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ORIGINAL CONTRIBUTION

Synthesis of biocompatible and biodegradable polymer particles in supercritical carbon dioxide

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Abstract The free radical copolymerization of *N*-vinyl-2-pyrrolidone and 2-methylene-1,3-dioxepane was carried out in supercritical carbon dioxide ($scCO_2$) using three kinds of dispersants and 2,2′-azobisisobutyronitrile as the initiator. Polymerization was performed with fluorinated polymeric dispersants synthesized in $scCO_2$ using the solution polymerization method and commercially available siloxane-based surfactant. Spherical biocompatible and biodegradable polymeric particles were prepared within the sub-micron size range. The effect of various ratios of the comonomer, reaction temperature, and concentration of initiator, in addition to the types and concentrations of the dispersants, on the particle size and morphology was investigated. The particle size and particle size distribution of copolymer particles were controlled using the above mentioned experimental parameters. Glass transition temperatures of copolymers were varied according to the comonomer ratios used.

Keywords 2-Methylene-1 · 3-dioxepane · *N*-vinyl-2-pyrrolidone · Dispersion polymerization · Supercritical carbon dioxide

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Introduction

In any drug delivery system, well-controlled spherical polymeric particles enable the uniformity of the chemical and physical properties exhibited by the drug, as well as minimize any potential irritant reaction at the drug injection site. The synthesis of polymeric drug carriers in the form of a spherical shape has been investigated in several studies [1–5]. Biodegradable and biocompatible polyesters have found wide usage in medicine as temporary bone replacements and/or fixing elements, as well as matrices for controlled drug release systems. In the synthesis of such polyesters, dispersion polymerization of lactides or ε-caprolactone (CL) using ring-opening polymerization (ROP) methods has been reported by some researches [1–5]. Catalysts for ionic ROP are not easily manageable due to their sensitivity to water. The ring-opening process for the ester can be enhanced by activation of a Zn- or Sn-based catalyst with the carbonyl ester. However, the introduction of a catalyst increases the risk of incorporating traces of potentially cytotoxic materials [6]. A few catalysts have been approved by the U.S. Food and Drug Administration in their use for biomedical applications [7–10].

2-Methylene-1,3-dioxepane (MDOP), a cyclic ketone acetal, can be polymerized by the free radical ring-opening method to produce poly(ε-caprolactone) (PCL) in commonly used radical initiators. MDOP has been shown to copolymerize with vinylic monomers such as styrene, *N*-isopropylacrylamide, methyl acrylate, and methyl methacrylate, with relative ease, using the conventional free radical polymerization technique with biodegradable ester units in the backbone chain [11–14]. However, it is not easy to construct a microsphere due to the low glass transition temperature (T_g) value (−61 °C) as well as low crystalline properties of poly(2-methylene-1,3-dioxepane) (PMDOP)

[15]. At room temperature, the homopolymer of MDOP exists in a viscous, wax-like state. Copolymerization of MDOP with other vinylic monomers is therefore required to obtain spherical biodegradable polymers containing biodegradable CL units. In this study, *N*-vinyl-2-pyrrolidone (NVP) was used with MDOP to produce copolymer microspheres using the dispersion polymerization technique.

Poly(vinyl-2-pyrrolidone) (PVP) has been used in a variety of fields such as in cosmetics (detergents, soaps, hair spraying agents, and dyes), medical devices (ophthalmic, lubricious coating, biocompatible coatings, and complex), and for pharmaceuticals (controlled release, bind agents, stabilizers for polymerization as well as thickeners) because of its excellent biocompatibility properties [8, 16].

Dispersion polymerization has been spotlighted and developed as a simple one-step method for constructing microspheres. Recently, supercritical carbon dioxide ($scCO_2$) was studied as a reaction medium for free radical dispersion polymerization [17–20]. $ScCO_2$ has many advantages regarding environmental apprehensions due to its low toxicity, inflammability, chemically inert nature, natural abundance, and its separation technology, which vented by simple depressurization [17–20]. Solvent-free and high-purity products are particularly useful in the fields of biomaterials. The $scCO_2$ process has therefore been called as the environmental green and energy saving technology.

A variety of polymers have been synthesized in CO_2 by heterogeneous polymerization methods. Among the various heterogeneous polymerization methods available (precipitation, dispersion, emulsion, and suspension polymerization), the dispersion polymerization technique has been one of the most widely studied. This is because most low molecular weight monomers are soluble in $scCO_2$, but polymers formed by the dispersion polymerization method are rarely soluble in $scCO_2$ with the exception of a few amorphous fluorinated polymers and siloxane-based polymers [17–20].

In the present study, free radical dispersion copolymerization of NVP and MDOP was performed in $scCO_2$ with conventional siloxane-based polymeric surfactant and fluorinated polymeric dispersants synthesized in $scCO_2$. Following this, the effects of concentration and type of dispersant, comonomer ratios, reaction temperature, and concentration of initiator on particle size and distribution of copolymer were investigated.

Experimental

Materials

MDOP (min. 98%) was obtained from Fluka and used without further purification. NVP was kindly supplied by BASF Korea and used as received. 2,2′-Azobisisobutyronitrile (AIBN, Junsei Chemical, min. 98%) was recrystallized from methanol. Carbon dioxide (min. 99.95%) was purchased from Korea Industrial Gases. 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl acrylate (HDFDA; min. 97%) and 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl methacrylate (HDFDMA; min. 97%) were purchased from Aldrich and the inhibitor (methoxyhydroquinone (MEHQ)) in the monomers was removed through an alumina column. Poly(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl acrylate) (PHDFDA) and poly (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl methacrylate) (PHDFDMA) were synthesized in the 30 ml reactor using the solution polymerization method in $scCO_2$ [21–23]. HDFDA or HDFDMA (4.00 g) was polymerized in $scCO_2$ (27.0 g) at 70.0±0.5 °C, 300–310 bar for 24 h with AIBN as the initiator (1.0 wt.% of monomer). CO_2 was vented after polymerization was completed. The polymer particles were washed with methanol to remove unreacted monomer and dried in vacuum at room temperature. Then, the yields from solution polymerization of HDFDA and HDFDMA in $scCO_2$ were 89.4% and 85.2%, respectively. PDMS-*g*-pyrrolidone carboxylic acid (Monasil PCA, Uniqema) was used without further purification. Monasil PCA has a molar weight of about 8,500 g/mol with approximately two carboxylic acid groups per molecule. The chemical structures of the dispersants are illustrated in Fig. 1.

