Enhancement of *Curcuma xanthorrhiza* Roxb Phytochemical Dissolution via Micronization Using a Supercritical Antisolvent Technique

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**ABSTRACT:** Fine particles comprising *Curcuma xanthorrhiza* Roxb (*C. xanthorrhiza*) rhizome extract were successfully generated using a supercritical carbon dioxide (SCCO$_2$) antisolvent technique. The SCCO$_2$ antisolvent process was performed at 40 °C with 8–16 MPa operating pressures. The CO$_2$ and feed solution flow rates were 15 and 0.25 mL min$^{-1}$, respectively. The mixture of *C. xanthorrhiza* rhizome extract and a polyvinylpyrrolidone (PVP) polymer in acetone–ethanol was used as a feed solution. The collected particle products seemed to possess spherical and spherical-like morphologies with a diameter of less than 500 nm. The infrared spectroscopy analysis showed that the structural properties of *C. xanthorrhiza* rhizome extract did not change after treatment with the SCCO$_2$ antisolvent. Furthermore, the addition of the PVP polymer in the *C. xanthorrhiza* rhizome extract particle products may improve their dissolution significantly in an aqueous solution medium.

**INTRODUCTION**

Supercritical fluids, in general, can be defined as any fluids at conditions above their critical points, where the diversities of liquid and gas phases are not present. At this condition, the fluids possess liquid-like densities with gas-like transport properties and moderate solvent power. These features can be adjusted by changing the temperature and pressure environments. Because of this, supercritical fluids have been employed at various applications, i.e., separations (extractions), particle generation, or chromatography.$^{1−3}$ For particle production by employing a supercritical fluid, mainly supercritical carbon dioxide (SCCO$_2$), based on the function of supercritical fluids as a medium, a different technique has been proposed. Nevertheless, there are three major ways to generate particles by employing supercritical fluids including SCCO$_2$: supercritical antisolvent (SAS), particles from gas-saturated solution (PGSS), and rapid expansion of supercritical solution (RESS) techniques.$^{4−6}$ In the RESS technique, a supercritical fluid is utilized as a solvent, and it shifts into an antisolvent in the SAS technique, while in the PGSS technique, a supercritical fluid may act as a solute. These three major techniques usually employed SCCO$_2$ to produce particles in the nano- to microscale because CO$_2$ can be applied as a solute, an antisolvent, or a solvent.$^5$ In addition to its critical point being relatively low ($T_c = 31.06$ °C; $P_c = 7.38$ MPa), CO$_2$ is also environment-friendly, inert, inexpensive, tasteless, odorless, easily available, nonflammable, and relatively nontoxic. This substance is also easily removed completely from the products.

*Curcuma xanthorrhiza* Roxb (*C. xanthorrhiza*) is known as a herbal plant that is extensively utilized as a traditional medicine and supplement in Southeast Asian countries including Indonesia. As a native Indonesian herbal plant, *C. xanthorrhiza* belongs to the Zingiberaceae family, and it is usually called Java turmeric or Temulawak.$^7−9$ As a health supplement ingredient, this herbal plant is employed traditionally to treat several health problems, i.e., diabetes, heart disorders, hypertension, rheumatism, liver complaints, and hepatitis. Usually, it is called “jamu”. Moreover, it also can be employed as an antidiabetic, antitumor, anticancer, anti-inflammatory, antimicrobial, and antioxidant agent. Moreover, *C. xanthorrhiza* also possesses hepatoprotective and skin care properties.$^7,9$ Despite these advantages, *C. xanthorrhiza* phytochemicals, especially curcumin, consist of a complex structure and have high hydrophobicity and poor solubility in pure water. It leads to rapid metabolism, rapid systemic elimination, and poor absorption, which may limit the usage of *C. xanthorrhiza* phytochemicals in...
pharmaceutical fields and functional food application. Due to these limitations, *C. xanthorrhiza* phytochemicals’ structural modification with a hydrophilic polymer is needed to enhance the water solubility. It also is expected to improve the application of *C. xanthorrhiza* phytochemicals in food and pharmaceutical applications.

