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Solubility and crystallization of ibuprofen in the presence of solvents and antisolvents

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Abstract−The solubility and crystallization behavior of ibuprofen was investigated in the presence of solvents (acetone and ethanol) and antisolvents (water and hydrogen peroxide). The solubility of ibuprofen was determined in the mixtures of acetone+water, acetone+hydrogen peroxide, ethanol+water, and ethanol+hydrogen peroxide. The phase boundaries of these ternary systems were determined as a function of the mixtures' concentration at 27, 35, and 40 °C. Based on the solubility data, ibuprofen was crystallized using the antisolvent crystallization technique. It was found that the external shape and internal structure of ibuprofen crystals were nearly independent of solvent and antisolvent, but the size distribution of the resulting particles changed. In the crystallization process, the application of ultrasound induced a significant reduction in particle size and caused severe agglomeration of micronized ibuprofen. This problem was solved by adding an external additive (Tween 80) to the solvent and antisolvent mixtures.

Keywords: Antisolvent, Crystallization, Ibuprofen, Solubility, Tween 80

INTRODUCTION

Crystallization is a typical separation process for producing pure solid materials from liquid solutions [1,2]. These solutions may consist of a pure solvent or mixtures of different types of solvents or antisolvents. The solubility of solid materials in liquid solvents is strongly dependent on solvent properties, such as density, polarity, and dielectric constant. Therefore, for a particular solute, the solubility in a mixture of solvents will change depending on the composition of solvents or antisolvents in the mixture.

In antisolvent crystallization, crystallization is induced by changes in the composition of the solution, i.e., the ratio of solvent+antisolvent in the mixture [3-5]. Therefore, prior to performing antisolvent crystallization, it is important to determine the solubility of a target solute in solvent+antisolvent mixtures as a function of their composition. The main function of the antisolvent is to diminish the solubility of the dissolved material and to cause rapid crystallization. Thus, the physical properties of the antisolvent, along with the mixing rate between the solvent and the antisolvent, will govern the nucleation rate and growth of crystal in the crystallizing system. These factors may influence the physical properties of the products, such as particle size distribution and shape of crystals. In contrast, the solubility of a solute in the solvent+antisolvent mixture affects the yield of crystallization, which corresponds to the amount of crystallized product obtained divided by the initial amount of solute fed. When the solution is supersaturated, the crystallization process continues until the solution reaches an under-saturation state. The yield of crystallization is then determined by the solubility difference between the supersaturation and the under-saturation states.

Antisolvent crystallization is commonly employed to recrystallize pharmaceutical compounds, because this technique does not require thermal energy, which can reduce the performance of biologically active drugs [6,7]. In the crystallization of pharmaceutical compounds, it is important to maintain product quality, including particle size distribution, crystal shape, and internal structure, to ensure that the medical effect of the drug is consistent. In addition, it is crucial to increase the yield of crystallization because pharmaceutical compounds are high-value products.

When a pharmaceutical compound is recrystallized, micronization of the precipitated particles is necessary to enhance its bioavailability. To achieve this purpose, ultrasound techniques can be used during crystallization [8-10]. The considerable advantages of using ultrasonic waves include induction of primary and secondary nucleation, reduction of crystal size, and modification of internal structure. However, one of the side effects of the use of ultrasound is the occurrence of agglomeration owing to the generation of extremely small particles. These particles can be easily aggregated to form undesirable large masses of agglomerated particles. This phenomenon can be relieved by adding a surface-active agent to crystallizing systems in order to prevent the microparticles from forming aggregates.

In this study, the solubility and antisolvent crystallization of a pharmaceutical compound was investigated in the presence of various solvent+antisolvent mixtures. Ibuprofen [11,12], a nonsteroidal anti-inflammatory ingredient, was selected as a pharmaceutical compound. Variations in the particle size and crystal properties of ibuprofen were examined as a function of the type of solvent and antisolvent, the presence of ultrasound and the concentration of surface-active agents.

EXPERIMENTAL METHODS

1. Materials

Ibuprofen (CAS 15687-27-1), acetone (CAS 67-64-1), ethanol (CAS 64-17-5), and hydrogen peroxide (CAS 7722-84-1) were pur-

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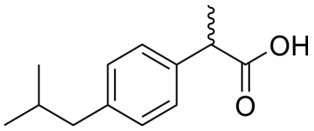
Table 1. Physico-chemical properties of ibuprofen

Properties	
Chemical formula	$C_{13}H_{18}O_2$
Chemical structure	
Molecular weight	206.29 g/mol
Density	1.03 g/cm^3
Solubility in water	0.021 mg/ml (20 °C)
Melting point	75-78 °C
Usage	Non-steroidal anti-inflammatory drug

chased from Sigma-Aldrich Co. As a surface-active agent, Tween 80 (CAS 9005-65-6) was also purchased from Sigma-Aldrich Co. Table 1 shows the physico-chemical properties of ibuprofen.

