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ARTICLE

Preparation of Curcumin Sub-micrometer Dispersions by High-Pressure Homogenization

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High-pressure homogenization (HPH) processing has been used to increase the water dispersity of curcumin, a popular spice and coloring and antioxidant agent, which shows anti-inflammatory and anti-cancer properties but poor water solubility and oral bioavailability. The optimized HPH treatment was achieved at the combined conditions of temperature at 2 °C, pressure at 150 MPa, and 10 HPH cycles. The mechanism behind the improved water dispersity of curcumin by HPH treatment was interpreted as a result of the reduced curcumin particle sizes and crystallinity caused by mechanical stresses, which were verified by particle size measurements, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) results. Spray drying of maltodextrin (MD)-entrapped curcumin can also increase the water dispersity of curcumin. A combination of HPH treatment and spray drying using MD exhibits a faster curcumin dissolution while retaining a higher water dispersity of curcumin than curcumin prepared by either spray drying using MD alone or the combination of HPH and freeze-drying using MD, suggesting that the combination of HPH processing with spray drying would be an excellent processing method for curcumin-based functional food products.

KEYWORDS: Curcumin; high-pressure homogenization (HPH); crystal−amorphous transition; X-ray diffraction

INTRODUCTION

Curcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a natural polyphenolic phytochemical extracted from the powdered rhizomes of turmeric, with anti-oxidative, anti-inflammatory, anti-microbial, anti-parasitic, and anti-mutagen properties and anti-tumor abilities (*1*−*4*). Nevertheless, curcumin has low bioavailability through an oral intake route compared to direct absorption by the gastrointestinal tract. After oral administration, curcumin was poorly absorbed (*5*) and only trace amounts of curcumin compound appeared in blood (*6*), while most orally administered curcumin was excreted in the feces and urine after rapid metabolization in the intestine to form several reduced products (*7*). One of the causes of reduced bioavailability of curcumin is due to its poor solubility in water at either acidic or physiological pH, which makes curcumin hard to absorb (*8*). Together with membrane permeability, drug solubility is among the key determinants for oral bioavailability. Besides, the latest determinant is the rate-limiting step for absorption of drugs from the gastrointestinal tract.

Because many nutraceuticals (i.e., flavonoids and carotenoids) and an increasing number of newly developed drug candidates present poor water solubility, approaches to improve their water solubility/dispersity are of great importance in functional food and drug formulations (*9*). Biomacromolecules, including gelatin, alginate, and maltodextrin (MD), have been used to improve the water solubility, stability, and bioavailability of curcumin (*10*−*12*). Physical processing methods, which reduce particle size and generate an amorphous state, have been applied to improve the dispersity of curcumin powder particles (*13*). Making very fine nutraceutical particle suspension is also an alternative approach for *in vivo* administration of poorly soluble nutraceuticals. One important prerequisite for *in vivo* injection of suspensions is small particle size below 1 μm because large particles can lead to thrombosis when surpassing a critical administered dose. Besides, conventional milling techniques, such as jet mill or pearl mill, result in high polydispersity of products and, thus, require subsequent removal of microparticles or abrasion of pearls in a mill (*14*). However, the finished product is prohibited to contain toxical excipients or materials from the production equipment. High-pressure homogenization (HPH) is a highly recommended technique to reduce particle size efficiently with high reproducibility and to process highly concentrated suspension. This technique has been widely applied to create stable emulsion systems (*15*−*17*). The HPH technique enjoys various advantages, such as simplicity, high efficiency, and needlessness of organic solvents (*9*).

In this paper, we aim to use HPH to reduce the particle size of curcumin, with a goal to improve its water solubility/dispersity and bioavailability. Processing parameters, such as temperature, pressure, and the number of processing cycles, have been optimized to achieve the optimized processing conditions for the formation of curcumin sub-micrometer dispersions. Curcumin powders prepared by a combination of HPH and the

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spray-drying method have been proven to be able to produce curcumin sub-micrometer dispersions with a high water dispersity and fast dissolution rate.

