Formation of Microcapsules of Medicines by the Rapid Expansion of a Supercritical Solution with a Nonsolvent

Kiyoshi Matsuyama,[1] Kenji Mishima,[1,2] Ken-Ichiro Hayashi,[1] Hideharu Ishikawa,[1] Hideto Matsuyama,[3] Toru Harada[4]

[1]*Department of Chemical Engineering, Faculty of Engineering, Fukuoka University, 8-19-1 Nanakuma Jonanku, Fukuoka 814-0180, Japan*
[2]*Advanced Materials Institute, Fukuoka University, 8-19-1 Nanakuma, Jonanku, Fukuoka 814-0180, Japan*
[3]*Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyoku, Kyoto 606-8585, Japan*
[4]*Mitsubishi Gas Chemicals Company, Incorporated, Tokyo Research Laboratory, Niijuku, Katsushikaku, Tokyo 125-0051, Japan*

Received 25 January 2002; accepted 21 October 2002

ABSTRACT: The rapid expansion from a supercritical solution with a nonsolvent (RESS-N) was applied to the formation of polymeric microcapsules containing medicines such as *p*-acetamidophenol, acetylsalicylic acid, 1,3-dimethylxanthine, flavone, and 3-hydroxyflavone. A suspension of medicine in carbon dioxide (CO_2) containing a cosolvent and dissolved polymer was sprayed through a nozzle to atmospheric pressure. The pre-expansion pressure was 10–25 MPa, and the temperature was 308–333 K. The polymers were poly(L-lactic acid) (molecular weight = 5000), poly(ethylene glycol) (PEG; PEG4000, molecular weight = 3000; PEG6000, molecular weight = 7500; and PEG20000, molecular weight = 20,000), poly(methyl methacrylate) (molecular weight = 15,000), ethyl cellulose (molecular weight = 5000), and PEG–poly(propylene glycol)–PEG triblock copolymer (molecular weight = 13,000). The solubilities of the polymers as coating materials and these medicines as core substance were very low in CO_2. However, the solubilities of these polymers in CO_2 significantly increased with the addition of low molecular weight alcohols as cosolvents. After RESS-N, polymeric microcapsules were formed according to the precipitation of the polymer caused by a decrease in the solvent power of CO_2. This method offered three advantages: (1) enough of the coating polymers, which were insoluble in pure CO_2, dissolved; (2) the microparticles of the medicine were encapsulated without adhesion between the particles because a nonsolvent was used as a cosolvent and the cosolvent remaining in the mixture was removed by the gasification of CO_2; and (3) the polymer-coating thickness was controlled with changes in the feed composition of the polymer for drug delivery. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 89: 742–752, 2003

Key words: microencapsulation; drug delivery systems

INTRODUCTION

The microencapsulation of medicines suitable for sustained-release preparation and transdermal preparation has been attracting a significant amount of attention in the field of controlled-release applications.[1–4] For controlled drug release in the body, it is often desirable to produce globular polymer particles, approximately 10 μm in diameter, containing medicine.[5] Many studies have investigated the preparation of medicines coated with polymers for controlled-release applications.[2,5,6] The development of microencapsulation methods with environmentally benign solvents has been difficult because solvent impurities are often toxic and also degrade medicines within the polymer matrix. Recently, the pharmaceutical industry has put significant effort into its social obligation to reduce the amount of toxic organic solvents and surfactants discharged into the environment and to form environmentally benign microcapsules of medicine without toxic organic solvents or surfactants.

Fluidized-bed coatings and spray coatings have been suitable only for particles greater than about 100 μm in diameter because of particle coalescence and adhesion.[1,3,5,7,8] For microparticles smaller than 100 μm, coating methods such as coacervation and *in situ* polymerization could be used.[1,5,7,8] However, these methods have some faults, such as the use of toxic organic solvents or surfactants and the difficulty in controlling capsule size. It is desirable to develop a novel microencapsulation method that avoids the use of toxic organic solvents and surfactants and allows easy control over capsule size. Therefore, we have been challenged to develop a novel polymer microencapsulation process that emits no such chemicals into

Correspondence to: K. Mishima (mishima@fukuoka-u.ac.jp).
Contract grant sponsor: Japanese Ministry of Education, Science, Sports, and Culture; contract grant numbers: 14550743 and 13750706.
Contract grant sponsor: Hosokawa Particle Technology Promotion Foundation.

our environment and controls the capsule size with the supercritical fluid (SCF) technique.

Carbon dioxide (CO_2) can be used as an environmentally benign solvent substitute for hydrocarbons, chlorofluorocarbons, and other organics.[9–16] Because CO_2 is essentially nontoxic, nonflammable, and inexpensive and has easily accessible critical conditions, such as T_c = 304 K and P_c = 7.37 MPa, SCFs including CO_2 have been used in a process called rapid expansion from a supercritical solution (RESS) to produce a variety of organic and inorganic powders and fibers by many investigators.[17–27] Most of the RESS studies of polymers have used organic solvents, such as C_1–C_5 alkanes and alkenes, as well as chlorofluorocarbons. In SCF technology, there is a great effort underway to attempt to replace these types of solvents with CO_2.[10–16,28,29] Although a few attempts have been made to use CO_2 for RESS of polymers,[9,24,25,27] RESS of polymer solutions of CO_2 has been limited by low polymer solubility in CO_2. Because CO_2 has no dipole moment and a low cohesive energy density, it dissolves only polymers with very low cohesive energy densities, such as poly(dimethyl siloxane)s, atactic polypropylene, and polymethacrylates with hydrocarbon branches.[9,30]

In our previous work,[31,32] a novel method, rapid expansion from a supercritical solution with a nonsolvent (RESS-N), has been reported for forming polymer microparticles containing proteins and for forming polymer microspheres to reduce the amount of toxic organic solvents and surfactants discharged into the environment. In the RESS-N process, a suspension of proteins in a CO_2-containing cosolvent and a dissolved polymer is sprayed through a nozzle to atmospheric pressure. The solubilities of the polymers in CO_2 increase significantly with low molecular weight alcohols as cosolvents. The particles do not tend to agglomerate after expansion because the pure cosolvent is a nonsolvent for the polymer. The thickness of the polymer coating on the protein, as well as the mean diameter and particle size distribution, can be controlled by changes in the feed composition of the polymer. However, this process has not been applied to the encapsulation of medicines, which are relatively dissolved in a mixture of supercritical carbon dioxide (SC-CO_2) and a cosolvent.

