Supplementary Material

1.Solubility and supersaturation data of 7-ACT

(1) We prepared 7-ACT solutions of different concentrations with a solvent of acetonitrile at a ratio of 1.6:1 to water. Then we use a Raman spectrometer to collect Raman spectra of various concentrations. Pre-processes such as baseline removal, normalization, and smoothing were performed on each spectrum, and the preprocessed spectra are shown in Fig. S1 (a). Fig. S1 (b) shows the magnified Raman spectra of 1500-1850cm-1. We can see from the graph that the Raman spectral intensity of 7-ACT exhibits a good correlation with concentration. Therefore, we established a PLS prediction model for 7-ACT concentration and Raman spectroscopy, and the model results are shown in Fig. S1 (c). The model results are shown in Fig. S1 (c), where R2 is 0.996.

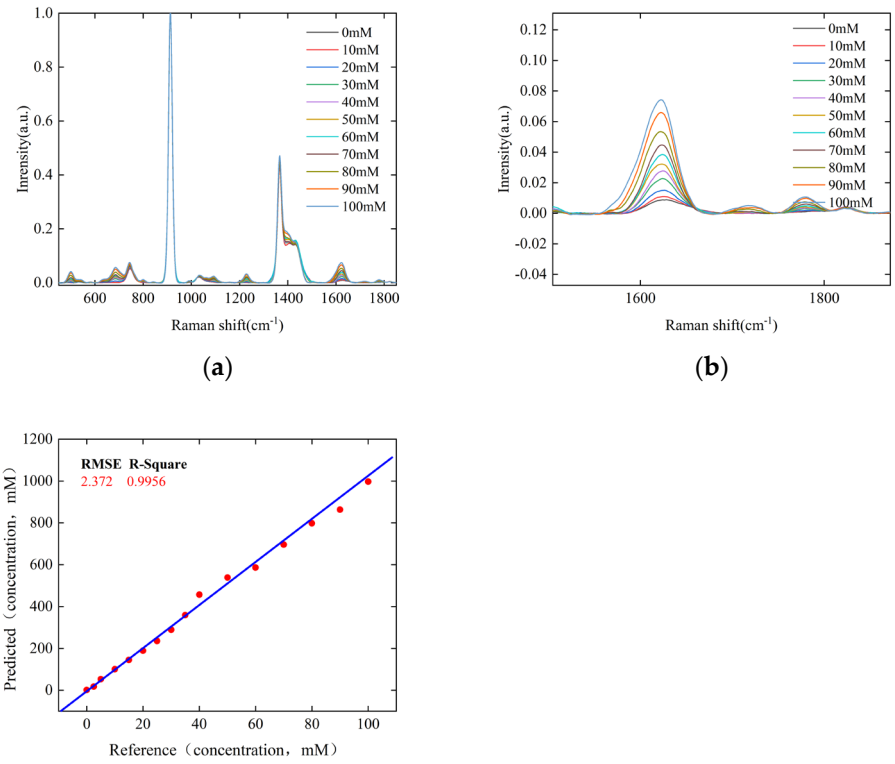


Figure S1 (a) Raman spectra of 7-ACT solution at different concentrations; (b) Raman spectroscopy with wave numbers 1500-1850cm-1 (c) PLS prediction model (Prediction and Reference)

(2) The correlation equation between solubility and pH

In considering the influence of acid-base dissociation equilibrium on drug solubility, Tsuji et al.[1], in 1978, introduced a relationship to depict the correlation between solubility C_T and the pH of the solution. This model, accounting for the protonated and deprotonated states of a drug at different pH levels, is expressed mathematically as follows:

$$C_T = C_0\left(\frac{a_{H+}}{K_1} + 1 + \frac{K_2}{a_{H^+}}\right) \tag{1-1}$$

C_T represents the molar solubility of the drug in solution, C_0 is the drug's intrinsic mola r solubility, a_{H^+} is the activity of protons in the solution, while K_1 and K_2 respectively repre sent the drug's dissociation constants at varying pH levels.

To simplify the handling of solidliquid equilibrium data in industrial applications, this e quation can be further simplified to:

$$C_T = C_0[10^{(pK_1 - pH)} + 10^{(pH - pK_2)} + 1] \quad (1\text{-}2)$$

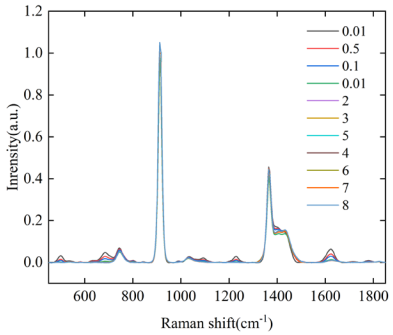
C_T is the molar solubility of the target solute in the system, C_0 is the intrinsic mol ar solubility of the target solute, pK_1 and pK_2 are the negative logarithms of the disso ciation constants of the target solute in the system, and pH is the acidity or alkalinity o f the system.