MATERIALS AND METHODS

Materials. Curcumin (85% pure, with 11% demethoxycurcumin and 4% bisdemethoxycurcumin as impurities) was obtained from Sabinsa Corporation (Piscataway, NJ) and used without further purification. MD (MaltrinM100, Lot M0808130) was purchased from Grain Processing Corporation (Muscatine, IA). Milli-Q water (18.3 MΩ) was used in all experiments.

HPH Processing. Curcumin suspensions in water (1%) were subjected to premilling treatments to reduce curcumin particle sizes to the micrometer range according to Möschwitzer's method by high-speed homogenization (High-speed homogenizer, ULTRA-TURRAX T-25 basic, IKA Works, Inc., Willmington, NC) for 5 min (*18*). HPH cannot be applied directly to suspended powders because they may clog the valve of the homogenizer. After filtration (5 μm mesh), the curcumin suspensions were further homogenized by a high-pressure homogenizer (EmulsiFlex-C3, Avestin, Inc., Ottawa, Ontario, Canada) at pressure levels ranging from 50 to 200 MPa and for up to 40 HPH cycles. Inlet, operation, and outlet temperatures were controlled by cooling or heating the inlet reservoir and the homogenization valve, while a heat exchanger was equipped to rapidly cool the processed fluids, which exhibited a temperature increase rate of 0.2 °C/MPa because of viscous heating during the homogenization step.

Spray Drying. Curcumin powder was retrieved by the spray-drying technique with Yamato Pulvis Mini-Spray GA32 (Yamato Scientific Co., Ltd., Tokyo, Japan). Curcumin suspensions were passed at a spray rate of 4 mL/min, with drying and outlet temperatures fixed at 200 and 120 °C, respectively. Dry air flow was set at 800 L/h, and the atomization pressure was set at 1.5 bar. MD with a final concentration of 30% (w/w) in the whole matrix was used as the carrier for curcumin.

Particle Size Measurements. Particle sizes of curcumin dispersions were determined by a photon correlation spectroscopy (PCS)-based BIC 90 plus particle size analyzer equipped with a Brookhaven BI-9000AT digital correlator (Brookhaven Instrument Corporation, New York, NY). The light source of the particle size analyzer is a solid-state laser operating at 658 nm with 30 mW power, and the signals were detected by a high-sensitivity avalanche photodiode detector. All measurements were made at a fixed scattering angle of 90° and temperature of 25.0 ± 0.1 °C. The mean diameter or z diameter was determined by Cumulant analysis of the intensity−intensity autocorrelation function, $G(q,t)$ (*19*).

Solubility/Dispersity Test. Saturation solubility/dispersity was measured through ultraviolet/visible (UV/vis) absorbance determination at 420 nm using a Cary Eclipse UV/vis spectrophotometer with a 1 cm optical path length. A total of 50 mL of curcumin suspensions (initial curcumin solid content is 1%, w/w), prepared from curcumin in powder state, were centrifuged for 10 min at 5000 rpm prior to analysis. It should be mentioned that the presence of residual fine solid particles, if not sedimented by the centrifugation method applied, may affect the UV/vis measurement. Nevertheless, particle size measurements after centrifugation showed that the mean sizes of residual solid particles dispersed in the liquid were always around 200 nm and never larger than 300 nm, with a relatively narrow distribution (polydispersity index of ~0.25) for all tested samples (at different pressures of treatment and a different number of cycles). On the basis of these considerations, the UV/vis measurement performed can be reasonably considered indicative of the curcumin concentration. At 25 °C, curcumin shows a water dispersity of 0.6 mg/L. It should be clarified that the initial curcumin solid content is not the same as the final curcumin concentration in water.

Dissolution Rate Measurements. The dissolution rate shows how fast dried particles re-disperse into sub-micrometer suspensions upon rehydration. Dried powder of MD-entrapped curcumin was prepared for dissolution experiment with a typical formulation of 0.5 g of powder in 5 mL of distilled water. The samples held in independent flasks were agitated at 140 rpm on an orbital shaker for different periods. At definite times, a flask was collected from the shaker and the content was filtered and assayed through UV/vis absorbance determination at 450 nm.