Our objectives are to apply the RESS-N process to the formation of microcapsules of medicines without adhesion and to develop a method for controlling the coating thickness of microcapsules for controlled-release applications. Figure 1 provides a conceptual framework for the process. Because the polymers are insoluble in CO_2 at our operating temperatures and pressures, several cosolvents are used to enhance the solubility of the polymer in the SCF. In the pure form, these cosolvents are nonsolvents for the polymers. They are only sparingly soluble in the polymer particles produced during expansion. Because a cosolvent does not swell the polymer product, it is not expected to cause adhesion.[31,32] For polymers, it has been demonstrated that cosolvents that cause large increases in solubility in CO_2 need not be good solvents for the polymer. The solubilities of polymers in mixtures of CO_2 and low molecular weight alcohols are much higher than those of low molecular weight solutes such as medicines. In this study, we take advantage of the differences in the solubilities of the medicine and polymer in the CO_2–cosolvent mixture. During RESS-N, the polymer precipitates and coats the medicine microparticles.

The first part of this study explores the solubility behavior for polymer and medicine weight percentages approaching 25 wt % as a function of the cosolvent concentration. The second part examines the performance of the RESS-N microencapsulation process for the medicine in terms of the particle morphology, particle size distribution, and other properties.

EXPERIMENTAL

Materials

To check the applicability of the RESS-N process, we used five pharmaceutically acceptable polymers as coating materials. The polymers were poly(ethylene glycol) (PEG) fractions (PEG4000, molecular weight = 4000; PEG6000, molecular weight = 7500; and PEG20000, molecular weight = 20,000), poly(methyl methacrylate) (PMMA; molecular weight = 15,000), poly(L-lactic acid) (PLA; molecular weight = 5000), ethyl cellulose (EC; molecular weight = 5000), and PEG–poly(propylene glycol) (PPG)–PEG triblock copolymer (molecular weight = 13,000; PEG/PPG = 0.85/0.15). PEG, PLA, and EC were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). PMMA was purchased from Aldrich Co., Ltd. (Milwaukee, WI). PEG–PPG–PEG copolymer samples were donated by Dai-ichi Seiyaku Co., Ltd. (Tokyo, Japan).

Five low molecular weight medicines were used as core materials. The medicines were *p*-acetamidophenol, acetylsalicylic acid, 1,3-dimethylxanthine, flavone, and 3-hydroxyflavone (Wako Pure Chemical Industries), which had purities greater than 95.0, 99.5, 97.0, 98.0, and 98.5%, respectively. The chemical structures of these medicines are listed in Table I. All the medicines were used without further purification. Methanol, ethanol, 1-propanol, and toluene, used as cosolvents, were purchased from Wako Pure Chemical Industries, and these purities were believed to be greater than 98%. All the alcohols were kept over activated molecular sieves (3 Å) and used without further purification. The purity of CO_2 (Fukuoka Sanso Co., Fukuoka, Japan) was greater than 99.9%. A 0.5 wt % aqueous solution of ruthenium tetroxide

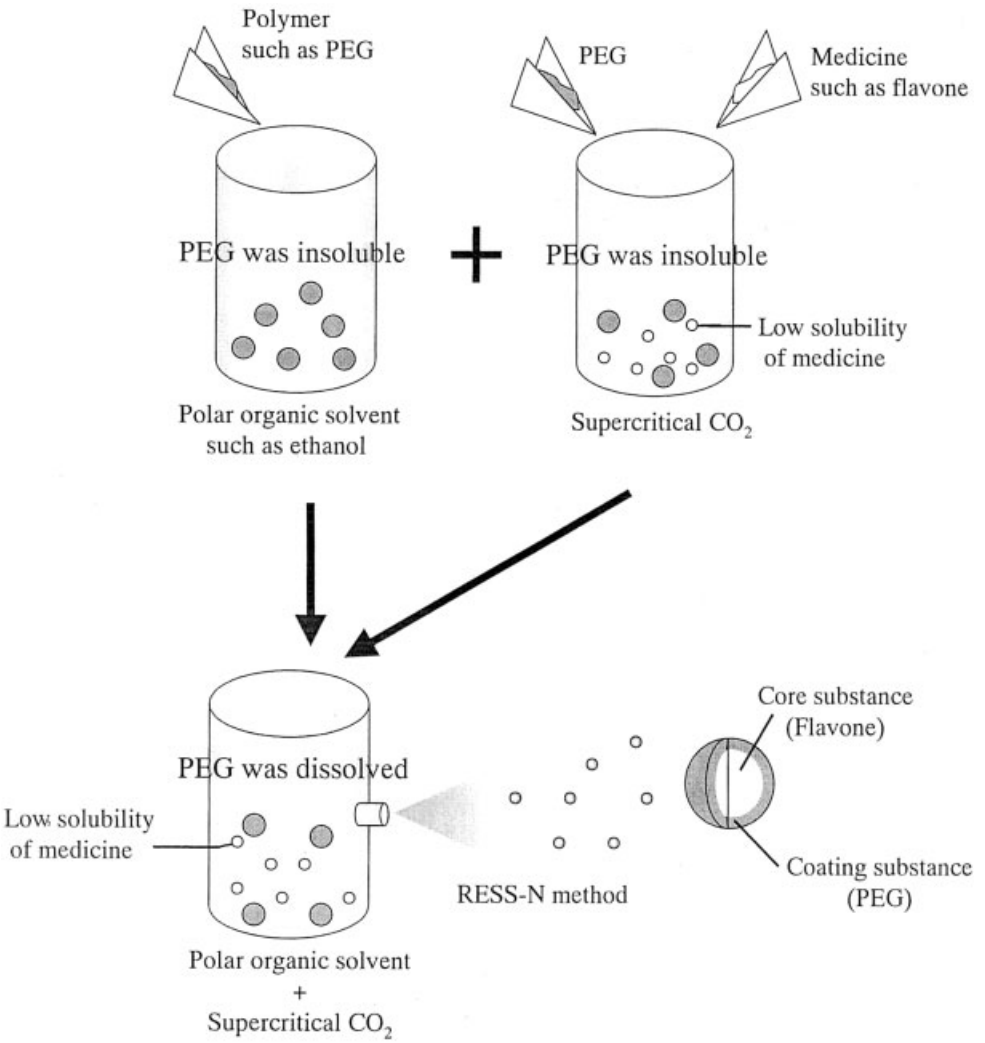


Figure 1 Formation of polymeric microcapsules with the rapid expansion of SCF.

(RuO_4) was used to stain medicines (Electron Microscopy Sciences Co., Fort Washington, PA) for transmission electron microscopy (TEM).

