CONFORMATIONAL EQUILIBRIA AT THE CRYSTAL-SUPERCRITICAL FLUID INTERFACE

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Supercritical fluids technologies(SCF) are increasingly being used for the synthesis and targeted modification of materials and composites. In pharmaceuticals, such materials are widely applied to enhance the bioavailability of drug formulations, control their release, and obtain multi-component crystals, among other applications. One promising SCF technology for pharmaceuticals is the formation of micronized particles for use in inhalers. The main advantages of SCF technologies for producing inhalation suspensions include the following: (a) the ability to obtain micronized forms of the target substance with control over the particle size of the resulting crystals across a wide range of state parameters; (b) a high degree of purity of the target product obtained using both rapid expansion of supercritical solution (RESS) methods and those based on the anti-solvent effect (SAS), and (c) control over the polymorphism of the obtained target product by varying the thermodynamic parameters of the supercritical fluid during crystallization, which allows producing samples with the desired polymorphic purity.

Polymorphism screening is typically a completely empirical procedure. This report presents a new methodology for screening conformational polymorphism, based on a correlation discovered in the authors' previous works between the distribution of conformers of a drug compound dissolved in a supercritical solvent and the polymorph that forms under the studied state parameters. A methodology was developed for predicting polymorph formation, based on a combination of experimental (IR and NMR spectroscopy) and computational (quantum chemical calculations, molecular dynamics simulation, density functional theory) approaches. In order to understand the origin of correlation between of conformer population at fluid state and polymorfism MD simulation of three curcumin polymorphs at vacuum interfaces. More specifically, we employ layer-resolved molecular dynamics simulations to investigate the temperature evolution of the free surfaces of the three curcumin polymorphs along their low-index crystallographic faces. Across all systems, substantial structural rearrangements emerge well below the bulk melting temperature, consistent with the onset of thermally activated interfacial softening. However, both the onset temperature and the magnitude of the response are strongly anisotropic. By combining normalized layer displacement δR_[klm], positional fluctuations, joint position-tilt distributions, intermolecular packing descriptors (θ1,θ2), hydrogen-bond distance distributions, and conformational analysis, we resolve the coupled structural changes underlying this behavior.

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