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Naproxen-bipyridine cocrystallization assisted by pressurized carbon dioxide

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Abstract

Cocrystals of S-naproxen (S-NPX) or RS-naproxen (RS-NPX) and 4,4'-bipyridine (BiPY) were prepared by the Gaseous Anti Solvent (GAS) method using CO₂ as antisolvent. S-NPX and BiPY cocrystals were also produced by Cocrystallization with Supercritical Solvent (CSS) using CO₂ as a solvent though leading to mixtures of cocrystals and homocrystals. Hydrogen-bond networks and stoichiometries of produced cocrystals were identical whatever the mode of preparation (evaporation, grinding and CO₂-assisted processes) and matched those already described in literature: S-NPX₂:BiPY₁ and RS-NPX₂:BiPY₁. The effects of the NPX:BiPY molar ratio and of the processing conditions were investigated. By GAS, an excess of BiPY in the initial processed mixture was mandatory to produce pure S-NPX₂:BiPY₁ cocrystals whereas pure RS-NPX₂:BiPY₁ cocrystals were identically produced from mixtures of 2:2 and 2:1 NPX:BiPY initial ratio. No enrichment of the product in any of the naproxen enantiomer was reached, even when mixtures of S- + RS-NPX were coprocessed with bipyridine.

Key-words. Cocrystal; CO₂; crystallization; naproxen; bipyridine; antisolvent

Abbreviations.

API active pharmaceutical ingredient

NPX Naproxen

BiPY Bipyridine

GAS gaseous anti solvent

CSS crystallization with supercritical solvent

PXRD powder X-ray diffraction

scCO₂ supercritical CO₂

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1. Introduction

Sustainability and environmental concerns have motivated the emergence of green chemistry, looking for instance to alternative products and manufacturing routes entangling less toxic inputs or lower solvent consumption. For the pharmaceutical sector, the need for improved manufacturing technologies is getting crucial notably because of the emergence of generic drugs that are considerably cheaper than the original drugs [1]. In such a competitive context, cocrystals and innovative technologies represent a broad patent space and provide additional options for lifecycle management for new and old drugs. Cocrystals are multicomponent assemblies of a given molecule and a coformer in a solid state that are held together by non-covalent interactions. In the pharmaceutical sector, the formation of a cocrystal whose one entity is an active pharmaceutical ingredient (API) is one of the strategies established to alter the physical-chemical properties of the drug, as the formation of salts, polymorphs, hydrates, or solvates [2,3]. Molecular interactions between components are a prerequisite to envisage the cocrystal formation. However, the presence of hydrogen-bonding is insufficient to predict the success of a cocrystallization experiment, since thermodynamics and kinetics are controlling the cocrystal formation as well. Slow evaporation, cooling, grinding, and melting are common techniques to explore cocrystal formation [2,4], but to move from small scale screening trials to a viable option for development and ultimately to products, scalable processes offering high cocrystal purity and yields must be devised and established [5]. Supercritical technologies have been investigated for decades to micronize or fabricate organic or inorganic compounds or composites [6] but application to cocrystal formation emerged more recently [7–15]. Compressed CO₂ can be used either as a solvent or as an antisolvent when mixed with a solution. The CO₂ solvent route is certainly the greenest option by regards of the organic solvent, especially in the CSS (crystallization by supercritical solvent) option in which components are brought in contact and suspended in CO₂. The cocrystallization is mediated by the dissolution of the components in the compressed CO₂, a dissolution that can be assisted by drops of solvent and stirring [12,15]. In the antisolvent route, CO₂ is mixed with an organic solution and the decreased solubility of compounds in the newly formed solution provokes their precipitation [9]. Compared to the conventional liquid antisolvent, the CO₂ method is run as a semi-continuous process in which the solvent and the unprecipitated species are flushed out of the vessel while a filter retains the particles in the crystallizer. The particles are then dried under pressure by a flow of compressed CO₂ so that no post-processing steps at atmospheric conditions are further required. GAS has been used for the production of several cocrystals, including naproxen:nicotinamide [9], posaconazole:4-aminobenzoic acid [12], or quercetin:nicotinamide [13].

In this work, naproxen (NPX) and 4,4'-bipyridine (BiPY) were selected as model substances. Naproxen contains a carboxylic function that can form homosynthons with molecules containing acid functional groups and heterosynthons with molecules containing amide and pyridine groups. In addition, aromatic rings can interact by π --- π and C-H--- π interactions which stabilize the packing[2]. Naproxen forms cocrystals with piperazine, 4,4'-bipyridine [16], pyridinecarboxamide isomers [17–19], amino acids

[20] and proline [21,22]. Cocrystals were mostly prepared by mechanochemistry or solvent drop grinding excepted in Manoj et al [16] in which cooling and slow evaporation were preferred. Using CO₂ antisolvent techniques, we previously produced cocrystals of naproxen with nicotinamide [9,10]. The purity in cocrystals of the produced powders and the yield of precipitation were found to be tributary of several parameters as the process variant, the CO₂-solvent composition, the API:coformer ratio and the concentrations. To our best knowledge, this is still the only reported work for naproxen cocrystallization assisted by CO₂. The bipyridine coformer was selected from a screening made by coprocessing naproxen and various coformers in the conditions of GAS next described in this work. Contrary to bipyridine, the formation of a cocrystal was unsuccessful with adipic acid, mandelic acid, salicylic acid, 4 amino benzoic acid and saccharine despite the presence of acid or amino groups in the molecules.

Naproxen is a chiral molecule. Manoj et al. reported the formation of a racemic cocrystal of RS-naproxen/bipyridine and of S-naproxen/bipyridine by cooling solution from 60°C to room temperature followed by slow evaporation [16]. In our previous work with RS-NPX:NCTA [23], we successfully produced either the racemic cocrystal or the metastable conglomerate cocrystal by CO₂ antisolvent, opening therefore new horizons for developing chiral resolution based on CO₂ assisted cocrystallization. This work investigates the ability of cocrystallization assisted by pressurized CO₂ to produce cocrystals of RS-naproxen/bipyridine and of S-naproxen/bipyridine, using scCO₂ as an antisolvent (GAS method) or as a solvent (CSS). When using CO₂ as antisolvent, the effect of processing conditions was studied for both S-NPX and RS-NPX in order to envisage future work on chiral resolution.

2. Materials and methods

2.1. Materials

S-naproxen ((S)-(+)-2-(6-methoxy-2-naphthyl)propionic acid, purity >98 %, S-NPX), RS-naproxen ((±)- 2-(6-methoxy-2-naphthyl)propionic acid, purity >99 %, RS-NPX) and bipyridine (4,4' bipyridyl, purity >98 %, BiPY) were supplied by TCI Chemicals (Belgium). R-naproxen ((2*R*)-2-(6-Methoxy-2-naphthyl)propionic acid, purity 99.99 %, R-NPX) was supplied by Santa Cruz Biotechnology (US). Molecules formulae are shown in Figure 1. Carbon dioxide (CO₂, purity 99.5 %) was supplied from Air Liquide (France). Acetone (99.5 %, Scharlau), methanol (HPLC grade), heptane (HPLC grade), ethanol (HPLC grade), isopropanol (HPLC grade), acetic acid, potassium dihydrogenophosphate and phosphoric acid were purchased from Atlantic Labo (France). Water was obtained from a Milli-Q water purification system.

