JOURNAL OF CHEMICAL & ENGINEERING DATA

Article

pubs.acs.org/jced

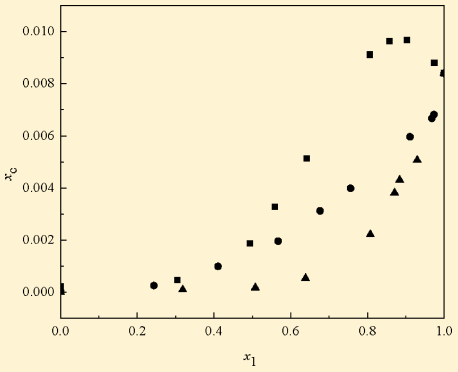
Determination of Thermodynamics in Various Solvents and Kinetics of Cefuroxime Sodium during Antisolvent Crystallization

Yingying Zhao,[†,‡] Baohong Hou,[‡] Xiaobin Jiang,[‡] Chuan Liu,[‡] and Jingkang Wang*[,‡]

[†]Engineering Research Center of Seawater Utilization Technology of Ministry of Education, Hebei University of Technology, 300130 Tianjin, P. R. China

[‡]School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, P. R. China

ABSTRACT: This work reports new measurements of solubility of cefuroxime sodium in pure water in the temperature range from (281.15 to 307.75) K and binary liquid mixture as a function of composition at atmospheric pressure. According to the results of solubility of cefuroxime sodium in various solvents, antisolvent crystallization was determined, and acetone was chosen as the antisolvent. Furthermore, the induction time of cefuroxime sodium was measured to deduce the nucleation and growth mechanism. It is found that only homogeneous nucleation occurred at the chosen supersaturation according to the classical nucleation theory equation. It was also speculated that the growth mechanism of cefuroxime sodium follows the diffusion-controlled growth in view of the value of the surface entropy factor.



INTRODUCTION

Cefuroxime is one of the second-generation cephalosporins, which overcomes some limitations in the spectrum of antibacterial activity of other cephalosporins. It has strong antibacterial activity against Gram-positive bacteria, as well as Gram-negative bacteria, and especially has preferred effects on mixed infections.[1,2] Due to its broad spectrum antibiotics, wide distribution in vivo, and low toxicity, cefuroxime sodium is not only used for the prevention of infection and anti-infective therapy in surgeries but also for the treatment after surgeries. Cefuroxime sodium is not metabolized by liver in the body, for it is excreted from urine in its primary form by the kidney. Therefore, it is nontoxic to the liver and kidney and very safe for adults and also for neonates.

Because of good market prospects, many investigators endeavor to study the production of cefuroxime sodium, but few scientists have paid attention to its crystallization process. It is well-known that crystallization is one of the most important industrial purification and separation processes in the pharmaceutical industry, which affects the crystal size distribution, crystal habit, morphology, purity, and so on. The knowledge of the solubility of pharmaceuticals in pure solvents and solvent mixtures is crucial for designing the crystallization process of drug substances.[3] The interpretation of the induction time reflects the nucleation characteristics of a system and is considered to be useful in exploring nucleation and growth kinetics.[4] The thermodynamics and kinetics are essential to the design of crystallization process. Therefore, in this paper, the solubility and induction time of cefuroxime sodium were measured to supply the valuable thermodynamic and kinetic data for crystallization.

EXPERIMENTAL SECTION

Materials. Cefuroxime sodium was prepared in our own laboratories as a creamy white crystalline solid with a molar mass of 446.4 kg·mol^{-1} from the analytical results of X-ray powder diffraction (XRPD) and high performance liquid chromatography. Ethanol, propan-2-ol, and acetone were supplied by Tianjin Ke-wei Chemical Reagent Co., Ltd., in China and were of analytical reagent grade. The mass fraction of the obtained products and all of the regents was higher than 0.995. In addition, all of the solutions for experiments were prepared with deionized water.

Apparatus. The solubility and induction time of cefuroxime sodium were measured using a laser method.[5] The apparatus for measurements of solubility and induction time are shown in Figures 1 and 2. During all of the experiments, solutions were prepared in the suitable jacketed glass vessels, and the temperature could be controlled by a water bath with a mercury thermometer reading the actual temperature in the inner chambers of the vessels. The masses of cefuroxime sodium and all of the solvents were weighed using an analytical balance with the accuracy of ± 0.1 mg. The solutions were well-mixed by a magnetic stirring apparatus. The disappearance and the appearance of solid phase were determined by the intensity change of laser penetrating through the solution.

