Transformation of Hemipentahydrate to Monohydrate of Risedronate Monosodium by Seed Crystallization in Solution

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The transformation from a hemipentahydrate to a monohydrate of risedronate monosodium was studied by seed crystallization in solution. By using the in-line measurement based on ultrasonic measuring technique and the off-line measurements such as optical microscopic and crystallography, transformation of hydrate forms and crystallization of monohydrate were observed. The effect of concentration of solution and solid fraction of suspension on the ultrasonic velocity was found. The hydrate composition, concentration of solution, and supersaturation during the transformation were estimated with elapsed time. The effect of monohydrate seed, agitation rate and temperature on the induction time, transformation, and crystallization was also investigated. Eventually, transformation from hemipentahydrates to monohydrates and crystallization of monohydrate were analyzed successfully from in-line measuring technique. © 2011 American Institute of Chemical Engineers *AIChE J,* 57: 3385–3394, 2011
Keywords: risedronate, hydrate, transformation, crystallization, ultrasonic velocity

Introduction

The polymorphism of solvates and hydrates is being important in the pharmaceutical field due to their different physical properties related to solubility, dissolution rate, bioavailability, and bioactivity of drug substance. Thus, the screening, the formation, and the transformation of different solid forms are an essential task for selection of the targeted forms and improvement of the properties and ability of drugs.

Risedronate is an effective active pharmaceutical ingredient in field of treatment of diseases of bone and calcium metabolism.[1–8] As reported in the previous studies on risedronate monosodium (RS), hemipentahydrate is most thermodynamically stable form under the typical processing conditions.[1] The hemipentahydrate is demonstrated to be more stable than monohydrate at below 37°C in presence of water.[4] On the other hand, hemipentahydrate of RS was transformed into the monohydrate form by heating the suspension of hemipentahydrate form in a mixture of water/ethanol.[2] Lester et al. presented that an overdried version of hemipentahydrate form of RS existed at low-relative humidity (<10% RH).[7] In the previous study,[8] solubilities of hemipentahydrate and monohydrate in water were found. It was found that there was at a definite temperature for transition between hemipentahydrates and monohydrates. Thus, the stability of hydrate forms is dependent on the temperature. To transform intentionally the hydrate forms is a challenging task. Transformation of monohydrate to hemipentahydrate was studied at room temperature and 37°C.[7] However, transformation of hemipentahydrate of risedronate to monohydrate by seeding hemipentahydrate crystals in the saturated solution was not reported. Mechanism of transformation between hydrate forms of RS has never been studied. It needs understanding the on-line measurement of transformation.

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Based on the change of solid, solution, or suspension properties, using the technique to characterize them can identify and elucidate the transformation. A lots of methods and techniques were applied by off-line analysis technique based on crystallography (X-ray diffraction), morphology (optical microscopic, hot-stage microscopic, scanning electron microscopy (SEM)), thermal analysis [thermogravimetric (TGA), different scanning calorimetry (DSC) and different thermal analysis), and in-line analysis technique such as powder X-ray diffraction (XRPD), Fourier transformation infrared, nuclear magnetic resonance, turbidity measurement, focused beam reflectance measurement and particle vision microscope, and ultrasonic measuring techniques.

The degree of interaction of the ultrasonic velocity in the crystallization depends on the solid fractions and properties of solution during the transformation of polymorphs.[8–10] In general, variations of ultrasonic velocity are a result of diffraction and reflection effects (scattering) on the solid particles determined by their size and morphology, and of dissipative processes, which may be related to the viscosity of the solution. Hence, significant changes of the ultrasonic velocity expected the transitions and crystallization in solution. This technique was more useful than the previous ways for determining the crystal forms and monitoring their change.[8–10] This study introduced ultrasonic velocity measuring technique to grasp the transformation of hydrate form of RS.

In this article, the transformation of hydrates (hemipentahydrates to monohydrates) was investigated by seeding RS in the saturated solution. The solid composition, concentration, and supersaturation, which were useful for analyzing the kinetic of transformation, nucleation, and growth, were estimated during the transformation by ultrasonic measuring technique.

Materials and Experimental Method

Materials

Monohydrates and hemipentahydrates of RS (99 mol %, supplied by JC) were used. RS was identified accurately by XRPD, HPLC, and DSC. Distillated water was used as solvent and other chemicals were purchased by Sigma Aldrich.

Characterization of solid forms

Thermal gravimetric analysis (TGA) and differential scanning calorimetry (DSC) of the solid forms were obtained by using thermogravimetric analyzer (TA instrument, TGA 2050, DSC 2010) up to 573 K with dried nitrogen at a flow rate of 70 mL min^{-1} and a heating rate of 10 K min^{-1}.

XRPD analysis of the solid samples was carried out by RIGAKU Power Diffractometer, model D/Max 2500H with $CuK\alpha_1$ radiation (40 kV, 100 mA) at scan speed of 10°/min and scan step of 0.05° in range of 0–45°.

Morphologies of the solid samples were observed by means of SEM (JEOL, JSM-6390) and optical microscopy.

Monitoring the transformation

The experiment apparatus for monitoring the transformation is identical to that used in the previous work.[9] By adding hemipentahydrate RS solid in the saturated solution at a constant temperature, suspensions of 0.04 wt % solid were prepared in a 300 mL of glass-jacket crystallizer. The temperature was kept constantly by adjusting the thermostatic bath (JEIO Tech, HTRC-30) using programmable PID controller within an accuracy of ±0.1 K. The suspension was agitated by the three-blade propeller. A sensor of Liquisonic30 (SensoTech GmbH, Magdeburg, Germany) was set inside crystallizer to measure the ultrasonic velocity and the temperature, which were recorded at interval of 2 s with a precision of 0.01 m/s and 0.01 K, respectively. A very low-frequency longitudinal ultrasonic wave (1.5 MHz) generated in ultrasonic probe had no cavitations effect in the transformation of hydrates. It was found that nucleation point was not changed by ultrasonic velocity measuring system.[11–14] Suspension was sampled during the experiment and separated into solid and solution parts by filtration. The solid was dried and analyzed by optical microscopic image and XRPD. The concentration of solution was determined by the volume titration with sodium hydroxide using phenolphthalein as an indicator. Experiments by seeding and unseeding the monohydrate crystals were carried out to understand the effect of seed. Effect of temperature of 318.0–346.5 K and agitation rate of 200–400 rpm was also investigated.