Here, to enhance the *C. xanthorrhiza* phytochemical solubility in pure water, SCCO$_2$ was utilized to act as a medium to form the *C. xanthorrhiza* phytochemical particles, which were mixed with a hydrophilic polymer modifier, namely, polyvinylpyrrolidone (PVP), in the nano- to microscale. In other words, SCCO$_2$ was employed as an antisolvent to form particles from the *C. xanthorrhiza* phytochemical–PVP solution with acetone–ethanol as a solvent mixture. Rossmann *et al.* conducted experiments for the formation of fine particles from PVP and ibuprofen using the SCCO$_2$ antisolvent technique with ethanol–acetone solvent mixtures. They found that, concerning the PVP polymer, varying the proportion of ethanol (good solvent) and acetone (poor solvent) led to a change in mean particle size significantly, where the increasing acetone portion in the feed solvent composition may result in a decrease in the size of particle products. Prosapio *et al.* also produced fine particles from PVP and β-carotene using ethanol–acetone solvent mixtures in the SCCO$_2$ antisolvent system because β-carotene is soluble in acetone whereas the PVP polymer is soluble in ethanol. They conducted experiments at pressures of 8.5−10 MPa and a temperature of 40 °C with the β-carotene and PVP polymer ratio from 1:10 to 1:20 as starting materials that were dissolved in 70:30 (v/v) acetone–ethanol solvent mixtures. Using the SCCO$_2$ antisolvent process, Matos *et al.* also successfully produced fine particles from curcumin with PVP as a coprecipitation polymer with an acetone–ethanol mixture as a feed solution solvent. They reported that nano- to submicroparticles were generated and the highest recovery of curcumin was achieved when 70:30 (v/v) acetone–ethanol solvent mixtures were used as a feed solution solvent. In the present work, the feed solution containing the *C. xanthorrhiza* rhizome extract and the PVP polymer was introduced through a coaxial nozzle into the SCCO$_2$ antisolvent system directly using a high-pressure pump. It is well-known that one of the prominent step processes in the SCCO$_2$ antisolvent system is the mixing between the feed solution and SCCO$_2$ as an antisolvent because the supersaturation achievement to generate particles from a solution is mainly obtained by the fast mixing between the SCCO$_2$ solvent and the feed solution. In this work, the coaxial nozzle was employed as a mixing device. It comprises two capillary pipes to pass the SCCO$_2$ solvent and the feed solution simultaneously. One of the merits of employing a coaxial nozzle device is that the flow rate of two coaxial streams can be tuned independently during the particle formation process; hence, the aggregation of collected particle products may be reduced.

In this work, PVP was selected as a hydrophilic polymer modifier. As a water-soluble polymer, this polymer consists of the monomer N-vinylpyrrolidone and is known as povidone or polyvidone. Given its physical and chemical features, PVP is nonionic, chemically inert, pH-stable, physiologically compatible, nontoxic, highly soluble in pure water, colorless, and temperature-resistant. Therefore, it is employed widely in several fields, i.e., medical, cosmetic, or pharmaceutical application. In addition, PVP is also widely used to encapsulate matrix substances because it may enhance the water dissolution rate of encapsulated matrix substances.

## RESULTS AND DISCUSSION

It is well-known that particles in the nano- and microscale can be produced by utilizing SCCO$_2$ via physical transformation or chemical reactions. In the physical transformation way, SCCO$_2$ usually acts as a fluid or solvent in the particle formation process, while in the chemical reaction way, SCCO$_2$ is employed as a reaction medium to generate particles. Hence, the mass transfer phenomenon plays an important role when SCCO$_2$ is employed as a fluid to form particles in a supercritical antisolvent system. This mass transfer takes place between SCCO$_2$ (antisolvent) and solvent droplets (usually organic solvents) from the starting solution during the particle generation process. Since this phenomenon, the success of SCCO$_2$ as an antisolvent to form particles in the nano- and microscale was affected by the feed solvent solubility in the SCCO$_2$ medium and the feed solute insolubility in the SCCO$_2$ medium.

