

Insights into the Mechanism of Concomitant Nucleation of Form II and Ethanol Solvate of Spirolactone in Cooling Crystallization

Supplementary Information

The solubility of form II and the ethanol solvate of spironolactone in ethanol at different temperatures are listed in Table S1. And the calculation of shape factors of the two polymorphs are listed in Table S2.

Table S1. Solubility data of spironolactone in ethanol

T/K	Ethanol solvate		Form II	
	C*(mole fraction)	Regular Residual	C*(mole fraction)	Regular Residual
308.15	0.00653	1.20E-7	0.00617	5.08E-5
310.15	0.00728	2.84E-6	0.00674	-1.45E-5
313.15	0.00852	-3.98E-5	0.00778	-4.25E-5
314.15	0.00904	1.13E-5	0.00821	-8.21E-6
317.15	0.01062	2.12E-5	0.00950	3.24E-6
319.15	0.01181	3.00E-5	0.01047	1.53E-5
322.15	0.01371	-8.01E-5	0.01229	-5.48E-5
323.15	0.01458	5.48E-5	0.01269	5.33E-5

Table S2. Calculation of the Shape Factor

		Area(um ²)	Volume(um ³)	f_s	f_v	
Ethanol solvate	Length(um)	226.79 ^a				
	Width(um)	9.40	8703.86	20038.79	98.50	24.13
	Thickness(um)	9.05				
Form II	Length(um)	92.43				
	Width(um)	34.05	14908.91	107178.48	12.86	2.71
	Thickness(um)	18.90				

^a Each size of the crystals in Table S2 is the average value of 30 crystals

The Simplification Process of Equation (10)

Usually, a general expression of the induction time has been proposed by Kashief et al. (*J. Cryst. Growth. 1991, 110, 373*) as follow:

$$t_{\text{ind}} = \frac{1}{JV} + \frac{\alpha}{(a_n JG^{n-1})^{1/n}} \quad (15)$$

So this expression takes into account the rate of primary nucleation and the growth rate of crystallites, which should be responsible for the loss of the metastability.

The first part is the time for appearance of the first nucleus, which brings the system out of its metastable state. The loss of the metastability equilibrium is due to a mononuclear nucleation mechanism.

$$t_{\text{MN}} = \frac{1}{JV} \quad (16)$$

where V is the volume of the solution and J is the nucleation rate.

The second part is the time for nucleation and growth of a statistically large number of nuclei (polynuclear mechanism).

$$t_{\text{PM}} = \frac{\alpha}{(a_n JG^{n-1})^{1/n}} \quad (17)$$

where a_n is a shape factor, $n = mv + 1$ ($m = 1, 2, 3$ is the dimensionality of the growth), and G is the crystal growth rate.

Generally, the relationship between G and S (supersaturation degree) is expressed by the following equation:

$$G = K_G f(S) \quad (18)$$

K_G is the growth rate constant. $f(S)$ is a the function of S related to growth mechanism, which reported by Teychene and Biscans (*Cryst. Growth Des. 2008, 8, 1133*).

So the equation (15) can be deduced as

$$F(S) = \ln A_u + \frac{B}{n \ln^2 S} \equiv \ln \left\{ S^{1/n} [f(S)]^{(n-1)/n} t_{\text{ind}} \right\} \quad (19)$$

Where $n = mv + 1$, m is dimensionality of the growth, and v a number ranging from 0.5 to 1.

By fitting the induction period with equation (19), the information on the different

possible mechanisms could be found. As referred to by Verdoes et al. (*J. Cryst. Growth. 1992, 118, 401*), the value of m for needlelike ethanol solvate was 1, while the value of m for prismatic form II was 3. Following this assumption, the experimental data were treated by using equation (19). The results show that the best agreement (according to the square coefficient) is obtained for the mononuclear mechanism (i.e., $n = 1$). Thus, it is the appearance of the first nucleus that brings the solution out of the metastable equilibrium and the induction time is governed only by the rate of primary nucleation: $t_{\text{ind}} \equiv 1/JV \gg (\alpha / a_n JG^{n-1})^{1/n}$. So equation (10) is rational in this study.