Dispersion copolymerization of NVP and MDOP in $scCO_2$

Dispersion copolymerization of NVP and MDOP was carried out with various dispersants in $scCO_2$ in order to obtain spherical particles. The experimental system was comprised of the same equipment described in our previous reports [24, 25]. All polymerization experiments were conducted in a 30-ml high-pressure reactor, with a window on the front. After the desired amount of comonomers, dispersant and AIBN were charged to the reactor, the reactor was purged with N_2 and CO_2 several times to remove any residual air. CO_2 was charged with a gas booster pump until ~100 bar at 30 °C. The reactor was gradually heated to the desired temperature and then filled with CO_2 using the booster pump until polymerization conditions were reached and maintained throughout the reaction time. After polymerization, the reactor was cooled down to room temperature and CO_2 was slowly vented through two glass traps. The white, dry, powdery particle polymer was collected directly. After complete polymerization, the bulk of the unreacted monomer and surfactant was removed using $scCO_2$ extraction [24]. The polymer was finally dried in vacuo overnight at room temperature.

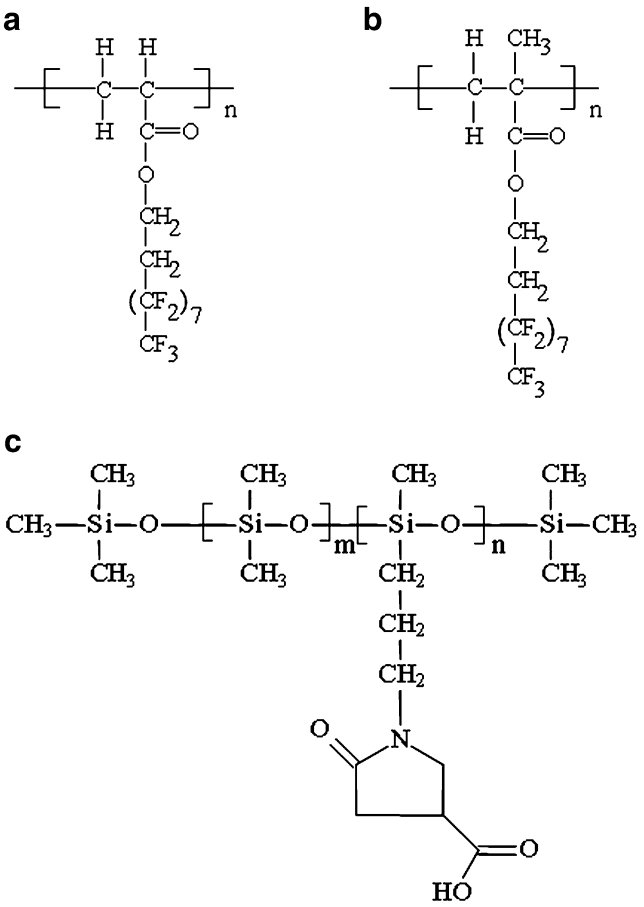

Fig. 1 Structures of dispersants: **a** PHDFDA, **b** PHDFDMA, and **c** Monasil PCA

Characterization

The particle size and morphology of the polymer were characterized using field emission scanning electron microscopy (FE-SEM; Jeol, JSM-6700F). The number and average particle size, as well as the particle size distribution, were measured by an image analyzer software (TDI Scope Eye™ ver 3.1) using the SEM images generated. Number (D_n) and weight (D_w) of average particle diameters were calculated from the following equations.

$$D_n = \frac{\sum_{i=1}^{N} d_i}{N} \tag{1}$$

$$D_w = \frac{\sum_{i=1}^{N} d_i^4}{\sum_{i=1}^{N} d_i^3} \tag{2}$$

where d_i is the diameter of particle i and N is the total number of particles (about 100–150 particles) measured in the SEM image. The particle size distribution was determined by the polydispersity index (PSD= D_w/D_n).

