Electronic Supplementary Material

Theoretical insights into influence of additives on sulfamethoxazole crystal growth kinetics and mechanisms

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The pure-component PC-SAFT parameters of SMX were obtained by regressing the experimental solubility data of SMX in water (measured in this work), methanol [1] and octanol [2]. The pure-component PC-SAFT parameters were summarized in Table S1. The binary interaction parameters between water and polymers were taken from the literatures [3, 4] and were displayed in Table S2. The binary interaction parameters between SMX and water were obtained by regressing the experimental solubility data of SMX in water. Furthermore, the binary interaction parameters between SMX and polymer were obtained by regressing the experimental solubility data of SMX in ternary systems including water and polymer. The fitted binary interaction parameters were listed in Table S2. The comparison between the modeled and experimental values were shown in Fig. S3. It was demonstrated that the PC-SAFT model can accurately correlate the solubility data. The modeled SMX solubility was in good accordance with the experimental data with the average ARD of 5.7% (see Table S3).

Table S1 The pure-component parameters of SMX, polymer and water within PC-SAFT.

	M/(g/mol)	m_i^{seg}	σi/(Å)	u_i/κ_B/(K)	$\varepsilon^{AiBj}/\kappa_B$/(K)	κ^{AiBi}	N_i^{assoc}
SMX	253.18	13.02	3.29	169.3	933.3	0.02	2/2
PEG 6000 [5]	6000	303.6	2.899	204.6	1799.8	0.02	2/2
PEG 20000 [3]	20000	1012	2.933	236.1	2405	0.0238	2/2
Water [6]	18.02	1.2047	2.793	353.945	2425.7	0.0451	1/1

Table S2 Binary interaction parameters.

System	$k_{ij,T}$	$k_{ij,0}$
SMX/water	1.08×10^{-4}	-0.196
SMX/PEG 6000	-8.13×10^{-4}	0.293
SMX/PEG 20000	-2.90×10^{-4}	0.0488
PEG/water [5]	2.344×10^{-4}	-0.1035

Table S3 Predicted SMX solubility by PC-SAFT and experimental SMX solubility in aqueous solutions with different polymer concentrations.

Polymer concentration	Predicted SMX solubility/(g/L)	Experimental SMX solubility/(g/L)	ARD%	Average ARD%
/	0.688	0.605	13.7	
2% PEG 6000	0.893	0.834	7.1	
4% PEG 6000	1.144	1.113	2.9	5.7
2% PEG 20000	0.929	0.907	2.4	
4% PEG 20000	1.244	1.215	2.5	

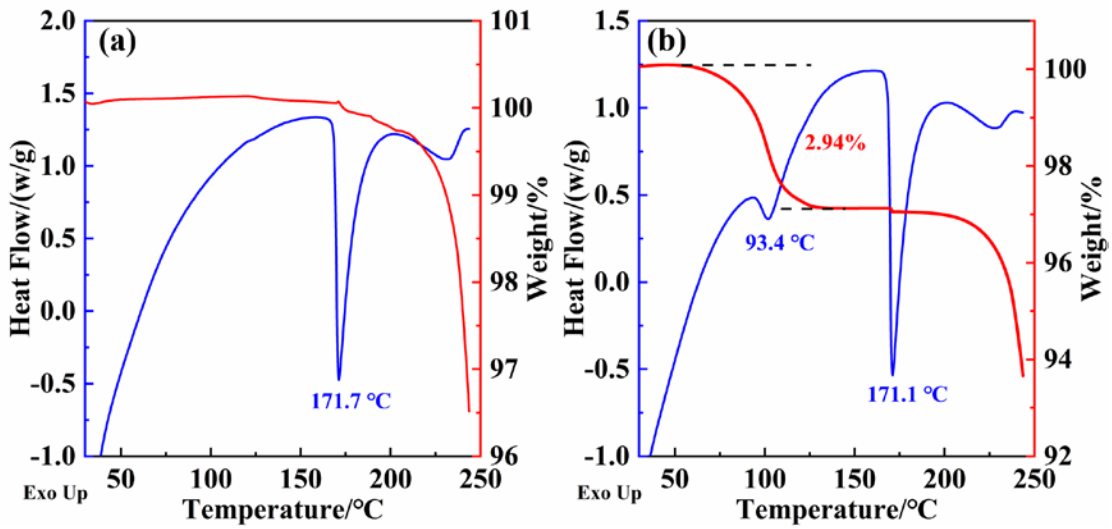

Fig. S1 The DSC-TGA curves of SMX seed crystals (a) and the crystalline products obtained from aqueous solutions containing 4% PEG 6000 (b).

