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On enhancing the solubility of curcumin by microencapsulation in whey protein isolate via spray drying

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ABSTRACT

The encapsulation of curcumin in whey protein microparticles by spray drying was done to improve solubility and thus, the bioavailability of curcumin. In solution, curcumin formed soluble complexes with whey protein isolate (WPI) via hydrophobic interactions and its solubility increased linearly with WPI concentrations. Solutions of WPI-curcumin complexes were spray-dried as uniform microparticles via a microfluidic jet spray dryer. Nearly 100% curcumin was retained in amorphous state and the microparticles could be easily rehydrated as transparent dispersions irrespective of the drying temperature. Antioxidant properties of these microparticles were studied by DPPH test, showing a higher DPPH radical scavenging activity for curcumin-loaded microparticles compared to that of WPI particles as benchmark. The ability to generate easily dissolved powders containing water-insoluble ingredients such as curcumin is a beneficial approach for pharmaceutical and functional foods applications.

1. Introduction

As a natural polyphenolic compound extracted from the rhizome of the herb *Curcuma longa* (Anand et al., 2007), curcumin has been reported to possess numerous biological and pharmacological properties, such as anti-tumour, anti-inflammatory, antioxidant and other desirable medicinal benefits (Srimal and Dhawan, 1973; Ruby et al., 1995). Its non-toxic nature has also been proven by several clinical trials, showing that curcumin is safe even at high doses (up to 8 g/day for 3 months) (Cheng et al., 2001). Due to these merits, curcumin has been considered as the third generation of cancer chemopreventive agent by the National Cancer Institute of America (Lin et al., 2009). However, due to its extremely low water solubility at acidic or neutral pH and the resulting low bioavailability, the application of curcumin in health-related products has been largely limited (Yan et al., 2011).

The technique of microencapsulation has been widely used to increase the efficacy of bioactive ingredients, such as fish oils (Pourashouri et al., 2014), polyphenols (Zheng et al., 2011), and natural colourants (Rajabi et al., 2015). An important step in microencapsulation process is the selection of a suitable wall material depending on properties of the bioactive ingredients, desired characteristics of the final products, and the microencapsulation methods (Jafari et al., 2008). Due to the excellent solubility, film forming and emulsification properties, food proteins like soy proteins and milk proteins are attracting increasing attention for use as wall materials to fabricate various delivery vehicles for bioactive ingredients (Jafari et al., 2008; Thongkaew et al., 2014; Faridi et al., 2015). Milk proteins are chemically and structurally versatile biopolymers that are categorized into two main groups: caseins and whey proteins (Tavares et al., 2014). In milk, caseins present in the form of highly hydrated colloidal particles which are known as casein micelles and the presence of hydrophobic and hydrophilic amino acids makes caseins excellent copolymers feasible for encapsulation of hydrophobic compounds. It has been reported that curcumin displayed significantly enhanced dispersibility and bioactivity after the incorporation in casein micelles (Pan et al., 2013, 2014). The ability of whey proteins to bind various hydrophobic and amphiphilic compounds such as flavour compounds, fatty acids, and vitamins has also been widely reported (Zhang and Zhong, 2012; Flores et al., 2014). Properties such as solubility and photo-stability of several bioactive ingredients were reported to improve after binding with whey proteins. The interactions

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between curcumin and β-lactoglobulin (one of the major components of WPI) in aqueous solution have been reported before (Sneharani et al., 2010; Li et al., 2013). However to the best of our knowledge, the encapsulation of curcumin using whey proteins, particularly in a dry powder form, and the resulting functional properties have never been reported before.

Here the use of whey proteins as a carrier for curcumin to enhance its aqueous solubility, produced via spray drying, were demonstrated by generating curcumin-loaded WPI microparticles. The effects of drying conditions on properties and functionalities of microparticles were investigated in terms of particle size, morphology, crystallinity, curcumin retention rate, and antioxidant activity. The study helped to improve the current understanding of interactions between water-insoluble components such as curcumin and whey proteins. The knowledge would lead to the design of better delivery systems for bioactive ingredients by spray drying.