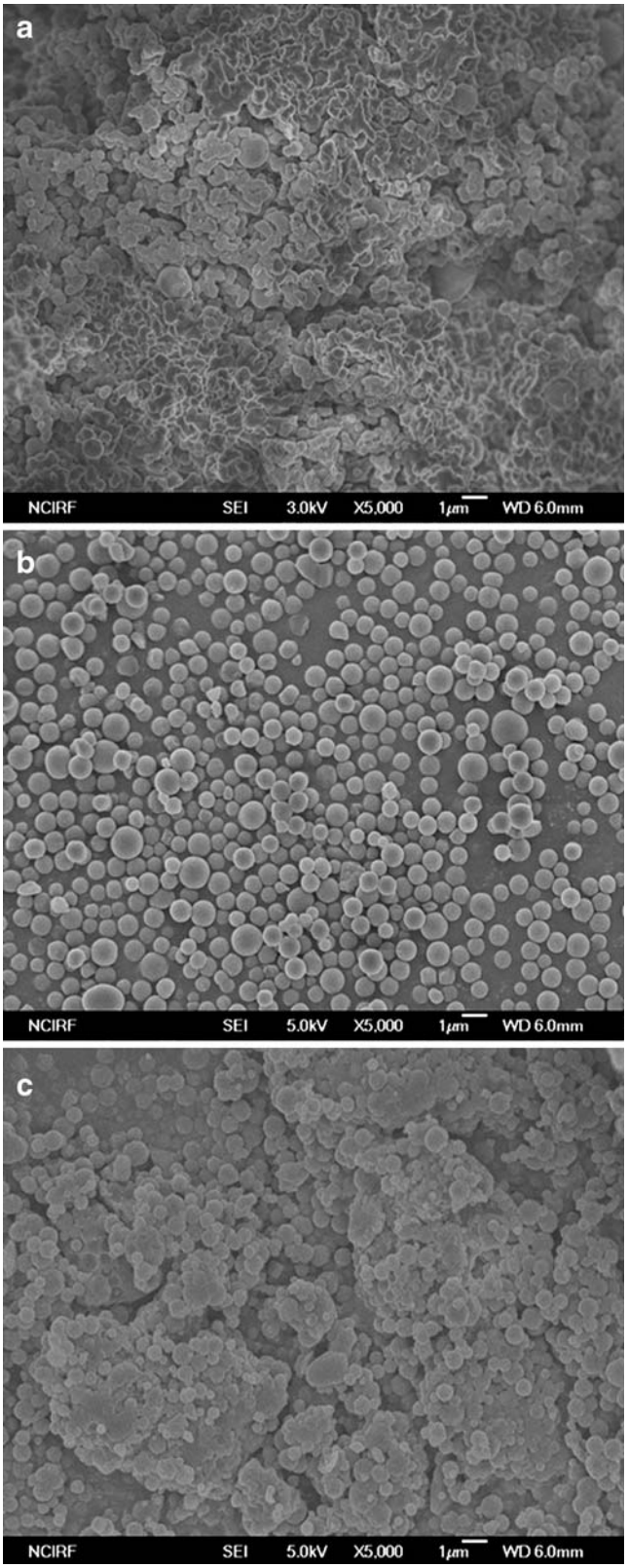

Fig. 2 FE-SEM images of copolymer particles: **a** with PHDFDA, **b** PHDFDMA, and **c** Monasil PCA

^{1}H-NMR (Bruker, 300 MHz, and $CDCl_3$ as a solvent) and Fourier transform infrared spectroscopy (FT-IR; JASCO, Model FT-IR 200, KBr as an internal reference) were used to confirm the chemical structure of the copolymers. The thermal properties of the polymers were investigated using differential scanning calorimetry (DSC; TA instrument Q100 DSC, using a scan rate of 10 °C/min, second heating scan, and temperature range of −60 to 180 °C) in N_2.

Results and discussion

Effects of various dispersants

Three types of dispersants were tested for efficient dispersion polymerization of NVP and MDOP in $scCO_2$. The basic experimental conditions were a temperature of 70 °C, pressure of 300 bar, concentration of MDOP at 11± 0.5 mol% of the total comonomer, concentration of dispersant at 10 wt.% of the total comonomer weight, and concentration of AIBN at 1.0 wt.% of the total comonomer weight.

The result of dispersion polymerization reaction using PHDFDA showed the strongly aggregated polymer particles in comparison with the results using PHDFDMA or Monasil PCA as shown in Fig. 2. Between PHDFDA and PHDFDMA as dispersants, PHDFDMA was the more effective stabilizer in the dispersion polymerization. This is attributed to the anchor groups in the PHDFDMA which might attach on the surface of the copolymer effectively.

Efficiency of dispersion polymerization of NVP and MDOP in $scCO_2$ was investigated with PHDFDMA and Monasil PCA under various experimental parameters (ratio of comonomer concentration, dispersant concentration, reaction temperature, and initiator concentration).

Effect of variations in comonomer ratios

As shown in Table 1 and Fig. 3, the mean particle size of polymer particles with PHDFDMA decreased slightly as the concentration of MDOP in the feed ratio increased from 7.21 to 16.94 mol% of the total comonomer concentration. When concentrations of MDOP greater than 16.94 mol% were used, the final particles were obtained as fine powder but the morphology of the particles was strongly aggregated as shown in the FE-SEM images (Fig. 3). This was attributed to the low T_g values of the formed copolymer as the concentration of MDOP increased. The low T_g values of the polymer obtained, rendered the surface of the polymer soft, thereby allowing for easy flocculation and agglomeration of the formed polymer particles by collision. In Table 1, T_g values of poly(NVP-*co*-MDOP) particles decreased from 142 to 110 °C as the concentration of MDOP increased within the monomer ratios.

The results of dispersion polymerization of Monasil PCA, with an increase in the MDOP content, are shown in Table 1 and Fig. 4. The morphology of the resulting polymer was intensely aggregated upon addition of increasing quantities of MDOP. The siloxane-based dispersants showed a low T_g value and were in the form of a viscous liquid at room temperature. This was attributed to

Table 1 Effects of dispersants structure and comonomer concentration on particle size and particle size distribution of poly(NVP-*co*-MDOP) particles

Dispersant[a]	MDOP in comonomer (mol%)	MDOP in copolymer (mol%)[b]	D_n (μm)[c]	PSD (D_w/D_n)[d]	T_g (°C)[e]	Polymer morphology[f]
PHDFDMA	7.21	4.10	0.86	1.04	142	Dry powder
	11.15	4.30	0.76	1.10	136	Dry powder
	16.94	5.77	0.60	1.05	132	Dry powder
	18.98	6.96	NA	NA	131	Slight aggregation
	24.80	7.38	NA	NA	110	Slight aggregation
Monasil PCA	5.55	4.74	NA	NA	138	Dry powder
	10.51	7.82	0.58	1.44	121	Dry powder
	14.93	9.16	NA	NA	79	Slight aggregation

Reaction conditions: 300±0.5 bar and 70±0.5 °C, 1 wt.% of AIBN on comonomer and 24 h
NA Not available
[a] 10 wt.% dispersant on comonomer
[b] Calculated by relative NMR spectra
[c] Determined by FE-SEM image
[d] Particle size distribution
[e] Determined by DSC analysis (heating and cooling rate=10 °C/min, N_2 gas)
[f] Appearance of copolymer after CO_2 venting