Atomic Force Microscopy (AFM). An image of curcumin nanoparticles was collected using commercial Nanoscope IIIa Multi-Mode AFM (Veeco Instruments, Goleta, CA) equipped with a J scanner, which was operated in tapping mode using a silicon cantilever. The curcumin sub-micrometer dispersion sample for AFM imaging was prepared by treating the mixture of 1% curcumin in water with a 10-cycle HPH at 150 MPa. A drop of curcumin sub-micrometer dispersion was deposited on a precleaned silicon wafer surface and evaporated naturally.

Differential Scanning Calorimetry (DSC) Measurements. Thermal properties of HPH-treated curcumin powder, obtained by spray drying using MD as a carrier, were investigated in comparison to the thermal properties of pure curcumin powder, with DSC (model 823, Mettler-Toledo Instruments, Columbus, OH). Powder samples were placed in perforated aluminum sealed pans at an amount of 5−10 mg. The thermal analyses were performed by a two-cycle model, with a temperature scanning range from 25 to 225 °C and a heating rate of 10 °C/min. Nitrogen was used as blanket gas. The first heating cycle was used to remove the thermal history of the samples. Therefore, only thermographs from the second heating cycle were used in this paper. The melting temperature of curcumin was recorded as the maximum peak temperature in the second heating process.

X-ray Diffraction (XRD) Measurements. XRD patterns of HPH-treated curcumin powder, obtained by spray drying using MD as a carrier, in comparison to pure curcumin powder, were collected by an X-ray diffractometer equipped with a Bruker HiStar multiwire area detector at diffraction angle 2θ and rotating anode X-ray generator. The wide-angle X-ray scattering (WAXS) patterns of curcumin prepared by two different methods were obtained using a Bruker HiStar area detector and an Enraf-Nonius FR571 rotating anode X-ray generator equipped with a graphite monochromator (Cu Kα; λ = 1.5418 Å) operating at 40 kV and 50 mA. All of the data were collected from fine powder placed on the slightly oiled outer surface of a 0.2 mm special glass capillary at room temperature. The sample−detector distance was 8.9 cm, and the standard spatial calibration was performed at that distance. Scans were 5° wide in ω [$-95° < \omega < -90°$] with a fixed detector or Bragg angle (2θ) of 27° and fixed χ angle of 45° and freely spinning Φ angle. Data were collected for 300 s, and the count rate for the area detector did not exceed 100 000 cps. Background-subtracted integration of the frame image in χ [$-120° < \chi < -80°$, bin-normalized, 0.01 step size] is processed for the final data.

RESULTS AND DISCUSSION

Effect of Processing Conditions on the Sizes of Curcumin Sub-micrometer Dispersions. The energy delivered by HPH into the curcumin system, which is directly proportional to the homogenization pressure and the number of homogenization cycles, results in a decrease of mean particle sizes of curcumin. Simultaneously, the reduction of the particle size caused an increase of the water dispersity of curcumin. **Figure 1** shows the effect of the number of cycles on the mean particle sizes of curcurmin suspensions, polydispersity, and water dispersity of curcumin at a fixed operating pressure of 150 MPa and 25 °C inlet temperature. The mean particle sizes of curcumin crystals exhibited a significant reduction from the starting value of approximately 2000 to less than 1000 nm after only 3 cycles. In the following cycles, the reduction rate decreased, and after the tenth pass, the z diameter reached a plateau with a 600 nm value. Polydispersity with a low initial value (0.2) increases during the first pass because not all curcumin particles underwent the dramatic size reduction in a single pass. Polydispersity of curcumin dispersions reached a steady value of 0.3 after 10 cycles, indicating that HPH-treated curcumin had a stable and narrow particle size distribution.

Meanwhile, HPH processing after 10 cycles could still influence the water dispersity of curcumin. HPH-treated curcumin exhibited a measurable increasing trend in the curcumin concentration even after 40 cycles of HPH. In the first 10 cycles, corresponding to the measurable particle size reduction, the increasing rate of curcumin water dispersity is the highest. After 10 cycles of HPH,