In this work, the solvent suitability of the SCCO$_2$ antisolvent to form particles from the mixture of *C. xanthorrhiza* rhizome extract—PVP solution was tested at a pressure of 16 MPa with a *C. xanthorrhiza* rhizome extract concentration of 2 mg mL$^{-1}$. The flow rates of CO$_2$ and feed solution were 15 and 0.25 mL min$^{-1}$, respectively, and the PVP was not added during the experimental test. The generated particle products were captured and collected on a stainless-steel filter (0.5 mm, SS-4F-K4-05, Swagelok), which was assembled at the end of the precipitator unit. Figure 1 shows SEM images and particle size distributions of particle products with different solution solvents when the experiment was performed at a pressure of 16 MPa. It can be observed that the collected particle products possessed flake (see Figure 1a) and spherical fine particle (see Figure 1c,e) morphologies. Their agglomeration seems to occur resulting in the relatively bigger particle sizes with rough surfaces, especially the collected particle products obtained from acetone as a solvent. The mean sizes of the collected particle products from acetone, ethyl acetate, and dichloromethane solvents were around 376, 261, and 175 nm, respectively. The collected particle products from ethyl acetate and dichloromethane solvents also seem to be narrower than the collected particle products from acetone. Probably, these results were associated with the solvent properties of acetone, ethyl acetate, or dichloromethane, which was employed as a feed solution solvent, where acetone possessed a relatively low dipole moment compared with ethyl acetate or dichloromethane.

Considering the Hansen solubility parameter (HSP), it seems that the solubility parameter of each solvent also affected the size and shape of the collected particle products due to the nucleation and nascent crystal growth in the SCCO$_2$ antisolvent system occurring within the mixture of the feed solution solvent and CO$_2$ environment (see Table 1). Here, the HSP value of each solvent was determined by HSiP 4.1.04 software, while the HSP for CO$_2$ at supercritical conditions was determined according to NIST data (https://webbook.nist.gov/chemistry/fluid/) and Williams *et al.* Based on this prediction, the near value of the HSP between the solvent and CO$_2$ might indicate high solubility.
\[ \delta_d = \delta_{d,\text{ref}} \left( \frac{V_{\text{ref}}}{V} \right)^{0.5} \]  
\[ \delta_p = \delta_{p,\text{ref}} \left( \frac{V_{\text{ref}}}{V} \right)^{0.5} \]  
\[ \delta_h = \delta_{h,\text{ref}} \exp \left[ 0.00132 \left( T_{\text{ref}} - T \right) + \ln \left( \frac{V_{\text{ref}}}{V} \right)^{0.5} \right] \]  

\( \delta_{d,\text{ref}}, \delta_{p,\text{ref}}, \) and \( \delta_{h,\text{ref}} \) are the HSP references (MPa\(^{1/2}\)). \( V_{\text{ref}} \) (39.13 cm\(^3\) mol\(^{-1}\)) is the molar volume at the reference pressure (\( P_{\text{ref}}, 0.1 \) MPa) and reference temperature (\( T_{\text{ref}}, 25 \) °C). In view of the fact that the existence of the liquid or the mixture of two or more solvents in the SCCO\(_2\) antisolvent system may affect the solvent power of SCCO\(_2\), the HSP values were determined using eqs 4 and 5.\(^{26}\)

\[ \delta = \delta_{\text{ref}} \times \left[ \frac{1 - \frac{T}{T_{c,i}}} {1 - \frac{T}{T_{c,\text{ref}}}} \right]^{0.34} \]  
\[ \delta_{\text{mixture}} = \sum x_i \delta_{T,i} \]  

where \( T \) is a given temperature, \( T_c \) is the critical temperature of substance \( i \), and \( x_i \) is the composition of each of the components (CO\(_2\) and ethanol, acetone, ethyl acetate, or dichloromethane, in percentage). As the solubility parameter deviation between the feed solution solvent and CO\(_2\) decreases, the nucleation rate may increase to result in a smaller precipitated particle product. Consequently, as shown in Figure 1, the mean sizes of the collected particle products from ethyl acetate and dichloromethane as feed solution solvents were smaller than the collected particle products from acetone as a feed solution solvent.

