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Formation of deagglomerated PLGA particles and PLGA-coated ultra fine powders by rapid expansion of supercritical solution with ethanol cosolvent

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Abstract−Rapid expansion of supercritical solution (RESS) was used for preparing polymer particles and polymer coating of ultra fine powders. The polymer of pharmaceutical interest was Poly(lactic-co-glycolic acid) (PLGA with PLA : PGA ratio of 85 : 15 and MW of 50,000-75,000) and the simulated core particles were 1.4-μm SiO_2 and 70-nm TiO_2 particles. The supercritical solution was prepared by dissolving PLGA in supercritical carbon dioxide with ethanol as a cosolvent. Supercritical solution of CO_2-PLGA was sprayed through capillary nozzles to ambient conditions, resulting in formation of submicron PLGA particles. Similarly, rapid expansion of supercritical solution of CO_2-PLGA suspended with the core particles could provide solvent evaporation and deposition of submicron PLGA particles on the surface of the core particles, resulting in the formation of coating films on dispersed particles of SiO_2 and agglomerates of TiO_2. The influences of the core particle size, spray nozzle diameter as well as powder-to-polymer weight ratio were also investigated and discussed with respect to the coating performance.

Key words: RESS, Powder Coating, Poly(lactic-co-glycolic acid), Agglomeration, Cosolvent

INTRODUCTION

Coating of powders has found its application in various industries, including pharmaceuticals, foods, agriculture and energetic materials. Normally, coating is considered as a shell-like barrier that protects powders from exposure to the environment or allows modification of powder surface functionality [1]. In the pharmaceutical industry, the general purposes of coating are to provide protection from rapid degradation, control of release rate and prevention of side effect of therapeutic agents. While the conventional process used for coating powders is generally based on fluidization technique, there is a limitation for powders smaller than 70 μm in diameter because of poor fluidization behavior [2]. Emulsion-based techniques, such as water-in-oil-in-water (w/o/w) double emulsions or solid-in-oil-in-water (s/o/w) emulsions, may be used for coating ultra fine powders. However, due to the common use of organic solvents and harsh processing conditions, these emulsion-based techniques involve some drawbacks including alteration of structure of therapeutic agent, presence of residual organic solvent in the coated powders and emission of volatile organic compounds to the environment [3,4].

In the last few decades, numerous attempts have been made on the application of supercritical fluids (SCFs) to overcome the problems of organic solvent in the conventional coating processes [5]. Supercritical fluids exhibit both liquid-like and gas-like properties with densities and solvating characteristics similar to those of the liquid and mass transfer similar to the gas. For pharmaceutical applications, carbon dioxide (CO_2) is the most commonly used SCF due to its inert properties, non-toxicity, non-polluting nature and mild critical conditions. Several studies have been reported on coating of microscale and nanoscale particles with polymers by using supercritical carbon dioxide (SC-CO_2) via different approaches [6-9]. Process variables, such as feed composition of polymer and size of the host particles, were experimentally found to be the key parameters affecting the coating performance in these processes.

The simplest SCF technique for formation of pharmaceutical particles and composite materials is the rapid expansion of supercritical solution (RESS) [10]. With the RESS technique, a solute is dissolved in SC-CO_2 and the solution is then instantaneously depressurized by spraying it through a capillary nozzle, causing precipitation of the solute as SC-CO_2 vaporizes. Submicron- and nano-sized dry particles with a narrow particle size distribution could be prepared from various pharmaceutical compounds and polymers [5]. Meanwhile, there are also other similar processes recognized as supercritical antisolvent (SAS) or gas antisolvent (GAS) [11], aerosol solvent extraction system (ASES) [12-14] and solution enhanced dispersion by supercritical fluids (SEDS) [15]. All of those processes exert both advantages and disadvantages depending on conditions of their applications.

In this study, the RESS process with a cosolvent is used to produce fine particles of polymer and the process is also modified for polymer coating of ultra fine powders. Microsize silica and nanosize titanium dioxide particles were chosen as preformed drug ultra fine powders, while Poly(lactic-co-glycolic acid) (PLGA) copolymer was used as the coating material. Basically, PLGA-coated ultra fine powders can be used to investigate simple-diffusion controlled release of the drugs in subcutaneous and intravenous applications [1]. Effects of the process parameters, which were the particle size of ultra fine core powder, spray nozzle diameter as well as powder-

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to-polymer weight ratio, and mechanism of the coating process are presented and discussed based on the characterization results of coated powders regarding morphology and internal structure of coated particles.

EXPERIMENTAL

1. Material

Microsize silica (SiO_2) particles with a mean size of 1.4 μm (Kojundo Chemical Lab, Japan) and nanosize titanium dioxide (TiO_2) particles with a mean size of 70 nm (Ishihara Sangyo Kaisha, Japan) were employed as core particles. Poly(lactic-co-glycolic acid) (PLGA) (PLA : PGA=85 : 15, molecular weight=62,000 and glass transition temperature=47.5 °C, Aldrich Chemicals Ltd.) and liquid CO_2 (critical temperature T_c=304 K, critical pressure P_c=7.4 MPa, Suzuki Shokan Co. Ltd., Tokyo, Japan) were used as coating agent and solvent. Due to the limited solubility of PLGA in SC-CO_2, ethanol (special grade; >99.5%; Kanto Chemical Co., Inc., Tokyo, Japan) was employed as cosolvent. All chemicals and materials were used as received.

2. Experimental Procedure

The experimental apparatus shown schematically in Fig. 1 consists of a high-pressure pump (3), a stirred high-pressure vessel (6), and a spray nozzle (9). The high-pressure pump was installed with a cooler before the suction part to avoid cavitation. The high-pressure vessel had a capacity of 1,500 ml and maximum allowable operating pressure and temperature of 30 MPa and 473 K, respectively. During each experiment, the vessel temperature was kept constant at 313 K by using an automatically controlled electric heater. The spray nozzle was simply made from a stainless steel tube with a length of 10 mm and was equipped with a shut-off valve. Two spray nozzles with different inner diameters of 0.1 mm and 0.3 mm were employed for investigating the effect of nozzle diameter on the coating process. Temperature of the nozzle was kept constant at 423 K by a ribbon heater to prevent the nozzle clogging with dry ice during spraying. A planar target (100 mm×100 mm×10 mm) covered with aluminum foil and a carbon-coated copper microgrid was employed to collect samples of particles generated from the spray for characterization.