Procedure of Solubility and Induction Time Measurement. For solubility measurement, a predetermined amount of solute and excess solvents were first prepared in the vessel and stirred at constant temperature for 1 h. More solutes were

Received: November 10, 2011
Accepted: January 17, 2012
Published: February 6, 2012

dx.doi.org/10.1021/je2012007 | *J. Chem. Eng. Data* 2012, 57, 952–956

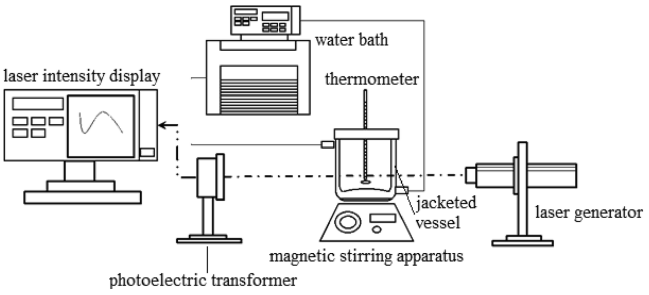


Figure 1. Equipment for solubility measurement.

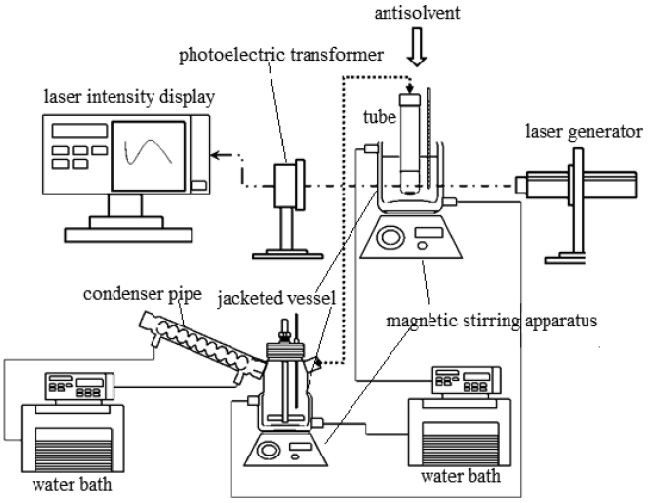


Figure 2. Sketch of the apparatus for the determination of the induction period of antisolvent crystallization of cefuroxime sodium.

added in small batches until the laser detected the superfluous solute and the intensity would not return 90 % of the number in 2 h as that detected when all of the solute could dissolve. Since cefuroxime sodium dissolved in the chosen solvents very fast and only a small batch was added every time, the intensity of the laser would return its maximum within 2 h if all of the added solute could dissolve, so 2 h was chosen as the duration for the solution to reach its equilibrium. Then certain solutions were extracted, filtered by membrane with a 0.45 μm aperture, and then dried. The filtrations were done at the same temperature with the equilibrium temperature to avoid the possibility of premature precipitation to be ruled out. The weights of extracted solutions and dried products were also weighted by an analytical balance. Then, according to the recorded data, the solubility of cefuroxime sodium was obtained by the following equation:

$$x_A = \frac{m_A/M_A}{m_1/M_1 + m_2/M_2 + m_A/M_A} \quad (1)$$

where m_1, m_2, and m_A represent the mass of water, the another solvent, and cefuroxime sodium, and M_1, M_2, and M_A are the molecular weights, respectively.

For the measurements of induction time, 6 mL of saturated solution of cefuroxime sodium was prepared in a tube that was immersed in the jacketed vessel. After the saturated solution was stirred for 1 h to reach equilibrium, a certain amount of acetone was quickly added into the saturated solution. The solution was kept stirring until the appearance of the solid phase was followed by a slight decrease of the laser intensity. The period from the addition of acetone to the formation of the solid phase was recorded as the induction time.