**Table 1. Hansen Solubility Parameters for Pure Substances**

| Substance          | Boiling Point (°C) | Dipole Moment (D) | Hansen Solubility Parameter (MPa\(^{1/2}\)) | Conditions          |
|--------------------|--------------------|------------------|---------------------------------------------|---------------------|
| acetone            | 56.3               | 2.69             | \( \delta_d = 15.5 \) \( \delta_h = 15.8 \) \( \delta_p = 17 \) 7 ordinary       |
| ethyl acetate      | 77.1               | 1.88             | \( \delta_d = 15.8 \) \( \delta_h = 15.8 \) \( \delta_p = 17 \) 7.2 ordinary   |
| dichloromethane    | 39.6               | 1.14             | \( \delta_d = 17 \) \( \delta_h = 17 \) \( \delta_p = 17 \) 7.1 ordinary   |
| ethanol            | 78.4               | 1.66             | \( \delta_d = 19.7 \) \( \delta_h = 19.8 \) \( \delta_p = 19.7 \) 19.4 ordinary |
| curcumin           |                    |                  | \( \delta_d = 19.7 \) \( \delta_h = 19.7 \) \( \delta_p = 19.7 \) 11 ordinary |
| CO\(_2\)           | -78                | 0                | \( \delta_d = 10.1 \) \( \delta_h = 10.1 \) \( \delta_p = 10.1 \) 6.8 16 MPa, 40 °C |
| CO\(_2\) + acetone |                    |                  | \( \delta_d = 15.1 \) \( \delta_h = 15.1 \) \( \delta_p = 15.1 \) 6.8 16 MPa, 40 °C |
| CO\(_2\) + ethyl acetate |              |                  | \( \delta_d = 15.1 \) \( \delta_h = 15.1 \) \( \delta_p = 15.1 \) 6.8 12 MPa, 40 °C |
| CO\(_2\) + dichloromethane |             |                  | \( \delta_d = 15.1 \) \( \delta_h = 15.1 \) \( \delta_p = 15.1 \) 6.8 8 MPa, 40 °C |
| CO\(_2\) + ethanol + acetone |             |                  | \( \delta_d = 15.1 \) \( \delta_h = 15.1 \) \( \delta_p = 15.1 \) 6.8 8 MPa, 40 °C |

\( \delta_d \): Dispersion force; \( \delta_p \): dipole force; \( \delta_h \): hydrogen-bonding force.

Figure 1. SEM images and particle size distributions of particle products with different feed solution solvents (a,b) acetone, (c,d) ethyl acetate, and (e,f) dichloromethane at 16 MPa.
Figure 2 shows the amounts of collected particle products from C. xanthorrhiza rhizome extract without PVP addition using different feed solution solvents. The feed concentration, \( \text{CO}_2 \) flow rate, and feed solution were 2 mg mL\(^{-1} \), 15 mL min\(^{-1} \), and 0.25 mL min\(^{-1} \), respectively. It showed that the amounts of collected particle particles could approach to 2.9, 2.6, and 5 mg with acetone, ethyl acetate, and dichloromethane as a feed solution, respectively, when the experiment was operated at a pressure of 8 MPa with a 90 min operating time. Their amount decreases with increasing operating pressure at the same operating conditions. As mentioned before, the solubility between the feed solution solvent and \( \text{SCCO}_2 \) may affect the size of particle products due to the change in the nucleation rate, where the solubility of pure solvents including acetone, ethyl acetate, or dichloromethane in \( \text{SCCO}_2 \) generally increased with increasing operating pressure owing to the improved solvent power of \( \text{SCCO}_2 \). It was followed by the increasing nucleation rate to result in the particle generation. As a result, the smaller-size particles were formed and precipitated on the particle product collector when the operating pressure of the \( \text{SCCO}_2 \) antisolvent was improved from 8 to 12 or 16 MPa. Since this phenomenon, the individual substance from C. xanthorrhiza rhizome extract in the feed solution did not shift into a solid form and precipitate as particles on the stainless filter, but they passed through this stainless filter, which was employed as a particle product collector.\(^{27} \) This, probably, can cause the decrease in the amount of particle products generated from C. xanthorrhiza rhizome extract at higher operating conditions.