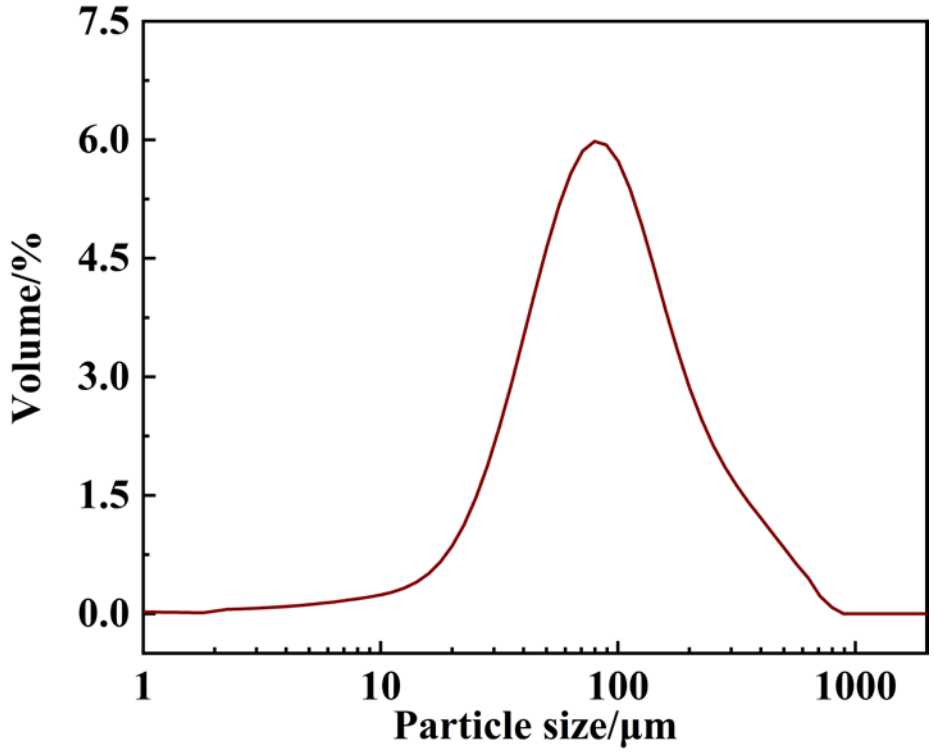

Fig. S2 The particle size distribution of SMX seeds.

