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An Investigation in Microencapsulating Astaxanthin Using a Monodisperse Droplet Spray Dryer

Qijing Dai,[1] Xiang You,[1] Liming Che,[1] Fei Yu,[1] Cordelia Selomulya,[2] and Xiao Dong Chen[1]

[1]*Department of Chemical and Biochemical Engineering, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, P. R. China*
[2]*Department of Chemical Engineering, Faculty of Engineering, Monash University, Clayton, Victoria, Australia*

Astaxanthin has stirred great interest in the research and health communities due to its antioxidant capacity and possible role in reducing the risk of some diseases. However, astaxanthin is a highly unsaturated molecule that can degrade and lose its bioactive properties during processing and storage. Microencapsulation is a possible preservation process and a product option. In this work, monodisperse astaxanthin-containing microparticles with high bioactivity retention were prepared using the monodisperse droplet drying technique. The morphology, microstructure, surface oil content, flowability, antioxidant capacity, and in vitro release properties of the microparticles were determined to test the reliability of the spray-drying technique. The results show that monodisperse astaxanthin-containing microparticles have smooth surface, low surface oil content, excellent flowability, prolonged release profile, and high antioxidant activity. The current work indicates that the monodisperse droplet spray-drying technique enhances both bioactivity retention and product properties of astaxanthin-containing microparticles.

Keywords Antioxidant; Astaxanthin; Monodisperse droplet spray drying; Monodisperse microparticles

INTRODUCTION

Astaxanthin is a high-value carotenoid with strong antioxidant activity belonging to the xanthophyll class. Astaxanthin is the main natural ketocarotenoid pigment responsible for the red to orange color in crustacean and salmon flesh.[1] This natural pigment serves as a biological antioxidant with an antioxidant activity 10 times greater than other carotenoids such as zeaxanthin, lutein, canthaxantin, and β-carotene.[2] Like other carotenoids, astaxanthin is a highly unsaturated molecule, which can degrade and lose its bioactive properties during processing and storage. This can cause the loss of their nutritive and biological desirable properties as well as the production of undesirable flavor or aroma compounds.

Correspondence: Dr. Liming Che and Dr. Xiao Dong Chen, Department of Chemical and Biochemical Engineering, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. China; E-mail: lmc@xmu.edu.cn; xdc@xmu.edu.cn

Microencapsulation may make it possible to transform extracted astaxanthin into a powdered form.[3] Microencapsulation has been shown to be an effective way to protect the stability of bioactive compounds from environmental factors.[4–6] Several techniques, including spray drying, spray–freeze drying, fluidized bed drying, extrusion, and centrifugal extrusion, can be used to produce microcapsules.

Spray drying can produce dry products of different types, having a wide range of production capacities.[7] Heat damage to the product is relatively low and the qualities of final product remain constant throughout production runs if drying conditions are held constant. Mathematical models have been formulated on the characterization of products. It is therefore the most commonly used microencapsulation technology in food industries.[8]

Recently, a monodisperse droplet generator was designed and equipped on spray dryers as an atomizer.[9,10] The droplets generated by this type of atomizer have a monodisperse size and thus undergo similar drying histories when they are dried under similar conditions (e.g., flow rate, temperature, and trajectories). Therefore, the powder obtained has similar properties that allow for more consistent analysis (i.e., interpretation not blurred by the wide size distribution and random trajectories).

The aim of this work is to investigate the properties of the astaxanthin-containing microparticles produced using the monodisperse droplet drying technique. The morphology, microstructure, surface oil content, flowability, antioxidant activity, and in vitro release properties of the microparticles obtained were determined to illustrate the potential of the spray-drying process for such microencapsulation.

MATERIAL AND METHODS

Materials

Astaxanthin (98 wt%), 2,2-diphenyl-1-picrylhydrazyl (DPPH), phosphate buffer saline (PBS, pH = 7.4), sodium caseinate, and dialysis bags were purchased from

Sigma-Aldrich (St. Louis, MO, USA). Whey protein concentrate (WPC) was donated by Xiamen Kingdomway Group Company (Xiamen, China). Dichloromethane and petroleum ether (bp 30–60°C) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). All chemicals and solvents were analytical grade and used without further purification.

