Study on Preparation of Monodispersed Poly(styrene-*co*-*N*-dimethylaminoethyl methacrylate) Composite Microspheres by SPG (Shirasu Porous Glass) Emulsification Technique

GUANG-HUI MA, MASATOSHI NAGAI, SHINZO OMI

Graduate School of Bio-Applications and Systems Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Nakamachi, Koganei, Tokyo 184-8588, Japan

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ABSTRACT: Monodispersed poly(styrene-*co*-*N*-dimethylaminoethyl methacrylate) [P(St-DMAEMA)] composite microspheres were prepared by employing a Shirasu Porous Glass (SPG) emulsification technique. A mixture of monomer, hexadecane (HD), and initiator *N,N′*-azobis(2,4-dimethylvaleronitrile) (ADVN) was used as a dispersed phase and an aqueous phase containing stabilizer [poly(vinyl pyrrolidone) (PVP) or poly(vinyl alcohol) (PVA)], sodium lauryl sulfate (SLS), and water-soluble inhibitor [hydroquinone (HQ), diaminophenylene (DAP), or sodium nitrite ($NaNO_2$)], was used as a continuous phase. The dispersed phase was permeated through the uniform pores of SPG membrane into the continuous phase by a gas pressure to form the uniform droplets. Then, the droplets were polymerized at 70°C. The effects of inhibitor, stabilizer, ADVN, and DMAEMA on the secondary nucleation, DMAEMA fraction in the polymer, conversion, and morphologies of the particles were investigated. It was found that the secondary nucleation was prevented effectively in the presence of HQ or DAP when PVP was used as the stabilizer. The secondary particle was observed when ADVN amount was raised to 0.3 g (/18 g monomer); however, no secondary nucleation occurred even by increasing DMAEMA fraction to 10 wt %. This result implied that the diffusion of ADVN into the aqueous phase was a main factor responsible to the secondary nucleation more than that of DMAEMA. The hollow particles were obtained when $NaNO_2$ was used, while one-hole particles formed in the other cases. By adding crosslinking agent, the hole disappeared and the monomer conversion was improved. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 79: 2408–2424, 2001

Key words: Shirasu porous glass; emulsification; monodispersity; poly(styrene-*co*-*N*-dimethylaminoethyl methacrylate); composite microspheres

INTRODUCTION

Monodispersed microspheres provide wide applications, for example, carriers of enzymes,[1–4] cells,[5] and DNAs.[6] Particularly, monodispersed large microspheres with several to 100 μm with functional groups found high performance as the carriers of the above-active substances in packing column or bioreactors, and of drugs in drug delivery system (DDS).[7–12] In these applications, functional groups are usually necessary to immobilize chemically the active substances on or in the particles. Monodispersity of the microspheres is also required in these applications. For example, when they are used in mass purification of protein, DNAs, and cells in a packing column, the pres-

Correspondence to: G.-H. Ma.

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sure loss can be minimized if the size distribution of particles is narrow. Furthermore, the theoretical evaluation will become simple if the microspheres are uniform in the above applications.

The large particle is usually prepared by the suspension polymerization method or seeded polymerization method by using the particle obtained in emulsion polymerization or dispersion polymerization as the seed. The former method provides the particles with broad size distribution; it is necessary to carry out postfiltration to eliminate large and small particles after the particles were obtained. Ugelstad developed a two-step swelling method[13,14] to prepare very uniform particles by using the particle obtained in the emulsion polymerization as the seed. Okubo et al. proposed a dynamic swelling method[15–17] to prepare large particles with the diameter around 7 μm by using the particles obtained in the dispersion polymerization as the seed. These swelling techniques can provide very uniform functional particles; the disadvantage is that they need more than two stages and a long time.

