

Kinetic and thermodynamic characteristics of crystallization of vancomycin

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(Received 15 February 2017 • accepted 24 May 2017)

Abstract—We investigated the effect of the major process parameters (crystallization temperature and time) on the efficiency of the vancomycin crystallization process and conducted a kinetic and thermodynamic analysis. The most clear and uniform vancomycin crystals with the highest yield (~98%) were obtained at the optimum crystallization temperature (283 K) and time (1,440 min). The electron microscope, SEM, and XRD analyses showed that intact crystalline vancomycin was obtained when using a crystallization temperature of 283, 288, and 293 K. The kinetic analysis results revealed that the Johnson-Mehl-Avrami-Kolmogorov (JMAK) model was suitable with a high value for r^2 (>0.9561) and low value for RMSD (<0.0170). Finally, from the thermodynamic analysis the Gibbs free energy change (ΔG^0), entropy change (ΔS^0), and enthalpy change (ΔH^0) were all negative, indicating that the crystallization process was spontaneous, irreversible, and exothermic.

Keywords: Vancomycin, Crystallization, Johnson-Mehl-Avrami-Kolmogorov Model, Kinetics, Thermodynamics

INTRODUCTION

Vancomycin is the first glycopeptide antibiotic to inhibit cell wall synthesis in Gram-positive bacteria, thereby lysing the bacteria [1,2]. It is widely used to treat methicillin resistant *Staphylococcus aureus* (MRSA) infection and endocarditis in patients who are allergic to penicillin and cephalosporin. In addition, vancomycin is the first therapeutic agent for MRSA infection to be widely used for preventive treatment during cardiac surgery involving an artificial implant, orthopedic surgery, and neurosurgery for the placement of a ventriculoperitoneal shunt [3]. For vancomycin now recorded in the United States and European pharmacopeia, the vancomycin content and the amount of total and individual impurities are strictly regulated [4]. Complying with these strict regulations necessitates several steps of isolation and purification. Generally, in producing a drug with high purity such as an antibiotic, a crystallization is introduced as the final purification step. Crystallization is the process of precipitating and producing a compound from a solution, and it corresponds to a core technology for the isolation and purification of a substance as well as the control of its physical properties and morphology. This process maximizes the quality of the final product and also results in a higher value-added product. Crystallization is a simple, energy efficient and environmentally friendly process that is widely applicable and has a low fixed investment cost [5,6]. In a previous study [7], the major process parameters (distilled water/acetone ratio, storage temperature, storage time, conductivity, pH, initial concentration, stirrer velocity) were optimized for vancomycin crystallization to obtain a high-yield ($>95\%$) of high-purity ($>97\%$) vancomycin crystals. However, crystal formation required a long period of time, resulting in low

productivity in the mass-production process. Thus, new crystallization processes were developed using glass beads, ion exchange resin, and silica gel to increase the surface area per volume of the reaction solution, thereby reducing the crystallization time [8-10]. Plus, the use of ionic liquids and various surface-area-increasing materials (e.g., silica gel) was found to reduce the crystallization time dramatically and produce high-quality vancomycin crystals [11-13]. However, most previous studies have focused on optimizing the experimental conditions or process factors and qualitative description of their effects, with very little quantitative analysis of the kinetics and thermodynamics of vancomycin crystallization, which is important for understanding the feasibility and nature of the process. The Johnson-Mehl-Avrami-Kolmogorov (JMAK) model has already been applied to the precipitation and crystallization process of inorganic substances, including polymers [14], metals [15], and glass [16], yet rarely applied to the crystallization of vancomycin from a microbial culture. Accordingly, we investigated the effect of the crystallization temperature and time on the crystallization efficiency of vancomycin and then used the kinetic and thermodynamic characteristics of the vancomycin crystallization to conduct a quantitative analysis of the crystallization behavior.

MATERIALS AND METHODS

1. Vancomycin Samples

The vancomycin used in this study was obtained through the fermentation of the microorganism *Nocardia orientalis* isolated from soil. Cells were removed from the fermentation solution containing vancomycin, which was then purified [17]. The solution was consecutively passed through cation exchange, anion exchange and porous cation exchange resins and eluted with ammonia to obtain 88% pure vancomycin in the form of hydrochlorate. Impurities such as pigment and protein were removed using alumina and a weak acidic cation exchange resin. The resulting product was used for the

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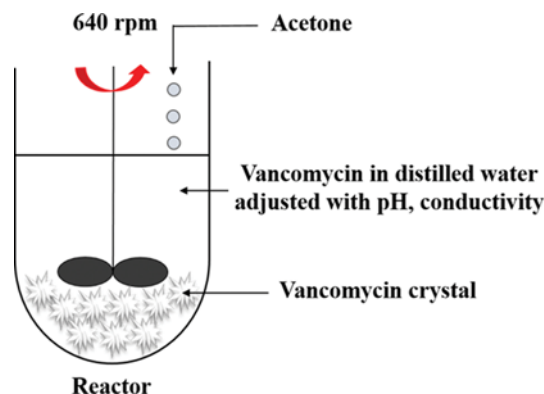


Fig. 1. Schematic diagram of crystallization process for purification of vancomycin.

crystallization process. The purified vancomycin sample (purity: 88%) for this study was provided by the Samyang Biopharm Company, South Korea.