RESULTS AND DISCUSSION

Solubility of Cefuroxime Sodium in Pure Water. From the description in U.S. Pharmacopeia, cefuroxime sodium is freely soluble in water, soluble in methanol, and very slightly soluble in other common reagents. Therefore, water or methanol is a possible solvent to dissolve cefuroxime sodium during the crystallization process. However, it was found that cefuroxime sodium could be esterified by methanol if the crystallization conditions were not strictly controlled. Furthermore, water is easier to obtain and more economic than methanol. Then water is more suited to be as the solvent of cefuroxime sodium. To investigate the effect of temperature on the solubility of cefuroxime sodium, the solubility of cefuroxime sodium in pure water was measured between (281.15 and 307.75) K, as listed in Table 1 and Figure 3. Then the experimental solubility values were fitted with the modified Apelblat equation which is a semiempirical equation as follows:[6]

$$\ln(x_C) = A + \frac{B}{T/\mathrm{K}} + C \ln(T/\mathrm{K}) \quad (2)$$

where A, B, and C are semiempirical constants. The solubility of cefuroxime sodium in water was correlated with temperature using eq 2. The values of parameters A, B, and C are listed in Table 2, and the calculated solubility data predicted by eq 2 are in good agreement with the experimental solubility data as shown in Figure 3. It could also be seen that the solubility of cefuroxime sodium increases greatly with the temperature

Table 1. Solubility Data of Cefuroxime Sodium in Water and Binary Solvents

water		water + acetone		water + ethanol		water + propan-2-ol	
T/K	x_c	x_1	x_c	x_1	x_c	x_1	x_c
281.15	0.0069	0.0000	0.0002	0.0000	0.0001	0.0000	0.0000
285.15	0.0072	0.3042	0.0005	0.2436	0.0003	0.3184	0.0001
289.15	0.0076	0.4945	0.0019	0.4104	0.0010	0.5079	0.0002
293.65	0.0080	0.5589	0.0033	0.5671	0.0020	0.6387	0.0005
298.25	0.0084	0.6413	0.0051	0.6764	0.0031	0.8078	0.0022
302.75	0.0091	0.8059	0.0091	0.7560	0.0040	0.8708	0.0038
		0.8572	0.0096	0.9111	0.0060	0.8842	0.0043
		0.9030	0.0097	0.9681	0.0067	0.9300	0.0051
		0.9742	0.0088	0.9736	0.0068	1.0000	0.0084
		1.0000	0.0084	1.0000	0.0084		

dx.doi.org/10.1021/je2012007 | J. Chem. Eng. Data 2012, 57, 952−956

Table 2. Fitting Parameters for the Solubility of Cefuroxime Sodium in Water[a]

parameters	A	B	C	ΔH_d / kJ·mol^{-1}	ΔS_d / J·mol^{-1}·K^{-1}
water	−14.46	−484.4	1.988	6.341	−7.430

[a]Data are fitted by eqs 2 and 3.

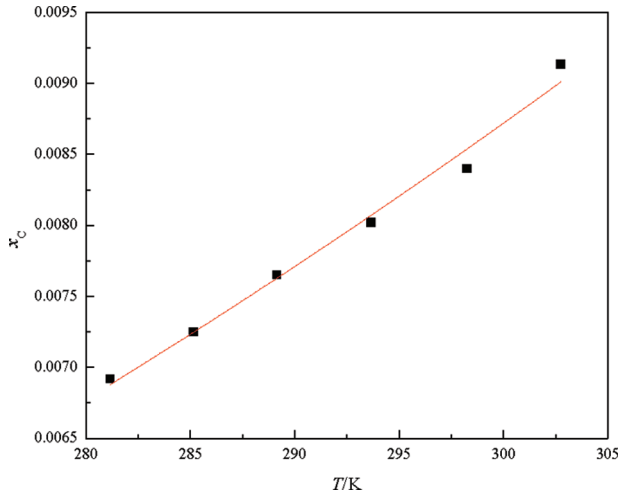


Figure 3. Solubility with temperature in water of cefuroxime sodium and fitting curve by eq 2.

increasing. Hence, water could probably be used as the solvent, and cooling crystallization was adopted to obtain the products. Nevertheless, the yield of cefuroxime sodium was only about 24.3 % if the above method was employed from (307.75 to 281.15) K.

For real solution, the van's Hoff equation used to predict solubility could be[7]

$$\ln(x_C) = -\frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R} \quad (3)$$

where ΔH_d and ΔS_d are the dissolution enthalpy and entropy, respectively, T is the absolute solution temperature, and x_C is the solubility with mole fraction. Using the natural logarithm of solubility of cefuroxime sodium $\ln(x_C)$ versus $1/T$ plot, as shown in Figure 4, then ΔH_d and ΔS_d could be obtained from the slope and intercept, which are also listed in Table 2.