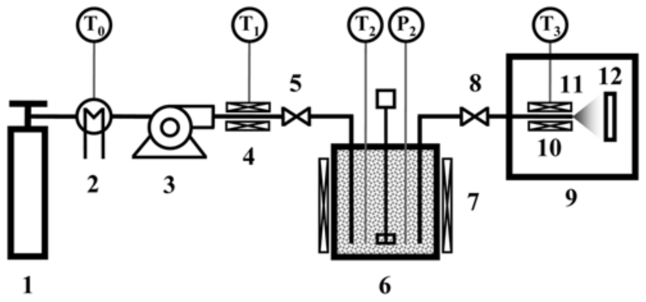


Fig. 1. Schematic diagram of the experimental apparatus.

1. CO_2 cylinder
2. Cooler
3. HPLC pump
4. Ribbon heater
5. Shut-off valve
6. Stirred high-pressure vessel
7. Vessel heater
8. Shut-off valve
9. Vacuum chamber
10. Ribbon heater
11. Nozzle
12. Target plate, or microgrid

The first part of the experimental work was carried out to investigate the applicability of the RESS process for generating polymer particles, which will be used to coat ultra fine powders. For RESS processing of a polymer, the information of its solubility in SC-CO_2 is crucial. To the best of our knowledge, there is no report on the solubility of PLGA in SC-CO_2. PLGA polymer used in our study has a limited solubility in SC-CO_2 because of its very high molecular weight (10). In order to increase the PLGA solubility in SC-CO_2 to a beneficial extent, ethanol was used as cosolvent. 2 g of PLGA with different amounts of ethanol were placed in the high-pressure vessel for preparation of SC-CO_2 solution. After being carefully sealed, the vessel was heated and fed with CO_2 via the high-pressure pump until the desired supercritical conditions were achieved. The mixture in the vessel was stirred by a mixing paddle rotating at 300 rpm, and was left for 3 hours to achieve equilibrium. The prepared supercritical solution was then sprayed through the nozzle to allow its rapid expansion. The target plate was placed against the sprayed flow at a distance of 300 mm from the nozzle tip within a chamber under atmospheric conditions.

In the second part of this work, performance of the RESS process to generate film coating of PLGA on ultra fine powders was investigated with the same apparatus. It is noteworthy that the ultra fine powder, PLGA and ethanol, in pure form, are not soluble in each other. Thus, they form an immiscible ternary mixture under atmospheric conditions. Experimental procedures similar to the first part were carried out so as to dissolve PLGA in SC-CO_2 with the aid of ethanol in the presence of fine SiO_2 or nanosize TiO_2 core particles. Under these conditions, the core particles were not dissolved but suspended in a single homogenous supercritical phase of CO_2, ethanol and the dissolved PLGA. The supercritical suspensions were then allowed to expand through the nozzle for a few seconds. It could be observed from each experiment that in the case of PLGA expansion without core powder, there is nothing remaining in the autoclave. However, when core powder and PLGA were taken into account, after expansion there would be some residues left in the vessel. After expansion, all coated particles were collected for characterization by using the target plate as already mentioned above. In order to evaluate the coating performance, effect of three process parameters, i.e., diameter of the spray nozzle, particle size of the core powder and powder-to-polymer weight ratio, on the coating characteristics was investigated. The experimental parameters and conditions used in this work are listed in Table 1. Fig. 2 depicts step-by-step conceptual representations of polymer particle formation and polymer coating of powder using RESS.

Field emission scanning electron microscopy (FE-SEM; Hitachi, S-900) was used to examine the particle samples obtained from each experiment. For SEM sample preparation, the aluminum foil uncovered from the target plate was cut into a small piece, mounted on a specimen stub with conductive paint and coated with platinum by a sputtering device (Hitachi, E-1030) for 20 s. The SEM was operated at an accelerating voltage of 10 kV and a magnification between 1,000 and 200 k. The SEM images were processed for particle size analysis by using image-analyzing software (Image-Pro Plus version 3.0; Media Cybernetics). For verification of polymer coating of the ultra fine powder, the particle samples on the microgrid were further analyzed by a transmission electron microscope (TEM; JEOL 2000-EX) operated at 200 kV in the bright-

Table 1. Experimental parameters and conditions of RESS processes

Material	Solvent	CO_2; P_c=7.4 MPa; T_c=304 K; T_0=266 K; T_1=353 K
	Cosolvent	ethanol; 0-21.8 wt%*
	Polymer	Poly(D,L-lactide-co-glycolide), PLGA; 85:15; M_w 50,000-75,000; T_g 318-323 K
	Powder	SiO_2; mean particle size 1.4 µm TiO_2; mean diameter 70 nm (for coating experiments)
	feed ratio**	1 : 1, 3 : 1 (for coating experiments)
Dissolution	Vessel	Cylinder; 1,500 ml
	Agitation	300 rpm; 180 min
	Conditions	P_2=25 MPa; T_2=313 K
Expansion	Nozzle	stainless steel; d=0.1, 0.3 mm; L=10 mm; T_3=423 K
	spraying time	3 s
	target distance	300 mm