2. Materials and methods

2.1. Materials

Curcumin (≥94% curcuminoid content, ≥80% curcumin) and 2, 2-diphenyl-1-picrylhydrazyl (DPPH) were purchased from Sigma–Aldrich (Australia). Whey protein isolate (WPI) with 92.5% protein content on dry basis was supplied by Mullins Whey Inc. (USA). Absolute ethanol of analytical grade was from Merck (Australia). Deionized water (Milli-Q) was used for all precursor preparation.

2.2. Curcumin saturation studies in WPI solutions

The ability of WPI to solubilize curcumin in an aqueous solution was evaluated by measuring curcumin concentrations in curcumin-saturated solutions with varying amounts of WPI (1–10 wt%). Curcumin (25 mg) was added to 100 mL WPI aqueous solution and homogenised at 1000 rpm for 5 min to disperse curcumin into the solution (Wise Mix Homogenizer, Daihan Scientific HG-15D). The solution was then stirred overnight at room temperature in the dark, followed by centrifugation (5000 rpm, 10 min) to remove the free curcumin. The amount of curcumin in the supernatant was quantified based on calibrations made with known amounts of curcumin loaded into 0.1 wt% WPI.

2.3. Binding of curcumin with WPI

The binding between curcumin and WPI was characterized by UV–visible and fluorescence spectroscopy using a microplate reader (SpectraMax M2e, Molecular devices, USA). The UV–visible spectra of WPI solutions containing different amounts of curcumin were acquired between 200 and 600 nm. The fluorescence of curcumin was measured by fixing its concentration at 20 μM and varying the concentration of WPI from 0 to 5 mg/mL. The emission spectra were recorded from 450 to 700 nm with an excitation wavelength of 420 nm. Protein intrinsic fluorescence was measured at a constant WPI concentration of 1 mg/mL in the presence of 0–20 μM curcumin concentration. The emission spectra were recorded from 300 to 450 nm at an excitation wavelength of 280 nm.

2.4. Spray drying of WPI-curcumin complexes

WPI solutions at the concentration of 5 wt% with saturated amounts of curcumin (59.5 ± 2.7 μg/mL) were spray dried by a microfluidic jet spray dryer (Wu et al., 2011a). Monodisperse droplets were generated from the precursor solution by a microfluidic aerosol nozzle system, with an orifice diameter of 75 μm. The liquid flow rate and applied disturbance frequency were adjusted to best achieve monodisperse droplet formation (Wu et al., 2011b). The obtained monodisperse droplets were well dispersed and dried at a specific drying temperature. Inlet temperatures of 150 °C and 110 °C were used to investigate the influence of drying temperature on properties of the produced microparticles.

2.5. Characterization of spray dried WPI-curcumin microparticles

Morphologies of the spray dried microparticles were observed by a field-emission scanning electron microscopy (FE-SEM, JEOL 7001F, Japan). For particle size analysis, images of spray dried microparticles were recorded by light microscopy (Motic B1-223A, UK) and analysed using the software package Motic Images Plus 2.0ML and ImageJ. The average particle size ($\bar{d}$) was defined as $\bar{d} = \sum_{i=1}^{n} \frac{d_i}{N}$ and the standard deviation of particle size was described as $SD = \sqrt{\frac{\sum (d_i - \bar{d})^2}{(N-1)}}$, where d_i was the diameter of the i-th particle, N was the total number of particles counted. At least 500 particles were measured and analysed for each sample. Powder X-ray diffraction (XRD) patterns of raw curcumin and spray dried WPI-curcumin microparticles were collected using a Rigaku Miniflex 600 X-ray diffractometer with Ni-filtered Cu Kα radiation (λ = 1.5406 Å). The tube voltage and amperage were set at 40 kV and 25 mA. Each sample was scanned between 5 and 40 °C in 2θ with a step size of 0.02 °C. The amount of curcumin retained in the microparticles was determined by dissolving an accurately weighed amount of microparticles in 10 mL of 0.1 N HCl solution. After dissolving the particles, the solutions were centrifuged for 5 min at 5000 rpm, and the amount of curcumin in the supernatant was determined using the microplate reader at 425 nm. Each sample measurement was performed in triplicate. The curcumin encapsulation efficiencies of WPI solution used for spray drying and the spray dried powder were calculated according to the following formula based on the amount of curcumin encapsulated in the solution/powder and the amount of curcumin added in the WPI solution for the preparation of curcumin saturated solution:

$$\textit{Curcumin encapsulation efficiency}(\%) = \frac{\textit{Amount of curcumin encapsulated}}{\textit{Total amount of curcumin added}} \times 100$$

The curcumin retention rate was calculated according to the following formula based on dry matter measurements:

$$\textit{Curcumin retention rate}(\%) = \frac{\textit{Curcumin in spray dried powder}(mg/g)}{\textit{Curcumin in feed solution}(mg/g)} \times 100$$

2.6. DPPH radical scavenging activity

DPPH scavenging activity was evaluated using a modified method according to a previous study (Yen et al., 2010). In brief, samples were dissolved in 0.1 N HCl solutions to obtain a

concentration of 0–10 mg/mL. Then, 1 mL of the sample solution was mixed with 2 mL 0.2 mM DPPH ethanol solution and subsequently incubated at room temperature in the dark for 30 min. The resulting solution was centrifuged at 5000 rpm for 5 min and the absorbance was measured at 517 nm using a microplate reader. The solution without any sample was used as the control. All tests were done in triplicate. The free radical scavenging activity of the sample was calculated according to the formula below:

$$\textit{Radical scavenging activity}(\%) = \frac{\textit{OD of control} - \textit{OD of sample}}{\textit{OD of control}} \times 100$$

3. Results and discussion

3.1. Curcumin saturation studies

A critical factor limiting the application of curcumin is its extremely low water solubility, which is reported to be around 11 ng/mL (Kaminaga et al., 2003). As shown in Fig. 1, only a very limited amount of curcumin could be dissolved in water and the curcumin-saturated solution did not show any noticeable colour change from water. The ability of WPI to promote the dissolution of curcumin was evaluated by measuring the curcumin saturation concentration in solutions with varying amounts of WPI. It was found that the curcumin saturation points linearly increased with WPI concentrations within the investigated range, with an upper limit of 124.9 ± 4.8 μg/mL curcumin dissolved in 10 wt% WPI solution. The enhanced solubility of curcumin in the presence of WPI might be attributed to the formation of soluble complexes with WPI. The possible interaction between curcumin and WPI was discussed in the next section.

3.2. Interaction between curcumin and WPI

UV–visible absorption spectroscopy and fluorescence spectroscopy were employed to investigate possible interactions between WPI and curcumin, as well as the formation mechanism of soluble complexes. UV–visible absorption spectroscopy could provide information about protein structural changes caused by complexation or reaction with other compounds (Zhang and Zhong, 2012). The UV–visible absorption spectra of WPI solutions

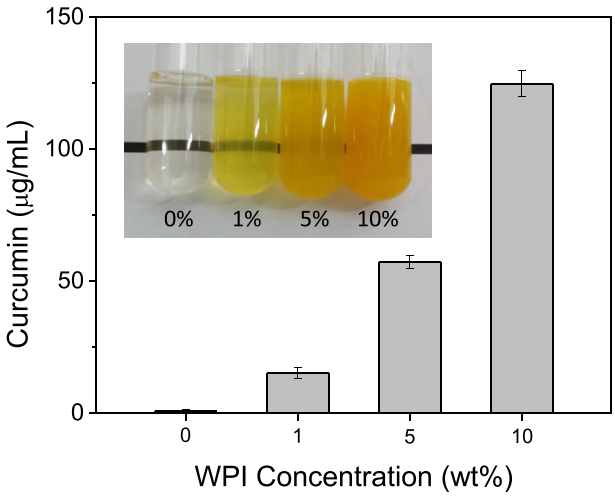

Fig. 1. Solubility of curcumin in WPI solutions of different concentrations (inset: appearance of curcumin-saturated WPI solutions).