2. Crystallization Method

A schematic diagram of the vancomycin crystallization process is shown in Fig. 1. The conductivity and pH of the distilled water were adjusted to 20 ms/cm and 2.5, respectively, using sodium chloride and 1N hydrochloric acid, and the vancomycin sample (purity: 88%) then dissolved in the distilled water. Next, acetone was slowly added drop by drop while stirring the solution (640 rpm) [7]. The distilled water/acetone ratio, pH, conductivity, initial concentration, and stirrer velocity were 1 : 3.5 (v/v), 2.5, 20 ms/cm, 0.1 g/mL, and 640 rpm, respectively. Crystallization patterns were investigated at different crystallization temperatures (263, 268, 273, 278, 283, 288, 293 K) and times (240, 480, 720, 960, 1,200, 1,440, 1,680 min) using a thermo-hygrostat (KCL-2000W, EYELA, Japan). After crystallization, the vancomycin crystals were washed with acetone to remove any impurities on the surface and filtered using filter paper (150 mm, Whatman). The crystals were then dried at room temperature. The purity and yield of vancomycin were measured using an HPLC analysis and the yield calculated as follows:

$$\text{Yield (\%)} = \frac{\text{Quantity of vancomycin after crystallization}}{\text{Quantity of vancomycin before crystallization}} \times 100 \quad (1)$$

3. Vancomycin Analysis

An HPLC system (SCL-10AVP, Shimadzu, Japan) and Cadenza CW-C18 column (4.6×100 mm, 3 μm, Imtakt, Japan) were used for the vancomycin analysis. Mobile phase A (formic acid/distilled water 0.1%, v/v) and B (formic acid/acetonitrile 0.1%, v/v) were injected at 0.8 mL/min for 0-10 min (95 : 5-30 : 70, v/v, gradient mode) and 10-20 min (95 : 5, v/v, isocratic mode). The sample injection volume was 20 μL and the eluate was detected at 260 nm [12]. A standard curve was used in the HPLC analysis based on a standard sample (purity: >97%).

4. Analysis of Vancomycin Morphology

An electron microscope (SV-35 Video Microscope system, Some Tech., Korea) was used to measure the morphology and size of the vancomycin particles [12]. Crystals were observed at a high magnification (×200). The morphology and size of the crystals were determined from video images using the IT-Plus System (Some

Tech., Korea).

5. SEM and XRD Analysis

The structure of the vancomycin crystals was confirmed as crystalline or non-crystalline (amorphous) by using a scanning electron microscope (SEM, MIRA LMH; Tescan, Czech Republic) with accelerating voltages of 10-15 kV and an approximately 1 mg sample [10]. Also, whether the structure of the vancomycin was crystalline was determined by means of an x-ray diffractometer (XRD, SMD 3000, SCINCO, Italy) operated by the WINHRD 3000 program at 40 kV and 15 mA with a range of 2-theta from 5° to 25° and an approximately 50 mg sample [12].

6. Kinetic Analysis

A kinetic analysis, which predicts the reaction rate, reaction pathway, and reaction extent, can be used for process development, optimization, and verification [18,19]. We used the JMAK model to investigate the characteristics and parameters of the vancomycin crystallization process. The JMAK model can be applied to a crystallization and precipitation process where the precipitates grow independently or are distributed randomly, and can describe the phase transition behavior (nucleation and growth) in an isothermal process [20,21]. The JMAK model is expressed in Eq. (2), and rearranged as shown in Eq. (3).

$$X(t) = 1 - \exp[-kt^n] \quad (2)$$

$$\ln\left(\ln\left(\frac{1}{1-X(t)}\right)\right) = \ln k + n \ln t \quad (3)$$

where $X(t)$ is the yield of vancomycin crystals at time, n is the JMAK exponent, and k is the crystallization rate constant (min^{-1}) [22-24].

7. Thermodynamic Analysis

Process behavior can be quantitatively interpreted by a thermodynamic analysis, which determines the spontaneity, heat of the reaction, and reversibility of the process [25,26]. The relationship between the activation energy and the second-order rate constant is expressed in Eq. (4) using Arrhenius' equation and as a linear equation in Eq. (5), plus $1/T$ were calculated using a linear regression analysis.

$$k = k_0 e^{-E_a/RT} \quad (4)$$

$$\ln k = \ln k_0 + \left(\frac{-E_a}{R}\right) \frac{1}{T} \quad (5)$$

where k is the crystallization rate constant (min^{-1}), k_0 is the pre-exponential factor ($\text{mL/mg} \cdot \text{min}$), E_a is the activation energy (kJ/mol), T is the absolute temperature (K), and R is the universal gas constant ($8.314 \text{ J/mol} \cdot \text{K}$).