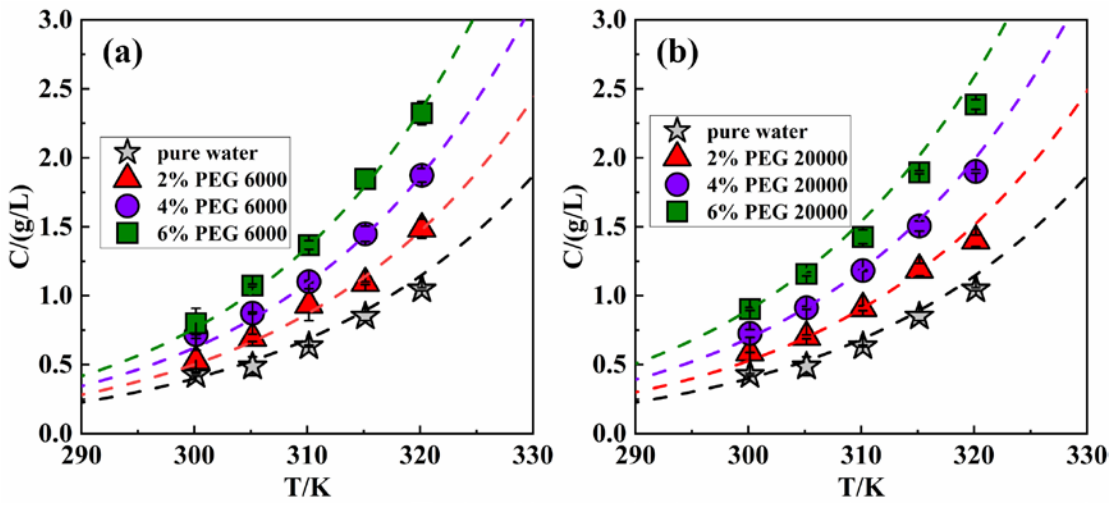

Fig. S3 SMX solubility in polymer/water ternary systems. PEG 6000/water (a), PEG 20000/water (b). The lines denote the modeled SMX solubility using PC-SAFT. The symbols represent the experimental SMX solubility in different solutions with different polymer concentrations.

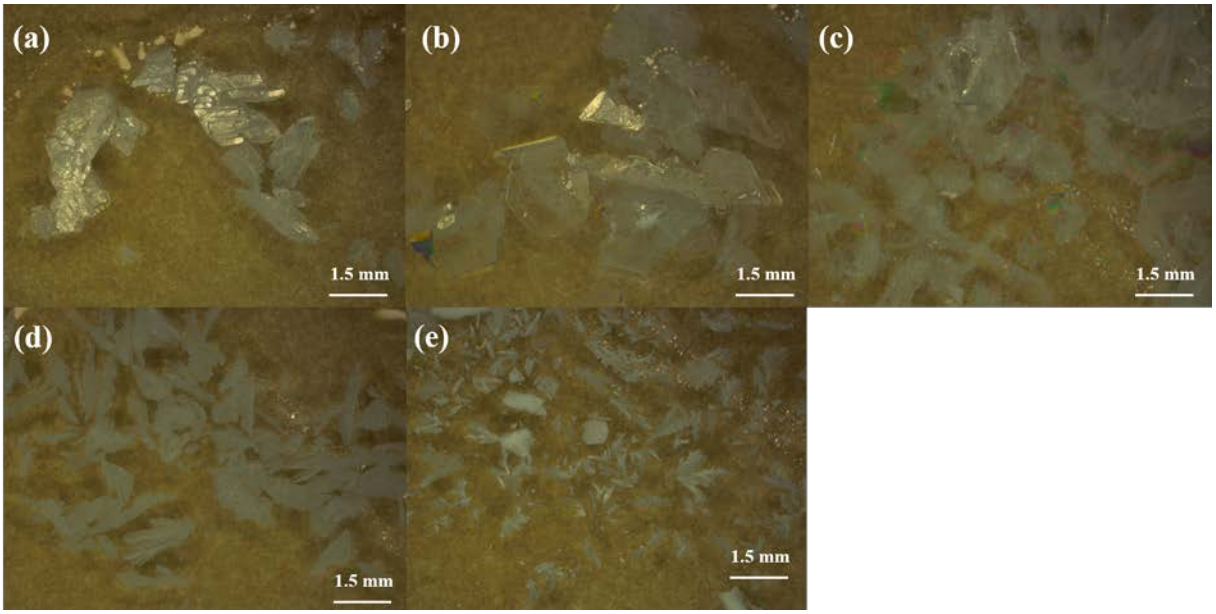

Fig. S4 Micrographs of SMX. The crystalline products obtained in solutions without polymer (a); solutions containing PEG 6000 (b); solutions containing PEG 20000 (c); solutions containing PVP (d); solutions containing HPMC (e).