* polymer-free basis; ** powder-to-polymer weight ratio

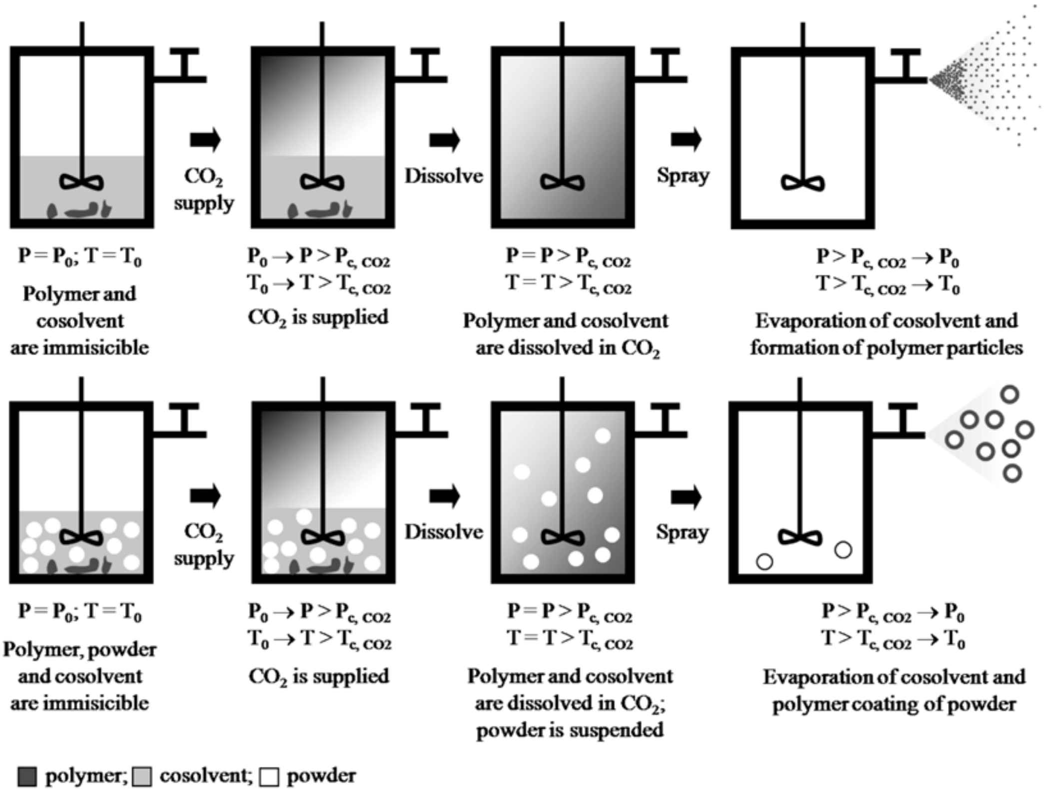


Fig. 2. Schematic representations of polymer particle formation process by RESS with a cosolvent (upper half) and powder coating process by rapid expansion of supercritical suspension with a cosolvent (lower half).

field mode. The mass-thickness contrast between the coating polymer and the core powder was analyzed to reveal the structures and morphology of the coated powders.

RESULTS AND DISCUSSION

1. Formation of PLGA Particles by RESS

Ethanol is a commonly used cosolvent in the RESS of CO_2-insoluble pharmaceutical materials due to its low toxicity. Although PLGA has limited solubility in either SC-CO_2 or ethanol, it was reported that the PLGA solubility becomes higher in the mixture of these two fluids [6]. Since ethanol is capable of being both donor and acceptor of hydrogen bonds, it can self-associate through hydrogen bonding with both CO_2 and PLGA, which leads to significantly improved PLGA solubility in SC-CO_2. The solubility enhancement of various polymers by ethanol cosolvent has been reported and discussed in several papers [16-20].

First, a solution of PLGA in SC-CO_2 plus ethanol was prepared at 25 MPa and 313 K. Under these conditions, CO_2 and ethanol become miscible at all compositions and form a single supercritical fluid phase [21-23]. A different amount of ethanol was added to the pressure vessel at 0, 100, 200, 300 and 400 ml, respectively. Because the amount of PLGA dissolved in the CO_2-ethanol mixtures was very small, compared to that of CO_2 and ethanol, the ethanol

