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Antisolvent Crystallization of Roxithromycin and the Effect of Ultrasound

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Antisolvent crystallization was performed to precipitate roxithromycin particles from organic solutions. Roxithromycin was dissolved in acetone at different concentrations and each solution was injected into an aqueous antisolvent leading to prompt particle formation. The effects of various experimental variables (solution injection rate, solution concentration, and temperature) on the particle size of roxithromycin were investigated. In addition to these variables, the effect of ultrasound on the resulting particle size was investigated by changing process parameters such as wave intensity (power output), sonication time, and the moment of ultrasonic application. When the drug solution was rapidly injected into the antisolvent, smaller crystals were obtained. Smaller crystals were obtained when solutions with high drug concentrations were used and also when the crystallization took place at lower temperatures. The particle size decreased with the increasing power output of ultrasound and with the increasing sonication time. It was also found that the ultrasonic wave induced the reduction of the particle size only when the ultrasound was applied to the solution at the initial stage of crystallization.

Keywords antisolvent; crystallization; particle size; roxithromycin; ultrasound

INTRODUCTION

Antisolvent crystallization has been used to produce granules or powders of drugs and polymers. The technology employs an antisolvent in order to precipitate a dissolved compound in various organic or inorganic solutions. An important feature of the antisolvent crystallization method is that it eliminates the use of thermal energy which can degrade the activity of the temperature-sensitive materials such as fine chemicals and pharmaceuticals. Therefore antisolvent crystallization can substitute for an evaporation-based crystallization which requires expensive energy-intensive equipment. In addition, versatile experimental variables involved in antisolvent crystallization can be utilized during the crystallization process, and therefore the solid-state properties of the resulting crystals can be altered over a wide range (1).

The core of antisolvent crystallization is the selection of an antisolvent that can successfully precipitate the dissolved compounds from their solutions. The role of the antisolvent is to reduce the solubility of a solute in the solution and to induce prompt precipitation. The physicochemical properties of the antisolvent influence the rate of mixing with the solutions and hence directly affects the rate of nucleation and crystal growth of the precipitating compounds. In addition, the conditions involved in crystallization experiments strongly affect the particle formation mechanism and govern the resulting particle size and its distributions. Recent studies have focused on employing gaseous antisolvents such as carbon dioxide in order to precipitate drugs and polymers from organic solutions. The main reasons for using carbon dioxide as an antisolvent are its relatively high miscibility with organic solvents and low solubility towards polymers and pharmaceuticals. However, the requirements of high-pressure equipment along with high operating costs can increase the expense of the crystallization process (2–4).

Other than gaseous antisolvents, aqueous media can be an attractive choice for an antisolvent if the target crystallizing materials are hydrophobic pharmaceutical compounds (5). Water has nearly zero solubility towards such compounds and shows complete miscibility with many polar organic solvents. These features enable the use of water as an antisolvent to precipitate drugs from their solutions. In addition, water is an environmentally safe option for processing pharmaceutical ingredients and can be easily separated from final products. A possible disadvantage of employing water as an antisolvent is a delayed mixing rate between the solution and antisolvent which attributes to a low diffusivity of water in organic solutions. The low rate of mixing may prohibit the fast local supersaturation and hence can decrease the rate of nucleation and subsequent particle formation, which can lead to the formation of large crystals with a broad size distribution. These problems can

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be resolved by utilizing an ultrasonic wave as an additional operational variable during the crystallization process (6).

Crystallization under the influence of ultrasonic waves is called sonocrystallization. This technique is applied to induce the formation of nuclei and to improve the particle size distribution (7–11). The presence of an ultrasonic wave normally reduces the particle size depending on the moment at which the sonication is applied. In the antisolvent crystallization process, an ultrasonic wave enhances the mixing between the solution and antisolvent, and accelerates the secondary contact nucleation. Operational parameters associated with the application of ultrasound, include the wave frequency, intensity, and the sonication time, and these variables may contribute to regulate the particle size and to modify crystal habit.

The objective of this study was to micronize a hard to comminute drug compound and to examine the effect of ultrasound on the size variation of particles. Through this study, the formation of micron size particles with a low particle size distribution was expected. In addition, we intended to generate submicron size drug particles by applying ultrasonic wave. In this study, we investigated the variation in particle size of a pharmaceutical compound when it was crystallized from organic solutions using an antisolvent. Roxithromycin (a hydrophobic macrolide antibiotic) was selected as a model compound because it precipitates in granular form (not acicular) so that the size of each particle can be clearly defined (1). In the crystallization experiments, water was used as an antisolvent, and in particular, the effect of ultrasound on particle size variation was explored. Operational parameters regarding the application of ultrasonic waves were manipulated and the experimental variables such as the mixing rate of solution and antisolvent, drug solution concentration and crystallization temperature were changed during the experiments. The solid-state properties of the resulting roxithromycin particles, such as crystallinity were also analyzed.