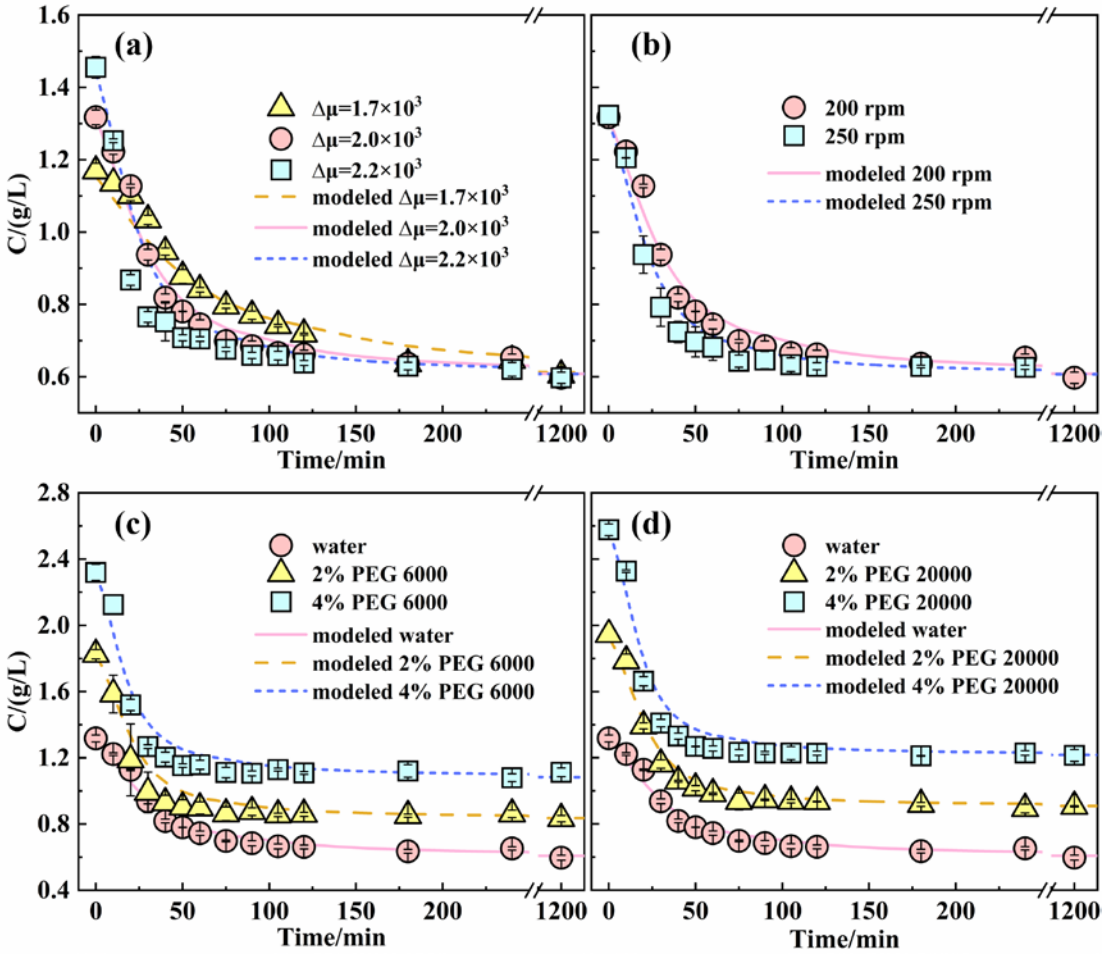

Fig. S5 Crystal growth kinetics of SMX at different conditions: the different initial chemical potential gradients (a), stirring speed (b), PEG 6000 (c), PEG 20000 (d). In Fig. S5 (a), the triangles, circles and squares represent the crystal growth kinetics of SMX at the initial chemical potential gradient of 1.7×10^3 J/mol, 2×10^3 J/mol and 2.2×10^3 J/mol, respectively. The dashed, full and dotted lines denote the modeled results of the two–step chemical potential gradient model with the initial chemical potential gradient of 1.7×10^3 J/mol, 2×10^3 J/mol and 2.2×10^3 J/mol, respectively. In Fig. S5 (b), the circles and squares denote the crystal growth kinetics of SMX at 200 rpm and 250 rpm. The full and dotted lines denote the modeled results of the two–step chemical potential gradient model at 200 rpm and 250 rpm. In Fig. S5(c), the circles, triangles and squares represent the crystal growth kinetics of SMX at 0%, 2% and 4% content of

PEG 6000, respectively. The full, dashed and dotted lines denote the modeled results of the two–step chemical potential gradient model at 0%, 2% and 4% content of PEG 6000, respectively. In Fig. S5 (d), the circles, triangles and squares represent the crystal growth kinetics of SMX at 0%, 2% and 4% content of PEG 20000, respectively. The full, dashed and dotted lines denote the modeled results of the two–step chemical potential gradient model at 0%, 2% and 4% content of PEG 20000, respectively.

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