We developed an alternate method to prepare large monodispersed particles by one step,[18–21] combining the SPG (Shirasu Porous Glass) membrane emulsion technique and subsequent suspension polymerization process. The SPG membrane is a special porous glass membrane with very uniform pores. By applying adequate gas pressure, the oil phase containing the initiator permeates through the uniform pores of the membrane into the aqueous phase to form uniform droplets. The stabilizer and surfactant dissolved in the aqueous phase are adsorbed on the surface of the droplets to stabilize them. Then, by elevating the temperature to over the decomposition temperature of the initiator, the suspension polymerization proceeds to form the uniform particles. During the polymerization, the monodispersity is maintained if the emulsification and polymerization conditions are adequate. With using this method, we have successfully prepared monodispersed polystyrene (PST),[18] PST–PMMA,[19] polyurethane,[20] and polystyrene–polyimide[21] microspheres. The CV value that indicates the size distribution of the particles is about 10%.

In this study, we tried to prepare composite P(St-DMAEMA) microspheres with the amino functional group on the surface of the particles. DMAEMA was selected for this study because (1) it can be used for immobilization of the active substances on the uniform particles; (2) its chemical properties, such as acidity, basicity, and hydrophilic and hydrophobic properties, can be modified. Its property can thus be designed for actual application; (3) PDMAEMA is a temperature-sensitive polymer;[22] it can be used in the adsorption and desorption of proteins by changing the temperature. However, it is quite difficult to incorporate a high amount of DMAEMA into the composite particles because a majority of DMAEMA will be partitioned in the aqueous phase. Furthermore, the secondary nucleation in the aqueous phase will become very serious due to the large amount of DMAEMA dissolved in the aqueous phase. Even when a low amount of DMAEMA is used, the secondary nucleation will possibly occur because the solubility in the aqueous phase of oligoradical containing DMAEMA unit is high so that it will diffuse into the aqueous phase easily. Therefore, it is an important task to prevent the formation of the secondary nucleation when DMAEMA is used.

For the preparation of particles in the previous studies as described above, we usually used benzoyl peroxide (BPO) as an initiator, because the hydrophobicity of BPO is high enough to prevent the secondary nucleation in the aqueous phase. However, it was found that BPO was not suitable for the polymerization of DMAEMA. Although very uniform droplets were prepared, no polymerization occurred when BPO was used as the initiator. This is because BPO primary radical reacted with DMAEMA and lost its activity. In fact, it was found by ^{1}H-NMR measurement that benzoic acid formed when DMAEMA was mixed with BPO in $CDCl_3$. It implied that BPO primary radical has lost its activity by abstracting a hydrogen from DMAEMA. In this study, we selected a popular azo-initiator ADVN as an initiator instead of BPO. Although the hydrophobicity of ADVN is higher than that of AIBN, its solubility in the aqueous phase is still high enough to diffuse into the aqueous phase to generate the secondary nuclei in the usual polymerization condition, because it contains two nitrile groups. Furthermore, the inhibitor that was used to prevent the secondary nucleation in the previous studies became ineffective any more after adding DMAEMA, due to the special amine property of DMAEMA. Therefore, in this study, we investigated in detail how we can prevent the secondary nucleation by changing the type and amount of inhibitor and stabilizer, and amount of initiator and DMAEMA, and also studied the effects of these factors on the fraction of DMAEMA in the copolymer, monomer conversion, and morphology of the particles.

EXPERIMENTAL

Materials

Styrene (St) and divinyl benzene (DVB) were commercial grade (Kishida Chemical Co.), *N,N′*-dimethylamino ethyl methacrylate (DMAEMA) was reagent grade (Tokyo Chemical Industries, Co., Ltd.). St and DVB were distilled under a vacuum to remove the inhibitor. DMAEMA was used as purchased.