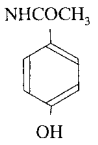
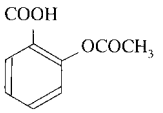
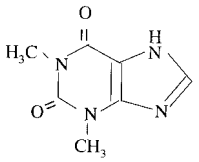
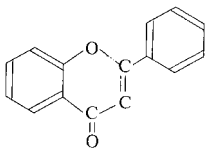
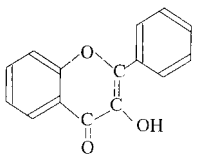
Supercritical fluid chromatography (SFC)

The solubilities of medicines, such as *p*-acetamidophenol, acetylsalicylic acid, 1,3-dimethylxanthine, flavone, and 3-hydroxyflavone, in mixtures of SC-CO_2 and 25 wt % cosolvent (polymer-free base) were measured by SFC (Super200, Jasco Co., Ltd., Tokyo, Japan). A detailed description of the apparatus and operating procedures has been given elsewhere.[33–35] The solubilities were determined from the degree of retention of the solute in SFC.

Observing the cloud point

The solubilities of the polymers in mixtures of SC-CO_2 and a cosolvent were determined by the visual observation of the cloud point with an experimental apparatus described previously.[36,37] Recently, several investigators determined the solubility of polymers by variable-volume view cells.[26] We used a similar experimental apparatus. In this work, the cloud point is defined as the point at which a solution turns slightly translucent. A 500-cm^3 high-pressure equilibrium cell (LC-5, Toyo Koatsu Co., Ltd., Hiroshima, Japan), equipped with sapphire windows (10 × 140 mm) for the observation of the phase behavior, was placed in a thermostated air chamber controlled to ±0.05 K. The temperature was measured within ±0.01 K with a thermocouple installed inside the cell. The system pressure was controlled by a back-pressure regulator (accurate to 0.1 MPa; model 26-1721-24, Tescom Co.) and measured with a precise Bourdon-tube gauge (accurate to ±0.3%; AT1/2, Yamasaki Keiki Co., Tokyo, Japan). After a known amount of the polymer was loaded, the entire system was purged with nitrogen. Known amounts of CO_2 and the cosolvent were charged into the equilibrium cell with a CO_2 pump (NRXM-90-G5M, Akico Co., Tokyo, Japan) and a sam-

TABLE I
Chemical Structures of *p*-Acetamidophenol, Acetylsalicylic acid, 1,3-Dimethylxanthine, Flavone, and 3-Hydroxyflavone

Substance	Chemical structure
p-Acetamidophenol	
Acetylsalicylic acid	
1,3-Dimethylxanthine	
Flavone	
3-Hydroxyflavone	

ple feed pump (HPD-200, Akico). The CO_2 pump was capable of delivering up to 590 bar at a rate of up to 5.2 $dm^3\ min^{-1}$ (liquid CO_2 basis). The impurities in CO_2 were removed through an in-line dryer (3001-17001, GL Science, Inc., Tokyo, Japan) and a filter (SS-2TF-2, Nupro Co., Tokyo, Japan). The refrigeration unit (Carry Cool, Orion Co., Tokyo, Japan) was equipped to prevent liquid CO_2 from vaporizing during the suction stroke of the pump. CO_2 was charged by the actual weight with a CO_2 pump that measured the total flow rate at a controlled temperature. The actual weight of CO_2 was calibrated with a wet-gas meter. The mixture of CO_2, cosolvent, and polymer was stirred with an agitator rotating at 150 rpm for 2 h and then was kept for more than 48 h without agitation at 308 K.

A certain amount of the cosolvent was added to the equilibrium cell until a cloud point was detected. When the cosolvent was added, the system pressure was maintained with a syringe tank (model 6010-1503, GL Science) equipped with a piston for adjusting the volume. The volume of the syringe tank was determined by the measurement of the piston position with a magnet installed in the piston. Near the cloud point, the cosolvent was carefully charged at longer than 30-min intervals. After we found the cloud point, the mixture was stirred for more than 1 h and then kept for more than 12 h without agitation to confirm that the polymer did not precipitate.

Details concerning the experimental apparatus and procedures for making polymeric microcapsules have been described in previous articles.[31,32] The parts of this apparatus for charging the CO_2 and cosolvent were similar to those for the polymer solubility measurements. A high-pressure cell (LC-3, Toyo Koatsu), about 500 cm^3 in volume, was equipped with sapphire windows (10 mm in diameter). The pre-expansion pressure was raised at 5-MPa intervals from 10 to 25 MPa. The system pressure was controlled by a back-pressure regulator (accurate to 1 bar; model 26-1721-24, Tescom) and monitored by a digital pressure gauge (accurate to $\pm 0.3\%$; model DD-501, Shinwa Electronics Co., Tokyo, Japan). The temperature was controlled to within ± 0.1 K with a water bath. Known amounts of the polymer, medicine, and cosolvent were placed in the high-pressure cell. SC-CO_2 was pumped through a stainless steel tube preheater (3 meter long $\times$ 1/8 in.) and then into the high-pressure cell. This mixture was magnetically stirred by an agitator rotating at 200 rpm for about 4 h and then kept for more than 1 h without agitation. Before the expansion of the polymer solution, it was confirmed visually that all of the feed polymer was dissolved and that the solution was homogeneous. The polymer solution was sprayed toward a target aluminum plate (30 mm $\times$ 60 mm $\times$ 1 mm) through a stainless steel capillary nozzle (model 500017-TC, Spraying Systems Co., Wheaton, IL) 0.28 mm in diameter and 0.5 mm long for a short time ($<$3 s) by the opening of a valve placed before the nozzle. The nozzle was maintained at 313 K with an electric heater. The target plate was placed in a chamber (70 cm $\times$ 80 cm $\times$ 80 cm) under atmospheric pressure. The distance from the tip of the nozzle to the plate was varied from 10 to 50 cm. The expansion produced polymer microcapsules. After sedimentation of the microcapsules, they were collected throughout the entire chamber.

