



HAL
open science

Cocrystallization of Naproxen and Bipyridine assisted by supercritical CO₂.

Fatma Ercicek, Christelle Harscoat-Schiavo, Patrick Layrisse, Mathieu Marchivie, Yohann Cartigny, Clément Brandel, Thierry Tassaing, Samuel Marre, Pascale Subra-Paternault

► **To cite this version:**

Fatma Ercicek, Christelle Harscoat-Schiavo, Patrick Layrisse, Mathieu Marchivie, Yohann Cartigny, et al.. Cocrystallization of Naproxen and Bipyridine assisted by supercritical CO₂.. EUROPEAN MEETING SUPERCRITICAL FLUIDS, ISASF, May 2023, BUDAPEST, Hungary. hal-04203052

HAL Id: hal-04203052

<https://hal.science/hal-04203052v1>

Submitted on 11 Sep 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Cocrystallization of Naproxen and Bipyridine assisted by supercritical CO₂. CO₂ solvent or CO₂ antisolvent, what is the best process?

Ercicek F.^{a,b} Harscoat-Schiavo^{a,*} Layrissé^a P. Marchivie^b M. Cartigny^c Y. Brandel^c C. Tassaing^d T. Marre^b S. Subra-Paternault^a P.

^aUniversité Bordeaux, CBMN-UMR5248, Allée Geoffroy St Hilaire, F-33600 Pessac, France

^bUniversité de Bordeaux, ICMCB-CNRS, 87 avenue du docteur Albert Schweitzer, F-33607 Pessac cedex, France

^cNormandie Univ, UNIROUEN, SMS, F-76000 Rouen, France

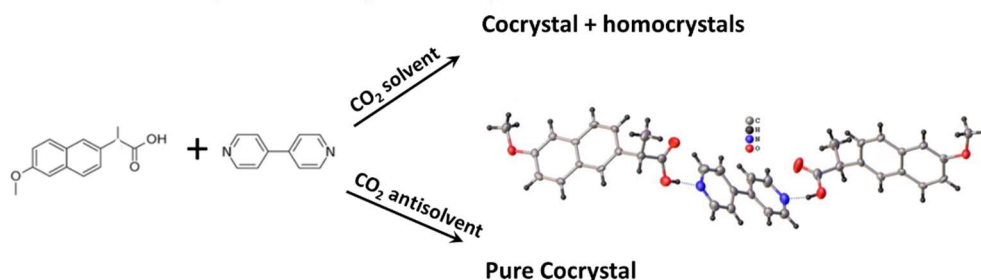
^dUniv. Bordeaux, CNRS, Bordeaux INP, ISM, UMR 5255, F-33400 Talence, France

*christelle.harscoat-schiavo@u-bordeaux.fr

Crystalline materials obtain many of their properties from the molecular arrangement within the solid. For active pharmaceutical ingredients, a recent strategy to alter such properties is the formation of cocrystals, i.e. molecular complexes of two entities in a solid state. Although cocrystal formation relies on molecular interactions, their presence is insufficient to predict if a cocrystallization will be successful. Cocrystals of S-naproxen (S-NPX) and RS-naproxen (RS-NPX) with 4,4'-bipyridine (BiPY) have been produced by Manoj [1] by evaporation (S-NPX₂:BiPY₁ and RS-NPX₂:BiPY₁ respectively). Cocrystallization assisted by supercritical fluids is in its infancy, with only few systems investigated so far [2–4]. Two different processes have been used for cocrystallization, using supercritical CO₂ as a solvent (CSS: Crystallization with Supercritical Solvent) and as an antisolvent (GAS: Gaseous AntiSolvent). This work presents for first time the formation of Naproxen-Bipyridine cocrystals by these two different processes and compares their performances.

The effects of the initial NPX:BiPY molar ratio and of the processing conditions were investigated. The influence of naproxen form, i.e. racemic or enantiopure, was also investigated. Precipitation yields were determined and the produced powders were characterized by powder X-Ray Diffraction, Differential Scanning Calorimetry, InfraRed spectroscopy and HPLC.

When S-NPX was processed, the powders obtained by the GAS method were of higher purity in S-NPX₂:BiPY₁ cocrystals than the products obtained by the CSS method, which presented also S-NPX homocrystals. The absence of BiPY in CSS product was explained by in-situ FTIR measurements of S-NPX and BiPY solubility in scCO₂. By GAS, an excess of BiPY in the initial 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. In appropriate conditions, pure RS-NPX₂:BiPY₁ and S-NPX₂:BiPY₁ cocrystal powders were produced, with precipitation yields as high as 65% and 56% respectively. Processing mixtures of S-naproxen and RS-naproxen with bipyridine produced mixtures of enantiopure and racemic cocrystals, in proportions corresponding to the initial mixture ratio. Therefore, it did not allow any enrichment of the product in any of the naproxen enantiomers.



References

- [1] K. Manoj, R. Tamura, H. Takahashi, H. Tsue, *CrystEngComm*. 16 (2014) 5811–5819. <https://doi.org/10.1039/C3CE42415D>.
- [2] C. Neurohr, A.-L. Revelli, P. Billot, M. Marchivie, S. Lecomte, S. Laugier, S. Massip, P. Subra-Paternault, *J.Supercrit Fluids*. 83 (2013) 78–85. <https://doi.org/10.1016/j.supflu.2013.07.008>.
- [3] B. Long, V. Verma, K.M. Ryan, L. Padrela, methods, *J.Supercrit Fluids*. 170 (2021). <https://doi.org/10.1016/j.supflu.2020.105134>.
- [4] I.A. Cuadra, A. Cabañas, J.A.R. Cheda, M. Türk, C. Pando, *J.Supercrit Fluids*. 160 (2020) <https://doi.org/10.1016/j.supflu.2020.104813>.