2. Experimental Procedure

Two sets of experiments were performed in this study: solubility measurements and antisolvent crystallization. The solubility of ibuprofen in four different solvent+antisolvent mixtures was measured before the crystallization experiments. The mixtures were acetone+water, acetone+hydrogen peroxide, ethanol+water, and ethanol+hydrogen peroxide. First, 20 ml of the solvent+antisolvent mixture was prepared. The ratios of solvent/antisolvent in the mixtures were 100/0, 95/5, 90/10, 85/15, 80/20, and 70/30 by volume. Next, 1.0 g of ibuprofen was loaded in a mixing vessel, which was kept at a constant temperature. Then, the prepared solvent+antisolvent mixture was slowly injected into the mixing vessel under vigorous agitation. The injection rate of the mixture was 0.01 ml/sec, and the injection was continued until complete dissolution of ibuprofen was observed. During the injection, we carefully observed the agitated mixture to determine the accurate solubility point. To identify the complete dissolution of ibuprofen, the agitation was occasionally stopped during the injection step. When ibuprofen particles were not shown and a clear solution was visually observed, it was regarded as a solubility point. The total volume of the used solvent+antisolvent mixture was not greater than 20 ml. The required volume of mixture was recorded, and the solubility of ibuprofen in a particular solvent+antisolvent mixture was calculated.

The experimental apparatus and operating methods for the crystallization experiments are well explained in our previous publication [13]. Briefly, for the experiments, ibuprofen solutions in a given solvent (acetone or ethanol) were prepared at concentrations of 0.1, 0.2, and 0.4 g/ml. Next, 10 ml of the solution was injected into 30 ml of antisolvent (water or hydrogen peroxide) under vigorous mixing. If necessary, ultrasonic waves were added to the system at a frequency of 22.5 kHz and an output of 5 W. In addition, as needed, an external additive (Tween 80) was mixed to the solution at a concentration range of 0.32-1.92 wt%. The crystallization experiments were performed at three temperatures (27, 35, and 40 °C). During

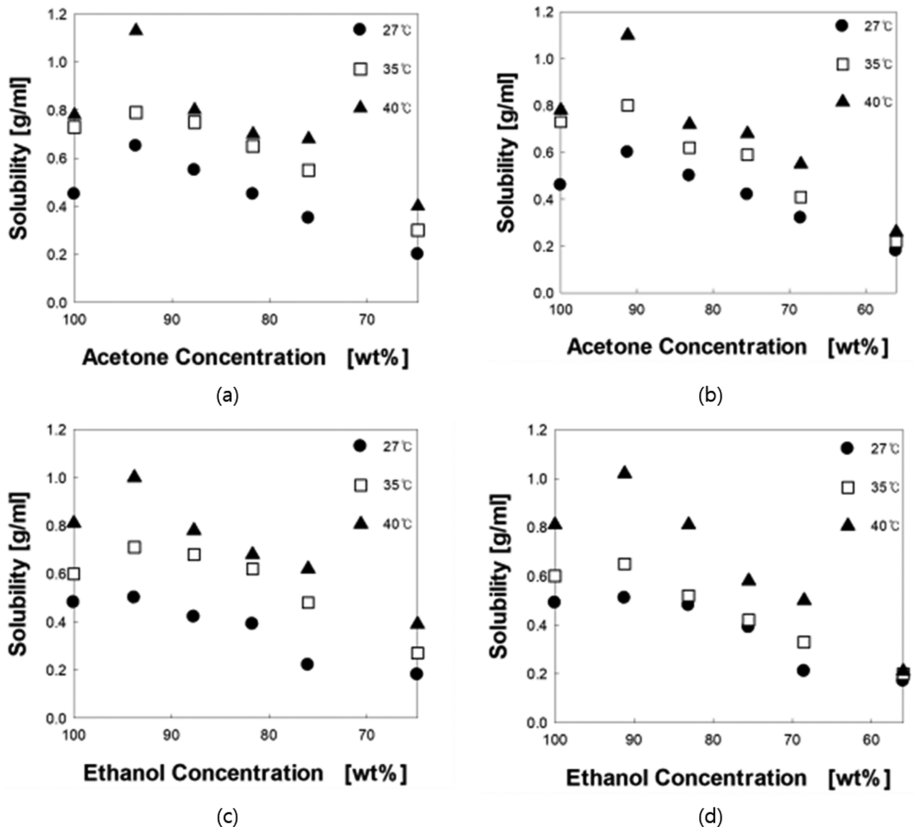


Fig. 1. Solubility of ibuprofen in mixtures of acetone+water (a), acetone+hydrogen peroxide (b), ethanol+water (c), and ethanol+hydrogen peroxide (d) at 27, 35, and 40 °C.

the injection of the ibuprofen solution, rapid precipitation of the solid particles occurred. After the solution injection was completed, the particles were separated from the suspension and dried for analysis. The obtained ibuprofen particles were analyzed by scanning electron microscope (SEM, Hitachi), differential scanning calorimeter (DSC, TA Instruments), and powder X-ray diffractometer (XRD, Rigaku). The particle sizes and particle size distributions of the crystals were measured using ImageJ software.