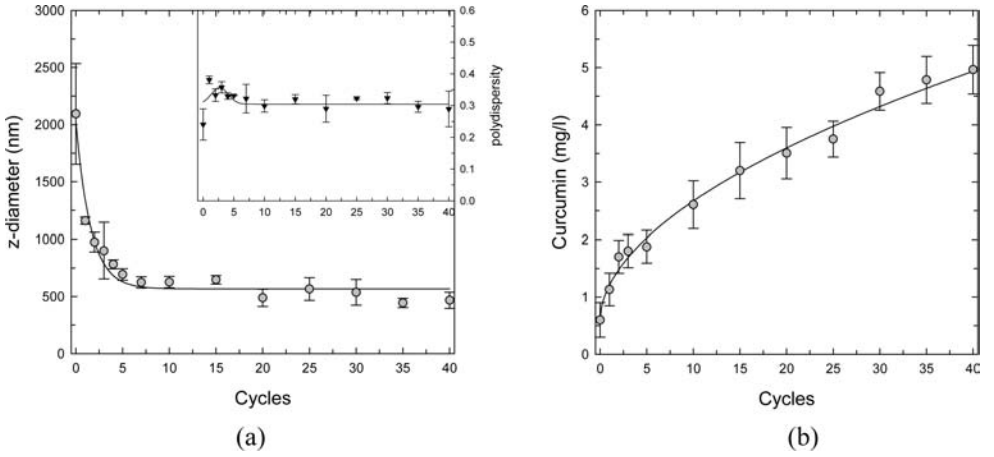

Figure 1. (Inset of a) Polydispersity index, (a) *z* average diameter, and (b) water dispersity of curcumin as a function of the number of HPH cycles. The HPH pressure and processing temperature were fixed at 150 MPa and 25 °C, respectively.

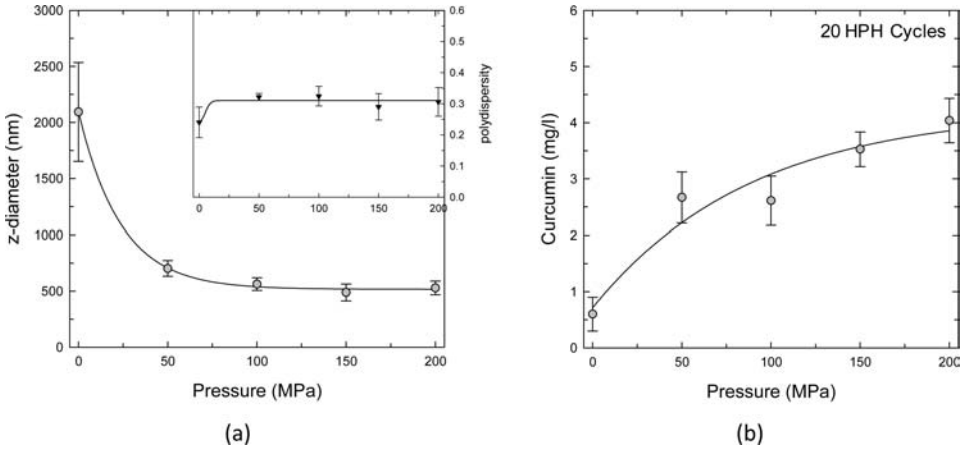

Figure 2. (Inset of a) Polydispersity index, (a) *z* average diameter, and (b) water dispersity of curcumin as a function of the HPH pressure. The number of HPH cycles and processing temperature were fixed at 20 cycles and 25 °C, respectively.

the increasing rate of the curcumin concentration reached a constant (**Figure 1b**), which might be correlated to a mechanism different from particle size reduction. It is worth noting that the water dispersity of HPH-treated curcumin is rather stable over time and no significant decrease of the curcumin water dispersity was observed after several days of storage.

Figure 2 shows the polydispersity, *z* diameter, and water dispersity of HPH-treated curcumin at different pressure levels for 20 cycles, with the inlet temperature fixed at 25 °C. In terms of mean particle size, for pressures up to 50 MPa, curcumin particle sizes were significantly reduced (i.e., from > 2000 to < 700 nm). A further increase of the pressure from 50 to 200 MPa caused only a slight reduction from less than 700 to around 500 nm. In accordance, the polydispersity index remained at a constant value of around 0.3, suggesting that 20 cycles at 50 MPa of HPH have already delivered enough energy for curcumin crystals to reach a maximum sustainable particle size reduction. The pressure difference tunes the energy input; thus, we observe that the curcumin particle size decreased as the applied pressure was increased. In terms of the water dispersity of curcumin versus HPH processing pressure curve, a linear regression was used to fit the raw data. The increasing rate of the water dispersity of curcumin at approximately 1 mg L^{-1} 100 MPa^{-1} was obtained from the slope of the curve.