Preparation of Astaxanthin Emulsion

Aqueous solution of wall materials was prepared by dissolving lactose (5 wt%), sodium caseinate (5 wt%), and WPC (10 wt%) in Milli-Q water in sequence at about 40°C. The mixture was stirred magnetically for 15–20 min to allow complete dissolution of the solids. Astaxanthin solution was prepared by dissolving astaxanthin in dichoromethane at 40°C. The astaxanthin solution obtained was added into the aqueous solution of wall materials (volume ratio 1:10). The resultant mixture was stirred mechanically (T25, IKA-Werke GmbH & Co. KG, Staufen, Germany) for 10 min at 5,000 rpm. Then the crude emulsion obtained was homogenized using a microfluidizer (M-110P, Microfluidics International Corporation, Newton, MA, USA) at a pressure of 140 MPa (one pass). The dichoromethane was removed from the fine emulsion via rotary evaporation at 0.1 MPa and at room temperature (N-1100, Ailang Instruments Co. Ltd., Shanghai, China). All feed solutions were prepared under an O_2-free atmosphere in a chamber with continuous purging of nitrogen gas to prevent astaxanthin from oxidation.

Preparation of Monodisperse Astaxanthin-Containing Microparticles

The detailed design of the rig and monodisperse droplet generator can be found everywhere.[10] Briefly, the feed emulsion was storied in a stainless steel reservoir and atomized by a specially designed microfluidic nozzle. The reservoir was connected to a compressed air supply that forced the feed emulsion to the jet through the orifice of the nozzle. The glass nozzle contained a glass capillary tube with an orifice of 75 μm, surrounded by zirconate/lead titanate ceramics. The piezoelectric ceramic component was connected to a Jet Drive III pulse controller (Microfab Technologies Inc., Bedford, MA, USA). In order to achieve uniform droplets, the flow rates and frequency of piezoelectric pulse were adjusted. The piezoelectric pulsing was adjusted to a frequency of 10,000 Hz for generation of monodisperse droplets. A photograph of successful generation of monodisperse droplets is shown in Fig. 1. The droplets formed were dried in a spray dryer chamber. The detailed design of the spray dryer is shown in Fig. 2. The main drying chamber was made from stainless steel with an inner diameter of 0.6 m and a length of 3.0 m, insulated with fiberglass lagging. Hot air was introduced with variable-temperature heat guns at the top of the drying chamber. The combined air flow from the guns was passed through an air dispersion plate with small holes to evenly distribute the air flow throughout the column. Thermocouples

FIG. 1. Monodisperse droplet generation: stream of feed solution consisting of monodisperse droplets, obtained with the optimized electrical frequency (color figure available online).

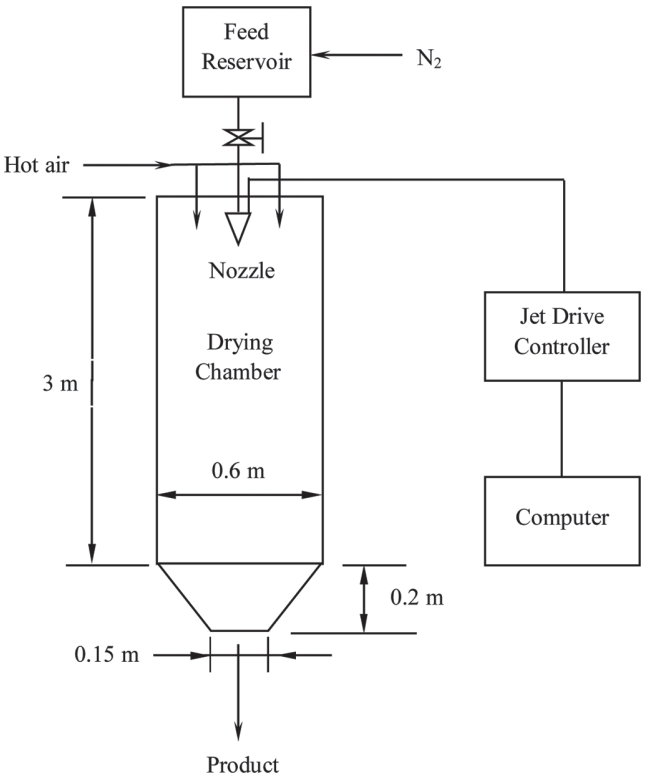

FIG. 2. Schematic diagram of the spray dryer.

