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Micronization of *p*-Aminosalicylic Acid Particles Using High-Gravity Technique

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An antisolvent precipitation process was adopted in this study to prepare micrometer-sized *p*-aminosalicylic acid (PAS) particles using the high-gravity technique. The effects of operating variables on the particle size were investigated. With an increase in the dispersant concentration and disk diameter or a decrease in the drug (PAS) concentration, the particle size of PAS was reduced. In addition, a circular-tube distributor was more effective than a straight-tube distributor for micronization. On the other hand, the effect of the liquid flow rate in the range between 0.25 and 1 L/min was less significant. The high-pressure homogenization following the high-gravity precipitation would effectively reduce the agglomeration of the particles in the suspension to produce drug particles with a mean size of 1 μm. The enhancement of the dissolution rate was significant for the micronized drug particles. The results indicate that the high-gravity process is a promising approach for micronizing drug particles.

Introduction

In the pharmaceutical industry, a large number of drugs are poorly soluble in water. Roughly 40% of all the investigated compounds failed to develop because of poor bioavailability, which is often associated with low aqueous solubility, thus, a low dissolution rate. There are several methods for enhancing the dissolution rate of poorly water-soluble drugs. Micronization, which reduces the particle size and increases the surface area of particles, is one of the most direct and safest ways to increase the solubility and dissolution rate of these drugs. Common methods for reducing particle size include ball milling, jet milling, and high-pressure homogenization.[1−3] There are, however, several drawbacks associated with the "top-down" mechanical comminution processes, such as a broad particle-size distribution due to crushing, physical and chemical instability resulting from disruptions in the crystal lattice, products denatured by exposure to high temperature and pressure, and contamination of the drugs. Viewing the disadvantages of mechanical comminution methods, a "bottom-up" recrystallization method has been developed to generate ultrafine particles and perhaps together with a modification of lattice structure to enhance solubility and dissolution rate. Conventionally, the recrystallization process is performed in a stirred vessel, which would give a broad size distribution and a large mean particle size due to low mixing efficiency. To overcome this problem, several novel techniques have been developed, including the microemulsion technique, supercritical fluid technique, and high-gravity technique.[4−8] However, disadvantages are associated with each technique. For the microemulsion system, the problems of low yield and contamination by using surfactants and organic solvents have to be solved. The supercritical fluid technique has been widely applied for particle design of pharmaceuticals, cosmetics, and specialty chemicals due to the nontoxicity of CO_2 used as a solvent or antisolvent. Nevertheless, the high capital cost and the difficulty in scale-up bound up with a high-pressure system restrict the development and application of this technique.

The investigation of the high-gravity technique has become one of the most significant subjects in the field of process intensification. In this technique, gravity force is replaced by a centrifugal force, which is up to several hundred *g*, to enhance mass-transfer rate and mixing efficiency, leading to a reduction in equipment size and operating cost. Two types of high-gravity equipment, i.e., rotating packed bed (RPB) and spinning disk reactor (SDR), are introduced as novel gas−liquid or liquid−liquid contactors, which have been used in many chemical processes, such as absorption, stripping, distillation, adsorption, and reactive precipitation.[9−22] For the liquid−liquid system, studies performed in our laboratory have shown that the micromixing efficiency can be improved considerably by the aid of centrifugal force.[23,24] In 1991, Marcant and David[25] demonstrated a simplified mixing model for qualitatively predicting the influence of micromixing on precipitation. They found that increasing the mixing intensity would increase the crystallization rate, thus, reducing the particle size in the primary nucleation process. Additionally, in 2002, Cafiero et al.[26] estimated the micromixing time and the induction time of $BaSO_4$ precipitation in a spinning disk reactor. They concluded that the micromixing time of reactant streams on the disk surface was shorter than the induction time of nucleation; therefore, small and uniform particles were generated. In our laboratory, nanosized $Mg(OH)_2$ particles were synthesized in an SDR.[21] The results indicated that a higher micromixing intensity would reduce the particle size, conforming to the findings of Marcant and David[25] and Cafiero et al.[26] In addition, silver nanoparticles were successfully synthesized in an SDR via a green chemical process, using environmental-friendly and inexpensive materials of glucose and starch as the reducing agent and protecting agent, respectively.[22]

Recently, the high-gravity technique has been proven to be useful in the pharmaceutical industry. Oxley et al.[6] used an SDR to manufacture pharmaceuticals and found that the particles had a narrow particle size distribution and a mean size of around 3 μm. In addition, the reaction time and the impurity level were significantly reduced when compared with those from a batch process performed in a stirred vessel. In 2004, Chen et al.[7] produced nanoparticles of benzoic acid precipitated in an RPB.

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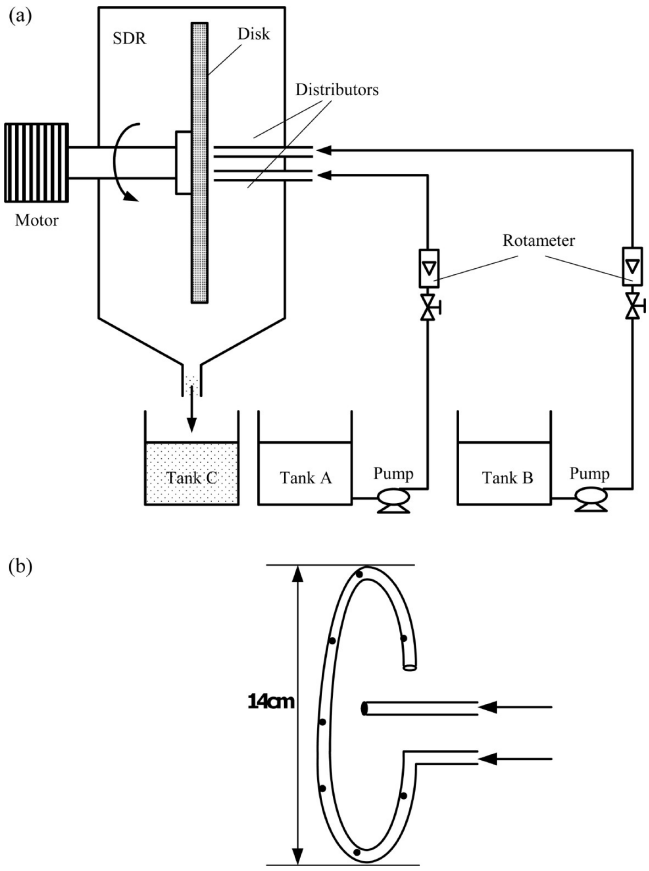

Figure 1. (a) Schematic diagram of the experimental setup and (b) the circular liquid distributor used in the SDR-L.

