

Naproxen-bipyridine cocrystallization assisted by pressurized carbon dioxide

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Supplementary Information 1. Solubility measurements of crystalline S-NPX, RS-NPX and BiPY in CO₂ at various pressure values, by in-situ FTIR.

The solubility (C (mol/mol of CO₂)) of the considered compound at a given pressure in scCO₂ was calculated from the Beer-Lambert law ($A = \epsilon \cdot l \cdot C$) knowing the absorbance A of the characteristic peak of the compound, its molar extinction ϵ , the cell path ($l = 2.6$ cm), and the amount of CO₂ (in mol) in the 4.8 mL cell at 40°C for the considered pressure. Calculation of the molar extinction coefficients of the characteristic peak of naproxen at 1758 cm⁻¹ has been calculated by using the reference data of the solubility of S-naproxen in scCO₂ previously published [1,2]. Then, as the peak used for S-NPX and RS-NPX are at the same frequency position and expected to have the same oscillator strength, the same extinction coefficient has been used for the solubility determination of RS-NPX. Thus, it was found to be $\epsilon_{1758} = 460$ L.mol⁻¹.cm⁻¹ for the characteristic peak of naproxen at 1758 cm⁻¹. For BiPY, the molar extinction coefficient of the characteristic peak at 1765 cm⁻¹ was determined when for a given pressure threshold, 100% of the initial quantity of BiPY introduced in the cell was dissolved in scCO₂ as verified by the fact that the absorbance of the characteristic peak did not rise with an increase of pressure above this pressure threshold. The reported data are the average of at least two replicates. Thus, it was found to be $\epsilon_{1765} = 0.96$ L.mol⁻¹.cm⁻¹ for the characteristic peak of 4,4'-bipyridine at 1765 cm⁻¹.

Solubility of S-NPX, RS-NPX and BiPY in CO₂ at 40°C for various pressure values are reported below.

Solubility at 40°C in CO ₂	10 MPa X 10 ⁵ mol / mol CO ₂	15 MPa X 10 ⁵ mol / mol CO ₂
S-NPX	0.55	1.6
RS-NPX	0.48	1.24
BiPY	180	420

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Supplementary Information 2.

The different homo and co-crystals ratios have been calculated using Rietveld refinements from the published crystal structures. The cell parameters were refined to account from Bragg peak position variation due to temperature difference and intensities were generated according to the atomic positions in the unit cell taken from the previously published crystal structures without refining them. The molecules or molecular complexes were thus introduced as rigid body in the refinement and the only refined variables were the background function (5 terms of Legendre polynoms combined with a manual background), the unit cell parameters, the Lorentzian and Gaussian peak broadening due to size and microstrain effects respectively, the overall isotropic atomic thermal displacement, the whole scale factor and the different phase fractions. The latter was then used to calculate the different weight proportion of each phase. Figure (below) shows the result of the Rietveld refinement for the powder obtained by the GAS2 sample (see table 2) that leads to an estimation of 69(3) % of S-Naproxen-bipyridine cocrystal and 31(3) % of S-Naproxen in good agreement with HPLC results (73% and 27% respectively).

