO_2 with and without menthol (37.5 mg).

First, the vessel was heated to the selected temperature. Then CO_2 was introduced from the thermostated pump into the vessel up to the desired pressure and the system was stirred. Experiments were performed at 50 and 70ºC and 15 and 25 MPa. These four points were combined to perform four tests and finally a central point at 60ºC and 20 MPa. The cosolvent tests were also carried out at 60ºC and 20 MPa. In the experiments with liquid cosolvents, the same volume of solvent (1.5 mL) was added (2.5% and 1.5% mol of ethanol and ethyl acetate in CO_2, respectively). In the experiments with menthol (solid), the mass of menthol used was varied (0.016–0.060% mol/mol menthol in CO_2). Even though the % menthol may seem very low in comparison to that of ethanol or ethyl acetate, it represents, for the higher concentrations, a mass larger than those of naproxen or support in the experiments. Experiments were performed at different concentrations of menthol to minimize the amount of cosolvent impregnated on the support. The impregnation tests were maintained for 24 h to ensure the solubilisation of the drug and to promote saturation of the mesoporous surface. Once the test was finished, the stirring was stopped and the system was depressurized at a rate of ca. 1 MPa/min. Experiments at 50ºC and 25 MPa and 70ºC and 25 MPa were performed in triplicate to determine the reproducibility of the method, obtaining average absolute standard deviations of ± 0.6% in both. Data shown in Fig. 4 are the average of at least two replicates.

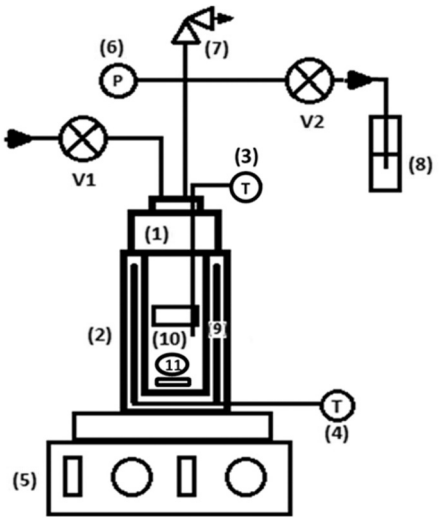
The solubility of naproxen in pure CO_2 and CO_2 modified with ethanol or ethyl acetate has been previously reported [44–46]. Solubility of naproxen in pure CO_2 is lower than 7 10^{-5} in mole fraction at pressures up to 25 MPa between 35 and 75ºC [44,45]. At pressures between 10 and 15 MPa, the solubility varies little with temperature, and the crossover of the curves is observed at ca. 16 MPa. However, at 35 MPa, solubility increases markedly with temperature. The moderate/low solubility of the drug seems to be related to its low vapor pressure, which increases significantly with temperature. The addition of cosolvents increases the solubility of naproxen in the supercritical mixtures reaching values of 4.8 10^{-4} and 1.4 10^{-4} in mole fraction when ca. 5% mol ethanol and ethyl acetate are used, respectively[46]. Considering these data, the impregnation experiments have been performed at every pressure and temperature condition using a very large excess of naproxen. Experiments performed with different amounts of support at saturation conditions led to the same drug load within the experimental uncertainty.

2.3. Liquid impregnation with solvent evaporation

For comparison purposes, liquid impregnation of naproxen followed by solvent evaporation was also performed on mesoporous SiO_2 SBA-15 following the procedure described in the literature [17,47]. ca. 10 mg of naproxen were dissolved in 10 mL of solvent and placed in a beaker containing a Teflon-coated magnet and 50 mg of SBA-15 support. The mixture was stirred at ca. 400 rpm for 24 h at room temperature in the fume hood. During this time, the solvent evaporated. The central part of the impregnated sample was then collected for further characterization. Impregnations were carried out using ethanol and chloroform as solvents.

2.4. Materials characterization

The amount of naproxen and cosolvents impregnated into the SiO_2 supports was determined by Thermogravimetric analysis (TGA) using an SDT- Q600 from TA at a heating rate of 10 ºC/min in N_2 flow. The amount of naproxen was further confirmed by UV–vis spectroscopy of the released drug using an Agilent Cary 8454 spectrophotometer. In a typical experiment, 5.0 mg of the impregnated material was added to



1. High-pressure vessel
2. Aluminium heating jacket.
3. Thermocouple inserted in thermowell
4. Thermocouple connected to a PID temperatura controller.
5. Stirring plate.
6. High Pressure transducer
7. Relief Valve.
8. Outlet line.
9. Cartridge heaters.
10. Basket to place support
11. Magnetic stirrer and drug

V1-2: High-pressure valves

Fig. 2. High-pressure vessel used in the SSI experiments.

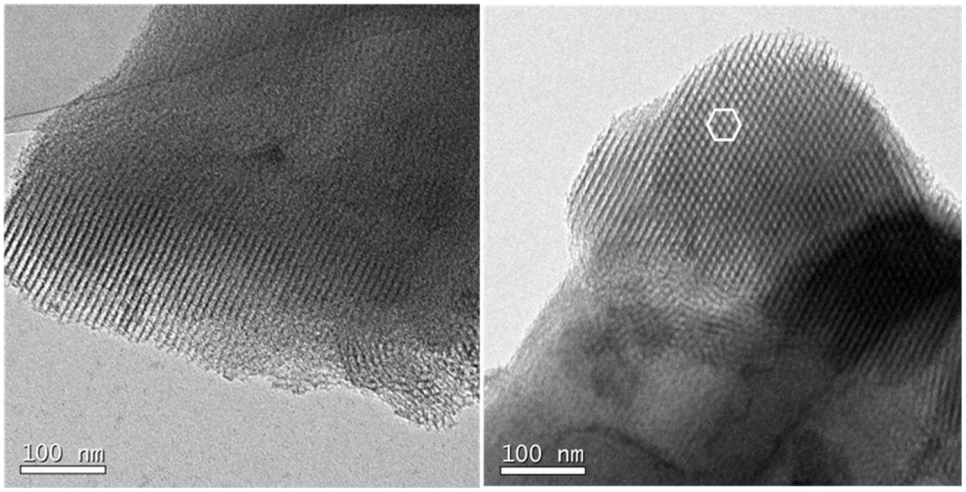


Fig. 3. TEM images of the SiO_2 SBA-15 support.

