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High-Pressure Solubility of Naproxen, Nicotinamide and their Mixture in Acetone with Supercritical CO_2 as an Anti-Solvent

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Cocrystals are receiving increased attention for improving the physicochemical characteristics of active pharmaceutical ingredients (APIs), such as solubility and stability. While various techniques are used to synthetize cocrystals at atmospheric conditions, cocrystallisation assisted by supercritical CO_2 was recently proposed as a new alternative to enhance the rate of cocrystal formation. Up to now, literature reports a lot of examples of compounds recrystallized by the addition of supercritical CO_2 to an organic phase (anti-solvent effect), while only few studies are devoted to cocrystal formation. By the so-called GAS version of the process, we successfully produced cocrystals of naproxen and nicotinamide. However, for the comprehension and development of a robust cocrystallization process, it is essential to address the thermodynamic outcomes, i.e. to evaluate the phase equilibria of the quaternary system API + coformer + solvent + supercritical CO_2 . Solubilities of binary mixtures in supercritical CO_2 have not been extensively investigated and most of the studies involved nonpolar aromatic hydrocarbons.To our knowledge, only one study is devoted to solubility measurements of two solids in CO_2 with ethanol as a cosolvent while the study of ternary system (API - solvent -CO_2) is generally not performed in the whole range of concentration (i.e. only few percents of solvent). In this work, a new equipment was designed in order to measure solubility of API-coformer mixture in a supercritical CO_2 - cosolvent mixture. An analytical method was used, based on a variable-volume cell with sampling and analysis of the fluid phase at high pressure by High-Performance Liquid Chromatography (HPLC). The equipment is suitable to operate at temperatures ranging from (293 to 333) K and pressures up to 20 MPa. Solubility of naproxen (NPX) and nicotinamide (NCTA) and their mixture in acetone + supercritical CO_2 systems were measured at two temperatures (298.15 and 310.65 K) and at 10 MPa over all range of CO_2 compositions. Nature of the solid phase was also investigated.