EXPERIMENTAL METHODS

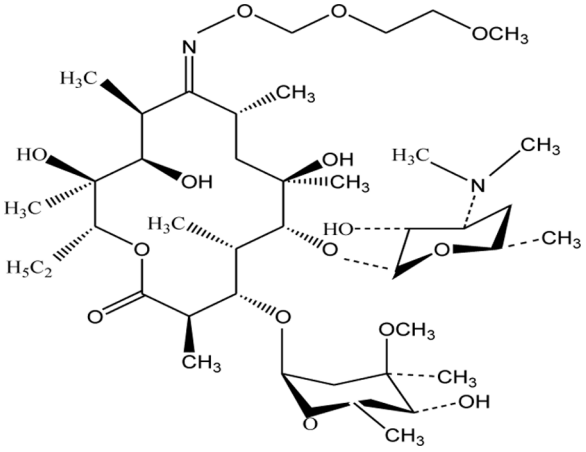
Materials

Roxithromycin (Cat. No. R4393) was purchased from Sigma Chemical Co. Acetone (Aldrich, 99.5%) was selected as a solvent for roxithromycin and distilled water was used as an antisolvent. All the chemicals were used without further purification. Table 1 summarizes the physico-chemical properties of roxithromycin.

Apparatus and Experimental Procedure

Figure 1 shows the experimental apparatus used for the antisolvent crystallization of roxithromycin. The main purpose of the equipment was to mix the drug solution and antisolvent, with the controlled mixing rate under the action of ultrasonic wave. The apparatus consisted of a

TABLE 1
Physico-chemical properties of roxithromycin

Properties	
Chemical formula	$C_{41}H_{76}N_2O_{15}$
Molecular weight	837.06 g/mol
Solubility	Soluble in acetone and alcohols Practically insoluble in water
Melting point	115~120°C
Usage	Used to treat respiratory tract, urinary and soft tissue infections
Chemical structure	

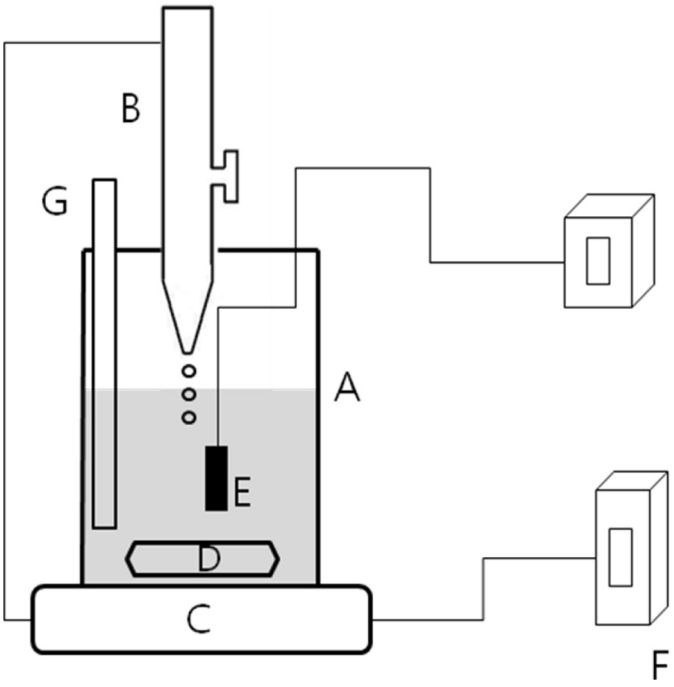


FIG. 1. Experimental apparatus for the antisolvent crystallization experiment. (A) crystallizing chamber, (B) drug solution injector, (C) constant temperature bath, (D) agitator, (E) ultrasonic wave probe, (F) temperature controller, (G) thermometer.

crystallizing chamber, a drug solution injector, a constant temperature bath, an agitator, and an ultrasonic generator (probe). The drug solution injector was equipped with a controlling valve that can regulate the injection rate of the drug solution into the antisolvent. The ultrasonic generator was designed to apply the ultrasonic wave for a specific time period during the crystallization experiment. The ultrasonic wave was supplied at a constant frequency of 22.5 kHz, and the power of the wave was changed within the range of 5–15 watts.

For the crystallization experiments, the solutions of roxithromycin in acetone were prepared at concentrations of 0.01–0.03 g/ml. At these concentrations, roxithromycin completely dissolved in acetone. First, 30 ml of distilled water was loaded in the crystallizing chamber as an antisolvent and the drug solution injector was filled with 10 ml of the prepared roxithromycin solution. Before the mixing of the drug solution and antisolvent, the crystallizing chamber was maintained at constant temperatures of 25, 35, and 45°C as necessary. The temperature of the drug solution injector was kept at room temperature. The crystallization experiment was performed by injecting the drug solution from the solution injector into the antisolvent. The diameter of the injector tip was ca. 1.0 mm, and we presumed that the diameter of the injector tip did not influence the resulting particle size. During the mixing of the two media, the solution was vigorously agitated. The solution was injected using three different injection rates: rapid, medium, and slow injections. For these injections rates, the solution was released into the antisolvent at the rates of 1.0, 0.05, and 0.02 ml/s, respectively. The solution injection was finished when 10 ml of the solution in the injector was used up. At this stage, the formation of solid particulate and the subsequent precipitation was visually observed. After the solution injection was finished, the solution was continuously agitated to complete crystal growth.

These experiments were repeatedly performed with and without the application of ultrasonic wave. The ultrasound was applied to the system during the solution injection and crystal growth stages. The crystallizing chamber was sonicated using an immersed probe with different times. Regarding the application of ultrasound, we used the following three experimental variables, ultrasonic power output, sonication time, and the time at which the sonication was applied. These variables were manipulated during the crystallization experiments as necessary. Details regarding the manipulation of the ultrasonic variables are described in the results section. In all the experiments in this study, the total time for the solution injection, sonication, and crystal growth was 10 min, which was the total residence time for the produced crystals in the solution. After the crystallization experiment was completed, the crystals were filtered from the solution and dried.