RESULTS AND DISCUSSION

1. Solubility of Ibuprofen

Fig. 1 shows the solubility of ibuprofen in four different solvent+antisolvent mixtures at 27, 35, and 40 °C. The solubility is plotted as a function of solvent (acetone or ethanol) concentration in mixtures of acetone+water (Fig. 1(a)), acetone+hydrogen peroxide (Fig. 1(b)), ethanol+water (Fig. 1(c)), and ethanol+hydrogen peroxide (Fig. 1(d)). Overall, the solubility of ibuprofen in these mixtures ranged from 1.120 to 0.147 g/ml as the solvent concentration changed from 100 to 60 wt%. For reference, we present the solubility data of ibuprofen in pure solvents (acetone and ethanol) that were reported in the literature [12]. In pure acetone, the reported solubility ranged from 0.467 to 0.612 g/ml (in the temperature range of 24-39 °C), and in pure ethanol, the solubility ranged from 0.472 to 0.631 g/ml (in the temperature range of 25-39 °C). These literature data can be compared to our data shown in Fig. 1. As expected, the solubility increased with increasing temperature. It was found that the solubility of ibuprofen slightly increased when a small amount of antisolvent was added to the solvent, but smoothly decreased as the antisolvent concentration increased. There was a solubility maximum when the solvent concentration was ca. 93 wt%, and the solubility slowly decreased as the solvent concentration decreased. This trend was observed in all four solvent+antisolvent mixture systems. In addition, the solubility maximum phenomenon was more evident at a high temperature (40 °C) than at a low temperature (27 °C). These results can be explained by the strongly nonideal behavior of the solvent+antisolvent mixtures. Indeed, the solvents (acetone and ethanol) and antisolvents (water and hydrogen peroxide) used in this study are strongly polar compounds, which may exhibit negative volume changes of mixing owing to molecular attraction. The negative volume change of mixing should result in the density increase of a solvent mixture. Thus, as the solvent power towards a

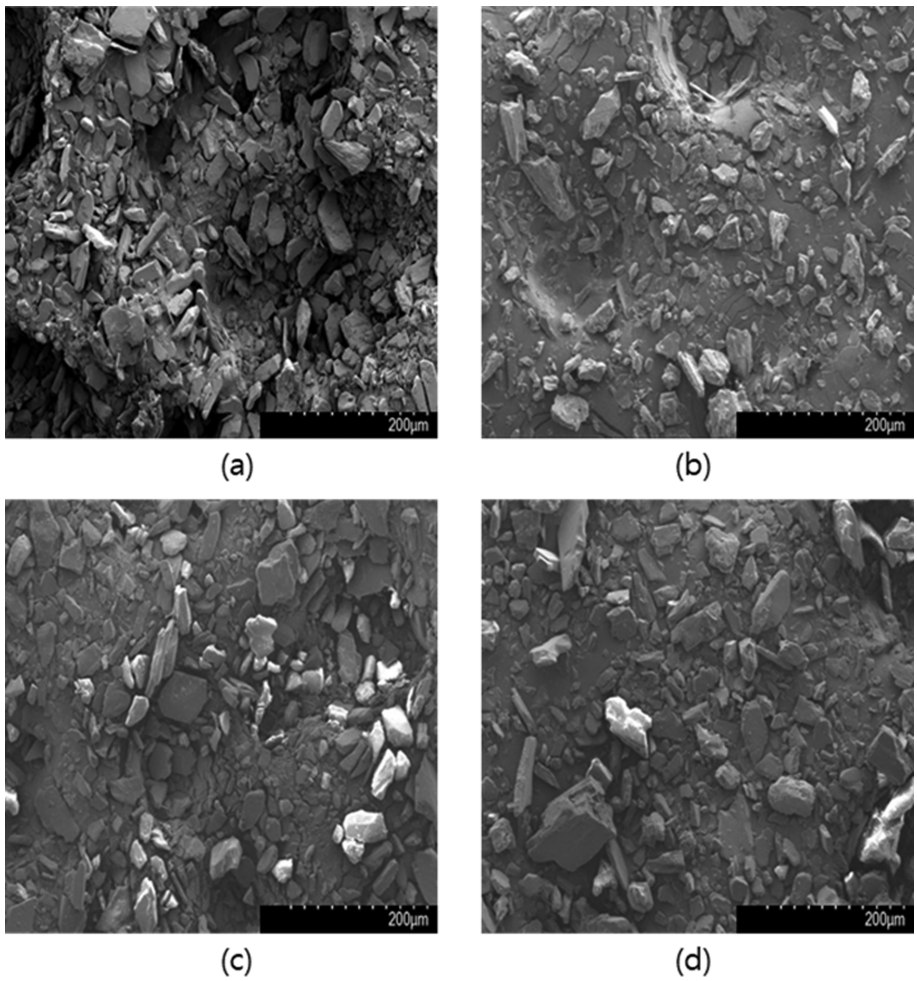


Fig. 2. SEM photomicrographs of ibuprofen particles crystallized from four different solvent+antisolvent mixtures: acetone as a solvent and water as an antisolvent (a), acetone as a solvent and hydrogen peroxide as an antisolvent (b), ethanol as a solvent and water as an antisolvent (c), and ethanol as a solvent and hydrogen peroxide as an antisolvent (d).

solute is proportional to the density of a solvent, the solvent mixtures exhibit a solubility maximum at a certain concentration (ca. 93 wt% solvent concentration). These results imply that the mixtures of the solvent+antisolvent have a maximum density at ca. 93 wt% solvent concentration, and as a result the maximum density induced the maximum solubility. A similar result was also found in our previous investigation published in the literature [13]. In that system, the solubility of griseofulvin in the mixed solvent of acetone+water was measured, and the solubility exhibited a maximum at ca. 92 wt% acetone in water.