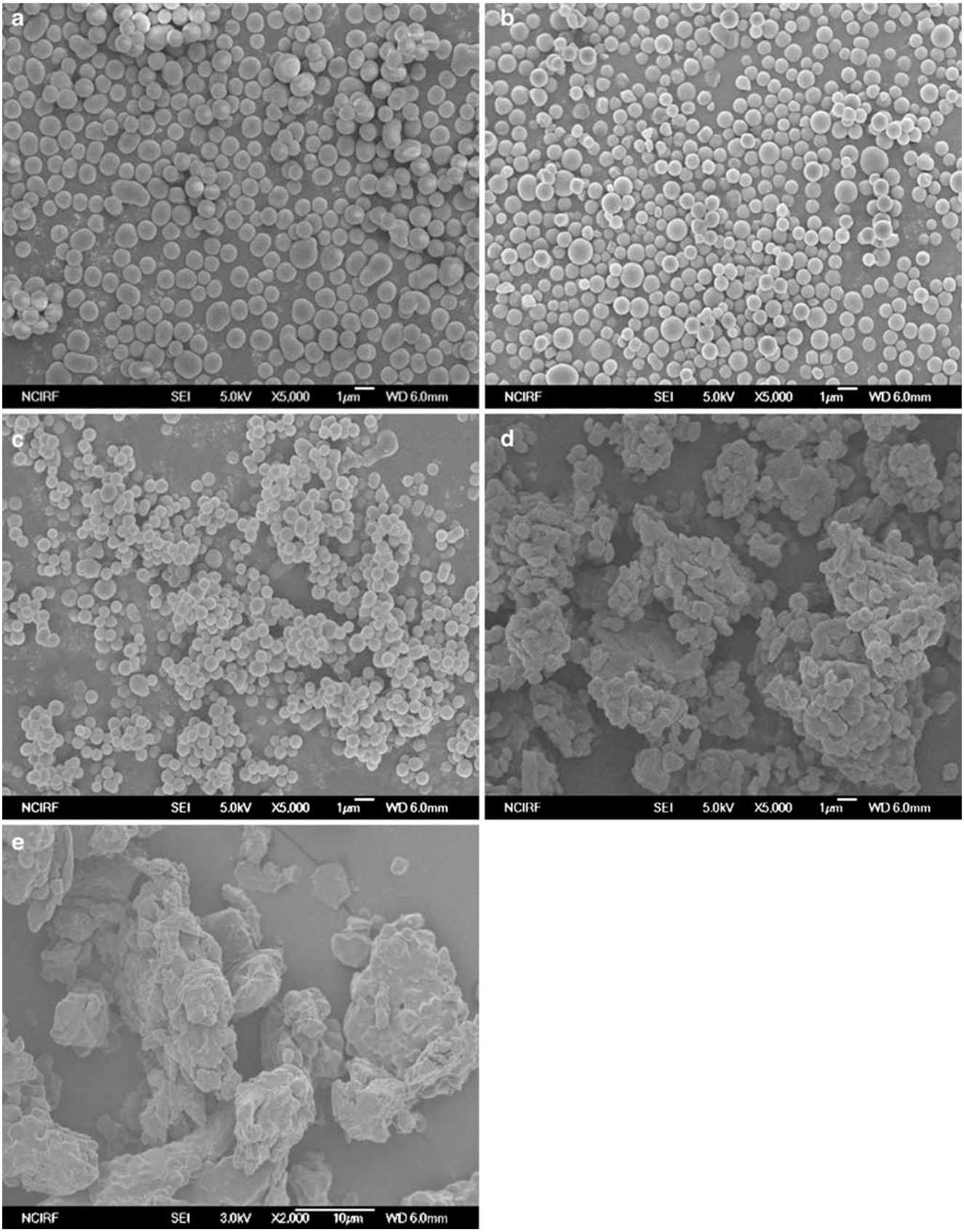

Fig. 3 FE-SEM images of copolymer particles with PHDFDMA containing **a** 7.21, **b** 11.15, **c** 16.94, **d** 18.98, and **e** 24.80 mol% of MDOP in comonomer