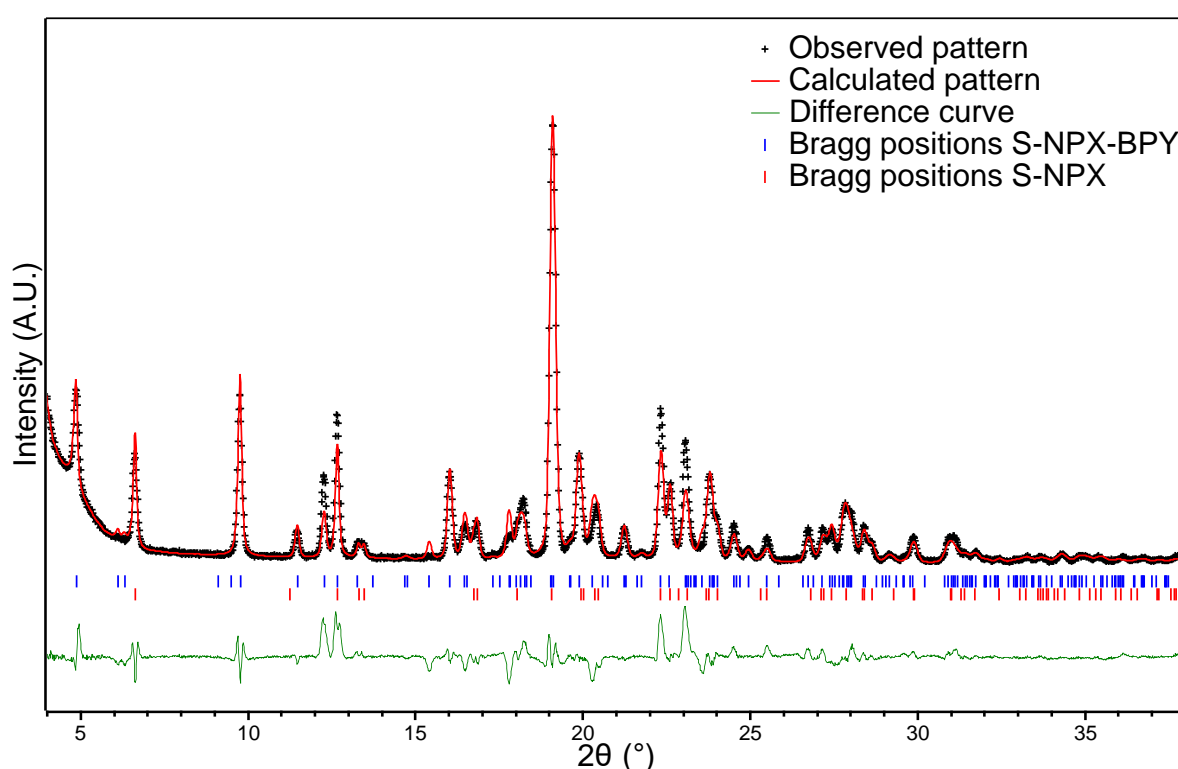


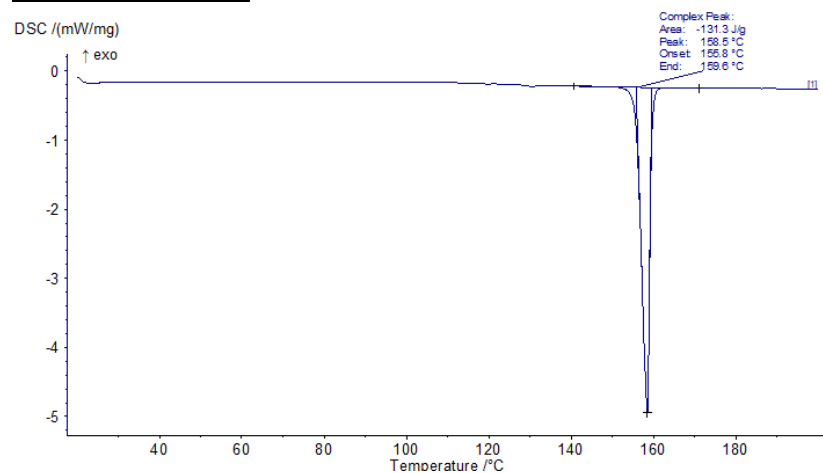
Figure: Rietveld refinement of GAS2 sample against the crystal structures of S-naproxen and S-Naproxen-bipyridine cocrystal found in the literature [3,4]. The refined parameters lead to $a = 15.430(14)$ $b = 5.802(4)$ $c = 19.378(23)$ $\beta = 110.93(5)$ for S-Naproxen-bipyridine cocrystal (slightly higher than those of the published structure that was recorded at low temperature) and $a = 13.327(18)$ $b = 5.772(5)$ $c = 7.882(6)$ $\beta = 93.96(9)$ for S-Naproxen. The profile and structural reliability factors were respectively:

