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Controlling Polymorph Crystallisation Using Structured Ternary Fluids

Structured ternary fluid (STF) mixtures consist of a small amphiphilic molecule, called a hydrotrope, that enhances the miscibility of two other immiscible components, typically oil and water. STFs, also called surfactant-free microemulsions or ultra-flexible microemulsions, have been shown to provide unprecedented control in the crystallisation of glycine polymorphs under ambient conditions.

Typically, crystallisation of glycine happens under kinetic control, resulting in the formation of the metastable α-glycine polymorph. However, restricted diffusion of glycine within the hydroxyl network of an octanol/water/ethanol (OWE) mixture allows crystallisation to proceed via a higher nucleation rate and slower crystal growth pathway. The STF mixture acts as a nanocrystal incubator, prolonging locally high glycine supersaturations and allowing nanocrystals to exist for extended times. This soft nanoconfinement means that crystallisation can occur under thermodynamic control, selectively producing slow-growing γ-glycine as the majority polymorph. Changing the STF composition and initial glycine supersaturation allows all three polymorphs to be targeted from the same OWE ternary mixture. The enhanced control of glycine crystallisation within this STF system has been investigated further using atomistic molecular dynamics simulations. Suitability of the glycine force field was assessed by calculating various solution and crystal-phase properties for the three ambient-pressure polymorphs. Namely, lattice energy, crystal density, hydration free energy, enthalpy of solution, solution density and polymorph free energy via the Einstein molecule method. Non-bonded parameters of the best-performing force field were calibrated using a multi-objective Bayesian optimisation approach to achieve better performance in reproducing crystal-phase properties.

STF structure was evaluated for various compositions through calculation of radial distribution functions and spatial density profiles. Additionally, computing shear viscosity, cluster lifetimes and diffusion coefficients for individual components allowed us to assess the degree of glycine nanoconfinement.

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