

This article was downloaded by: [University of Haifa Library]

On: 01 October 2013, At: 05:37

Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Drying Technology: An International Journal

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/ldrt20>

Supercritical CO₂ Spray Drying of Ethyl Cellulose (EC) for Preparing Microparticles

Bao-Guo Li^a, Yan Zhang^b, Wu-Jie Zhang^a & Ze-zhao Hua^a

^a Institute of Food and Biotechnology, University of Shanghai for Science and Technology, Shanghai, P.R. China

^b College of Food, Qingdao Agricultural University, Qingdao City, Shandong Prov., P.R. China

Published online: 02 Apr 2008.

To cite this article: Bao-Guo Li, Yan Zhang, Wu-Jie Zhang & Ze-zhao Hua (2008) Supercritical CO₂ Spray Drying of Ethyl Cellulose (EC) for Preparing Microparticles, *Drying Technology: An International Journal*, 26:4, 464-469

To link to this article: <http://dx.doi.org/10.1080/07373930801929441>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

Supercritical CO₂ Spray Drying of Ethyl Cellulose (EC) for Preparing Microparticles

Bao-Guo Li,¹ Yan Zhang,² Wu-Jie Zhang,¹ and Ze-zhao Hua¹

¹*Institute of Food and Biotechnology, University of Shanghai for Science and Technology, Shanghai, P.R. China*

²*College of Food, Qingdao Agricultural University, Qingdao City, Shandong Prov., P.R. China*

Even though common spray drying has been widely used for drying food and related products, the effect of drying conditions of supercritical CO₂ spray drying on the particle sizes of dried products has not been well studied. The objective of this study was to study the effect of drying conditions and design parameters on the particle sizes of biomaterials dried with supercritical CO₂ spray drying. The ethyl cellulose (EC) microparticles were prepared with supercritical CO₂ as the dry medium using an experimental spray-drying apparatus. This research studied the influences of spray nozzle diameter, mass ratio of gas to liquid, solution concentration, temperature, and pressure on the physical characteristics of ethyl cellulose microparticles. The results indicated that the average size of the dried particles ranged from 1.07 to 9.84 μm. The spray nozzle with 8-mm diameter produced smaller microparticles with narrower distribution than the 4-mm spray nozzle. The average particle size increased with the increase of the ratio of gas to liquid. Also, the average size and distribution of the microparticles increased with the rise of temperature and solution concentration but decreased with the increase of pressure.

Keywords Ethyl cellulose; Microparticle; Spray drying; Supercritical CO₂

INTRODUCTION

Spray drying is the most commonly used technique for drying liquid products. In spray drying, a water-soluble material is atomized into a stream of hot air. The atomized particles dry very rapidly, and then the dried powder is recovered via cyclone collectors.^[1,2] Although spray drying has been widely used for drying foods, agricultural products,^[3–5] and drugs,^[6,7] there are still limitations of spray drying for drying biomaterials, heat-susceptive materials, and lipid-soluble materials.^[8] Some of the major problems in spray drying are stickiness, thermoplasticity, and oxidation of some flavor compounds. Due to surface effect,

the aggregation of powder could be formed when using conventional spray-drying techniques.

Supercritical carbon dioxide spray drying, which uses supercritical carbon dioxide as drying medium instead of heated air, is a new particle preparation technology developed in recent years.^[9] Supercritical fluid spray drying can produce high-quality dried products similar to freeze drying.^[10,11] Supercritical fluids have unique properties that their densities and solubility power are similar to those of the liquids and their compressibility are like those of gases. Since the density increases in proportion to compressibility and the solubility power can be enhanced, the solubility power could maintain in a wide range by large compressibility. The main feature of supercritical fluid drying is nonoccurrence of liquid–gas phase change during the drying process. This phenomenon means that no cohesion along the evaporation process occurs due to lack of surface tension effects. Compared to the traditional spray-drying method, there are many advantages of supercritical carbon dioxide spray drying. The shapes, sizes, and size distributions can be easily controlled by adjusting the operation pressure and temperature. The particles with small size, narrow size distribution, and spherical morphology characteristics can be obtained through the supercritical carbon dioxide spray drying.^[12] In addition, the critical temperature of carbon dioxide is as low as 31.1°C, which can avoid overheating the products and damaging the effective ingredients during the process. This new technology has already raised interest in particle preparation for drying the heat-sensitive materials in food, biomaterials, and pharmaceutical industries.^[13]