The habit of the crystals was examined using a field emission scanning electron microscope (FE-SEM, Hitachi S-4300&EDX-350). The samples were coated with platinum in an argon atmosphere. Crystal size and size distribution were measured using a particle size analyzer (PSA, Ankersmid CIS-50). The detection range of the instrument was 0.1 to 1000 μm. The crystallinity was analyzed by a powder X-ray diffractometer (XRD, Rigaku D/Max-2500) with a scanning 2θ range of 5 to 45 deg.

RESULTS AND DISCUSSION

Effect of Mixing Rate of Drug Solution and Antisolvent

The mixing rate of the drug solution and antisolvent governs the supersaturation of the solution and hence could affect the rate of nucleation. The supersaturation occurs during the mixing process between the drug solution and antisolvent. Initially, when the small amount of antisolvent is added to the solution, the solution still contains the solvent power towards the drug compound (solute), and the solution remains undersaturated without the precipitation of the solute. As the amount of antisolvent added to the solution increases, the solubility towards the solute continuously drops and finally reaches the saturation point at which the solution becomes saturated with the given amount of solute. Further, when the excess amount of antisolvent is added to the solution, the solution experiences

the supersaturation and the dissolved solute starts to precipitate from the solution. Therefore, if the rate of mixing between the solution and antisolvent is controlled, the time at which the solution supersaturated can be regulated. For example, if a given amount of drug solution and antisolvent is mixed rapidly, the solution would be rapidly supersaturated and accordingly the number of nuclei formed per unit time (nucleation rate) would be increased. The change in nucleation rate directly influences the size of the precipitating particles.

In this study, the mixing rate of the drug solution and antisolvent was changed by controlling the injection rate of the drug solution into the antisolvent. Figure 2 shows the SEM images of roxithromycin crystals that were obtained when the drug solution was injected into the antisolvent at the rates of 1.0–0.02 ml/s (Figs. 2(b)−2(d)). Figure 2 also shows the image of as received (raw material) roxithromycin particles (Fig. 2(a)). It should be noted that the magnification of the images of Figs. 2(b)−2(d) is identical (×1500) and that of Fig. 2(a) is × 150. These experiments were conducted at 25°C with a solution concentration of 0.02 g/ml. Figure 2 shows that the size of the as received roxithromycin particles significantly reduced after the antisolvent experiments were conducted. The crystal habit of the processed roxithromycin particles was rhombic tabular and the crystal habit was not modified by changing the injection rate. According to the results, the particle size of roxithromycin tends to increase as the rate of mixing (solution injection rate) of the drug solution and antisolvent decreased (Figs. 2(b)−2(d)). This result was confirmed by measuring the particle size as shown in Figure 3.

Figure 3 shows the cumulative particle size distribution of roxithromycin that was precipitated when different injection rates were used. The graph also shows the size distribution of the raw material. The cumulative distribution represents the percentage of particles that are smaller than a given particle size. For example, in Fig. 3, ca. 25% of the raw material particles are smaller than 70 μm, and ca. 68% of the particles produced with an injection rate of 1.0 ml/s are smaller than 70 μm. It was found that as the solution injection rate decreased, larger particles were produced. When the injection rates were 1.0, 0.05, and 0.02 ml/s, the average particle sizes were 58.4, 64.7, and 70.3 μm, respectively. These results imply that the rate of mixing between the solution and antisolvent directly affects the degree of supersaturation and hence it could control the number of nuclei that form per unit volume of the solution. In addition, the rate of mixing could change the growth rate of each nucleus. The crystal growth rate reflects the mass transfer rate of the drug molecules from the solution

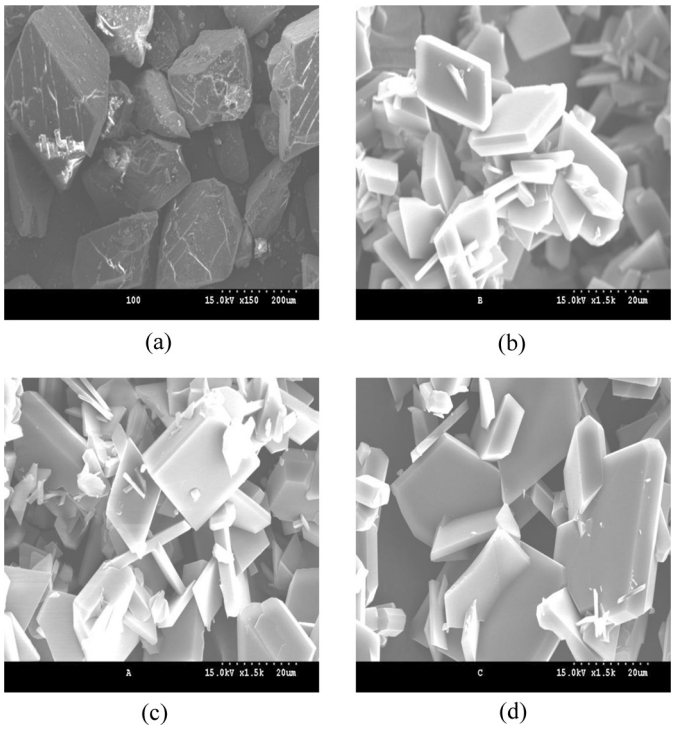


FIG. 2. SEM photomicrographs of roxithromycin crystals obtained when the drug solution was injected into antisolvent at various injection rates. The experiments were conducted at 25°C with the solution concentration of 0.02 g/ml. (a) raw material, (b) 1.0 ml/s, (c) 0.05 ml/s, (d) 0.02 ml/s.