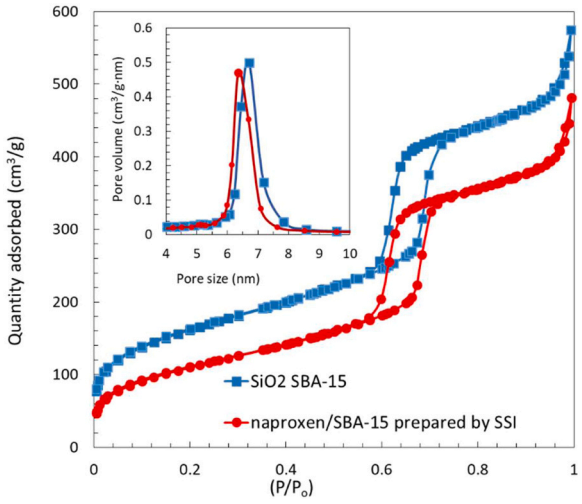


Fig. 4. N_2 adsorption-desorption isotherms of mesoporous SiO_2 SBA-15 and naproxen impregnated on SBA-15 by SSI. Inset shows the pore size distributions obtained from the adsorption branch of the isotherm.

10 mL of water and stirred for 6–12 h for the total dissolution of the drug. The solution was filtered through a filter paper and the UV–vis spectrum of the samples was recorded. The concentration of naproxen was calculated from the absorption band at 262 nm, subtracting the absorbance at 350 nm for baseline correction due to the scattering of colloidal SiO_2 particles. Uncertainty in the determination was large.

Differential Thermal Analysis (DTA) provided by the SDT- Q600 apparatus was used to follow the thermal transition upon heating, such as the melting of the crystalline drug. Fourier-Transform Infrared (FTIR) spectra were recorded using Perkin Elmer 1000 apparatus using KBr disks at a spectral resolution of 4 cm^{-1} between 4000 and 450 cm^{-1}. FTIR was used to assess the interaction between naproxen and the support and the crystallinity of the drug. The porosity of the bare support and the impregnated materials was determined by measuring N_2 adsorption-desorption isotherms at 77 K using Micromeritics ASAP-2020. Samples were out-gassed at 110 ºC for 6 h before the measurement. Textural properties were obtained using standard procedures [48]. The BET equation and the BJH method were used for the specific surface area and pore size distribution calculation. The total pore volume was calculated from the amount adsorbed at a relative pressure of 0.95. Wide angle X-Ray Diffraction (XRD) patterns of the composite materials were collected using an X´PERT MPD diffractometer with Cu Kα radiation at 2θ values between 5 and 35º. TEM images of the mesoporous SiO_2 support were obtained using a JEOL JEM 1400 transmission electron microscope. The material was dispersed in 1-butanol over a copper grid and dried in air.

2.5. Drug release tests

Drug release tests were performed using dialysis bags following a procedure previously described [47]. Tests were performed in 0.01 M PBS at pH 7.4 at 37.0 ± 0.5 °C. The dialysis bags were pre-treated with deionized water for 24 h and placed before the tests for a few minutes in the PBS medium. Bags were filled with 10 mL PBS and 100 mg of the naproxen-SiO_2 samples, sealed and placed into a flask containing 190 mL of PBS. Aliquots of 5 mL were taken from the medium every 5–10 min up to 120 min. The same volume of solvent was refilled to the solution after each sample extraction. Tests were performed under sink conditions. The concentration of naproxen in the samples was determined using an Agilent Cary 8454 UV–vis spectrophotometer following the naproxen absorption band at 262 nm. Experiments were performed in triplicate. The data shown are averages.

3. Results and discussion

Mesoporous SiO_2 SBA-15 supports were impregnated with naproxen by SSI. The influence of pressure and temperature and the use of cosolvents on the amount of impregnated drug was studied to see the dependence on these parameters and thus on the density of the supercritical fluid and the solubility of the drug in CO_2. Ethanol, ethyl acetate and menthol were tested as cosolvents. Results are summarized in Table 1.

Fig. 3. shows TEM images of the SiO_2 SBA-15 support. Images show cylindrical mesopores with very regular pore sizes around 6–7 nm, which are packed in a hexagonal way.

Adsorption-desorption isotherms for the support and a sample impregnated by SSI at 50ºC and 25 MPa are compared in Fig. 4. Isotherms exhibit a type IV, subtype H1 hysteresis loop, which is characteristic of mesoporous materials with well-defined cylindrical-like pore channels. BET surface area value for the SiO_2 SBA-15 support was 580 m^2/g. Using the BJH method for a cylindrical pore model, the pore size distribution obtained from the adsorption branch of the isotherm presented a maximum at 6.8 nm. After drug impregnation by SSI in pure CO_2 at 50ºC and 25 MPa, the BET surface area and the maximum in the pore size distribution decreased to 402 m^2/g and 6.4 nm, respectively. The pore volume of the support was also reduced from 0.75 to 0.61 cm^3/g indicating the successful adsorption of the drug into the support pores.

Table 1
Summary of SSI experiments of naproxen on SiO_2 SBA-15 showing the % mass of naproxen and cosolvent impregnated on the support by TGA and UV–vis, an estimate of the number of monolayers (NML) adsorbed onto the support[4] and some characteristics determined from FTIR and XRD.

