585c Synthesis of Supercritical Crystallization Processes

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Supercritical crystallization using carbon dioxide has become the favorite alternative to conventional processes such as evaporative crystallization and antisolvent crystallization particularly for processing pharmaceuticals. Such processes have been routinely designed based on pure component solubilities as a function of pressure. This approach is not reliable for multicomponent and multiphase systems since many important issues that impact process design cannot be addressed. For example, operating under different phase equilibria can affect the product properties such as size and morphology, but solubility diagram does not specify the type of phase equilibrium involved, such as whether the solubility data represent solid-vapor or solid-liquid-vapor equilibrium. This highlights the importance of understanding high-pressure phase behavior and its phase diagram representation, which can provide a more complete picture and deeper insights into the process.

To meet such a challenge, a framework for the conceptual design of supercritical crystallization processes based on better understanding of high-pressure solid-fluid equilibria and phase diagram representation is proposed. Based on a given process objective, a relevant phase diagram is generated and used to guide the process synthesis and determine feasible operating conditions, including temperature, pressure, and supercritical solvent-to-feed ratio. Compared to the conventional approach of determining such conditions by performing a series of bench-scale experiments in a trial-and-error manner, the proposed approach leads to speedier process development by offering a better workflow integrating modeling, experimental, and synthesis activities. Two examples are provided to illustrate the proposed approach. The first one illustrates how the phase diagram representation is useful in the design of the precipitation with compressed antisolvent (PCA) process using the ternary mixture of salicylic acid, ethanol, and CO2 as the model system. The second example illustrates the conceptual design of the rapid expansion of supercritical solutions (RESS) process using the ternary mixture of palmitic acid, tripalmitin, and CO2 as the model system.