Extrapolation of the solubility curves in Figs. 1(a)-1(d) reveals that ibuprofen solubility in the solvent+antisolvent mixtures approaches zero at solvent concentrations of <30 wt%. This result confirms that water and hydrogen peroxide can successfully act as antisolvents for ibuprofen solutions in crystallization experiments, in which a given volume of ibuprofen solution is mixed with an excess amount of antisolvent. In addition, the changes in ibuprofen solubility with temperature became very small when the solvent (acetone or ethanol) concentration reached 60 wt% (Figs. 1(a)-1(d)). This result indicates that increasing the antisolvent concentration in the solvent+antisolvent mixture, and therefore reducing the solvent power towards ibuprofen, diminishes the effect of temperature on ibuprofen solubility. Thus, it can be told that the role of antisolvent may be more important than the temperature change as long as the induction of supersaturation and nucleation is concerned.

2. Crystal Habit

Fig. 2 shows the SEM photomicrographs of ibuprofen particles that crystallized from four different solvent+antisolvent mixtures. Ibuprofen particles were crystallized using acetone as a solvent and water as an antisolvent (Fig. 2(a)), acetone as a solvent and hydrogen peroxide as an antisolvent (Fig. 2(b)), ethanol as a solvent and water as an antisolvent (Fig. 2(c)), and ethanol as a solvent and hydrogen peroxide as an antisolvent (Fig. 2(d)), respectively. Note that the magnifications of these four images are the same. Observation indicated that the type of solvent and antisolvent rarely influences the external crystal habit of ibuprofen within the experimental range investigated. The particle shape was almost constant and an irregular particulate crystal habit was formed in all four solvent+antisolvent systems. In addition, the crystal habit was not affected by the change of experimental conditions, such as temperature, solution concentration, and the application of ultrasonic waves. These

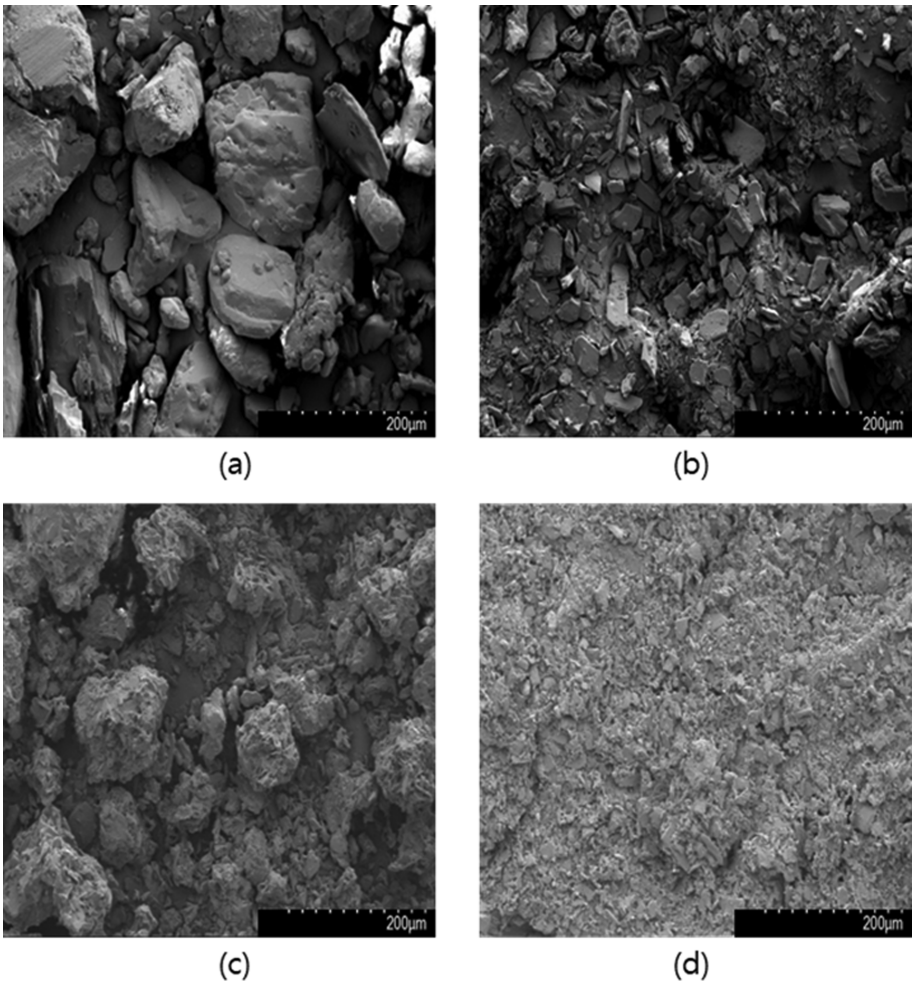


Fig. 3. SEM photomicrographs of the raw material (a), and ibuprofen particles crystallized from acetone+water (b), crystallized using ultrasonic waves (c), and crystallized using ultrasonic waves with added Twee 80 (d).

results imply that nucleation and crystal growth behavior of ibuprofen molecules are not significantly influenced by the conditions of the crystallizing environment, such as solvent polarity, temperature, and external disturbances. Thus, the change of experimental conditions used in this study could not overcome the strong interaction forces among ibuprofen molecules, so that the formation of the internal crystal lattice was not affected by the external solution conditions.