In comparison to the homogenization pressure and the number of homogenization cycles, the processing temperature has a negligible effect on the particle size after 10 cycles at 150 MPa. However, the water dispersity of curcumin was affected by the processing temperature. As shown in **Figure 3**, no significant difference in mean particle size was observed when the processing temperature changed from 2 to 50 °C. In contrast, it was found that the water dispersity of curcumin was influenced by the temperature. Interestingly, the water dispersity of pure curcumin increased by about 50% when the temperature increased from 2 to 50 °C, which is in agreement with the results from Kurien and co-workers (*20*). The temperature increase has an opposite effect on the water dispersity of curcumin during HPH processing, with the highest water dispersity at a processing temperature of 2 °C (4.2 mg/L) and the lowest (2.8 mg/L) at 50 °C.

To further visualize the improved water dispersity of curcumin sub-micrometer dispersion after HPH, photographic pictures of curcumin treated by 10 cycles of HPH at 150 MPa as well as nontreated pure curcumin in water (insoluble part of curcumin was removed by centrifugation) were taken and presented in **Figure 4**. The nontreated curcumin water solution was nearly colorless (**Figure 4b**). In contrast, HPH-treated curcumin sub-micrometer dispersion afforded a yellowish liquid with no noticeable free curcumin powder (**Figure 4a**). Sub-micrometer-sized curcumin particles were confirmed by an AFM height image, as shown in **Figure 4c**. The AFM image suggested that most curcumin particles were mainly irregular-shaped, while some of them were sphere-like.

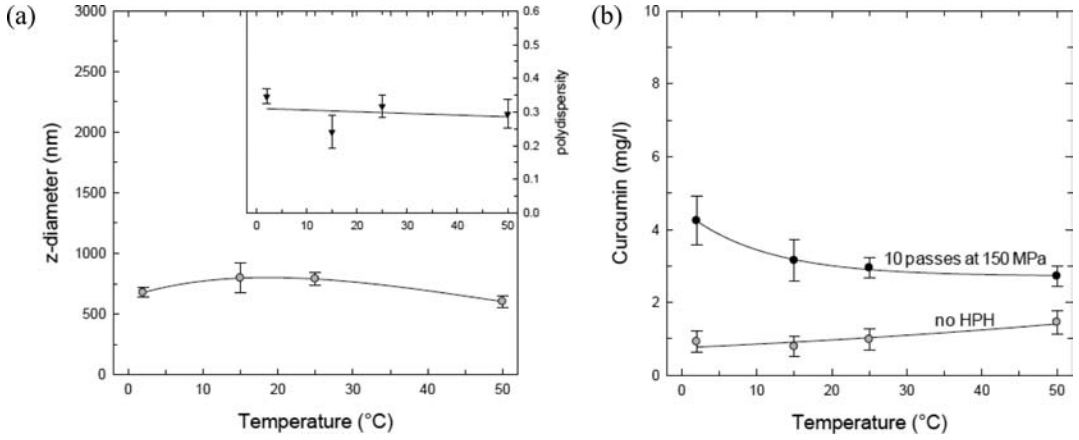

Figure 3. (Inset of a) Polydispersity index, (a) *z* average diameter, and (b) water dispersity of curcumin as a function of the HPH processing temperature. The number of HPH cycles and processing pressure were fixed at 20 cycles and 150 MPa, respectively.