Table 1. Range of Operating Variables Used in This Study

operating variables	range
precipitation in SDR	
disk diameter (cm)	12 and 50
rotational speed (rpm)	2100
flow rate of feeding stream (L/min)	0.25−1.0
PAS concentration in the alkaline solution (g/L)	40−100
PVP concentration in the alkaline solution (g/L)	5−20
high-pressure homogenization process	
homogenization pressure (psi)	10000−30000
homogenization cycle number	2−8

The results showed that the particle size decreased with an increase in rotational speed of a packed bed and flow rate of reactants. The particles obtained were as fine as 10 nm in size, and the reduction in size was attributed to the intensified micromixing of reactant streams in an RPB that enhanced nucleation rate while suppressing crystal growth. In 2006, Chen et al.[8] prepared cefuroxime axetil particles by an antisolvent precipitation process in an RPB. Amorphous cefuroxime axetil

Table 2. Particle Size Distributions of the PAS Particles Precipitated in a SDR at Various PVP Concentrations; Other Fixed Operating Variables Are PAS Concentration (40 g/L), NaOH Concentration (11 g/L), Propionic Acid Concentration (37 g/L), Liquid Rate (0.25 L/min), and Rotational Speed (2100 rpm)

PVP concentration (g/L)	particle size (μm)		
	D_{10}	D_{50}	D_{90}
5	3.36	13.6	36.4
10	1.80	8.94	19.6
15	1.20	6.58	21.5
20	1.23	7.18	17.8

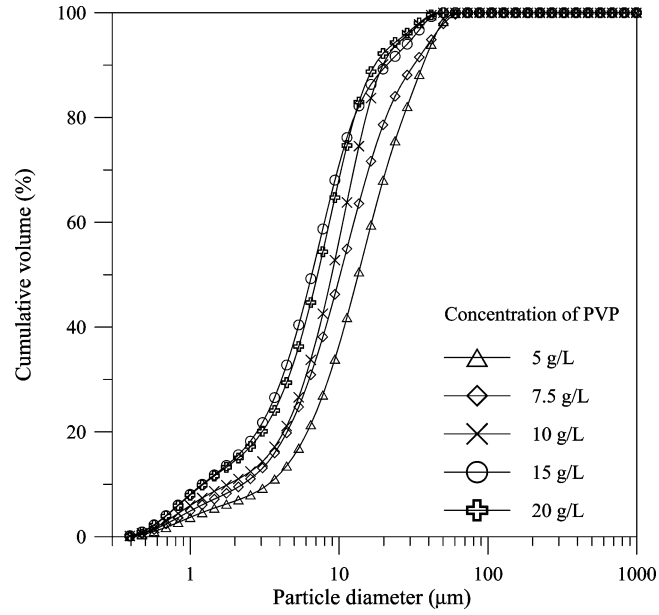

Figure 2. Particle size distribution of PAS particles prepared at various concentrations of PVP. Other operating variables kept constant are as follows: PAS concentration, 40 g/L; NaOH concentration, 11 g/L; propionic acid concentration, 37 g/L; liquid rate, 0.25 L/min; rotational speed, 2100 rpm.

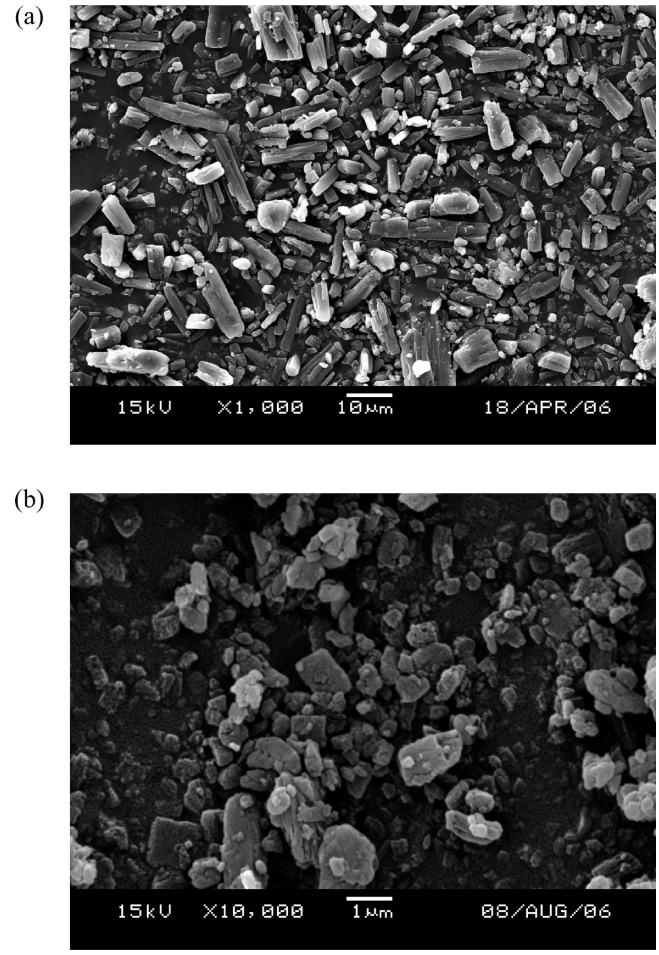

Figure 3. SEM micrographs of (a) commercial PAS and (b) micronized PAS produced from the SDR-S operated at PAS concentration of 40 g/L, PVP concentration of 15 g/L, NaOH concentration of 11 g/L, propionic acid concentration of 37 g/L, liquid rate of 0.25 L/min, and rotational speed of 2100 rpm.

