Formation of Fine Particles from Curcumin/PVP by the Supercritical Antisolvent Process with a Coaxial Nozzle

Siti Machmudah,* Sugeng Winardi, Wahyudiono, Hideki Kanda, and Motonobu Goto

ABSTRACT: The production of fine particles via the supercritical carbon dioxide (SC-CO₂) antisolvent process was carried out. The experiments were conducted at temperatures of 40–60 °C and pressures of 8–12 MPa with a 15 mL min⁻¹ carbon dioxide (CO₂) and 0.5 mL min⁻¹ feed solution flow rate. As a feed solution, the curcumin and the polyvinylpyrrolidone (PVP) powder were dissolved in acetone and ethanol at concentrations of 1.0 mg mL⁻¹ and 2.0–4.0% in weight, respectively. Scanning electron microscopy (SEM) images described that most of the precipitated particle products have spherical morphologies with a size of less than 1 μm. The Fourier transform infrared spectroscopy (FT-IR) spectra exhibited that the curcumin structural properties did not shift after the SC-CO₂ antisolvent process. Moreover, the PVP addition in the curcumin particle products can enhance the curcumin dissolution in distilled water significantly.

INTRODUCTION

Curcumin is known as a natural colorant isolated from the Curcuma longa L. plant (known as turmeric) where this rhizomatous herbaceous perennial plant was a plant native to tropical South Asia and nowadays extensively cultivated in the tropical and subtropical countries. As a major active component of turmeric, curcumin possesses a low molecular weight polyphenol responsible for the turmeric color (bright yellow). This compound has been applied in pharmaceutical applications to process anticarcinogenic, antibacterial, antimicrobial, anti-inflammatory, and antifungal activities.¹ Some reports also informed that curcumin has been applied to treat diverse diseases such as Alzheimer’s disease, myelodysplastic syndrome, multiple myeloma, anti-human immunodeficiency virus (anti-HIV) cycle replication, and psoriasis.²–⁴ In spite of these favors, due to the fact that curcumin consists of a complex structure and possesses poor solubility in water and high hydrophilicity, this compound seems to have a rapid systemic elimination, rapid metabolism, and poor absorption, which can restrict curcumin usage in pharmaceutical applications and functional food development. Hence, the curcumin structural modification by using a hydrophilic polymer was required to improve its solubility and to broaden its utilization in pharmaceutical and food fields.⁵,⁶

In this work, to improve the solubility of curcumin, especially in water media, supercritical carbon dioxide (SC-CO₂) was employed as a medium to produce fine particles from curcumin, which is mixed with polyvinylpyrrolidone (PVP) as a hydrophilic polymer modifier. This polymer, also usually recognized as polyvidone or povidone, is a water-soluble polymer composed of the monomer, N-vinylpyrrolidone. Due to its chemical and physical properties such as being nontoxic, physiologically compatible, nonionic, temperature-resistant, colorless, pH stable, chemically inert, and highly soluble in water, PVP has been applied in many applications such as pharmaceutical, cosmetic, and medical applications. It also has been broadly utilized to encapsulate matrix materials.⁷ Even the matrix material encapsulation with PVP may manage the release rate and improve the encapsulated matrix material solubility.⁸–¹² In other words, PVP is well suited to improve the dissolution rates of poorly water-soluble drugs in pharmaceutical applications.

A supercritical fluid including SC-CO₂ is any fluid at conditions above its critical point where diverse gas and liquid phases do not exist. At supercritical conditions, the fluid possesses liquid-like densities with gas-like transport properties and moderate solvent power, which can be tuned with turns in temperature and pressure. Hence, a supercritical fluid has been utilized at diverse applications, such as chromatography, extractions (separations), or particle formation.¹³–¹⁶ Several processes for particle generation by using the supercritical fluid have been proposed where the supercritical fluid performed different functions. However, there are two common methods to form particles by using supercritical fluids, mainly SC-CO₂: rapid expansion of supercritical solution (RESS) and supercritical antisolvent (SAS) methods. In the SAS process, the...
supercritical fluid was used as an antisolvent while it became a solvent in the RESS process. When the supercritical fluid was employed as a medium for particle generation, the solute–solvent, usually an organic solvent, can be eliminated from the precipitated particles owing to its high solubility in the supercritical fluid. Furthermore, the utilization of the organic solvent also can be decreased.

