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### ► To cite this version:

Pierre Guillou, Samuel Marre, Arnaud Erriguible. Thermodynamic assessment of two-step crystallization occurrence in supercritical fluid. 20th European Meeting on Supercritical Fluids, International Society for the Advancement of Supercritical Fluids; European Federation of Chemical Engineering; University of Maribor, May 2024, Maribor, Slovenia. pp.1-1. hal-04624296

**HAL Id: hal-04624296**

**<https://hal.science/hal-04624296>**

Submitted on 25 Jun 2024

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## THERMODYNAMIC ASSESSMENT OF TWO-STEP CRYSTALLIZATION OCCURRENCE IN SUPERCRITICAL FLUID

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A consensus is emerging to rule that the classical nucleation theory is not the only pathway of crystallization: recent works [1] proposed the demonstration of two-stage nucleation for different media, liquid-solid, solid-solid and vapour-solid, with possible spinodal decompositions.

In the case of the crystallization of an Active Pharmaceutical Ingredient (API) in supercritical CO<sub>2</sub>, a possible way to describe a two-step crystallization mechanism involves the apparition of transient metastable liquid droplets in the vapour phase of the API dissolved in the scCO<sub>2</sub>, before crystallization. In order to find out under which pressure and temperature conditions such a two-step mechanism could be observed in supercritical conditions, we proposed a thermodynamical modelling of the stability / metastability / unstability for {(S)-Naproxen + CO<sub>2</sub>} and {(RS)-Ibuprofen + CO<sub>2</sub>} vapour binary mixtures at 313K, based on the well-known Peng – Robinson equation of state.

The binary interaction parameters of the PREOS describing the fluid phases have been fitted using solid solubility experimental data from literature [2,3]. We have compared two different fugacity models for the solid phase: the first one is based on a classical subcooled liquid like approximation, whereas the second one is based on the Lee – Kesler equation to estimate the sublimation pressure of (S)-Naproxen or (RS)-Ibuprofen in scCO<sub>2</sub>.

A classical fugacity approach then shows that the binary vapour can condense in a liquid phase, metastable relatively to the solid phase, on condition for which moderate supersaturation levels are reached. We have shown, that the compositions of the predicted metastable liquid phases depend slightly on the pressure.

A study of the curvature of the Helmholtz free energy is then performed, based on Hessian matrices, in order to find the limits of intrinsic stability of the mixtures (the spinodal limits): it shows that the vapour mixtures can become intrinsically unstable at higher supersaturation.

Phase diagrams have been presented with stable, metastable and unstable domains (Figure 1). Finally, we rationalised the probability of occurrence of two-step crystallisation by estimating the supersaturation ratio required to reach the metastability and unstability limits.

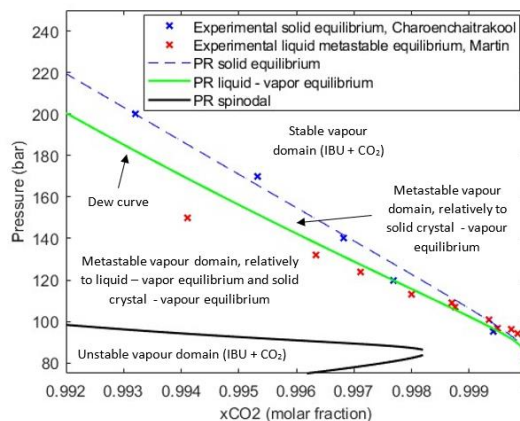


Figure 1: {(RS)-IBU + CO<sub>2</sub>} mixtures at 313.1K

[1] H. Fu, X. Gao, X. Zhang, L. Ling, *Crystal Growth & Design*, **2022**, 1476–1499

[2] S.S.T. Ting, D.L. Tomasko, N.R. Foster, S.J. Macnaughton, *Industrial & Engineering Chemistry Research*, **1993**, 1471–1481

[3] M. Charoenchaitrakool, F. Dehghani, N.R. Foster, H.K. Chan, *Industrial & Engineering Chemistry Research*, **2000**, 4794–4802



Additional information:

- Primary topic area: Thermodynamics & High-Pressure Equilibria
- Secondary topic area: Particle formation
- Just for oral presentation