at five positions on the inside wall of the drying chamber were used to monitor the temperature profile. The inlet temperature was measured by the thermocouple at the entrance of the dryer. In this work, the inlet temperature was maintained at 140°C, and the outlet temperature was 30°C. Monodisperse astaxanthin-containing microparticles obtained were stored at −18°C for further analysis.

Determination of the Moisture Content of Astaxanthin-Containing Microparticles

To measure the moisture content of resultant monodisperse astaxanthin-containing microparticles, 0.2 g of the sample collected was oven dried for 2 h at 105°C to remove all of the moisture in the sample. The sample weights before and right after drying were measured using an analytical balance (AL204, Mettler-Toledo Corporation, China). The moisture content of the sample was then calculated using the following equation:

$$w = \frac{W_0 - W_e}{W_0} \times 100\%, \quad (1)$$

where w is the moisture content of the sample on a wet basis (wt%), W_0 is the weight of the sample before drying, and W_e is the weight after drying.[11]

Microscopy of the Astaxanthin-Containing Microparticles

The microstructure of astaxanthin-containing microparticles was visualized with an LEO 1530 scanning electron microscope (SEM; LEO Elektronenmikroskopie GmbH, Oberkochen, Germany) located at Xiamen University. The microparticles obtained were fixed to an aluminum sample stub using double-sided conducting tape followed by sputter-coating with Au for 30 s to produce a conductive surface for SEM observation. SEM images were recorded at 5–15 kV accelerating voltage.

The astaxanthin-containing microparticles were also observed under an optical microscope (BX410, Olympus Corporation, Japan) equipped with a CCD camera module to take pictures. The average diameters and particle size distributions were analyzed using Image J 1.47 (National Institutes of Health, USA) from the pictures recorded.

Determination of the Surface Oil Content of Astaxanthin-Containing Microparticles

The surface oil content of astaxanthin-containing microparticles was determined using the approach proposed by Varavinit et al. with some modification.[12] Ten milliliters of petroleum ether (bp 30–60°C) was added to 0.5 g of powder in a 50-mL flask and shaken for 2 min. The slurry was then filtered through filter paper, and each filter paper with solid particles was washed three times by passing 5 mL of petroleum ether through each filter paper each time. The petroleum ether in the filtrate was allowed to evaporate for approximately 10–15 min at 60°C. To completely remove the solvent, the flask was oven dried at 100°C until a constant weight was achieved. The surface oil content is expressed as the mass of astaxanthin at the surface of microparticles per 100 g sample.

Determination of the Flowability of Astaxanthin-Containing Microparticles

To minimize the influence of moisture in the sample and ambient air, the sample was oven dried for 12 h at 60°C prior to the test and the test was conducted in a desiccator. The flowability of the sample was determined by measuring the angle of repose (a static measure of relative flowability). The method is similar to that described by Kim et al.[13] The experimental rig is illustrated schematically in Fig. 3. One gram of sample was placed in the top chamber of the rig carefully with the trap door closed. If the powder was highly flowable, the trap door was then opened to let the sample flow downwards freely and form a heap. The more free-flowing powders tend to have lower drained angles of repose.