Because the apparatus used for the supercritical carbon dioxide spray drying is different from the traditional spray drying, the related new drying mechanism and the differences in the particle properties obtained with different operation parameters exist.^[14] At present, the theoretical research of supercritical fluid spray drying is mainly focused on the phase behavior of multicomponent solutions and

Correspondence: Bao-Guo Li, Institute of Food and Biotechnology, University of Shanghai for Science and Technology, No. 516 Jungong Rd., Shanghai, P.R. China; E-mail: lbaoguo@126.com

optimization of the operation parameters. The influence of operation parameters, such as temperature and pressure, on the particle size, shape, and size distribution has also been investigated.^[15–17] Due to the differences in the apparatus, ranges of studied parameters, and analytical methods used in different studies, the conclusions from those studies were also different. Therefore, there is a need to conduct more research to study the new processing technology.^[18,19]

Ethyl cellulose is a derivative of cellulose in which ethoxy is substituted by hydroxy in the molecule chain. Since it has the characteristics of low toxicity, strong viscosity, and easily forming membrane, ethyl cellulose has been widely used in food, pharmaceutical, chemical, and cosmetics industries and can be used as a model ingredient for supercritical spray-drying research. The principle of supercritical spray drying of ethyl cellulose solution containing acetone is that the solution is dispersed into fine droplets and acetone solvent was absorbed by supercritical CO₂. When continuously extracted by supercritical CO₂, the droplets shrank and the ethyl cellulose concentration on the droplet surface gradually increased. As the concentration reached the critical saturation, nucleation occurred in the droplets. According to the theory of nucleation and nuclear growth, the quick formation of nucleation and separation will result in small size of particles produced. Since the supersaturation of solvents influences the speed of nucleation and crystal growth rate, desirable particle size and distribution could be obtained by adjusting the operation parameters, such as pressure, temperature, flow velocity, and concentration of samples and nozzle diameter.

The objective of this study was to study the effect of design and operation parameters of supercritical carbon dioxide spray drying on the characteristics of ethyl cellulose microparticles. The investigated parameters included the nozzle diameter, mass ratio of gas to liquid, solution concentration, operating temperature, and pressure.

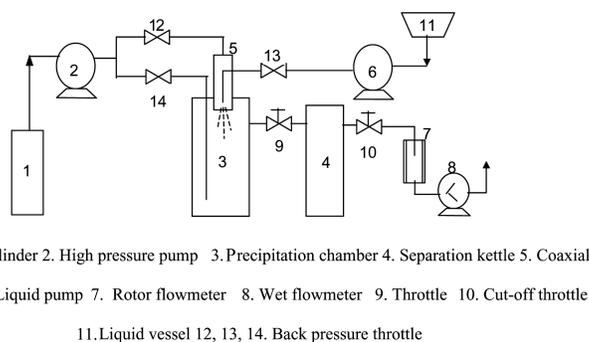
MATERIALS AND METHODS

Materials

The ethyl cellulose (EC) used in this study was provided by Pharmaceutical College of Fudan University, Shanghai, China. Acetone with a purity of 99.5% (analytical reagent) was purchased from Shanghai Fine Chemical Science and Technology Research Institute, Shanghai, China. The concentrations of ethyl cellulose and acetone solution used in the tests were 1 and 3%, respectively. The purity of CO₂ (Shanghai Steel Service & Development Company, Shanghai, China.) was 99.9%.

Apparatus

The schematic diagram of the experiments is shown in Fig. 1. Carbon dioxide was liquefied in a chiller to prevent cavitations and fed into a 500-mL deposit chamber through



1. CO₂ cylinder 2. High pressure pump 3. Precipitation chamber 4. Separation kettle 5. Coaxial nozzle 6. Liquid pump 7. Rotor flowmeter 8. Wet flowmeter 9. Throttle 10. Cut-off throttle 11. Liquid vessel 12, 13, 14. Back pressure throttle

FIG. 1. Schematic diagram of supercritical CO₂ spray-drying experimental apparatus.