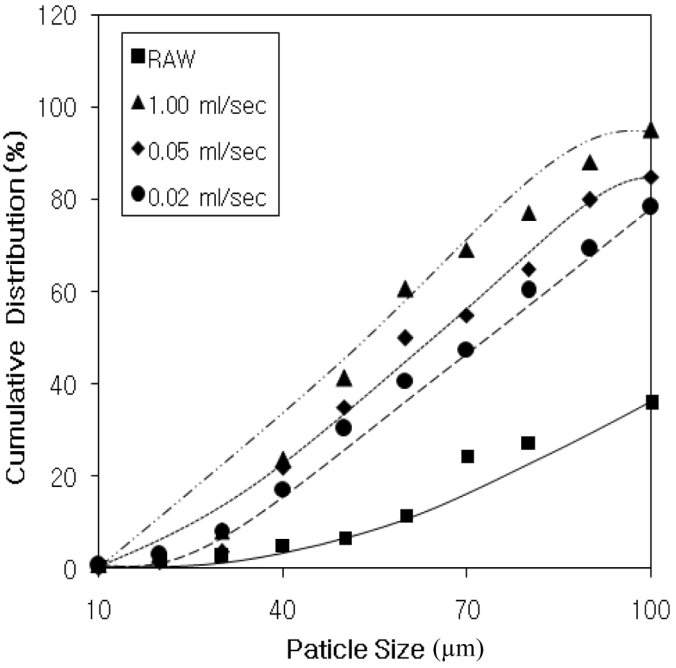


FIG. 3. Cumulative particle size distribution of roxithromycin crystals obtained when the drug solution was injected into antisolvent at various injection rates. The experiments were conducted at 25°C with the solution concentration of 0.02 g/ml.

phase to the crystal surface, and the mass transfer rate depends on how rapidly the solution is added to the antisolvent. Therefore, the solution injection rate influences the rate of crystal growth and the resulting particle size. In this experiment, when the solution is injected at a high rate, supersaturation is accelerated and hence the nucleation rate will increase. This induces the formation of a larger number of nuclei in the first stage of the nucleation process, and therefore the size of each crystal will be reduced (12,13). If the solution is slowly added to the antisolvent, the initial nucleation rate would be decreased and this would induce the formation of a smaller number of nuclei and as a result the size of the resulting crystals will be increased. Even though the data are not shown here, the produced particle was also analyzed by XRD and DSC. It was found that the crystallinity and thermal stability of the particles were not influenced by the solution injection rate.

Effect of Concentration of Drug Solutions

The effect of the concentration of the drug solution on the resulting particle size was investigated by using three different solutions. Roxithromycin solutions with concentrations of 0.01, 0.02, and 0.03 g/ml were injected into the antisolvent. In these experiments, the rapid solution injection rate (1.0 ml/s) was used at a temperature of 25°C. It was found that the concentration of the drug solution did not influence the crystal habit of roxithromycin and the precipitated particles consistently exhibited the tabular habit as shown in Fig. 2. The particle size, however, was altered by changing the concentration of the drug solutions.

Figure 4 shows the particle size distribution of roxithromycin as a function of solution concentration. The average particle sizes of crystals obtained from solution concentrations of 0.01, 0.02, and 0.03 g/ml were 72.7, 58.4, and 47.1 μm, respectively, showing that the particle size significantly decreased when the concentration of the drug solution increased from 0.01 to 0.03 g/ml. These results can be interpreted by considering the dependency of the nucleation rate on the concentration of roxithromycin in the solutions from which the drug was crystallized. Higher concentrations of drug solution should produce a higher degree of supersaturation upon the mixing with the antisolvent, and as a result, rate of nucleation should increase. The high rate of nucleation represents the formation of a large number of nuclei per unit time and leads to an increase in the number of crystals. This could make the size of each crystal smaller as explained in the previous section. In contrast, a lower concentration of drug solution leads to a low degree of supersaturation and as a result, fewer nuclei are formed. Hence there is a much greater chance that each nucleus could grow further, rather than forming new nuclei, which would make each crystal larger. The explanations regarding the effect of the solution concentration on particle size can also be found in the literature (14).

