FORMATION THERMODYNAMICS FOR IPRONIAZID MULTICOMPONENT CRYSTALS WITH DIHYDROXYBENZOIC ACIDS

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The rational design of pharmaceutical multicomponent crystals has emerged as a key strategy for tailoring the physicochemical properties of drug substances without compromising their therapeutic efficacy. While structural characterization provides essential insights into molecular recognition patterns, a fundamental understanding of formation thermodynamics (Gibbs energy, enthalpy, and entropy) is crucial for predicting stability and guiding the selection of optimal solid forms for pharmaceutical development. This work focuses on the quantitative thermodynamic characterization of five iproniazid multicomponent crystals with 2,3-, 2,5-, 2,6-, 3,4-, and 3,5-dihydroxybenzoic acids.

The Gibbs energy of formation (ΔG_f) for the studied multicomponent crystals was determined using a solubility-based method in acetonitrile within the temperature range of 20 to 40 °C, which directly probes the equilibrium between the solid phase and the solution. The negative values of ΔG_f confirm that the formation of all investigated systems is a spontaneous process, ensuring their thermodynamic stability relative to the pure components. The temperature dependence of the solubility products allowed for the calculation of the enthalpies and entropies of formation. The results reveal that the process of multicomponent crystal formation between iproniazid and dihydroxybenzoic acids is primarily enthalpy-driven, indicating the dominant role of strong intermolecular interactions, such as hydrogen bonding, in the stabilization of the crystal lattice.

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