the high-pressure pump. The temperature and pressure of the CO₂ in the chamber can be controlled from room temperature to $100 \pm 1^\circ\text{C}$ and from 0 to 50 ± 0.1 Mpa, respectively. Compressed CO₂ was preheated to the desired temperature and pressure before valve 14 was closed and then valve 12 was opened, which allowed the same conditions of CO₂ in the cylinder and precipitation chamber. Another high-pressure liquid pump 6 was used for delivery of the ethyl cellulose and acetone solution from liquid vessel 11 through pressure throttle 13. The two pressurized streams from valves 12 and 13 were sprayed into precipitation chamber from the top through a coaxial injection nozzle. The ethyl cellulose and acetone solution and supercritical CO₂ were injected into the precipitation chamber through the inside and outside tubes, respectively. The acetone solvent inside ethyl cellulose droplets was dissolved by supercritical CO₂, resulting in dried ethyl cellulose droplets. If it was necessary, valve 9 and 10 can be adjusted to maintain the pressure in chamber 3 until the acetone solvent completely dissolved in the supercritical CO₂. The dried ethyl cellulose particles were collected in the precipitation chamber and separation kettle after valves 9 and 10 were opened to release the pressure.

The particles size and size distribution of ethyl cellulose were measured by using FAM Laser Particle Measure Apparatus (University of Shanghai for Science and Technology, Shanghai, China). The average size, Sauter average size, was calculated by the rate between total particles average volume and average surface area. Size distribution was calculated as the percentage of the numbers of particles with a specific size and total numbers of particles.

RESULTS AND ANALYSIS

Influence of Nozzle Diameter on Particle Size

The average particle sizes and distributions of ethyl cellulose produced with two nozzle diameters, 4 and 8 mm, under three different solution velocities are shown in Table 1 and Fig. 2. The processing conditions were temperature of 35°C and pressure of 9 Mpa with 1% initial

TABLE 1

Influence of nozzle diameters on particle size ($T = 40^{\circ}\text{C}$,
 $P = 9 \text{ Mpa}$, $C = 1\%$)

Average size of microparticles (μm)			
Solution velocity $\text{m} \cdot \text{s}^{-1}$	0.147	0.193	0.307
Nozzle diameter			
4 mm	2.65	4.62	8.32
8 mm	1.07	2.26	5.38

ethyl cellulose. The size of the particles prepared with the 8-mm nozzle was much smaller than that produced with the 4-mm nozzle when using the same velocity. This could be because the increased nozzle diameter resulted in a thin liquid membrane, which formed small droplets during the supercritical CO_2 extraction. Meanwhile, the mass transfer between the supercritical CO_2 and droplets was strengthened with the increased total surface area of droplets and the droplets reached supersaturation status very quickly as the evaporation of solvents accelerated. The results also showed that the average particle sizes increased with the increase of solution velocity. Based on such results, it is believed that the particle formation was mainly through nucleation processing and a rapid nucleation formation could result in small particle size. Figure 2 shows the particle size distributions of ethyl cellulose particles produced with 4- and 8-mm nozzles and solution velocity of 0.307 m/s . The particle size and distribution varied with the nozzle diameter. The 8-mm nozzle was used in the following experiments due to smaller particle size produced compared to 4-mm nozzle.

Influence of Mass Ratio of Gas to Liquid on Particle Size

The average particle sizes varied significantly with the ratio of CO_2 gas and ethyl cellulose solution under the processing conditions of temperature of 40°C , pressure of 9 MPa , solution velocity of 0.108 m/s (Fig. 3). With the

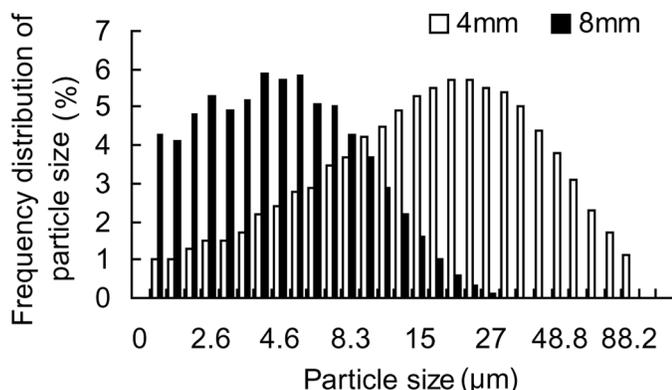


FIG. 2. Particle size distribution frequency of particles produced with two different nozzle diameters. ($T = 40^{\circ}\text{C}$, $P = 9 \text{ Mpa}$, $C = 1\%$).