T (°C)	P (MPa)	% mol cosolvent in CO_2	% mass solvents (TGA 50–200°C)	%mass naproxen ± 0.6 (TGA 200–700°C)	%mass naproxen ± 1.0 (UV–vis)	NML[a]	Crystallinity
50	25	-	2.9	7.4	7.7	0.37	Amorphous
50	15	-	1.3	9.9	9.2	0.52	Amorphous
70	25		1.5	9.0	9.1	0.46	Amorphous
70	15	-	2.1	11.1	10.4	0.59	Amorphous
60	20	-	1.5	9.4	9.7	0.49	Amorphous
60	20	2.5% EtOH	2.8	6.0	7.1	0.30	Amorphous
60	20	1.5% Ethyl acetate	2.9	4.4	5.1	0.22	Amorphous
60	20	0.060% Menthol	15.3	11.9	4.3	0.21	Amorphous
60	20	0.030% Menthol	11.0	12.5	3.1	0.15	Amorphous
60	20	0.024% Menthol	1.9	12.4	7.8	0.40	Amorphous
60	20	0.016% Menthol	2.0	13.6	6.3	0.32	Amorphous
Liquid EtOH		-	2.2	14.4	17.2	0.79	Crystalline + Amorphous
Liquid $CHCl_3$		-	2.5	17.1	16.0	0.97	Crystalline + Amorphous

[a] Values calculated from %mass naproxen by TGA for all samples except those with menthol, estimated from %mass by UV–vis.

The relatively low change in pore size and pore volume may be due to the partial evaporation of naproxen during the sample degassing procedure previous to the gas adsorption measurements [25].

The drug content, defined as the ratio of the mass of adsorbed naproxen to the mass of the support was determined by TGA of the impregnated samples. The total drug content was also measured by UV–vis of the solutions after the total release of the drug.

TGA and DTA analyses were performed on all prepared samples, as well as on the pure drug and the SiO_2 SBA-15 support. From the heat flow curve, information about the crystallinity of the drug before and after the SSI process was obtained. TGA was also used to quantify the amount of cosolvent present in the samples.

Fig. 5 shows the TGA of the pure drug showing that naproxen decomposes in one step at temperatures between 200 and 300 °C. The heat flow curve of pure naproxen shows several peaks associated with endothermic (downward) and exothermic (upward) processes. The endothermic peak at 153 °C indicates the melting of the drug [49] as no mass loss is observed at that temperature. The other two exothermic peaks with maxima at ca. 290 and 450 °C are associated with the decomposition of the drug.

TGA analysis of the sample impregnated at 70°C and 25 MPa and the SiO_2 support is also shown in Fig. 5. The thermal analysis of the support shows that after the stabilization of the equipment, a practically insignificant loss of mass close to 2% is observed, which is due to the condensation of the silanol groups and the dehydroxylation of the sample [47]. TGA of the impregnated sample shows a small mass loss below 100 °C, which may be associated with the evaporation of water present in the sample. Then the decomposition of the impregnated drug only starts at temperatures close to 300 °C and proceeds in two steps: the first pronounced mass loss occurs between 300 and 400°C and a second one between 400 and 650 °C. From this temperature onwards, the slope of the curve is very small and follows the same behaviour as the SiO_2 support. The heat flow curve of naproxen/ SBA-15 impregnated using $scCO_2$ shows only one exothermic peak with broad maxima between 340–360 °C. It appears that naproxen impregnated on the mesoporous SiO_2 support becomes more stable and starts decomposing at a higher temperature than the native drug. The decomposition profile indicates that the drug is stabilized due to its adsorption and confinement within the pores of the support [50]. As the criterion to determine the amount of impregnated naproxen, the percentage of mass loss between 200 and 700 °C was chosen. The mass loss between 50 and 200 °C was also estimated to determine the presence of water and cosolvent residues in the samples. The reproducibility of the method was estimated ± 0.6%.

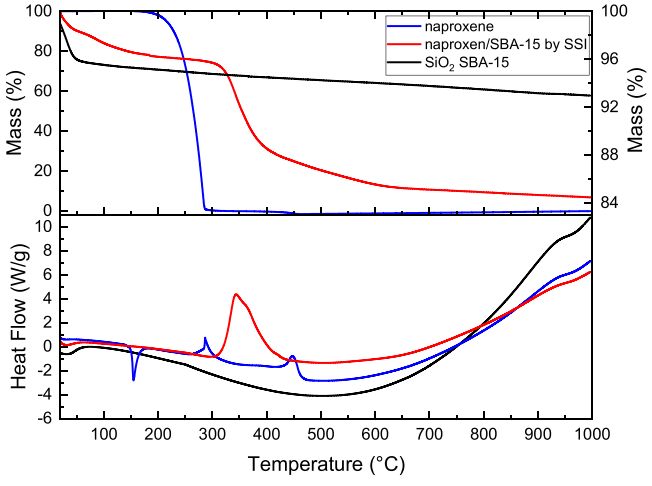


Fig. 5. Thermal analysis of (–) pure naproxen, (—) SiO_2 SBA-15 support and (–) naproxen/SiO_2 SBA-15 prepared by SSI at 50°C and 25 MPa in pure CO_2 showing (a) the % mass loss and (b) the heat flow associated.

Values obtained by UV–vis from the drug release in water are also presented in Table 1. For the SSI experiments in pure CO_2 and using ethanol and ethylacetate cosolvents, the values obtained by the different techniques agree with each other within experimental error. Because of the larger uncertainty of the UV–vis measurements (±1%), for these samples, the percentages of naproxen impregnated determined from TGA were used for the following discussion. However, for the experiments using menthol as a cosolvent the differences were large enough to confirm that the actual amount of loaded naproxen was lower and, as will be explained later, the percentages obtained from UV–vis were more realistic.

The results for all samples impregnated in pure supercritical CO_2 (Table 1) show that naproxen is impregnated on the SBA-15 support in percentages between 7.4% and 11.1% mass. In every case, the mass loss below 200 °C was close to 2.0%.