Determination of solid composition

The solid composition of hydrates was estimated from area of the XRPD peaks.[15,16] The area of XRPD peaks obtained in the known compositions of hydrate mixture was measured to obtain a quantitative calibration. Thus, the composition of hydrate forms during the transformation and the crystallization was estimated from this calibration curve.

Titrimetric analysis

The concentration of solution was determined by the volume titration of acid–base reaction. The precious amount (2 g) of mother solution, which was weighted by a Mettler Toledo AB204-S balance with an accuracy of ±0.0001 g was collected after filtration. It was diluted with 20 g of water and retained at 25°C to get a titrated solution. Then, the titrated solution was used for titrimetric experiment with analysis grade of sodium hydroxide (0.1 N) as a reactant and phenolphthalein as an indicator. The titrimetric experiments were conducted in triplicate to check the reproducibility for all solution. The concentration of mother solution was calculated from the volume of sodium hydroxide, which had been consumed by the titration.

Results and Discussions

Characterization of solid forms and solid composition

The examples of DSC and TGA for monohydrates and hemipentahydrates are shown in Figure 1a. The DSC curve of the monohydrate exhibited two clear endothermic transitions. The first broad peak at a temperature of 496.5 K in DSC curve attributed to the dehydration process corresponding to the weight loss of 6% in TGA curve at the range from 451 to 502.5 K, which meant a loss of one water molecules per one molecule of monohydrate RS. The second endothermic peak at 541.97 K was due to melting of the

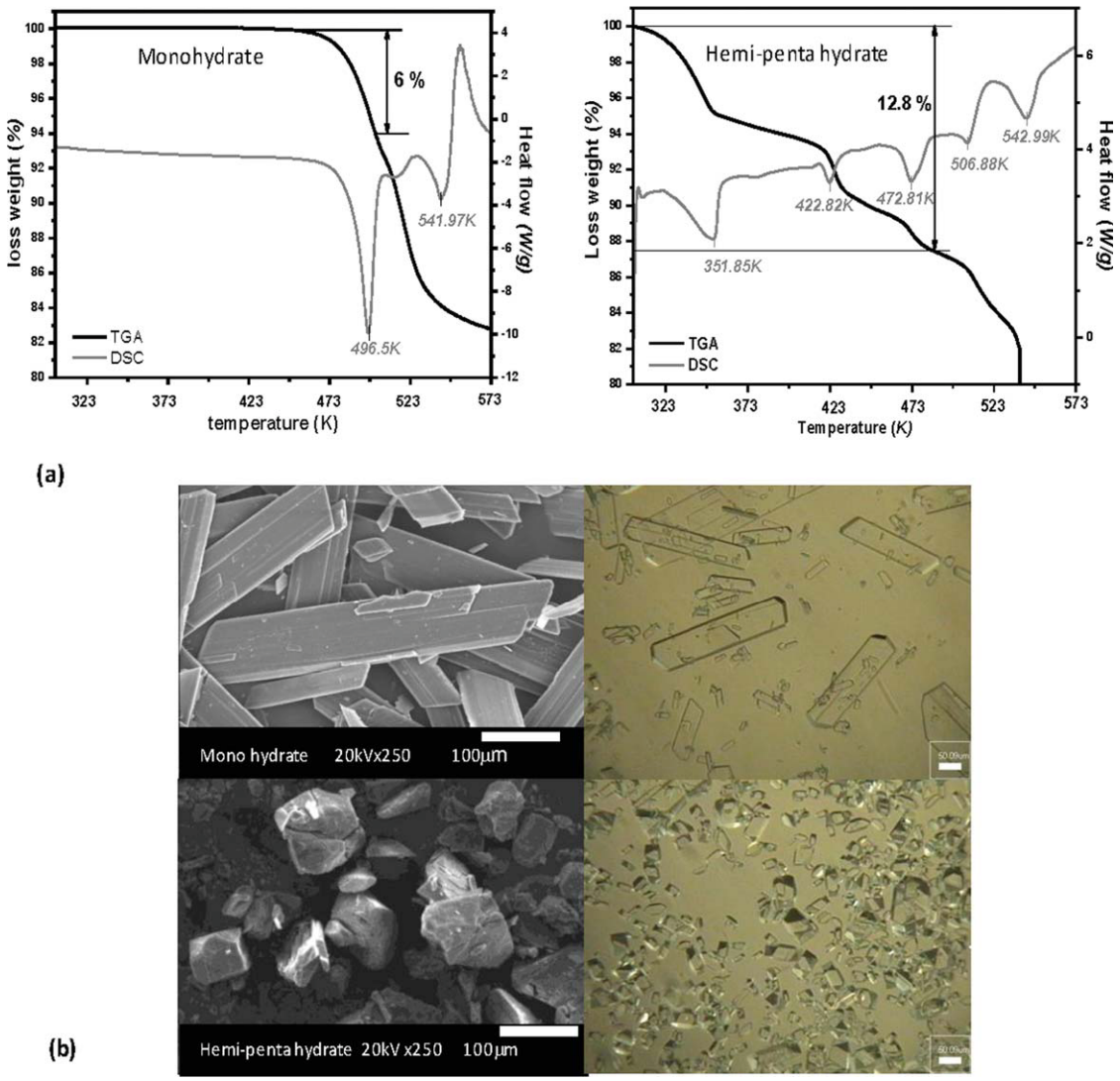

Figure 1. Characterization of monohydrates and hemipentahydrates.