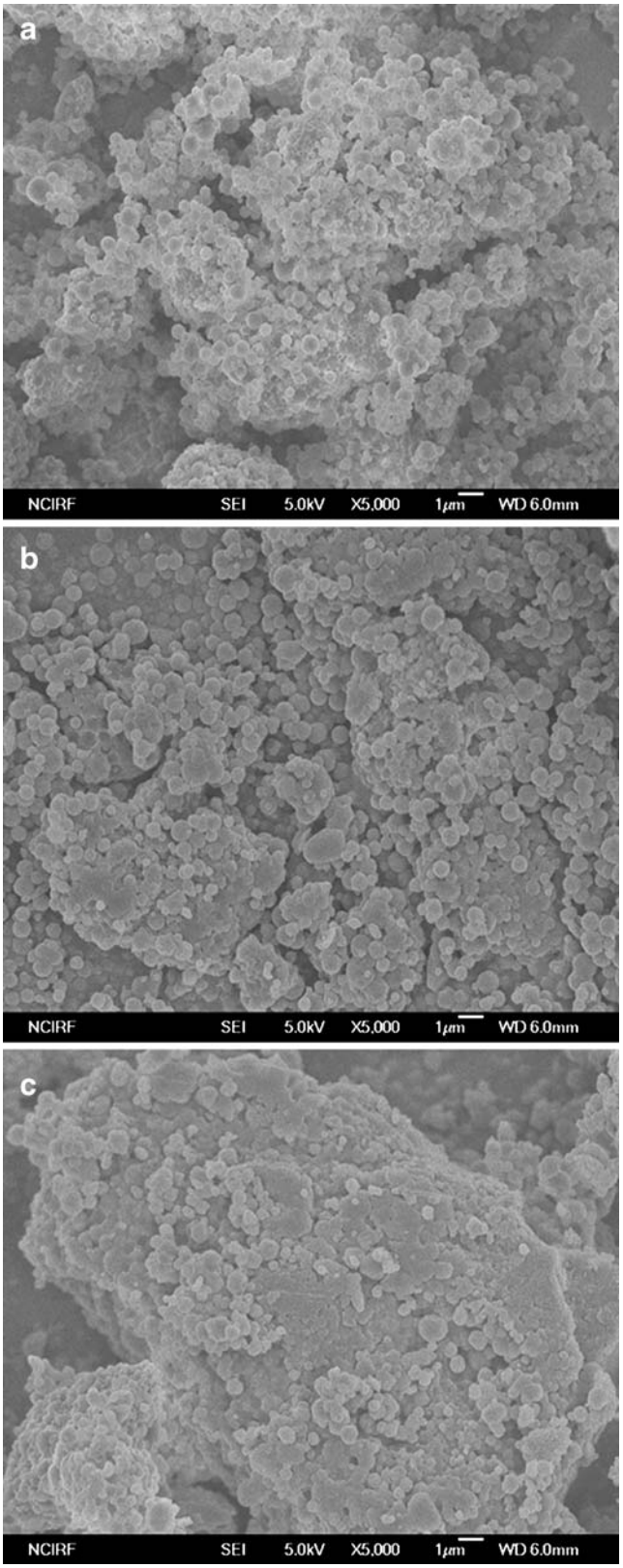

Fig. 4 FE-SEM images of copolymer particles with Monasil PCA containing **a** 5.55, **b** 10.51, and **c** 14.93 mol% of MDOP in comonomer

the ease of aggregation of polymer particles owing to their soft surface. The copolymer was found to be increasingly aggregated when T_g values were reduced by the incorporation of MDOP, in addition to the surface-softening effect of Monasil PCA (Table 1). The integration of the –NCH_2– peak at 3.24 ppm (PVP) and of the –CH_2COO– peak at 4.05 ppm (PMDOP) was used to estimate the MDOP content in the copolymer, as shown in ^{1}H-NMR spectra (Fig. 5). Elemental analysis by calculation of ^{1}H-NMR spectra in Fig. 5 confirmed that the composition of MDOP in the final copolymer was much smaller than that of the initial comonomer. This is in agreement with the reactivity of NVP being assumed to be higher than that of MDOP, as deduced from the reactivity ratio data on precipitation polymerization of NVP and MDOP in $scCO_2$ [15]. Reactivity ratios of NVP and MDOP during precipitation polymerization in $scCO_2$ were 9.252 (r_{NVP}) and 0.081 (r_{MDOP}) at 70 °C and 300 bar. A tendency for large deviations in the reactivity ratios of copolymerization with MDOP was also observed in the reference data [12, 26]. The reactivity ratio of MDOP in copolymerization with styrene or methyl methacrylate was much smaller than that of styrene or methyl methacrylate. The FT-IR spectrum of poly(NVP-*co*-MDOP) synthesized with Monasil PCA showed a characteristic C=O stretching vibration of the ester group in the copolymer at 1,730 cm^{-1} (Fig. 6).

Effect of various concentrations of dispersant

Table 2 and Fig. 7 show that variations in dispersant concentration had an effect on the particle size and distribution of the polymer formed. The concentration of MDOP was held at 11±0.5 mol% of the total comonomer. The surface area of the polymer particle was stabilized with an increase in the concentration of the dispersant. The particle size of the polymer decreased and the number of particles increased as the concentration of the dispersant increased [27–30]. When PHDFDMA was used as the dispersant, the amount of stabilized surface area of the copolymer increased with increasing concentrations of the dispersant. Following this, the particle size of the copolymer was reduced to 0.37 μm and the morphology showed improvement (PSD=1.08). The morphology of poly(NVP-*co*-MDOP) copolymer particles with Monasil PCA also showed improvement with increasing concentrations of the dispersant. However, the copolymer particles obtained with Monasil PCA were more agglomerated in comparison to those obtained with PHDFDMA.

Effect of variations in reaction temperature

A variation in the reaction temperature of the CO_2 phase as the reaction medium was related to a change in the fluid

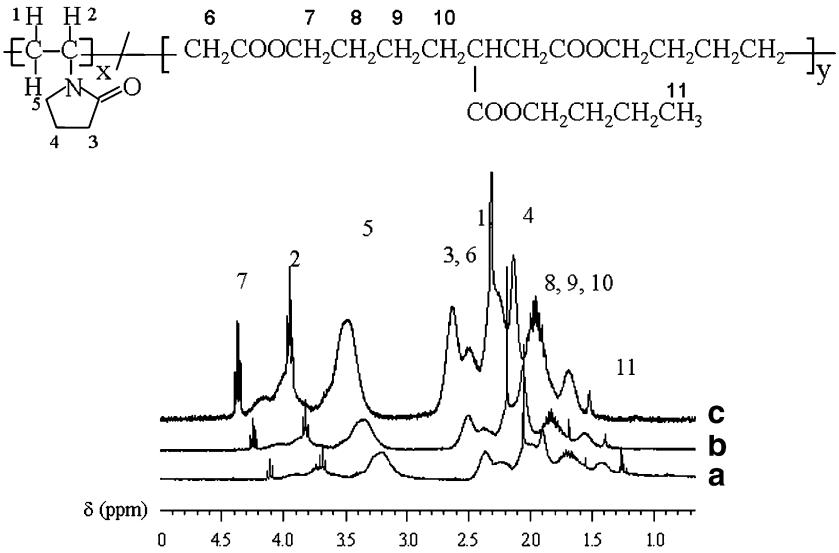

Fig. 5 ^{1}H-NMR spectra of poly (NVP-*co*-MDOP) containing **a** 5.55, **b** 10.51, and **c** 14.93 mol% of MDOP in comonomer

density or solvency power. Under constant reaction pressure, the density of CO_2 decreased with an increase in the reaction temperature. Table 3 and Fig. 8 show the result of copolymerization of NVP and MDOP with PHDFDMA while the reaction temperature was varied from 60 to 80 °C. This was followed by a change in the density of CO_2 from 0.83 to 0.75 g/ml (http://webbook.nist.gov/chemistry/ and NIST Standard Reference Database). The used basic experimental conditions were a pressure of 300 bar, concentration of MDOP at 17±0.5 mol% of the total comonomer, concentration of dispersant at 10 wt.% of the total comonomer weight, and concentration of AIBN at 1.0 wt.% of the total comonomer weight. With an increase in the reaction temperature and a decrease in the density of CO_2, the particle size of the copolymer showed a slight increase. In a typical radical polymerization reaction, the rate of polymerization and the final monomer conversion increase as the reaction temperature increases. This leads to an increase in the average particle size and a broader particle size distribution. The decomposition rate of the thermal initiator is predicted to be faster and more nuclei are produced at higher temperatures. In Table 3 and Fig. 8, the yield of copolymers showed an increase with the increase in the reaction temperature. Furthermore, the particle size of poly(NVP-*co*-MDOP) increased and showed a slightly increased broadening of the particle size distributions. The dominant effect of higher temperatures on the particle size and particle size distribution of copolymers may be a faster decomposition rate of the initiator. The solubility of the reactant in $scCO_2$ could be