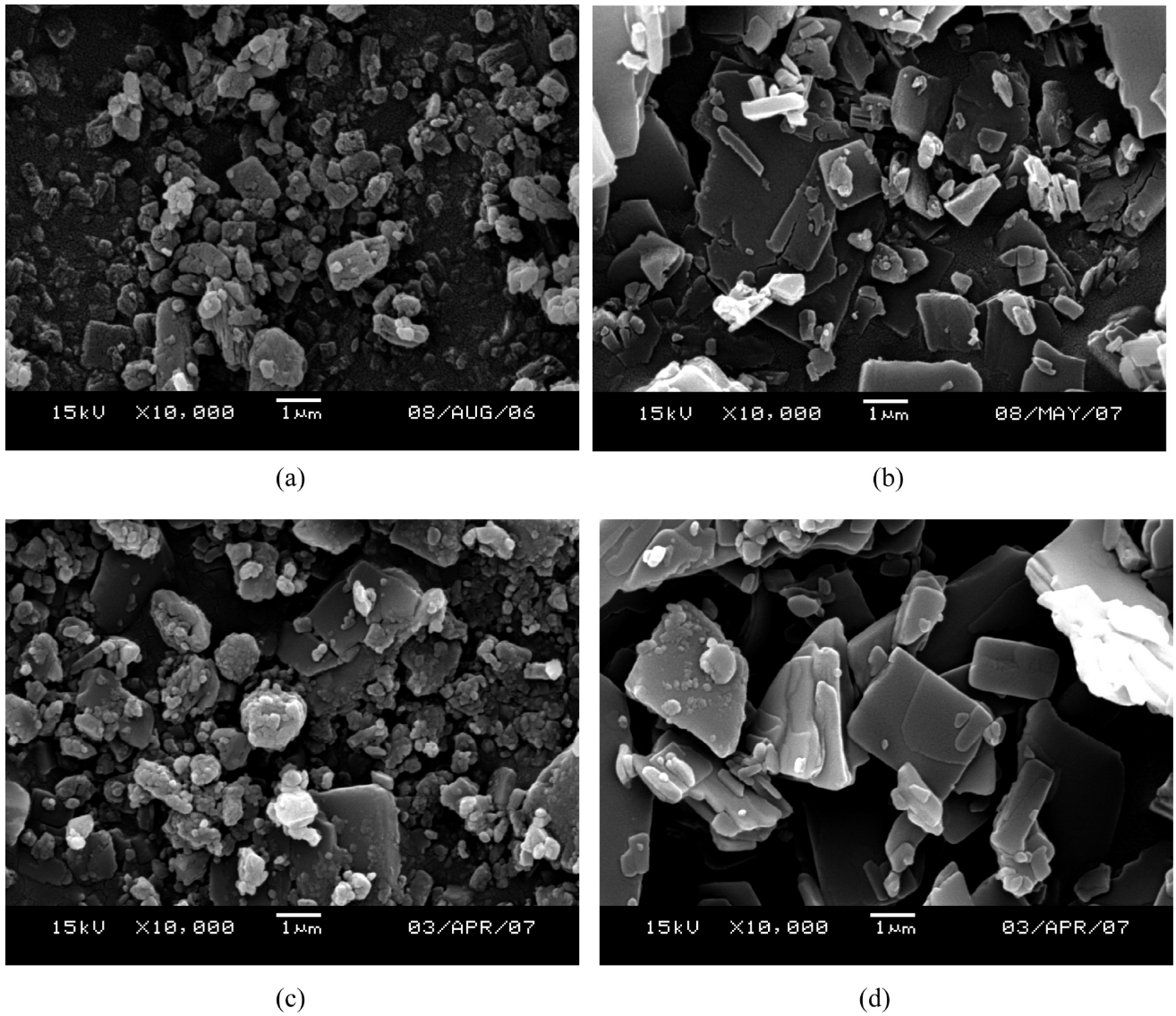

Figure 4. SEM micrographs of the micronized PAS prepared by the SDR-S for the PAS concentrations of (a) 40 g/L, (b) 60 g/L, (c) 80 g/L, and (d) 100 g/L. Other operating variables kept constant are the concentration ratios of NaOH:PVP:PAS (0.275:0.375:1), liquid rate (0.25 L/min), and rotational speed (2100 rpm).

particles of 300 nm with no significant agglomeration were obtained with no dispersant added. The dissolution rate of the recrystallized drug particles was greatly enhanced. Agglomeration of the water-insoluble drug particles, however, is generally observed during a precipitation process because the generated small particles tend to increase the hydrophobic surface. To reduce the agglomeration of particles, dispersants are usually added in a precipitation process.[27]

In this study, an antisolvent precipitation process proceeded in an SDR, which combined with high-pressure homogenization and freeze-drying, was proposed to generate fine drug particles. The model compound investigated was *p*-aminosalicylic acid, which is an antibiotic for treatment of tuberculosis. The solubility of PAS is quite low (<1 g/L) in low and medium pH aqueous solutions, but much higher in a basic aqueous solution.[28] Viewing the variation in solubility, PAS and a dispersant, polyvinylpyrrolidone (PVP), were first dissolved in a NaOH solution. Then the solution was mixed with an acidic antisolvent, i.e., propionic acid solution, in the SDR to precipitate drug particles. The effects of the feeding rate, and the concentration of solute (PAS) and additive (PVP), on the morphology and size of the PAS particles were investigated. Then a high-pressure homogenizer was used to break up the agglomerated particles. Furthermore, dissolution experiments of the commercial and micronized drug particles were carried out to evaluate the difference in dissolution rate between the two particles.

Experimental Section

A schematic diagram of the high-gravity system used in this study is shown in Figure 1a. The main part of the apparatus is a spinning disk reactor, which consists of a stainless-steel disk driven by a variable speed motor and a stationary cylindrical acrylic chamber. In this study, two spinning disk reactors, SDR-S and SDR-L, were used. The disk diameters of SDR-S and SDR-L are 12 and 50 cm, respectively. For the SDR-S, the liquid distributors are two straight tubes in parallel and 5 mm apart. Both tubes have a 3-mm hole at the end, being placed at a distance of 5 mm from the disk. For the SDR-L, one of the distributors is replaced by a circular tube, as shown in Figure 1b. The circular tube is 14 cm in diameter and has seven holes on the side facing the disk. The design purpose of the circular tube is to evenly distribute the acid stream and to improve the mixing efficiency.