Fig. 3 shows the SEM photomicrographs of ibuprofen crystals that illustrate the variation of particle size depending on the experimental conditions. Fig. 3 includes the image of raw material (as received) ibuprofen particles (Fig. 3(a)). Fig. 3(b) shows the typical shape of crystallized particles using acetone as a solvent and water as an antisolvent. A comparison of these figures clearly demonstrates the considerable size reduction of ibuprofen particles upon the antisolvent crystallization performed in present experiment.

Fig. 3(c) shows the ibuprofen particles obtained when ultrasonic waves were employed during the crystallization. A detailed examination of the image indicates that severe aggregation of tiny particles occurred. Thus, the large bundles of particles shown in Fig. 3(c) are clusters of small ibuprofen crystals that are stacked together. These aggregations may result from the generation of microparticles caused by the ultrasonic waves. As the crystal size was reduced, the surface area of a given amount of ibuprofen increased, increasing the chance of particle stacking. In addition, during the drying period of precipitated product, it became more difficult to completely remove liquid compounds (solvent or antisolvent) that exist between the microparticles. These effects may cause large aggregates of ibuprofen particles to form, as shown in Fig. 3(c).

Fig. 3(d) shows the ibuprofen particles obtained when ultrasonic waves were applied and 0.96 wt% of a surface-active agent (Tween 80) was added to the crystallizing system. It was found that the presence of a surface-active agent at low concentrations obviously prevented the aggregation of ibuprofen particles. This result shows that the addition of a small amount of surfactant is an effective method of avoiding aggregation. In present study, the influence of a surfactant on preventing aggregation was investigated by conducting experiments at different concentrations of Tween 80. Fig. 4 shows the number of aggregated bundles observed in SEM photomicrograph when different amounts of Tween 80 (0.0-1.92 wt%) were added to the system. The ordinate axis of Fig. 4 represents the number of aggregated bundles observed in SEM image per unit area (1 mm^2 in real scale). The aggregated bundles visually found on the printed SEM images (for example, Fig. 3(c)) were counted manually. The result shows that aggregation was drastically reduced when Tween 80 was used as an additive, and the degree of reduction was proportional to the additive concentration.

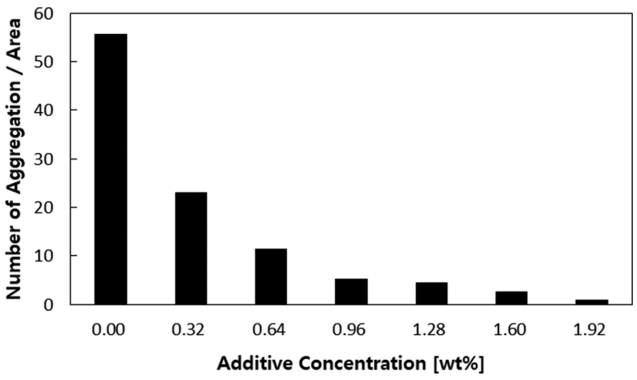


Fig. 4. Number of aggregated bundles observed in SEM images per unit area when different amounts of Tween 80 were added to the crystallizing system.

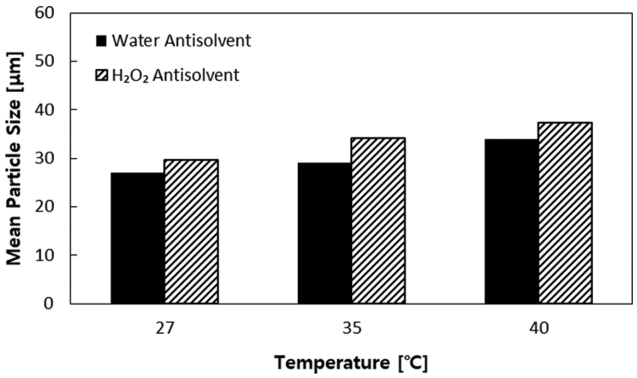


Fig. 5. Variation of the mean particle size of ibuprofen particles as a function of crystallizing temperature (27, 35 and 40 °C). Acetone was used as a solvent and two different antisolvents (water and hydrogen peroxide) were employed.