In Vitro Release Study of Astaxanthin-Containing Microparticles

In a typical experiment, 200 mg of astaxanthin-containing microparticles was dispersed in 20 mL deionized water, and the resultant suspension was then added to a dialysis bag. The dialysis bag with the sample was put into a 250-mL conical flask, and 200 mL release medium (100 mL of PBS with 100 mL of acetone)[14] was transferred into the flask. The release of astaxanthin from microparticles into PBS was conducted using a shaking incubator at 100 rpm and 25°C. The flask was sealed carefully to prevent the acetone vapor from escaping. At certain time intervals, a 3 mL sample was removed and replaced with an equivalent quantity of the release medium. The sample collected

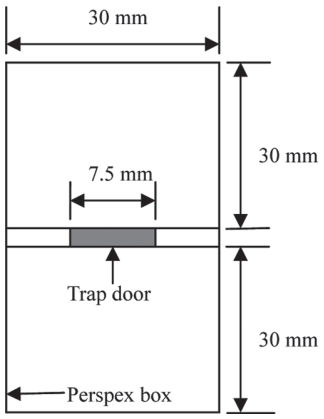

FIG. 3. Schematic diagram of the flowability test rig.

was transferred into a 4.5-mL microtube and then centrifuged at 10,000 rpm for 5 min (Legend Micro 17 R, Thermo Electron LED, Germany). The optical density of the sample at 480 nm was read by a ultraviolet-visible spectrophotometer (UV-2550, Shimadzu Corporation, Kyoto, Japan). The amount of released astaxanthin was determined by referencing the calibration curve prepared using the following procedure:

A weighed amount of astaxanthin was dissolved in 100 mL acetone. Then 1.0, 2.0, 3.0, 4.0, 5.0, and 6.0 mL of the astaxanthin solution was transferred to 50-mL volumetric flasks and diluted to give final concentrations of 1.8×10^{-4}, 3.6×10^{-4}, 5.4×10^{-4}, 7.2×10^{-4}, 8.9×10^{-4}, and 1.0×10^{-3} mol/L with acetone, respectively. These samples were analyzed using the ultraviolet-visible spectrophotometer, monitoring the absorbance at 480 nm. The Beer's law plot (calibration curve) was constructed by plotting absorbance (y) as a function of the calculated concentration of astaxanthin (x). The calibration curve is shown in Fig. 4. The equation of the best-fit line was determined by linear least-squares fitting of the data. Pure acetone was used as a reference blank.

Determination of DPPH Radical Scavenging Activity of Astaxanthin-Containing Microparticles

DPPH is a stable free radical. Upon mixing with a hydrogen donor such as active astaxanthin, the color of DPPH solution will turn from violet to pale yellow.[15] DPPH radical scavenging activity (RSA) of astaxanthin-containing microparticles was determined using a modified method of Brand-Williams et al.[16] In brief, 1 mL of various dilutions of astaxanthin microparticles was mixed with 5 mL of 60 μM DPPH in methanol. After an incubation period of 30 min, the optical density (OD) of 6 mL of sample was read at 517 nm using the UV-2550. Assay control (AC) consisted of 1 mL of methanol and 5 mL of DPPH solution. The DPPH radical stock solution and samples were prepared fresh daily. The DPPH RSA of astaxanthin at each dilution was calculated by:

$$RSA(\%) = \frac{OD_{AC} - OD_{sample}}{OD_{AC}} \times 100\% \qquad (2)$$

The results were used to calculate the EC50 (the amount of astaxanthin necessary to decrease the initial DPPH concentration by 50%) of astaxanthin on superoxide radical scavenging. A lower EC50 value represents a higher antioxidant activity.[15]

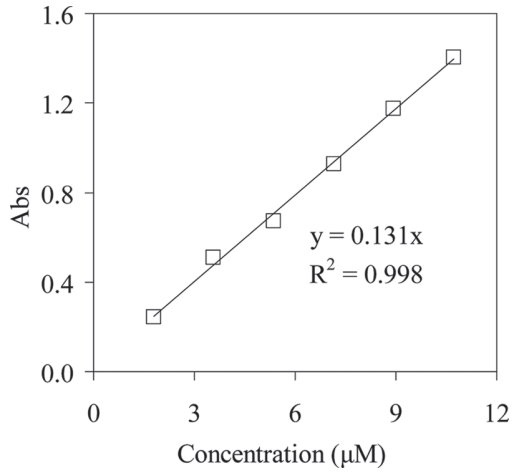

FIG. 4. Calibration curve for the determination of astaxanthin content.