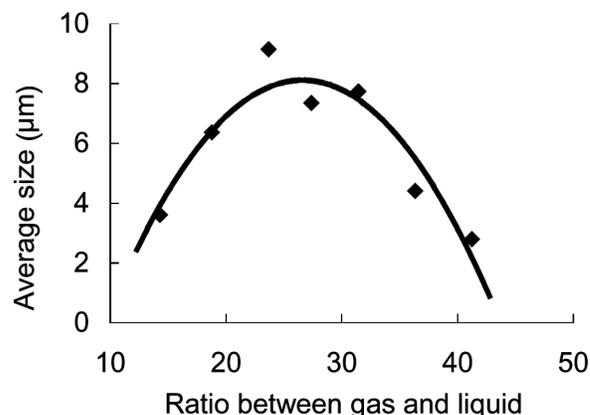


FIG. 3. Influence of mass ratio of CO_2 gas to solution on the microparticles size ($T = 40^{\circ}\text{C}$, $P = 9 \text{ Mpa}$, $V = 0.108 \text{ m} \cdot \text{s}^{-1}$, $C = 1\%$).

increase of the mass ratio of CO_2 gas to solution, the average particle sizes increased and then decreased after the mass ratio was greater than 27. At the low ratio, the growing particle conglomeration might result in increased particle size with the increase of the mass ratio. The increased gas velocity at the high mass ratio might cause the decreased particle size. It could carry more CO_2 gas through the nozzle and accelerated particle movement, which led to strong collision among the particles, resulting in the fine particles. The structure design of the nozzle may also affect the final particle sizes, which needs to be further investigated. Within the range of mass ratio of gas to liquid investigated, the average particle sizes were ranged from 2.8 to $9.15 \mu\text{m}$.

Influence of Solution Concentration on Particle Size

The average particle size was also closely related to the liquid concentration and mass flow rate (Fig. 4). In general, the particles with high initial concentration (3.5%) had

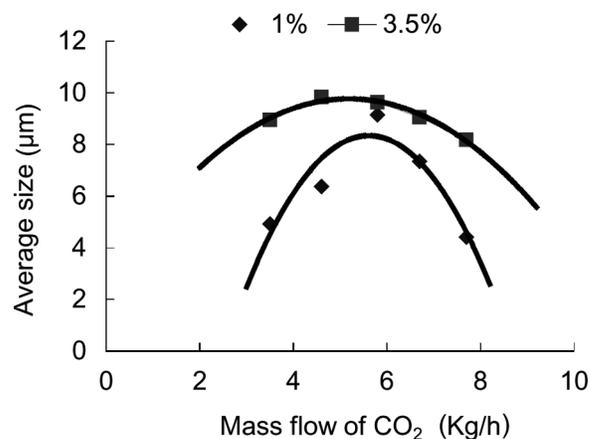


FIG. 4. Influence of solution concentration on the average size of particles ($T = 40^{\circ}\text{C}$, $P = 9 \text{ Mpa}$, $V = 0.108 \text{ m} \cdot \text{s}^{-1}$).

larger average size than that of low initial concentration. The high viscosity of the solution with high concentration could be the major reason of forming the large droplets and particles compared to the low concentration solution at the same flux of supercritical CO₂. At a certain cubage of droplets, large droplets might have small specific surface, reducing the mass transfer rate and increasing the time to reach supersaturation, which resulted in reduced numbers of nucleation formed and finally formed large particles. In addition, the particles might be more easily conglomerated together at higher solution concentration than at a low concentration. The observed results in this study were similar to that found by Taki et al.^[20] With poly-lactic acid as an example, it was found that the upper limit in the concentration for effectively producing particles was approximately 3.0%.

The effect of flow rate of carbon dioxide on the average size of particles was very similar to the influence of mass ratio of gas to solution on the particle size. In the tested range of solution flow rate, the average particle diameters ranged from 3.61 to 9.15 μm and from 8.19 to 9.84 μm when the ethyl cellulose concentrations were 1.0 and 3.5%, respectively.