3. Particle Size Analysis

The change in the particle size of ibuprofen was investigated when three experimental parameters (temperature, concentration of ibuprofen in solvent, and the presence of ultrasonic waves) were changed. Fig. 5 shows the variation in the mean particle size of ibuprofen crystals as a function of crystallizing temperature (27, 35, and 40 °C). In these experiments, the solvent was acetone (0.2 g ibuprofen/ml acetone) and two different antisolvents (water and hydrogen peroxide) were employed. It was observed that the particle size of ibuprofen increased with increasing temperature, and this trend was consistently observed regardless of the kind of antisolvent. In addition, larger particles were obtained when the antisolvent was hydrogen peroxide rather than water. These results could be explained by two effects: 1) the influence of temperature on the rate of nucleation of ibuprofen molecules, and 2) the influence of temperature on the solubility of ibuprofen in acetone. Generally, the rate of nucleation decreases with increasing temperature, and as a result, fewer nuclei could be formed at elevated temperatures. In addition, a higher temperature increases the solubility of ibuprofen in acetone, which could induce delayed crystallization from the solution. Because of these effects, at high temperatures, the presence of fewer nuclei leads to more growth of each crystal and the formation of larger particles.

Fig. 6 shows the cumulative size distribution (a) and mean particle size (b) of ibuprofen crystals as a function of ibuprofen concentration. In these experiments, ibuprofen concentration in acetone was 0.1, 0.2, and 0.4 g/ml and the experiments were carried out using water as an antisolvent at 27 °C. It was found that smaller particles were formed when crystallization was conducted at higher con-

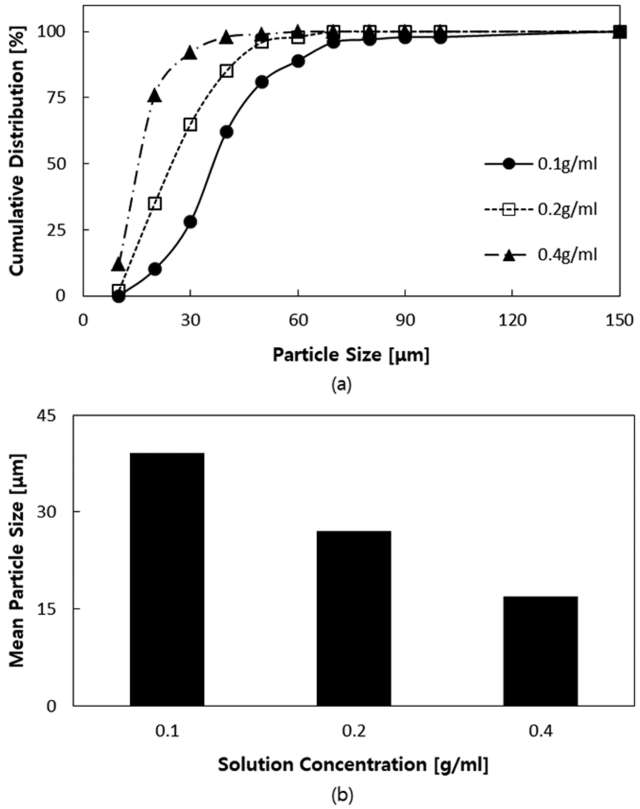


Fig. 6. Cumulative size distribution (a) and mean particle size (b) of ibuprofen crystals as a function of ibuprofen concentration in acetone solution at 27 °C when water was used as the antisolvent.

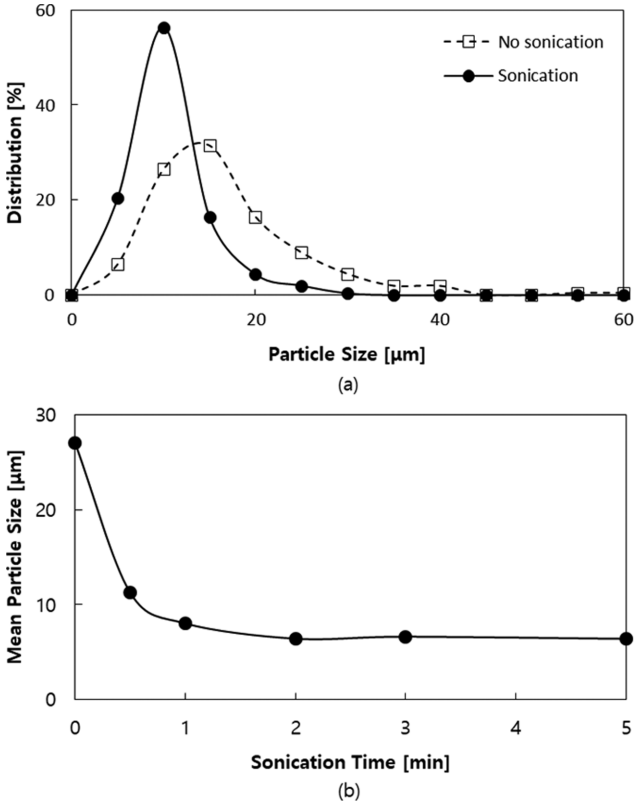


Fig. 7. Effect of ultrasound on the particle size distribution of ibuprofen crystals (a) and mean particle size of ibuprofen as a function of sonication time (b).

centrations. The distribution curves in Fig. 6(a) shifted to the left as the concentration increased, and the mean particle size decreased with increasing concentration (Fig. 6(b)). Indeed, a higher concentration of acetone solution should lead to a greater degree of supersaturation upon mixing with a given amount of antisolvent, and as a result, the nucleation rate should increase. A high rate of nucleation corresponds to the precipitation of an increased number of nuclei, which results in a large number of particles. Obviously, this will make the size of each crystal smaller.