At each temperature, the % mass of the impregnated drug decreases as the pressure increases. At constant pressure, the amount of naproxen impregnated increases with temperature. The temperature dependence is different from that found when experiments are not performed under saturation conditions [4]. These results can be better understood in terms of CO_2 density. Fig. 6 shows the % mass of naproxen as a function of (a) the density of CO_2 [51] and (b) the solubility of the pure drug in CO_2. Solubility values were interpolated from data in reference [44]. The impregnation of the drug is directly related to the CO_2 density. Fig. 6a shows that an increase in density decreases the amount of drug impregnated. The higher the density, the higher the solubility of the

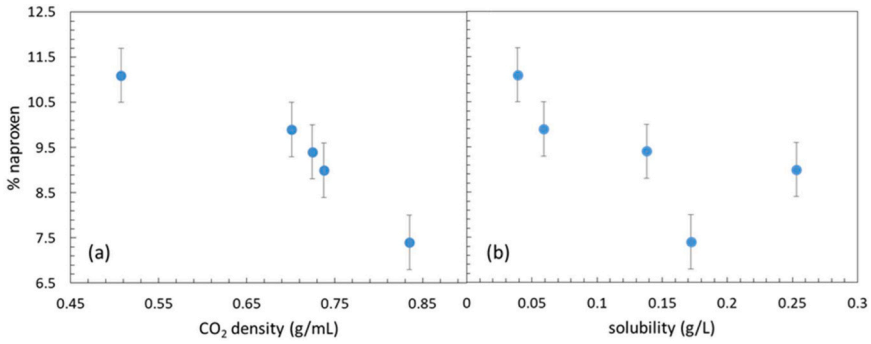


Fig. 6. Variation of the % naproxen impregnated on SiO_2 SBA-15 by SSI from TGA as a function of (a) CO_2 density [51] and (b) solubility of naproxen in CO_2 [44].

drug in CO_2 and the lower the amount impregnated (Fig. 6b). At higher densities, naproxen has more affinity for the solvent and the impregnation on the support decreases. In contrast, when the solubility is lower, the impregnation is more effective. This behavior reveals a not very strong interaction between the drug and support.

The influence of cosolvents on the impregnation process was further studied as some studies report an increase in the drug load adding cosolvents [40,41]. Experiments were carried out at the central point at 60 °C and 20 MPa since it is not necessary to increase the pressure and temperature too much to increase the solubility, due to the effect of the modifiers.

TGA of the samples impregnated with naproxen in CO_2 using ethanol and ethyl acetate as cosolvents are compared in Fig. 7 with that obtained in pure CO_2. As can be seen, after the stabilization temperature of the equipment, a mass loss is observed below 200 ºC. The values measured in the experiments using cosolvents in this range are slightly larger than those found in samples prepared by SSI in pure CO_2. Ethanol and ethyl acetate boiling points are 77.1 and 78.4 ºC, respectively [51]. Solvents adsorbed on the SiO_2 support may evaporate at a temperature slightly higher than their boiling temperatures. Thus this mass loss corresponds to the desorption of the cosolvents adsorbed on the support and water. From 200 ºC onwards, the decomposition of naproxen is observed.

The percentages of naproxen impregnated using CO_2 modified with ethanol and ethyl acetate were at the same conditions much lower than the percentages impregnated using pure CO_2 (9.4% mass). The use of ethanol and ethyl acetate as modifiers, although improving the solubility of naproxen in supercritical carbon dioxide, does not favour its impregnation on the support. TGA shows that naproxen impregnated on SiO_2 SBA-15 decomposes at the same temperature as that observed in the samples impregnated in pure CO_2. Then, although less drug is loaded on the support, its interaction with the support is similar. Apart from the higher solubility of naproxen in the CO_2-modified mixture, the competitive adsorption of the cosolvent on the support may also be responsible for the lower drug content. Similar results have been observed when loading ibuprofen into mesostructured silica using CO_2 modified with small amounts of ethanol, methanol, acetone or cyclohexane [32,33].

We have also tested the use of menthol as cosolvent. Menthol has been used to increase the solubility of different drugs in the Rapid Expansion of Supercritical Solution (RESS) process [52,53]. Furthermore, menthol has pharmacological activity, being a penetration enhancer in skin delivery, nasal decongestant and pain reliever [54]. It is also widely used in topical analgesic products, often combined with different NSAID [55].

Fig. 8 shows TGA of the samples impregnated with naproxen using menthol as cosolvent compared with that of the sample impregnated in pure CO_2. Menthol is solid at room temperature which melts and boils at 41.5 and 212.1 ºC, respectively [51]. However, because of its high vapour pressure, menthol evaporates continuously with heating in N_2 flow from 120 to 165 ºC [56]. When menthol is adsorbed on the SiO_2 support, it evaporates at a slightly higher temperature. Thus, the large mass loss observed below 200 °C corresponds to the menthol desorption. The concentration of menthol was reduced from 0.06% to 0.016% mol in CO_2 to minimize its adsorption on the SiO_2 support. In all cases, an increase in the %mass loss between (200–700 ºC), previously ascribed to

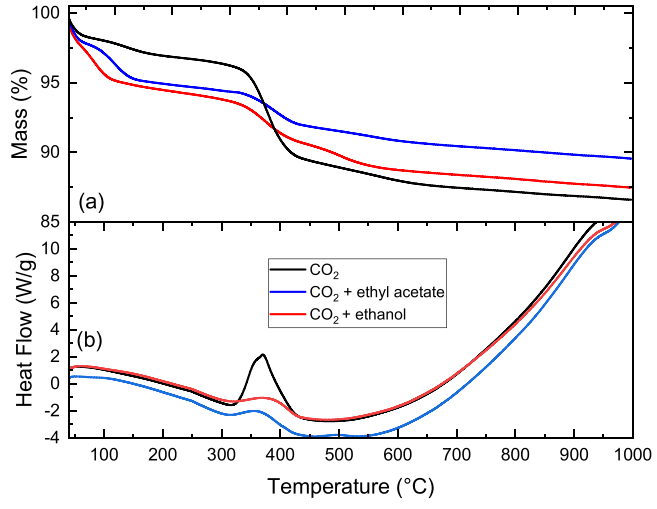


Fig. 7. Thermal analysis of naproxen/SiO_2 SBA-15 prepared by SSI at 60ºC and 20 MPa in pure CO_2, CO_2 + 2.5% mol EtOH and CO_2 + 1.5% mol ethyl acetate, showing (a) the % mass loss and (b) the heat flow associated.