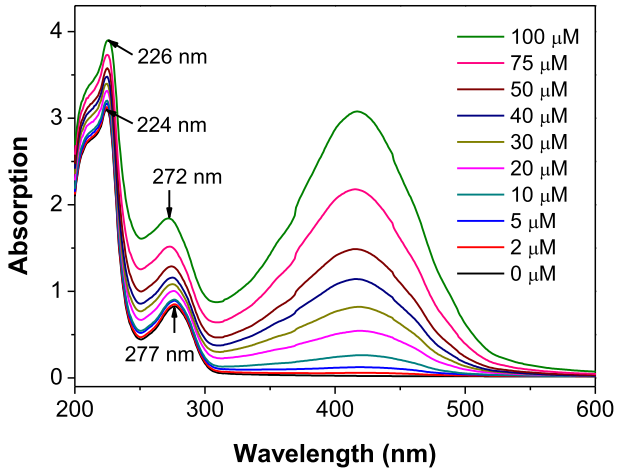

Fig. 2. UV–visible absorption spectra of WPI solutions (1.0 mg/mL) containing different amounts of curcumin (0–100 μM).

containing 0–100 μM curcumin were shown in Fig. 2. Prior to the addition of curcumin, the absorption spectrum of WPI solution displayed a strong peak at 224 nm and another peak centred at 277 nm. The 224 nm peak is characteristic of the peptide bones, while the 277 nm peak is related to the aromatic amino acids in proteins (Frederix et al., 2003). Upon the addition of curcumin, the absorbance intensity of WPI was intensified as curcumin increased, accompanied with a slight red shift of the 224 nm peak and a blue shift of the 277 nm peak. The above observations indicated that the interaction between curcumin and WPI led to changes in the microenvironment around the protein and also in the protein tertiary structure, e.g. increased polarity around the tyrosine and tryptophan residues and more extended peptide strands in the protein (Aitken and Learmonth, 2009; Zhang and Zhong, 2012; Rub et al., 2014).

Fluorescence spectroscopy is a useful approach to study the interactions between ligands and proteins, since the fluorophore is sensitive to the polarity of its surrounding environment (Liang et al., 2007; Tang et al., 2008). The fluorescence emission spectra of curcumin solutions in the presence of different amounts of WPI were displayed in Fig. 3A. It was observed that curcumin displayed a low-intensity broad peak at around 540 nm when it was excited at 420 nm in the absence of WPI. Addition of a small amount of WPI led to a sharp increase in the fluorescence intensity and the emission peak shifted to around 505 nm. Further enhancement of fluorescence intensity and a blue shift of the emission peak were observed as the WPI concentration increased, suggesting that curcumin was transferred from a polar to a less polar environment by binding to the hydrophobic domain of protein molecules (Li et al., 2013).

Since all the major components of WPI contain tryptophan or tyrosine residues which possess intrinsic fluorescence, fluorescence quenching of the protein was further studied at different curcumin concentrations to estimate the accessibility of curcumin to fluorophore groups of WPI (Zhang and Zhong, 2012). As shown in Fig. 3B, WPI demonstrated a strong fluorescence emission with a peak at around 330 nm upon excitation at 280 nm. The fluorescence intensity of WPI gradually decreased with more curcumin added, suggesting that curcumin was able to bind the tryptophan or tyrosine residues in the protein. However, it would be difficult to estimate the exact binding position of curcumin molecules since WPI consists of a mixture of proteins (Tapal and Tiku, 2012). The fluorescence quenching of WPI by curcumin might be caused by both dynamic and the static quenching. It is known that dynamic