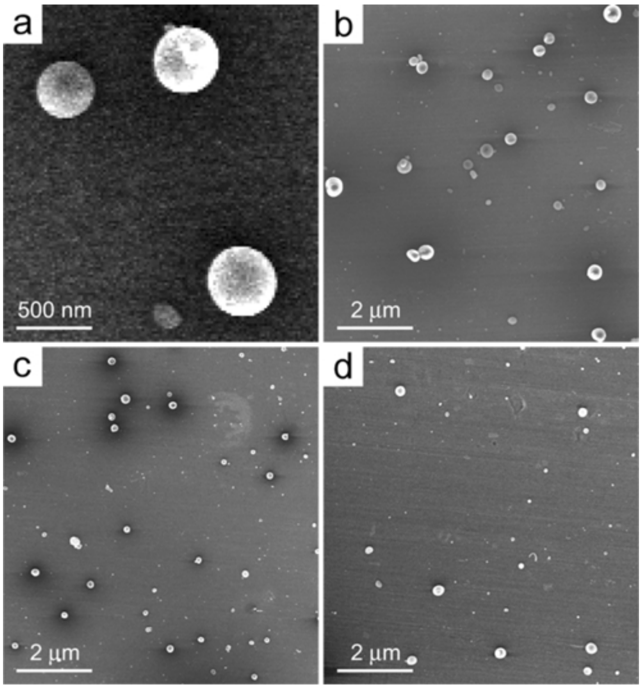


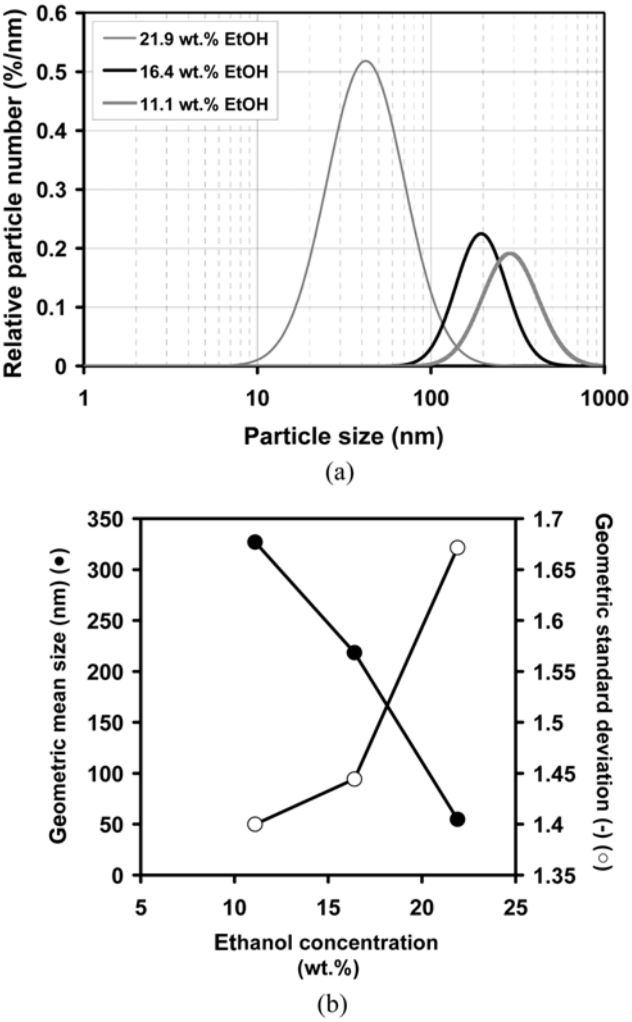
Fig. 3. SEM images of PLGA particles produced by RESS using ethanol cosolvent at different ethanol concentrations: (a) and (b) 11.1 wt%; (c) 16.4 wt%; (d) 21.8 wt%.

concentration in the mixtures could be estimated from the Patel-Teja cubic equation of state extended to binary mixtures [24], regardless of PLGA presence in the mixtures. The CO_2-ethanol interaction parameters used in the calculation were obtained from data reported in the literature [24,25]. According to the varied amount of ethanol mentioned above, the calculated values of polymer-free concentration of ethanol are 0, 5.7, 11.1, 16.4 and 21.8 wt%, respectively.

In experiments using pure CO_2 and CO_2 with 5.7 wt% ethanol, negligible amounts of polymer particles were detected in the collected samples under SEM observations, thereby indicating negligible particle formation during the RESS process. This implied that both the pure CO_2 and the CO_2 mixed with ethanol at 5.7 wt% were unable to dissolve PLGA to a sufficient extent; as a result, supersaturation was not achieved to trigger particle nucleation in these cases. On the other hand, Fig. 3 shows typical SEM images of PLGA particles produced by RESS using CO_2 mixed with ethanol at 11.1, 16.4 and 21.8 wt%. The charged amount of PLGA in SC-CO_2 with 21.8 wt% ethanol was approximately 0.17 wt% of the total amount of supercritical solution. Also in Fig. 3 it is clearly observable that the generated particles exhibit a nearly spherical shape with submicron size distributed in a narrow range.

Based on the experimental results, the formation of PLGA particles via RESS could be described as follows. Under the equilibrium condition of SC-CO_2, PLGA, CO_2 and ethanol would form a single homogeneous supercritical solution though saturation of PLGA was not yet achieved. During the rapid expansion, phase transition of CO_2 taking place in the post-expansion free jet would result in a drastic increase in PLGA concentration in the droplets, leading to precipitation of the dissolved polymer. As mentioned previously, since ethanol could not single-handedly dissolve PLGA, it also vaporized out during the expansion and then did not remain in the polymer [26]. Therefore, it is reasonable to consider that the precipitated polymer particles were solvent-free and did not undergo an agglomeration process because of its dilute solid content. These results suggested that the generated polymer particles could be used to coat some core particles.

Image analyses of typical SEM images of particle samples obtained from the experiments were carried out to determine their size distribution and morphology. At least 300 particles dispersed in different regions of the SEM images were taken into account in the determination of their size distribution. Fig. 4(a) reveals that the PLGA particles produced by RESS at different ethanol concentrations all exhibit log-normal size distribution behavior. The obtained geometric mean and standard deviation of the distribution were plotted as function of the ethanol concentration, as shown in Fig. 4(b). It is clearly seen that the particle size distribution of the prepared PLGA particles was strongly dependent on the ethanol concentration. As the ethanol concentration increased from 11.1 to 21.8 wt%, the particle geometric mean decreased to a minimum of 55 nm, while



(a)

(b)

Fig. 4. Dependence of particle size distribution of PLGA particles on ethanol concentration: (a) log-normal particle size distributions; (b) mean particle size and standard deviation of particle size distribution as function of ethanol concentration.

the geometric standard deviation increased to a maximum of 1.67. An increase in the ethanol concentration in the SC-CO_2 mixture resulted in an increase in the PLGA solubility, leading to higher supersaturation of PLGA in the sprayed mixture after its rapid expansion. According to the classical nucleation theory [27,28], higher nucleation rate and smaller critical nucleus size could be expected if the dissolved polymer concentration becomes increased. Meanwhile, a higher supersaturation ratio would also result in the occurrence of "nucleation bursts" which could generate several families of random size particles in the early stage of nucleation [29]. It is also noteworthy that an increase in the particle number concentration could provide higher coagulation frequency. These opposing phenomena were responsible for a smaller mean size but wider distribution of the resulting PLGA particles when a higher concentration of ethanol was used.