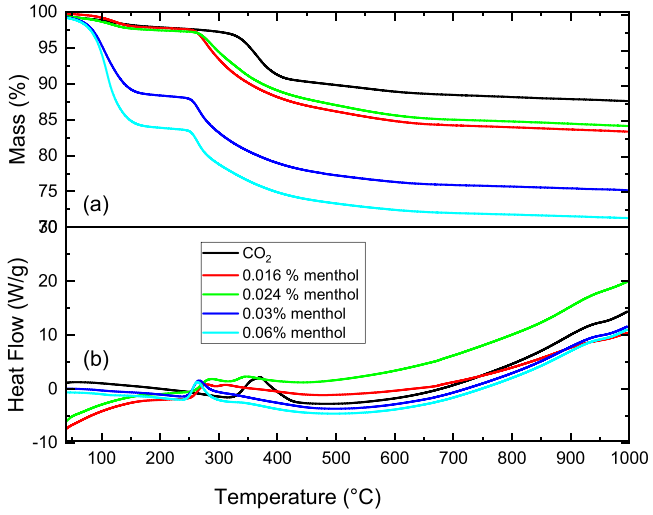


Fig. 8. Thermal analysis of naproxen/SiO_2 SBA-15 prepared by SSI at 60ºC and 20 MPa in CO_2 modified with menthol at different concentrations: 0.06%, 0.03%, 0.024% and 0.016% mol showing (a) the % mass loss and (b) the heat flow associated.

naproxen impregnated on the support was observed (11.9–13%). These values were however much larger than the values determined from UV–vis (3.1–7.8%). The higher the menthol concentration the lower the naproxen content which suggests that menthol and naproxen compete for the adsorption sites.

Furthermore, the decomposition of naproxen in the samples impregnated using CO_2 modified with menthol occurred below 250 ºC, at slightly lower temperatures than that found in the samples impregnated using pure CO_2 (above 300 ºC). This temperature was still higher than that observed for the pure drug. This suggests that the interaction of the drug with the support was weaker in these samples, or that different interactions among the support, drug and cosolvent were taking place.

In all samples impregnated by SSI using pure CO_2 and the different cosolvents, analysis of the heat flow curves of the DTA revealed that the melting point of naproxen was no longer observed at 153 °C. This indicates a loss of naproxen crystallinity in the mesoporous support. The samples impregnated by SSI with naproxen and menthol did not show a clear endotherm below 200 ºC related to the evaporation of the cosolvent as expected from the TGA, but just two exothermic peaks in the DTA previously associated with the decomposition of naproxen. The maxima in the heat flow curves of the DTA for these samples appear at 270–285 and 360–380 ºC, whilst in the samples impregnated with CO_2 pure or liquid cosolvents only the broad peak with a maximum at 360–380 ºC was observed. The different thermal behaviour suggests that naproxen is adsorbed on the support in two different ways. It appears that menthol and naproxen compete for the adsorption sites. Thanks to its lower size and higher volatility, menthol could reach the SiO_2 active sites faster than naproxen and interact with the silanol groups. If menthol did not saturate the surface, naproxen could also adsorb directly on the SiO_2 support. But naproxen could adsorb on the menthol molecule forming a bilayer. Thus the second exothermic peak in the DTA at 360–380 ºC would be ascribed to the decomposition of naproxen adsorbed on the SiO_2 support and it is also observed in samples impregnated in CO_2 in absence of menthol. The first one at 270–285 ºC could be due to the desorption of the menthol-naproxen complex forming a bilayer. At the lowest menthol concentration, this peak weakens and shifts to slightly higher temperatures. Thus when menthol is used as a cosolvent, the mass loss determined from the TGA between 200 and 700 ºC cannot be used to estimate the % naproxen as it may include the desorption of a small amount of menthol, particularly in the samples with the highest menthol concentration. This hypothesis is also confirmed by the smaller % mass of naproxen determined from UV–vis of the released drug. Then when menthol is used as cosolvent even at smaller concentrations than ethanol or ethyl acetate, the amount of naproxen adsorbed on the support decreases.

For comparison purposes, experiments were also performed using liquid ethanol and chloroform as described before. The results obtained for the liquid impregnation showed large percentages of naproxen on the mesoporous support with values equal to 14.4% and 17.1% mass for the samples impregnated in liquid ethanol and chloroform, respectively. Although the maximum amount of naproxen that could be impregnated considering the masses of support and drug used is 20% mass, the values measured by TGA were slightly lower. This is because for the TGA measurements only the central part of the sample was studied as excess naproxen crystals were observed in the border regions. In contrast, values determined by UV–vis from the mixture were closer to the theoretical one. In both cases, the % mass loss below 200 ºC due to the solvent adsorption was close to 2.5%, similar to the values obtained in samples prepared by SSI using cosolvents.

As in the previous samples, the melting point of the drug was not observed in the heat flow curves of the thermal analysis, indicating changes in the crystallinity of the drug. In these samples, however, the decomposition of naproxen occurred at lower temperatures than in the samples prepared by SSI, both at almost 200 ºC, coincident with the value measured for pure naproxen. This indicates that the interaction of the drug with the support has not occurred in the same way as in the samples prepared in the supercritical phase.

In comparison to previous reports, drug loadings obtained are similar to those previously given for the liquid impregnation of naproxen solutions in ethanol into pristine and surface functionalized SiO_2 SBA-15 by Žid et al. [11] but much lower than those given by Halamová on mesoporous SiO_2 SBA-15 and MCM-41 [6,17].