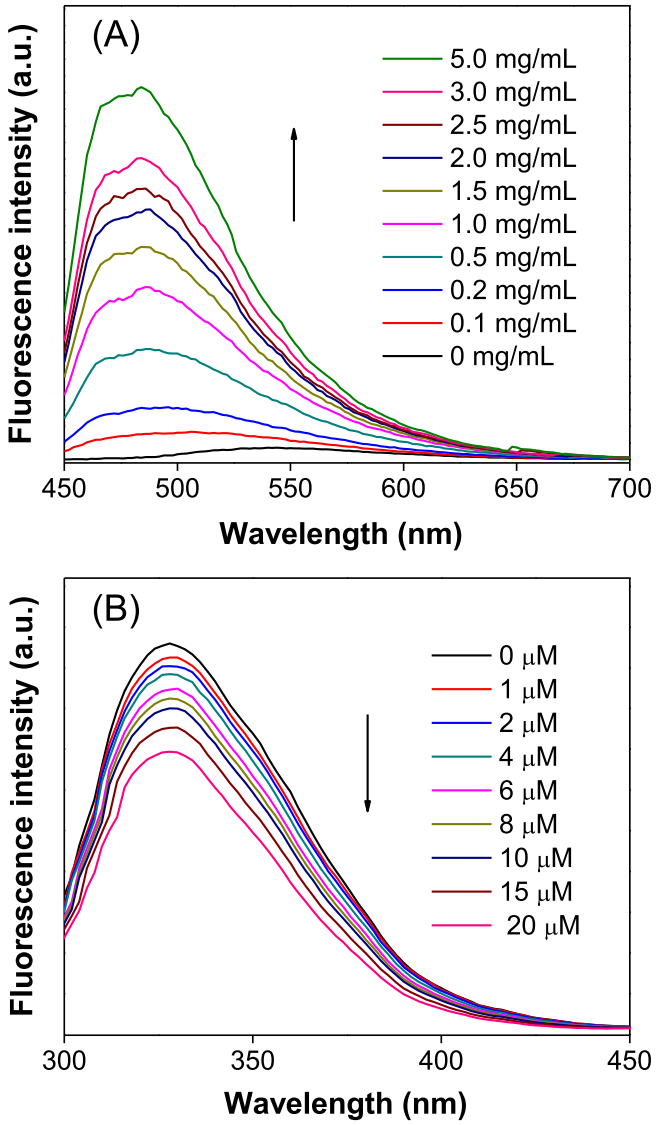

Fig. 3. (A) Fluorescence emission spectra of 20 μM curcumin solution at the excitation wavelength of 420 nm in the presence of WPI at different concentrations (0–5.0 mg/mL); (B) Fluorescence emission spectra of 1.0 mg/mL WPI solution at the excitation wavelength of 280 nm in the presence of curcumin at different concentrations (0–20 μM).

quenching is due to the collision between a fluorophore and a quencher during the lifetime of the excited state, while static quenching is caused by the formation of complexes at the group state (Zhang and Zhong, 2013). Since dynamic quenching does not change the UV spectrum of protein, the changes in UV–visible absorption spectra of protein after the binding of curcumin (Fig. 2) confirmed that the main mechanism of quenching is a static quenching process due to the complexes' formation (Sahoo et al., 2009; Rub et al., 2014).

The results from UV–visible absorption spectroscopy and fluorescence spectroscopy confirmed that the enhanced solubility of curcumin was due to the formation of soluble complexes with WPI, which increased with the amount of WPI in solutions. The complexes were formed via hydrophobic interactions with curcumin binding to the hydrophobic domains of protein molecules (especially the aromatic amino acid residues) and quenching the intrinsic fluorescence of WPI upon binding.