2,2′-Azobis(2,4-dimethylvaleronitrile) (V-65, ADVN) was reagent grade (Wako Pure Chemical Industries, Ltd.), and was used as an initiator. Hexadecane (HD) was reagent grade (Tokyo Chemical Industries, Co., Ltd.), and was used as a hydrophobic additive to retard the monomer diffusing into the aqueous phase. Hydroquinone (HQ), sodium nitrite ($NaNO_2$), and diaminophenylene (DAP) were reagent grade (Kishida Chemical Co.), and were used as inhibitors, respectively, to prevent the secondary nucleation in the aqueous phase. Sodium lauryl sulfate (SLS) was of the grade for biochemical use (Merck). Poly(vinyl alcohol) (PVA-217, degree of polymerization 1700, degree of hydrolysis 88.5%) was provided by Kuraray, and was used as a stabilizer. Poly(*N*-vinyl pyrrolidone) (PVP, K30, M_w = 40,000 g/mol) was reagent grade (Tokyo Chemical Co.), and was used as an alternate stabilizer. Electrolyte Na_2SO_4 was reagent grade (Wako Pure Chemical Industries, Ltd.), and was used to adjust the electrolyte concentration of the aqueous phase. Methyl alcohol was a commercial grade (Kishida Chemical Co.), and was used to precipitate and wash the particles obtained. All these reagents were used as received. Water was purified by distillation followed by deionization using ion-exchange resins.

Table I A Standard Recipe for SPG Emulsification

Ingredients	Weight (g)
Continuous phase	
PVP (or PVA)	**1.0** (or **2.0**)
Inhibitor (HQ, $NaNO_2$, NH_2—(C_6H_4)—NH_2)	0.02, 0.05 **0.10**
Na_2SO_4	**0.10**
SLS	**0.075**
Water	**225**
Dispersion phase	
ADVN	0.05, **0.1,** 0.2, 0.3, 0.5
Total Monomer	**18.0**
HD	**2.0**

Bold characters represent the standard recipe.

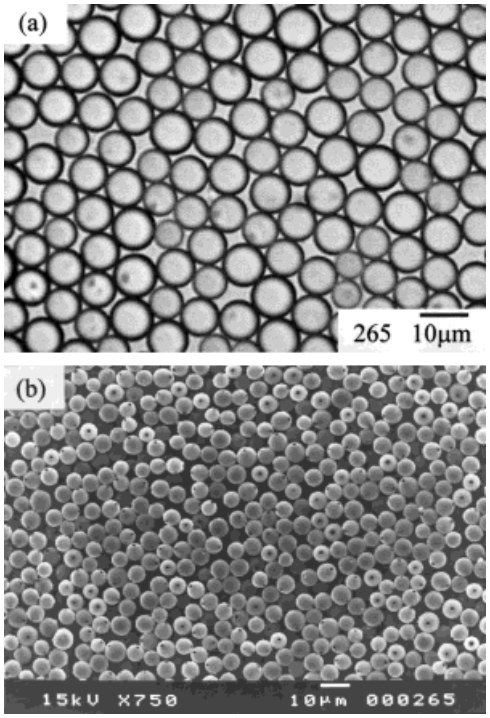

Figure 1 Typical OM micrograph of monodispersed droplets and SEM of polymer particles (run 265). (a) OM of droplets; (b) SEM of polymer particles.

Apparatus

A miniature kit for emulsification with an MPG module (microporous glass, a brand name of SPG) installed was purchased from Ise Chemical Co. A schematic diagram of this kit and the detailed emulsification process were shown in a previous article.[23] A membrane with the pore sizes of 1.42 μm was used in this study. Usually, the droplet size prepared is about six times as large as the pore size of the membrane.[18]

Preparation of Microspheres

Emulsification

A standard recipe of emulsification conditions is shown in Table I. The mixture of monomer and HD dissolving initiator ADVN was used as the dispersed phase (oil phase), and water, where the stabilizer (PVA or PVP), surfactant SLS, electrolyte Na_2SO_4, and inhibitor (HQ, $NaNO_2$ or DAP) were dissolved, was used as the continuous phase