$Rwp = 0.14$, $wR2(S-NPX-BPY) = 0.10$ and $wR2(S-NPX) = 0.09$

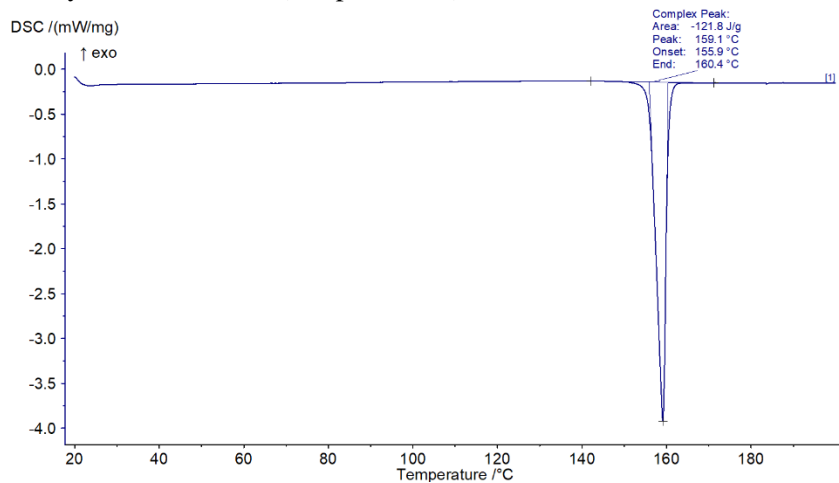
$$\left(\text{where } Rwp = \left[\frac{\sum \omega_i (y_{i,obs} - y_{i,calc})^2}{\sum \omega_i y_{i,obs}^2} \right]^{1/2} \text{ and } wR2 = \left[\frac{\sum (\omega_k (F_{k,obs}^2 - F_{k,calc}^2))^2}{\sum \omega_k (F_{k,obs}^2)^2} \right]^{1/2} \right)$$

Supplementary Information 3. DSC plots of S-NPX, commercial and recrystallized, commercial BiPY, and of produced powders by S-NPX and BiPY coprocessing;RS-NPX, commercial and recrystallizedand of the product obtained by RS-NPX and BiPY coprocessing

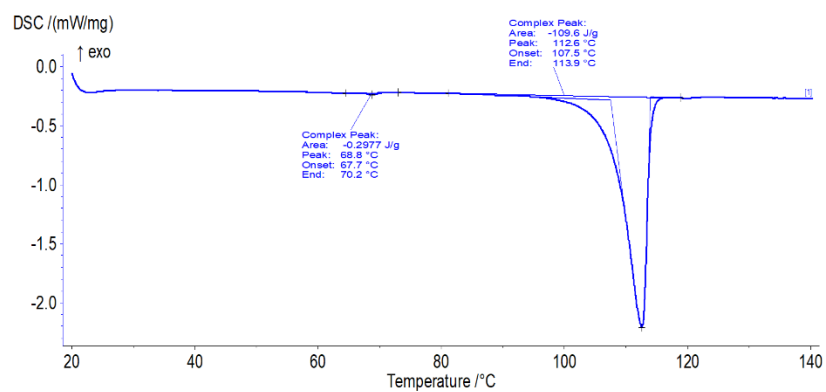
Commercial S-NPX



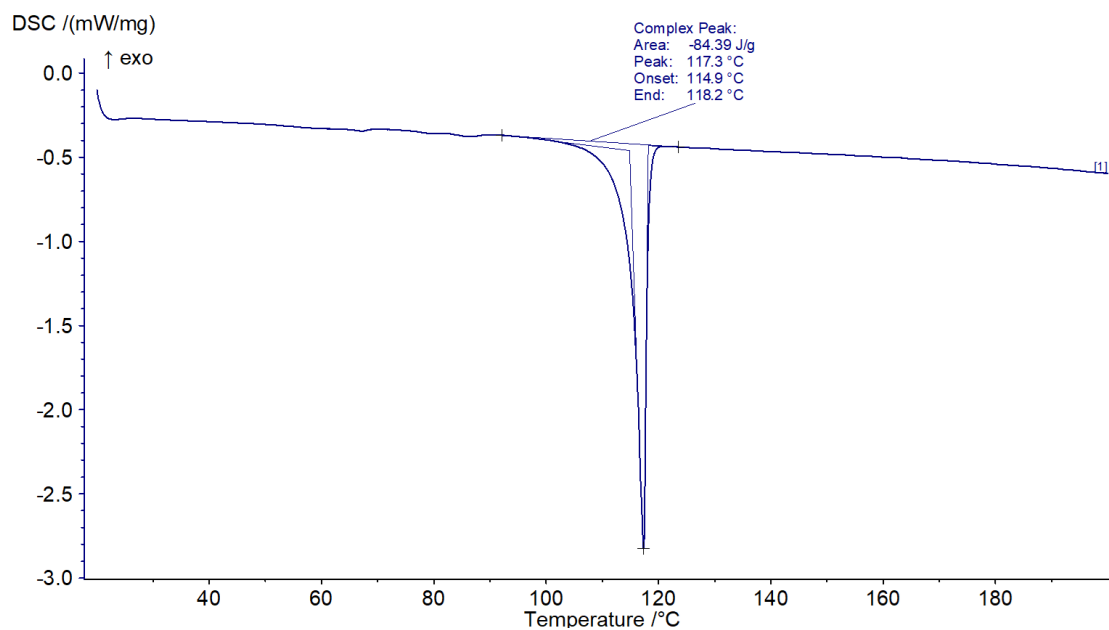
Recrystallized S-NPX (sample GAS1)