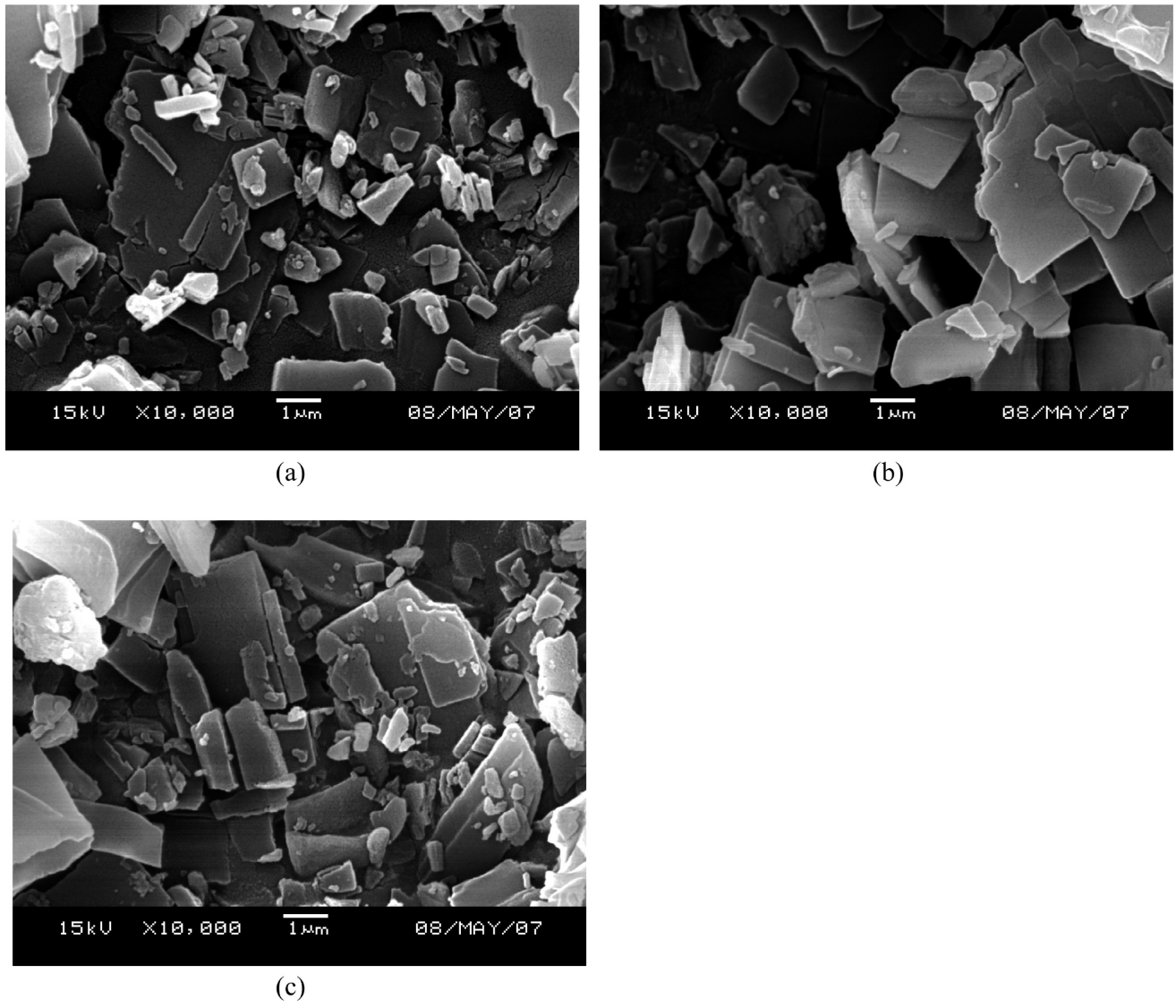

Figure 5. SEM micrograph of the micronized PAS prepared by the SDR-S for different flow rates at (a) 0.25 L/min, (b) 0.5 L/min, and (c) 1.0 L/min. Other operating variables kept constant are PAS concentration (60 g/L), PVP concentration (22.5 g/L), NaOH concentration (16.5 g/L), propionic acid concentration (110 g/L), and rotational speed (2100 rpm).

At the beginning of an experiment, an aqueous solution containing PAS, NaOH, and PVP was placed in Tank A and a propionic acid solution in Tank B. Both solutions were continuously pumped at a specific flow rate, which was measured by a rotameter, onto the center of the spinning disk with a rotational speed of 2100 rpm. The two liquid streams mixed well with each other on the disk surface under a centrifugal force and the drug particles were thereon precipitated. The slurry then hit the chamber wall and flowed down into Tank C.

To study the homogenization effect, a high-pressure homogenizer was used to break up the agglomerate of particles in the slurry. The slurry from the SDR was first filtered by a 0.2-μm membrane and the cake was washed with a PAS-saturated aqueous solution. Then the washed cake was dispersed in a PAS-saturated aqueous solution and the suspension was homogenized at 5 °C and at pressures ranging from 10,000 to 30,000 psi, using a high-pressure homogenizer (Mini DeBEE, BEE International, USA). The cycle number, which is defined as the operating time divided by the retention time of the homogenizer, was also tested between 2 and 8 cycles. The resulting suspension was then dried in a freeze-dryer (FD45, KingMech, Taiwan). A 100-mL suspension was first frozen at −20 °C and then placed in an environment of 20 Pa for 24 h to obtain drug powder. The operating variables and their ranges used in the precipitation and homogenization steps are summarized in Table 1.