Characterization

The microparticles were analyzed by TEM (200CX, JEOL, Tokyo, Japan) and scanning electron microscopy (SEM; S-2100B, Hitachi, Tokyo, Japan). For the sample preparation for TEM, the microparticles obtained from RESS were hardened with an epoxy-resin glue as blocks. These blocks were trimmed with a razor blade to form blocks of approximately 5 mm $\times$ 5 mm $\times$ 2 mm. These blocks were further trimmed into pyramids with the tips faced off to an area of 0.2 mm $\times$ 0.2 mm. A microtome (Ultracut E, Reichert-Jung, New York) was used to obtain ultrathin sections (15–50 nm thick) of the samples. Sectioning was performed under cryogenic conditions (223 K) with a

TABLE II
Solubilities of the Polymers and Medicines in Ethanol and Mixtures of SC-CO_2 and Ethanol at 308 K and 16 MPa

Substance	Solubilities of the polymer [wt %]			
	Measured		Calculated[a]	
	In pure solvent (pure ethanol)	In 25 wt % cosolvent solution of SC-CO_2, w_p^{exp} (polymer-free basis)	Mean value of solubilities in 25 wt % cosolvent solution of SC-CO_2, w_p	Cosolvency effect[b] Δw_p (wt %)
p-Acetamidophenol	13.2	0.21	3.30	−3.09
Acetylsalicylic acid	11.5	0.12	2.86	−2.74
1,3-Dimethylxanthine	1.56	0.18	0.39	−0.21
Flavone	9.61	0.31	2.40	−2.09
3-Hydroxyflavone	0.08	0.15	0.02	0.13
EC	12.8	8.2	3.20	5.0
PEG4000	2.50	11.2	0.61	10.6
PEG6000	0.42	13.0	0.11	12.9
PEG20000	0.23	11.1	0.07	11.0
PLA	16.8	4.11	4.20	−0.09
PMMA	0.0	0.78	0.0	0.78
PEG–PPG–PEG	32.6	19.6	8.16	11.4
PS	0.0	0.0	0.0	0.0

[a] Calculated as 0.25 × Solubility (in solvent) + 0.75 × Solubility (in SC-CO_2).
[b] Cosolvency effect, $\Delta w_p = w_p^{exp} - w_p^{cal}$.

diamond knife. To achieve phase contrast between the different components of the microparticles, a 0.5 wt % aqueous solution of ruthenium tetroxide (RuO_4) was used to stain the medicines and epoxy-resin phases. The sections were observed with TEM at 120 kV. For the sample preparation for SEM, collected polymeric microparticles were mounted on a small piece cut from the glass plate and sputter-coated with silver/palladium.

To explore the performance of the polymer coatings, we analyzed the concentrations of the medicines in microparticles and the surface components for all produced microparticles with an ultraviolet (UV) spectrometer (Uvidec-505, Jasco) and a Raman spectrometer (NR-1800, Jasco). The particle size, particle size distribution, and coating thickness of the microcapsules were determined with a laser diffraction particle size analyzer (Microtrack HRA, Nikkiso Co., Ltd., Tokyo, Japan) and SEM. To analyze the particle size and distribution, we dispersed the product microcapsules in ethanol or water with a surfactant. The physical properties of the polymeric microparticles were investigated by high-performance liquid chromatography (HPLC; HPLC-8000, Tosoh Co., Ltd., Tokyo, Japan) and differential scanning calorimetry (DSC; DSC-120, Seiko Instruments, Inc., Tokyo, Japan). The residual solvent in the particles was measured by the recording of the weight loss after the heating of a 5-g sample at 383 K for 2 h.

RESULTS AND DISCUSSION

Phase behavior

The solubilities of the medicines in the mixtures of SC-CO_2 and ethanol at 308 K and 16 MPa are shown in Table II. The solubility data for flavone and 3-hydroxyflavone in SC-CO_2 are reported in our previous article.[38] In pure CO_2, the solubilities of flavone and 3-hydroxyflavone were only about 10^{-4} and 10^{-5} (molar fraction), respectively, at this temperature and pressure. However, the solubilities of flavone in SC-CO_2 increased with an increase in the addition of ethanol as a cosolvent. With the addition of 25 wt % ethanol (high boiling compounds, such as medicines; free basis), the solubilities of flavone reached about 10^{-2} (molar fraction). The obtained cosolvent effects on the solubilities are consistent with literature data.[39] Similar results were obtained for the other medicines, as shown in Table II. In our previous work,[31] proteins used as core substances were insoluble in mixtures of SC-CO_2 and low molecular weight alcohol. The proteins were suitable for the RESS-N process because microencapsulation was carried out through the precipitation of the polymer. The medicines used in this work were relatively dissoluble in mixtures of SC-CO_2 and alcohol. However, the solubility of the medicines was relatively low ($<10^{-4}$ in a molar fraction). Under our experimental conditions, an excess amount of medicine was used in comparison with the saturate solubility. Many medicines were suspended in mixtures of SC-CO_2 and ethanol. The difference in the solubilities of the core medicines and coating polymer is the key novel feature of this work. During the encapsulation of medicine with RESS-N, the solubility of the polymers used as coating material should be higher than that of the core substances.

The solubilities of PEG4000 in mixtures of SC-CO_2 and ethanol at 308 K and 16 MPa are shown in Figure 2. Without the polymer, the mixtures of CO_2 and

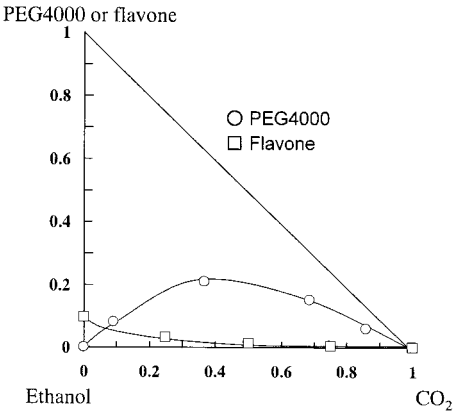
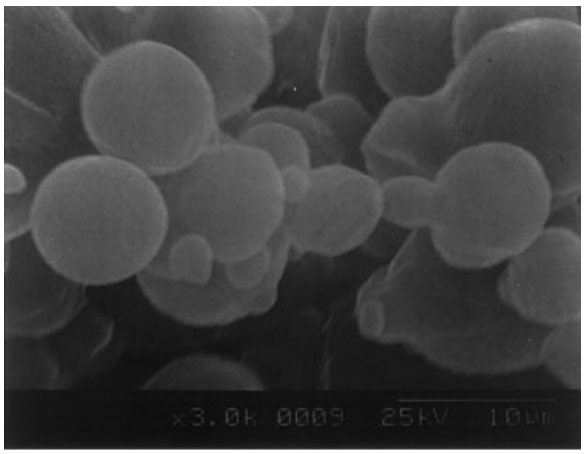


Figure 2 Solubilities of PEG4000 and flavone in mixtures of CO_2 and ethanol at 308 K and 16 MPa.