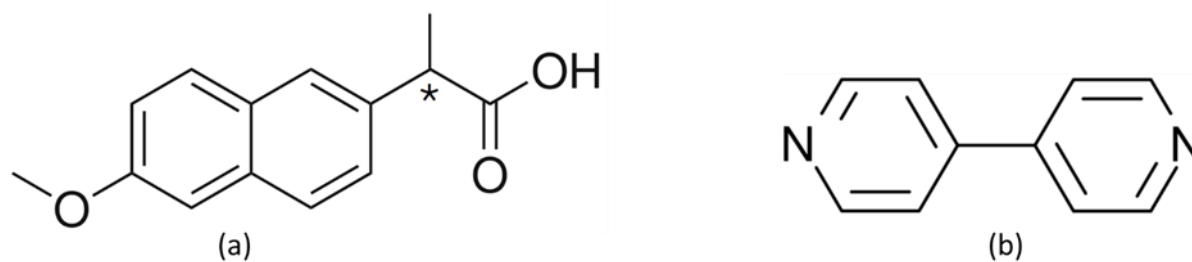


Fig. 1. RS-naproxen (a) and 4,4'-bipyridine (b) formulae

2.2. Solubility measurements of reactants in CO₂

Infrared Spectrophotometry coupled to a high pressure cell was used for in situ measurements of solubilities of each compound in supercritical CO₂, as previously described [24,25]

The experimental procedure was the following: a determined amount of solid compound was disposed at the bottom of the cell: 1.7 mg of S-NPX, or 2.9 mg of RS-NPX or 98.2 mg of BiPY to measure the solubility of each compound in scCO₂. These initial quantities were chosen in order to have an excess amount of compound for the CO₂ pressure range of interest of this study. The powder layer was well below the incoming infrared beam so that the CO₂ phase could be analyzed. Then, the cell was heated up to 40°C, the powder was stirred at 1250 rpm and CO₂ was slowly added to reach the required pressure and to avoid any spread of compound inside the cell. The system was kept under isobaric and isothermal conditions for a period between 10 min and 2 h. The stabilization of the operating conditions was controlled by recording several consecutive spectra. The equilibrium was reached when no changes of the spectral bands were noticed. The experiments were performed in the pressure range 3-26 MPa. For S-NPX and RS-NPX, the absorbance at 1758 cm⁻¹ was exploited while for BiPY the spectral band at 1765 cm⁻¹ was used (see supplementary data SI 1). The solubility of the considered compound at a given pressure in scCO₂ was calculated from the Beer-Lambert law knowing the absorbance of the characteristic peak, its molar extinction coefficient ($\epsilon_{1758} = 460 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ for S-NPX and RS-NPX and $\epsilon_{1765} = 0.96 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ for BiPY), the cell path (2.6 cm), and the amount of CO₂ in the 4.8 mL cell at 40°C for the considered pressure [26].

2.3. Solubility measurements of naproxen mixtures in acetone

The solubility of various S- and R-naproxen proportion mixtures in acetone at 40°C was measured by weighing the mixture in a cuvette equipped with a stirring bar and a cap. Then, acetone was added stepwise to the powder and the mixture was stirred, in a water bath at 40°C. At least one minute was awaited before more acetone was added. Addition was stopped as soon as last naproxen crystals disappeared (cloud-vanishing point method). The closed cuvette was then weighed to determine the total amount of added acetone and to calculate naproxen solubility.

2.4. Preparation of cocrystal by conventional crystallization

Conventional recrystallization was carried out by evaporation. S-naproxen (0.24 g, 1.0 mmole) and bipyridine (0.08 g, 0.5 mmole or 0.16 g, 1.0 mmole) were dissolved in 6 mL acetone. Evaporation was performed under the fume hood at room temperature.

2.5. Preparation of cocrystal by CO₂ recrystallization

2.5.1. Gaseous Antisolvent setup

The set-up was an home-made GAS (Gaseous Anti Solvent) equipment shown in Fig. 2A [27]. GAS technique proceeds by loading the vessel with a volume of solution and adding CO₂. Naproxen and bipyridine were dissolved in 30 mL of acetone at various concentrations and molar ratios. The concentration of NPX was fixed at 40 mg/mL whereas the concentration of BiPY was varied to fit with the desired ratio. The solutions were placed in an ultrasonic bath for approximately 3 min to ensure all starting material had dissolved. The vessel of 0.49 L was equipped with three sapphire windows and with a magnetically-driven impeller whose end fitted with a Rushton turbine plunged into the solution to allow for dispersing the antisolvent CO₂ directly into the solution. The stirring rate was set to 300 rpm. The temperature of the vessel was controlled by a heating tape and monitored by a sensor whose tip ended at half reactor height, in the centre. Temperature was set to 35-40°C. CO₂ was introduced by a LEWA (EM1, Lewa, Germany) or a SFE (Model HPP400-B, SFE Process, France) pump at variable introduction rate. Once the desired pressure of 10.0 MPa was attained, the formed CO₂-solvent mixture was drawn down at the vessel bottom whilst fresh CO₂ flew through the vessel at 30 g/min for 90 min to maintain the pressure and to dry the generated powder (stirring set at 500 rpm). The pressure in the vessel was controlled at 10.0 ± 0.5 MPa by an exit metering valve. A stainless-steel filter overtopped by a 0.2 µm pore size membrane held back the produced particles whilst the mixture was evacuated to a cyclonic separator. At the end of the period, the vessel was depressurized through the exit line and particles were collected, weighed and characterized.

2.5.2. Cocrystallization by Supercritical Solvent (CSS)

The set-up is shown in Fig. 2B. A vessel of 50 mL (AutoclaveMaxitech, France) in which a pre-mix of powders was introduced, was put in an oven to ensure the control of temperature. The vessel was filled with CO₂ at 5 MPa at ambient temperature before heating up to 40-45°C, unless mentioned. Once the vessel reached the desired temperature, monitored by inner thermocouple, CO₂ was introduced at a rate of 3 g/min up to the desired pressure of 15.0 MPa (Isco 260 D pump; Teledyne, USA). The magnetic stirring was then set to 500 rpm and the system was maintained under pressure and stirring for a 2.5-3 h before being depressurized in about 50-60 min. A second vessel, identical to that for CO₂ and equipped with a stirrer was introduced into the oven as well. That vessel experienced the same events than the CO₂ vessel except it did not contain CO₂ (and thus no pressure). The powders were placed in the vessels according two options. In option A, powders were deposited on a grid overtopped by a thin paper filter located at 2.5 cm above the vessel bottom. Powders were thus not in contact with the stirrer and only

the contact with CO₂ could induce the transformation into cocrystal. In option B, the powders were placed at the bottom of the vessel, they were in contact with the magnetic bar so a grinding could occur. The pre-mix of powders was made by gently mixing with a spatula the accurate amounts of each powder, typically in the range of 0.26-0.4 g for NPX and 0.13-0.18 g for BiPY.