The Gibbs free energy change (ΔG^0 , kJ/mol) indicates the spontaneity of a reaction, where a negative value means a spontaneous reaction, while a positive value means a nonspontaneous reaction. The enthalpy change (ΔH^0 , kJ/mol) indicates the heat of a reaction, where a negative value means an exothermic reaction, while positive value means an endothermic reaction. Finally, the entropy change (ΔS^0 , $\text{J/mol} \cdot \text{K}$) indicates the degree of randomness, where 0 means a reversible reaction, while >0 means an irreversible reaction. The equilibrium constant (K_e) was calculated using Eq. (6), ΔH^0 and ΔS^0 were calculated from the slope and intercept using a

linear regression analysis of $\ln K_e$ and $1/T$ using the van't Hoff equation in Eq. (7), and ΔG^0 was calculated using Eq. (8) for each temperature range.

$$K_e = \frac{C_e}{C_{se}} \quad (6)$$

$$\ln K_e = -\frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R} \quad (7)$$

$$\Delta G^0 = -RT \ln K_e \quad (8)$$

where C_{se} is the concentration of vancomycin in the supernatant at equilibrium (mg/mL) and C_e is the concentration of vancomycin in the crystalline phase at equilibrium (mg/mL).

8. Validity of Kinetic Model

The applicability of a kinetic model can be identified using the coefficient of determination (r^2) and root mean square deviation (RMSD) [27,28]. A coefficient of determination closer to 1 and a smaller value for the root mean squared deviation indicate a higher coincidence between the experimental values and the calculated values. The RMSD can be expressed as Eq. (9):

$$\text{RMSD} = \sqrt{\frac{1}{m} \sum_{i=1}^m (\text{experimental} - \text{calculated})^2} \quad (9)$$

where m is the number of experimental runs.

RESULTS AND DISCUSSION

1. Effect of Crystallization Temperature and Time

It is already well established that the crystallization temperature and time have a direct effect on the crystallization efficiency (yield, purity, morphology, etc.) in the crystallization process of most bio-products [7,12]. Therefore, we investigated the effect of the crystallization temperature and time on the crystallization process of vancomycin, and applied the JMAK model for a quantitative analysis of the crystallization process to determine the kinetic charac-

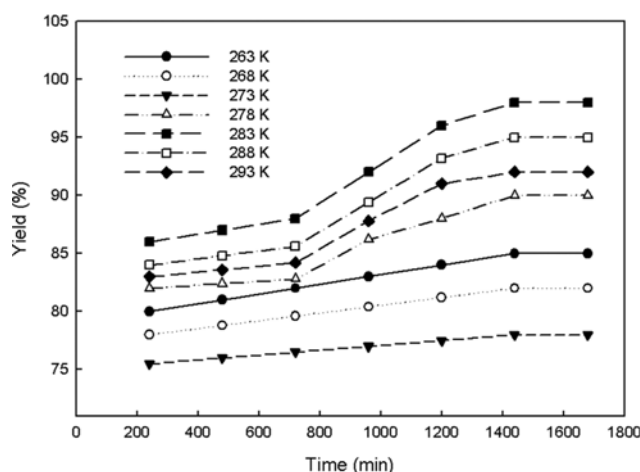


Fig. 2. Effect of crystallization temperature and time on the yield of vancomycin. The distilled water/acetone ratio, conductivity, pH, initial concentration, and stirrer velocity were 1 : 3.5 (v/v), 20 ms/cm, 2.5, 0.1 (g/mL), and 640 rpm, respectively.

teristics. To confirm the crystal behavior of vancomycin according to the crystallization temperature and time, different crystallization temperatures (263, 268, 273, 278, 283, 288, 293 K) and times (240, 480, 720, 960, 1,200, 1,440, 1,680 min) were used along with the conditions of the optimum distilled water/acetone ratio 1 : 3.5 (v/v), a conductivity of 20 ms/cm, pH 2.5, initial concentration of 0.1 (g/mL), and stirring rate of 640 rpm, as previously reported [7]. As shown in Fig. 2, the yield of vancomycin gradually increased at 278, 283, 288, and 293 K during 720 min of crystallization and then increased markedly and steadily until reaching equilibrium after 1,440 min of crystallization. The highest yield of vancomycin (~98%) was at 283 K. Meanwhile, the yield gradually increased at 263, 268 and 273 K over time and the reaction reached equilibrium after 1440, min of crystallization. The purity of the vancomycin (>97%) remained unchanged, regardless of the crystallization temperature and time (data not shown).