Influence of Operation Temperature on Particle Size

The influences of temperature on the particle size and distribution are shown in Figs. 5 and 6. The average particle sizes increased with the increase of temperature. The particle size distribution was much wider at high temperature than at low temperature. This phenomenon could be explained through the characteristics of supercritical carbon dioxide. The density of supercritical carbon dioxide decreased with the temperature increase. This could lead to decreased solvency capacity of supercritical carbon dioxide, prolonged the time for droplets to reach supersaturation, and reduced rate of nucleation and the numbers of nuclears. As a result, the average size of particles increased

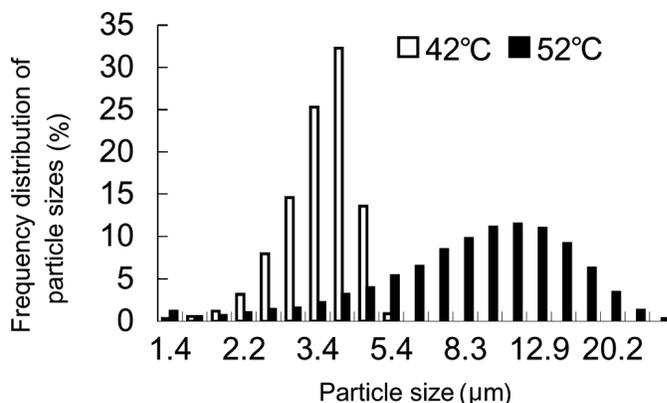


FIG. 6. Particle size distributions at different temperatures ($P = 9 \text{ Mpa}$, $V = 0.108 \text{ m} \cdot \text{s}^{-1}$, $C = 1\%$, $L = 3.5 \text{ kg} \cdot \text{h}^{-1}$).

since the particles were precipitated and separated out with a manner of nuclear growth. Meanwhile, the probability of the collision and conglomeration among those droplets increased due to the prolonged time for forming nucleation, which could reduce the uniformity of particles sizes and lead to a wide particle size distribution.

The particle size change under different processing temperatures was also related to the mass transfer process between droplets and supercritical carbon dioxide. The solvents in the droplets were gradually transferred toward the surface driven by the concentration gradient between the inner and surface of droplets. When the temperature increased, the solvency capacity of supercritical carbon dioxide decreased, which led to the reduced solvent transfer from the surface of droplets into supercritical carbon dioxide. The reduced transfer rate could decrease the concentration gradient between supercritical carbon dioxide and the solvents of droplets and further lower the evaporation of the solvent and increase the time for the droplets to reach supersaturation. Thus, the average size of particles was larger and the particle size distributions became wider

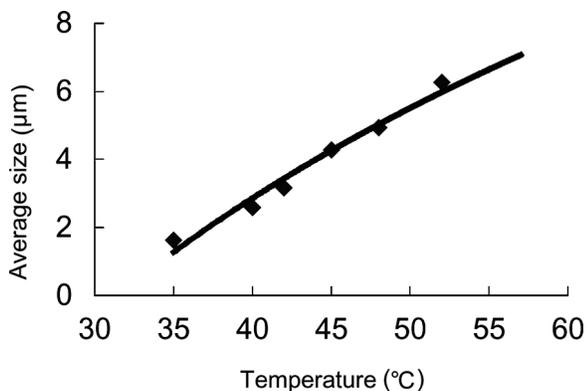


FIG. 5. Influence of temperature on the average size of particles ($P = 9 \text{ Mpa}$, $V = 0.108 \text{ m} \cdot \text{s}^{-1}$, $C = 1\%$, $L = 3.5 \text{ kg} \cdot \text{h}^{-1}$).

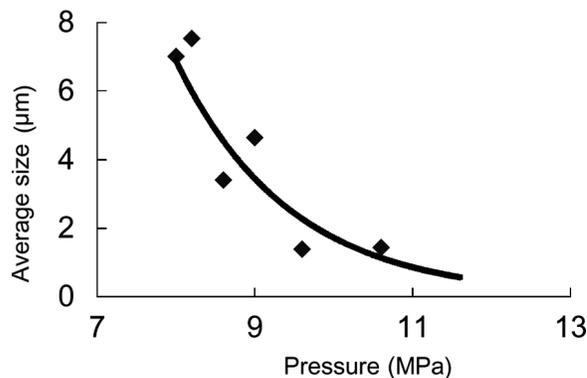


FIG. 7. Influence of pressure on the average size of particles ($T = 40^\circ\text{C}$, $P = 9 \text{ Mpa}$, $V = 0.108 \text{ m} \cdot \text{s}^{-1}$, $C = 1\%$, $L = 3.5 \text{ kg} \cdot \text{h}^{-1}$).