(3) We collected Raman spectra of 7-ACT acetonitrile solutions at different pH levels and used the same spectral preprocessing operation. Next, we will import the spectral data into the prediction model established in the first step to obtain the solubility of 7-ACT at different pH values. The spectral data at different pH values are shown in Fig.2 (a) and Fig.S2 (b). We fitted the solubility curve of 7-ACT using formulas (1-2). The fitted solubility curve is shown in Fig.S2 (c). From Fig.S2 (c), we can observe that the solubility of 7-ACT in acetonitrile solution reaches its lowest point between pH 3-4. The supersaturation of the solution can be calculated by the following equation:

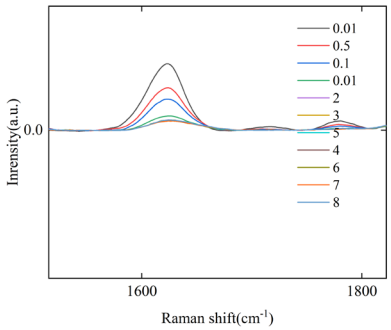
$$\sigma = (C - C_0) / C_0 \quad (1\text{-}3)$$

σ is the supersaturation of the solution, C is the actual concentration of the solution, and C_0 is the saturation concentration of the solution.

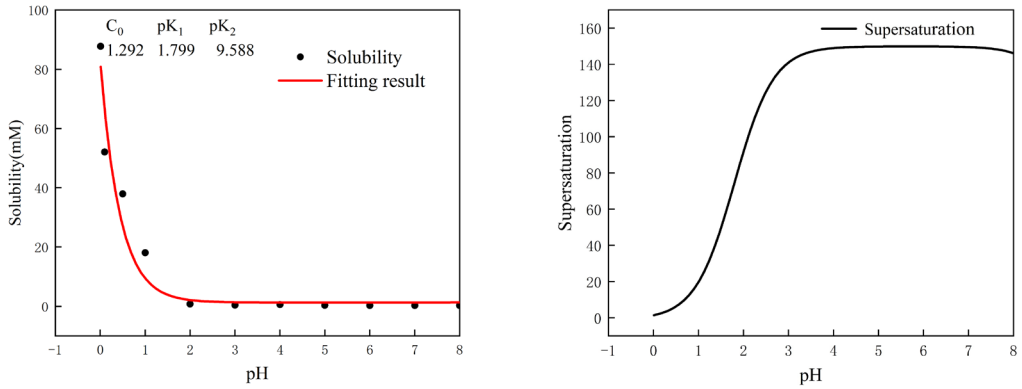
We used liquid chromatography to measure the 7-ACT concentration of the pre crystallization solution as 195mM (mmol/L). Therefore, We calculated the supersaturation value at a solution concentration of 195mM based on the supersaturation calculation formula (1-3), and we plotted the supersaturation curve in Fig.S2 (d).



(**a**)



(**b**)



(**c**) (**d**)

Figure S2 (a) Raman spectra of 7-ACT solution at different pH values; (b) Raman spectroscopy with a wavenumber of 1500-1850cm^{-1};(c) Solubility curves of 7-ACT in acetonitrile solution at different pH values;(d) Supersaturation curves of 7-ACT in acetonitrile solution at different pH values.

(4) We added the effect of temperature on the solubility of 7-ACT at different pH values, as shown in **Figure S3**. The solubility of 7-ACT increases with temperature across all pH values studied. Specifically, at pH 1.0, there is a marked rise in solubility corresponding to the increase in temperature, signifying a significant temperature dependency. At pH 1.5, the solubility of 7-ACT also increases with temperature. In contrast, at pH 2.0, solubility is relatively low regardless of temperature, with minimal increases observed as temperature rises. This pattern indicates that while temperature has a general effect on enhancing solubility, pH is a more decisive factor, with lower pH values leading to higher solubility of 7-ACT.

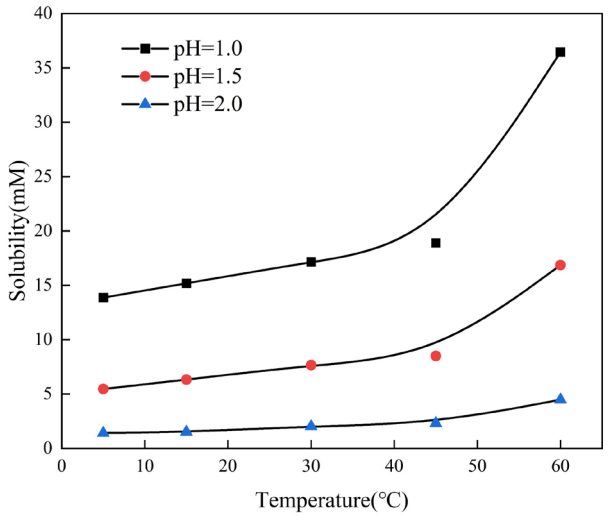


Figure S3 The change of solubility with temperature under different pH conditions.