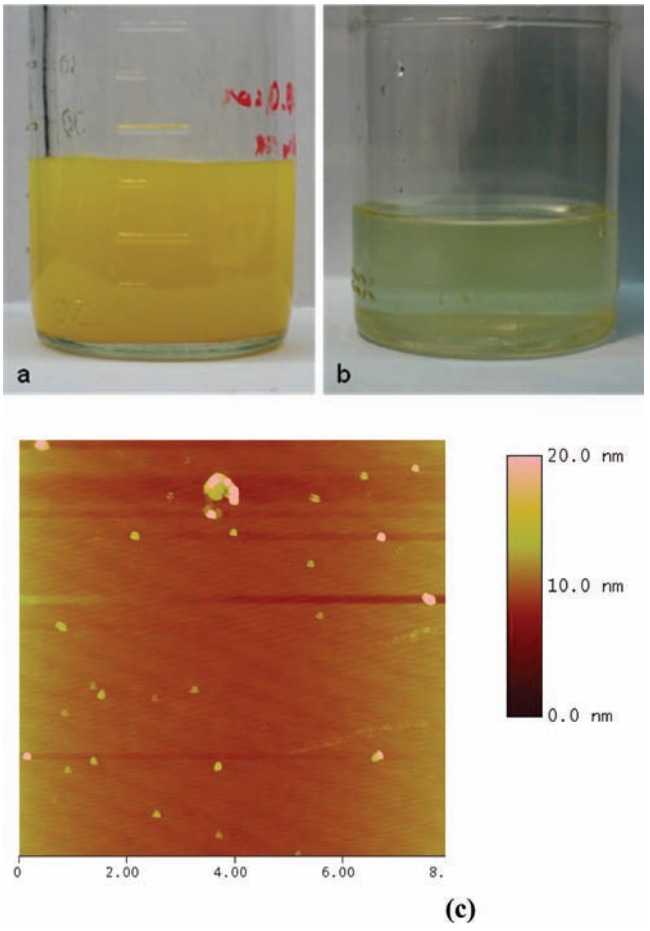

Figure 4. Photographic pictures of (a) curcumin treated with HPH at 150 MPa for 10 cycles and (b) nontreated curcumin, as well as (c) AFM height image of HPH-treated curcumin nanodispersion deposited on a precleaned silicon surface.

For some soft drug crystals with high melting temperatures, the temperature increase contributes to their dispersion and solubility. The temperature of the fluids increases from the inlet initial value close to its melting temperature when they pass through the homogenization valve (about 20 °C/100 MPa). Thus, the increase of inlet or operation temperature promotes the dissolution of a drug. Nevertheless, for curcumin crystals with a high melting temperature (about 180 °C), water dispersity decreased with the increase of the temperature during HPH processing. This phenomenon is probably due to the relatively high rigidity and elasticity of crystals at low temperature compared to crystals at high temperature. The rigid nature of crystals at low temperature decreases the critical stress required to propagate a crack or cause a phase transition in the stress field generated by HPH. The above results give us an optimal HPH condition for curcumin crystals, including a temperature at 2 °C, pressure at 150 MPa, and 10 cycles. This optimized processing condition maximized the overall performance of curcumin powder with balanced water dispersity improvement and energy consumption.

In general, water dispersity of a particle increases with a decrease of the particle size because it causes a linear increase of the specific surface area, which is in an inverse relationship with the particle diameter. In **Figure 1**, the water dispersity of curcumin is dependent upon the mean particle size only during the first 10 cycles. After 10 cycles, the mean particle size remains constant at around 600 nm, while the water dispersity continues to increase the severity of the treatment, e.g., number of cycles (**Figure 1**), pressure level (**Figure 2**), and decrease in the temperature (**Figure 3**). The decrease of the particle size can be explained by the Ostwarld−Freundlich theory for curcumin dispersion as described by Müller et al. (*14*). The water dispersity increase is linearly dependent upon the interfacial tension and molar volume of the particle material but inversely proportional to the absolute temperature, density, and solid dimension. Hence, size reduction not only increases water dispersity but also increases interfacial energy, defined as the interfacial tension times the interfacial area, by raising the interfacial area, during which the transition among different polymorphic forms occurs. In particular, the delivery of higher energy to the curcumin system caused more transitions from the crystal to amorphous phase during HPH processing, which can be used to explain the water dispersity increase of curcumin.