Here, SC−CO₂ acting as an antisolvent was employed to produce fine particles from curcumin–PVP that is dissolved in ethanol−acetone. The curcumin–PVP solution was injected directly to the SC−CO₂ antisolvent system via a coaxial nozzle. Since the SAS system was particularly proceeded by the quick mixing between the feed solution and the supercritical fluid to attain supersaturation to form particles, the mixing of ethanol−acetone containing curcumin−PVP as a feed solution and SC−CO₂ as an antisolvent became one of the important step processes. The coaxial nozzle is known as the nozzle that consists of two capillary tubes to flow the feed solution and the SC−CO₂ as an antisolvent simultaneously. By utilizing this device, the agglomeration of precipitated particle products also can be reduced due to fact that the velocity of two coaxial flows may be adjusted independently.

RESULTS AND DISCUSSION

Figure 1 illustrates the powders of PVP (Figure 1a) and curcumin (Figure 1b) before treatment by the SC−CO₂ antisolvent and the collected particle products from curcumin feed solution without (Figure 1c) and with (Figure 1d) PVP after treatment by the SC−CO₂ antisolvent. It could be seen that the raw materials of curcumin and PVP seem to have flakes and spherical or wrinkled spherical morphologies, respectively. Apparently, they have a broad diameter range. It is already known that SC−CO₂ can be applied as a medium to alter the existing particles, mainly their surface or to produce particles in the nano- and microscale. To generate a particle, there are two means: chemical reaction and physical transformation. In the chemical reaction manner, the SC−CO₂ was utilized as a medium of reaction, while in the physical transformation manner, the existing method for the formation of particles by using SC−CO₂ is frequently classified upon the act of the fluid in the process. Therefore, when the CO₂ was utilized as a solvent in the supercritical antisolvent, mass transfer has to be a key factor. The mass transfer occurs between a compressed CO₂ as an antisolvent and an organic solvent droplet from feed solution to generate a particle.

As shown in Figure 1d, the uniform morphologies of the collected curcumin−PVP particle products with a narrow diameter range were found after treatment by the SC−CO₂ antisolvent. Their morphologies were spherical shapes with a size of less than 1 μm. It exhibited that, as a SC−CO₂ antisolvent treatment, the droplet of feed solution was swelled and stabilized by the surface tension of acetone−ethanol solvents. Meanwhile, the mass transfer between the SC−CO₂ and acetone−ethanol solvents may decline these solvent surface tensions that are sufficient to control the droplet form. On the other hand, the diffusion phenomenon during the SC−CO₂ treatment may also drive the acetone−ethanol solvents volume from expanding, declining their density, and consequently, the solvating acetone−ethanol solvents power declines, resulting in the curcumin−PVP precipitation. Due to this process, at supercritical conditions, CO₂ as an antisolvent may reduce the size of curcumin−PVP particle products.