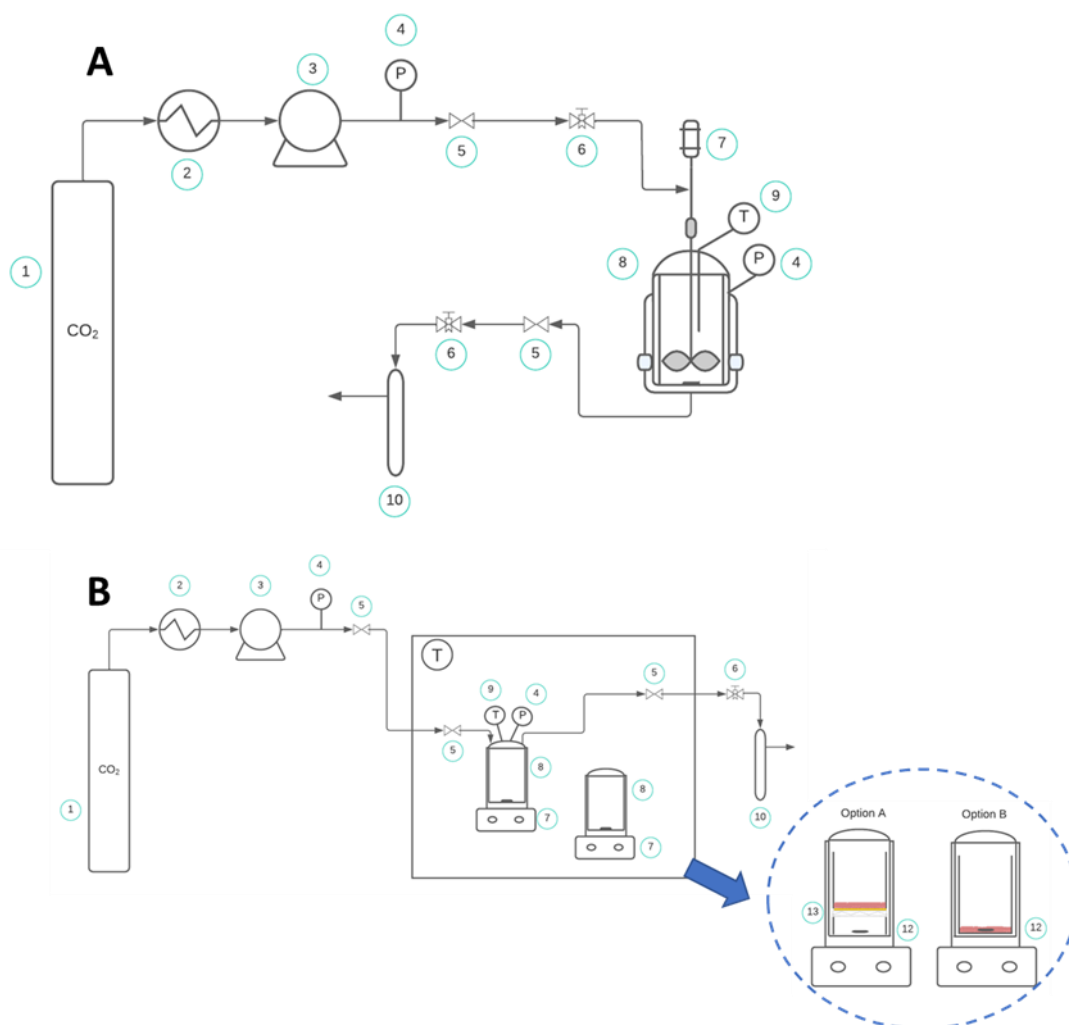


Fig. 2. Schematic diagram of the A) GAS set-up and B) CocrySTALLIZATION by Supercritical Solvent (CSS) apparatus with schematic configurations of powders inside the reactor option A: no contact with stirring bar; option B: contact with stirring bar. 1, CO₂ cylinder; 2, chiller; 3, CO₂ pump; 4, pressure gauge; 5, valve; 6, metering valve; 7, stirrer; 8, vessel; 9, thermocouple; 10, solution recovery; 11, temperature-controlled air chamber; 12, stirring bar; 13, grid and thin paper filter.

2.6. Product characterization

Crystallinity and phase identification were obtained by powder X-ray diffraction analysis (PXRD) performed on a PANalytical X'pert PRO MPD diffractometer in Bragg-Brentano θ - θ geometry equipped with a secondary monochromator and X'Celerator multi-strip detector with copper radiation. The samples were first gently ground to avoid preferred orientations, then placed uniformly on sample holders made of aluminum alloy and flattened with a piece of glass or a razor blade. Data were collected

for 2 θ angles of 4–38° with a step size of 0.02° at a scanning speed of 0.015° to 0.06°/min depending on the sample.

Interactions between naproxen and bipyridine that would evidence cocrystal formation were assessed by infrared spectroscopy. ATR-FTIR spectra on germanium crystal were recorded with Nicolet 6700 FTIR spectrometer from Thermo Fisher equipped with a liquid nitrogen cooled mercury-cadmium-telluride detector. Analyses were performed at room temperature between 800 and 4000 cm⁻¹ with a resolution of 4 cm⁻¹ and 200 scans. Physical mixtures of S-naproxen or RS-naproxen with bipyridine were prepared for comparison.

Differential scanning calorimetry (DSC) analyses were performed on a DSC 214 Polyma Netzsch equipped with a -70°C intracooler. Dry samples of circa 5 mg were weighted in 25 μ L aluminum pans equipped with pierced lids. Heating rate of 5K/min was applied between 20 and 200°C, under nitrogen atmosphere. Data treatment was performed by using Netzsch Proteus® software v7.1. The composition of the produced powders in naproxen and bipyridine was determined by high performance liquid chromatography (HPLC) after dissolution in methanol. Analyses were performed by an Agilent Infinity 1200 system (Agilent Technologies) equipped with a degaser, a quaternary pump, an automatic injector, a diode array detector (DAD) and Chemstation software for data acquisition. The column was a Zorbax Eclipse XBD C18 (100 x 4.6 mm, 3.5 μ m particle size, Agilent Technologies, France). The injection volume and temperature were 2 μ L and 25°C respectively. The mobile phase, flowing at 1.2 mL/min, consisted in a mixture of phosphate buffer 20 mM pH 7 and methanol. The separation was achieved in 10 min comprising 5 min with the 50/50 mixture followed by 5 min elution with phosphate buffer 20 mM pH 7 and methanol (5/95 v/v). The used wavelength for UV detection was 230 nm for NPX and 263 nm for BiPY. The calibration curves ranged from 7.5 to 90 μ g/mL for both NPX and BiPY. Analyses were performed in triplicate.