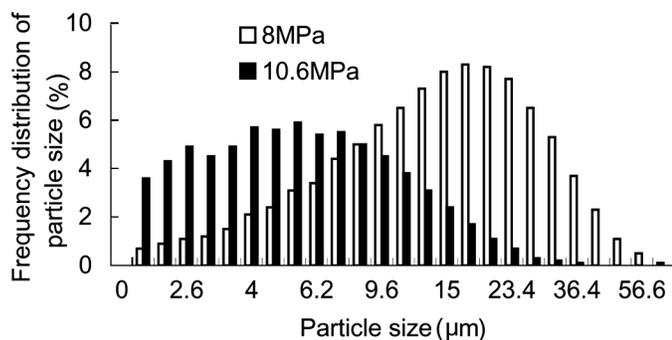


FIG. 8. Particle size distributions at different pressures ($T = 40^{\circ}\text{C}$, $P = 9\text{ Mpa}$, $V = 0.108\text{ m}\cdot\text{s}^{-1}$, $C = 1\%$, $L = 3.5\text{ kg}\cdot\text{h}^{-1}$).

at a high processing temperature than at a low temperature. Cocero also reported that conglomeration among particles was another reason causing the particle size increase at a high temperature.^[21] However, no obvious conglomeration of particles was observed in this study. The obtained average sizes of the particles ranged from 3.16 to 6.26 μm when the temperature was in the range of 40 to 52 $^{\circ}\text{C}$.

Influence of Pressure on Particle Size

Figures 7 and 8 show the influence of pressure on the average size and size frequency distributions of particles produce with the conditions of 40 $^{\circ}\text{C}$ temperature, carbon dioxide flow rate of 3.5 kg/h, liquid velocity at 0.108 m/s, and ethyl cellulose solution concentration of 1.0%. The average size of particles decreased and particle sizes were more uniform when the pressure increased.

Because the solvency of supercritical carbon dioxide can be enhanced with the increased density achieved by the increase of pressure, the evaporation and drying speed of the solvents inside droplets increased and resulted in small particle size. In addition, when the pressure of nozzle increased, the ethyl cellulose solution was atomized into small droplets resulting in increased contact area between CO_2 gas and the droplets and enhanced the rate of mass transfer between the two phases. Both favorable conditions could shorten the required time for the droplets to reach supersaturation. Therefore, the rate of nucleation and numbers of nuclear increased and the small particles and uniform particle size distributions were obtained at high pressure. However, if the pressure was too high, it could produce particles with undesirable shapes. Moshashae^[22] found that the dumbbell shape of particles and the conglutination of particles appeared under excessively high pressure.

CONCLUSIONS

The Influences of spray nozzle diameter, mass ratio of gas to liquid, solution concentration, temperature, and pressure on the physical characteristics of ethyl cellulose

particles were investigated. It is concluded that supercritical CO_2 could be used as drying medium of spray drying, and particles size ranged from 1.07 to 9.84 μm . The 8-mm nozzle produced smaller and more uniform particles than the 4-mm nozzle. The average particle size can be controlled from 2.80 to 9.15 μm by changing the mass ratio of CO_2 gas to liquid. High solution concentration can be used to produce large particles and wide particle size distribution. The average particle sizes ranged from 8.19 to 9.84 μm and from 3.61 to 9.15 μm , respectively, when the ethyl cellulose concentrations were 3.5 and 1.0%. The increased temperature resulted in increased particle size and size distribution. At the temperatures of 40 to 52 $^{\circ}\text{C}$, the average particle size was from 3.16 to 6.26 μm . The high processing pressure produced the particles with small and uniform sizes. When the pressures were from 8.0 to 10.6 MPa, the average sizes of ethyl cellulose particles were from 1.39 to 7.53 μm .

ACKNOWLEDGMENTS

This research was supported by Shanghai Leading Academic Discipline Project (No. T0503), and the National Natural Science Foundation of China (No. 30772183).

