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Micronization of arbutine using supercritical anti-solvent

Chan Ik Park, Moon Sam Shin and Hwayong Kim†

School of Chemical and Biological Engineering and Institute of Chemical Processes,
Seoul National University, Seoul 151-744, Korea
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Abstract−Arbutine has been used as skin whitening agent in cosmetics and pharmaceuticals. The objective of this study was to precipitate arbutine micro-particles using a supercritical anti-solvent. Ethanol and supercritical CO_2 were used as solvent and anti-solvent, respectively, under various conditions. The effects of pressure, temperature and solution flow rate on the particles were studied. The particle size and morphology were analyzed by field emission scanning electron microscopy.

Key words: Arbutine, ASES, Supercritical, Anti-solvent

INTRODUCTION

Tyrosinase, a copper-containing enzyme, is involved in two reactions in melanin synthesis. One is the hydroxylation of a monophenol and the other is the conversion of an o-diphenol to the corresponding o-quinone. Too large an amount of melanin causes skin diseases, such as discolorations and freckles. Therefore, inhibitors to suppress the synthesis and activity of tyrosinase are required [1]. To date, hydroquinone, kojic acid, azelaic acid, corticosteroids, and retinoic acid have been used for this purpose. Hydroquinone is the most effective agent, but it is unstable and causes irritation. Thus, arbutine, 4-hydroxyphenyl-β-D-glucopyranoside, is the drug of choice because it has fewer negative side effects [2].

Many pharmaceutical and cosmetic drugs including arbutine are insoluble or only slightly so in water. The drugs, however, must be dissolved in water in order to be absorbed and to exert their effects. The bioavailability of the drug, the percentage of the drug absorbed compared to its initial dose, is limited by insolubility. Micronization of the drugs can be enhanced a drug's dissolution rate in a biological environment. Dissolution rates are a function of solubility and particle surface area, and the surface area can be increased through reduction of particle size [3]. The aerosol solvent extraction system (ASES) has been widely used for the production of fine particles using supercritical CO_2 [4-13]. It consists of atomizing a solution of the substrate in an organic solvent into a vessel. ASES uses the principle that supercritical CO_2 causes the solvent to lose affinity for the solute. The advantages of ASES are semi-continuous processing and a narrow particle size distribution. During the wash step, residual solvent is removed from the final particle.

We prepared arbutine micro-particles using supercritical anti-solvent, and then measured the effects of pressure, temperature and solution flow rate on the particles.

MATERIALS, APPARATUS, AND METHODS

1. Materials

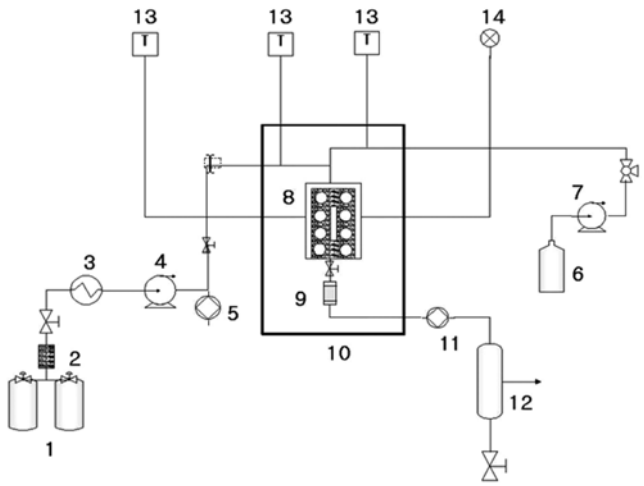


Fig. 1. Schematic diagram of the experimental apparatus.

1. Carbon dioxide bomb	8. Precipitator
2. Filter	9. Filter
3. Heat exchanger	10. Oven
4. High pressure pump	11. Back pressure regulator
5. Relief valve	12. Separators
6. Solution reservoir	13. Thermometer
7. High pressure pump	14. Pressure transducer

Arbutine (min. 99.0%) was supplied from BIOLAND. Ethanol (min. 99.5%) was supplied from Aldrich. Carbon dioxide (99.5%) was supplied from Korea Industrial Gases.

2. Apparatus and Methods

A schematic diagram of the semi-continuous ASES apparatus is shown in Fig. 1. The volume of the precipitator is about 100 cm^3 and the height is 200 mm. We prepared a 0.5 wt% solution of arbutine and ethanol. The solution was pumped with an HPLC pump (Hitachi, L-7110). The liquid CO_2 was pumped with a non-pulsating high pressure pump (Nihon Seimitsu Kagaku, NP-AX-70). The nozzle was made by Valco Instruments Co., and its inner diameter was 0.127 mm. The precipitator was heated in an air convection oven and pressurized with CO_2. The pressure precipitator was controlled with a backpressure regulator (Tescom, 26-1726-24-161).