HPLC results were used to determine the NPX:BiPY ratio in the generated powders as well as to estimate the amount of cocrystals in the produced powder[9]. The set of mass balance equations for NPX and BiPY is:

$$NPX_{total} = NPX_{cocrystal} + NPX_{homocrystal} \quad (1)$$

$$BiPY_{total} = BiPY_{cocrystal} + BiPY_{homocrystal} \quad (2)$$

$$\frac{NPX_{cocrystal}}{BiPY_{cocrystal}} = R_s \times \frac{MW_{NPX}}{MW_{BiPY}} \quad (3)$$

$$M_{collected} = NPX_{total} + BiPY_{total} \quad (4)$$

with NPX_{total} , $NPX_{cocrystal}$, $NPX_{homocrystal}$ the amount of naproxen in the collected powder, the amount of NPX as cocrystal and the amount of NPX as homocrystal, $BiPY_{total}$, $BiPY_{cocrystal}$, $BiPY_{homocrystal}$ the amounts of bipyridine in

powder, cocrystal and homocrystal, R_s the cocrystal stoichiometry, $MW_{NPX, BiPY}$ the molecular weight of naproxen and bipyridine, respectively and $M_{collected}$, the collected amount of powder.

Provided that only one compound precipitated as homocrystals (as it is the case for those GAS experiments, in which only NPX homocrystals were detected) and that the cocrystal stoichiometry is known (informations given by the PXRD analysis), the content of the powder in cocrystals $M_{cocrystal}/M_{collected}$ can be calculated thanks to the $NPX_{total}/M_{collected}$ and $BiPY_{total}/M_{collected}$ content given by the HPLC analysis,

$$\frac{M_{cocrystal}}{M_{collected}} = 1 - \frac{NPX_{total}}{M_{collected}} + \frac{BiPY_{total}}{M_{collected}} \times R_s \times \frac{MW_{NPX}}{MW_{BiPY}} \quad (5)$$

in case of homocrystals of naproxen.

With the same HPLC equipment, chiral chromatography was also performed to determine the ratio of each NPX enantiomer in the produced powders. The column was a Chiralpak IC (250 x 4.6 mm, 5 μ m particle size, Daicel Chiral Technologies Europe, Illkirch, France). The temperature was set at 25°C and the injection volume was 5 μ L. The mobile phase, flowing at 1.0 mL/min, consisted of a mixture of heptane, isopropanol and ethanol. The separation was achieved in 20 min comprising 10 min with heptane / isopropanol / acetic acid (96/4/0.1 v/v/v) followed by a gradient to reach heptane / ethanol 75/25 (v/v) in 10 min. The used wavelength for UV detection was 230 nm. Analyses were performed in triplicate.

3. Results and discussion

3.1. Processing enantiopure S-NPX with BiPY

3.1.1. Cocrystals prepared by CO₂ solvent

Literature has suggested that scCO₂ as solvent has the potential to be a simple, scalable, organic solvent-free alternative for cocrystallization of several APIs [4,28,29]. The method was hence tested for S-NPX and BiPY while several options were implemented to identify the parameters responsible for a successful cocrystallization. The options differed by the existence or not of a direct contact between the powders and the magnetic stirrer (option B versus A), and by the presence or not of pressurized CO₂ (scCO₂ experiments versus control experiments in air). The configuration named option B in which powders are in contact with the stirrer corresponds to a set-up usually described in literature [12,28]. The coprocessing of naproxen and bipyridine was investigated from mixtures prepared either in the stoichiometric ratio of the known cocrystal, i.e. 2 NPX:1 BiPY, molar basis, or in a 2 NPX:2 BiPY ratio. Results are summarized in table 1. The solid-state forms present in the resulting samples were identified by comparison of PXRD patterns (Figure 3) with those of the raw compounds or of the 2NPX:1BiPY cocrystal reported by Manoj et al.[16]. The content of powders in cocrystals was estimated

by treating XRD data, by Rietveld refinement. Indeed, beyond the identification of the phases, the Rietveld method allows to evaluate the weight ratio of each phase in case of mixtures, the intensities of the peaks being calculated from the crystal structure directly and moderated by a scale factor (supplementary data SI 2).

Table 1. Results of CSS experiments for S-NPX with BiPY, in which powders are either in contact with the magnetic stirrer (option B) or set above it (option A).

run	NPX :BiPY stoichiometry	scCO ₂ or air	Stirrer contact	Product (w%)
CSS1*	2 :1	CO ₂	yes	CC 89% + NPX 11%
CSS2*	2 :1	air	yes	CC 70% + NPX 25% + BiPY 5%
CSS3	2 :2	CO ₂	yes	CC 94% + NPX 6%
CSS4	2 :2	air	yes	CC 55% + NPX 30% +BiPY 5%+ BiPY-H ₂ O 5-10%
CSS5	2 :2	CO ₂	no	CC 86%+ NPX 14%