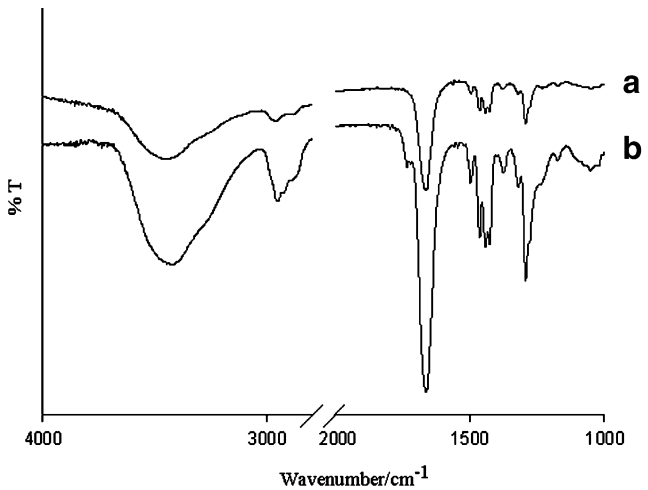

Fig. 6 FT-IR spectra of **a** PVP and **b** poly(NVP-*co*-MDOP) containing 14.93 mol% of MDOP in comonomer

Table 2 Effects of dispersant concentration on particle size and particle size distribution of poly(NVP-*co*-MDOP) particles

Dispersant[a] (wt.%)		MDOP in comonomer (mol%)	D_n (μm)[b]	PSD (D_w/D_n)[c]
PHDFDMA	5.0	11.0±0.5	NA	NA
	10.0		0.76	1.10
	15.0		0.37	1.08
Monasil PCA	5.0		NA	NA
	10.0		0.58	1.44
	15.0		0.27	1.36

Reaction conditions: 300±0.5 bar and 70±0.5 °C, 1 wt.% of AIBN on comonomer and 24 h
NA Not available
[a] Weight percent dispersant on comonomer
[b] Determined by FE-SEM image
[c] Particle size distribution

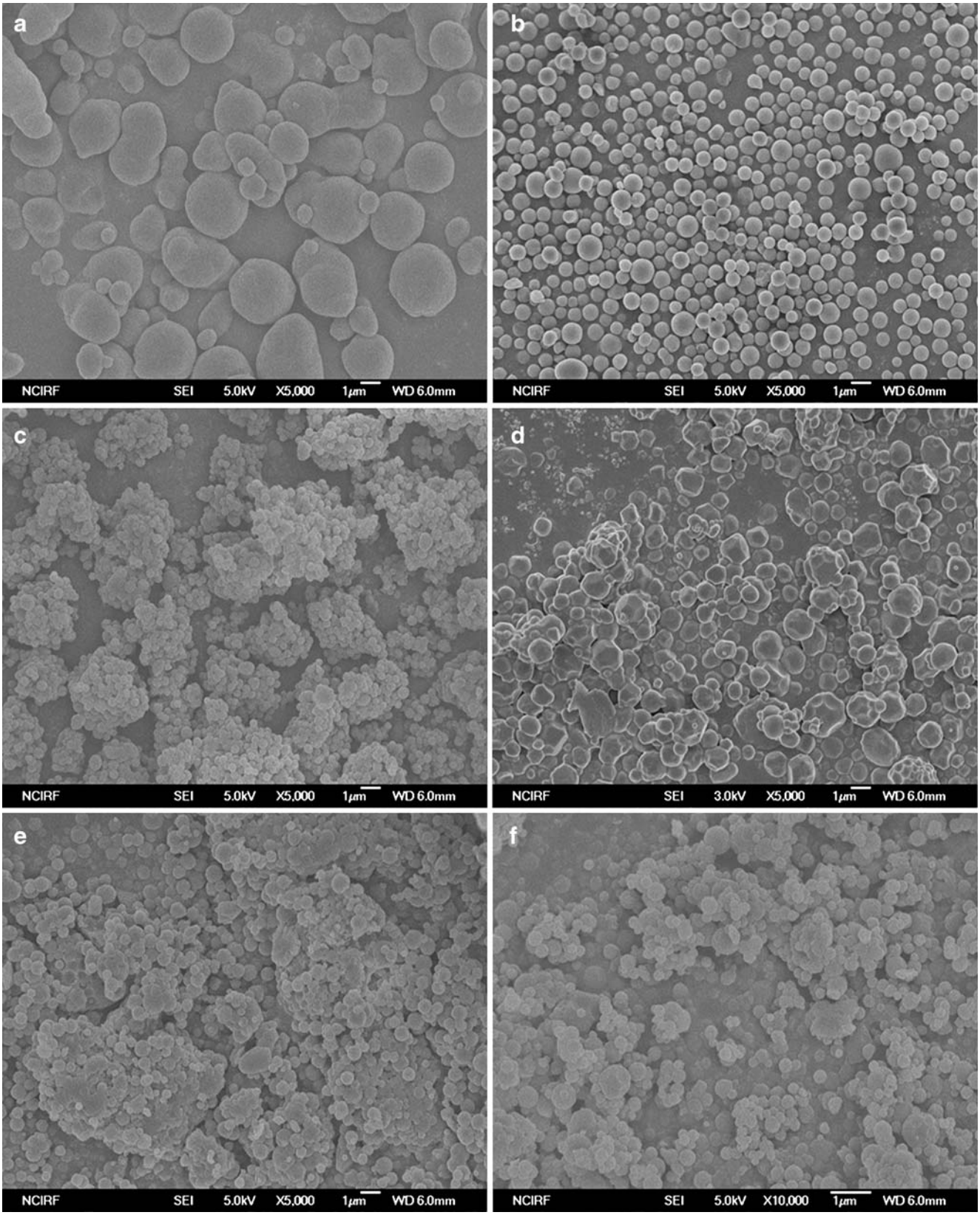

Fig. 7 FE-SEM images of copolymer particles with **a** 5.0, **b** 10.0, and **c** 15.0 wt.% of PHDFDMA on comonomer and with **d** 5.0, **e** 10.0, and **f** 15.0 wt.% of Monasil PCA on comonomer. Magnification: ×5,000 (**a**–**e**), ×10,000 (**f**)