Next, the amount of the curcumin content in the collected particle products was determined. As one of the main components of C. xanthorrhiza rhizome extract,\(^{26,29} \) curcumin is widely employed in medicine to treat various diseases, i.e., antihuman immunodeficiency virus (anti-HIV) cycle replication, myelodysplastic syndrome, Alzheimer’s disease, multiple myeloma, and psoriasis.\(^{30−32} \) Figure 3 illustrates the yield of curcumin in the collected particle products from acetone, ethyl acetate, and dichloromethane as a feed solution solvent at various operating pressures. The curcumin yield was determined as the curcumin mass in the collected particle products divided by the total mass of collected particle products (yield = (mass of curcumin/mass of collected particle products) \( \times 100% \)). It seems that, at each operating pressure, the higher yield of curcumin was obtained in the collected particle products when acetone was employed as a feed solution solvent. Even though the reason for this is not clear yet, as described above, when the value of the HSP between the solvents and \( \text{CO}_2 \) is near, the solubility among them was high. In this case, acetone seems to possess the highest difference in the HSP value with \( \text{SCCO}_2 \) compared to ethyl acetate or dichloromethane. Consequently, the very fine particle products containing curcumin as an individual substance with ethyl acetate or dichloromethane as a feed solution solvent may pass through the stainless filter as a particle product collector.\(^{27} \) On the contrary, the particle products from acetone as a feed solution solvent can be precipitated and accumulated in the particle product collector. Evaluating the results, it could be said that based on the HSP value, it may be possible to adjust the particle size of products containing phytochemical compounds by the suitable organic solvent selection. Next, acetone would be mixed with ethanol, and these solvent mixtures would be employed as a feed solution solvent when the PVP was added as a hydrophilic polymer modifier for the following micronization experiments using the \( \text{SCCO}_2 \) antisolvent technique.

Figure 4 shows the SEM images of the collected particle products without and with the addition of PVP in the feed solution and their diameter when the experiments were carried out at a pressure of 12 MPa. It seems that the difference in PVP amount addition in the feed solution resulted in the difference in the particle size distributions of particle products. In the \( \text{SCCO}_2 \) antisolvent system for particle generation, the \( \text{SCCO}_2 \) diffusion into the droplet of feed solution and the removal or evaporation of the feed solution solvent into the \( \text{SCCO}_2 \) medium are important steps during the particle formation process. Hence, in addition to the physical properties of \( \text{SCCO}_2 \), which was employed as an antisolvent, the feed solution concentration also has a high influence and is a key factor in mass transfer between \( \text{SCCO}_2 \) as a medium and the feed solution solvent to promote and to generate particles. In general, when the feed solution in a low concentration is introduced into the \( \text{SCCO}_2 \) antisolvent system, the super-saturation process of the solute for particle generation takes place very slow. This may delay the precipitation of the solute. At this condition, the solute nucleation process was superior to the solute growth process. As a result, the smaller precipitated particle was formed. Contrariwise, the larger precipitated particle was generated when the feed solution in a high concentration was injected into the \( \text{SCCO}_2 \) antisolvent system.
This may be because the solute supersaturation may occur faster and the solute growth process was superior to the nucleation process. Moreover, the feed solution in a high concentration may also improve the viscosity and surface tension of solution that can promote the formation of large droplets. This also may promote the bigger size of the precipitated particle. Therefore, as exhibited in Figure 4, the bigger size of the particle diameter was found on the collected particle products when the feed solution containing C. xanthorrhiza rhizome extract and PVP addition with a ratio of 1:20 was fed into the SCCO2 antisolvent system. The diameter mean size of the collected particle products increases from 177 to 344 nm with increasing the C. xanthorrhiza rhizome extract and PVP addition ratio from 1:10 to 1:20. In addition to the bigger particle products, many irregular and agglomerated particle products were also found from the feed solution with the high ratio of C. xanthorrhiza rhizome extract and PVP. This result revealed that the changes in the feed solution concentration by enhancing the PVP addition amount may affect the collected particle product size.