*Temperature of the vessel at 52°C instead of 40-45°C

CC: S-NPX₂:BiPY₁ cocrystal

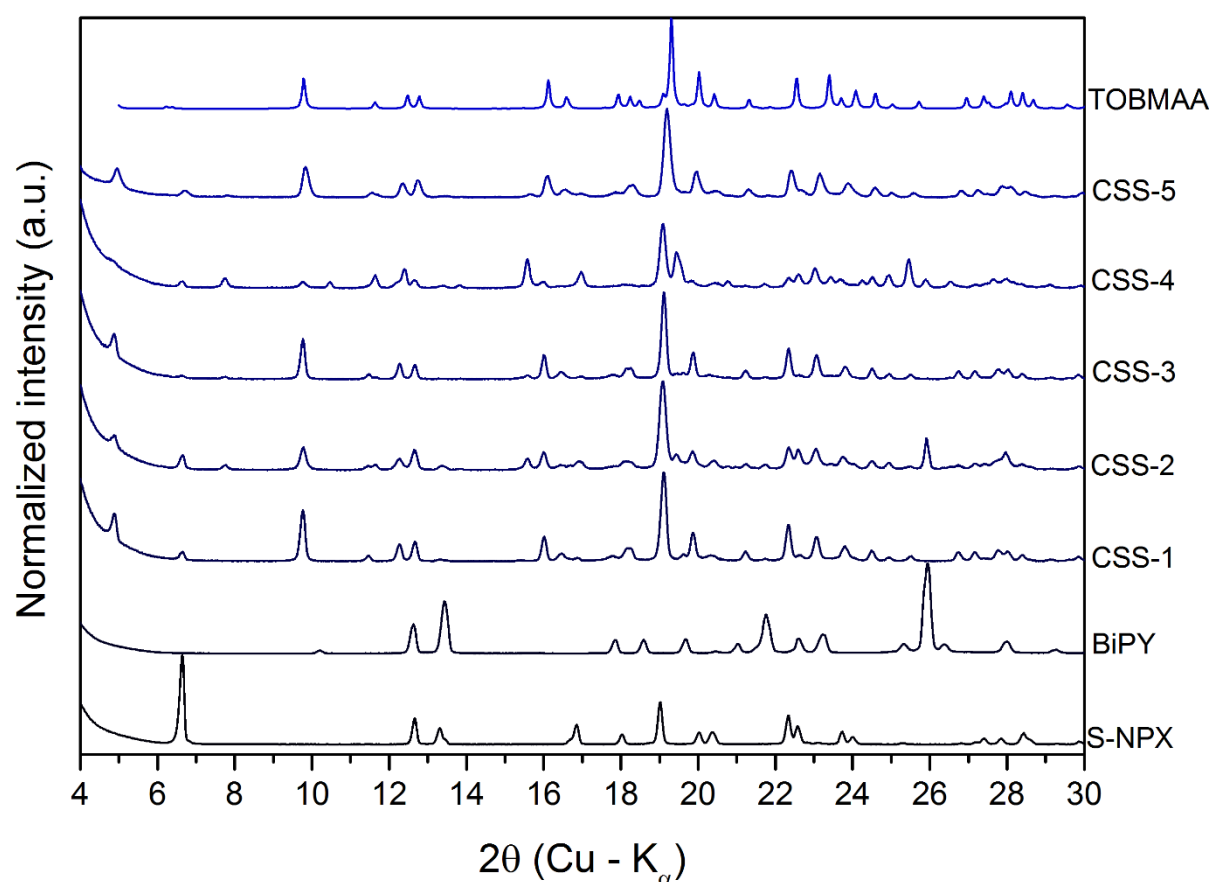


Fig. 3. Powder X-ray diffraction patterns of raw S-NPX, raw BiPY and theoretical S-NPX₂:BiPY₁ cocrystal from cif found in the Cambridge Structural Database (CSD) [16](TOBMAA) and samples processed by the CSS method, and without scCO₂. Experimental conditions as described in Table 1 (CSS 1–5).

For all samples, the formation of S-NPX₂:BiPY₁ was evidenced by the characteristic peaks at 2θ values of at 4.8°, 9.7°, 16.0° and 19.1°. However, the PXRD patterns of samples CSS1 and CSS3 closely matched the S-NPX₂:BiPY₁ cocrystal pattern, thus indicating a high purity of powders in cocrystal (estimated at 89% and 94% respectively). Therefore, the contacts with the stirring bar and with scCO₂ were mandatory to obtain a powder with high cocrystal purity. Interestingly, in the absence of supercritical solvent, but under stirring (run CSS2 and CSS4), cocrystals were produced but to a lesser extent than with CO₂ (70% and 55% respectively). The only grinding effect thus did allow the start of the transformation. Similarly, the action of CO₂ alone without grinding, (CSS5) was sufficient to induce significantly the transformation, since the obtained powder contained 86% cocrystals. Cocrystallization by CSS is subject to a discrete solubilization of the species. By analogy with the conventional method of preparing cocrystals by grinding, it is plausible that when powders are in contact with the stirrer, both phenomena of dissolution in CO₂ and grinding contribute to the cocrystal formation. In contrast, when powders and stirrer are not in direct contact, the mechanism of dissolution is involved but this process is slower. The results showed that cocrystals could be formed either by grinding or by contact with the supercritical solvent, but the combination of both actions is required to produce high-purity cocrystals. It is also worth noting that none of the conditions was able to produce a 100% pure cocrystal powder. This was already noticed by Long et al, when comparing CSS and GAS for the production of posaconazole:4-aminobenzoic acid [12].

In regards to the ratio inserted initially, it was surprising that no BiPY homocrystals were found in the CO₂-processed powders whereas significant amounts were found in air processed samples. For instance, CSS1 was performed from a mixture of S-NPX and BiPY in ratio 2:1, the same as that of the cocrystal and the product; though not pure in cocrystals, the powder did not contain BiPY homocrystals. Since the cocrystallization by CSS is driven by the solubilization of the species, data about their solubilities in scCO₂ were desirable. A literature review indicated that S-NPX is weakly soluble in scCO₂ with a solubility of 1.54 - 1.72 x 10⁻⁵ mol/mol CO₂ at 40°C and 15 MPa [30,31]. No data were found for 4,4' BiPY, but its isomer 2,2 BiPY is quite soluble in scCO₂ with a value in the range of 10⁻² mol/mol at 10 MPa, 40 and 50°C [32]. Solubility measurements of both compounds in scCO₂ were thus performed by in-situ FTIR at 40°C and various pressure values. At 15 MPa, the results presented in supplementary data (SI 1) confirmed the solubility value of 1.6 x 10⁻⁵ mol S-NPX/mol CO₂ and showed that 4,4' BiPY solubility was 420 x 10⁻⁵ mol/mol CO₂. The very high solubility of BiPY in CO₂ might explain the absence of BiPY homocrystals in the produced powder.

DSC plots of CSS 3 and CSS 5 presented in supplementary data (SI 3) showed an endothermic melting peak close to 118°C, a value consistent with the melting peak of S-NPX₂:BiPY₁ reported in literature[16]. One can add that some other small endothermic phenomena can also be observed in DSC curves (close to 85-86°C for CSS3 and CSS5) that are consistent with the description of Manoj et al. [16] who suggest the presence of a solid-solid transformation of this cocrystal at this temperature.

3.1.2. Cocrystals prepared by CO₂ antisolvent cocrystallization (GAS)

The coprecipitation of S-naproxen and bipyridine was investigated at two NPX:BiPY ratio, 2:1 and 2:2 (table 2). In order to distinguish the effect of CO₂ from that of acetone, recrystallization by evaporation of acetone solution was carried out for comparison purposes. Samples named P* and Q* were produced by solvent evaporation from mixtures of 2 NPX and 1 BiPY, and of 2 NPX and 2 BiPY in acetone respectively. Comparison of P* and Q* PXRD patterns with S-NPX₂:BiPY₁ cocrystal pattern (TOBMAA, indicated as dotted lines in figure 4) showed that P* powder pattern matched exactly the cocrystal one whereas Q* powder pattern showed peaks attributable to both the cocrystal and to BiPY homocrystals. The good agreement of the patterns (figure 4) with the calculated one indicated that the stoichiometry of cocrystals produced by evaporation-induced crystallization from acetone were alike and of 2:1 (S-NPX₂:BiPY₁), as cocrystals produced by the classical routes in methanol [16].

The precipitation by GAS of the single S-NPX specie was first investigated. When single processed, naproxen was recovered with a yield of 50% (collected amount / initial amount) that indicates a high residual solubility in the CO₂+acetone mixture as already observed by Ting et al [31]. PXRD pattern of CO₂- S-NPX exhibited the characteristic peaks of the supplied product, at 2θ values of 6.6°, 12.6° and 13.3° (Fig.4). DSC plot (supplementary SI 3) showed the same melting peak at 159°C as in the case of commercial S-NPX. The recrystallization by CO₂ antisolvent therefore did not change the crystallographic properties of S-NPX. On the contrary, the macroscopic aspect of particles changed significantly since needles as long as 1 cm were obtained for recrystallized naproxen (supplementary information SI 4). Conditions were thus promoting particle growth over nucleation indicating that the supersaturation reached in the formed CO₂-acetone mixtures was low.