XRD analysis confirmed the amorphous state of naproxen in the samples impregnated by SSI. Fig. 9 compares the diffraction patterns of naproxen and naproxen/SiO_2 SBA-15 materials prepared by SSI in pure CO_2, CO_2 modified with 0.03% menthol and impregnated in liquid EtOH and $CHCl_3$. Naproxen is crystalline and its diffraction pattern fits the pattern reported in the literature [57]. The naproxen/SiO_2 SBA-15 composite materials showed however a broad band between 20° and 25° associated with the amorphous SiO_2 support. A very weak peak at 28.4° is an artifact that comes from the Si sample holder. Close inspection of the XRD patterns showed in the sample prepared in liquid $CHCl_3$ reflections at ca. 6.7, 12.7, 18.1 and 19.1° coincident with some of the peaks of pure naproxen, which indicates some crystallinity in this sample. As the melting peak of the crystalline phase did not appear in the DTA of this sample, this also indicates that the sample is not homogeneous.

An estimate of the number of monolayers (NML) of naproxen adsorbed into the mesoporous SiO_2 SBA-15 support was calculated following Gurikov and Smirnova [4] using the formula

$$NML = \frac{L\, N_A\, A_{drug}}{M_{drug}\, S_{BET}}$$

where L is the drug loading expressed in mass of drug per mass of support easily obtained from the drug content, N_A is the Avogadro number, A_{drug} is the projection area of the molecule, M_{drug} is the molar mass of naproxen equal to 230.26 g/mol and S_{BET} is the BET area of the SiO_2 SBA-15 support equal to 580 m^2/g. Using the length and width for naproxen of 1.41 nm and 0.74 nm, respectively, reported in reference [58], an area equal to 1.04 10^{-18} nm^2 can be calculated. NML values are given in Table 1. Values varied from 0.22 to 0.5 in the samples prepared by SSI, whilst were somewhat larger, up to 1, in samples impregnated in the liquid medium. These values are in the range of those collected by Gurikov and Smirnova [4] but are slightly lower than those reported by Reiser for the adsorption of ibuprofen in different mesoporous materials [25].

FTIR of the impregnated samples was performed to study the interaction of the drug with the support. Fig. 10 compares the FTIR of the

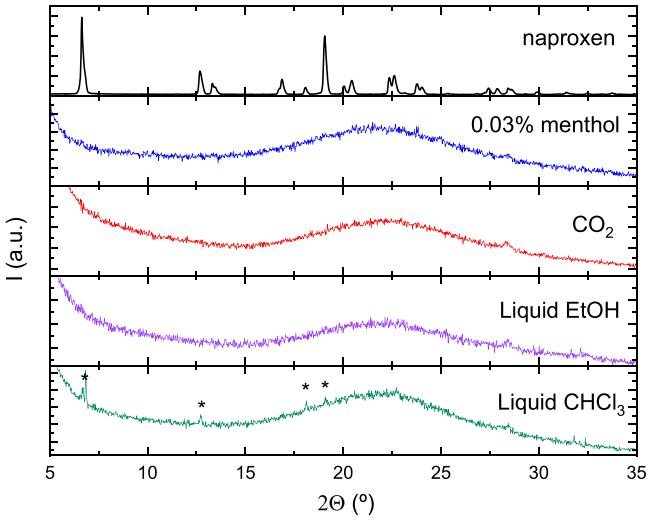


Fig. 9. XRD patterns of naproxen and naproxen/SiO_2 SBA-15 impregnated by SSI in CO_2 and CO_2 modified with 0.03% mol menthol at 60ºC and 20 MPa and impregnated in liquid EtOH and $CHCl_3$.

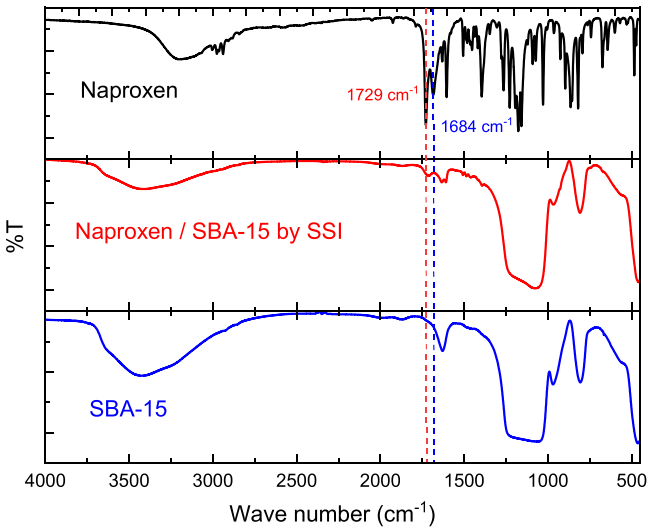


Fig. 10. FTIR spectrum of naproxen, SiO_2 SBA-15 and naproxen/SiO_2 SBA-15 impregnated by SSI in CO_2 at 50ºC and 25 MPa.

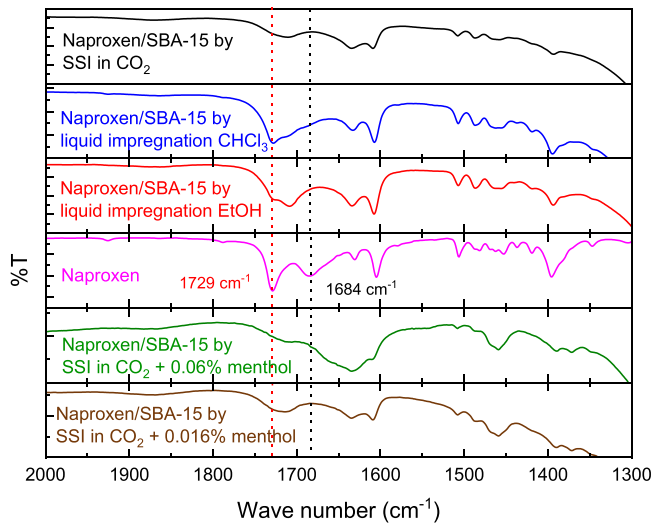


Fig. 11. FTIR spectrum of naproxen, naproxen/SiO_2 SBA-15 impregnated by SSI in pure CO_2 and CO_2 modified with 0.06% and 0.016% mol menthol in CO_2 at 60ºC and 20 MPa and naproxen/SiO_2 SBA-15 prepared by liquid impregnation in EtOH y $CHCl_3$.

bare support, the drug and the sample prepared by SSI in CO_2 at 50ºC and 25 MPa.