Electron microscopy, XRD, and SEM analyses were used to investigate the crystal size and morphology of the vancomycin. At 278, 283, 288, and 293 K, it was possible to identify a crystalline morphology by electron microscopy (Fig. 3). Crystalline particles of vancomycin were evident by XRD analysis in Fig. 4, which was confirmed by SEM analysis (Fig. 5). The XRD analysis revealed meaningful peaks in all the ranges, also corresponding with the results from a previous XRD analysis of vancomycin [13]. As shown

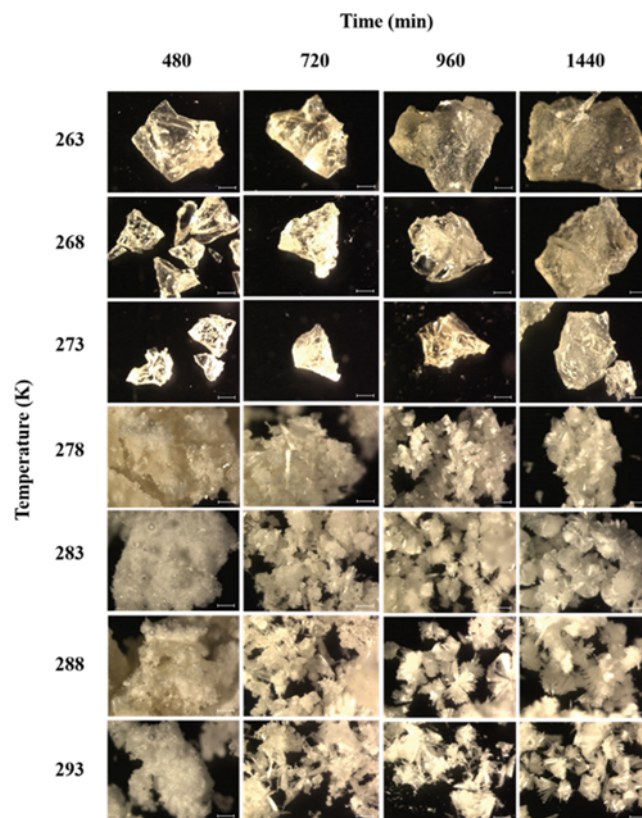


Fig. 3. Electron microscope images of vancomycin crystals formed by crystallization at various times and temperatures. The distilled water/acetone ratio, conductivity, pH, initial concentration, and stirrer velocity were 1 : 3.5 (v/v), 20 ms/cm, 2.5, 0.1 (g/mL), and 640 rpm, respectively. Scale bar indicates 100 μm .