When coprocessed with BiPY at the cocrystal stoichiometric ratio of 2:1 (assay GAS2) the generated powder was recovered with a yield of 56%. The calculation of the specific yield of precipitation for naproxen in GAS 1 and GAS 2 allows for concluding about a slight positive effect of BiPY presence since a higher amount of NPX (+24%, 0.14g) was precipitated. The powder exhibited characteristic peaks of the S-NPX₂:BiPY₁ cocrystals at 2θ values of at 4.8°, 9.7°, 16.0° and 19.1° together with characteristic peaks of S-NPX at the 2θ values of 6.6°, 12.6° and 13.3° (figure 4). No characteristic peak of BiPY could be detected. HPLC analysis provided a molar ratio of 3 NPX for 1 BiPY, which was consistent with the coexistence of S-NPX homocrystals and S-NPX₂:BiPY₁ cocrystals. The content in cocrystal of GAS2 was calculated as being 73 wt%.

By contrast, processing a mixture of 2 S-NPX and 2 BiPY allowed for producing a powder pure in cocrystals (figure 4, sample GAS3), though it did not change the overall recovery yield (54%). The perfect matching of GAS3 PXRD pattern with that of the S-NPX₂:BiPY₁ cocrystal was also consistent with HPLC analysis that provided a ratio value of 2 NPX for 1 BiPY and the FTIR analysis sample (SI 5) that evidenced interactions already described by Manoj [16]. Thermal analysis of GAS3 sample by DSC showed a sharp endothermic peak at 116°C (SI 3) with a small one at lower temperature, as already

reported for S-NPX₂:BiPY₁ cocrystal [16]. The absence of BiPY homocrystals in the powders, whatever the conditions investigated, indicated a significant residual solubility of this compound in the CO₂-acetone mixture. This was confirmed by the HPLC analysis of the effluents collected from the GAS reactor, where high proportions of BiPY were measured. When one compound is introduced in excess in the solution compared to the cocrystal stoichiometry (as BiPY in the 2:2 case), this excess is susceptible to precipitate provided it is present at higher concentration than the compound solubility [9]. Since no BiPY homocrystals were evidenced in the sample, the excess was obviously below the solubility limit. Because of that solubility, in the case of initial ratio of 2:1, there was not enough BiPY in solution to accommodate all molecules of NPX to form a cocrystal, therefore, some NPX were available to precipitate as homocrystals. Contrarily, in the case of excess of BiPY (initial ratio 2:2), all molecules of NPX were involved in cocrystal formation and residual BiPY was withdrawn with the acetone-CO₂ solvent. This behaviour of crystallizing a cocrystal starting from a higher molar ratio between cocrystal formers is often encountered in solution crystallization when a solid phase presents a non-congruent solubility in a solvent. By analogy regarding our case, one can say that the S-NPX₂:BiPY₁ cocrystal seems to present a non-congruent solubility in the acetone-CO₂ solvent under GAS conditions. Noteworthy is that coprecipitation with BiPY increased the percentage of S-NPX that recrystallized. Indeed, from 50% (GAS1), the yield of S-NPX precipitation (amount of NPX in collected powder / amount of NPX initially processed) increased to 61% (GAS2) and to 68% (GAS3). This was linearly ($R^2 = 0.99$) related to the total concentration of species in initial solution (40/54/67 mg/mL in these experiments).

Table 2. Cocrystallization of S-NPX with BiPY by GAS. NPX:BiPY molar ratio and cocrystal content (wt%) in obtained product were determined by HPLC.

run	NPX :BiPY stoichiometry	NPX/BiPY (mg/mL) concentration	Yield (%)	Product (w%)	NPX :BiPY molar ratio
GAS1	1 : 0	40/0	50 %	NPX 100 %	1 : 0
GAS2	2 : 1	40/14	56 %	CC 73% + NPX 27%	3 : 1
GAS3	2 : 2	40/27	54 %	CC 100%	2 : 1