In supercritical conditions, the physical properties of fluids including CO2 can be tuned by the changing the environment temperature and/or pressure. They are such as the solvating power that was affected by the density and the occurring quick mass transfer in supercritical fluids due to the high diffusivity, low viscosity, and low surface tension. Consequently, as presented in Figures 5 and 6, the difference in amounts of particle products and their curcumin contents without and with PVP addition was found when the SCCO2 antisolvent was carried out at a constant temperature and at various operating pressures from 8 to 16 MPa. The SCCO2 density may increase with increasing operating pressure at a constant temperature. This causes the SCCO2 antisolvent system at a higher operating pressure to become a suitable medium to generate a lot of particle nuclei because it favors the faster nucleation process. However, as exhibited in Figure 5, the amount of collected particle products without and with PVP addition seems to decrease with increasing operating pressure. Without PVP addition, the amount of collected particle products was 2.9 mg at an 8 MPa operating pressure. This amount decreased significantly to 0.2 mg with increasing operating pressure at 16 MPa. The same phenomenon was also found when the PVP polymer was added into the feed solution. The amount of collected particle products could approach to 18 mg at an 8 MPa operating pressure when the C. xanthorrhiza rhizome extract with PVP addition with a ratio of 1:10 was injected into the SCCO2 antisolvent system. It decreases drastically to 1.4 mg when the SCCO2 antisolvent was performed at a 16 MPa operating pressure. As mentioned before, at the higher operating pressure, the precipitated particle with a smaller size was generated, and accordingly, the stainless filter was not able to capture and to collect these very fine precipitated particle products. Probably, it is the reason why the amount of collected particle products decreases with increasing operating pressure. Interestingly, the curcumin content in the collected particle products did not decrease with increasing operating pressure. Conversely, it seems to increase with increasing operating pressure (see Figure 6). As listed in Table 1, according to the HSP value of curcumin and CO2, the curcumin substance did not seem to dissolve in CO2 even under supercritical conditions. Perhaps, other substances that existed in the C.
xanthorrhiza rhizome extract that was used as a feed solution had an HSP value near to that of SCCO₂. They will not land and precipitate in the particle product collector during the SCCO₂ antisolvent process, but these substances will pass through the stainless filter. It may lead to the increasing curcumin fraction in the collected particle products at the higher operating pressure.

Figure 7 shows the FTIR spectra of C. xanthorrhiza rhizome extract (a) and particles (c), the PVP raw material (b), and particle products (d) containing C. xanthorrhiza rhizome extract and PVP with a ratio of 1:20 obtained at a pressure of 16 MPa. This analysis can be employed to observe the possibility of a change in structure of substances including C. xanthorrhiza rhizome extract and PVP after SCCO₂ antisolvent treatment. The intermolecular interaction between C. xanthorrhiza rhizome extract and PVP as a polymer modifier also can be observed. As control substances, C. xanthorrhiza rhizome extract and the PVP raw material were directly placed into the FTIR device to observe the unidentified objects and the types of chemical bonds in the collected particle products. It can be seen that the absorption band at 3328 cm⁻¹, which is associated with the existence of −OH hydroxyl groups in plant matrices, can be found in the spectra of C. xanthorrhiza extract. This absorption band was also found in the spectra of the PVP raw material and particle products. Other peaks at 2922, 1514, and 1031 cm⁻¹ associated with CH₂, C=O, and C−O aliphatic groups, respectively, were also found in the spectra of C. xanthorrhiza extract. In the spectrum of the PVP raw material, it shows that the absorption peaks at 2960 and 1642 cm⁻¹ revealed the presence of asymmetric stretching of CH₂ and stretching of C−O, respectively. The C−H bending, CH₂ wagging, CH₂ rocking, and N−C=O bending were confirmed at 1423, 1288, 1020, and 571 cm⁻¹ absorption bands, respectively.13,37,38 As shown in Figure 7a,c, before and after SCCO₂ antisolvent treatment, the FTIR spectra of C. xanthorrhiza rhizome extract and its particle are the same. It revealed that the structure of the C. xanthorrhiza rhizome did not shift after applying the SCCO₂ antisolvent. The same phenomenon was also found when the PVP was added into the feed solution as a starting material. Without and with PVP addition, their FTIR spectra are essentially the same. However, with the addition of PVP in the feed solution material, it seems that the C=O absorption peak intensity of the PVP raw material changed into a lower intensity owing to the intermolecular interaction between C=O groups of C. xanthorrhiza rhizome extract and the PVP raw material. Similar to that, the C−O and O−H absorption peak intensities in the C. xanthorrhiza rhizome extract spectra also decrease significantly due to the occurring similar interaction between carbon and hydrogen bonds of C. xanthorrhiza rhizome extract and the PVP raw material. This revealed that PVP as a hydrophilic polymer modifier successfully encapsulated C. xanthorrhiza rhizome extract during the precipitation process in the SCCO₂ antisolvent system.13,38