The size and the shape of the particles were examined by a scanning electron microscope (J-5600, Jeol, Japan), and the size distribution of the particles was measured by a laser-light scattering analyzer (Coulter LS230, Beckman, USA) using a saturated PAS solution as the solvent. The crystallinity of the particles was identified by an X-ray diffractometer (MXP-3, Mac, Japan). The dissolution rate of the PAS powder was measured in a dissolution apparatus (DT-3, Shin Kwang, Taiwan) by following the USP apparatus II (paddle) method.[29] The paddle speed was set at 50 rpm. At the beginning of an experiment, 50 mg of PAS powder was placed into a vessel containing 900 mL of 0.1 M HCl solution, which had been heated slowly to 60 °C to remove the dissolved air and then equilibrated at 37 °C. A 2-mL aliquot of sample was withdrawn at specific intervals using a syringe fitted with a 0.45-μm filter until the solid in the vessel was completely dissolved. Under the agitation of 50 rpm, most of the PAS particles were swirling at the bottom of the vessel, thus reducing the chance of catching drug particles in sampling. The PAS concentration of the

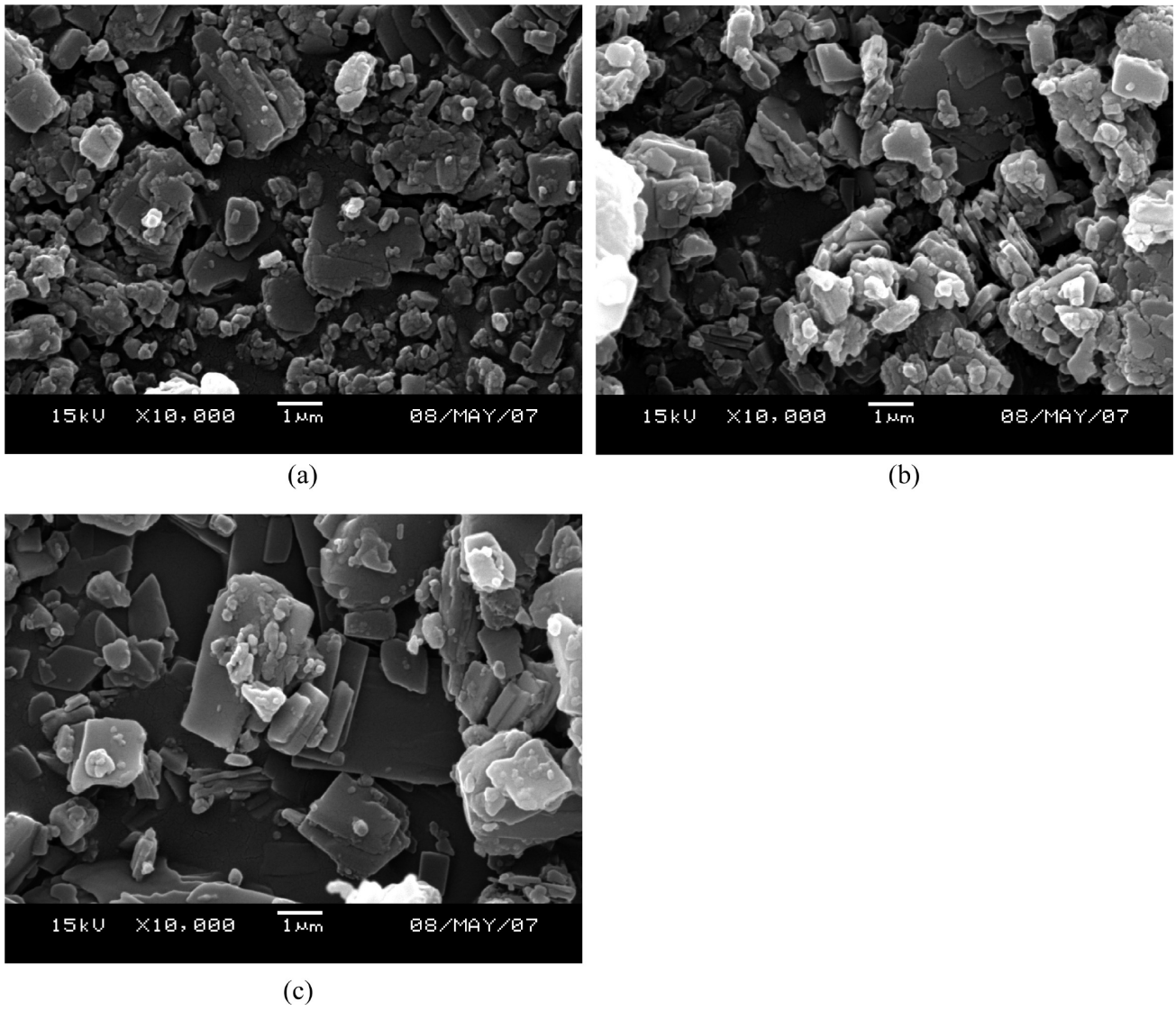

Figure 6. SEM micrograph of the micronized PAS prepared by the SDR-L with straight-tube distributors for the flow rates of (a) 0.25 L/min, (b) 0.5 L/min, and (c) 1.0 L/min. Other operating variables kept constant are PAS concentration (60 g/L), PVP concentration (22.5 g/L), NaOH concentration (16.5 g/L), propionic acid concentration (110 g/L), and rotational speed (2100 rpm).

solution sample was measured by an ultraviolet spectrophotometer (Spekol 1300, Analytik Jena, Germany) at 300 nm.

Results and Discussion

Effect of Operating Variables on Particle Size. The effect of PVP concentration on the size of the drug particles was first investigated in the SDR-S. The PVP concentration in the alkaline solution varied from 5 to 20 g/L, while the concentrations of PAS and NaOH were kept at 40 and 11 g/L, respectively. The antisolvent was a propionic acid solution of 37 g/L. The flow rates of the two streams were fixed at 0.25 L/min, and the rotational speed of the disk was set at 2100 rpm. The pH values of the slurry collected at the bottom of the SDR were about 4.2, and the particle size distributions of PAS particles in the slurries are shown in Figure 2. The values of D_{10}, D_{50}, and D_{90} of the distributions are listed in Table 2. The particle size decreased with an increase in the PVP concentration ranging between 5 and 15 g/L, and a further increase to 20 g/L was not effective. During the precipitation process, small particles tended to agglomerate due to the hydrophobic surfaces of the drug particles. When a protective polymer, such as PVP or other protecting agent, was present in the solution, the particles would be stabilized sterically to prevent the crystals from agglomeration and growth. When the polymer concentration was high, the protecting effect was more significant. The particle size, however, became slightly larger again when the concentration of PVP was further increased to 20 g/L. It is presumed that the increased viscosity to reduce the mixing intensity was responsible for the increase in particle size.