CC: S-NPX₂:BiPY₁ cocrystal

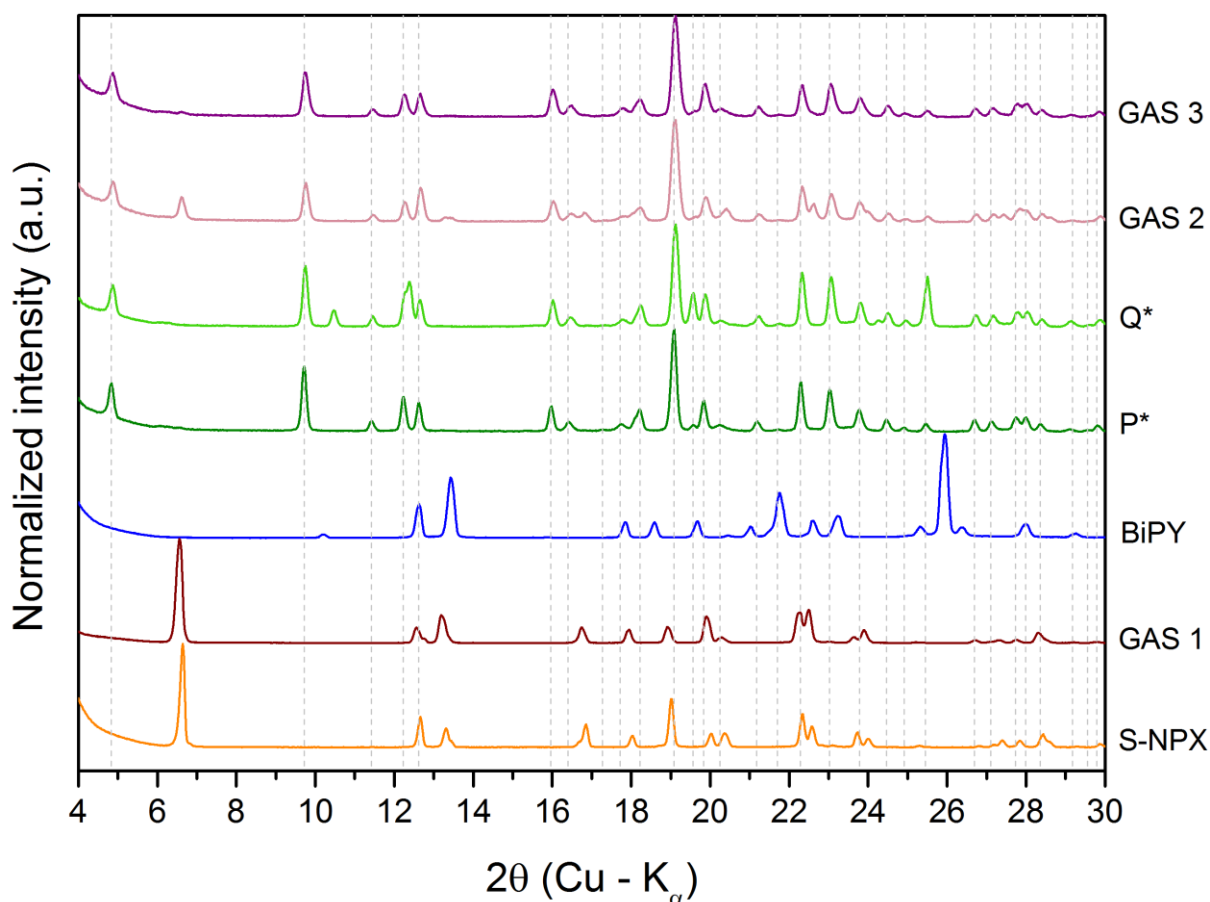


Fig. 4. PXRD patterns of raw S-NPX, raw BiPY and samples processed by the GAS method, and by solvent evaporation (P* and Q*). Experimental conditions of GAS as described in Table 2 (GAS 1–3). Dotted lines, highlighting characteristic peaks of reference cocrystal TOBMAA, are included.

To summarize, cocrystals produced by CO₂-recrystallization processes from initial mixtures of S-NPX and BiPY exhibited the same stoichiometry (S-NPX₂:BiPY₁) and crystalline structure as cocrystals produced by more conventional routes. CSS route produced mixtures of cocrystals and homocrystals (up to 94% cocrystal purity). Contrarily, GAS method produced pure cocrystal powder starting from an initial mixture of 2 BiPY with 2 NPX: an excess of BiPY was thus mandatory to produce pure S-NPX₂:BiPY₁ cocrystals (the cocrystal presents a non-congruent solubility in these experimental conditions).

3.2. Processing racemic RS-NPX with BiPY

3.2.1. Identification of cocrystals prepared by CO₂ antisolvent cocrystallization (GAS)

Since CSS was unlikely to generate pure cocrystals, only the GAS process was implemented for the coprecipitation of the racemic RS-naproxen and bipyridine. The precipitation of RS-NPX alone was first investigated. When single processed, naproxen was recovered with a yield of 57%, what is slightly

higher than when S-NPX was CO₂-recrystallized (aforementioned 50%). Solubility measurements of S-NPX and RS-NPX in CO₂ at 40°C and 10 MPa by in-situ FTIR showed a slightly higher solubility of S-NPX as compared to RS-NPX (Supplementary information SI 1). Furthermore, solubility measurements of mixtures of R and S-NPX in various ratio in acetone at 40°C also showed a lower solubility of the racemic mixture (Supplementary information SI 6). Hence, it can be inferred that S-NPX solubility in the CO₂-acetone mixture at 10 MPa and 40°C was higher than that of RS-NPX, leading to a lower precipitation yield. Similarly to the S-NPX recrystallization, the produced powder (sample GAS4) exhibited the same PXRD pattern as the supplied product, with characteristics peaks at 2θ values of 6.8°, 8.9°, 11.5° and 13.3° (figure 5). DSC plot (supplementary information SI 3) showed the same melting peak at 158°C as the DSC thermogram of commercial RS-NPX. The recrystallization by CO₂ antisolvent therefore did not change the crystallographic properties of RS-NPX.

The coprocessing of naproxen and bipyridine was then investigated from mixtures of 2 RS-NPX and 1 BiPY, according to the stoichiometry of the known cocrystal [16] and from a 2:2 mixture (table 3). The powder generated from a 2:1 ratio (sample GAS5) was recovered with a yield of 65 ± 3% (collected amount / initial amount). Its PXRD pattern exhibited peaks that were all attributable to the RS-NPX₂:BiPY₁ cocrystal with characteristics peaks at 2θ values of 4.9°, 9.8°, 11.3° and 12.4° (figure 5). The HPLC analysis confirmed that the powder was pure in RS-NPX₂:BiPY₁ cocrystals since a molar ratio of 2:1 NPX:BiPY was measured. Thus, contrary to the recrystallization of the enantiopure S-NPX, the processing of the racemic RS-NPX with BiPY at the initial ratio of 2:1 allowed the production of pure cocrystals, moreover at a significantly higher yield (65% vs 56%).

Table 3. Cocrystallization of RS-NPX with BiPY by GAS. NPX:BiPY ratio (molar basis) and cocrystal content (wt %) in produced powders were determined by HPLC. Molar ratio of R- and S-NPX were determined by chiral HPLC.

run	NPX :BiPY stoichiometry	NPX/BiPY (mg/mL) concentration	Yield (%)	Product (w%)	NPX :BiPY molar ratio	R-:S-NPX molar ratio
GAS4	1:0	40/0	57 %	NPX 100 %	1:0	1:1
GAS5	2 : 1	40/14	65± 3%	CC 100%	2:1	1:1
GAS6	2 : 2	40/27	61 %	CC 100%	2 :1	1 :1

CC: RS-NPX₂:BiPY₁ cocrystal

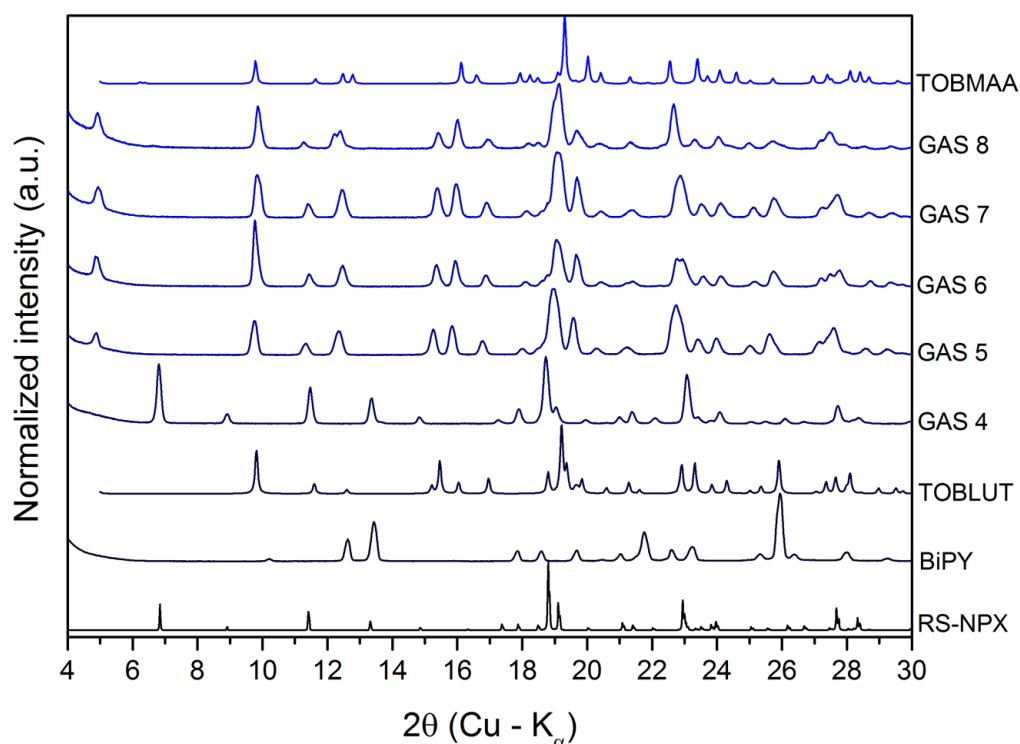


Fig. 5. PXRD patterns of raw RS-NPX, raw BiPY and theoretical RS-NPX₂:BiPY₁ and S-NPX₂:BiPY₁ cocrystals from cif found in the Cambridge Structural Database (CSD)[16] (TOBLUT and TOBMAA) and samples processed by the GAS method. Experimental conditions of GAS as described in Tables 3 and 4 (GAS 4-8).