To observe the particle product dissolution from C. xanthorrhiza rhizome extract with PVP addition, the C. xanthorrhiza rhizome extract and the collected particle products from C. xanthorrhiza rhizome extract with PVP addition obtained from the SCCO₂ antisolvent at an 8 MPa operating pressure were dissolved in distilled water (10 mL). The amount of each sample was 1 mg. After 12 h, the collected particle products from C. xanthorrhiza rhizome extract with PVP addition were soluble completely in distilled water resulting in a clear yellow color. Regardless of the size of particle products, Figure 8 depicts the profile of the collected particle product dissolution in distilled water with PVP addition ratios of 1:10 and 1:20 when the SCCO₂ antisolvent processes were carried out at a pressure of 8 MPa. Conversely, the collected particle products from C. xanthorrhiza rhizome extract without PVP addition were not soluble in distilled water. Hence, they were not shown herein. It reveals that the existence of the PVP polymer in the collected particle products may improve the water solubility of C. xanthorrhiza rhizome extract. As illustrated in Figure 8, the amount of C. xanthorrhiza rhizome extract release in an aqueous medium increases with increasing dissolution time.

However, it seems that the release of C. xanthorrhiza rhizome extract into an aqueous medium was affected by the content of the PVP polymer in the particle products, where the release rate of C. xanthorrhiza rhizome extract increased with the increasing PVP polymer amount in the particle products.
solution comprising \(C.\ xanthorrhiza\) rhizome extract and PVP with a ratio of 1:10 in distilled water. As exhibited in this figure, the predominant peaks were found around 430 nm. The predominant peak around 210 nm might originate from the hydroxyl groups from the samples that were dissolved in distilled water, while the peak in the wavelength region at around 430 nm was originated from the existence of the curcumin compound in the \(C.\ xanthorrhiza\) rhizome extract. The PVP polymer is known to have both a hydrophilic and hydrophobic side owing to its structure consisting of the highly polar five-membered ring lactams and the carbon chain atoms. Due to this physical structure, PVP may dissolve highly in distilled water. In agreement with the results obtained by infrared spectroscopy, the intermolecular interaction between the \(C.\ xanthorrhiza\) rhizome extract, especially the curcumin compound, and the PVP modifier occurs during the precipitation process in the \(SCCO_2\) antisolvent. Consequently, the \(C.\ xanthorrhiza\) rhizome extract can be released from the collected particle products with the PVP polymer addition and dissolved completely into distilled water.

**CONCLUSIONS**

Fine particle formation from a solution containing \(C.\ xanthorrhiza\) rhizome extract without or with the PVP polymer addition using the \(SCCO_2\) antisolvent was proven. The \(SCCO_2\) antisolvent process was carried out at a 40 °C operating temperature and 8–16 MPa operating pressures with 15 and 0.25 mL min\(^{-1}\) for \(CO_2\) and feed solution flow rates, respectively. The SEM images presented that the collected particle products seemed to possess spherical and spherical-like morphologies with a diameter of less than 500 nm. The FTIR analysis showed that the structural properties of \(C.\ xanthorrhiza\) rhizome extract did not change after treatment with the \(SCCO_2\) antisolvent. The addition of the PVP polymer to modify the \(C.\ xanthorrhiza\) rhizome extract particles’ surface under the \(SCCO_2\) antisolvent system can improve their solubility significantly in an aqueous solution medium.

**MATERIALS AND METHODS**

**Materials.** The \(C.\ xanthorrhiza\) rhizome was bought from a local market in Jember, East Java, Indonesia. Crystalline curcumin and polyvinylpyrrolidone (PVP; average molecular weight of 29,000) were purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan and Sigma–Aldrich Co. (St. Louis, MO, USA). Ethanol (>99.5%), acetone (>99.7%), dichloromethane (>99.5%), and ethyl acetate (>99.5%) were obtained from Merck. Carbon dioxide (\(CO_2\)) was received from PT. Samator Gas Industri, Gresik, Indonesia.

**Sample Preparation.** The \(C.\ xanthorrhiza\) rhizome was washed using tap water, and it was then rinsed with distilled water and dried naturally at room temperature for around 3 h. To reduce the size of the \(C.\ xanthorrhiza\) rhizome, it was shredded mechanically to a particle size of <2 mm and passed through 16-mesh sieves. Next, the shredded \(C.\ xanthorrhiza\) rhizome was placed into a freeze-drying device (Freeze Dryer Model TF-FD-1, Shanghai Selon Scientific Instrument Co., Ltd., China) to remove the water content. The sample was then stored in a desiccator at room temperature.