(a) DSC and TGA curve, (b) SEM (left side) and microscopic (right side) image. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

dehydrated phase. In case of hemipentahydrate, the DSC curve was more complicated with various peaks related to different dehydration levels. It is the same to the result presented in the previous study.[7]

As mentioned in the previous study,[8] these hydrate forms performed different XRPD patterns due to the difference in crystal structure and arrangement of molecules. The structure data of unit cell of monohydrate and hemipentahydrate crystals was reported in the previous studies.[4,17] The characterized peak position in XRD charts of monohydrate and hemipentahydrate is listed in Table 1. Furthermore, it was also found that the morphology, crystal shape of these hydrate forms is totally different (see Figure 1b). It suggests that two phases are distinctly different in thermal stability, crystalline structure, crystal size, and morphology. Therefore, the transition between hydrate forms could be readily monitored by XRPD, SEM, DSC, and TGA. However, these are off-line measurement method. To find out exact transformation of hydrates, in-line measurement is necessary.

Solubility and experiment design

As the result was shown in the previous study,[8] monohydrate and hemipentahydrates differ in solubility, which offers a significant information for the design of crystallization process and the prediction and estimation of stability of different solid form. In this article, the solubility data of these hydrate forms in the range of 293–353 K was redrawn with the operating scheme for seeding crystallization using hemipentahydrate crystals and concept of metastable zone(see

Table 1. The Characterized Peak Position in XRD Charts of Monohydrate and Hemipentahydrate

	Monohydrate	Hemipentahydrate
2θ	6.0°, 12.0°, 13.4°, 14.3°, 16.5°, 17.1°, 18.1°, 19.0°, 19.6°, 21.8°, 22.8°, 23.4°, 25.4°, 26.1°, 26.5°, 27.4°, 28.7°, 29.7,° 30.2°	9.0°, 12.2°, 12.9°, 13.5°, 15.4°, 15.7°, 17.2°, 19.8°, 20.5°, 22.9°, 23.9°, 24.6°, 27.8°, 28.1°, 31.3°, 31.8°

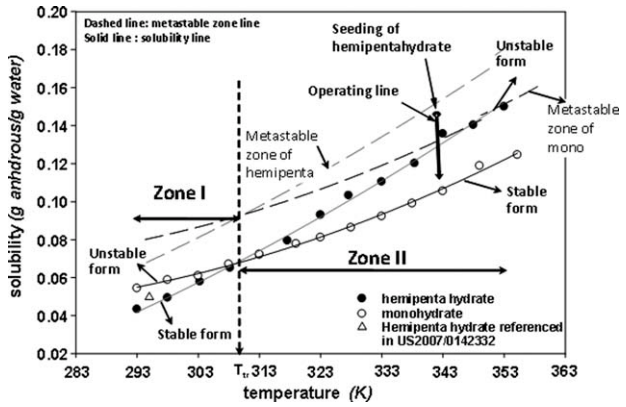

Figure 2. Solubility curves of hydrate forms and operating scheme.

Figure 2). The stability of these hydrates was dependent on the temperature even though they suspended in the aqueous solution at the normal pressure. It means that the transition from the metastable form to stable form at the suitable temperature and operating condition occurs. The contact point of two solubility curves refers to the transition temperature (T_{tr}) for stability of hydrates and divides two zones. Zone I ($T < T_{tr}$) is the stable zone of hemipentahydrate, in which the solubility of hemipentahydrate is smaller than that of monohydrate, whereas zone II is a stable zone for monohydrate, as in $T > T_{tr}$ monohydrate form is the more stable phase due to the lower solubility. It suggests that hemipentahydrate can be transformed from monohydrate in the presence of water under $T_{tr} = 310$ K, which was also supported by Redman-Furey et al.[4] Because risedronate is used at a room temperature, the hemipentahydrate is known as the most stable phase at a typical process. However, it is extremely possible to be changed into monohydrate form at a high-temperature during the thermal manufacturing process even though it is suspended in aqueous solution.

To understand the hydrate formation and transformation, the transition from hemipentahydrates to monohydrates was investigated by seeding hemipentahydrate crystals in a saturated solution at a constant temperature in zone II. The transformation occurs based on the different thermodynamic properties of hydrate forms. In zone II, the hemipentahydrate form is the metastable form. Hemipentahydrate dissolved to solution can be crystallized as stable form—monohydrate. Because the solubility of monohydrate is lower than that of hemipenta, the supersaturation can be generated from the saturated solution of hemipentahydrate. As the point adding the hemipentahydrate solids is inside the metastable zone, the hemipentahydrate crystals added were not dissolved, and so new hemipentacrystals could be formed. Then, as the solution went through the metastable curve of monohydrate, hemipentahydrate was transformed into monohydrate. After the transformation, crystallization of monohydrate occurred. During the transformation, solution concentration moves according to the operating line as can be seen in Figure 2. Transformation occurs in overlapping zone inside metastable zone widths of two hydrates. However, metastable zone width depends on the supersaturation. Thus by controlling the supersaturation, transformation condition can be changed.

When the transformation occurs, the properties of solution such as concentration, density, viscosity, and solid fraction are changed. They cause the variation on the compressibility and the density of liquid media, which induces a significant change on the ultrasonic velocity. Therefore, ultrasonic measuring technique can be used as in-line technique to detect and analyze the transformation as well as the formation of different forms in crystallization process.[8–10]

Ultrasonic velocity curve

The solution-mediated transformation of hemipentahydrate in suspensions at a constant temperature was monitored by ultrasonic measuring technique. The typical curve of ultrasonic measuring system at a temperature of 346.5 K and an agitation rate of 300 rpm is shown in Figure 3. It is divided into four sections associated with the formation of hemipentahydrate in solution, the transformation of hemipentahydrates to monohydrates, growth of monohydrate, and completion of transformation. The kinetic of transformation from hemipentahydrate to monohydrate can be obtained in section II.

