Title of the thesis : Structure and dynamics of active pharmaceutical ingredients-supercritical CO2 interface

For the pharmaceutical industry in particular, controlling the polymorphic form is essential. During the evolution of the production process, it aids in the optimization of material qualities and inhibits the emergence of unanticipated new forms. Organic crystals frequently exhibit polymorphism, which is the property of a substance that allows it to form in numerous different crystal shapes. It has a major effect on the physicochemical characteristics of solid materials in a number of crucial industries, such as the manufacture of high-energy materials, dyes and pigments, and food. Recent studies have demonstrated the solid surface's important significance in the polymorphic synthesis of active pharmaceutical ingredients (APIs). [1] [2] Because they have fewer neighbors, the molecules near the solid interface are different spatially from those in the bulk, showing greater mobility and conformational changes. Although the kinetics and structural alterations that underlie the mechanism are still poorly understood, these surface molecules have an impact on polymorphism selection mechanisms and crystal nucleation rates. Our latest research demonstrates a relationship between the polymorph state and distribution conformations of API molecules dissolved in supercritical CO2 (scCO2). [3]
This thesis focuses on the structural and dynamics changes at the interface between the solid API and $scCO_2$ by combining melt and solvent (scCO2) crystallization methods. The goal of this PhD thesis is to develop an environmentally friendly method for selectively synthesizing a certain polymorph form of an active pharmaceutical ingredient (API) using scCO2. The solubility and kinetic dissolution of CUR in scCO2 will be measured using in situ IR and Raman spectroscopy. (ii) The API's conformations at the scCO2 interface will be sampled, and structural changes of the solid form will be monitored. We will employ chemometric techniques (Principal Components Analysis) on the measured spectra data to identify the parameters that primarily influence the polymorph transformation processes due to their intrinsic complexity.
The force field for the chosen API and CO_2 will initially be optimized using molecular dynamics simulations, with a particular emphasis on how well these models can replicate experimental data on the latent heat of melting and API melting temperature. The investigation of interfacial characteristics using molecular dynamics (MD) simulations is the second phase. Examining the kinetics and structure of the API-scCO2 interface is the aim of this phase. The candidate will use the 'Identification of Truly Interfacial Molecules' (ITIM) algorithm to identify the API molecules at the interface. *[5]*

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[5] M. Lbadaoui-Darvas, A. Idrissi, P. Jedlovszky, Computer Simulation of the Surface of

Aqueous Ionic and Surfactant Solutions, J. Phys. Chem. B. 126 (2022) 751–765. https://doi.org/10.1021/acs.jpcb.1c08553.

keywords :
Supercritical fluids, polymorph transformations, in situ vibration spectroscopy, molecular dynamic simulation, interfacial properties.

Candidates profile
The candidates should have recently obtained a master's degree in condensed matter physics or physical-chemistry and strong interest in multidisciplinary approaches at the interface between physics and chemistry of materials and pharmacy. The candidate also have a good practice of English language.

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