Thermal Properties and Structure of Curcumin before and after HPH Treatment. Figure 5 exhibits the thermograms of pure curcumin and HPH-treated and spray-dried curcumin with scanning temperatures ranging from 25 to 225 °C. For pure curcumin, a single well-defined peak at ~180 °C corresponds to the melting of the curcumin crystal. In contrast, HPH-treated curcumin showed multiple peaks. The first peak, observed at 30 °C, and the second broad and wide peak, centered at around 120 °C, can be attributed to the MD glass transition and to the disruption of hydrogen bonds with water, as previously observed by different authors (*21*, *22*). The third peak that can be observed in the DSC profile was located at 180 °C, which corresponded to

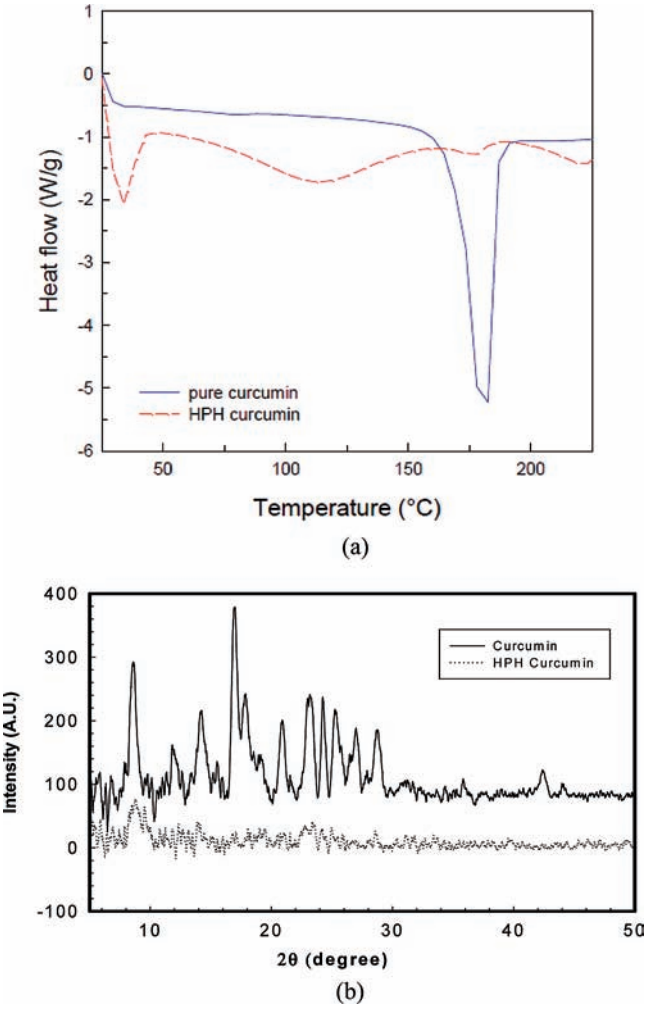

Figure 5. (a) DSC thermograms and (b) XRD results of pure curcumin and curcumin treated with HPH at 150 MPa for 10 cycles.

the melting peak of original curcumin, suggesting the preservation of at least a part of the crystal structure of the original curcumin.

The XRD patterns of pure curcumin and HPH-treated curcumin were shown in **Figure 5b**. The characteristic peaks of pure curcumin appeared at a series of diffraction angles 2θ at 8.43°, 11.76°, 14.14°, 16.91°, 17.87°, 20.80°, 23.10°, 24.21°, 25.24°, 26.98°, 27.86°, and 28.65°, which indicates that pure curcumin is in a highly crystalline form. Similar XRD patterns of curcumin can be found in the Cambridge Structure Database. Among the XRD patterns of curcumins performed by different groups, our XRD pattern results are greatly in agreement with the results of Ishigami et al. (*23*). In comparison to the XRD curve of pure curcumin, the majority of Bragg peaks disappeared for HPH-treated curcumin, which suggested that HPH processing could partly break down the crystalline structure of curcumin and turn the curcumin crystalline phase into the amorphous phase. However, small peaks located at 7−9°, 22−24°, and 28° in the XRD curve of HPH-treated curcumin indicated that a small amount of curcumin crystals may still coexist with the large amorphous domain of HPH-treated curcumin, in agreement with DSC thermograms.