RESULTS AND DISCUSSION

Morphology of Astaxanthin-Containing Microparticles

As shown in Fig. 5, the astaxanthin-containing microparticles obtained had very smooth surfaces. Figure 6 shows that the microparticles were similar in size and appearance. The microparticles were all buckled.[17] The particle size distributions of the microparticles is shown in Fig. 7. The microparticles had a relatively narrow size distribution and precise measurement showed that the mean diameter (d[4, 3])[18] was 122 μm (>500 microparticles). The moisture content of the microparticles was 4.55 wt% (wb).

Flowability of the Monodisperse Astaxanthin-Containing Microparticles

The flowability of powders is an important attribute for processing, handling, and in end-user applications. The flowability generally depends on the physical properties of the powder, such as particle size and shape, surface structure, particle density, bulk density, moisture content, and fat content.[19,20] Despite the influence of these parameters, the flowability of powders is a surface-related property and is therefore thought to be influenced to some extent by the powder surface composition. Of most importance is the oil content of the powder surface. The presence of oil may render the powder surface sticky and act as a bridge between particles, reducing the flowability of some powders. This is more significant when the temperature is near or above the melting point of fat. It is common sense that the microstructure of a material determines its macroscopic properties.[21] Therefore, it is supposed that such smooth surfaces would facilitate the flow of the powders.

The surface oil contents of the astaxanthin-containing microparticles with different initial solid concentrations are listed in Table 1. No trend was found between the surface oil content and initial solid concentration of the sample.

In this work, the angle formed by a heap of powder can provide indications of relative flow characteristics. The results for flowability are shown in Fig. 8. The samples with

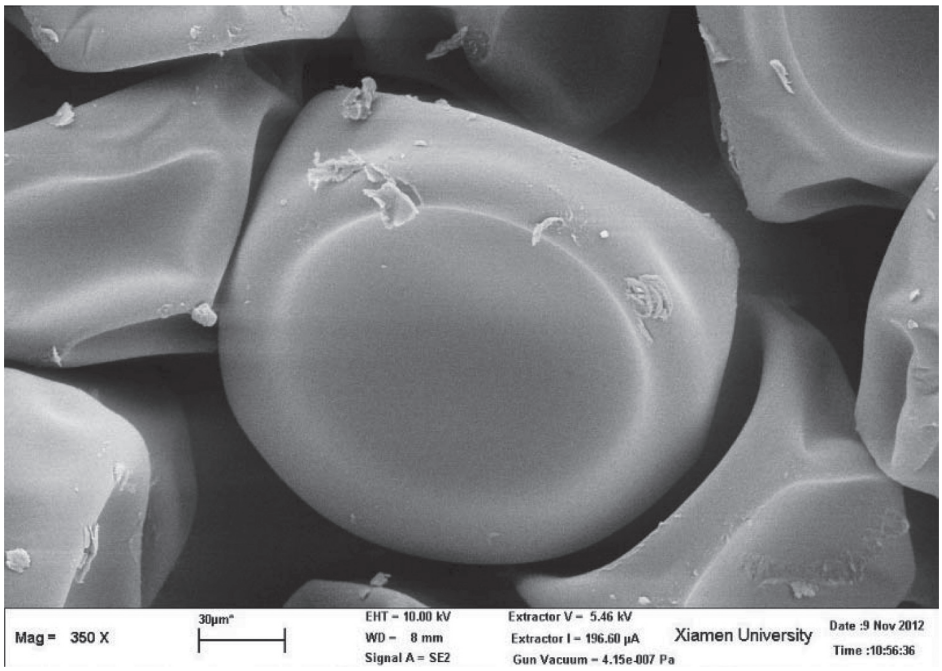

FIG. 5. SEM photograph of astaxanthin-containing microparticles.

surface oil contents of 358.9, 649.1, and 587.4 mg/100 g powder showed angles of repose of −80, −75, and −85°, respectively. No trend was found between the flowability and the surface oil content of the sample.