3.3. Properties of spray dried WPI-curcumin microparticles

The original WPI and curcumin powders were shown in Fig. 4A and B. Solutions of the WPI-curcumin complexes were spray dried at different inlet temperatures to investigate the effects of drying conditions on properties and functionality of the microparticles. Uniform microparticles (size and morphology) were formed using the microfluidic dryer (Fig. 4C and D). For the temperature range investigated here, the microparticles from each batch generally exhibited pot-like shapes (round or slightly wrinkled). The possible mechanism for the formation of pot-like particle shape was given as below. The particle formation process during spray drying could be described by solvent evaporation and diffusion of solutes in the atomized droplet caused by the heat and mass transfers (Vehring, 2008; Liu et al., 2011). The solvent evaporation rate determined the time required for the droplet to dry, τ_d, while the diffusion rate of a solute controlled the time required for the solute to diffuse from the surface of the droplet to its centre, R^2/D_s, where R was the radius of the droplet and D_s was the diffusion coefficient of the solute. The relative significance of the solvent evaporation and solute diffusion during drying could be defined as a dimensionless Peclet number, $Pe = R^2/\tau_d\ D_s$, which critically determined the morphology of final dried microparticles (Tsapis et al., 2002; Hadinoto et al., 2007). In the scenario of $Pe > 1$ (*i.e.* solvent evaporation rate > solute diffusion rate), the solutes would have inadequate time to diffuse from the surface to the centre of the droplet, so that a shell was formed on the early drying stage. Upon further evaporation of the solvent from the core of the droplets, the shell might experience folding or bucking forming dried microparticles with pot-like shapes (Rizi et al., 2011; Liu et al., 2013). The slightly wrinkled surface of particles dried at higher inlet temperature (150 °C) indicated that the droplets experienced more extreme drying histories (such as earlier shell formation and faster solvent evaporation) thus the tendency to deform increased. The particle size produced at 150 °C and 110 °C were 111.2 ± 5.0 μm and 108.4 ± 3.8 μm (Table 1), respectively, suggesting that the inlet drying temperature had little effect on particle size in this case.

According to curcumin saturation results in Fig. 1, the estimated amount of curcumin loaded in the microparticles would be 1.19 ± 0.12 mg/g in dry weight. After spray drying, the curcumin content in microparticles obtained at 150 °C and 110 °C were 1.13 ± 0.17 mg/g and 1.16 ± 0.14 mg/g (Table 1), respectively. Based on the formula presented in section 2.5, curcumin retention rate of microparticles spray dried at 150 °C and 110 °C were 95.0% and 97.5% (Table 1), respectively. The high retention of curcumin confirmed that spray drying was a viable approach for drying heat sensitive polyphenols. When rehydrated with water, microparticles dried at both 150 °C and 110 °C could be rapidly dissolved as transparent solutions, without any noticeable curcumin precipitates (Fig. S1, Supporting Information). In theory, aqueous solution of 1% (w/v) WPI-curcumin microparticles obtained at 150 °C would give 11.6 μg/mL solubilized curcumin, i.e. increased solubility of curcumin by 1055-fold through the WPI-curcumin complex. The curcumin content of fresh reconstituted 1% (w/v) WPI-curcumin aqueous solution was 10.9 ± 0.19 μg/mL and 11.3 ± 0.11 μg/mL for the powders dried at 150 °C and 110 °C, respectively, which were practically the same amount of curcumin as in the curcumin-WPI powders. Thus, solutions with specific curcumin concentrations would be readily prepared through the reconstitution of WPI-curcumin powders as the amount of curcumin solubilised would be directly proportional to the concentration of dissolved WPI-curcumin microparticles.