Table II Effect of Stabilizer and Inhibitor on the Secondary Nucleation in the Absence of DMAEMA

		Run No.					
		255	256	257	263	262	261
Preparative conditions	Continuous phase (g)						
	PVP	1.0	1.0	1.0	—	—	—
	PVA	—	—	—	2.0	2.0	2.0
	HQ	—	—	0.10	—	—	0.10
	$NaNO_2$	—	0.10	—	—	0.10	—
	NH_2—(C_6H_4)—NH_2	0.10	—	—	0.10	—	—
	Na_2SO_4			0.10			
	SLS			0.075			
	Water			225			
	Dispersion phase (g)						
	ADVN			0.10			
	St			18.0			
	HD			2.0			
Polymerization result	D_p (μm)[a]	5.75	6.32	5.65	11.03	11.33	8.93
	CV (%)	10.19	9.75	10.00	14.07	12.92	16.38
	Conversion (%)	76.0	98.8	100.0	67.0	50.7	100.0
	$M_n/10^4$ (g/mol)	1.78	1.93	1.69	1.95	1.88	1.70
		—[b]	87.02	44.14	—[b]	—[b]	52.90
	Secondary particles	No	A few	A lot	No	No	A lot
	Morphology	One-hole	One-hole	Hollow	One-hole	One-hole	One-hole

[a] D_p: diameter of particle after polymerization.
[b] The peak due to the secondary particles was not observed.

(aqueous phase). Because it has been found in the previous studies that adding a small amount of HD can improve the stability of the droplets, 10 wt % of HD based on the oil phase was added into the oil phase. The oil phase was pressed by nitrogen gas through the SPG membrane into the aqueous phase continuously. Then, the stabilizer and SLS dissolved in the aqueous phase will be adsorbed onto the surface of the droplets to stabilize them. The concentration of the monomer was always around 10 wt %. The detailed SPG membrane emulsification process was described elsewhere.[23]

Polymerization

The obtained emulsion was transferred to a four-neck glass separator flask equipped with a semicircular anchor-type blade, a condenser, and a nitrogen inlet nozzle. After the emulsion was bubbled with nitrogen gas for 1 h, the nozzle was lifted up above the surface of the emulsion and the temperature was elevated to 70°C gradually for the polymerization. The polymerization was carried out for 24 h under a nitrogen atmosphere.

Analyses

Optical Microscopic (OM) Observation

Droplets of the emulsion before and after polymerization were observed with an optical microscope.

SEM Observation

The diameter and surface features of polymer particles were observed by a JSM-5300 (JEOL) scanning electron microscope (SEM). The specimens for SEM observations were prepared by coating a thin gold film (approx. 60 Å in thickness) on sample under reduced pressure below 8 Pa with a JFC-1200 fine coater (JEOL). Diameter of about 300 particles were counted to calculate the average diameters and size distribution of the polymer particles.

GPC Measurement

To check whether the secondary particles formed or not quantitatively, gel permeation chromatography (GPC) (HLC-801, Toso Co. Ltd.) measurement was carried out by employing tetrahydrofu-