First, in section I, the hemipentahydrate solid was fed in the solution (seeding in metastable zone of hemipentahydrate, shown in Figure 2) and the ultrasonic velocity reached to the stable value until the occurring of spontaneously nucleation and crystal growth of hemipentahydrate, which caused the remarkable change of ultrasonic velocity. Second, transformation of hemipentahydrate into monohydrate occurred in section II (in intercepting metastable zone of monohydrate, shown in Figure 2). At the end point of section II, only monohydrate form (Form M) was obtained and the slope of curve was remarkable changed. The curve decreased continuously against time in section III (inside metastable zone of monohydrate, shown in Figure 2), in which growth of Form M proceeded and, finally, reached at a steady state. It reflects the completion of growth of monohydrate. It indicates obviously that the slope of curve is related to the degree of transformation from hemipentahydrate to monohydrate and growth of monohydrate form. Furthermore, the induction time of monohydrate, time required for transformation, and time for the crystallization of monohydrate were determined.

As can be also seen in Figure 3, the XRPD patterns and microscopic images support that ultrasonic data are reasonable for expecting transformation of hydrate forms. As mentioned previously, hemipentahydrates and monohydrates have different crystal morphologies. Hemipentahydrate has the hexagonal prism, whereas monohydrate performs the flat-needle-like shape. It is easy to distinguish these forms by XRPD pattern and microscopic images. In section I, only hemipentahydrate form exists as can be seen from XRPD patterns and microscopic photos. In section II, the occurring of new flat-needle-like crystal and new peak at 6° of 2θ proves the formation of monohydrate form. The gradual disappearance of hemipentahydrate and the continuous increase in the amount of monohydrate crystal make the transformation be occurred. In sections III and IV, monohydrate increases with elapsed time. The data obtained from these offline techniques gives a good evidence for the accuracy of ultrasonic measuring technique.

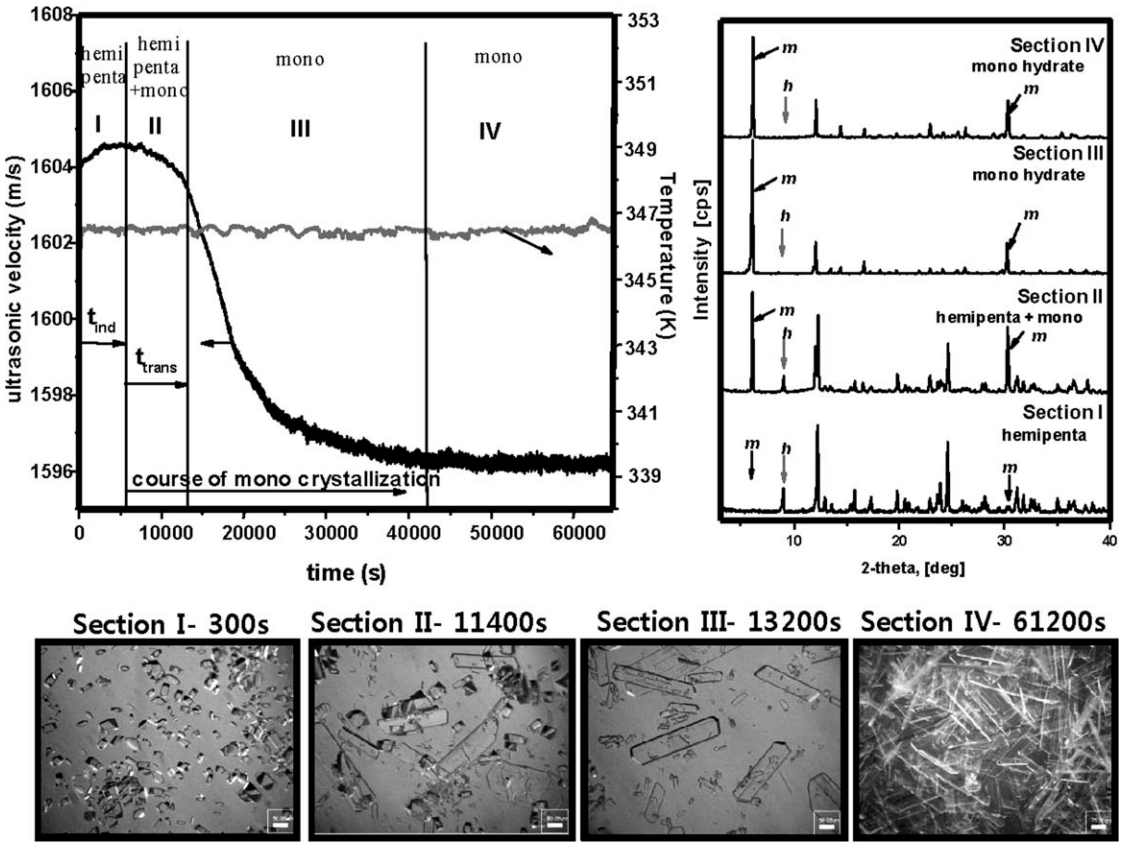

Figure 3. Plot of ultrasonic velocity against time, XRPD patterns and microscopic images at T = 346.5 K and an agitation rate of 300 rpm.