Dissolution Rate. The powder of HPH-treated curcumin (treated with 150 MPa and 10 cycles at 25 °C) was obtained by the spray-drying technique. The obtained powder is convenient for handling and storage and is ready for redispersion in water. Dissolution rates were measured under gentle agitation

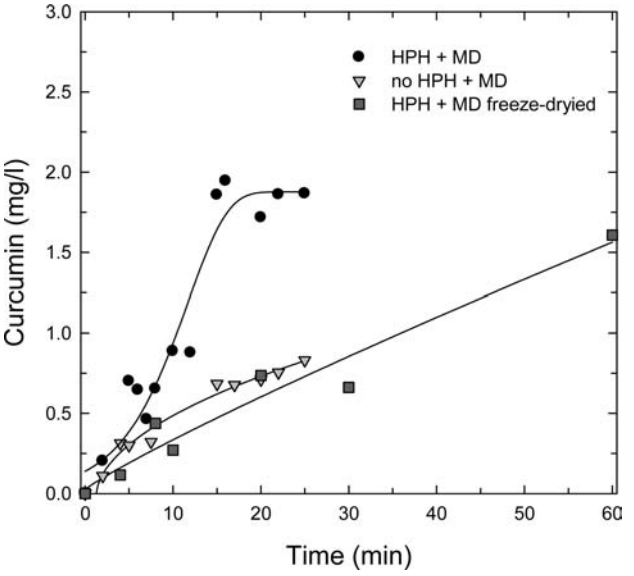

Figure 6. Dissolution of curcumin powders in water as a function of the agitation time: (●) powder of HPH-treated curcumin spray-dried with MD, (▼) powder of nontreated curcumin spray-dried with MD, and (■) powder of HPH-treated curcumin freeze-dried with MD. HPH was carried at 150 MPa and 10 cycles.

for spray-dried pure curcumin and HPH curcumin and compared to freeze-dried HPH-treated curcumin. MD, which accounted for 30% in the curcumin suspension, was used as a carrier material to acquire the curcumin suspension. **Figure 6** shows the plot of the water dispersity of curcumin as a function of the agitation time. The dissolution times (time to reach the concentration plateau) for spray-dried HPH curcumin and pure curcumin were nearly the same within a 10 min period under the same experimental conditions. However, the final curcumin concentration obtained is obviously lower for unprocessed curcumin. On the other hand, it takes a significantly longer time for freeze-dried HPH-treated curcumin to become fully dissolved. Even after 60 min, the freeze-dried curcumin sample still did not reach full dissolution. The faster dissolution rate of spray-dried samples can be attributed to the more porous structure of the spray-dried powder. In contrast, freeze-dried curcumin was entrapped in a vitreous structure, which is more impervious to water. The effect of spray drying on water dispersity can be evaluated by comparing the final values of water dispersity after complete powder dissolution to the dispersity of the original curcumin dispersion. For the HPH-treated sample, spray drying causes a certain reduction of water dispersity, from 2.5 to about 1.8 mg/L, probably because of particle coalescence induced by heat. Instead, for untreated curcumin, spray drying resulted in a slight increase of dispersity, from 0.6 to 0.8 mg/L. The effect of spray drying on the increasing water dispersity of curcumin can be ascribed to the reduced crystallinity of the curcumin powder through the incorporation of MDs (*24*). Nevertheless, the temperature effect is minor compared to HPH treatment, and HPH processing is still necessary to obtain readily dispersible curcumin powders with high water dispersity.

In summary, HPH was used to increase the water dispersity of curcumin crystals, by producing a very fine suspension in the nanometric range (about 600 nm) and promoting the transition from the crystalline phase to the amorphous phase. We optimized the HPH processing condition for curcumin crystals after examining effects of the temperature, homogenization pressure, and number of HPH cycles on the particle size and water dispersity of

curcumin. The optimal HPH condition for curcumin crystals involves a temperature at 2 °C and 10 HPH cycles at the homogenization pressure of 150 MPa. The water dispersity of curcumin was increased 10 times with respect to the untreated curcumin. The increased water dispersity was attributed to particle size reduction as well as the decrease in overall crystallinity of the final sample, both generated by the mechanical stress on curcumin crystals because of the treatment of HPH. Spray-drying treatment for MD-entrapped curcumin could also decrease the particle size of curcumin. However, it made less contribution to the particle size decrease and water dispersity increase of curcumin than HPH treatment. HPH has been proven to be a mature method to create readily dispersible curcumin powders with high water dispersity, which is of vital importance for the enhancement of the oral bioavailability of curcumin.

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