FTIR spectra of the SiO_2 support show intense broad bands which are attributed to the Si-O-Si asymmetric stretching from 1000 to 1250 cm^{-1} and Si-O-Si symmetric stretching at ca. 800 cm^{-1}. The bending vibrational mode of Si-O-Si appears at ca. 460 cm^{-1}. Finally, the band appearing between 3000 and 3500 cm^{-1} and the peak around 1630 cm^{-1} are ascribed to the bending and stretching vibrations, respectively, of the water physisorbed on the support [59].

The FTIR spectrum of pure naproxen shows the characteristic bands of the functional groups of the naproxen molecule (Fig. 1). The bands associated with the carbonyl group are observed in the 1680–1720 cm^{-1} region. Signals corresponding to the C═C vibration of the aromatic rings are also observed in the 1500–1600 cm^{-1} range. The band at 1396 cm^{-1} is due to the naproxen in the plane O-H deformation vibration. The symmetric and antisymmetric C-H stretching vibrational modes of CH_3 substituents appear between 2940 and 3000 cm^{-1}, whilst the C-H out-of-plane bending modes of the aromatic rings are observed below 900 cm^{-1}. The broad band centered at 3200 cm^{-1} is due to the O-H stretching vibration of the carboxylic acid group[47]. The infrared absorption of the impregnated support sample shows a combination of the characteristic signals of the support and naproxen.

The most characteristic signals to be analysed are those associated with the carboxylic acid group. An enlargement of this region from 1300 to 2000 cm^{-1} is shown in Fig. 11. In the case of pure naproxen, two signals are observed at 1729 and 1684 cm^{-1} which correspond to the free and associated carbonyl groups, respectively. When carboxylic acid groups form hydrogen bonds (HB), the C═O bond weakens and its vibrational frequency decreases. The crystalline structure of naproxen is known [60]. In the crystal, each naproxen molecule interacts with two other adjacent molecules through hydrogen bonds and aromatic interactions, but due to the crystalline chain-like structure, some C═O groups remain free. Then the signal observed in the carbonyl region at 1729 cm^{-1} is due to the free C═O groups that do not interact, whilst the band at 1684 cm^{-1} is due to HB carboxylic acid groups; both groups are present in the crystalline form [47]. When the drug becomes amorphous, however, the linear structure of the crystal is lost and most C═O groups hydrogen bond to other molecules forming dimers [61,62], disappearing the carbonyl higher frequency signal. At the same time, because molecules in the amorphous state are not as organized as they were in the crystal, the band at 1684 cm^{-1} shifts to slightly larger wave numbers. The analysis of the frequencies of the carbonyl group in naproxen can be used to get an insight into the crystalline or amorphous state of the impregnated drug.

In the sample impregnated by SSI in CO_2, the C═O band associated with free COOH, which is present in crystalline naproxen, disappears and the HB carbonyl band is shifted to 1711 cm^{-1}. This is in agreement with previous results (XRD and DTA) which indicate that the impregnated naproxen is in the amorphous state. The large shift observed in the carbonyl band also suggests that the interaction of the drug with the support may also happen via the carboxyl group. The change in crystallinity of the drug indicates that the impregnation on the support has been effective and has taken place inside the pores of the support.

Fig. 11 also compares the FTIR spectra of pure naproxen and naproxen/SiO_2 SBA-15 prepared by SSI in pure CO_2, CO_2 modified with 0.06% and 0.016% mol menthol in CO_2 and impregnated in liquid ethanol and chloroform. In the samples prepared using liquid solvents, spectra show carbonyl bands that are very different from those observed in the materials prepared from SSI. In the sample impregnated using chloroform, the band at 1729 cm^{-1} associated with crystalline naproxen is very intense and appears at the same position as in pure naproxen. Then there is a small shoulder at ca. 1707 cm^{-1} due to the HB carbonyl group of naproxen, which suggests a weaker interaction of the drug and the support. In the sample impregnated using ethanol, however, the band at ca. 1707 cm^{-1} associated with the amorphous drug is the most intense. Then in samples impregnated using liquid solvents, naproxen forms both crystals and an amorphous phase. Due to the small pore size of the mesoporous support, crystalline naproxen is most likely placed on the external surface of the support. In contrast, in the samples impregnated by SSI in CO_2, the drug impregnates the support pores and appears only in an amorphous state.

Infrared spectra of the samples impregnated by SSI in CO_2 using ethanol and ethyl acetate as cosolvents (not shown here) have been also analysed. Although the amount of drug impregnated is smaller, spectra confirmed the loss of crystallinity of the drug and its interaction with the support. Fig. 11 also shows the FTIR spectra of two materials prepared using solid menthol as cosolvent. The carbonyl band due to amorphous naproxen appears at the same position as in the samples prepared in CO_2. A new band at 1460 cm^{-1} is associated with the C-H bending mode. New intense bands between 2960 and 2850 cm^{-1} due to the C-H stretching bands of menthol also appear (not shown here). The sample prepared with the largest menthol content also shows a shoulder at ca. 1665 cm^{-1} which could be due to the interaction of the carbonyl group of naproxen with menthol. This band does not appear at the lower

concentrations of menthol. The combination of ibuprofen with naturally occurring phenolic compounds to form the prodrug ester derivative has been proposed as a method to improve the therapeutic efficacy of the drug by retarding gastrointestinal side effects [63]. Ibuprofen and naproxen are chemically similar NSAI drugs, with a carboxylic acid group that can interact with the OH group of menthol. Although the reaction between naproxen and menthol does not take place under these conditions, its interaction may be beneficial for the same purpose.