Transformation kinetic

In this study, a simple theoretical equation to establish a relationship between the ultrasonic velocity of Form H (hemihydrate) and Form M (mono) was used. To a first approximation, the ultrasonic properties of a multiphase material can be described according to McClements[18]

$$\frac{1}{c^2} = \sum_{j=1}^{n} \varphi_j \rho_j \sum_{j=1}^{n} \frac{\varphi_j}{c_j^2 \rho_j} \tag{1}$$

where ρ_j, c_j, and φ_j are density, ultrasonic velocity, and volume fraction of phase j, respectively. The phase consists of solvent, dissolved monohydrate, dissolved hemipentahydrate, solid monohydrate, and solid hemipentahydrate. As can be seen in Figure 4a, the points that indicate 100% hemipentahydrate (Form H) and 100% monohydrate (Form M) were indicated as c_H and c_M, respectively, from measuring ultrasonic measuring system. Therefore, c_H means sum of ultrasonic velocities of solvent, dissolved RS and Form H solid, whereas c_M means sum of ultrasonic velocities of solvent, dissolved RS and Form M solid. Even though the water is released during the transformation of hydrate forms, the amount of water released is very small compared with that of solvent and so is neglected in this study. Thus, the solvent fraction was assumed to be constant. During the transformation, the dissolved RS content in solution decreases, and the solid RS content increases. To simplify Eq. 1, the phases can be divided into the dissolved RS and solid Form H as C_H, and the dissolved RS and solid Form M as C_M.

$$C_H = c_H - c_S \tag{2}$$

$$C_M = c_M - c_S \tag{3}$$

where c_S is ultrasonic velocity of water, and its value is 1556 m/s as can be found in Figure 5a. The solid density of Forms H and M are very similar. The density of Forms H and M dissolved in solvent is same. Thus, it can be assumed that volume fraction is converted into the mass fraction.[10]

This simple relationship gives a good description of the ultrasonic properties in the case that the densities of the two forms are similar and the scattering of ultrasound is negligible. The x_H can be expressed as follows:[10]

$$x_H = \frac{1/C^2 - 1/C_M^2}{1/C_H^2 - 1/C_M^2} \tag{4}$$

where x_H is the mass fraction of the Form H, and C_H and C_M are the ultrasonic velocities of 100% solid Form H and of 100% solid Form M at the measurement temperature in section II, respectively. Thus, transformation from Form H into Form M can be determined by measuring ultrasonic velocity, providing that the ultrasonic velocities of 100% Form H and 100% Form M are known at the same temperature.

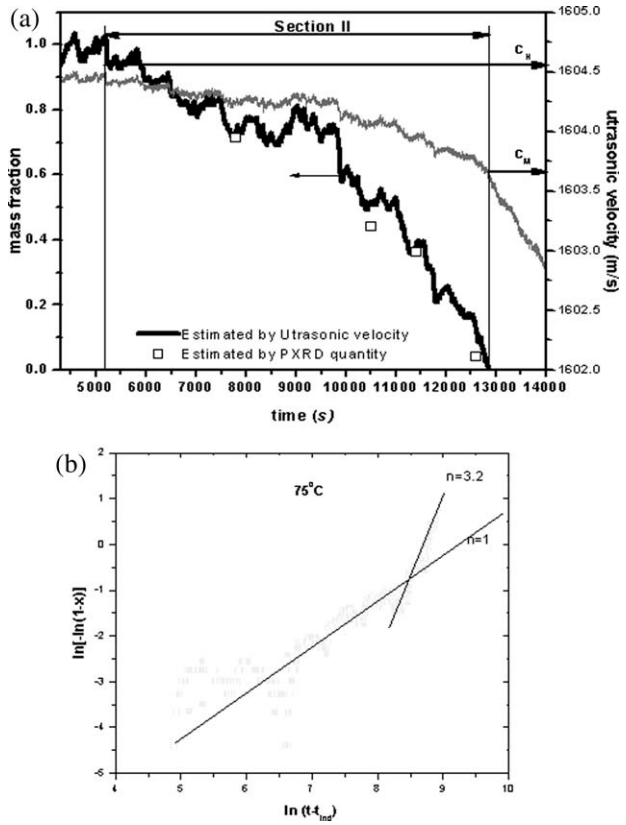

Figure 4. (a) Mass fraction of hemipentahydrate and (b) plot of ln[-ln(1 − x)] vs. ln($t - t_{ind}$) at 346.5 K.

The mass fraction of Form H obtained from the ultrasonic velocity in Section II is shown in Figure 4a. As be seen in this figure, the mass fraction of Form H decreases with the transformation time. Decrease in mass fraction of Form H suggests that transformation occurred. The mass fraction estimated from area fraction of the peaks of hydrates using XRPD chart is also presented to get the confirmation. It is obvious that the data obtained from two methods is well agreed with each other. It concludes that ultrasonic velocity can be applied to monitor the solid fraction and transformation of hydrates in suspension with high-accuracy.

To get kinetic of transformation, the J–M–A equation can be used.

$$x(t) = 1 - \exp\{-K(t - t_{\text{ind}})^n\} \tag{5}$$

where, $x(t)$ is transformed fraction at time t, referred as weight fraction of monohydrate (weight fraction of monohydrate = 1 − weight fraction of hemipentahydrate), t_{ind} is the induction time of monohydrate, K is nucleation and growth rate dependent constant, and n is the order of kinetic of transition. Solvent is not crystallized during transformation.

Plot of ln[−ln(1 − x)]] against ($t - t_{\text{ind}}$) is shown in Figure 4b. As can be seen in this figure, two slopes in the plot were found. It means that two mechanisms dominated during the transformation. The data is fitted as line with the slope value $n = 1$ even though in the end of section II the slope value $n = 3.2$ is obtained. It means that the transformation is mostly controlled by the diffusion, and crystallization of Form M is dominated in the end of section II. It is interesting that transformation and crystallization of monohydrate occurs simultaneously at the transition section. The mechanisms during the phase transition can be explained by the combination of transformation (from Form H to Form M) and crystallization (Form M crystallization) from the supersaturated solution.