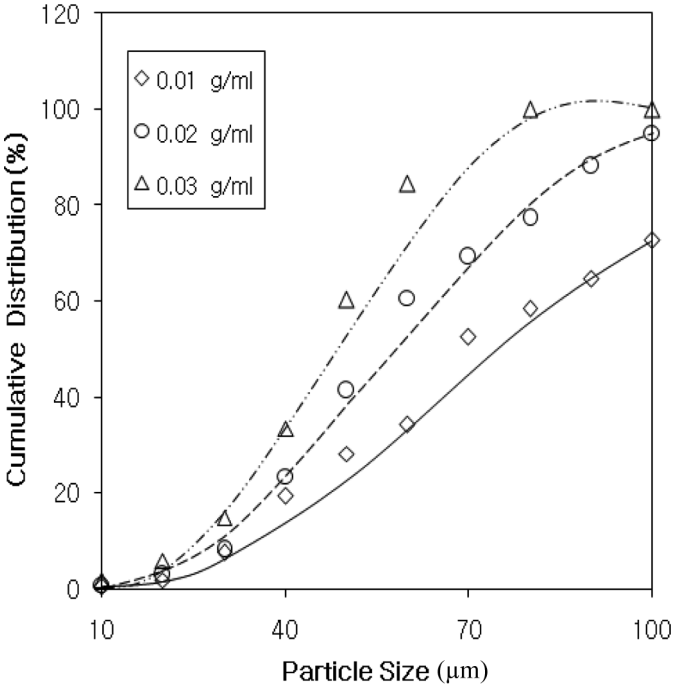


FIG. 4. Cumulative particle size distribution of roxithromycin as a function of solution concentration. The solution injection rate of 1.0 ml/s was used at 25°C.

Effect of Temperature

According to the theory of crystallization, the rate of nucleation is inversely proportional to temperature (15). Moreover, the mass transfer coefficient that governs the crystal growth rate is a strong function of system temperature. Therefore, the temperature is an important governing factor that can control the final particle size and distribution. Table 2 shows the variations of particle size range as a function of crystallization temperature. In these experiments, a solution concentration of 0.02 g/ml was used and the solution was injected at the rate of 1.0 ml/s. Table 2 represents the size range of crystals excluding the

TABLE 2
Size ranges of particles that precipitated at different temperatures. The solution concentration of 0.02 g/ml and the solution injection rate of 1.0 ml/s were used

	Particle size range (μm)	
Temperature (°C)	D (20)	D (80)
25	39.5	86.1
35	42.6	102.1
45	44.6	107.7

particles whose sizes are in the upper 20% (D (80)) and lower 20% (D (20)) of the particles counted. For example, the crystals size ranged from 42.6 to 102.1 μm at 35°C, indicating that 20% of the produced particles were larger than 102.1 μm and another 20% was smaller than 42.6 μm. The overall observation indicated that larger crystals were produced when crystallization occurred at higher temperatures. When the crystallization took place at the temperatures of 25, 35, and 45°C, the average particle sizes were 58.4, 61.5, and 74.1 μm, respectively. These results can be explained by considering the dependency of the nucleation rate on temperature and the solubility of the drug compound in the organic solvent. In general, the nucleation rate decreases with temperature and therefore fewer nuclei are formed at higher temperatures. In addition, high temperature leads to an increase in the solubility of a drug compound in the organic solvent, which causes the delayed precipitation from its solution. Therefore, at high temperatures, fewer numbers of nuclei are formed, leading to the further growth of individual crystals and the production of larger particles. Similar temperature effect trends were also observed in previous studies in which crystallization was carried out using different types of antisolvent, such as supercritical fluids (12,16).

Effect of Ultrasonic Wave

The influence of an ultrasonic wave on particle size was investigated by changing three parameters: ultrasonic power output, sonication time, and the time at which the sonication was applied. Figure 5 shows the SEM images of roxithromycin particles when the ultrasonic wave was applied with different power outputs of 5, 10, and 15 watts. In these experiments, the drug solution (with a concentration of 0.02 g/ml) was rapidly injected (1.0 ml/s) into the antisolvent at 25°C. Immediately after the injection of the drug solution into the antisolvent was completed, the ultrasonic wave was applied for 20 s using different power output. Figure 5 also contains an image of particles obtained without using ultrasound (Fig. 5(a)). The figure illustrates that the presence of ultrasound significantly reduced the particle size of roxithromycin, while it did not modify the overall crystal habit (rhombic tabular habit) of particles. In addition, Figs. 6(b)–(d) demonstrate the reduction of particle size with the increase of power output from 5 to 15 watts. Figure 6 shows the cumulative size distributions of roxithromycin particles that were shown in Fig. 5. It should be noted that the horizontal axis of Fig. 6 is plotted on a log-scale. According to Fig. 6, it was confirmed that the particle size significantly decreased with increasing power output of the applied ultrasound. The average sizes of particles produced with the power outputs of 5, 10, and 15 watts were 27.7, 19.3, and 14.6 μm, respectively, and the average size of particles obtained without ultrasound was 58.4 μm.