†To whom correspondence should be addressed.
E-mail: hwayongk@snu.ac.kr

When temperature and pressure arrived at the set point, the solution of arbutine in ethanol was pumped through the CO_2, which was continuously supplied. After 60 min, the flow of the solution was stopped. Supercritical CO_2 was washed out of the precipitator, and any residual ethanol was washed from the particles for about 15 min. The arbutine particles were collected by filtration (Swagelok, pore size 0.5 m). The powder samples were observed with a field emission scanning electron microscope (FE-SEM, JSM-6700F). Particle size was analyzed directly in the laser diffraction beam as an aerosolized dry powder by using an RODOS dry powder accessory (Sympatec Gmbh, HELOS/BF). The measuring range of particle size was from 0.1 to 35 μm.

RESULTS AND DISCUSSION

The ASES process consists of atomizing a solution of the substrate in an organic solvent into a precipitator and causing precipitation of the product by rapid mass transfer of supercritical fluid and organic solvent. The solution-containing arbutine was injected into the precipitator, and was broken up into droplets by a fine nozzle. As the atomized droplet came in contact with the anti-solvent CO_2, the latter diffused into the solution and the solvent evaporated from the droplet surface. At this time, the solution became cloudy and nucleation followed. Particle size in the ASES process is controlled by the nucleation and growth rates of the particles. As the nucleation rate increases or growth rate decreases, the mean size of the particles decreases.

1. Effect of Temperature

The SEM image of unprocessed arbutine is shown in Fig. 2. The particles have a rod-like morphology and the mean particle size is about 20.43 μm. We performed experiments at various temperatures (313.15, 323.15, and 333.15 K). The experimental conditions are shown in Table 1, and the SEM images are shown in Fig. 3. As temperature was increased, the particles became larger and more aggregated.

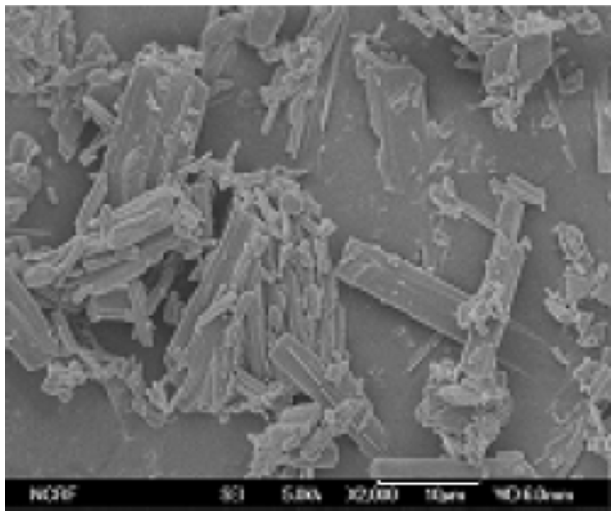
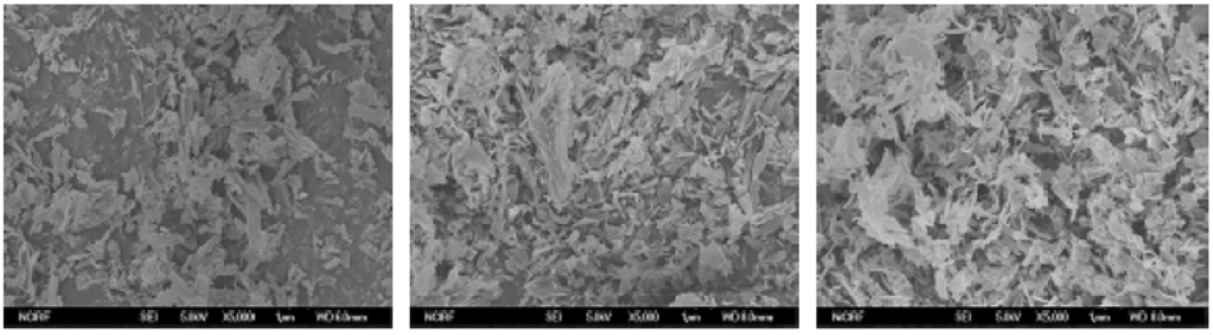


Fig. 2. SEM image of unprocessed arbutine.

As temperature was increased from 313.15 K to 333.15 K, CO_2 density was decreased from 0.641 g/cm^3 to 0.297 g/cm^3. As a result, a higher diffusivity and mass transfer were achieved. Consequently, particle size decreases with increasing temperature. On the other hand, particle size was analyzed by dimensionless Weber number [12,13] defined as the ratio of the deformation and the reformation