On the contrary, the morphology and the size of the collected particle products from the curcumin feed solution without PVP addition does not seem to change after treatment by the SC−CO₂ antisolvent (see Figure 1c). They have flake morphologies with a size larger than 1 μm. It seems that the collected particle products from the curcumin feed solution without PVP underwent agglomeration during the SC−CO₂ antisolvent treatment. It indicates that, although the formation of curcumin particles from curcumin solution with or without PVP addition by using SC−CO₂ antisolvent is in principle the same process, the addition of biodegradable polymer such as PVP as a carrier in the curcumin feed solution is a promising way to prevent particle product agglomeration.
Figure 2 exhibits the solubility of curcumin particle products in distilled water at 40 °C and 12 MPa without and with 2% PVP. Obviously, the curcumin particle products without PVP addition did not dissolve in distilled water, and conversely, the curcumin particle products with PVP addition can dissolve completely in distilled water. It is well known that the solubility of solutes can be improved by the reduction of their sizes and the encapsulation to modify their surface by using hydrophilic polymers.26 Here, to reduce the powder size of curcumin and to encapsulate the curcumin powder, the feed solution consisting of curcumin and PVP was sprayed via a coaxial nozzle into the SC-\(\text{CO}_2\) antisolvent system. Due to the SC-\(\text{CO}_2\) antisolvent effect, the smaller particles of curcumin containing PVP, compared with those of the curcumin raw material, were obtained via precipitation during the process. At these conditions, encapsulation of curcumin with PVP may occur and grow simultaneously to form a particle. In this work, encapsulation was expressed as the particle formation process from a feed solution consisting of two substances in the solvent that is injected in the SC-\(\text{CO}_2\) antisolvent system in which one substance may grow over an already precipitated substance particle. During the encapsulation process, the hydrophobic part of PVP may wrap the curcumin, while at the hydrophilic part of PVP, the hydrogen bonds would be generated.27 As a result, as shown in Figure 2, the encapsulated curcumin particle products with PVP is completely soluble in distilled water.

To identify the possible shift structure of curcumin or PVP molecules after treatment by the SC-\(\text{CO}_2\) antisolvent, the collected particle products were characterized by FT-IR spectroscopy in the wavelength range from 4000 to 400 \(\text{cm}^{-1}\). This analysis also can observe the possible intermolecular interaction between curcumin and PVP as a carrier. Curcumin or PVP as a starting material was used directly as a control to identify the unknown objects and the chemical bond types of the compounds in those objects. Essentially, the diverse compounds in a similar organic group can absorb approximately in a similar spectral range. Hence, curcumin or PVP was also constructed from many various chemical bonds, which are slightly elastic and may bend, vibrate, or stretch. Figure 3 describes the FT-IR spectra of raw materials of PVP (Figure 3a) and curcumin (Figure 3b) and the collected particle products from SC-\(\text{CO}_2\) antisolvent treatment at 40 °C and 12 MPa without (Figure 3c) and with 2% PVP (Figure 3d). The PVP starting material (Figure 3a) provided an absorption band at 3410 \(\text{cm}^{-1}\), corresponding to the O–H stretching vibration. The absorption bands at 2960 and 1642 \(\text{cm}^{-1}\) confirmed the existence of asymmetric CH\(_2\) and C–O stretching, respectively. The C–H bending and CH\(_3\) wagging were noticed at 1423 and 1288 \(\text{cm}^{-1}\) absorption bands, respectively. The absorption bands at 1020 and 571 \(\text{cm}^{-1}\) were indicated as the CH\(_2\) rocking and N–C–O bending, respectively.28,29 As illustrated in this figure, the FT-IR spectra of untreated curcumin (Figure 3b) and treated curcumin without PVP addition (Figure 3c) by the SC-\(\text{CO}_2\) antisolvent treatment were the same. They showed the characteristic absorption bands at 3512 \(\text{cm}^{-1}\) due to the O–H stretching vibration, at 1627 \(\text{cm}^{-1}\) due to C=C benzene stretching ring, at 1509 \(\text{cm}^{-1}\) due to C=O stretching, at 1428 \(\text{cm}^{-1}\) due to C=H bending, at 1280 \(\text{cm}^{-1}\) due to C–O stretching, at 1025 \(\text{cm}^{-1}\) due to C–O–C stretching vibration, and at 856 \(\text{cm}^{-1}\) due to C=H aromatic hydrogen. These FT-IR spectra (Figure 3b,c) indicated that the curcumin structure did not change after SC-\(\text{CO}_2\) antisolvent treatment without PVP addition. In the case of the treated curcumin containing PVP, due to the hydrogen-bond intermolecular interaction between O–H of curcumin and C=O of PVP, the O–H absorption band of curcumin completely disappeared and the C=O absorption band of PVP shifted to a lower intensity. There are no other chemical bands in the collected particle products from the feed solution containing curcumin and PVP after the SC-\(\text{CO}_2\) antisolvent treatment. Perhaps it indicated that PVP as a polymer carrier successfully encapsulated curcumin during the precipitation process.29