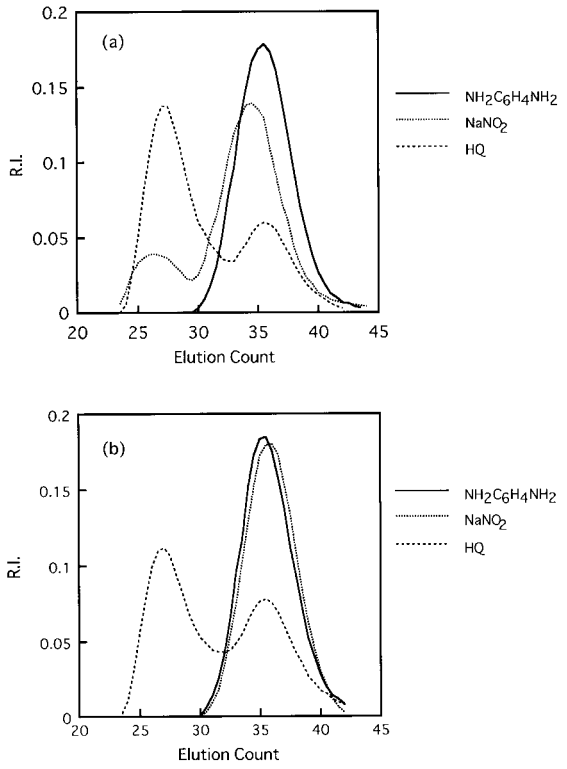

Figure 2 Normalized GPC results of polymer particles obtained in the absence of DMAEMA as a function of inhibitor types. Stabilizer: (a) PVP; (b) PVA.

ran (THF) as an elution solvent. The polymerization in the droplets and the secondary nuclei followed different polymerization mechanism, the former followed homogeneous bulk or solution polymerization, and the latter proceeded by emulsion polymerization mechanism. It has been well known the molecular weight obtained in emulsion polymerization is higher than that obtained by bulk or solution polymerization, attained to 10^5–10^6 (g/mol) The bulk or solution polymerization usually provides the polymer with the molecular weight of $\sim 10^4$ (g/mol). Therefore, two peaks should be detected by GPC measurement if the significant secondary nucleation occurred.

Measurement of Fraction of DMAEMA in the Polymer

The DMAEMA fraction in the polymer was measured by ^{1}H-NMR spectrometry. The ^{1}H-NMR spectra were recorded by a 500-MHz spectrometer (JEOL α-500) at 40°C with trichloromethane-d_3 ($CDCl_3$) as the solvent and locking agent. Spectra were obtained after accumulating 200 scans, by using a sample concentration of 5 wt %. The areas of peaks of —CH_3 of DMAEMA and —C_6H_5 of St were used to calculate the DMAEMA fraction in the polymer.

Measurement of Monomer Conversion

The monomer conversion was determined gravimetrically. The polymer was precipitated by methyl alcohol from the serum, separated by centrifugation, dried in a vacuum, and weighed.

RESULTS AND DISCUSSION

General Features of Emulsion Droplets and Polymer Particles

Fairly uniform droplets were obtained when less than 20 wt % of DMAEMA was added, irrespective of the types of stabilizer and inhibitor. A typical OM micrograph of droplets after SPG emulsification is shown in Figure 1(a) (run 265). After polymerization, the monodispersity of the droplets was maintained, the CV values of the particles obtained in most cases are below 10%. The average diameters of the particles were around 6–10 μm. A typical SEM of the polymer particles after polymerization is shown in Figure 1(b) (run 265). However, the secondary nucleation often occurred after polymerization, many small new particles were found. There are three main factors responsible to the secondary nucleation. (1) The initiator or oligoradical containing initiator fragment in terminal was not hydrophobic enough to escape into the aqueous phase easily. (2) The oligoradical that contains hydrophilic DMAEMA units exited into the aqueous phase easily. (3) The stabilizer was not able to stabilize the droplets during the polymerization.

To prevent the secondary nucleation, it is necessary to add a water-soluble inhibitor into the aqueous phase. The effectiveness of inhibitor depends on the respective monomer and initiator. Furthermore, the amounts of initiator, inhibitor, and DMAEMA also affect the secondary nucleation. Therefore, the effects of types of stabilizer, types and amount of inhibitor, amount of initiator and DMAEMA on the secondary nucleation, as well as on the monomer conversion, DMAEMA fraction in the polymer, and morphology, were investigated as follows.