Coprocessing of naproxen and bipyridine was then investigated with a mixture of 2 RS-NPX and 2 BiPY, similarly to the study of S-NPX and BiPY coprecipitation. The collected powder (GAS6) exhibited exactly the same PXRD pattern as the calculated RS-NPX₂:BiPY₁ and the HPLC analysis confirmed it was composed of NPX and BiPY in a 2:1 ratio (table 3 and Fig 5). Additionally, thermal analysis of sample GAS6 (DSC plot in SI 3) showed the same melting peak at 136°C as that already reported for RS-NPX₂:BiPY₁ cocrystals[16] and FTIR analysis of GAS6 sample (SI 5) evidenced interactions already described for the RS-NPX₂:BiPY₁ cocrystal. Thus, increasing the initial BiPY ratio in the processed mixture had no influence on the composition of the generated powder. The pure RS-NPX₂:BiPY₁ cocrystals were formed, and only a slight decrease was observed in the powder recovery yield (61% vs 65%).

Produced powders were also analysed by chiral HPLC in order to quantify their content in R-NPX and S-NPX, expressed as a molar ratio: R-NPX:S-NPX. As shown in table 3, GAS5 and GAS6 were 1:1 in R-NPX:S-NPX ratio, that is the same ratio as that of reactants. This result was expected since no difference in PXRD patterns, as compared to the reference racemic cocrystal pattern (TOBLUT), was noticeable. Noteworthy is that some experiments were conducted under various CO₂ introduction rates, in an attempt to generate the metastable conglomerate cocrystal rather than the racemic cocrystal, as

achieved by Neurohr et al. with naproxen and nicotinamide [23]. Unfortunately, these experiments were unsuccessful.

3.2.2. Processing mixtures of RS-NPX and S-NPX with BiPY

Some experiments were performed by coprocessing BiPY with various mixtures of S-NPX and RS-NPX (GAS7 and GAS8). Results are reported in table 4. The generated powders were mixtures of racemic and enantiopure cocrystals in various ratio (figure 5). A higher precipitation yield was observed when the initial mixture contained more RS-NPX (58 % vs 51 %), what is consistent with the lower solubility of RS-NPX - BiPY as compared to that of S-NPX - BiPY, as discussed earlier. Coprecipitation of enantiopure and racemic mixtures of naproxen with bipyridine did not lead to any significant enrichment of the produced powder in any of the naproxen enantiomer. Indeed, the R-NPX:S-NPX ratio in the powders was similar to the initial processed ratio, i.e. 0.17:1 from initial 0.14:1 and 0.67:1 from initial 0.6:1.

Table 4. Cocrystallization of RS-NPX and S-NPX mixtures with BiPY by GAS. NPX:BiPY ratio (molar basis) and cocrystal content (wt %) in produced powders were determined by HPLC. Molar ratio of R- and S-NPX were determined by chiral HPLC.

run	NPX :BiPY stoichiometry	S-NPX/RS-NPX/BiPY (mg/mL) concentration	Yield (%)	Product (w%)	NPX :BiPY molar ratio	R-:S-NPX molar ratio
GAS7	2 : 2	30/10/27	51 %	CC 100 %	2 : 1	0.17 : 1
GAS8	2 : 2	10/30/27	58 %	CC 100%	2 : 1	0.67 : 1

CC: mixture of S-NPX₂:BiPY₁ cocrystal and RS-NPX₂:BiPY₁ cocrystal, in various proportion.

To summarize, RS-NPX₂:BiPY₁ cocrystals were produced very easily and at a yield as high as 65% by CO₂ antisolvent cocrystallization. The behaviour of RS-NPX in the presence of BiPY during coprecipitation in GAS was very different from that of S-NPX, though these differences were not likely to envisage chiral resolution.

Conclusion

For the first time, the feasibility of CO₂-antisolvent cocrystallization (GAS) to prepare cocrystals of the enantiopure S-naproxen or the racemic mixture RS-naproxen with 4, 4' bipyridine was demonstrated. The cocrystallization of S- naproxen with bipyridine was also achieved by the Cocrystallization with Supercritical Solvent (CSS) method. In CSS experiments, results showed that cocrystals could be formed either by grinding without CO₂, or by contact with scCO₂, but it is the combination of the two actions that produced the highest yields in cocrystals, i.e. above 94%. Whatever the CO₂ production

route (GAS or CSS), the powder X-ray analysis evidenced the same crystalline pattern and the stoichiometry for cocrystals produced by CO₂ assisted methods, grinding and evaporation techniques (this work and literature results), i.e. S-NPX₂:BiPY₁. When the processed mixture was composed of S-NPX and BiPY in a ratio corresponding to the cocrystal 2:1 molar ratio, S-NPX homocrystals coexisted with the cocrystals in the final product. The fact that GAS and CSS powders did not significantly contain homocrystals of BiPY indicated a rather high solubility of that component in CO₂ and in CO₂-acetone mixtures. Both techniques yielded to the fabrication of the S-NPX₂:BiPY₁ cocrystal though powders were not cocrystal pure. As a solvent-free route, CSS holds however an appreciable advantage for industrialization, but the technique has to be further optimized to improve the cocrystal purity. In addition, criteria of particle size distribution and energy demand, not investigated in this work, should be considered in future work to better appraise the techniques. In GAS, the improvement of the cocrystal content in the product was achieved by increasing the concentration of BiPY in the processed solution. Changing the enantiopure S-NPX for the racemic RS-NPX induced some differences in the process outcomes. The precipitation yields were slightly higher suggesting that the solubility of the RS-NPX – BiPY mixture in CO₂-acetone is slightly lower than that of the S-NPX – BiPY mixture. The sensitivity of the NPX-BiPY ratio was also different. Whereas a 2:2 processing ratio was mandatory for S-NPX based system to avoid the coprecipitation of NPX homocrystals, the 2:1 ratio enabled to recover a pure cocrystal powder when the RS-NPX system was processed. Regarding the crystalline phase, the CO₂ process produced cocrystals of same stoichiometry as the conventional methods, for both systems. So far, changing the ratio of R and S NPX by processing mixtures of S and RS NPX with BiPY did not allow any enrichment of the product in any of the naproxen enantiomers.

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