In this work, to observe the shifts in the thermal properties of curcumin or PVP as a starting material and the collected particle products after the SC-\(\text{CO}_2\) antisolvent treatment, they were characterized by using thermogravimetric analysis, as described in Figure 4. This analytical technique can be applied to determine the thermal stability of the substance, and its fraction of volatile components by observing the weight shift.
that occurs as a sample is heated. The weight loss of sample versus time was recorded, and this weight loss was assumed to describe the thermal decomposition of curcumin or PVP and the collected particle products containing them.30 Essentially, all samples underwent the same decomposition pathway during thermogravimetric analysis, but the starting temperature of each sample losing weight seems different. Below 100 °C, generally, the weight loss of substances can be due to the elimination of the moisture content. This could be found only in the TGA (thermal gravimetric analysis) thermogram of PVP, and this might be because PVP is a highly hygroscopic substance. As described in Figure 4, it can be known that the thermal degradation of curcumin, PVP, and the collected particle products did not result in significant differences. Below 100 °C, there is essentially no more weight loss above this temperature. Although the thermal decomposition curves of curcumin, PVP, and the collected particle products did not result in significant differences, it seems that the intermolecular interaction between curcumin and PVP can improve the thermal stability of curcumin via O−H and C==O bond conjugations.31 This result is in good agreement with the results given by infrared spectroscopy (see Figure 3).

Mostly, in the antisolvent process including SC−CO2 as an antisolvent, the desired substance was dissolved in an organic solvent to form a solution as a feed solution. The desired substance should be virtually insoluble in SC−CO2 and vice versa, and the organic solvent should have relatively high miscibility in SC−CO2 at the desired operating pressure and temperature. During the SC−CO2 antisolvent process, the solvent power of the feed solution was declined by saturating it with antisolvent, resulting in precipitation of the dissolved substance. In this work, the contact between the feed solution and the SC−CO2 as an antisolvent was performed at the top of the precipitator through a coaxial nozzle continuously when the operating condition achieved a steady state (temperature, pressure, and CO2 flow rate). The SC−CO2 will soon interact with antisolvent, resulting in precipitation. A faster nucleation, resulting in the increasing yield of precipitation.

Figure 5 and 6 exhibit the SEM images of the collected particle products and their diameter produced from feed solution containing 2 to 4% PVP at various operating conditions (temperatures and pressures). In the physical transformation process, there are two potential ways to form a particle under the SC−CO2 antisolvent. They are the solvent removal or evaporation into the antisolvent phase and the diffusion of antisolvent into the feed solution droplet. Therefore, aside from the physical properties of SC−CO2 as an antisolvent, the concentration of the starting material also has a significant effect and has to be an important parameter in the precipitation yields, and the curcumin contents collected from each experiment. The yield of collected particles was determined as the percentage ratio of the mass of the collected particles to the initial mass delivered to the precipitator particle product collector (yield = (mass-collected particles/mass-delivered feed) × 100%), while the content of curcumin in the collected particles was determined by dividing the curcumin mass in the analyzed collected particle products by the total mass of collected particle products. The yield of collected particles and the content of curcumin in the collected particles ranged between 53.01−77.19 and 63.37−78.51%, respectively, depending on the operating conditions operated in the SC−CO2 antisolvent process. De Marco et al.32 conducted an experiment for supercritical antisolvent precipitation using PVP as a solute and the organic solvent mixture as a solvent. They reported that the precipitation yields could approach to 90% when the various acetone−ethanol mixture compositions were used as a solvent. However, as summarized in Table 1, the results of precipitated particles and the curcumin content in the precipitated particles were less than 80%. This can be attributed that the individual substance might pass through the stainless filter as a particle product collector during the SC−CO2 antisolvent experiments.33 The results also showed that the increasing amount of PVP addition was almost followed by the increasing precipitation yield at each condition. It is well known that the PVP solubility is much higher in ethanol (over 10% w/w at room temperature) than in acetone (less than 10% w/w at room temperature).34 Hence, when the amount of PVP addition in the feed solution with acetone−ethanol (9:1 in volume ratio) as a solvent was increased, the curcumin−PVP precipitation occurred earlier in time during the expansion process due to increasing the degree of supersaturation and faster nucleation, resulting in the increasing yield of precipitation.