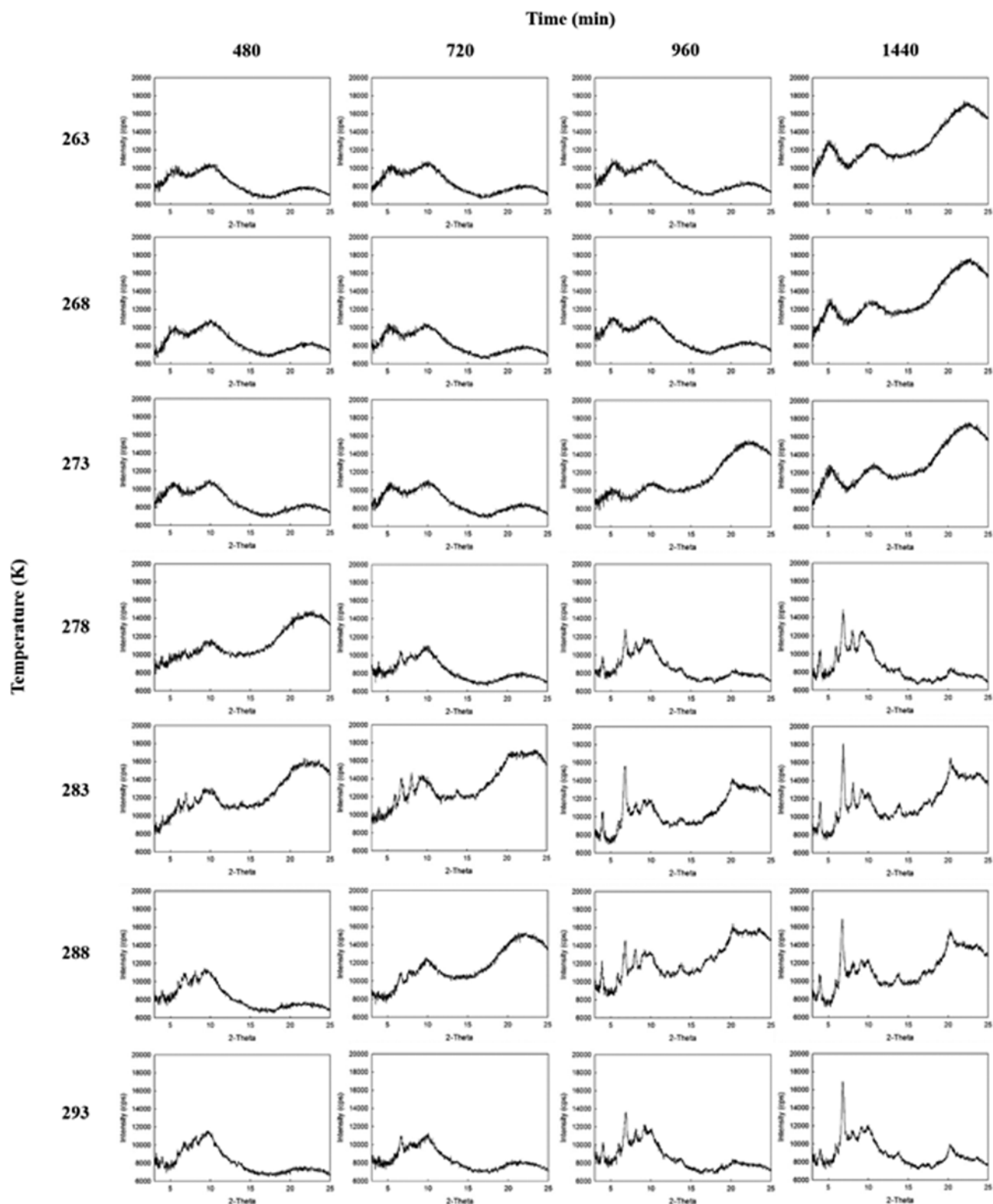


Fig. 4. XRD patterns of vancomycin crystals formed by crystallization at various times and temperatures. The distilled water/acetone ratio, conductivity, pH, initial concentration, and stirrer velocity were 1 : 3.5 (v/v), 20 ms/cm, 2.5, 0.1 g/mL, and 640 rpm, respectively.

in Figs. 4 and 5, the most clear and uniform vancomycin crystals with the highest yield (~98%) were obtained when using the optimum crystallization temperature (283 K) and time (1,440 min).

This phenomenon was caused by the solubility and supersaturation of vancomycin at the optimum crystallization temperature [12,29,30]. At relatively low temperature (278 K), amorphous van-