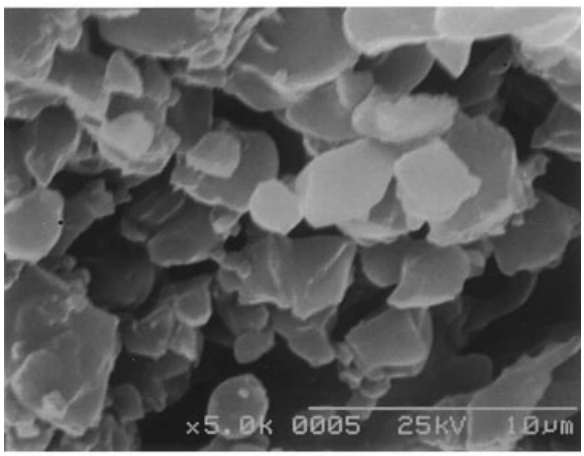
ethanol formed a single SCF phase at this temperature and pressure according to vapor–liquid equilibria data in the literature.[40] The dissolution of the polymer was strongly dependent on the concentration of the cosolvent. For a binary system without a cosolvent, Daneshvar et al.[41] reported that the solubility of PEG1000 (molecular weight = 1000) in SC-CO_2 was about 0.1 wt % at 323 K and 16 MPa. The solubility of PEG4000 at 308 K and 16 MPa in this study was in general agreement. However, with the addition of about 30 wt % ethanol (polymer-free basis), the solubility of PEG4000 reached about 10 wt %. It is interesting that ethanol was such a good cosolvent despite the fact it was a nonsolvent for the polymer. The solubilities of the polymer in the pure cosolvent are shown in Table II. The solubilities of PEG4000 were very low. High molecular weight PEG4000 was insoluble in ethanol. Even with the addition of 20 wt % CO_2 to ethanol, the solubility was not so high. The maximum solubility was achieved at about 50 wt % ethanol (polymer-free basis). Similar results were also obtained for some other polymers, including PMMA, PEG, PEG–PPG–PEG, and EC, as shown in Table II. The solubilities of the polymers in mixtures of SC-CO_2 and 25 wt % ethanol were higher than those calculated by the sum of the solubilities in each pure solvent (0.25 $\times$ the solubility in the pure cosolvent + 0.75 $\times$ the solubility in pure CO_2). This indicates the cosolvency effect of the SC-CO_2 and cosolvent. Similar effects were also observed with other small alcohols, such as methanol and 1-propanol. For some other nonpolar polymers such as poly(styrene) (molecular weight = 10,000), the addition of ethanol as a cosolvent did not raise the solubility significantly. This type of solubility phenomenon (cosolvency) has been observed for iodine in ethanol–benzene mixtures and may be understood thermodynamically.[42] In this case, ethanol was too polar for iodine. A mixture of the two solvents was a better solvent than either solvent alone. However, a similar cosolvency has not been reported for a polymer in the SC-CO_2 systems. In our case, the van der Waals forces and polarity of CO_2 were too small for the polymer, whereas ethanol was too polar and self-associated. In the mixed solvent, the polarity was better matched to the polymer, and ethanol self-association was diluted, so that it was more available to hydrogen bonds on the polymer.

Evaluation of microencapsulation

SEM and TEM images of the polymeric microcapsules containing medicines produced by RESS-N and collected on the surface of a target plate 30 cm from the nozzle are shown in Figures 3 and 4. The pre-expan-



(a)



(b)

Figure 3 SEM images of polymeric microcapsules of flavone from a polymer produced by RESS-N under pre-expansion conditions: (a) PEG6000 microcapsules containing flavone and (b) flavone microspheres. Temperature = 308 K; pressure = 20 MPa; core substance = flavone (3.0 wt %); cosolvent = ethanol (27.1 wt %); coating material = PEG6000 (2.2 wt %).

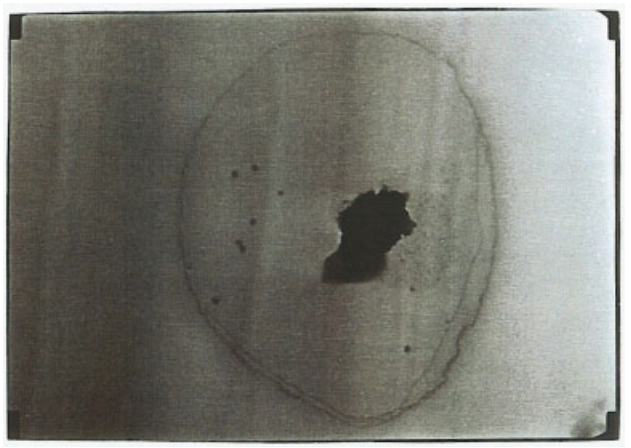


Figure 4 TEM image of polymeric microcapsules of flavone from a polymer produced by RESS-N under pre-expansion conditions. Temperature = 308 K; pressure = 20 MPa; core substance = flavone (0.3 wt %); cosolvent = ethanol (27.1 wt %); coating material = PEG6000 (8.1 wt %).

sion pressure was 20 MPa, and the temperature was 308 K. Ethanol was used as a cosolvent at a concentration of 27.1 wt %. The observed polymer morphologies produced by RESS containing a cosolvent are shown in Table III.

In the SEM photograph, we can see that the particles did not adhere to one another because the ethanol was volatile and a nonsolvent for the polymer. The globular particles had a fairly monodisperse particle size distribution. Similar results were observed for other cosolvents, including methanol and 1-propanol. No hollow was observed on the surface and in the cross section of the microparticles because the microparticles were formed by precipitation from mixtures of CO_2 and low molecular weight alcohol. This precipitation of polymer microparticles can be explained by the disappearance of the cosolvency effect of the mixture at atmospheric pressure. Through the expansion of the solution from a nozzle, the distance between the solvent molecules of CO_2 and alcohol abruptly increased, and this expansion lost the cosolvency and solvent power of the mixture. At low pressures, CO_2 and alcohol were separated and formed vapor and liquid phases. Pure CO_2 and alcohol were nonsolvent for the polymers. They were only sparingly soluble in the polymer particles formed through the expansion. In the RESS-N method, the easy separation of CO_2 and low molecular weight alcohols makes it possible to use the cosolvency to produce polymeric microcapsules without adhesion. It is difficult to use the cosolvency of a liquid–liquid solvent for a polymer process because the residual liquid solvent causes coalescence and adhesion of polymer products. The formation of polymeric microparticles is realized with the cosolvency of gaseous CO_2 and a liquid cosolvent. In RESS-N, in which a cosolvent is a nonsolvent and gas–liquid cosolvency can be used , all the polymer exhausted from a nozzle can be formed into microparticles. However, microcapsules formed with toluene or acetone as a cosolvent adhered after RESS. Because toluene and acetone were volatile and good solvents for the polymers, the microspheres adhered to one another.