Table 3 Effects of reaction temperature on particle size and distribution of poly(NVP-*co*-MDOP) particles

Reaction temperature (°C)	Density of CO_2 (g/ml)[a]	MDOP in comonomer (mol%)	Yields (%)	D_n (μm)[b]	PSD (D_w/D_n)[c]
60	0.83	17.0±0.5	85	0.49	1.02
70	0.79		92	0.58	1.04
80	0.75		98	0.68	1.06

Reaction conditions: 300±0.5 bar, 1 wt.% of AIBN on comonomer, 10 wt.% of PHDFDMA on monomer and 24 h

[a] Density of CO_2 (gram/milliliter) was determined by NIST Standard Reference Database.

[b] Determined by FE-SEM image

[c] Particle size distribution

improved or reduced with variations in the reaction temperature. In our previously published report, the solubility of the reactant (NVP + Monasil PCA) in $scCO_2$ was shown to have been reduced and particles were aggregated at higher temperatures [31]. However, in case of dispersion polymerization of *N*-isopropylacrylamide, the solubility of the reactant (*N*-isopropylacrylamide + PHDFDMA) in $scCO_2$ increased, and the particle size distribution of resulting polymer was improved with an increase in temperature [24]. In the present study, a growing chain length of formed oligomeric particles of copolymers increased with high temperatures. Furthermore, a large amount of radicals were shown to initiate many polymer chains. The larger particles obtained by high temperature reactions could be attributed to particle nucleation possibly due to coagulation at the neighboring softened and sticky surfaces. This, therefore, led to an increase in the particle size of the copolymer and its broadened size distribution as the reaction temperature was increased.

Effect of variations in initiator concentration

The effect of the concentration of the initiator on dispersion polymerization of NVP and MDOP was investigated with three different concentrations of AIBN. The concentration of Monasil PCA used was 10 wt.% of the total weight of the comonomer. Table 4 and Fig. 9 show the results of polymerization with 0.5, 1.0, and 2.0 wt.% of AIBN of the weight of the comonomer. Polymer yields higher than 90% were obtained under all experimental conditions. The morphology of the final copolymer was dry powder. However, FE-SEM images showed the presence of slightly aggregated particles in Fig. 9. There were no significant changes in the morphology of the copolymer obtained with different concentrations of AIBN. At higher concentrations of AIBN, the particle size of the copolymer was slightly reduced.

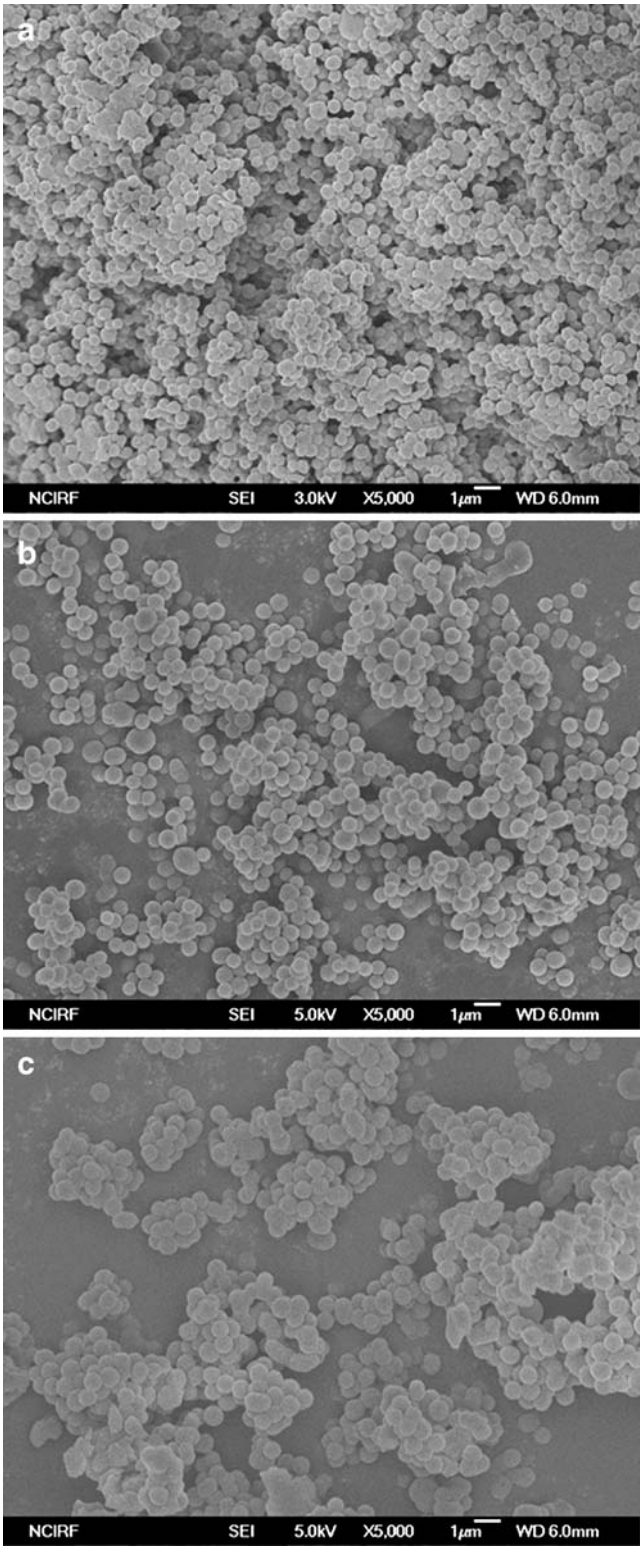

Fig. 8 Effect of reaction temperature on copolymerization: **a** 60, **b** 70, and **c** 80 °C