The flowability of powders depends on some physical properties of the powder. Particle size has a major influence on powder flowability. More contact surface area is available for cohesive forces, in particular, and frictional

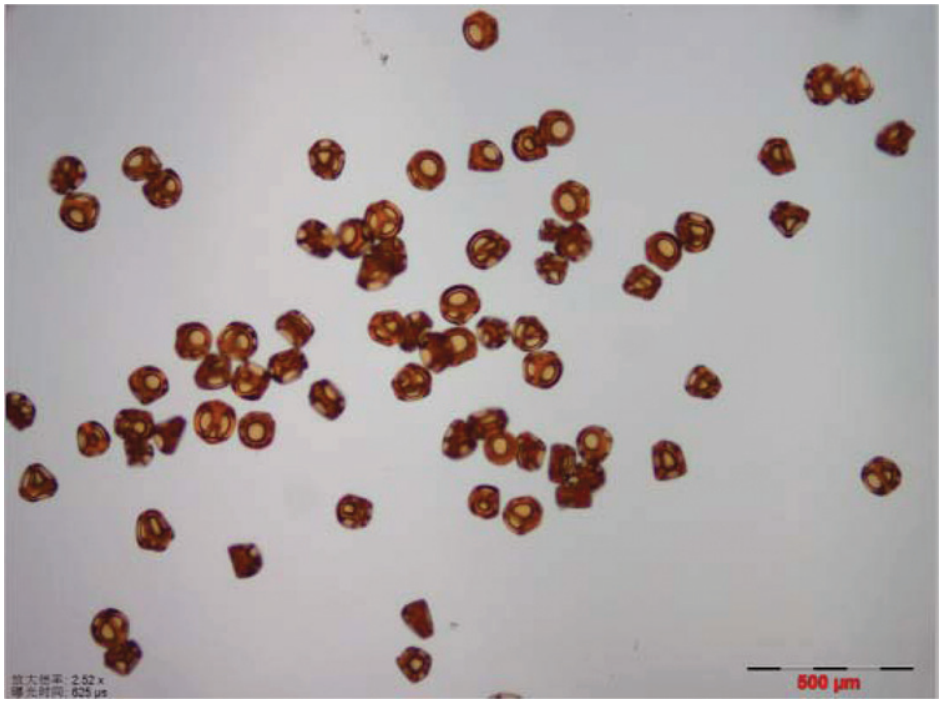

FIG. 6. Microscope photograph of astaxanthin-containing microparticles (color figure available online).

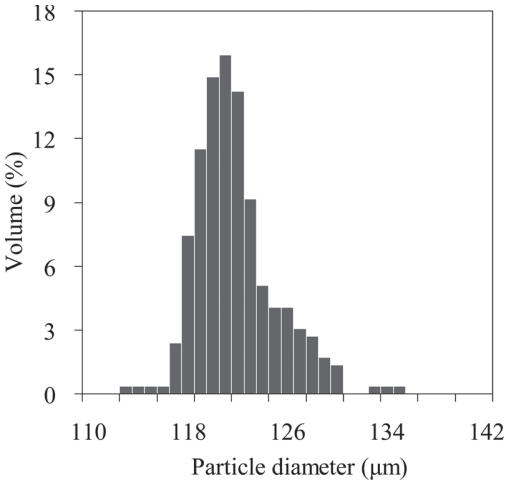

FIG. 7. Particle size distribution of astaxanthin-containing microparticles.

forces to resist flow. Particle shape also has an influence on powder flowability. It influences the surface contact between particles. Powder moisture content has a significant impact on powder flowability. Increasing moisture content leads to reduced flowabiltiy due to the increase in liquid bridges and capillary forces acting between the powder particles. In addition, increased moisture content can soften (plasticized) the powder material, especially the water-soluble constituents, which results in deformation of the powder, giving a higher contact surface area. Fat on the surface of powders also has a tendency to cause the particles to adhere to one another or agglomerate, deteriorating the flowability of the powders.[13]

Antioxidant Activity of the Astaxanthin-Containing Microparticles

It is well known that the antioxidant activity of astaxanthin is sensitive to temperature and prolonged exposure to air. In order to determine the loss of antioxidant activity during spray drying, the EC50 value of astaxanthin-containing microparticles was compared to that of native astaxanthin. The RSA of native astaxanthin and astaxanthin-containing microparticles is shown in Fig. 9.