In the TEM photograph, the flavone phase, stained by a 0.5 wt % aqueous solution of RuO_4, is shown as a dark area. It is completely covered by the PEG phase, shown as a bright area not stained by RuO_4. As shown in the microcapsule, the area ratio of the flavone phase to the PEG phase was almost identical to the feed composition ratio of flavone to PEG. The boundary between the PEG phase in the microcapsule and the epoxy resin can clearly be observed. It is likely that the suspended medicines in the expanding jet served as nucleating agents for the precipitating polymer. When the composition ratio of flavone to PEG6000 in the feed was 3.7×10^{-2}, the volume ratio of the dispersed flavone particles to the volume of the continuous PEG phase in the microcapsules approximately agreed with the feed composition, as shown in Figure 4. The volume ratio was determined by visual observation (e.g., TEM). Approximately 95% of the area of the flavone phase was located in the center of the polymeric microcapsules. Some other small areas of the flavone phase were distributed in the microcapsules and not out of the microcapsules in the matrix of the epoxy resin. The epoxy resin out of the microcapsules was also slightly stained by RuO_4, and the boundary between the PEG phase in the microcapsules and the matrix of epoxy resin can clearly be observed.

It was difficult to check the coating performance for all collected microcapsules by a TEM photograph because the RESS process produced an extremely large number of microspheres. To evaluate the performance of the polymer coating, we examine Raman and UV spectra for all the collected microcapsules. The existence of flavone in the microspheres was confirmed with a UV spectrometer. The UV spectrum of a 20% aqueous ethanol solution dissolving the microspheres was identical to that of feed materials of flavone. The produced microspheres involved the flavone. The surface compositions of the produced microspheres were analyzed with a Raman spectrometer. The Raman spectra of the source material and microspheres obtained from RESS are shown in Figure 5. The intensity of flavone at 1640 cm^{-1} in the microspheres was about 100 times lower than that of the source flavone. As the result of spectroscopic analyses, it may be considered that most of the feed flavone molecules were coated with PEG and existed inside the produced microcapsules. Similar results were obtained for other medicines.

TABLE III
Observed Polymer Morphology Produced by the Rapid Expansion of SC-CO_2 Solution Containing Ethanol at 308 K and 20 MPa

No.	Core material	Coating material	Cosolvent	Core substance (wt %)	Cosolvent (wt %)	Polymer (wt %)	CO_2 (wt %)	Primary particle diameter[b] (μm)	Geometric Standard deviation of particle diameter[c]
1	*p*-Acetamidophenol	EC	Ethanol	0.3	27.1	2.2	70.4	21	1.76
2	*p*-Acetamidophenol	PEG6000	Ethanol	0.3	27.1	2.2	70.4	17	1.65
3	*p*-Acetamidophenol	PEG6000	Methanol	0.3	27.1	2.2	70.4	18	1.79
4	*p*-Acetamidophenol	PEG6000	l-Propanol	0.3	27.1	2.2	70.4	18	1.79
5	*p*-Acetamidophenol	PEG6000	Acetone[a]	0.3	27.1	2.2	70.4	—	—
6	*p*-Acetamidophenol	PEG6000	Toluene[a]	0.3	27.1	2.2	70.4	—	—
7	*p*-Acetamidophenol	PEG4000	Ethanol	0.3	27.1	2.2	70.4	18	1.74
8	*p*-Acetamidophenol	PLA	Ethanol	0.3	27.1	2.2	70.4	23	1.78
9	*p*-Acetamidophenol	PMMA	Ethanol	0.3	27.1	2.2	70.4	18	1.87
10	*p*-Acetamidophenol	PEG–PPG–PEG	Ethanol	0.3	27.1	2.2	70.4	24	1.83
11	*p*-Acetamidophenol	PS	Ethanol	0.3	27.1	2.2	70.4	—	—
12	*p*-Acetamidophenol	—	Ethanol	0.3	27.1	0.0	72.6	6	1.92
13	Acetylsalicylic acid	PEG6000	Ethanol	0.3	27.1	2.2	70.4	22	1.74
14	Acetylsalicylic acid	PEG4000	Ethanol	0.3	27.1	2.2	70.4	18	1.80
15	1,3-Dimethylxanthine	PEG6000	Ethanol	0.3	27.1	2.2	70.4	17	1.74
16	1,3-Dimethylxanthine	PEG4000	Ethanol	0.3	27.1	2.2	70.4	19	1.80
17	1,3-Dimethylxanthine	EC	Ethanol	0.3	27.1	2.2	70.4	21	1.84
18	Flavone	PEG6000	Ethanol	0.3	27.1	2.2	70.4	12	1.79
19	Flavone	PEG6000	Ethanol	0.2	26.5	4.6	68.7	36	1.87
20	Flavone	PEG6000	Ethanol	0.1	17.8	5.8	76.3	55	2.02
21	Flavone	PEG4000	Ethanol	0.3	27.1	2.2	70.4	24	1.81
22	Flavone	PLA	Ethanol	0.3	27.1	2.2	70.4	21	1.81
23	Flavone	PEG–PPG–PEG	Ethanol	0.3	27.1	2.2	70.4	21	1.84
24	Flavone	—	Ethanol	0.3	27.1	0.0	72.6	7	1.87
25	3-hydroxyflavone	PEG6000	Ethanol	0.3	27.1	2.2	70.4	18	1.75
26	3-hydroxyflavone	PEG4000	Ethanol	0.3	27.1	2.2	70.4	17	1.74

[a] Polymer microstructure is cracked film.
[b] Primary particle diameter $\bar{D_p} = \Sigma\, nD_p/\Sigma n$, where n is the number of particles and D_p is the particle diameter.
[c] Geometric standard deviation σ, $\ln \sigma = (1/n)\sqrt{\Sigma\, n(\ln D_p - \ln \bar{D_p})^2}$, where n is the number of particles, D_p is the particle diameter, and $\bar{D_p}$ is the primary particle diameter.

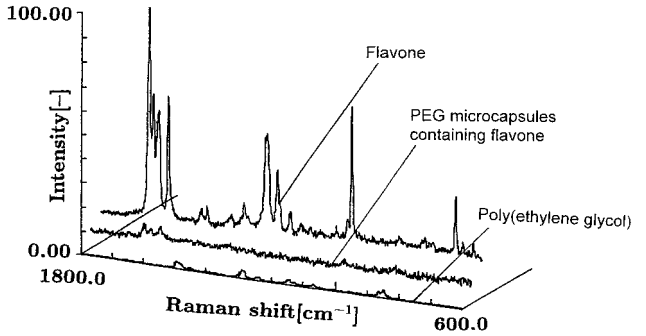


Figure 5 Raman spectra of the source materials PEG and flavone and the produced microspheres.