As a comparison, the SEM micrographs of the commercial PAS particles and the produced particles directly from the SDR-S operated at a PVP concentration of 15 g/L are shown in (a) and (b), respectively, of Figure 3. The commercial particles, shown in Figure 3a, were mainly rodlike with a mean particle size of around 10 μm and a wide particle size distribution, while the produced particles, shown in Figure 3b, were mainly granular with most of the primary particles being smaller than 1 μm. Consequently, it is concluded that a remarkable reduction in the size of PAS particles was achieved by the high-gravity technique. The possible mechanism for producing micrometer *p*-aminosalicylic acid particles is described below. The precipitation process generally consists of three main steps, i.e., generation of supersaturation, nucleation, and crystal growth. To produce ultrafine particles with uniform

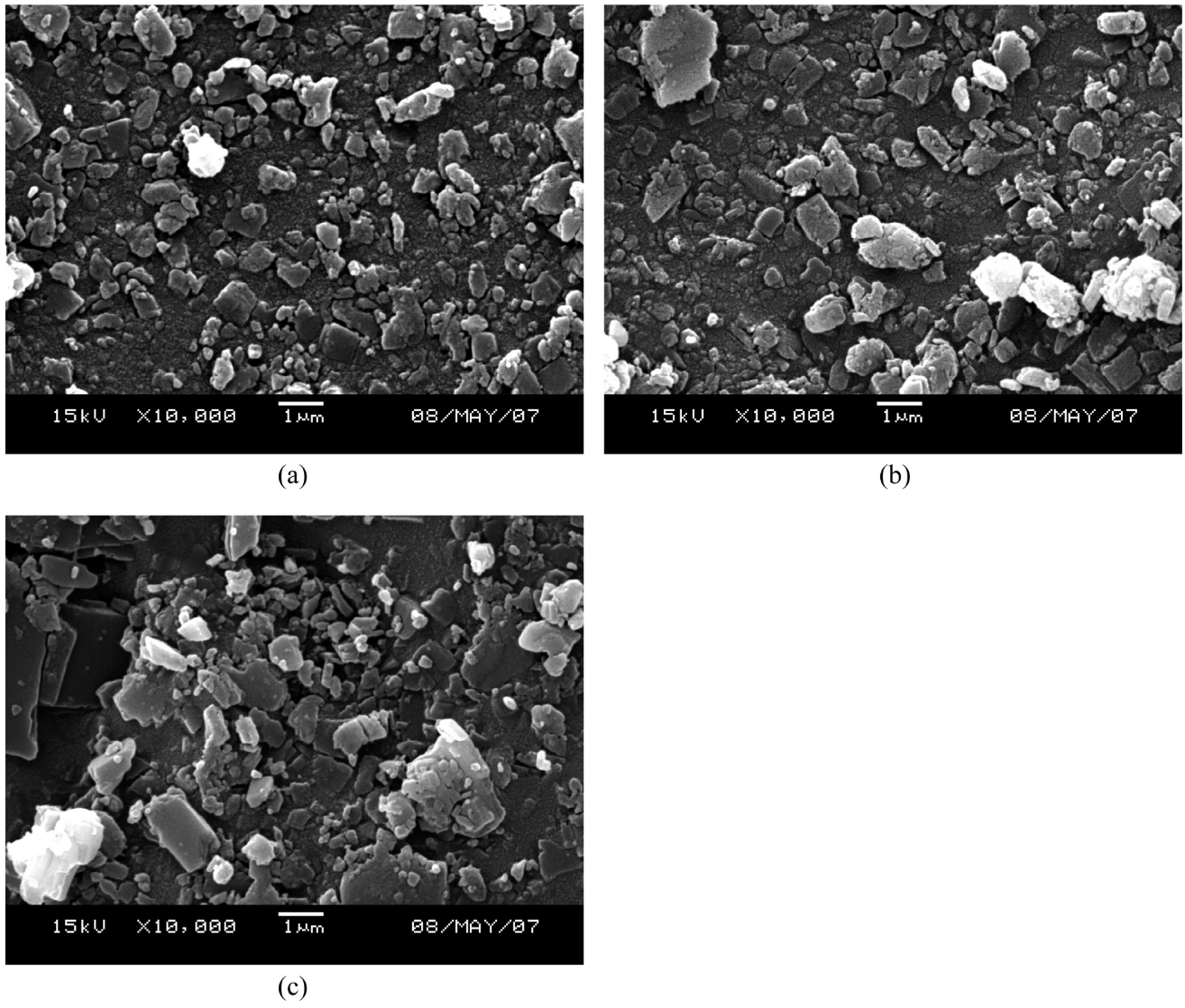

Figure 7. SEM micrograph of the micronized PAS in the slurry prepared by the SDR-L with a circular-tube distributor for the flow rates of (a) 0.25 L/min, (b) 0.5 L/min, and (c) 1.0 L/min. Other operating variables kept constant are PAS concentration (60 g/L), PVP concentration (22.5 g/L), NaOH concentration (16.5 g/L), propionic acid concentration (110 g/L), and rotational speed (2100 rpm).

size, a high and uniform supersaturation should be generated. In addition, a protecting agent should be added to suppress the agglomeration and growth of crystals. On the surface of the spinning disk used in this experiment, the mixing was so intensive that uniform concentration of all components, including the protecting agent, was achieved immediately when the feeding streams were injected onto the SDR. Since the micromixing time of the alkaline and acid streams was shorter than the induction time of PAS nucleation, the PAS particles were generated in an environment of uniform and high supersaturation. Meanwhile, the PAS particles were protected by the protecting agent uniformly distributed in the solution once they were generated. Therefore, small and uniform particles were obtained. It is also noted that the volume mean size of the sample shown in Figure 3b was 9.1 μm, analyzed by the light-scattering analyzer. It is obvious that the size determined by the analyzer was larger than that observed by SEM. The larger particle size was caused by the agglomeration of drying particles in the suspension.