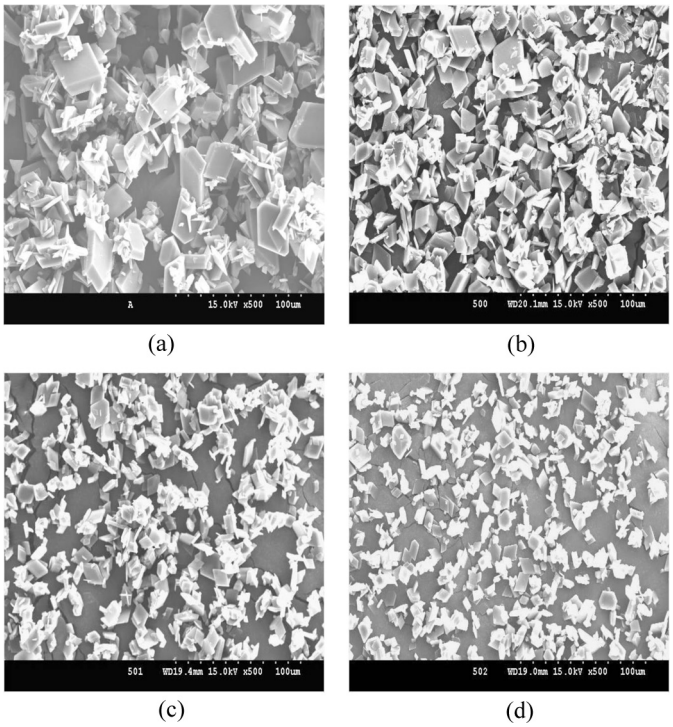


FIG. 5. SEM photomicrographs of roxithromycin when the ultrasonic wave was applied with different power outputs. Experiments were conducted with the drug concentration of 0.02 g/ml and with the solution injection rate of 1.0 ml/s at 25°C. (a) no sonication, (b) 5 watts, (c) 10 watts, (d) 15 watts.

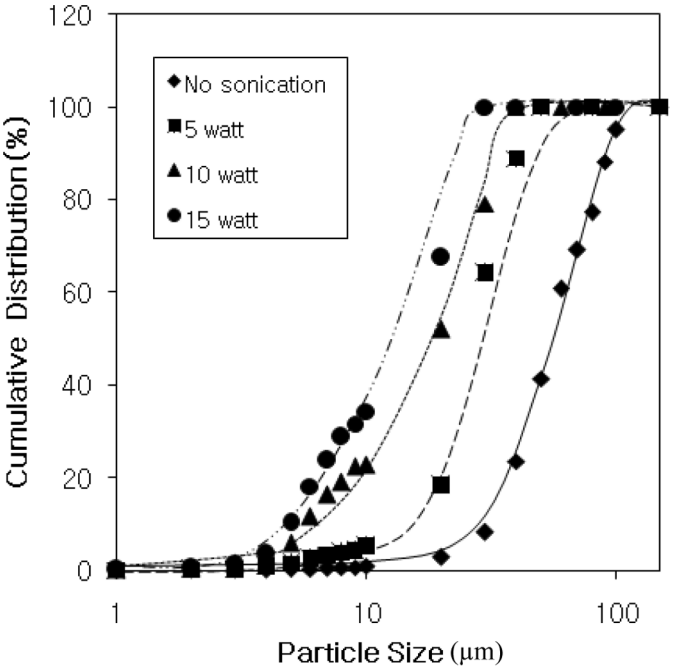


FIG. 6. Cumulative particle size distributions of roxithromycin when the ultrasonic wave was applied with different power outputs. Experiments were conducted with the drug concentration of 0.02 g/ml and with the solution injection rate of 1.0 ml/s at 25°C.

The presence of an ultrasonic wave during crystallization leads to the reduction of both the nucleation induction time and the width of the metastable zone (7). The main action of ultrasound is the consecutive formation and burst of cavitation bubbles that cause severe disturbance inside the solution. Therefore, the ultrasound may control the rate of nucleation and crystal growth and hence the resulting size of each particle. The induction time stands for the elapsed time between the time of supersaturation and the advent of the crystal. The metastable zone is the boundary region between the stable single-solution phase and the nuclei formation regime. The reduction of these two factors accelerates the change of drug solution from a stable to unstable state, and hence the rate of nucleation is increased. Therefore, the birth of more numerous nuclei leads to the reduction of average particle size. In addition, their average particle size decreases with an increase in the power output of the ultrasound as shown in Fig. 6. It has been shown that an increase in the level of power output of sonication produces more clouds of cavitation bubbles inside the solution, which increases the chance of particle collisions (8). This induces the high rate of secondary contact nucleation and the reduction of the final size of individual particles.

Figure 7 shows the cumulative size distribution of roxithromycin particles when the ultrasonic wave was applied to the solution with different times. In these experiments, the ultrasonic power output of 5 watts was constantly used, and other experimental conditions were identical to the conditions that were used to produce particles in Fig. 5. Sonication was applied for 20, 40, and 60 s, immediately after the injection of the drug solution into the antisolvent was completed. The total time of crystallization (residence time of each crystal in the solution) for each of these individual experiments was 10 min. It was found that the particle size decreased with increasing sonication time. The average particle sizes of roxithromycin were 27.7, 19.9, and 11.1 μm, when the solution was sonicated for 20, 40, and 60 s, respectively. These results indicate that the effect of increasing sonication time is similar to the effect of increasing the sonication power output. The longer sonication time likely provides more persisting cavitation bubbles and increases the probability of collision between the particles (6). This generates the greater number of nuclei and causes the subsequent reduction in particle size.