Solubility of Cefuroxime Sodium in Binary Solvents. From the discussion of the solubility in water, it concluded that water could be the solvent to dissolve cefuroxime sodium, but cooling crystallization is not a suitable crystallization method in the view of the yield. Therefore, another solvent was introduced, such as the common solvents: acetone, ethanol, and propan-2-ol. From Figure 5 and Table 1, it could be seen that the dissolving capacity of cefuroxime sodium in the three solvent systemsis water−propan-2-ol < water−ethanol < water−acetone. Another obvious phenomenon is that the solubility has a maximum in water−acetone with the fraction of water, while it increased with the fraction of water in other systems without the appearance of maximum. The hydroxy group of water, ethanol, and propan-2-ol and the carbonyl group of acetone indicates that the hydrogen bond could form between solvents. According to the electronegativity, the strength of the hydrogen bond between the above three binary solvents was in the following order: water−propan-2-ol < water−ethanol < water−acetone. The solubility order of cefuroxime sodium was identical with the order of strength of hydrogen bonds between the three binary solvents. Thus it was speculated that the hydrogen bond between solvents enhanced the solubility of cefuroxime sodium. The influencing factors of the solubility of solids in liquids are comparatively complex, and the formation of hydrogen bond between solvents is only one of the factors affecting the dissolution behavior. Further analysis of the dissolution process is complicated and beyond the scope of this article.

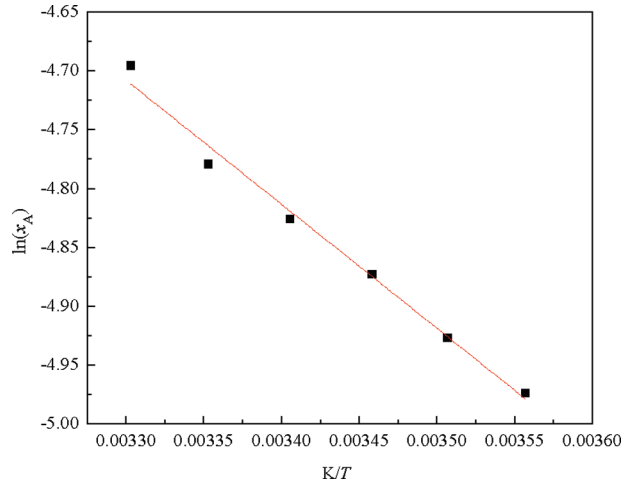


Figure 4. van't Hoff plots of $\ln(x_A)$ versus $1/T$ in water.

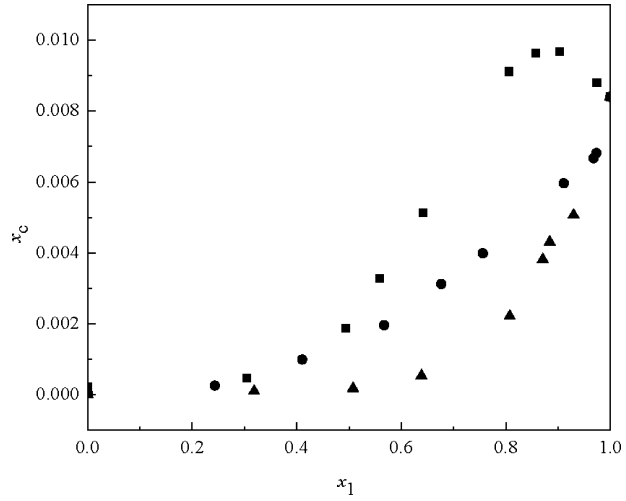


Figure 5. Solubility with temperature in binary solvents of cefuroxime sodium. ■, the solubility data of cefuroxime sodium in water + acetone; ●, the solubility data of cefuroxime sodium in water + ethanol; ▲, the solubility data of cefuroxime sodium in water + propan-2-ol.

Compared between the solubility in different solvents, it was found that antisolvent crystallization can be used to produce cefuroxime sodium and acetone is a preferred antisolvent. It could also surmise that the hydrogen bond between solvents enhanced its solubility. The theoretically maximum yield to use this method is about 97.6 %. The effect of temperature on the solubility of cefuroxime sodium was very slight, so the solubility at different temperatures was excluded in this paper.

Nucleation and Growth Mechanism of Cefuroxime Sodium Using Antisolvent Crystallization. For homoge-

dx.doi.org/10.1021/je2012007 | J. Chem. Eng. Data 2012, 57, 952−956

neous nucleation the nucleation rate can be expressed by the following classical nucleation theory equation[8]

$$J = A \exp(-B/(\ln S)^2) \quad (4)$$

where $B = (16\pi\gamma^3 v_m^2)/(3\nu^2 k^3 T^3)$ if crystal nucleus was assumed to be spherical. J is the nucleation rate; k is the Boltzmann constant; T is the absolute temperature, S is the supersaturation ratio; ν is the moles of ions per mole of the solute; γ is the solid−liquid interfacial tension, and V_m is the volume of molecule. The relation between induction time and nucleation rate is:

$$t_{ind} = J^{-1} \quad (5)$$

$$\text{then } \ln t_{ind} = A_m + B/\ln^2 S \quad (6)$$

where $A_m = \ln(1/A)$.