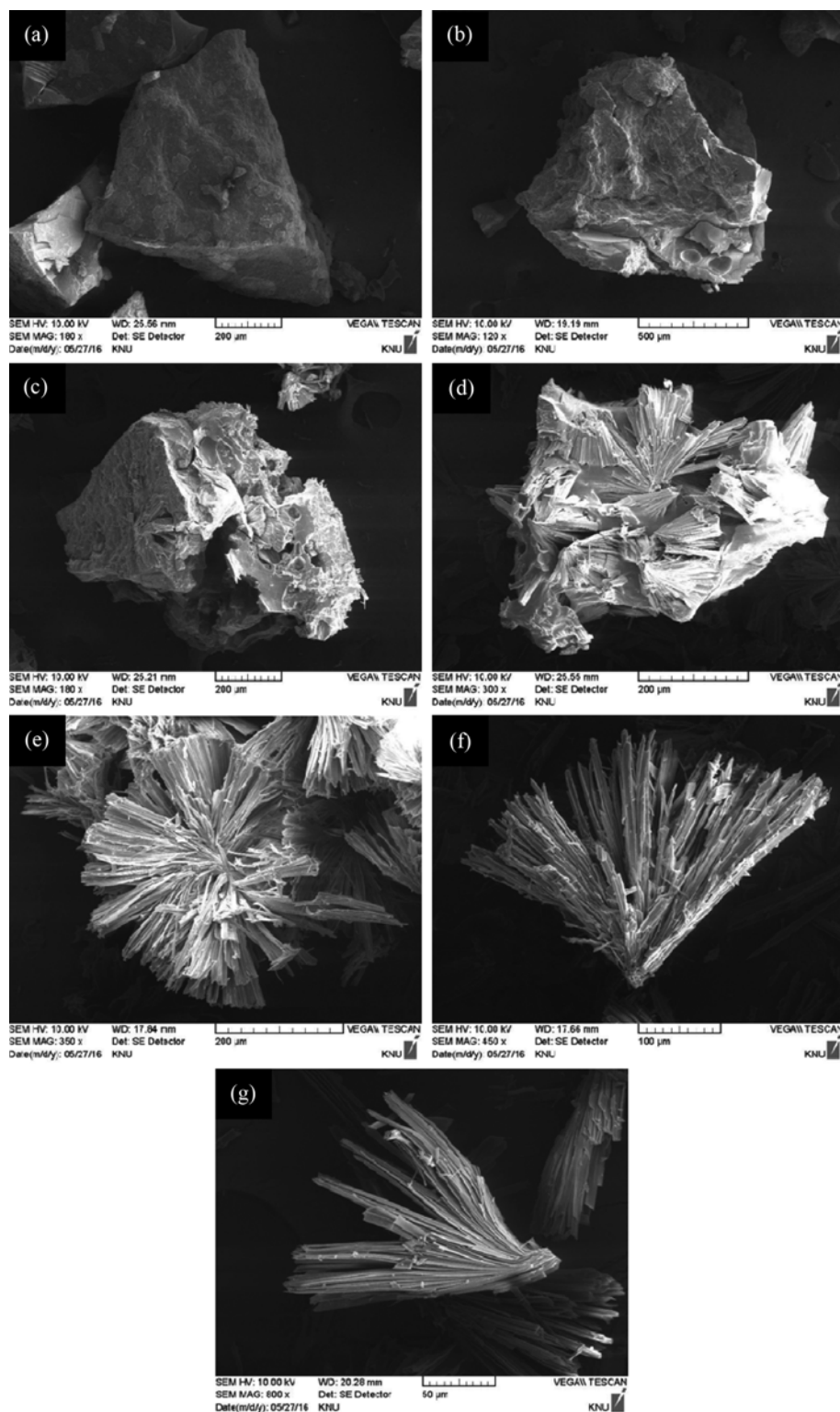


Fig. 5. SEM images of vancomycin crystals at various temperatures after 1,440 min of crystallization. (a) 263 K; (b) 268 K; (c) 273 K; (d) 278 K; (e) 283 K; (f) 288 K; (g) 293 K.

comycin was partially observed due to conglomeration [7] (Fig. 5(d)). Thus, intact crystalline vancomycin was obtained at 283, 288, and 293 K. Meanwhile, the XRD analysis revealed no meaningful peaks at 263, 268 and 273 K, regardless of the crystallization time,

indicating amorphous vancomycin (Fig. 4). In addition, the crystal density in the crystallization solution became higher when the crystallization temperature became lower, indicating conglomeration of the precipitate [12,31] (Fig. 5(a)-(c)).

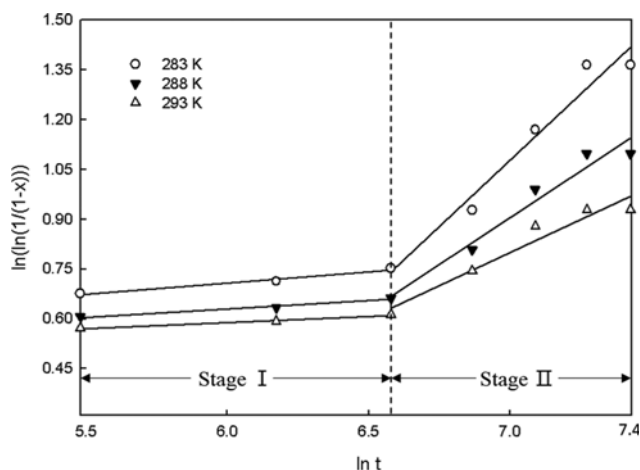


Fig. 6. Johnson-Mehl-Avrami-Kolmogorov (JMAK) plots at different temperatures (○ 283 K; ▼ 288 K; △ 293 K).

2. Analysis of Crystallization Kinetics

The production of crystals generally has two stages, nucleation and growth [29]. Thus, the experimental data from Fig. 2 were applied to the JMAK model to investigate the kinetic characteristics and parameters of the model. The applicability of the JMAK model was determined based on the values of r^2 and RMSD. The crystallization behavior was quantitatively interpreted using a kinetic analysis. The results were applied to the linear equation in Eq. (3) of the JMAK equation, and the parameters and values of r^2 and RMSD were then determined in a linear regression analysis (Fig. 6 and Table 1). As shown in Fig. 6, two straight lines were obtained at 283, 288, and 293 K, when intact crystalline vancomycin was observed. Thus, stage I and stage II were divided based on the point where the slope changed. The value of n at 283, 288, and 293 K was 0.0670, 0.0496, and 0.0359, respectively, for stage I and 1.0793, 0.7157, and 0.4565, respectively, for stage II. As the value of n differed for stage I and stage II, this confirmed a phase transformation and that the two mechanisms were consecutive, i.e., there was no time overlap for the two transformation mechanisms [20, 29,30,32]. As the production process of crystals has two stages, nucleation and growth, stage I was determined as nucleation and stage II as growth. As the temperature became lower, the value of n increased, whereas the value of k decreased. Thus, at a lower temperature, the crystals grew slowly, resulting in uniform and clear crystals. The kinetic analysis results revealed that the JMAK model was suitable with the high value of r^2 (>0.9561) and low value of RMSD (<0.0170). The results revealed a correlation between the crystallization temperature and the crystal size, yield, and value of the JMAK exponent (n) and crystallization rate constant (k) at