REFERENCES

- David, H.H. The Influence of the spray drying process on product properties. *Drying Technology* **2004**, *22* (6), 1261–1287.
- Gary, A.R. The spray drying of food flavors. *Drying Technology* **2004**, *22* (6), 1289–1324.
- Athanasia, M.G.; Konstantinos, G.A.; Nikolaos, A.K. Influence of spray drying conditions on tomato powder properties. *Drying Technology* **2004**, *22* (5), 1129–1151.
- Rodríguez-Hernández, G.R.; González-García, R.; Grajales-Lagunes, A.; Ruiz-Cabrera, M.A.; Abud-Archila, M. Spray-drying of cactus pear juice (*Opuntia streptacantha*): Effect on the physicochemical properties of powder and reconstituted product. *Drying Technology* **2005**, *23* (4), 955–973.
- Roustapour, R.; Hosseinalipour, M.; Ghobadian, B. An experimental investigation of lime juice drying in a pilot plant spray dryer. *Drying Technology* **2006**, *24* (2), 181–188.
- Mahmoud, A.; Yuh-Fun, M. Spray drying of biopharmaceuticals: Stability and process considerations. *Drying Technology* **2006**, *24* (6), 763–768.
- Maria, I.R. Formulating drug delivery systems by spray drying. *Drying Technology* **2006**, *24* (4), 433–446.
- Ozmen, L.; Langrish, T.A.G. A study of the limitations to spray dryer outlet performance. *Drying Technology* **2003**, *21* (5), 895–917.
- Junn, J.; Perrut, M. Particle design using supercritical fluids: Literature and patent survey. *The Journal of Supercritical Fluids* **2001**, *20*, 179–219.
- Bisson, A.; Rigacci, A.; Lecomte, D.; Rodier, E.; Achard, P. Drying of silica gels to obtain aerogels: Phenomenology and basic techniques. *Drying Technology* **2003**, *21* (4), 325–334.
- Tachiwaki, T. Supercritical fluid drying of aqueous 2-propanol suspension. *Drying Technology* **2004**, *22* (1&2), 325–334.
- Santos, I.; Richard, J.; Pech, B.; Thies, C.; Benoit, J.P. Microencapsulation of protein particles within lipids using a novel supercritical fluid process. *International Journal of Pharmaceutics* **2002**, *242*, 69–78.

13. Sieves, R.E.; Karst, L.; Milewski, P.D.; Sellers, S.P.; Miles, B.A.; Schaefer, J.D.; Stoldt, C.R.; XU, C.Y. Formation of aqueous small droplet aerosols assisted by supercritical carbon dioxide. *Aerosol Science and Technology* **1999**, *30*, 3–15.
14. Debenedetti, P.G.; Lim, G.B.; Prudhomme, R.K. Formation of protein microparticles by antisolvent precipitation. European Patent No. 0542314 A I, 1992.
15. Hile, D.; Mary, L.; Amirpour, A. Active growth factor delivery from poly (D, L-lactide-co-glycolide) foams prepared in supercritical CO₂. *Journal of Controlled Release* **2000**, *66*, 177–185.
16. Kompella, U.B.; Koushik, K. Preparation of drug delivery systems using supercritical fluid technology. *Critical Reviews in Therapeutic Drug Carrier System* **2001**, *18*, 173–199.
17. Reverchon, E. Supercritical antisolvent precipitation of micro-and nano-particles. *The Journal of Supercritical Fluids* **1999**, *15*, 10–21.
18. Reverchon, E.; Porta, G.D.; Falivence, M.G. Process parameters and morphology in amoxicillin micro and sub-microparticles preparation by supercritical antisolvent precipitation. *The Journal of Supercritical Fluids* **2000**, *17*, 239–248.
19. Thiering, R.; Dehghani, F.; Dillow, A. The influence of operating conditions on the densens precipitation of model proteins. *Journal of Chemical Technology and Biotechnology* **2000**, *75*, 29–41.
20. Taki, S.; Badens, E.; Charbit, G. Controlled release system formed by supercritical antisolvent coprecipitation of a herbicide and a biodegradable polymer. *The Journal of Supercritical Fluids* **2001**, *21*, 61–70.
21. Cocero, M.J.; Ferrero, S. Crystallization of carotene by a GAS process in batch effect of operating conditions. *The Journal of Supercritical Fluids* **2002**, *22*, 237–245.
22. Moshashae, S.; Bisrat, M.; Forber, R.T.; Quinn, E.A.; Nygvist, H.; York, P. Supercritical fluid processing of proteins I: Lysozyme precipitation from organic solution. *European Journal of Pharmaceutical Science* **2000**, *11*, 239–245.