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Investigations of pharmaceutical compounds co-crystallization for application to chiral resolution assisted by supercritical CO₂

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Co-crystalline products are becoming increasingly important in the pharmaceutical industry, due to the chirality, low water solubility and low bioavailability of most active pharmaceutical ingredients (API). Solids with a single crystalline phase composed of two entities (API + cofomer COF) linked *via* non-covalent interactions are called co-crystals. The modification of the API crystal lattice through the incorporation of the COF enhances the physicochemical properties of the initial drug without altering its therapeutic purposes. Thus, understanding crystallization processes can help to obtain products with desired properties. The formation of metastable conglomerates by co-crystallization can be a solution for optical resolution [1].

With the rising demand for green technologies, a co-crystal manufacturing strategy has been coupled with supercritical fluids. Supercritical CO₂ (scCO₂) is non-toxic, inexpensive, and manageable, which is frequently employed as an anti-solvent, like in the Gaseous Anti-Solvent (GAS) method. It enables reaching high supersaturation and directly obtaining dry products [2].

This work, first, highlights the manufacturing process (batch inox reactor) and the characterization of unknown co-crystals of chiral compounds produced by supercritical CO₂. The solubility of the selected chiral API and COF in the initial solvent system is reduced by the anti-solvent effect of CO₂, resulting in co-precipitation. The parameters influencing the purity of the co-crystals, such as the choice of solvents, temperature, and stoichiometric ratio were studied. The results demonstrate the obtaining of unidentified co-crystal structures, which were elucidated by XRD.

In parallel, a high-pressure microfluidic device has been developed to investigate crystallization phenomena under scCO₂. Thanks to optical access being provided by such a device, *in-situ* observations of time-related events are possible. Visualization of racemic naproxen crystals is shown in Figure 1. From these data, knowledge on the growth kinetics under scCO₂ can be acquired. *In-situ* precipitation monitoring of racemic and enantiopure co-crystals in a high-pressure optical cell thanks to FTIR spectroscopy is in progress. Relevant information on the behavior of racemic and enantiopure compounds precipitation are being obtained thanks to *in-situ* analysis. These first results could be an opening perspective for enantioseparation in supercritical conditions.

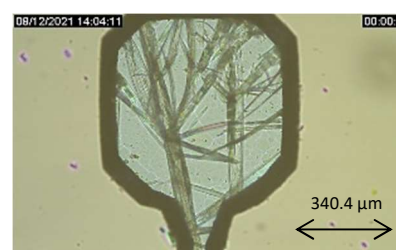


Figure 1: On-chip precipitation of RS-NPX by optical microscope in a micro-pool

[1] L. C. Harfouche, C. Brandel, Y. Cartigny, S. Petit, and G. Coquerel (2020): **Resolution by Preferential Crystallization of Proxyphylline by Using Its Salicylic Acid Monohydrate Co-Crystal**, *Chemical Engineering & Technology*, 43, 1093-1098.

[2] C. Neurohr, A.L. Revelli, P. Subra-Paternault (2013): **Naproxen–Nicotinamide Cocrystals Produced by CO₂ Antisolvent**, *J. Supercrit. Fluids*, 83, 78-85.