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## Cocrystallization of Naproxen and Bipyridine assisted by supercritical CO<sub>2</sub>. CO<sub>2</sub> solvent or CO<sub>2</sub> antisolvent, what is the best process?

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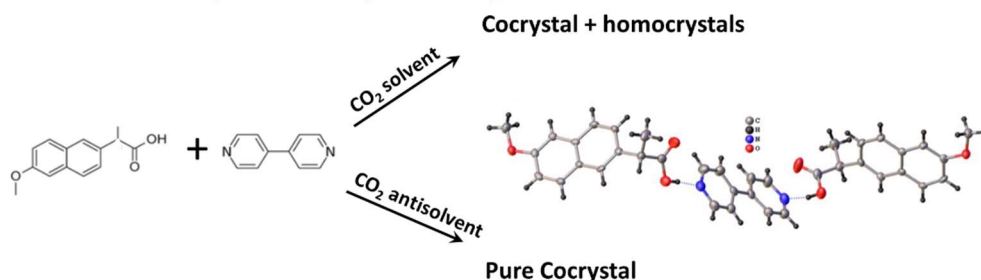
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Crystalline materials obtain many of their properties from the molecular arrangement within the solid. For active pharmaceutical ingredients, a recent strategy to alter such properties is the formation of cocrystals, i.e. molecular complexes of two 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-NPX<sub>2</sub>:BiPY<sub>1</sub> and RS-NPX<sub>2</sub>:BiPY<sub>1</sub> 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 CO<sub>2</sub> 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-NPX<sub>2</sub>:BiPY<sub>1</sub> 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 scCO<sub>2</sub>. By GAS, an excess of BiPY in the initial mixture was mandatory to produce pure S-NPX<sub>2</sub>:BiPY<sub>1</sub> cocrystals whereas pure RS-NPX<sub>2</sub>:BiPY<sub>1</sub> cocrystals were identically produced from mixtures of 2:2 and 2:1 NPX:BiPY initial ratio. In appropriate conditions, pure RS-NPX<sub>2</sub>:BiPY<sub>1</sub> and S-NPX<sub>2</sub>:BiPY<sub>1</sub> 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

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