**Thermodynamic Study of Acetaminophen in the Presence of an Impurity: Solubility and Melting Phase Diagram.**

**Peerapon Rapeenun** 1, Jeremy Merritt 2, Jon Selbo 2, Gerard Capellades 1

*1 Department of Chemical Engineering, Rowan University, Glassboro, NJ 08028, United States*

*2 Synthetic Molecule Design and Development, Lilly Research Laboratories,   
Eli Lilly &Company, Indianapolis, Indiana 46221, United States*

**Purpose:**

Impurity incorporation is not only an undesirable byproduct of pharmaceutical processing but has also been reported to act as a poison in a crystallization process, surpassing particle size control and secondary nucleation attempts (seed poisoning) [1]. This study aims to investigate the change in solubility due to impurity presence and/or the face poisoning in the crystal lattice via solid solution. Here, acetaminophen (ACM) and sulforhodamine B (SB, dye) were used as a model.

**Methods:**

To investigate the equilibrium solubility of ACM at varying levels of SB, both isothermal suspension and temperature cycling methods were employed. Experiments were performed with SB contents ranging from 10 to 80 wt% (solvent-free) under precisely controlled conditions, 25 °C for the isothermal measurements and 25–45 °C for the temperature-programmed experiments. Finally, the solid phases were characterized by X-ray powder diffraction (XRPD) for phase identification, optical microscope (OM) for SM incorporation, and differential scanning calorimetry (DSC) for melting phase diagram construction, while the saturated solutions were analyzed by high-performance liquid chromatography (HPLC) to establish the ternary phase diagram.

**Results and Conclusions:**

The temperature program offers a faster method to reach an equilibrium compared to isothermal suspension, producing a well-crystallized morphology and impurity incorporation. The presence of SB increases the solubility of ACM, with the system eventually reaching the eutectic composition observed as constant solubility in the middle region of the ternary phase diagram. To identify the crystal phases along SB compositions, the melting phase diagram will be determined.

**Keywords:**

Solubility, Solid Solution, Seed Poisoning, and Temperature Cycling.

**References:**

[1] Nong, A., et al. Impurity Retention and Pharmaceutical Solid Solutions: Visualizing the Effect of Impurities on Dissolution and Growth Using Dyed Crystals. CrystEngComm 2024, 26 (38), 5337–5350.