From eq 6, it is known that the linear relation between $\ln t_{ind}$ and $1/\ln^2 S$ can be obtained if the nucleation is homogeneous and solid−liquid interfacial tension can be calculated from the slope B:

$$\gamma = \left(\frac{3B\nu^2 k^3 T^3}{16\pi V_m^2}\right)^{1/3} \quad (7)$$

For the real solution growth system, Davey[9] suggested that surface entropy factor f could be calculated by using interfacial tension data given by:

$$f = \frac{4V_m^{2/3}\gamma}{kT} \quad (8)$$

The surface entropy factor f is a measure of the roughness degree of the crystal surface. A larger f means that the crystal surface becomes smoother and crystal growth becomes more difficult.[10] Generally, it is expected that continuous growth will occur when f is below 3, spiral growth or screw dislocation is predominate if the value of f is above 5, and birth and spread growth is to be expected if the value of f is between 3 and 5. Therefore, from the f value, crystal growth mechanism can be roughly determined.

The induction time of cefuroxime sodium in water + acetone at 298.15 K is shown in Figure 6. The volume proportion of acetone and water is 2.25:1 in the initial saturated solution for this system which is the best to dissolve cefuroxime sodium during the recrystallization process according to the solubility data. It can be seen that the plot of $\ln t_{ind}$ against $1/\ln^{-2} S$ is a straight line. It also could be inferred that the induction time increased as the supersaturation slowed down for the formation of nuclei became more difficult. Therefore, the nucleation mechanism of cefuroxime sodium in water + acetone system accorded with the classical homogeneous nucleation. The solid−liquid interfacial tension calculated from the slope is 1.746 as shown in Table 3. The value of solid−liquid interfacial tension is less than 3; hence, continuous growth mechanism is speculated to occur for cefuroxime sodium in the water + acetone system.

To investigate the effect of the initial content of acetone, several induction time data were measured at constant temperature and supersaturation as shown in Figure 7. It clearly revealed that the induction time became shorter as the initial content of acetone increases. It is suggested that the supersaturation level for primary nucleation is much higher in

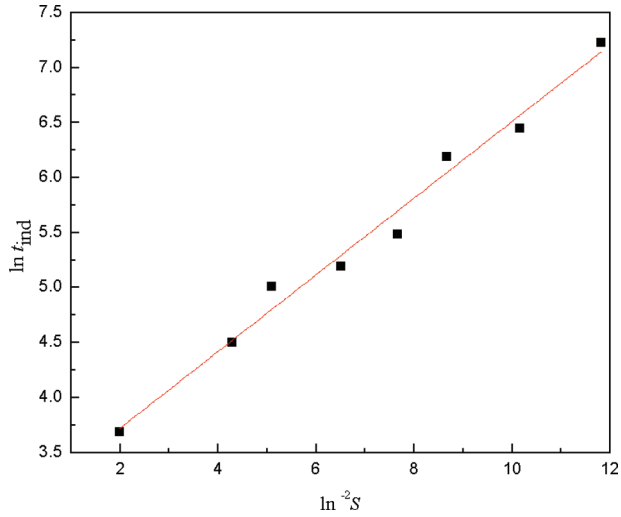


Figure 6. Plot of $\ln t_{ind}$ against $1/\ln^{-2} S$ for cefuroxime sodium in water + acetone and fitting curves by eq 6.