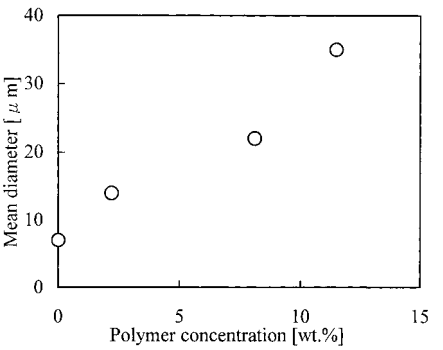


Figure 7 Influence of the polymer concentration on the particle size distribution of PEG6000 microcapsules with flavone. Temperature = 308 K; pressure = 20 MPa; cosolvent = ethanol; coating material = PEG6000; core substance = flavone.

Effects of the various factors on the particle size

The effects of various operating factors, such as the pre-expansion pressure, temperature, feed compositions, injection distance, and polymer molecular weight, on the mean particle diameter and geometric standard deviation of the particle diameter were examined, as shown in Table III. The particles were analyzed with a laser diffraction particle size analyzer. The particle size distribution of PEG6000 microparticles obtained under pre-expansion conditions of 20 MPa and 308 K was considered to be a monodispersed distribution, as shown in Figure 6. The particle size distribution of PEG6000 microparticles obtained under pre-expansion conditions of 20 MPa and 308 K was considered to be a relatively broad distribution, as shown in Figure 6. Several investigators reported that the RESS process generally produced monodispersed distributions.[17–26] It may be considered that a pressure drop caused the precipitation of the polymer in the vessel through RESS because the pressure was not kept constant experimentally through RESS. Similar results were obtained for other polymers with the RESS-N method. In this case, the mean particle diameter and standard deviation were 14 μ m and 1.74, respectively.

The effect of the PEG6000 feed concentration on the mean particle diameter of the microcapsules containing flavone is shown in Figure 7. The mean particle diameter of the microcapsules, and likewise the coating thickness, increased with an increase in the PEG6000 concentration. For flavone, one flavone particle was coated with PEG6000, as shown in Figure 4. The size of the core substance (the dark area in Fig. 4) in the flavone–PEG6000 composite by RESS-N was almost the same as that of the flavone particle produced by RESS without the polymer [Fig. 3(b)]. The method for the determination of particle sizes of flavone and other medicines without a polymer can be described as follows. Medicines were dissolved and dispersed in mixtures of SC-CO_2 and ethanol, and the dissolved and dispersed medicines were sprayed. The particle sizes of the resulting medicines were determined with a laser differential particle size analyzer. The thickness of the coating increased with an increase in the polymer concentration for flavone, as shown in Figure 7. Furthermore, the standard deviation in the particle diameter increased with an increase in the feed composition of the polymer. A key result of this study was the ability to control the thickness and particle size distribution of the microcapsules with the feed concentration of the polymer.

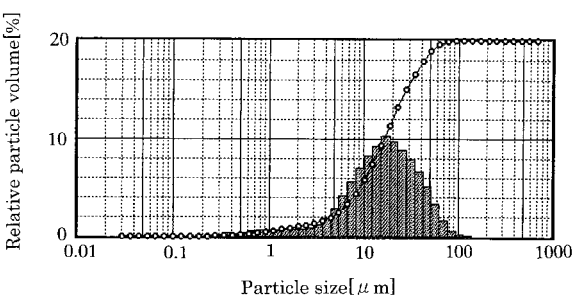


Figure 6 Particle size distribution of microcapsules with flavone. Temperature = 308 K; pressure = 20 MPa; core substance = flavone (0.3 wt %); cosolvent = ethanol (27.1 wt %); coating material = PEG6000 (8.1 wt %).

The mean particle diameter of the PEG particles was almost constant for several conditions, including the pre-expansion pressure, temperature, molecular weight of the polymer, and injection distance. The standard deviation of the particle diameter decreased slightly with an increase in the pre-expansion pressure and injection distance. A linear relationship was observed between the standard deviation and these factors. For each of these variables, except the polymer feed composition, the particle size of the polymeric microcapsules was almost constant under these experimental conditions. Therefore, the polymer feed composition was a key variable for controlling the particle size of the microcapsules. Similar results were obtained for the other polymers in this study. Recently,

some theories of particle morphology with SC-CO_2 were reported.[25,43,44] The effect of operating conditions on particle morphology was discussed. Tom and Debenedetti[25] discussed the effect of operating conditions of RESS, such as the expansion device, pre-expansion pressure and temperature, and solvent composition, on particle morphology. They tried to produce PLA particles by the rapid expansion of SC-CO_2 with $CHClF_2$. Although PLA was dissolved in SC-CO_2 with $CHClF_2$ as a cosolvent, the solubility was relatively low (<1 wt %). Furthermore, it was indicated that the particle morphology strongly depended on the length/diameter ratio of the orifice as the expansion device. However, the particle morphology in the RESS-N process strongly depended on the polymer feed composition. It may be considered that the particle morphology in RESS-N was responsible for the high solubility of PEG6000 in the mixtures of SC-CO_2 and ethanol.

The various physical properties of the microspheres were compared with those of the source polymers. The glass-transition temperatures of the feed polymer and polymeric microspheres were measured by DSC and found to be the same. Consequently, the residual solvent remained in the polymer, or it would have depressed the glass-transition temperature. For the determination of the amount of the residual solvent in the microcapsules, they were dried at about 373 K, and the change in mass was measured. The amount of the residual ethanol in the microcapsules was less than 1 wt % for all the polymers. The HPLC retention times of the feed and product polymer were identical; this indicated that the molecular weight did not change. This result suggests that the CO_2–cosolvent mixture dissolved all of the polymer, rather than a fraction of the molecular weight distribution. For reasons given previously, it became clear that physical properties, such as the molecular weight and glass-transition temperature, of the polymer materials did not vary through the RESS processing.

CONCLUSIONS

RESS-N was used to produce polymeric microcapsules of medicines such as *p*-acetamidophenol, acetylsalicylic acid, 1,3-dimethylxanthine, flavone, and 3-hydroxyflavone without agglomeration. The cosolvent ethanol was far less toxic than most organic solvents, and no surfactant was required. The solubilities of the polymers—the homopolymers were PEG (PEG4000, PEG6000, PEG20000), PMMA, and EC, and the copolymer was PEG–PPG–PEG—increased drastically with the addition of a small amount of a lower alcohol, such as methanol, ethanol, or 1-propanol, which were nonsolvents for the polymer but could become good cosolvents when mixed with CO_2. Because ethanol was a nonsolvent for the polymers, polymeric microparticles produced by RESS-N had no agglomeration. The microcapsules had a globular form and a fairly monodispersed particle size distribution. The mean particle diameter and standard deviation of the particle diameter were 14.6 μm and 0.41. The particle size distribution of the microcapsules could be controlled by changes in the polymer concentration. It changed very little with the pre-expansion pressure, temperature, injection flow rate, injection distance, and polymer molecular weight. The feed compositions were more effective than other factors for controlling the particle size.