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### Table 1. Experimental Conditions, the Precipitation Yield, and the Curcumin Recovery

| operating condition | product recovery (%) | curcumin recovery (%) |
|---------------------|----------------------|-----------------------|
| P (MPa) T (°C) | PVP addition (%) | PVP addition (%) |
| 8 40 | 67.33 71.96 77.19 | 74.84 78.51 |
| 50 60 | 58.46 66.67 67.89 | 65.86 73.71 |
| 60 60 | 53.01 68.07 65.81 | 63.64 72.07 |
| 10 40 | 61.43 70.84 73.72 | 71.06 76.37 |
| 50 50 | 54.54 63.48 64.71 | 69.03 68.61 |
| 60 60 | 60.86 65.60 61.35 | 68.22 72.24 |
| 12 40 | 65.04 65.25 64.52 | 69.47 77.01 |
| 50 60 | 60.08 63.96 64.75 | 63.37 63.74 |
| 60 60 | 59.68 62.22 63.66 | 63.49 64.57 |

*T, temperature; P, pressure.*
mass transfer between solute solvents and \( \text{CO}_2 \), resulting in particle formation. Generally, the solute supersaturation occurs very late when the lower concentration of feed solution was fed in the SC–\( \text{CO}_2 \) antisolvent to produce particles. Next, the solute precipitation will delay, and the nucleation of solute dominates growth, resulting in smaller precipitated particles. Contrariwise, by enhancing the feed solution concentration, the supersaturation of the solute may occur sooner where the solute growth dominates the nucleation process, resulting in bigger precipitated particles. In addition, the higher concentration of feed solution may enhance the solution viscosity and the solution surface tension, promoting the large droplet; consequently, the precipitated solute with the larger size will be generated.\(^{6,14,21,35}\) As a result, as shown in Figures 5d and 6f, the larger diameter of the precipitated curcumin–PVP particles was formed when the feed solution concentration at 4% was

Figure 5. SEM images of the collected particle products and their diameter obtained from feed solution containing 2% PVP at 60 °C with different pressures.
introduced in the SC–CO₂ antisolvent system. On average, the diameter was around 164 nm. The diameter of the precipitated curcumin–PVP particles decreased to 124 nm when the feed solution concentration at 2% was fed in the SC–CO₂ antisolvent system at the same operating conditions. Although it is not significant, the result indicated that the changes in the feed solution concentration may affect the size of particle products.

It was well known that, even if there are several types of supercritical fluids that exist and they have been applied in various industrial applications, mostly their dissolving power depends on their density and owing to their higher diffusivity, lower viscosity, and lower surface tension than liquid solvents, the fast mass transfer with supercritical fluids may occur. These physical properties including SC–CO₂ properties can be manipulated by shifting operating pressure and/or temperature.36,37

Figure 6. SEM images of the collected particle products and their diameter obtained from feed solution containing 4% PVP at 10 MPa with different temperatures.
At a constant operating temperature, the density of SC–CO₂ will increase with increasing operating pressures. In most cases, a higher operating pressure of the SC–CO₂ antisolvent system became in favor of the nucleation process to construct and to form a lot of particle nuclei.38–40 This condition might lead to generating particle products with a smaller size. Therefore, the rising operating pressure of the SC–CO₂ antisolvent from 8 to 12 MPa at a constant operating temperature was hoped to be followed by the smaller size of curcumin–PVP particle products. As depicted in Figure 5, the size of curcumin–PVP particle products was produced dominantly at ranges of 250–750 nm with an average diameter of 538 nm when the SC–CO₂ antisolvent process was performed at 8 MPa with a 60 °C operating temperature. At the same operating temperature, the size of curcumin–PVP particle products decreased significantly to 124 and 115 nm on average when the SC–CO₂ antisolvent process was carried out at 10 and 12 MPa, respectively. The results indicated that the fast mass transfer between feed solution solvents and CO₂ promoted the high supersaturation for the curcumin–PVP solutes and led to the rapid curcumin–PVP solute precipitation, resulting in smaller curcumin–PVP particle products that, at the higher operating pressures at this system, might provide the higher fluid density that can highly influence the mass transfer between SC–CO₂ and acetone–ethanol solvents during the precipitation process, which results in particle formation.31,42