Concentration of solution

The ultrasonic velocity in suspension is significantly affected by the concentration of solution and the solid fraction. To monitor the concentration of solution during transformation and crystallization, the behavior of ultrasonic velocity for solution concentration and solid fraction was investigated at a constant temperature of 346.5 K and is shown in Figure 5a. In general, ultrasonic velocity rises

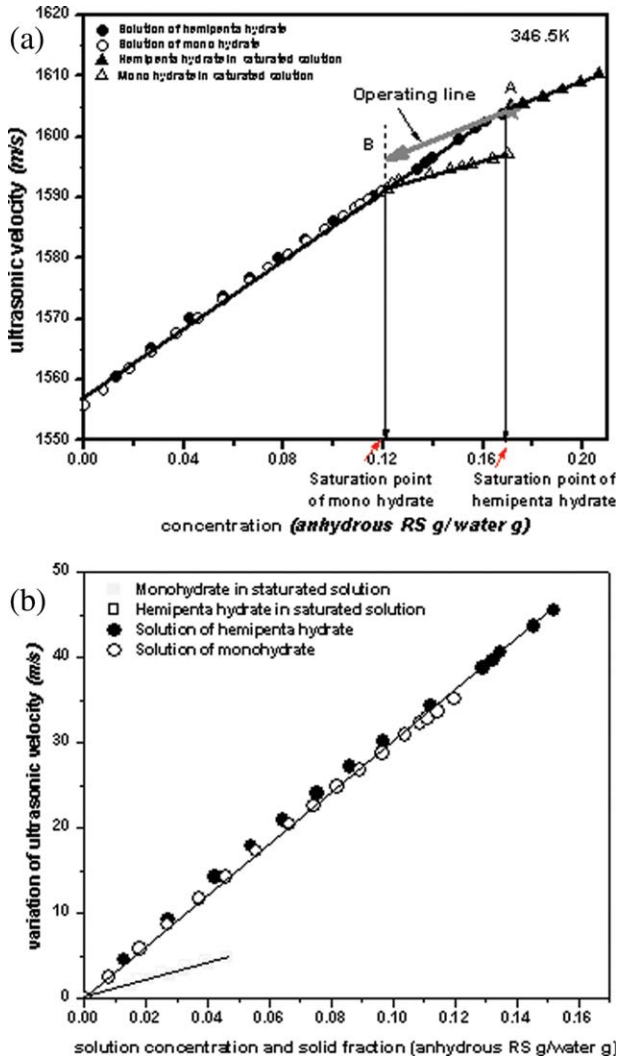

Figure 5. (a) Effect of solution concentration and solid fraction on ultrasonic velocity and (b) variation of ultrasonic velocity against solution concentration and solid fraction.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

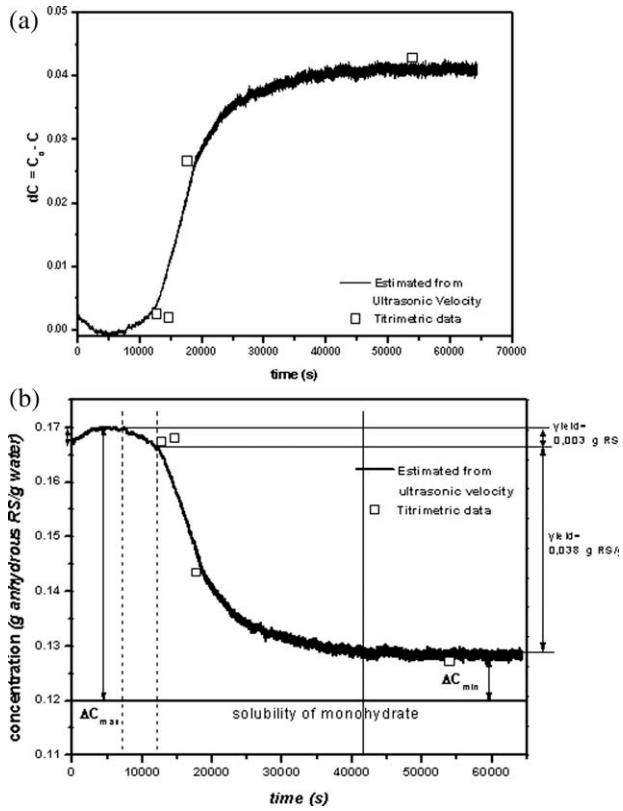

Figure 6. Change of (a) supersaturation and (b) solution concentration with elapsed time.

linearly with the increase in both solution concentration and the solid fraction. From this figure, the undersaturated solution of monohydrates and hemipentahydrates displays the same slope due to the same effect of the solution on ultrasonic velocity. There are the remarkable differences at the slope of the undersaturated solution and the saturated solution with solids for all hydrates. The slope of curve in undersaturated solution is higher than that in solid. It means that the property of solution (especially concentration) has the stronger effect on ultrasonic velocity than that of solid. From this figure, the operating line was also performed. To model the function of ultrasonic velocity with the variation of concentration and solid fraction, the plot of variation in concentration and solid fraction against ultrasonic velocity was created in Figure 5b. From this figure, effect of solid content for hemipentahydrate and monohydrate in saturated solution on the ultrasonic velocity is almost same. Eventually, solution effect on ultrasonic velocity is much higher than the solid effect.

Because the fraction of hemipentahydrate crystal in the starting suspension is 0.0004 (anhydrous RS g/water g), formation of monohydrate by transformation of the fed crystals is not expected. In end of section II, fraction of monohydrate solid in solution is about 0.0037 anhydrous RS g/water g). It concludes that the hemihydrate seed solids are changed into monohydrate by mean of the phase transition and induce hemipentahydrate formation to be changed into monohydrate. During the crystallization of the constant volume, the increase of the solid fraction results from the nucleation and growth of monohydrate, which results in the decrease of solution concentration. The operating line was created to model the coexist effect of concentration and solid fraction during the crystallization and transformation. The change of concentration (dC) and solution concentration (C) during the transformation and crystallization were obtained from the change of ultrasonic velocity (see Figure 6). As can be seen in this figure, solution concentration decreases following the S-curve according to ultrasonic velocity. The square points represent for the solution concentrations, which were determined by the volume titration with sodium hydroxide. It is found that titrated data are well matched with the values estimated by ultrasonic velocity. Following the obtained concentration curve, the end point of concentration is higher than solubility of monohydrate. It can be explained by the limitation of kinetic effect. It is obvious that the concentration data can be obtained by measured ultrasonic velocity. This is a useful information for further kinetic studies of crystallization.