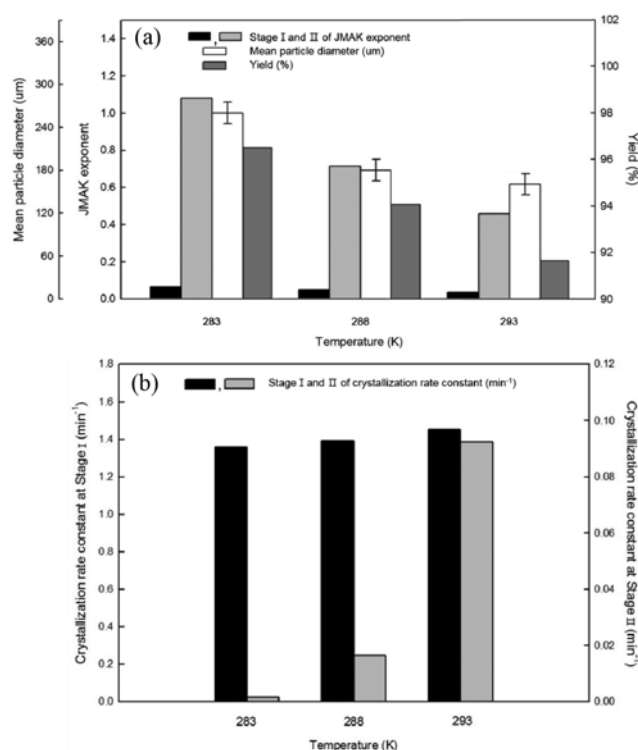


Fig. 7. Relationship between vancomycin yield, mean particle diameter, JMAK exponent (a), and crystallization rate constant (b), depending on the temperature for intact crystalline vancomycin. The storage time, distilled water/acetone ratio, conductivity, pH, initial concentration, and stirrer velocity were 1,440 min, 1 : 3.5 (v/v), 20 ms/cm, 2.5, 0.1 g/mL, and 640 rpm, respectively.

1,440 min when the crystallization process reached equilibrium, as shown in Fig. 7. At 283, 288, and 293 K when intact crystalline vancomycin was observed, the yield, crystal size, and value of n during nucleation (Stage I) and growth (Stage II) all increased when decreasing the crystallization temperature, while the value of k decreased. So, the crystal size, yield, and value of the JMAK exponent (n) and rate constant (k) are all closely related in the vancomycin crystallization process.

3. Analysis of Crystallization Thermodynamics

A thermodynamic analysis was conducted at the crystallization temperature (283, 288, and 293 K) at which the crystallization reached an equilibrium state. $\ln k$ vs. $1/T$ was linearized using k obtained at each crystallization temperature (Fig. 8(a) and Table 2). E_a was 56.3537 kJ/mol for intact crystalline vancomycin. In this case, the crystallization increases as the temperature decreases,

Table 1. Johnson-Mehl-Avrami-Kolmogorov (JMAK) model parameters and statistical correlation values for crystallization of vancomycin

Temperature (K)	Stage I/Stage II			
	n	k	r^2	RMSD
283	0.0670/1.0793	1.3579/0.0015	0.9742/0.9999	0.0013/0.0170
288	0.0496/0.7157	1.3931/0.0165	0.9755/0.9927	0.0010/0.0098
293	0.0359/0.4565	1.4527/0.0924	0.9762/0.9561	0.0007/0.0076

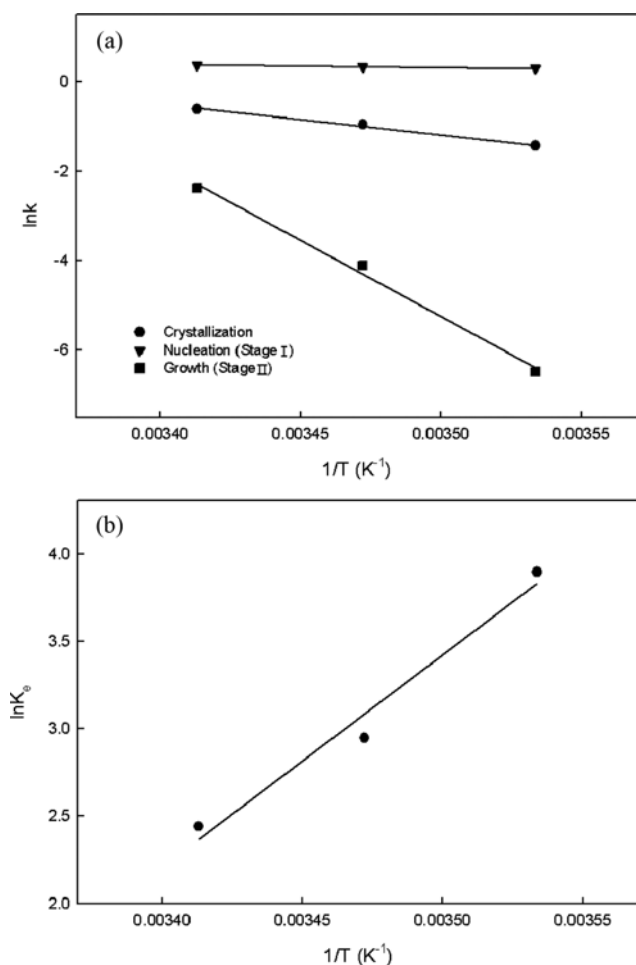


Fig. 8. Plot of $\ln k$ versus $1/T$ (a) and $\ln K_e$ versus $1/T$ (b) for crystallization of vancomycin.