**Physicochemical Extraction.** Using the Soxhlet technique, the bioactive fraction was extracted from the dried and shredded \(C.\ xanthorrhiza\) rhizome (12 g). The ethanol solvent (250 mL) was employed as an extraction solvent for 24 h. The sample was then placed into a vacuum rotary evaporator at 50 °C (B-One Rotary Evaporator Model RE-1000 VN, China) to remove the ethanol solvent. After that, the crude extract was stored at 5 °C till further use.

**Solution Preparation.** The feed solution consisted of the mixture of \(C.\ xanthorrhiza\) rhizome extract and PVP, which were dissolved in the mixture of acetone and ethanol with a ratio of 9:1 (v/v) as a solvent. The concentration of \(C.\ xanthorrhiza\) rhizome extract in the feed solution was 2 mg mL\(^{-1}\). The ratio of \(C.\ xanthorrhiza\) rhizome extract to PVP was varied from 1:10 to 1:20 in weight percent (w/w).

**SCCO\(_2\) Antisolvent.** The apparatus scheme for the particle formation from the mixture of \(C.\ xanthorrhiza\) rhizome extract–PVP via the \(SCCO_2\) antisolvent is shown in Figure 10. The main parts of this apparatus are two high-pressure pumps (PU-1586 and PU-980, Jasco, Japan), a back pressure regulator (BPR; AKICO, Tokyo, Japan), a nozzle (SUS-316), and an oven (Tokyo Rikakikai, WFO-400, Tokyo, Japan). The two high-pressure pumps were used to supply \(CO_2\) as an antisolvent and to inject the feed solution into the apparatus.
system via a coaxial nozzle, while the BPR and oven devices were employed to adjust the operating pressures and temperatures, respectively. To observe the operating pressures during the process, a pressure gauge was attached and placed between the BPR and the particle product precipitator. The precipitator was constructed from a stainless-steel tube with a volume of approximately 20 mL (length of 5.4 m, 1/8 inch, SUS-316). K-type thermocouples were also employed to monitor the operating temperatures during the particle formation process. They were placed in the particle product precipitator part and between the nozzle and the coil preheater parts. After the particle precipitation process was finished, the washing process employing SCCO₂ with the solvent mixtures (ethanol:acetone with a volume ratio of 1:1) was frequently performed to sustain the supercritical state and to avoid the condensation of the liquid phase. This also favored overcoming the accumulation of the particle precipitation that can clog the SCCO₂ antisolvent pipeline apparatus. Moreover, to avoid particle blockage in the BPR device and to keep a constant outlet flow during the particle formation process, the BPR device was equipped and heated with a heater at around 70 °C by a cartridge heater connected to a digital temperature controller (model TR-200, AS ONE Corp., Japan). In this work, particle formation was performed at a temperature of 40 °C and pressures of 8–16 MPa. The flow rate of CO₂ was 15 mL min⁻¹, while the flow rate of the feed solution was 0.25 mL min⁻¹. The operating time for the particle formation at each operating condition was 90 min. After the elapsing operating time, the operating pressure was released, and the particle precipitation process was completed. The precipitator was then removed from the system via a coaxial nozzle, while the BPR and oven devices were employed to adjust the operating pressures and temperatures, respectively. To observe the operating pressures during the process, a pressure gauge was attached and placed between the BPR and the particle product precipitator. The precipitator was constructed from a stainless-steel tube with a volume of approximately 20 mL (length of 5.4 m, 1/8 inch, SUS-316). K-type thermocouples were also employed to monitor the operating temperatures during the particle formation process. They were placed in the particle product precipitator part and between the nozzle and the coil preheater parts. After the particle precipitation process was finished, the washing process employing SCCO₂ with the solvent mixtures (ethanol:acetone with a volume ratio of 1:1) was frequently performed to sustain the supercritical state and to avoid the condensation of the liquid phase. 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**Analytical Methods.** A scanning electron microscope (SEM; S-4300, Hitachi, Japan) was employed to characterize and to inspect the collected particle products’ morphologies, and the image analyzer software ImageJ 1.42 was used to determine the diameters of these collected particle products. A Spectrum Two Fourier transform infrared (FTIR) spectrophotometer (PerkinElmer Ltd., Buckinghamshire, England) was also employed to characterize the collected particle products. The collected particle product dissolution was inspected using a UV–vis spectrophotometer (UV–vis Genesys 10S, Thermo Fisher Scientific, Waltham, MA).

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