To increase the production rate, the effect of PAS concentration was investigated. Figure 4 shows the SEM micrographs of the produced particles for different PAS concentrations of the feeding streams. The experiments were carried out in the SDR-S for PAS concentrations ranging from 40 to 100 g/L. The concentration ratios of NaOH:PVP:PAS were fixed at 0.275:0.375:1, respectively, while the propionic acid concentrations were varied from 37 to 180 g/L to keep the pH value of the slurry at 4.2. The graphs revealed that the concentration of PAS significantly affected the particle size, which increased with an increase in the PAS concentration. For example, the particle size increased more than 5 times, i.e., from submicrometer to 3 μm, when the concentration of PAS increased from 40 to 100 g/L. The PAS crystals probably grew to larger particles in the collecting tank for those runs of higher PAS concentration because the high supersaturation did not release completely on the disk surface, especially for the case of the highest concentration.

Effect of SDR Geometry. The effects of the SDR geometry on the particle size were investigated by using the SDR-S and SDR-L with disk diameter of 12 and 50 cm, respectively, and both fitted with a straight-tube distributor. In addition, a circular-tube distributor was tested in place of a straight-tube distributor in the SDR-L. The flow rates of feeding streams for the three cases were varied between 0.25 and 1.0 L/min, while keeping the concentration of PAS fixed at 60 g/L. The SEM micrographs of the produced particles for each case, which are presented in

Figures 5−7, were used for judging the particle size. In general, the effect of the SDR geometry was more significant than that of the flow rate, although the particle size increased slightly with an increase in flow rate. For the case of SDR-S shown in Figure 5, the flow rate had little effect on the particle size, which had a distribution from submicrometer to several micrometers and was much larger than that of the case of SDR-L equipped with the circular-tube distributor as shown in Figure 7. Using the SDR-S of shorter retention time, it was suspected that the crystals grew further in the collection vessel due to incomplete release of supersaturation on the disk surface. When the disk diameter increased from 12 to 50 cm, the particle size decreased at the low flow rate of 0.25 L/min but was not affected at high flow rates as shown in Figure 6. It is understood that the longer retention time caused a complete release of supersaturation on the disk surface at the lowest flow rate of feeding streams but not for the higher flow rates. From the experience accumulated in the above experiments, we realized that the micromixing was not as good as we expected when the two feeding streams were charged simultaneously into the disk center. Therefore, the straight-tube distributor was replaced by a circular tube with seven holes, through which the acid stream was charged to the SDR-L. This arrangement would be able to provide a better spreading of the antisolvent and a higher impingement velocity between the two liquid streams and thus, more effective micromixing. As a result, most of the particles were reduced to submicrometer levels with a few agglomerates exceeding a micrometer at higher flow rates as shown in Figure 7.

Effect of Homogenization. Although primary particles of PAS as fine as 1 μm were obtained using the high-gravity technique, it was noticed that agglomeration of particles occurred in the precipitation process. Therefore, high-pressure homogenization was used in this study to break up the agglomeration of particles. In the high-pressure homogenization step, the pressure range from 10000 to 30000 psi and the cycle number from 2 to 8 were tested, while the temperature was set at 5 °C to lower the solubility of the PAS particle. When a pressure of 30000 psi was applied, a significant portion of the drug particles would dissolve in the medium as observed by the naked eye. On the other hand, most of the agglomerate still existed in the suspension for the case of 10000 psi. Consequently, an optimum pressure of 20000 psi was used in the homogenization step.

Figure 8 shows the effect of cycle number on the particle size distribution at 20000 psi. The particle size reduced with increasing cycle number and the distribution remained the same after 6 cycles. The mean particle size was reduced from 9 to 1 μm after 8 cycles of homogenization. Figure 9 shows the SEM micrograph of the particles after 8 cycles of homogenization. The size and the shape of the PAS primary particles did not change as compared with that of the particles before homogenization as shown in Figure 3b, indicating that the reduction of particle size in the high-pressure homogenization step was mainly due to the break-up of particle agglomerate, instead of the comminution of the particles.

Dissolution Curve of Drug Samples. The dissolution curves of the commercial sample and the micronized PAS particles after freeze-drying (shown in Figure 9) are presented in Figure 10. The results showed that over 90% of the micronized PAS particles dissolved in 1 min, while only 24% of the commercial drug particles dissolved in the same time interval. Then all of the micronized particles dissolved in 2 min, but it took almost 30 min for the commercial drug to dissolve completely.

In addition, XRD analyses were performed in this study to investigate the crystallinity of the micronized PAS particles.

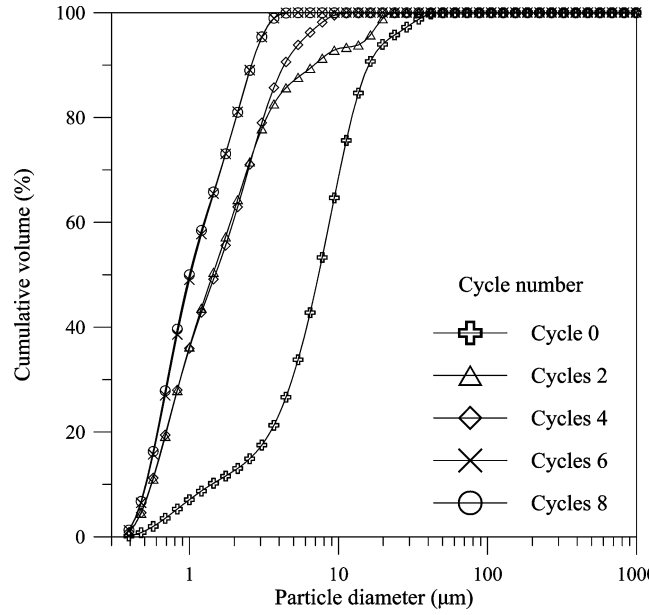

Figure 8. Particle size distribution of PAS after various cycles of high-pressure homogenization.

