**In-Situ pH Modulation as a Crystallization Strategy for Low-Solubility APIs**

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**Purpose:**

Determining a robust crystallization process is a critical step in drug development. However, crystallization can be hindered by low solubility in typical process-relevant solvent systems. These cases often necessitate the use of high-boiling solvents or high-volume processes which can lead to the retention of residual solvent or increased production costs. As such, other methods to modulate solubility are an attractive alternative. The main goal of this research was to investigate *in-situ* pH modulation to transiently generate, and neutralize, salts of target compounds that are more soluble in process-relevant media.

**Methods:**

Initially, benzoic acid was employed as a model compound. Solubility in ethanol (EtOH)/water mixtures, followed by proof-of-concept EasyMax experiments, were performed to establish the dissolution and crystallization profile. During base addition, both the solution pH and concentration were monitored using ATR-IR and pH probes. Following this, neutralization was carried out, leading to crystallization of the free acid. Once established, a modified procedure was extrapolated to theophylline (with acid and base addition respectively). This methodology has also been extrapolated to a current API developmental candidate.

**Results:**

Benzoic acid showed only slight dissolution at EtOH:water (3:7 vol.) while sodium benzoate was highly soluble (> 333 mg/mL) in the same system. As such, crystallization could be carried out in low (8-10) volumes of EtOH:water (3:7 vol.). Additionally, monitoring the correlation between dissolution and pH revealed full dissolution at sub-stoichiometric amounts of base, resulting in less solution-bound sodium chloride byproduct. Applying this principle to theophylline also showed sub-stoichiometric acid was required to dissolve, followed by crystallization upon base addition. When this method was applied to an API developmental candidate, parameters such as temperature, rate of addition, and wash volumes were all deemed important criteria to examine.

**Conclusions:**

For crystallization development, solubility is the primary metric that guides initial solvent system selection for further process refinement. However, while industry guidance is focused on typical ICH Class 3 solvents, these may not be amenable to dissolution of low-solubility APIs without resorting to high-boiling components. The work herein shows that *in-situ* salt formation and neutralization is an attractive alternative to traditional cooling and antisolvent crystallization.

**Keywords:**

(Reactive crystallization, neutralization, pH modulation, solubility)