Effect of monohydrate seeding

Experiments adding seed of monohydrate in the initial suspension were carried out. Figure 7 shows the comparison of seeded and unseeded processes. Mean size of seeded hemipentahydrate crystals was about 60 μm. Induction time for seeded and unseeded processes is 900 and 5300 s, respectively. Amount of the monohydrate seed fed is 0.0001 (anhydrous g/ water g). Transformation time from hemipenta to mono for seeded and unseeded processes is 2400 and 7600 s, respectively. It is proved that the monohydrate seed reduces significantly time for induction, transformation, and crystallization of monohydrate. Seeding is contributed to activation of secondary nucleation. It also indicates that the nucleation of monohydrate is the very important stage, which could affect strongly the kinetic of transformation and crystallization.

Effect of temperature

Experiments with different temperatures from 318 to 346.5 K in seeded process were investigated. At a temperature below 318 K, there was no transformation from Form H

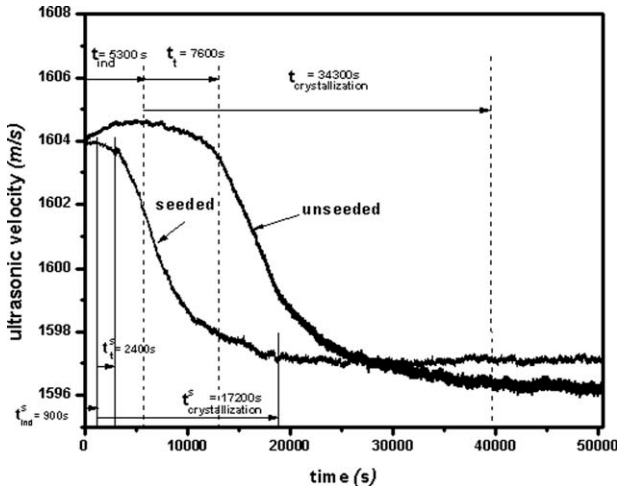

Figure 7. Effect of monohydrate crystal seed on the transformation.

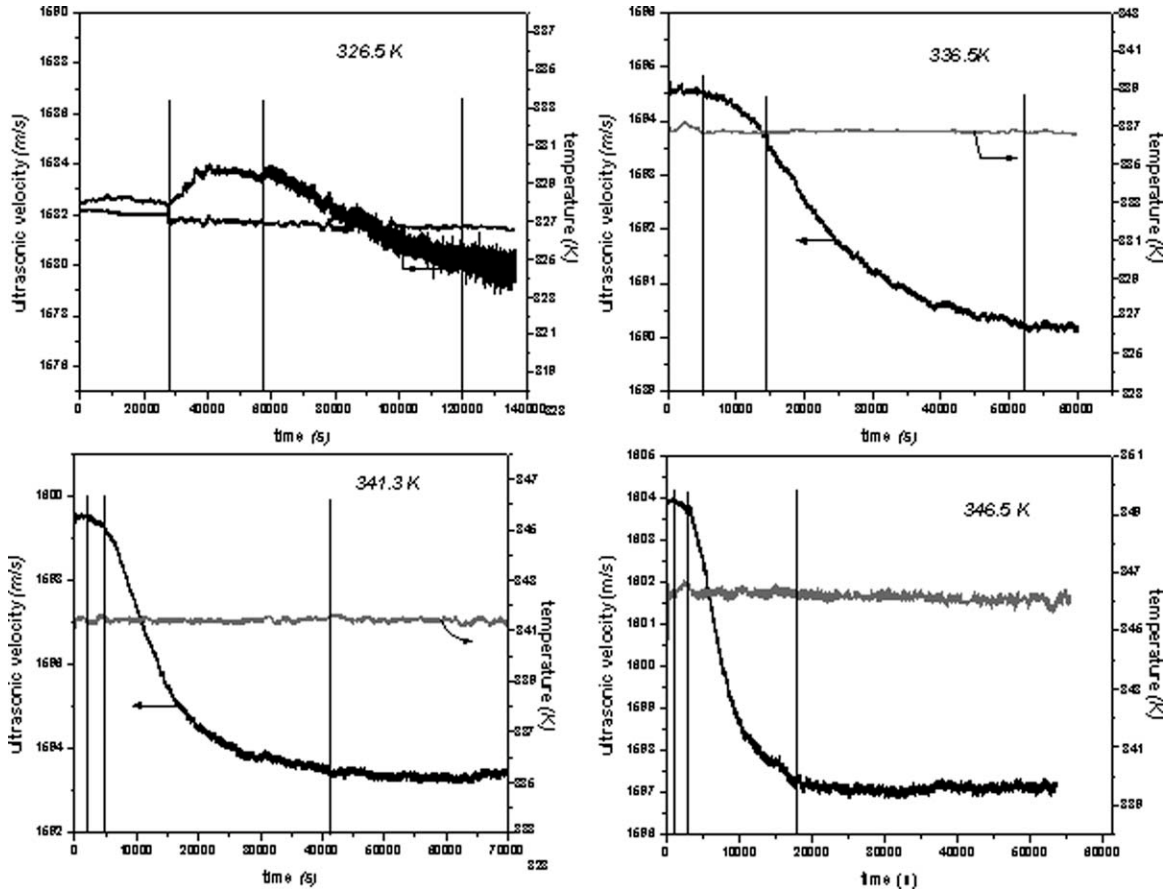

Figure 8. Ultrasonic velocity curves at various temperatures.

to Form M for 4 days. The ultrasonic velocity curves of experiments carried out in range of 326.5–346.5 K were shown in Figure 8.