Fig. 7 shows the effect of ultrasound on the particle size distribution of ibuprofen crystals. In these experiments, the solvent was acetone, the antisolvent was water, and the temperature was 27 °C. Ultrasound with a power output of 5 W was applied to the system when the ibuprofen solution was injected to antisolvent. In Fig. 7(a), the particle size distribution data obtained in the absence of ultrasonic waves are also presented. Comparison of the two data sets in Fig. 7(a) indicates that the crystal size became significantly smaller when sonication was applied to the system, i.e., the particle size distribution curve shifted to the left. In addition, the particle size distribution curve became narrower with the application of ultrasound. Fig. 7(b) shows the mean particle size of ibuprofen as a function of sonication time (0.5, 1, 2, 3, 4, 5 min). The result shows that the particle size significantly was reduced when the sonication time was 0.5 min. However, at sonication times longer than 1 min, the ultrasonic waves had little effect on further particle size reduction. These results can be interpreted by the effect of cavitation bubbles on the primary nucleation stage. Therefore, the results in Fig. 7(b) imply that presence of ultrasonic waves during the initial state of nucleation (<0.5 min) accelerated primary nucleation and generated more nuclei, resulting in smaller crystals. In contrast, if the ultrasonic waves were applied for longer times (>1 min), which may correspond to the secondary nucleation stage, the ultrasonic waves did not significantly affect the formation of nuclei, and this might have produced crystals with nearly constant particle size.

4. Thermal Analysis

Ibuprofen particles were analyzed by DSC to examine the thermal behavior of the solid crystals. DSC measurements provide information on the fusion temperature and the enthalpy change involved in phase transitions. The DSC curves reflect the degree of crystallinity and the thermal stability of crystals and may indicate the existence of different polymorphic forms. In this study, DSC analysis was performed on all the ibuprofen samples produced under various experimental conditions, including different solvents and antisolvents, different concentrations and temperatures, application and ultrasonic waves, and addition of external additives. Fig. 8 shows typical DSC curves for the obtained ibuprofen samples and that for the raw material. The figure includes the DSC curves of particles that crystallized without ultrasonic waves (No sonication), with ultrasonic waves (Sonication), and with ultrasonic waves and added Tween 80 (Sonication with additive). Observation of these patterns indicates that the melting temperature (T_m) and enthalpy of fusion

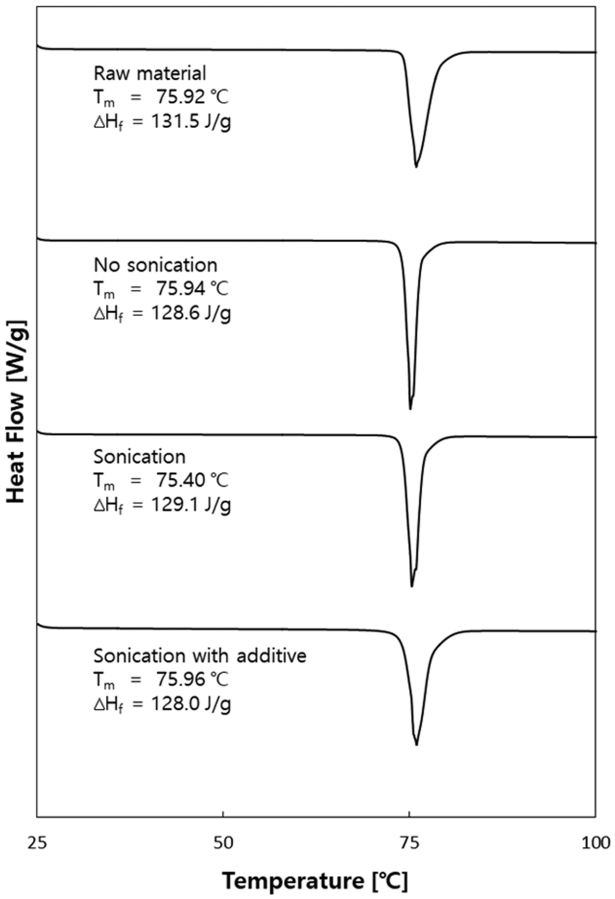


Fig. 8. DSC curves of raw ibuprofen (Raw material), and ibuprofen crystals obtained from acetone solution (No sonication), obtained from acetone in the presence of ultrasonic waves (Sonication), and obtained in the presence of ultrasonic waves with added Tween 80 (Sonication with additive).