2. Effect of RESS on the Deagglomeration of Microsize Silica and Nanosize Titanium Dioxide Powders

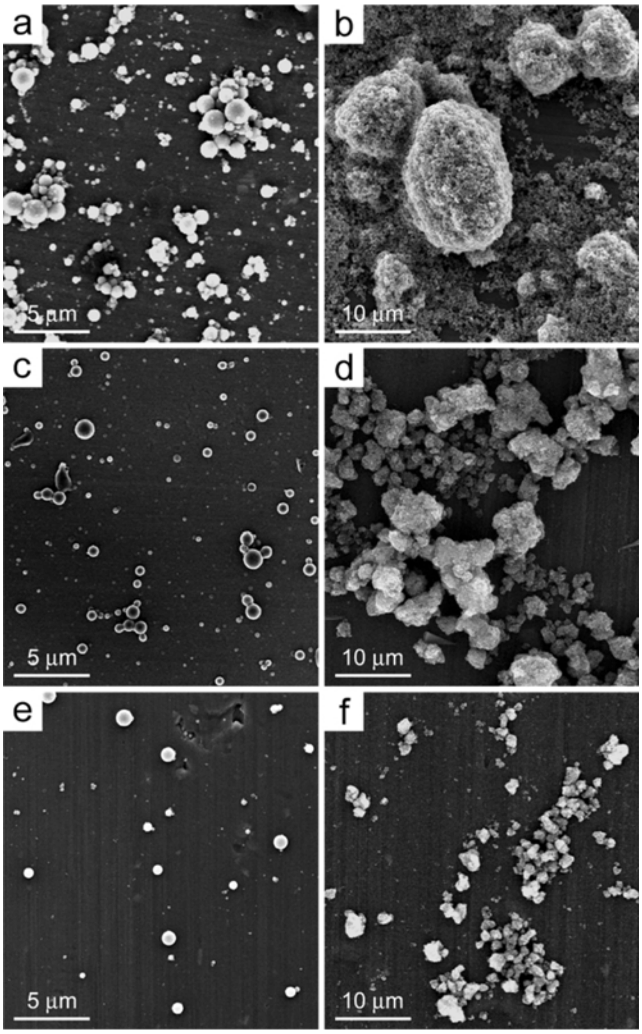


Fig. 5. Effect of diameter of spray nozzle on the deagglomeration of ultra fine powders. 1.4-μm silica: (a) before expansion; (c) after expansion (nozzle diameter 0.1 mm); (e) after expansion (nozzle diameter 0.3 mm). 70-nm titanium dioxide: (b) before expansion; (d) after expansion (nozzle diameter 0.1 mm); (f) after expansion (nozzle diameter 0.3 mm).

Ultra fine particles have a strong tendency to agglomerate due to their van der Waals interactions. In general, spontaneous agglomeration of ultra fine powders could take place and result in particle size enlargement and unstable processing conditions in the conventional coating processes [27]. In the RESS process, in which the expansion flow is considered as a supersonic or at least free jet, tempestuous turbulence is expected to be developed in the rapid expansion flow [30,31]. This turbulence could provide an advantageous contribution to the disintegration of agglomerates of ultra fine powders to facilitate the formation of a coating layer on the primary particles.

Fig. 5 shows typical SEM images of silica and titanium dioxide ultra fine particles before and after performing the rapid expansion of their suspensions in mixtures of SC-CO_2 and ethanol. The suspensions were prepared with 21.8 wt% ethanol in SC-CO_2 under conditions of 25 MPa and 313 K. Before rapid expansion, it could be observed that ultra fine powders could agglomerate to form large particles as revealed in Fig. 5(a) and Fig. 5(b). The agglomerate sizes are approximately 2-5 μm for the fine silica powder and 3-20 μm for the ultra fine titanium dioxide powder. Fig. 5(c), Fig. 5(d) and Fig. 5(e), Fig. 5(f) illustrate the change in the morphology of the ultra fine powders prepared by rapid expansion through nozzles with different diameters of 0.1 and 0.3 mm, respectively. Deagglomeration of the ultra fine powders was observed and consistently indicated by a decrease in the agglomerate size and an increase in the number concentration of primary particles. It could be implied that the dispersion and deagglomeration of the ultra fine powders were achieved as a combined result of boundary friction due to flow along the nozzle wall, turbulence in the high-velocity fluid and collisions between the ultra fine powder particles along the rapid expansion path. The boundary friction and the turbulence were responsible for fragmentation of large powder agglomerates into smaller ones, whereas the particle collisions could result in either particle coagulation or particle dispersion depending on relative velocities and collision angles of the particles. Comparison between the SEM images of particle samples produced by these two nozzles suggests that a better dispersion and deagglomeration effect was achieved with the bigger 0.3-mm diameter nozzle, and the effect was stronger for the larger silica fine powder. This reveals the influences of nozzle diameter and particle size of the ultra fine powder on the performance of dispersion and deagglomeration of the ultra fine powder in the rapid expansion process. As pointed out by Smith et al. [32], at the same pre- and post-expansion conditions, an increase of the nozzle diameter results in a higher Reynolds number, more turbulence, a higher total flow rate and a larger friction loss. In addition, with shorter residence time the probability of particle coagulation becomes lower. These lead to an improvement of the dispersion and deagglomeration of the ultra fine powders. Accordingly, the cohesive forces are smaller, the number concentration lower and the probability of particle coagulation lower for large particles compared with the small ones. The reasoning supports our experimental results that the dispersion and deagglomeration of the 1.4-μm silica powder were better than that of the 70-nm titanium dioxide powder. It should be noted that in case of the ideal condition, individual core particles should be obtained if agglomeration can be completely suppressed by the rapid expansion. Therefore, a smaller nozzle would reasonably be expected to provide the well dispersed core particles after the expansion. However, it was coincidentally found that the smaller nozzle was easily clogged. To avoid this difficulty as well as to obtain a favorable coating process with low-agglomeration tendency, the 0.3-mm diameter nozzle was selected for the coating of the ultra fine powders, which will be discussed in the next section.

3. Coating of Microsize Silica and Nanosize Titanium Dioxide Powders with PLGA by Rapid Expansion of Supercritical Suspensions

A series of experiments was carried out on coating 1.4-μm silica particles and 70-nm titanium dioxide particles with PLGA by rapid expansion of supercritical suspensions to investigate the effect of experimental parameters on coating performance. In all experiments, the supercritical suspensions were prepared by using the conditions at which the solubility of PLGA in the mixture of SC-CO_2 and ethanol could be determined, i.e., the supercritical pressure and temperature of 25 MPa and 313 K, the ethanol concentration of 21.8 wt% and the polymer solubility of 0.17 wt%. The powder-to-polymer weight ratio was varied through an adjustment of the powder concentration in the suspension by changing the amount of powder added to the high-pressure vessel at the beginning of each experiment.