Figure 9 shows the summary for induction, transformation, and crystallization time. As can be seen, time of induction, transformation, and crystallization decrease with increasing the temperature. In crystallization section, secondary nucleation and crystal growth by ripening and desupesaturation can occur simultaneously. As the solubility of two hydrate forms increases with increasing temperature, the higher temperature generates the lower supersaturation (see Figure 2). The crystallization time is much higher than induction and transformation time. It indicates that there is a more significant effect of supersaturation on the crystallization than transformation. K values in Eq. 5 were found to be 0.000226, 0.000720,

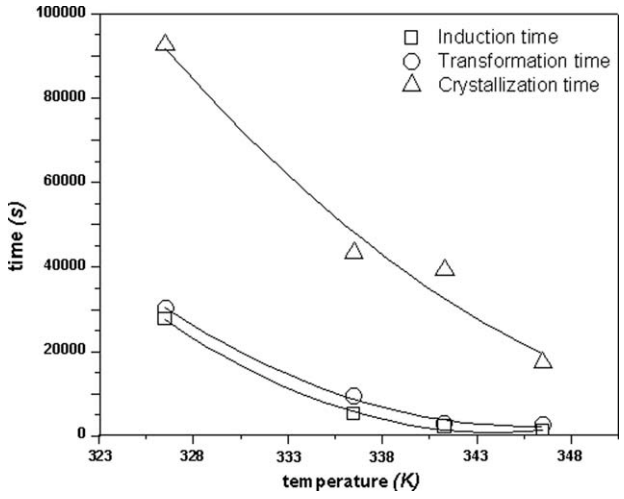

Figure 9. Effect of temperature on induction, transformation and crystallization time.

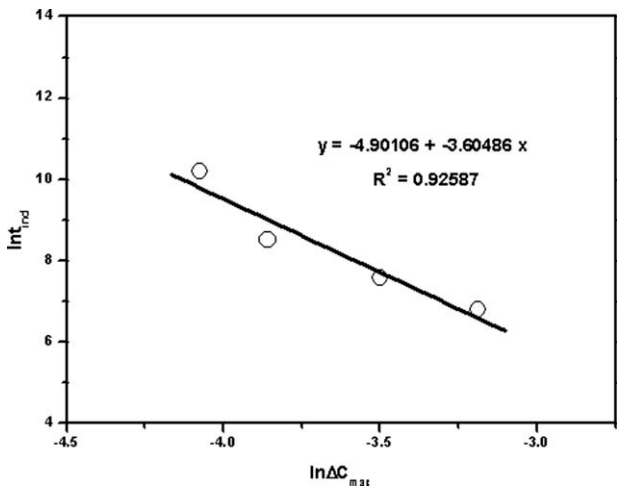

Figure 10. Plot of $\ln t_{ind}$ against $\ln \Delta C_{max}$.

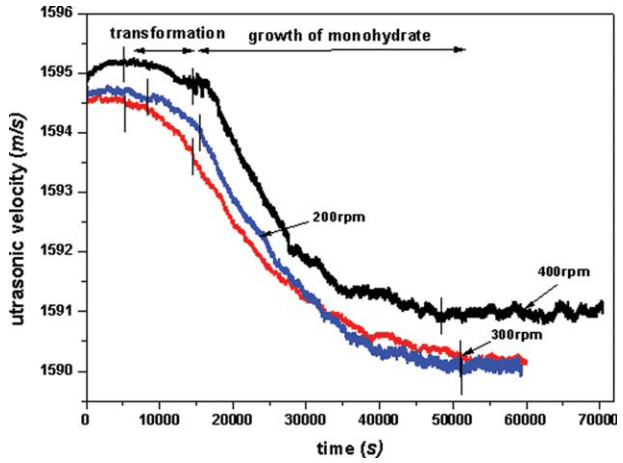

Figure 11. Effect of agitation rate on transformation and crystallization.

[Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

0.002295, and 0.003289 s^{-1} for 326.5, 336.5, 337.5, and 338.5 K, respectively.

Nucleation kinetic of monohydrate

The nucleation rate (B) is the exponent function of maximum concentration suspersaturation (ΔC_{max}):

$$B = k_n \Delta C_{max}^{b} \tag{6}$$

In addition, it also has the inversely proportional relation with the induction time, $t_{ind} \propto B^{-1}$.

$$t_{ind} \propto \frac{1}{k_n} \Delta C_{max}^{-b} \tag{7}$$

Based on the Eq. 7, the order of nucleation was calculated from the slope of $\ln t_{ind} - \ln \Delta C_{max}$ curve. As can be seen in Figure 10, it was found that nucleation order is about 3.6.

Effect of agitation rate

The agitation rate of 200–400 rpm was investigated in the seeded process at temperature of 336.5 K. Figure 11 shows the effect of agitation rate. It was found that time of induction, transformation, and crystallization were almost same at 200–400 rpm despite data were scattered a little. It reflects that the agitation rate in investigated range had a weak effect on the solvated mediated transformation from hemipentahydrate to monohydrate and crystallization of monohydrate.

Conclusions

Analysis using ultrasonic velocity measurement detected successfully the transformation from hemipentahydrates to monohydrates of RS in the suspension. Particularly, the measurement of ultrasonic velocity disclosed that the transformation and crystallization occurred separately in the transformation of RS hydrates. The induction time, solution concentration, and supersaturation were determined during the transformation and the crystallization. The kinetic of transformation was analyzed in the course of transition and formation of hydrates. Furthermore, it was found that monohydrate seed and increase of temperature had a significant improvement on the transformation from hemipentahydrates to monohydrates and the crystallization of monohydrate.

Notation

B = nucleation rate, #/m^3s
b = order of nucleation
C_H = ultrasonic velocity of 100% solid Form H, m/s
C_M = ultrasonic velocity of 100% solid Form M, m/s
ΔC_{max} = maximum suspersaturation
c = ultrasonic velocity, m/s
K = nucleation and growth rate dependent constant
n = order of kinetic of transition
T = temperature, K
t = time, s
t_{ind} = induction time of monohydrate, s
x = mass fraction of the hydrate

Greek letters

ρ = density, kg/m^3
φ = volume fraction

Subscripts

j = phase
H = hemipentahydrate of RS
M = monohydrate of RS

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