Since excessive amount of curcumin was added into the WPI solution for the curcumin saturation process and undissolved curcumin was removed via the centrifuging step prior to spray drying,

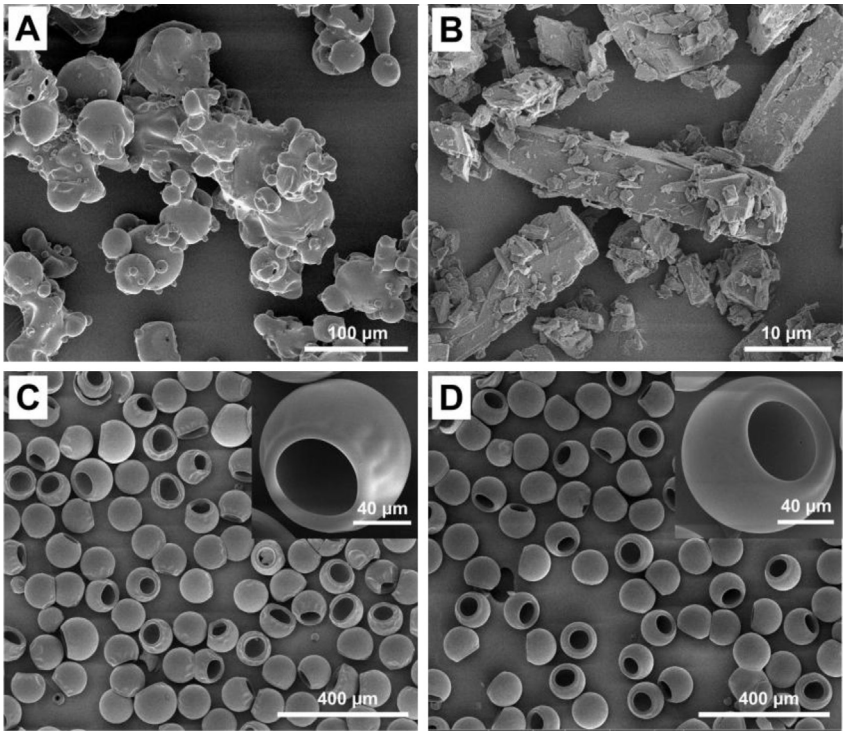

Fig. 4. SEM images of (A) raw WPI powder; (B) raw curcumin powder; microparticles of WPI-curcumin complexes spray dried at inlet temperatures of (C) 150 °C and (D) 110 °C.

Table 1
Summary of the properties of spray dried WPI-curcumin microparticles.

Inlet temperature	Particle size	Curcumin content	Encapsulation efficiency
150 °C	111.2 ± 5.0 μm	1.13 ± 0.17 mg/g	95.0%
110 °C	108.4 ± 3.8 μm	1.16 ± 0.14 mg/g	97.5%

the curcumin encapsulation efficiency of WPI solution as well as the spray dried powder was relatively low in this study (~23%). However, with the results obtained from the curcumin saturation study, the amount of curcumin required to saturate the WPI solution could be easily calculated. Thus, the encapsulation efficiency could be possibly improved by reducing the amount of curcumin added for curcumin saturation process.

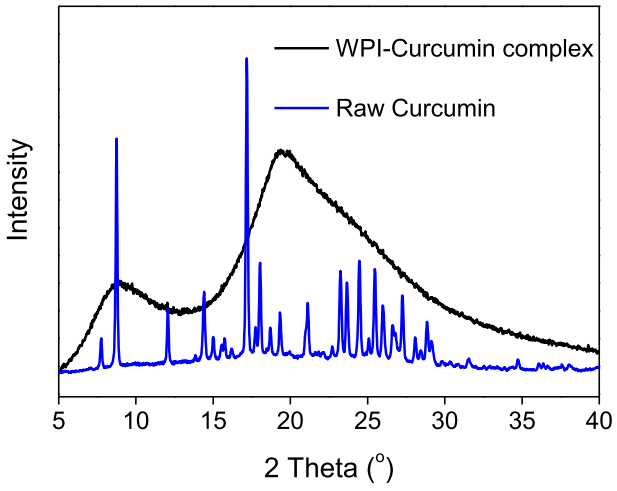

Fig. 5. Powder X-ray diffraction patterns of raw curcumin powder and WPI-curcumin microparticles spray dried at 110 °C.