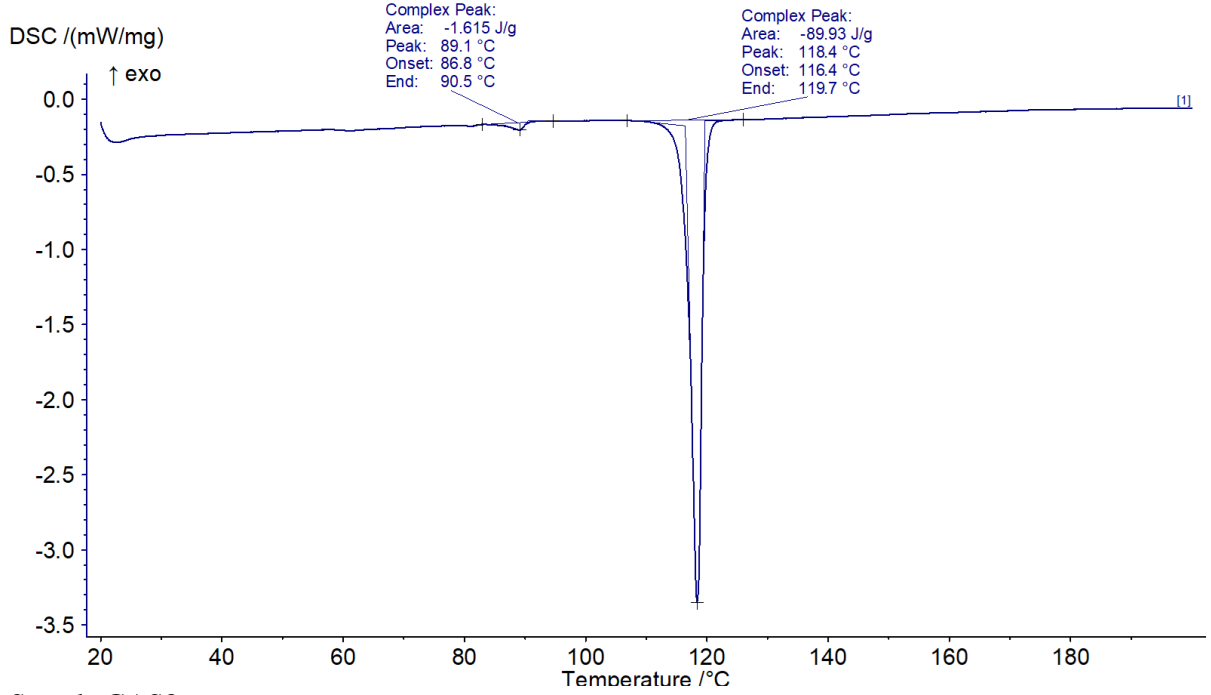
Commercial BiPY



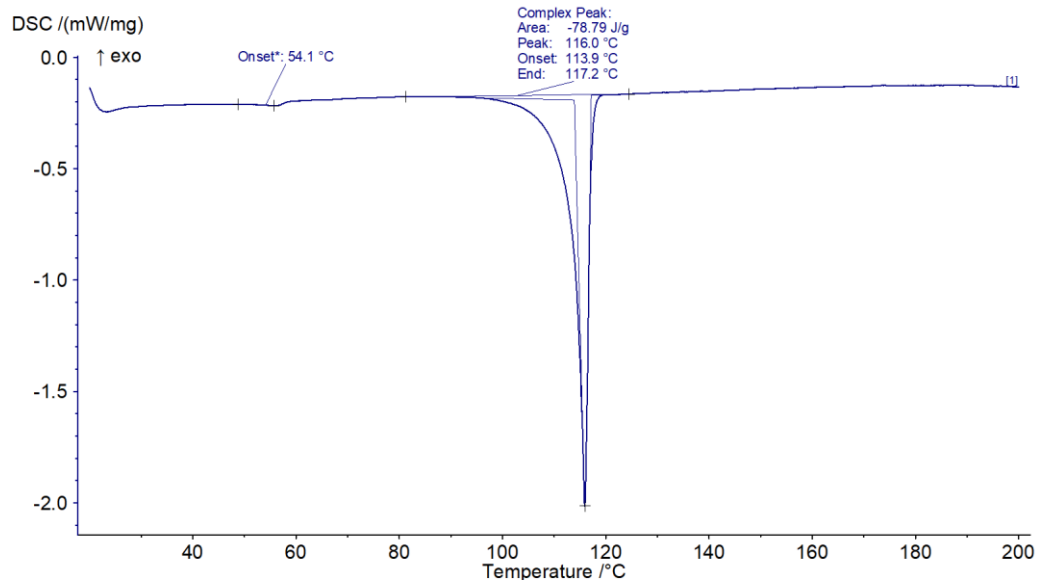
Sample CSS3



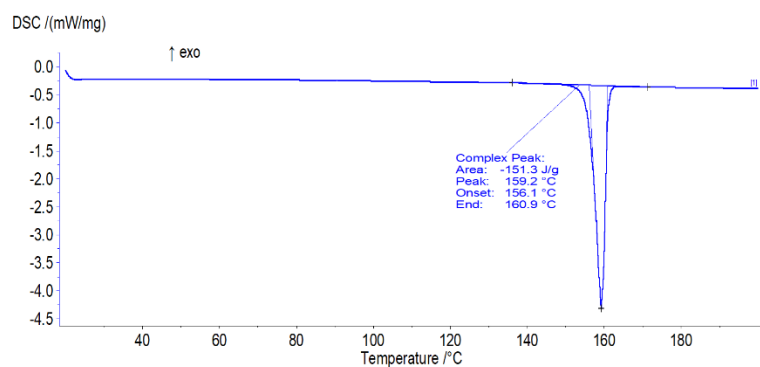
Sample CSS5



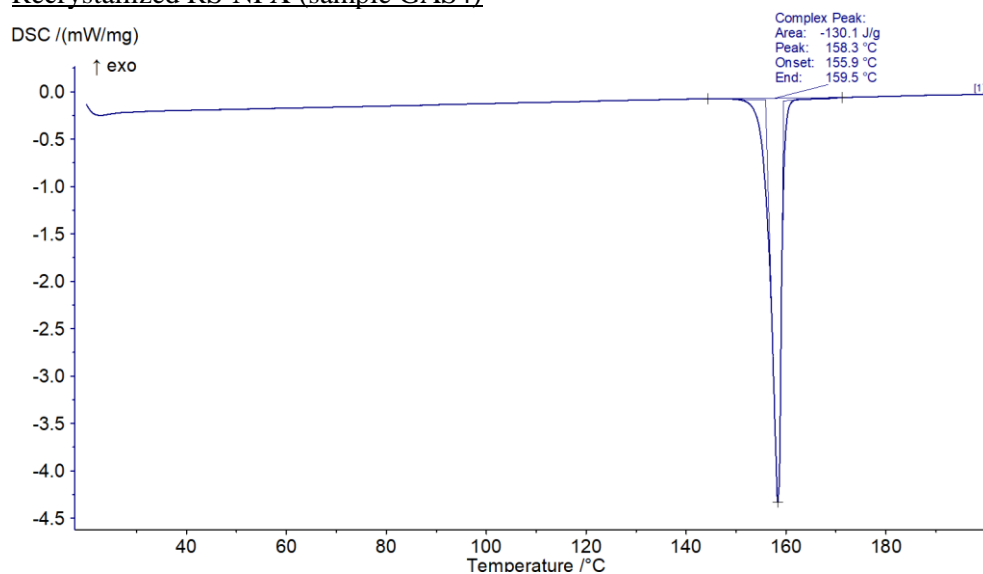
Sample GAS3



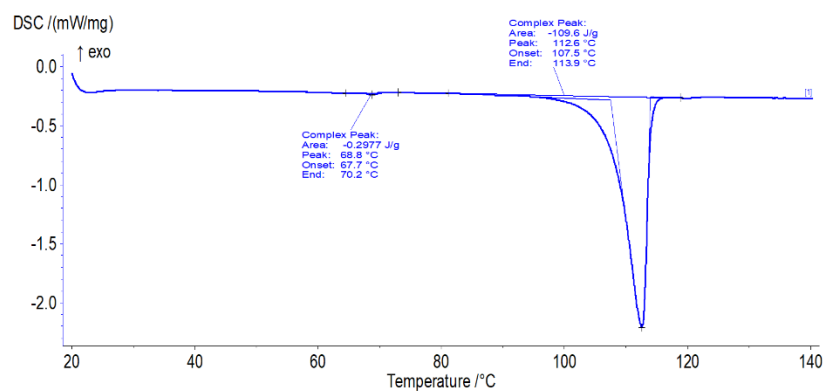
Commercial RS-NPX



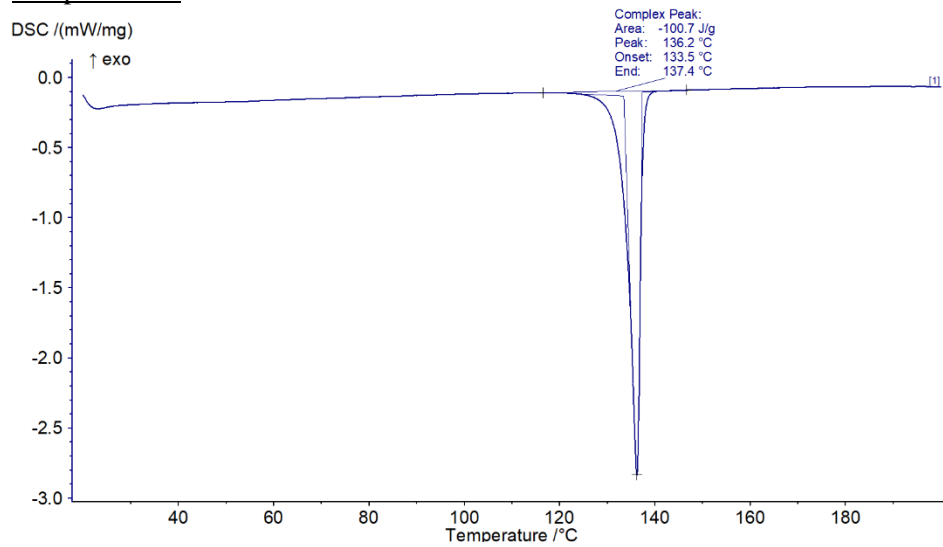
Recrystallized RS-NPX (sample GAS4)



Commercial BiPY



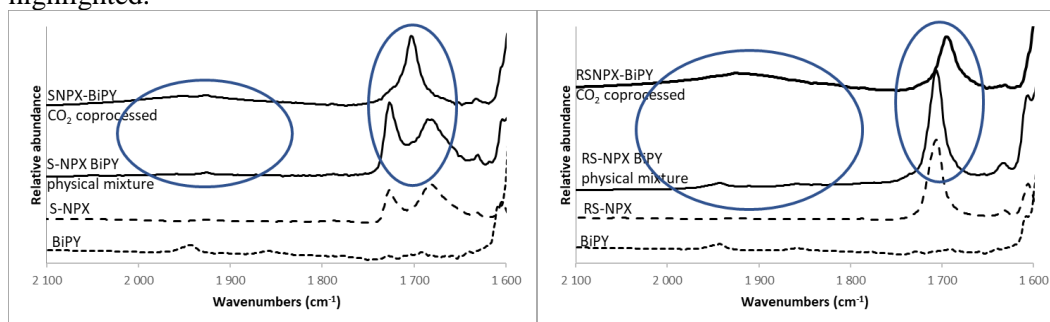
Sample GAS6



Supplementary information 4. Picture of recrystallized S-NPX (sample GAS1)



Supplementary information 5. ATR-FTIR spectra of a) S-NPX, BiPY, physical mixture of S-NPX and BiPY in ratio 2:1, the product obtained by S-NPX and BiPY coprocessing (GAS3); b) RS-NPX, BiPY, physical mixture of RS-NPX and BiPY in ratio 2:1, the product obtained by RS-NPX and BiPY coprocessing (GAS6). The main differences between physical mixture and product spectra are highlighted.



Supplementary information 6. Solubility measurements in acetone at 40°C of S-NPX, R-NPX and various S-NPX + R-NPX proportion mixtures. Table with concentration of naproxen determined at the 'Clear point' for the different R-Naproxen ratio.

R-Naproxen ratio	Clear point (g NPX / g acetone)
0	0.28
0.27	0.23
0.5	0.21
0.75	0.23
1	0.31

References

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- [3] K. Manoj, R. Tamura, H. Takahashi, H. Tsue, Crystal engineering of homochiral molecular organization of naproxen in cocrystals and their thermal phase transformation studies, *CrystEngComm.* 16 (2014) 5811–5819. <https://doi.org/10.1039/C3CE42415D>.
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