Similar to the operating pressure, because SC–CO₂ possesses high compressibility, the minor changes in the operating temperature may also result in large changes in the SC–CO₂ density, which means that its solvent power was also changed. The higher operating temperature leads to the mass transfer between SC–CO₂ and feed solution solvent where, at these conditions, the high supersaturation occurs, resulting in the smaller precipitated particle products. On the other hand, the higher operating temperature also promotes the decreasing SC–CO₂ density and the declining SC–CO₂ ability to dissolve organic solvents. Next, the decreasing supersaturation occurs to promote the bigger precipitated particle product formation. Hence, it could be said that the operating temperature in SC–CO₂ possesses two different effects on particle formation.35,43 As shown in Figure 6, the SC–CO₂ operating temperature of 40 °C resulted in the curcumin–PVP particle products with size ranges of 50–125 nm with an average particle size of 82 nm. The size ranges and the average of these particle products increase significantly to 100–200 nm and 164 nm, respectively, when the operating temperature was increased to 60 °C with the same operating pressure. This result indicated that, at this experiment, the SC–CO₂ dissolving ability declines with increasing operating temperature, resulting in the decreasing supersaturation. Next, the bigger size of curcumin–PVP particle products was generated.

As shown above, the curcumin particles can dissolve entirely in distilled water after treatment by the SC–CO₂ antisolvent to modify their surface with a PVP polymer. Regardless of their particle size, Figure 7 illustrates the profile of precipitated curcumin particle dissolution in distilled water without and with PVP polymer addition at 2 and 4% when the experiments were performed at an operating temperature of 60 °C and an operating pressure of 8 MPa. As depicted in this figure, except for the precipitated particle from curcumin solution without PVP polymer addition, the amount of curcumin release in distilled water increases with the increasing dissolution time. It indicated that the presence of PVP in the curcumin precipitated particle can improve its aqueous solubility. It may be attributed to the formation of intermolecular hydrogen bonding between the PVP carbonyl group and the hydrogen atom in the curcumin hydroxyl group, and it is well known that PVP possesses both a hydrophobic and hydrophilic part due to the existence of the chain carbon atoms in its structure and the highly polar five-membered ring lactams. It caused this polymer to be highly water soluble, and it even may dissolve in a small amount of water.34 Because of this, the release of curcumin from the precipitated particles into distilled water increased significantly with the addition of the PVP polymer, especially a higher concentration of PVP polymer addition.34

### CONCLUSIONS

The production of fine particles by using the SC–CO₂ antisolvent process from a solution of curcumin with or without a PVP polymer was demonstrated. The experiments were performed at temperatures of 40–60 °C and pressures of 8–12 MPa with a 15 mL min⁻¹ CO₂ and 0.5 mL min⁻¹ feed solution flow rate. The SEM images illustrated that most of the precipitated particle products have spherical morphologies with a size of less than 1 μm. The FT-IR spectra indicated that the curcumin structural properties did not change after the SC–CO₂ antisolvent process, and the curcumin particles can dissolve entirely in distilled water after SC–CO₂ antisolvent treatment to modify their surface with a PVP polymer. Next, this experiment demonstrated that the SC–CO₂ antisolvent is likely to be fruitful for the fabrication of phytochemical compound particles containing biodegradability as a carrier to enhance its solubility in the distilled water.