TABLE 1
Surface oil content with different mass concentrations

Mass concentration (%)	Surface oil content (mg/100 g)
10.8	587
16.5	977
17.9	674
25.2	359
30.1	817

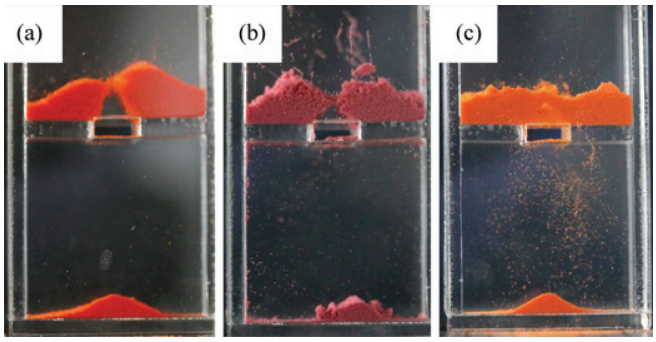

FIG. 8. Flowability of astaxanthin-containing microparticles for samples with surface oil contents of (a) 358.9 mg/100 g powder, (b) 649.1 mg/100 g powder, and (c) 587.4 mg/100 g powder (color figure available online).

The RSA of native astaxanthin and astaxanthin-containing microparticles increased linearly with increasing astaxanthin concentration. The RSA of native astaxanthin was slightly higher than that of astaxanthin-containing microparticles. Pure astaxanthin has an EC50 value of 1.588×10^{-4} g/mL, and astaxanthin-containing microparticles have an equivalent one of 1.872×10^{-4} g/mL. This suggests that the loss of antioxidant activity is relatively low, though the air temperature employed in spray drying is 140°C. The approach of encapsulation prevented the astaxanthin from deactivation. The results show that astaxanthin-containing microparticles with high bioactivity retention can be prepared by emulsion spray drying.

In Vitro Release Profile of Astaxanthin-Containing Microparticles

The in vitro release profile of astaxanthin-containing microparticles is shown in Fig. 10. There was no detectable

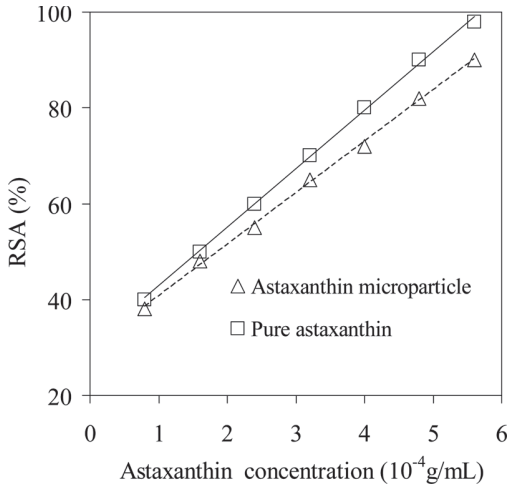

FIG. 9. RSA of astaxanthin-containing microparticles and astaxanthin evaluated by DPPH assay.

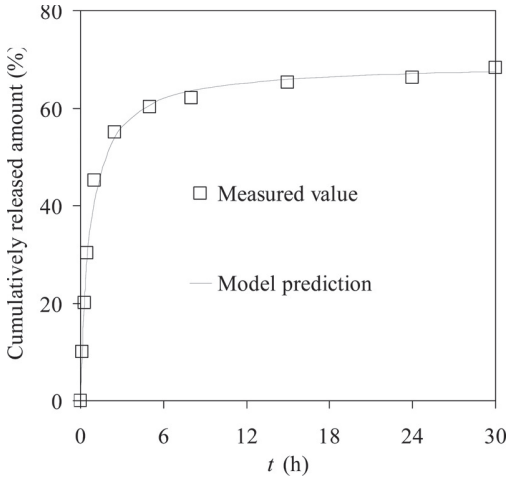

FIG. 10. In vitro release profile of astaxanthin-containing microparticles.