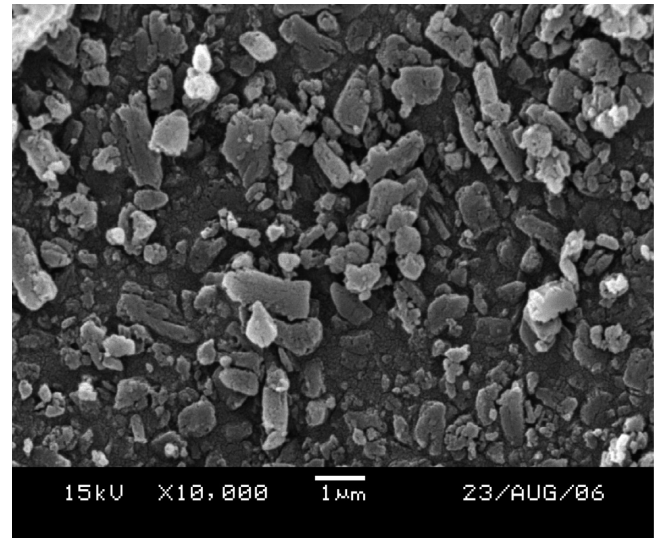

Figure 9. SEM micrograph of the micronized PAS after 8 cycles of homogenization and freeze-drying.

The XRD patterns of the commercial and the micronized PAS particles are shown in Figure 11. It should be noted that (a) and (b) of Figure 11 are the commercial sample and micronized particles, respectively, of the same intensity scale, and Figure 11c is the micronized particles on an enlarged scale. Comparing (a) and (b) in Figure 11, it is found that the peak intensity of the micronized PAS particles was significantly lower than that of the commercial one. However, the morphology of the two drug particles were similar, shown in (a) and (c), respectively, of Figure 11 because the positions of the major peaks were the same. This indicates that the crystal structure of the micronized PAS particles prepared by the high-gravity technique did not change, but the crystallinity was weak compared to that of the commercial drug. As reported by Panagopoulou-Kaplani and Malamataris[30] and Chauhan et al.,[31] the weak crystallinity of the drug particles might enhance the dissolution rate as well. Hancock and Zografi[32] also reported that the amorphous state may be introduced to enhance the biopharmaceutical properties of the drugs with very poor aqueous solubility. Therefore, the

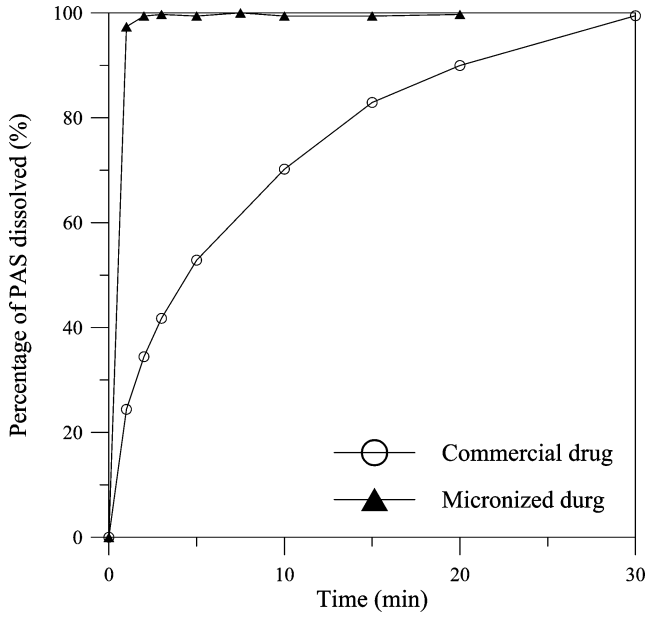

Figure 10. Dissolution curves of the commercial and the micronized PAS.

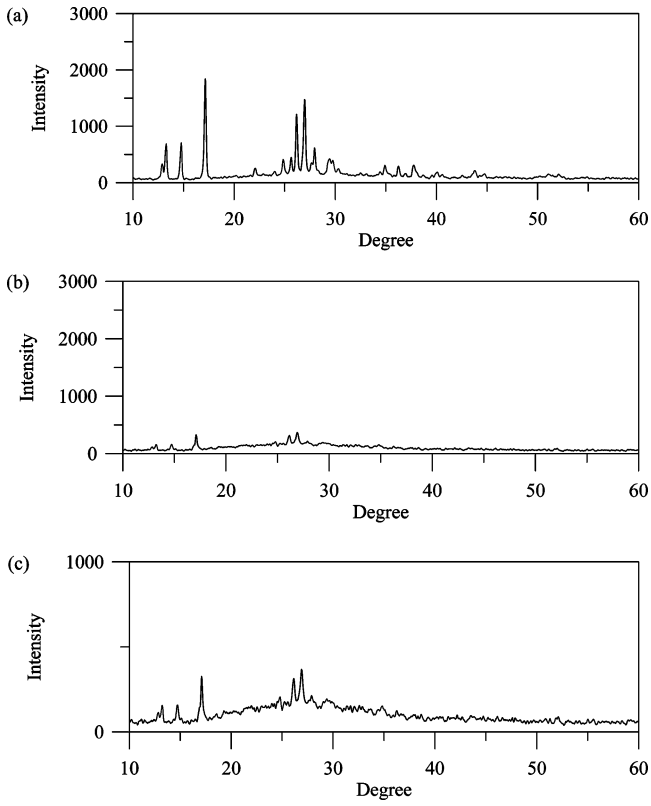

Figure 11. XRD patterns of the PAS samples: (a) commercial particles, (b) micronized particles, and (c) micronized particles on an enlarged scale.

enhancement of the dissolution rate of the micronized drug can be attributed mainly to the increase in the particle surface area resulting from the reduction in particle size as well as the weak crystallinity of the particles.

Conclusions

Micronization of PAS particles was demonstrated in an antisolvent precipitation process using a spinning disk reactor. The precipitation was followed by a high-pressure homogenization to break up the agglomerate. The effects of operating variables in the precipitation and homogenization steps were investigated. The concentration of the drug and the protecting agent, the diameter of the rotating disk, and the type of distributor influenced the size of PAS particles in the precipitation step. In the homogenization step, 20000 psi and 6 to 8 cycles were suitable for breaking up the particle agglomerate. As a result, PAS particles smaller than 1 μm were obtained. The dissolution rate was enhanced significantly for the micronized drug particles because of larger surface area and weaker crystallinity of the particles. It is concluded that the high-gravity technique together with high-pressure homogenization is a promising alternative for micronizing drug particles that are prone to agglomeration.

Acknowledgment

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