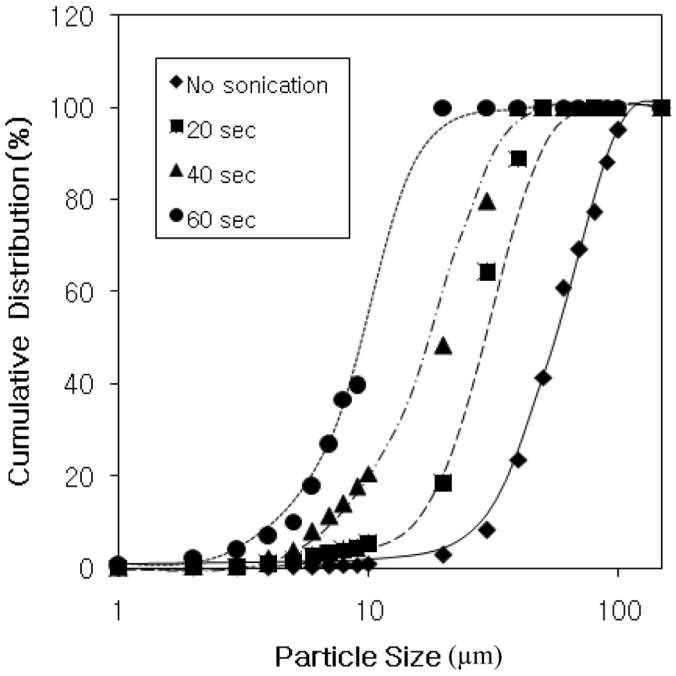


FIG. 7. Cumulative particle size distribution of roxithromycin when the ultrasonic wave was applied to the solution with different times. Ultrasonic power output of 5 watts was used and other experimental condition was identical to data shown in Figure 6.

The sonication experiments were also conducted by changing the time at which the sonication was applied during the crystallization. In above experiments, all the drug solution injected was 10 ml and the solution injection rate was 1.0 ml/s. Therefore, the total time needed for the completion of the solution injection was 10 s. In the experiments conducted so far (Figs. 7 and 8), the sonication was applied for a particular time (for example 5 or 20 s) immediately after the injection of the drug solution was completed. In other words, the sonication was applied for 5 or 20 s after 10 s had passed after the solution started to mix with the antisolvent. After the sonication was finished, the mixed solution was continuously agitated for 10 min allowing complete crystal growth. In this experiment, in order to investigate the effect of time at which the sonication was applied, the sonication was momentarily applied at a particular time during the crystallization procedure. First, as mentioned above, the solution was sonicated for 5 or 20 s when 10 s had passed after the mixing of the solution and antisolvent took place. After that, the sonication was stopped and the solution was continuously agitated for 10 min allowing crystal growth. Then, the crystals were collected and their size was analyzed. Second, the same experiment was conducted by varying the time at which the sonication was applied, i.e., the solution was sonicated for 5 or 20 s when 20 s had passed after the mixing. After that, the sonication was stopped and the solution was continuously agitated for 10 min, and the crystals were collected for size analysis. Third, the solution was sonicated for 5 or 20 s when 30 s has passed after the mixing. Then, the total agitation time was maintained constant (10 min) as in the previous experiments. Following this procedure, experiments were repeated by changing the time at which the sonication was applied, i.e., the solution was sonicated for 5 or 20 s when 40, 50, 60, 70, 80, 90, 120, 130, and 150 s had passed after the mixing,

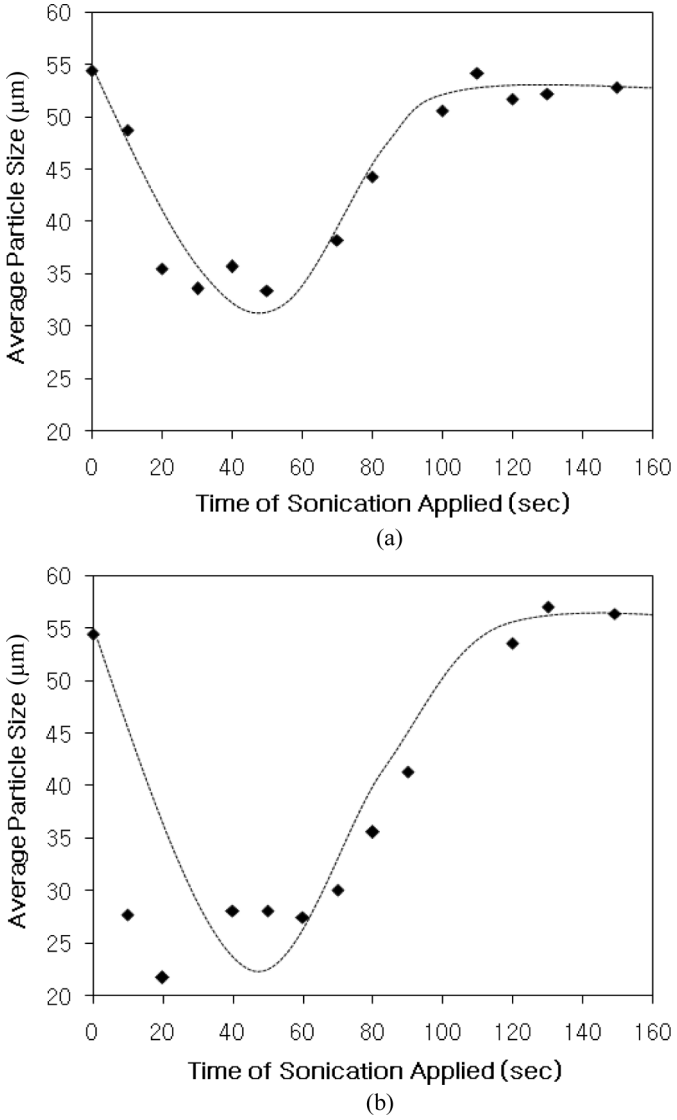


FIG. 8. Average particle size of roxithromycin when the time at which the sonication was applied after the mixing had been changed from 10 to 150 s. Ultrasound was applied for (a) 5 s, (b) 20 s. Power output was 5 watts for both experiments.

respectively. For each of these experiments, the total time of crystal growth inside the solution was equally 10 min.

