In situ microfluidic investigations of APIs crystallization dynamics in srCO2 : from thermodynamic equilibrium to growth kinetics

Fatma Ercicek, Arnaud Erriguible, Pascale Subra-Paternault, Christelle Harscoat-Schiavo, Samuel Marre

▶ **To cite this version:**

Fatma Ercicek, Arnaud Erriguible, Pascale Subra-Paternault, Christelle Harscoat-Schiavo, Samuel Marre. In situ microfluidic investigations of APIs crystallization dynamics in srCO2 : from thermodynamic equilibrium to growth kinetics. Workshop - "Recent Trends in Microfluidics", Fédération de Microfluidique en Aquitaine, Jun 2024, Talence, France. hal-04654543

HAL Id: hal-04654543
https://hal.science/hal-04654543v1

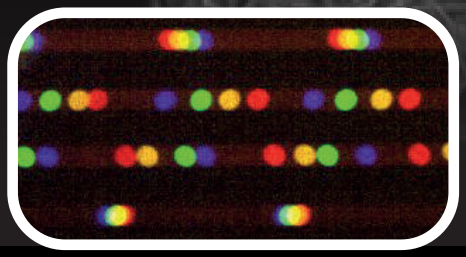
Submitted on 19 Jul 2024

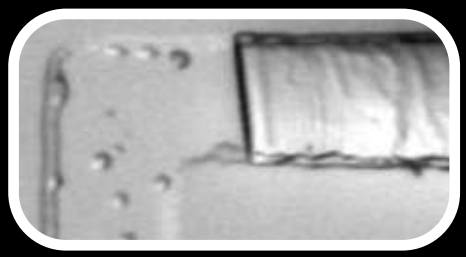
HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

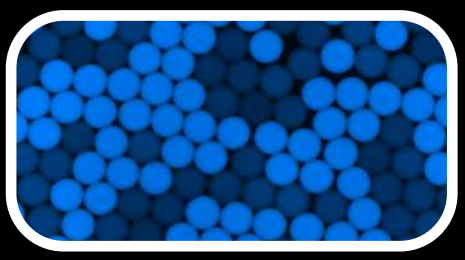
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

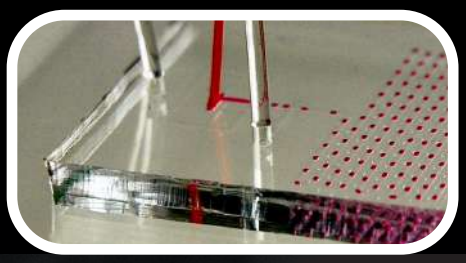
Recent Trends in Microfluidics

workshop @ ENSMAC, Pessac
10 June 2024









Shaping **a local network** for **academics** and **industry** working with **microfluidics**

Biology - Health - Chemistry
Physics - Energy - Materials - ...

Submission of contributions
before 15 April 2024
at https://microflu2024na.sciencesconf.org
talk 10 min + 5 min | **poster** (& flash-com)

Organising & Scientific Committee

Antoine ALLARD (LOMA UMR5798)
Jean-Christophe BARRET (CRPP UMR5031)
Thomas BENEYTON (CRPP UMR5031)
Stéphane CHEVALIER (I2M UMR5295)
Damien COUDREUSE (IBGC UMR5095)
Ulysse DELABRE (LOMA UMR5798)
Jacques LENG (LOF UMR5258)
Claire-Line MARAIS (BFP UMR1332)
Mickael MAUCOURT (BFP UMR1332)
Adeline PERRO (ISM UMR5255)
Jean-Baptiste SALMON (LOF UMR5258)

Réseaux **BEST & FOL**
Départements
SIN, SMR, SBM

Université de BORDEAUX

cnrs

Inserm

BORDEAUX INP

INRAE

RÉGION Nouvelle-Aquitaine

Crédit Photo : BFP - CRPP - LOF - LP2N

Recent Trends in Microfluidics
workshop @ ENSMAC, Talence, 10 June 2024

In situ microfluidic investigations of APIs crystallization dynamics in $scCO_2$: From thermodynamic equilibrium to growth kinetics

Fatma Ercicek[a,b*], **Arnaud Erriguible**[a], **Pascale Subra-Paternault**[b], **Christelle Harscoat-Schiavo**[b], **Samuel Marre**[a]

[a] *CNRS, Univ. Bordeaux, ICMCB, UMR 5026, F-33600 Pessac, France*
[b] *CNRS, Univ. Bordeaux, CBMN, UMR 5248, F-33600 Pessac, France*

* *fatma.ercicek@icmcb.cnrs.fr*

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 CO_2, 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 CO_2 ($scCO_2$) 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 CO_2 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 CO_2-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 CO_2 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 CO_2 conditions. The fusion of $scCO_2$ 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 $scCO_2$[4].

References

[1] J.M. Schall, J.S. Mandur, R.D. Braatz, A.S. Myerson, *Crystal Growth & Design*, **2018**, 18, 1560-1570.

[2] M. Garel et al., *Microbiology*, **2022**. doi: 10.1101/2022.07.29.501982.

[3] F. Ercicek et al., *J. Supercrit. Fluids* **2023**, 200, 105976, doi: 10.1016/j.supflu.2023.105976.

[4] F. Ercicek et al., *Lab on a Chip,* submitted **2024**.