Conclusions

Dispersion copolymerization of NVP and MDOP was carried out in $scCO_2$ using fluorine- or siloxane-based

Table 4 Effects of initiator concentration on particle size and distribution of poly(NVP-*co*-MDOP) particles

AIBN (wt.%)[a]	MDOP in comonomer (mol%)	D_n (μm)[b]	PSD (D_w/D_n)[c]	Polymer morphology[d]
0.5	11.0±0.5	0.58	1.20	Dry powder
1.0		0.58	1.44	Dry powder
2.0		0.51	1.25	Dry powder

Reaction conditions: 300±0.5 bar and 70±0.5 °C, 10 wt.% of Monasil PCA on comonomer and 24 h
[a] Weight percent based on comonomer concentration
[b] Determined by FE-SEM image
[c] Particle size distribution
[d] Appearance of copolymer after CO_2 venting

dispersants. Dry, powdery, spherical particles of poly(NVP-*co*-MDOP) were produced directly after venting of CO_2. The experimental parameters of copolymerization included variations in comonomer ratios and dispersant concentrations as well as the reaction temperature and concentration of the initiator used. Particle size of the copolymers showed a reduction with increasing molar concentrations of MDOP in the feed. When the amount of MDOP was greater than 16.94 mol% in the case of using PHDFDMA as a dispersant, the copolymer particles were aggregated due to their low T_g values. T_g values of poly(NVP-*co*-MDOP) particles decreased from 142 to 110 °C with an increase in the concentration of MDOP in comonomer ratios. The particle size of the copolymer was reduced, and the morphology of the particles showed a narrow distribution with an increasing concentration of dispersants. The particle size of the copolymer increased and its size distribution was broadened due to the large amount of radicals that were initiated upon an increase in the reaction temperature. There were no significant changes in the morphology of the copolymer produced with different concentrations of AIBN.

These biocompatible and degradable polymer microspheres can be applied to polymeric carrier in drug delivery system. Encapsulation of special drugs using supercritical CO_2 impregnation process and release behavior of drugs will be the subject of future investigations.

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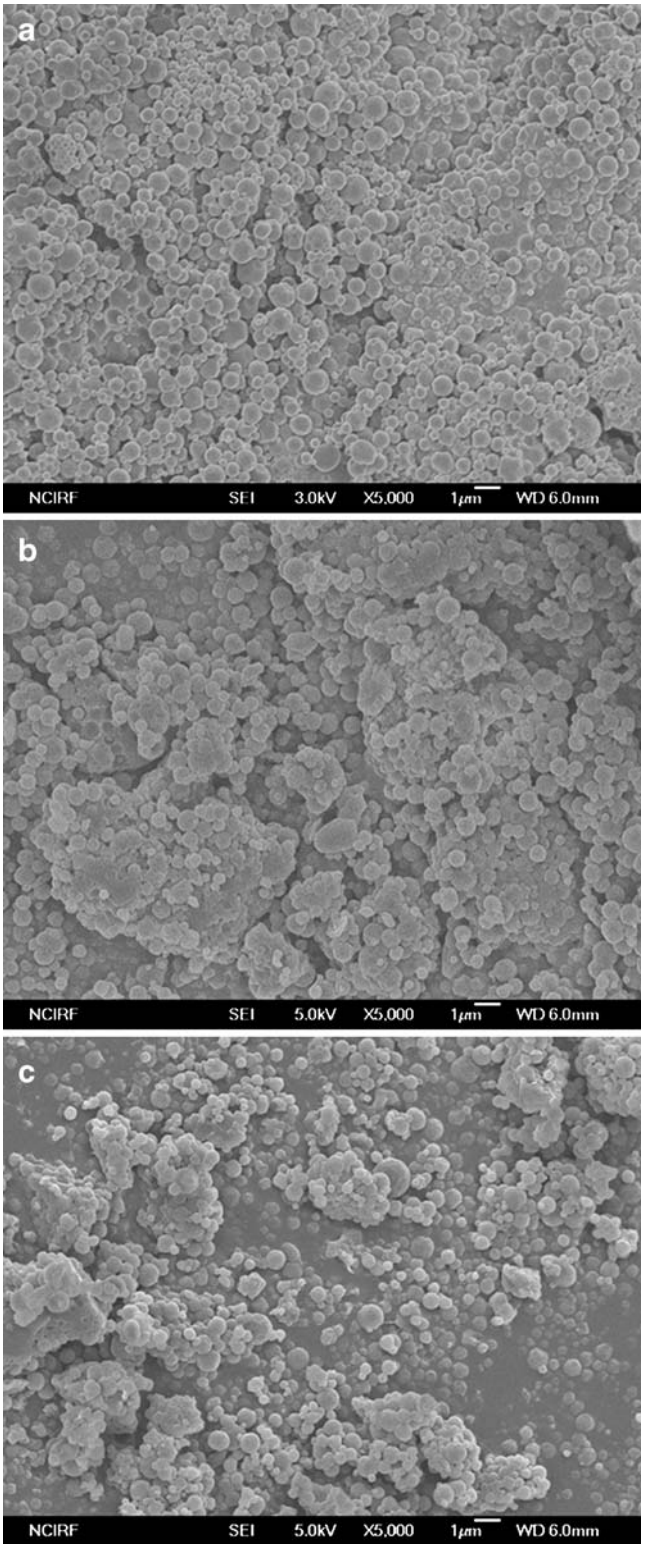

Fig. 9 FE-SEM images of copolymer with **a** 0.5, **b** 1.0, and **c** 2.0 wt.% of AIBN on comonomer

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