Figure 8 shows the average particle size of roxithromycin when the time of ultrasonic application (the time at which the sonication was applied after the mixing took place) had been changed from 10 to 150 s. It should be noted that the sonication was applied for 5 s (Fig. 8(a)) and 20 s (Fig. 8(b)) for each experiment, and the total crystallization time (residence time of each crystal in the solution) was also exactly to 10 min for each of the experiments. The data point at the origin of the abscissa is the size of the particle obtained when no sonication was applied. As shown in Fig. 8, the average particle size of the produced crystals was 48.7 μm (Fig. 8(a)) and 27.7 μm (Fig. 8(b)) if the sonication was applied when 10 s had passed after the mixing of solution and antisolvent. Crystals with an average size of 44.3 μm (Fig. 8(a)) and 35.5 μm (Fig. 8(b)) were obtained if the sonication was applied when 80 s had passed after the mixing occurred. Crystals with a size of 52.2 μm (Fig. 8(a)) and 57.0 μm (Fig. 8(b)) were obtained if the sonication was applied when 130 s had passed after the mixing. Particle size was not much changed when the sonication was applied after 150 s had passed.

These results indicate that an ultrasonic wave induced a reduction of the particle size when it was applied to the solution only at the initial stage of crystallization. In addition, the degree of particle size reduction was directly proportional to the ultrasonic application time, as compared in Fig. 8(a) and Fig. 8(b). The initial stage of crystallization is the particle formation period during which the nuclei were formed and the crystal growth was about to start. Therefore, the ultrasound significantly affected the particle formation mechanism including the collision-induced secondary nucleation and as a result the average particle size was decreased. Figure 8 shows that the nucleation and crystal growth procedure has been completed in ca. 150 s, and the ultrasonic wave no longer influenced the final particle size when it was applied after that time. These results imply that the ultrasound, in addition to other process parameters such as solution injection rate, drug concentration and crystallization temperature, can be adopted as a useful tool that can regulate the particle size when it is applied

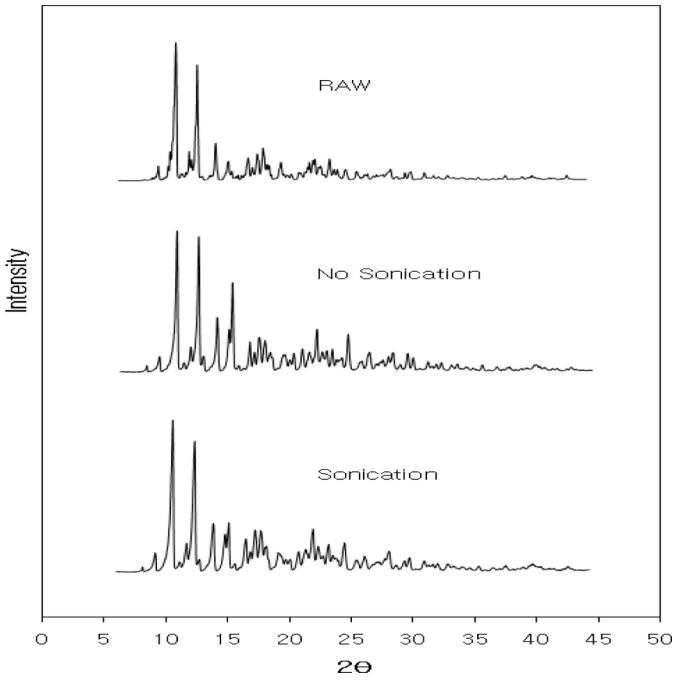


FIG. 9. XRD patterns of roxithromycin samples: raw material, produced particles with and without ultrasound at 25°C.

at a properly selected time during the crystallization. The roxithromycin particles produced in the presence of ultrasound were analyzed by XRD. Figure 9 shows the XRD patterns of the raw material and produced crystals with and without sonication. Observation indicated that the crystallinity of roxithromycin was not significantly affected by the presence of ultrasound.

CONCLUSIONS

Antisolvent crystallization of roxithromycin was conducted using acetone and water as a solvent and as an antisolvent, respectively. Experimental variables such as the mixing rate of the drug solution and antisolvent, concentration of the solution, and crystallization temperature were manipulated in order to investigate their effect on the particle size. The influence of an ultrasonic wave on the resulting particle size was also examined. The particle size of roxithromycin tended to increase as the rate of mixing of the drug solution and antisolvent decreased. The crystal habit was not modified with the change of mixing rate. The particle size of crystals decreased when the concentration of the drug solution increased. Larger crystals were produced when crystallization occurred at higher temperatures. It was found that the particle size was significantly reduced when the solution was sonicated during the crystallization. The particle size decreased with increasing power output of the ultrasound and with increasing sonication time. The ultrasonic wave induced a reduction in particle size when the ultrasound was applied to the solution only at the initial stage of crystallization.

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