Fig. 6 shows some samples of the morphology and internal structure of PLGA-coated silica fine powder produced by the rapid expansion of supercritical suspension process at different powder-to-polymer weight ratios. It appears that the coating of silica fine powder was achieved in the form of both individual dispersed particles and agglomerates. The coated silica particles exhibit a core-shell structure, as shown in the bright-field TEM images (Fig. 6(b) and Fig. 6(d)). Due to the stronger interactions between the electrons and silicon than that between the electrons and carbon (a major component of the polymer) in the TEM, the silica particles appear as a darker contrast area than the PLGA phase in these images. It is clearly seen that the darker contrast area is thoroughly covered by the lighter contrast area, indicating that the silica particles were completely coated with a layer of PLGA. The rapid expansion of a suspension of SC-CO_2-insoluble particles in the supercritical CO_2 solution of a polymer led to deposition of the polymer on the surface of the suspended particles, thereby generating polymer film coating on the particle surfaces [6,8]. Our experimental results are consistent with this explanation. When Fig. 6 is compared with Fig. 5(a), it is clear that, as a concurrent result of the rapid expansion of supercritical suspension, the dispersion and deagglomeration of the silica fine powder contributed to the low agglomeration tendency of the coated particles. It was observed that, at the powder-to-polymer weight ratio of 1, there was no significant agglomeration of coated silica particles that took place during the coating process (Fig. 6(a) and Fig. 6(b)), while the agglomeration process appeared to be enhanced when the powder-to-polymer weight ratio was increased to 3 (Fig. 6(c) and Fig. 6(d)). This is mainly attributable to the increased number concentration of silica particles in the rapid expansion flow, resulting in more frequent collisions and higher coagulation probability of the silica particles within the nozzle, and consequently an increase in the degree of agglomeration of the particles. In addition, it can be observed in the TEM images that the thickness of the coating layer was not uniform and estimated to be around 10-100 nm from the scale bar. It is likely that the PLGA particles, which precipitated and then deposited on the silica particle surface, spread and formed solid bridges between them, thereby resulting in growth of the coating layer. The strong turbulence in the rapid expansion flow dissipated much of the eddy energy [30], which can be considered to cause significant disturbances to the just-formed coating layer. It is interesting to note that, from our experimental results, the coating layer thickness seems not to be sensitive to the change in the powder-to-polymer weight ratio. As a possible assumption, the particle coagulation along the length of the nozzle during the rapid expansion flow plays a significant role in the coating process. Particle coagulation results in a drastic decrease in the particle number and a drastic reduction of the particle surface area, on which coating takes place. The higher the probability of particle coagulation, the more pronounced the reduction of the coating surface area and capability. Since the particle coagulation probability is proportional to the powder-to-polymer weight ratio in the coating process, it might be assumed that the change in powder-to-polymer weight ratio did not provide a significant change in the total coating surface area and it had no influence on the coating layer thickness.

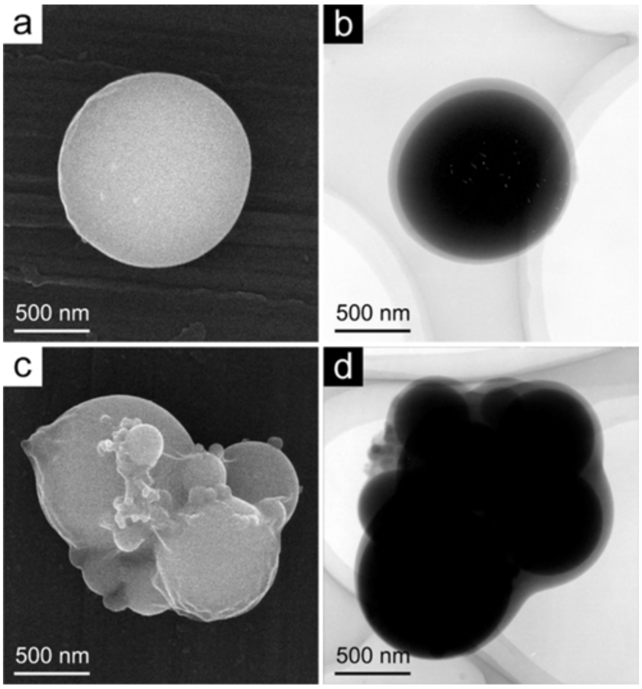


Fig. 6. SEM and TEM images of PLGA-coated silica fine powder produced by the rapid expansion of supercritical suspension process at powder-to-polymer weight ratios: (a) and (b) 1 : 1; (c) and (d) 3 : 1.

Similar results were obtained for the coating of 70-nm titanium dioxide ultra fine powder with PLGA, as shown in Fig. 7. When compared with Fig. 6, the experimental results shown in Fig. 7 suggest that the coating of titanium dioxide ultra fine powder with PLGA could also be achieved in the same process as that of silica fine powder. However, SEM and TEM images reveal that the coating of titanium dioxide ultra fine powder always took place in the form of agglomerates of primary particles. In Fig. 7(b) and Fig. 7(d), the coated particles are composed of an agglomerate of titanium dioxide particles in the core and a coat of PLGA as shown by the darker