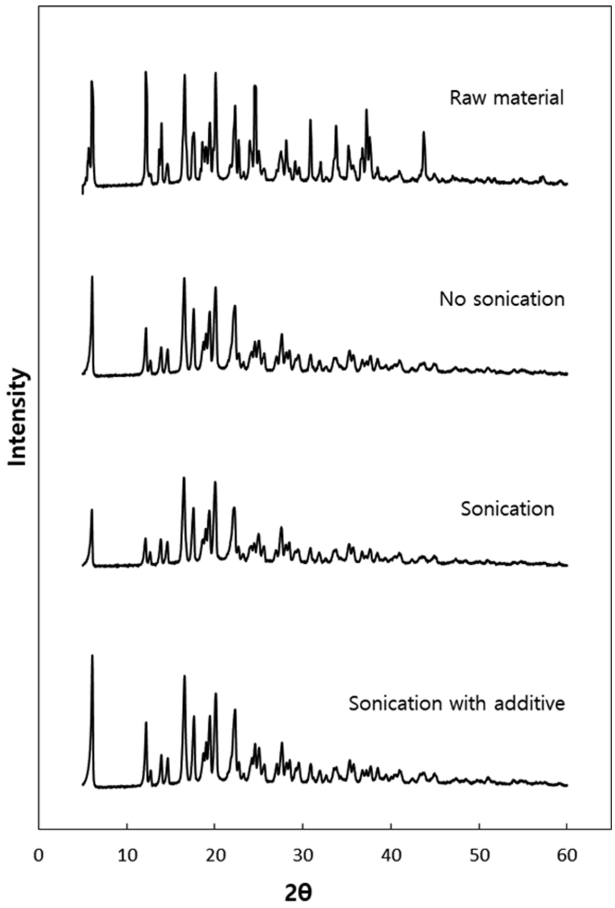


Fig. 9. XRD patterns of raw ibuprofen (Raw material), and ibuprofen crystals obtained from acetone solution (No sonication), obtained from acetone in the presence of ultrasonic waves (Sonication), and obtained in the presence of ultrasonic waves with added Tween 80 (Sonication with additive).

(ΔH_f) of the raw material are quite similar to those of the crystallized samples. In addition, the DSC patterns of the three samples are almost identical. Moreover, although not shown here, the DSC curves of the ibuprofen crystals obtained under other experimental conditions (different solvents, antisolvents, concentrations and temperatures) are similar. These results imply that the variation of experimental conditions did not alter the thermal behavior of the obtained ibuprofen particles or change the thermal properties of the raw ibuprofen material. It was also revealed that the presence of ultrasonic waves and an external additive did not influence the melting point and heat of fusion of the crystallized ibuprofen. It would be worth to compare these results to other findings observed in our previous publication [14], in which sulfa drugs were crystallized using the antisolvent technique. In these investigations, the crystallized sulfa drugs were measured by DSC and it was revealed that their thermal behavior was significantly affected by the experimental conditions. These results may imply that ibuprofen is thermally more stable than sulfa drugs under the condition used in the antisolvent crystallization technique.

5. XRD Patterns

The XRD patterns of crystal particles reflect the crystallinity and molecular orientation inside a solid crystal. Each peak shown in the XRD pattern represents an orientation of molecular arrangement towards a given 2θ direction. Fig. 9 shows the XRD patterns of raw ibuprofen and the samples obtained in this study. Comparison of the four patterns indicates that the peak locations of the raw material ibuprofen are somewhat different from those of the processed samples (No sonication, Sonication, and Sonication with additive). It was revealed that the several reflection peaks shown in the XRD pattern of raw material ibuprofen (Raw material) were not found in the patterns of ibuprofen that crystallized in this study. The major peaks that were not found in the patterns of crystallized samples were at 2θ=24.5, 30.8, 33.7, 37.2, and 43.7°. These results indicate that the molecular orientations corresponding to these reflection angles disappeared when the raw material was crystallized. This means that the crystallinity and preferred crystal orientation of raw material was changed by the crystallization of ibuprofen. Similar results were observed in our previous investigation [15], in which chlorpropamide was recrystallized using carbon dioxide as an antisolvent. Comparison of the XRD patterns of the three processed samples demonstrates that there was no variation in XRD patterns when the experimental conditions were

changed. These results imply that the internal crystal structure of the ibuprofen was not influenced by the experimental conditions. Moreover, the result is consistent with the DSC analysis, which showed that the thermal properties of the crystals were not affected by changes in the experimental conditions.

CONCLUSIONS

The solubility of ibuprofen in acetone+water, acetone+hydrogen peroxide, ethanol+water, and ethanol+hydrogen peroxide mixtures showed a maximum at a solvent concentration of ca. 95%. Extrapolation of the solubility curves revealed that ibuprofen solubility in the solvent+antisolvent mixtures approaches nearly zero at solvent concentration of <50 vol%. The particle size of ibuprofen increased with increasing temperature, and this trend was consistently observed regardless of the kind of solvent and antisolvent. However, larger particles were obtained when the antisolvent was hydrogen peroxide rather than water. Further, smaller crystals were produced when crystallization took place at higher concentrations. The particle size was significantly reduced and the particle size distribution curve became narrower when the system was sonicated. Comparison of the DSC and XRD patterns of the crystallized ibuprofen demonstrates that there was no variation in these patterns when the experimental conditions were changed. These results imply that the internal structures of the ibuprofen were not affected by the experimental conditions investigated in this study.

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