### MATERIALS AND METHODS

**Materials.** Crystalline curcumin and PVP \((\text{C}_6\text{H}_9\text{NO})_n\), average molecular weight, 29,000) were bought from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) and Sigma-Aldrich Co. (St. Louis, MO, USA). Ethanol \((\text{C}_2\text{H}_6\text{O}, >99.5\% )\) and acetone \((\text{C}_3\text{H}_6\text{O}, >99.7\% )\) were purchased from Merck. Carbon dioxide \((\text{CO}_2)\) was provided by PT. Samator Gas Industri (Gresik, Indonesia). All chemicals were received and used without further purification. For preparing the feed solution, the curcumin and the PVP powder were dissolved in...
acetone and ethanol at concentrations of 1.0 mg mL\(^{-1}\) and 2.0–4.0% in weight, respectively. Next, they were mixed at different ratios of 9:1 (volume ratio). However, the pump did not work properly after a few minutes of pumping when the concentration of PVP in the feed solution was higher than 4%. Hence, the higher concentration of PVP (higher than 4%) was not fed as feed solutions.

**Supercritical CO\(_2\) Antisolvent.** Figure 8 describes the apparatus scheme for curcumin–PVP precipitation through the SC–CO\(_2\) antisolvent. The SC–CO\(_2\) antisolvent apparatus system consisted of the following main parts: two high-pressure pumps (one for the feed solution and the other for CO\(_2\); PU–980 and PU–1586, Jasco, Japan), a heating chamber (Tokyo Rikakikai, WFO–400, Tokyo, Japan), a nozzle device (SUS–316), and a back pressure regulator (BPR; AKICO, Tokyo, Japan). The nozzle device was constructed from a 1/16 in. tube (0.5 mm i.d.) for the feed solution, placed inside a 1/8 in. tube (2.17 mm i.d.) for the SC–CO\(_2\) antisolvent. This nozzle was connected to a 1/8 in. tube (2.17 mm i.d., SUS–316) as a precipitator part with a 5.0 m length by using union Tee (SS–200–3, Swagelok). To observe the precipitation temperature, K-type thermocouples were attached in the nozzle part and in the coil preheater that was located in a heating chamber with a length of 3.0 m (2.17 mm i.d., SUS–316). The pressure gauge was also assembled between BPR and the precipitator product collector to monitor the operating pressure during experiments. In this work, the experiments were carried out at 40–60 °C and 8–12 MPa with a 15 mL min\(^{-1}\) CO\(_2\) and 0.5 mL min\(^{-1}\) feed solution flow rate. At each condition, the experiment was performed at 60 min. The curcumin–PVP particle products were collected in the bottles after releasing the pressure. Next, it was stored in a vacuum desiccator at room temperature until the next analysis.

**Analytical Methods.** The collected curcumin–PVP particle products were characterized by using a scanning electron microscope (S–4300, Hitachi, Japan) after gold coating to observe their morphologies. Their diameters were measured from the SEM images by using an image analyzer software (ImageJ 1.42). The SC–CO\(_2\) antisolvent products were also characterized by using a Spectrum Two Fourier transform infrared spectroscopy (FT-IR) spectrophotometer (PerkinElmer Ltd., Buckinghamshire, England). This FT-IR consisted of the standard optical system with KBr (potassium bromide) windows and a universal attenuated total reflectance (UATR) sampling accessory for a spectral data collection. The thermal decomposition behavior of different samples was characterized by thermogravimetric–differential thermal analysis (TGA–50, Shimadzu, Japan) under a nitrogen flow rate of 50 mL min\(^{-1}\) with a 10 °C min\(^{-1}\) temperature rate from room temperature to 500 °C. The dissolution of the collected curcumin–PVP particle products was observed using a UV–vis spectrophotometer (V–550, JASCO, Japan). Initially, 4 mg of the sample was dissolved in 40 mL of distilled water at a temperature of 37 °C. After 12 h, it was filtered with a 0.2 μm disposable membrane filter. Next, the solution sample absorbance was measured by using the UV–vis spectrophotometer at 430 nm. The curcumin concentration (stated as mg curcumin L\(^{-1}\)) was determined based on the standard calibration curve of curcumin in ethanol. The same method was used for the curcumin content determination in the collected curcumin–PVP particle products.

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ABBREVIATIONS
SC–CO₂: supercritical carbon dioxide; CO₂: carbon dioxide; PVP: polyvinylpyrrolidone; SEM: scanning electron microscopy; FT-IR: Fourier transform infrared spectroscopy

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