Table 2. Thermodynamic parameters for crystallization of vancomycin

Thermodynamic parameters	Temperature (K)		
	283	288	293
K_e	49.2714	19.0378	11.4831
ΔG^0 (kJ/mol)	-9.1704	-7.3907	-5.9463
ΔH^0 (kJ/mol)		-100.5810	
ΔS^0 (J/mol·K)		-323.5760	
E_a (kJ/mol)		56.3537	
$E_{a, \text{Stage I}}$ (kJ/mol)		4.6453	
$E_{a, \text{Stage II}}$ (kJ/mol)		283.1530	

which indicates an exothermic process [33]. Thus, as the crystallization temperature decreases, the solubility is reduced, whereas the supersaturation increases. As a result of that the crystallization yield of vancomycin increases. The temperature influence in the reaction is determined not only by temperature level but also by E_a , because reactions with higher E_a values are more dependent on the temperature while reactions with lower E_a values are relatively independent on temperature [34]. E_a for nucleation (stage I) and

nucleus growth (stage II) was 4.6453 and 283.1530 kJ/mol, respectively, confirming that the activation energy significantly increased during crystal growth. This result may have been due to an increase in the mobility of the solute grain boundary during the crystallization [15,35]. ΔH^0 and ΔS^0 were calculated using Eq. (7), and ΔG^0 was calculated using Eq. (8) (Fig. 8(b) and Table 2). K_e was 49.2714, 19.0378, and 11.4831 at 283, 288, and 293 K, respectively, confirming that the equilibrium yield increased when increasing the value of K_e with a lower temperature. The ΔG^0 values were negative (-9.1704 kJ/mol at 283 K, -7.3907 kJ/mol at 288 K, -5.9463 kJ/mol at 293 K) and decreased as the temperature decreased. Crystallization was more spontaneous and feasible at lower temperatures. The ΔH^0 value was negative (-100.5810 kJ/mol), and the crystallization process was exothermic, meaning heat was released and the temperature decreased [33]. Then ΔS^0 value was negative (-323.5760 J/mol·K), and the crystallization process was irreversible. The negative value of ΔS^0 suggested a decrease in the degree of freedom of the crystallized vancomycin. Similar results were reported for the fractional precipitation of (+)-dihydromyricetin and paclitaxel [36,37]. Therefore, the results indicated that the vancomycin crystallization process was exothermic, irreversible, and spontaneous.

CONCLUSIONS

We investigated the effect of the major process parameters, including the crystallization temperature and time, on the efficiency of the vancomycin crystallization process. Based on the results, a kinetic and thermodynamic analysis of the crystallization process was then conducted. The optimum crystallization temperature and time were 283 K and 1,440 min, respectively. Under these optimum conditions, clear and uniform crystals were obtained with the highest yield of vancomycin (~98%). In electron microscopy, SEM, XRD analyses, intact crystalline vancomycin was observed at 283, 288, and 293 K, mixed morphologies of vancomycin at 278 K, and amorphous vancomycin at 263, 268, and 273 K. When intact crystalline vancomycin was observed, the kinetic analysis results revealed that the Johnson-Mehl-Avrami-Kolmogorov (JMAK) model was suitable with a high value for r^2 (>0.9561) and low value for RMSD (<0.0170), plus consecutive mechanisms of nucleation and growth were determined. When decreasing the crystallization temperature, the vancomycin yield, crystal size, and JMAK exponent all decreased, indicating they were inversely proportional to the temperature, whereas the crystallization rate constant increased, indicating it was proportional to the temperature. Finally, the thermodynamic analysis revealed that the Gibbs free energy change (ΔG^0), enthalpy change (ΔH^0), and entropy change (ΔS^0) were all negative, indicating that the crystallization process was spontaneous, exothermic, and irreversible.

ACKNOWLEDGEMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Korean Ministry of Education, Science and Technology (Grant Number: 2015016271).

NOMENCLATURE

C_e	: concentration of vancomycin in the crystalline phase at equilibrium [mg/mL]
C_{se}	: concentration of vancomycin in the supernatant at equilibrium [mg/mL]
E_a	: activation energy [kJ/mol]
ΔG^0	: gibbs free energy change [kJ/mol]
ΔH^0	: enthalpy change [kJ/mol]
k	: crystallization rate constant [min^{-1}]
k_a	: pre-exponential factor [mL/mg·min]
K_e	: equilibrium constant [C_e/C_{se}]
m	: number of experimental runs
n	: JMAK exponent
r^2	: coefficient of determination
R	: universal gas constant [8.314 J/mol·K]
ΔS^0	: entropy change [kJ/mol·K]
t	: time [min]
T	: absolute temperature [K]
$X(t)$: yield of vancomycin crystals at time

Subscript

RMSD : root mean square deviation

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