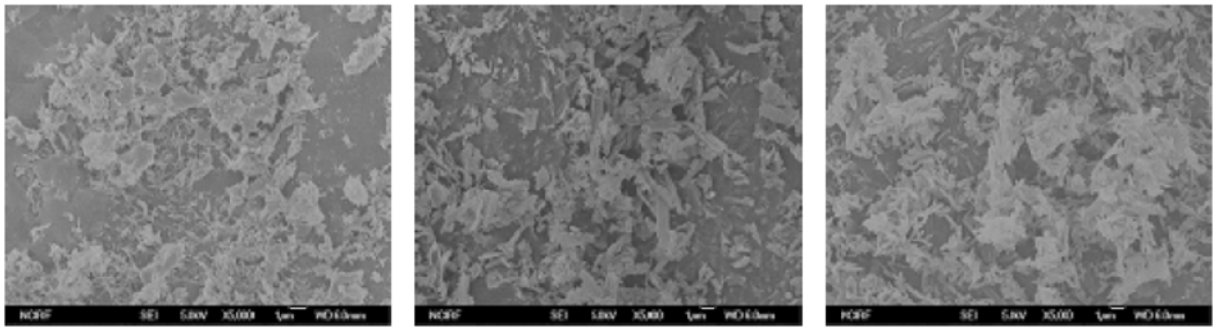
Table 1. ASES experimental conditions

Experiment no.	T [K]	P [MPa]	CO_2 flow rate [kg/hr]	Solution flow rate [cm^3/min]	Mean particle size (μm)
1	313.15	15.0	2.5	0.5	2.452
2	323.15	15.0	2.5	0.5	2.738
3	333.15	15.0	2.5	0.5	3.414
4	313.15	13.0	2.5	0.5	2.132
5	313.15	17.0	2.5	0.5	2.719
6	313.15	15.0	2.5	1.0	4.189
7	313.15	15.0	2.5	1.5	4.752



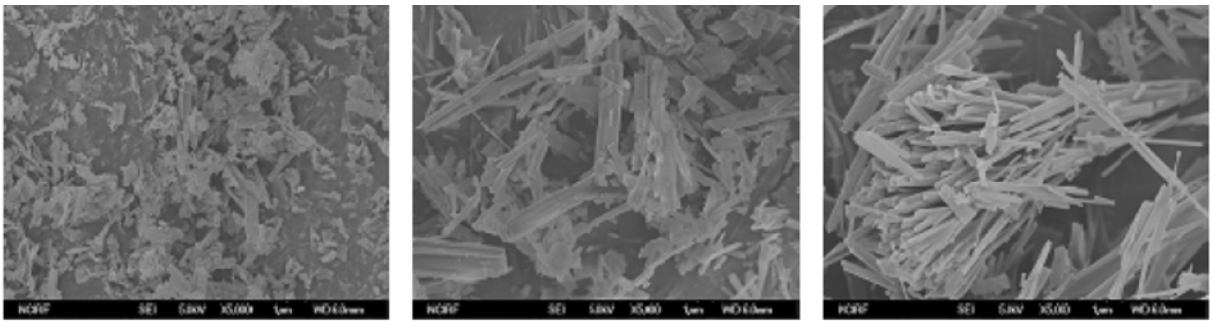
(a) (b) (c)

Fig. 3. SEM images of arbutine processed at various temperatures. (a) 313.15 K (b) 323.15 K (c) 333.15 K.



(a) (b) (c)

Fig. 4. SEM images of arbutine processed at various pressures. (a) 13 MPa (b) 15 MPa (c) 17 MPa.



(a) (b) (c)

Fig. 5. SEM images of arbutine processed with different solution flow rates. (a) 0.5 cm^3/min (b) 1.0 cm^3/min (c) 1.5 cm^3/min.

forces. In general, the higher the Weber number, the smaller the droplets are as a result of atomization. As the temperature was increased, a lower CO_2 density in the numerator of Weber number caused the lower Weber number. As a result, particle size increases with increasing temperature. Therefore, it can be explained that the effect of atomization dominates that of mass transfer in this experiment.

2. Effect of Pressure

We conducted the experiment at various pressures (13, 15, and 17 MPa). The SEM images are shown in Fig. 4. As pressure increased, the particle size also increased. As pressure was increased, CO_2 density and viscosity were increased and diffusivity of CO_2 was decreased. In general, reduced diffusivity and increased viscosity hinder mass transfer between the droplets and the surrounding CO_2, so particle size must be increased with increasing pressure. But, increasing pressure led to fine droplets due to increasing aerodynamic force and breakup. Thus, various particle sizes were obtained with every pressure increment due to the contrary effect of mass transfer and atomization on particles.

3. Effect of Solution Flow Rate

Experiments were performed at various solution flow rates (0.5, 1.0, and 1.5 cm^3/min). The SEM images are shown in Fig. 5. As solution flow rate increased, the particle size increased. High solution concentrations increased particle size as a consequence of the higher particle growth rate and coagulation among the particles.

CONCLUSIONS

In this study, microsized particles of arbutine were successfully produced by the ASES process. The atomization and mass transfer, which affect the particle size, were adjusted by controlling the temperature, pressure and solution flow rate. The particle size was increased with increasing temperature because of the predominant effect of atomization by jet breakup and hydrodynamics than enhancing the mass transfer which occurred between the droplets and the surrounding CO_2. The particle size was also increased with increasing pressure due to the predominant effect of reducing mass transfer rather than enhancing atomization. Increasing solution flow rate increased particle size because of the higher particle growth rate and coagulation among the particles. Therefore, the particle size of arbutine can be easily adjusted by using the ASES process by controlling the temperature, pressure and solution flow rate.

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