astaxanthin released into deionized water (data not reported in this article). However, the release of astaxanthin from microparticles commenced immediately when the sample was exposed to a mixture of PBS buffer and acetone. This demonstrates the need for ions in the elution medium in order to displace the protonated astaxanthin from the protein binding sites, further supporting the mechanism of ionic interaction between astaxanthin and wall materials.[22] Because wall materials are not soluble in acetone, whereas astaxanthin is, acetone was used as a medium to investigate the release of astaxanthin from wall materials. However, the mechanism of biological transportation of astaxanthin within the human body has yet to be elucidated but likely involves lipophilic carrier complexes or proteins. To this end, it will be interesting to evaluate the stability—that is, the release rate—of astaxanthin from WPC-encapsulated microspheres in both digestive tract systems (with both food and bile salt–derived emulsifiers and fats) and plasma-based solutions.[14] The release curve indicates that encapsulated astaxanthin diffused out of the WPC spheres relatively slowly. The reduced diffusion may be due mainly to the protection by encapsulation, the short drying time, and the relatively low spray-drying temperature (140°C) compared to traditional spray drying. Sixty percent of the encapsulated astaxanthin was released in the first 6 h. After 12 h, the cumulative release rate remained fairly constant. The release of astaxanthin into the mixture of PBS buffer and acetone can be described using the second-order model

$$\frac{t}{q_t} = \frac{1}{h} + \frac{t}{q_e}, \tag{3}$$

where t is time (h), q_t is the amount of astaxanthin (mg/g) released at time t, h is a constant [g/(mg · h)], and q_e is the equilibrium amount of astaxanthin (mg/g) released into the mixture of PBS buffer and acetone.[23] As shown in Fig. 10, the release of astaxanthin can be predicted well using the second-order model ($R^2 = 0.9$).

Monodisperse Droplet Drying Technique for Investigation of Astaxanthin-Containing Microparticles

Spray-dried monodisperse microparticles (size and morphology) offer various advantages compared to conventional particles with similar average sizes but a broader size distribution. Monodisperse particles enable more precise controlled drug release. So far, however, spray drying has not been found to be a cost-effective way to produce monodisperse particles mostly due to the lack of an automization technique that can handle large capacities.

Though not economical for large-scale production, the current technique does produce monodisperse particles. For research purposes, it has great advantages. Foremost is the ability to ensure that the conclusions are more definitive for the particles of concern. The ability to obtain droplets with a narrow size distribution ensures accurate control of drying conditions such that each particle experiences similar conditions, so the moisture content can be controlled precisely, particularly for the drying of heat- and oxygen-sensitive materials. When drying astaxanthin-containing microparticles, if each antioxidant particle underwent a different drying history in spray dryer, considerable variation in moisture content would be found in products, consequently inducing large variations in antioxidant activity because the denaturation of such material is usually a function of temperature and moisture content.

The monodisperse spray-drying technique described in this article produced astaxanthin microparticles with high antioxidant activity. Compared to other formulation methods such as emulsification, homogeneous precipitation, and template-assisted method, the current spray-drying technique does not require a purification step to remove solvents, which would enable rapid and single-step production at a large scale. Traditional spray-drying techniques generate droplets with a broad size distribution and thus are unable to guarantee similar drying histories for individual particles.[24,25] Although spray-dried particles with a narrow size distribution have been reported from other spray drying approaches, the narrow size distribution was often achieved with the use of a specially designed cyclone for particle separation, where only a fraction of the spray-dried particles was used as the final product.[26]

For smaller production capacities, such as a few kilograms per hour, it will be possible to scale up the present technique in the near future. There are challenges in this. In the meantime, the technique allows one to obtain more consistent experimental results for the same kind of powder and interpret the data without the interference of the size distribution effect. It will be useful in the future in studying

the bioavailability of astaxanthin-containing microparticles when different wall materials and excipients are used.

CONCLUSION

This article shows the use of a relatively low-temperature spray-drying system equipped with the monodisperse droplet generator to prepare astaxanthin-containing microparticles. Monodisperse astaxanthin-containing microparticles with high bioactivity retention—that is, antioxidant capacity—were prepared successfully. The monodisperse spray-drying technique shows great potential as a technique for making of heat- and oxygen-sensitive microparticles for drug release studies.

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