Table 3. Regression Value in Equation 6 for the Induction Time and Supersaturation of Cefuroxime Sodium in Water + Acetone and the *f* Value

solvent	A_m	B	rmsd	f
water + acetone	3.019	0.3486	0.1346	1.746

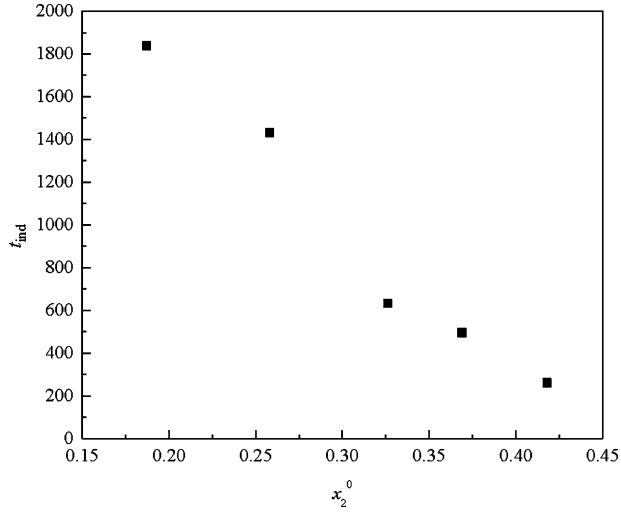


Figure 7. Effect of initial concentration of acetone on induction time at 298.15 K.

pure water and tends to become lower after adding acetone, which implied that the formation of primary nuclei in antisolvent crystallization is easier than in cooling crystallization for cefuroxime sodium. In other words, as the content of acetone increased, cefuroxime sodium would keep in the metastable state for shorter time.

■ CONCLUSIONS

Solubility and induction time are essential data for the design of a crystallization process. In this paper, the solubility in pure and mixture solvents of cefuroxime sodium was first measured to determine the optimal crystallization method in the view of thermodynamics. As expected, the solubility of cefuroxime sodium increases with temperature in pure water. However, in

dx.doi.org/10.1021/je2012007 | J. Chem. Eng. Data 2012, 57, 952−956

consideration of yield, water is the best solvent of cefuroxime sodium, but cooling crystallization is not the best choice. Then another solvent was drawn in, and the solubility was measured in the normal binary systems. It shows acetone is the suitable antisolvent to crystallize for cefuroxime sodium in antisolvent crystallization.

After crystallization solvents and method were determined, the induction time was studied in water + acetone. Afterwards, the nucleation and growth mechanism were speculated from the relationship between induction time and supersaturation. Results showed that homogeneous nucleation is dominant and then continuous growth played a leading role of cefuroxime sodium in water + acetone. Finally, the effect of the initial content of acetone on the induction time was also studied.

AUTHOR INFORMATION

Corresponding Author

*Tel.: +86 22 27405754; fax: +86 22 27374971. E-mail address: wangjkch@tju.edu.cn.

Notes

The authors declare no competing financial interest.

REFERENCES

(1) O'Callaghan, C. H.; Sykes, R. B.; Griffiths, A.; Thornton, J. E. Cefuroxime, a new cephalosporin antibiotic: activity in vitro. *Antimicrob. Agents Chemother.* **1976**, *9*, 511−519.

(2) Jelinska, A.; Zajac, M.; Jakubowska, M. Kinetics of cefuroxime sodium salt decay in solid phase. *React. Kinet. Catal. Lett.* **2001**, *73*, 325−331.

(3) Ruether, F.; Sadowski, G. Modeling the solubility of pharmaceuticals in pure solvents and solvent mixtures for drug process design. *J. Pharm. Sci.* **2009**, *98*, 4205−4215.

(4) Söhnel, O.; Mullin, J. W. Interpretation of crystallization induction periods. *J. Colloid Interface Sci.* **1988**, *123*, 43−50.

(5) Zhao, Y.; Jiang, X.; Hou, B. Measurement and Correlation of Solubility of Cefuroxime Acid in Pure and Binary Solvents at Various Temperatures. *J. Chem. Eng. Data* **2010**, *55*, 3369−3372.

(6) Apelblat, A.; Manzurola, E. Solubilities of o-acetylsalicylic, 4-aminosalicylic, 3,5-dinitrosalicylic, and p-toluic acid, and magnesium−aspartate in water from T = (278 to 348) K. *J. Chem. Thermodyn.* **1999**, *31*, 85−91.

(7) Mo, Y.; Dang, L.; Wei, H. Solubility of α-form and β-form of L-glutamic acid in different aqueous solvent mixtures. *Fluid Phase Equilib.* **2011**, *300*, 105−109.

(8) Jones, A. G. *Crystallization Process Systems*; Elsevier Science: Oxford, 2002.

(9) Davey, R. Solvent effects in crystallization processes. *Curr. Top. Mater. Sci.* **1982**, *8*, 454−462.

(10) Hao, H.; Wang, J.; Wang, Y. Determination of induction period and crystal growth mechanism of dexamethasone sodium phosphate in methanol-acetone system. *J. Cryst. Growth* **2005**, *274*, 545−549.