References

1. Gutcho, M. H. Microcapsules and Microcapsulation Technique; Noyes Data: Park Ridge, NJ, 1976.
2. Martin, Y. C. Quantitative Drug Design; Marcel Dekker: New York, 1978.
3. Harris, J. M. Poly(ethylene glycol) Chemistry; Plenum: New York, 1992.
4. Benita, S. Microencapsulation: Methods and Industrial Applications; Marcel Dekker: New York, 1990.
5. Deasy, P. B. Microcapsulation and Related Drug Process; Marcel Dekker: New York, 1984.
6. Whatelyey, T. L. Microcapsulation of Drugs (Drug Targeting and Delivery); Harwood Academic: Newark, NJ, 1992.
7. Nixon, J. R. Microcapsulation; Marcel Dekker: New York, 1976.
8. Kondo, A. Microcapsule Processing and Technology; Marcel Dekker: New York, 1979.
9. McHuch, M. A.; Kurukoics, V. In Encyclopedia of Polymer Science and Engineering, 2nd ed.; Bikales, N. M.; Overberger, C. G.; Menges, G., Eds.; Wiley: New York, 1988.
10. Goel, S. K.; Beckman, E. J. Polym Eng Sci 1994, 34, 1137.
11. Goel, S. K.; Beckman, E. J. Polym Eng Sci 1994, 34, 1148.
12. DeSimone, J. M.; Guan, Z.; Eisbernd, C. S. Science 1992, 257, 945.
13. Johnston, K. P. Nature 1994, 368, 187.
14. Harrison, K.; Goveas, J.; Johnston, K. P.; O'Rear, E. A., III. Langmuir 1994, 10, 3536.
15. McFann, G. J.; Johnston, K. P.; Howdle, S. M. AIChE J 1994, 40, 543.
16. Hoefling, T. A.; Enick, R. M.; Beckman, E. J. J Phys Chem 1991, 95, 7127.
17. Matson, D. W.; Petersen, R. C.; Smith, R. D. J Mater Sci 1987, 22, 1919.
18. Matson, D. W.; Fulton, J. L.; Petersen, R. C.; Smith, R. D. Ind Eng Chem Res 1987, 26, 2298.
19. Chang, C. J.; Randolph, A. D. AIChE J 1989, 35, 1876.
20. Mohamed, R. S.; Debenedetti, P. G.; Prud'homme, R. K. AIChE J 1989, 35, 325.
21. Ohgaki, H.; Kobayashi, K.; Katayama, T. J Supercrit Fluid 1990, 3, 103.
22. Lele, A. K.; Shine, A. D. AIChE J 1992, 38, 742.
23. Lele, A. K.; Shine, A. D. Ind Eng Chem Res 1994, 33, 1476.
24. Tom, J. W.; Debenedetti, P. G. Biotechnol Prog 1991, 7, 403.
25. Tom, J. W.; Debenedetti, P. G.; Jerome, R. J Supercrit Fluid 1994, 7, 9.
26. Mawson, S.; Johnston, K. P.; Combes, J. R.; DeSimone, J. M. Macromolecules 1995, 28, 3182.
27. Lele, A. K.; Shine, A. D. Polym Prepr (Am Chem Soc Div Polym Chem) 1991, 31, 677.
28. Donohue, M. D.; Geiger, J. L.; Kiamos, A. A.; Nielsen, K. A. In Green Chemistry: Designing Chemistry for the Environment;

Anastas, P. T.; Williamson, T. C., Eds.; American Chemical Society: Washington, DC, 1996.
29. Nielson, K. A.; Argyropoulos, J. N.; Clark, R. C.; Goad, J. D. Presented at the 3rd Annual Advanced Coating Technology Conference, Dearborn, MI, 1993.
30. O'Neill, M. L.; Cao, Q.; Fang, M.; Johnston, K. P.; Wilkinson, S. P.; Kerschner, J. L.; Jureller, S. H. Ind Eng Chem Res 1998, 37, 3067.
31. Mishima, K.; Matsuyama, K.; Tanabe, D.; Yamauchi, S.; Young, T. J.; Johnston, K. P. AIChE J 2000, 46, 857.
32. Matsuyama, K.; Mishima, K.; Umemoto, H.; Yamaguchi, S. Environ Sci Technol 2001, 35, 4149.
33. Bartle, K. D.; Clifford, A. A.; Jarar, S. A. J Chem Eng Data 1990, 35, 355.
34. Ekart, M. P.; Bunnett, K. L.; Ekart, S. M.; Gurdial, G. S.; Liotta, C. L.; Eckert, C. A. AIChE J 1993, 39, 235.
35. Yang, J.; Griffiths, P. Anal Chem 1996, 68, 2353.
36. Mishima, K.; Tokuyasu, T.; Matsuyama, K.; Komorita, N.; Enjoji, T.; Nagatani, M. Fluid Phase Equilib 1998, 144, 299.
37. Mishima, K.; Matsuyama, K.; Nagatani, M. Fluid Phase Equilib 1999, 161, 315.
38. Uchiyama, H.; Mishima, K.; Oka, S.; Ezawa, M.; Ide, M. J Chem Eng Data 1997, 42, 570.
39. Koga, Y.; Iwai, Y.; Hata, Y.; Yamamoto, M.; Arai, Y. Fluid Phase Equilib 1996, 125, 115.
40. Jennings, D. W.; Lee, R. J.; Teja, A. S. J Chem Eng Data 1991, 36, 303.
41. Daneshvar, M.; Kim, S.; Gulari, E. J Phys Chem 1990, 94, 2124.
42. Nakanishi, S.; Asakura, S. J Phys Chem 1977, 81, 1745.
43. Alessi, P. A.; Cortesi, A.; Kikic, I.; Foster, N. R.; Macnaughton, S. J.; Colombo, I. Ind Eng Chem Res 1996, 35, 4718.
44. Weber, M.; Thies, M. C. In Supercritical Fluid Technology in Materials Science and Engineering; Sun, Y.-A., Ed.; Marcel Dekker: New York, 2002.