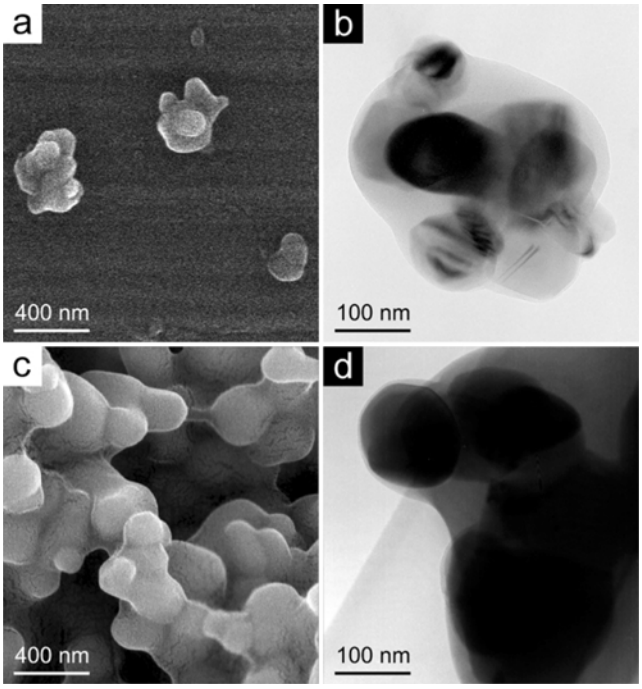


Fig. 7. SEM and TEM images of PLGA-coated titanium dioxide ultra fine powder produced by the rapid expansion of supercritical suspension process at different/specified powder-to-polymer weight ratios: (a) and (b) 1 : 1; (c) and (d) 3 : 1.

and the lighter contrast areas, respectively. It should be noted that no PLGA is observed in the void among the titanium dioxide particles, suggesting that the PLGA coat was formed as a growing layer on the titanium dioxide agglomerate surface, not a coalescence of coated primary particles. The agglomerate sizes are in the range of some hundred nanometers to a few microns, which is consistent with the typical size of agglomerates shown in Fig. 5(f). Obviously, the flow turbulence and friction loss generated during the rapid expansion of supercritical suspension process was not sufficient to disintegrate agglomerates into primary particles. This is attributable to the extremely strong adhesion forces among the nanosize titanium dioxide particles. The nonuniformity of the coat can also be observed in the TEM images, indicating the deposition of relatively large PLGA particles on the irregular surfaces of the titanium dioxide agglomerates. Anyway, the change of powder-to-polymer weight ratio from 1 : 1 to 3 : 1 did not cause a significant change in the coating layer thickness. The thickness is estimated from the scale bar to be around 10-100 nm, which is comparable to that of the fine silica particles. Based on all the experimental data shown previously, the potential mechanisms that would possibly contribute to the formation of coating on the ultra fine powders are schematically summarized as depicted in Fig. 8. Under the high-pressure condition, PLGA dissolved in supercritical CO_2 could be absorbed (wet) onto the surface of the core particles. In the figure, the wet coating layer on the surface of the core particles is represented by the dotted line covering the particle flowing within the nozzle. During the rapid expansion, the vaporization of CO_2 to the ambient leads to the formation of solidified PLGA film on the surface of core particles. Such coating layers would experience impaction among particles and shear forces due to high flow of surrounding gas, resulting in relatively uniform coating layer on the coated particles which would have

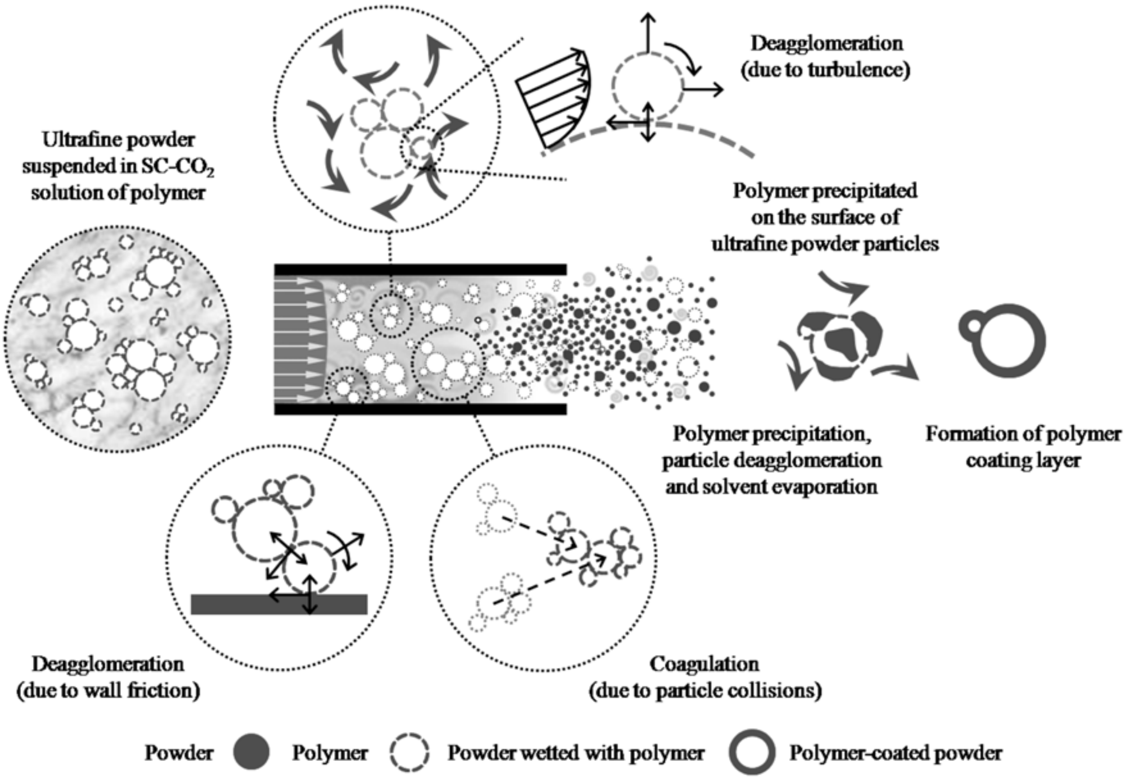


Fig. 8. Potential mechanism of polymer coating of ultra fine powder by the rapid expansion of supercritical suspension process.

some remaining agglomeration. The solidified polymer coating layer is represented by a thick solid line covering images of particles after being sprayed out of the nozzle.