Drug release experiments in pH 7.4 buffer solution of the pure drug and the drug impregnated on the SiO_2 support by SSI and liquid impregnation using ethanol are compared in Fig. 12. The SSI sample was impregnated using pure CO_2 at 70 ºC and 25 MPa. Under these conditions, the amount of naproxen impregnated on the support was 9.0% mass. The drug amount on the sample impregnated in liquid ethanol was 14.4%. The release test of the sample impregnated using 0.024% mol menthol in CO_2 was also performed.

The pure drug took 3 h to release completely, whilst the formulation prepared from supercritical carbon dioxide took up to 5 h. This contrasts with some reports in which a faster release profile is observed upon amorphization of the drug [25,64,65]. Both the diffusion of naproxen outside the mesopores and the interaction of the drug with the support seem to slow down the release, resulting in an almost constant drug release profile. This near zero-order kinetics with a constant release rate is highly desirable for long-term drug delivery. Then a time-controlled therapeutic effect can be achieved with constant drug release. This system would avoid any adverse effects due to naproxen overdose, as the body would not be exposed to an excess drug concentration at any time, due to the interaction of the drug and the SiO_2 carrier.

On the other hand, the study with the formulation obtained using menthol was not complete because the released menthol formed an organic phase that was immiscible with the aqueous phase and clogged eventually the dialysis membrane before the total amount of naproxen was released. Considering the large uncertainty in the % naproxen content in these samples, this resulted in a slightly faster release of naproxen. The release test of the sample impregnated using liquid ethanol reveals a behaviour very similar to that of pure naproxen in agreement with the lower interaction of the drug with the support as determined by FTIR.

4. Conclusions

This work presents the preparation of naproxen impregnated into SiO_2 SBA-15 by SSI technique as a model system for the preparation of a sustained drug release system. The effect of pressure and temperature on impregnation and drug content has been further studied. The highest drug content of 11.1% has been obtained at the lowest pressure and the highest temperatures, 70ºC and 15 MPa, which are the conditions of lower CO_2 density and lower solubility of naproxen in CO_2. This indicates that although the solubility of naproxen in supercritical CO_2 is not very high, the interaction of the carboxylic acid group with the silanols groups from the SiO_2 surface drives the adsorption of naproxen to the SiO_2 support. However, at higher CO_2 densities the affinity of the drug for CO_2 and therefore its solubility increases, to the detriment of the amount adsorbed.

The influence of cosolvents on the impregnation process has been also studied. Ethanol and ethyl acetate have been proven good liquid cosolvents to increase the solubility of naproxen in CO_2. However, these polar substances increase the affinity of naproxen for the fluid phase and compete with the drug for the adsorption sites, leading to significantly lower adsorption values. The use of the solid cosolvent menthol, even at much lower concentrations (0.016–0.06% mol in CO_2) also leads to a decrease in the amount of naproxen adsorbed. Menthol adsorbs at large concentrations on the support impeding the direct adsorption of naproxen on the SiO_2 surface. However, naproxen can still adsorb on the adsorbed menthol layer. Menthol has pharmacological activity and can add beneficial properties to the system.

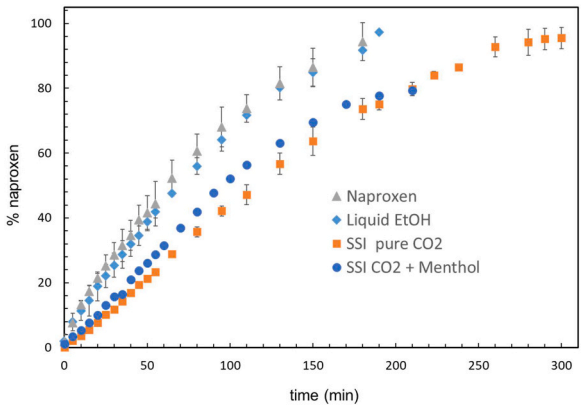


Fig. 12. Drug release tests in PBS pH 7.4 as a function of time for pure naproxen, and SiO_2 SBA-15 formulations prepared in liquid EtOH, by SSI in pure CO_2 at 70ºC and 25 MPa and by SSI in CO_2 modified with 0.024% mol menthol at 60 ºC and 20 MPa.

As confirmed by XRD, DTA and FTIR, naproxen impregnated on SiO_2 by SSI changes its crystalline form and becomes amorphous. The release tests also confirm that the drug release profile is modified when it is impregnated on the SiO_2 support using $scCO_2$. In contrast to some reports in the literature, in this case, a longer sustained release has been achieved, which may help to achieve a longer therapeutic effect with less naproxen dose, increasing the bioavailability and decreasing the adverse effects of the drug.

Besides the better properties of the drug delivery system prepared, the supercritical impregnation process in comparison to the liquid one using organic solvents has clear advantages which have been already demonstrated in different industrial processes: (i) elimination of polluting and toxic organics solvent; (ii) lower cost of CO_2 in comparison to organic solvent, (iii) reduction in time, both in the impregnation and in the subsequent drying steps and (iv) decrease of the energy cost due to solvent evaporation which may be comparable to that of the compression and decompression of CO_2. As a disadvantage, the installation cost of high-pressure equipment is higher. Nevertheless, if the production capacity increases a lot and there is a disruptive advantage in eliminating organic solvent residues, the process could be competitive. These are practical aspects that can tip the balance towards supercritical impregnation, as has happened in the wood or textiles industries.

CRediT authorship contribution statement

Juan González: Investigation (impregnation experiments and characterization of the materials). **Eduardo Pérez:** Formal Analysis, Writing – review & editing. **Marzena Pepczynska**: Investigation (characterization of the materials, Writing – review & editing; **Lourdes Calvo**: Writing – review & editing, Funding acquisition. **Albertina Cabañas**: Conceptualization, Supervision, Formal analysis, Writing – original draft, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

Acknowledgments

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