Powder X-ray diffraction measurements were performed to study the effects of encapsulation on the crystallinity of curcumin. The XRD pattern (Fig. 5) of raw curcumin displayed several characteristic peaks due to its high crystalline structure (i.e. 2θ at 8.74°, 14.42°, 17.18°, 21.14°, 24.48°, 28.84°, etc.) (Donsi et al., 2010). Its SEM image (Fig. 4B) showed the original rectangular curcumin crystals. However, no characteristic peak of curcumin was observed in the spray dried WPI-curcumin microparticles. The typical amorphous XRD pattern of spray dried microparticles clearly indicated the formation of curcumin-WPI in solid state dispersion, which might also contribute to the fast dissolution of curcumin from the spray dried powder.

The antioxidant activity of spray dried WPI-curcumin microparticles was quantified via DPPH radical scavenging assay, with the raw WPI powder used as a control (Fig. 6). It was shown that WPI alone exhibited antioxidant activity in agreement with previous reports (Chiang and Chang, 2005; Kerasioti et al., 2014). When compared to WPI alone, the WPI-curcumin microparticles demonstrated higher antioxidant activity due to the presence of curcumin. Despite limited amounts of curcumin in the powders (1.13 ± 0.17 mg/g and 1.16 ± 0.14 mg/g for microparticles dried at 150 °C and 110 °C, respectively), the increased antioxidant activities of WPI-curcumin particles indicated the effectiveness of curcumin to donate its hydrogen atom to radicals (Tapal and Tiku, 2012). The microparticles dried at different inlet temperatures showed very similar DPPH radical scavenging activities, demonstrating that the drying temperature in this range did not adversely influence the antioxidant activity of curcumin.

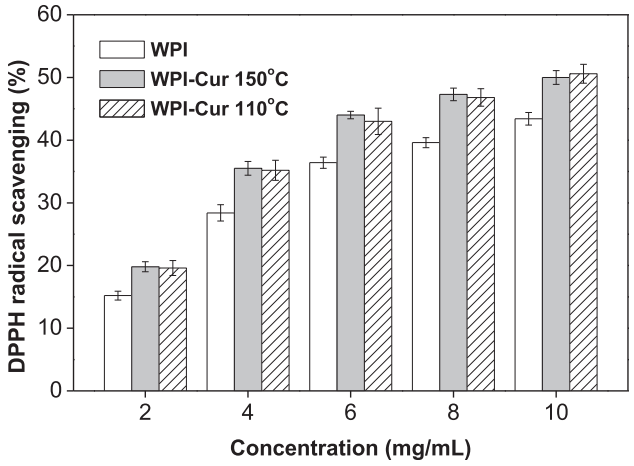

Fig. 6. DPPH free radical scavenging activity of WPI and spray dried WPI-curcumin microparticles at different concentrations.

4. Conclusions

The improvement of curcumin solubility in water by complexation to WPI prior to spray drying of WPI-curcumin microparticles was demonstrated here. The complexation was achieved through hydrophobic interactions of curcumin molecules bound to non-polar regions of WPI. After complexation, the solubility of curcumin was effectively increased up to 124.9 ± 4.8 μg/mL at 10 wt% WPI solution, thereby indicating increased solubility of 11,355-fold compared to the raw curcumin crystals. The WPI-curcumin solution was successfully transformed into uniform microparticles via microfluidic jet spray drying. The obtained microparticles displayed high curcumin retention rates (>95%) with amorphous curcumin present in the WPI matrix. WPI-curcumin microparticles displayed 4.4%–7.7% higher antioxidant activity than the WPI powder depending on the concentration of WPI-curcumin complex in the solutions. Spray drying at inlet temperature 110 °C was adequate to generate microparticles, while no obvious curcumin degradation was observed at 150 °C. The same strategy could be extended for microencapsulation of other lipophilic bioactive ingredients in the development of functional foods and pharmaceutical products.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfoodeng.2015.08.034.

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