CONCLUSIONS

The rapid expansion of supercritical solution process using ethanol as a cosolvent can produce non-agglomerated submicron particles of PLGA, which could favorably be used for coating ultra fine particles. The cosolvent concentration was found to play a key role in the control of PLGA particle size and size distribution. According to competitive influences of phase transition, turbulent flow, boundary friction and particle coagulation along the expansion path, the rapid expansion of supercritical suspension process exhibited two major phenomena, polymer precipitation and deagglomeration of ultra fine powders. These phenomena further resulted in a layer growth of polymer on the surface of deagglomerated ultra fine powders. Coating of the silica fine powder could be achieved in the form of both agglomerates and dispersed particles, depending on the powder-to-polymer weight ratio; whereas, coating in the agglomerate form was inevitable for the titanium dioxide ultra fine powder. In addition, nonuniformity of the coating layer was also observed. Surprisingly, the powder-to-polymer weight ratio appeared to have an insignificant effect on the thickness. To reduce agglomeration tendency, larger spray nozzle diameter, smaller powder particle size and low powder-to-polymer weight ratio are favorable. It is noteworthy that, in pharmaceutical applications, the RESS process with a cosolvent could be a promising environmentally friendly technique for coating CO_2-insoluble ultra fine drug particles with a high molecular-weight polymer with limited solubility in CO_2.

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REFERENCES

1. K. Jono, H. Ichikawa, M. Miyamoto and Y. Fukumori, *Powder Technol.*, **113**, 269 (2000).
2. D. Geldart, *Powder Technol.*, **7**, 285 (1973).
3. K. Fu, K. Griebenow, L. Hsieh, A. M. Klibanov and R. Langer, *J. Control. Release*, **58**, 357 (1999).
4. J. Wang, K. M. Chua and C. Wang, *J. Colloid Interf. Sci.*, **271**, 92 (2004).
5. J. Jung and M. Perrut, *J. Supercrit. Fluids*, **20**, 179 (2001).
6. K. Mishima, D. Tanabe and S. Yamauchi, *AIChE J.*, **46**, 857 (2000).
7. I. Ribeiro Dos Santos, J. Richard, B. Pech, C. Thies and J. P. Benoit, *Int. J. Pharm.*, **242**, 69 (2002).
8. A. Tsutsumi, M. Ikeda, W. Chen and J. Iwatsuki, *Powder Technol.*, **138**, 211 (2003).
9. Y. Wang, R. N. Dave and R. Pfeffer, *J. Supercrit. Fluids*, **28**, 85 (2004).
10. J. W. Tom, P. G. Debenedetti and R. Jerome, *J. Supercrit. Fluids*, **7**, 9 (1994).
11. S.-D. Yeo, P. G. Lim, G.-B. Lee and H. Debenedetti, *Biotechnol. Bioeng.*, **41**, 341 (1993).
12. P. G. Debenedetti, G. B. Lim and R. K. Prud'Homme, European Patent EP 0 542 314 (1992).
13. Y.-H. Choi, J.-W. Kim, M.-J. Noh, E.-M. Park and K.-P. Yoo, *Korean J. Chem. Eng.*, **13**, 216 (1996).
14. G-H. Li, J.-H. Chu, E.-S. Song, K.-H. Row, K.-H. Lee and Y. W. Lee, *Korean J. Chem. Eng.*, **23**, 482 (2006).
15. M. Hanna and P. York, Patent WO 95/01221 (1994).
16. M.-J. Noh, T.-G. Kim, I.-K. Hong and K.-P. Yoo, *Korean J. Chem. Eng.*, **12**, 48 (1995).
17. M. Zhong, B. Han and H. Yan, *J. Supercrit. Fluids*, **10**, 113 (1997).
18. B. Guan, Z. Liu, B. Han and H. Yan, *J. Supercrit. Fluids*, **14**, 213 (1999).
19. Q. Li, Z. Zhang, C. Zhong, Y. Liu and Q. Zhou, *Fluid Phase Equili.*, **207**, 183 (2003).
20. A. Chafer, T. Fornari, A. Berna and R. P. Stateva, *J. Supercrit. Fluids*, **32**, 89 (2004).
21. D. W. Jennings, R. J. Lee and A. S. Teja, *J. Chem. Eng. Data*, **36**, 303 (1991).
22. T. Susuki, N. Tsuge and K. Nakahama, *Fluid Phase Equili.*, **67**, 213 (1991).
23. C. Y. Day, C. J. Chang and C. Y. Chen, *J. Chem. Eng. Data*, **41**, 839 (1996).
24. N. C. Patel and A. S. Teja, *Chem. Eng. Sci.*, **37**, 463 (1982).
25. H. P. Gros, S. B. Bottini and E. A. Brignole, *Fluid Phase Equili.*, **139**, 75 (1997).
26. D. J. Dixon, K. P. Johnston and R. A. Bodmeier, *AIChE J.*, **39**, 127 (1993).
27. R. S. Mohamed, D. S. Halverson, P. G. Debenedetti and R. K. Prud'homme, *ACS Symp. Series*, **406**, 355 (1989).
28. P. G. Debenedetti, *Metastable liquids: Concepts and principles*, Princeton University Press, New Jersy (1996).
29. M. Giulietti, M. M. Seckler, S. Derenzo, M. I. Re' and E. Cekinski, *Braz. J. Chem. Eng.*, **18**, 423 (2001).
30. X. Y. Sun, T. J. Wang, Z. W. Wang and Y. Jin, *J. Supercrit. Fluids*, **24**, 231 (2002).
31. B. Helfgen, M. Turk and K. Schaber, *J. Supercrit. Fluids*, **24**, 231 (2003).
32. R. D. Smith, J. L. Fulton, R. C. Petersen, A. J. Kopriva and B. W. Wright, *Anal. Chem.*, **58**, 2057 (1986).