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Fatma Ercicek, Arnaud Erriguible, Pascale Subra-Paternault, Christelle Harscoat-Schiavo, Samuel Marre. In situ microfluidic investigations of APIs crystallization dynamics in scCO₂: from thermodynamic equilibrium to growth kinetics. 20th European Meeting on Supercritical Fluids (EMSF 2024), International Society for the Advancement of Supercritical Fluids; European Federation of Chemical Engineering; University of Maribor, May 2024, Maribor, Slovenia. pp.1-1. hal-04579249

HAL Id: hal-04579249

<https://hal.science/hal-04579249v1>

Submitted on 7 Jun 2024

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***In situ* microfluidic investigations of APIs crystallization dynamics in scCO₂: From thermodynamic equilibrium to growth kinetics**

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In the intricate landscape of pharmaceutical manufacturing, crystallization stands as a fundamental unit operation, constituting approximately 90% of the isolation of active pharmaceutical ingredients (API) [1]. Supercritical fluids, notably CO₂, are gaining prominence as environmentally sustainable alternatives due to their unique properties. Furthermore, in an era of miniaturization, microfluidic technology enhances heat and mass transfer, reduces preparation volumes and waste, improves reproducibility, and, crucially, provides optical accessibility for *in situ* analyses such as optical microscopy, UV, IR, and Raman spectroscopy. This study focuses on utilizing a specialized microfluidic platform under supercritical CO₂ (scCO₂) conditions to crystallize APIs, enabling an in-depth understanding and real-time observation of crystallization under elevated pressures.

The development of the microfluidic platform presented a significant technical challenge, requiring the design of tailored micro-reactors. The validated design ensures precise CO₂ diffusion within a micro-well system, presenting a pioneering approach for observing and studying. Prior to crystallization, the study addresses the rapid attainment of phase equilibrium through the microfluidic system, particularly focusing on the CO₂-acetone mixture. The experimental setup and protocol detail the reliability of the microfluidic device in examining phase equilibria in binary and ternary systems under pressure. Raman spectroscopy emerges as a key *in situ* characterization tool, facilitating the quantification of CO₂ composition over time, with values validated through numerical simulations.

Experimental efforts concentrate on the crystallization of naproxen, our model pharmaceutical compound. Parameters such as initial concentration, pressure, and stereoisomerism are explored. Results indicate that near-saturation concentrations reduce crystallization time, regardless of pressure, aligning with classical crystallization theories. The presence or absence of a counter-enantiomer significantly influences crystallization times, suggesting potential avenues for enantiomeric separation. In the context of crystal growth kinetics, the analysis of 2D images acquired via optical microscopy facilitates the estimation of growth kinetics through an inline model [2]. Unexpectedly, observations at 8 MPa demonstrate higher growth values than those at 10 MPa. The occurrence of liquid-liquid phase separation, a rare phenomenon, is observed, accompanied by theoretical thermodynamic propositions.

The microfluidic platform is also repurposed as a mini GAS (Gaseous Anti-Solvent) reactor for the rapid characterization of the S-NPX₂:BiPY₁ co-crystal under high pressure [3], thanks to Raman spectroscopy, showcasing its versatility.

In brief, this in-depth study not only broadens our understanding of pharmaceutical crystallization but also offers a unique perspective on the process under supercritical CO₂ conditions. The fusion of scCO₂ and microfluidic technology suggests a potential shift in how we produce pharmaceutical compounds, especially those with low solubility to increase it. Overall, this study stands out by highlighting the synergy between advanced technology and scientific exploration, providing profound insights into the complex dynamics of crystallization under scCO₂ [4].

References

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