Effects of Type of Inhibitor and Stabilizer on the Secondary Nucleation

At first, the effects of type of inhibitor and stabilizer on the formation of the secondary particles

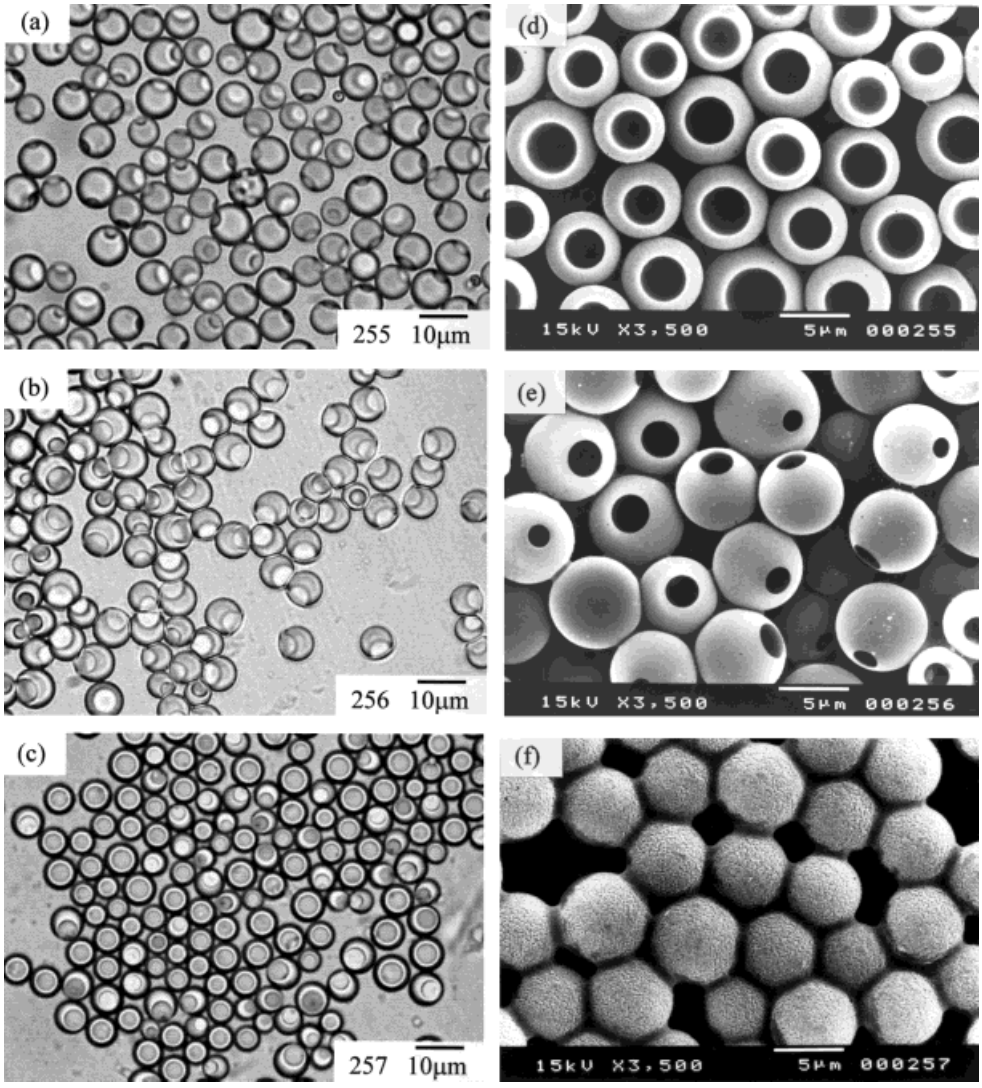

Figure 3 OM and SEM of polymer particles in the absence of DMAEMA as a function of inhibitor types. (a)–(c): OM; (d)–(f) SEM. Stabilizer: PVP. Inhibitor: (a),(d) DAP (run 255); (b),(e) $NaNO_2$ (run 256); (c),(f) HQ (run 257).

were investigated in the absence of DMAEMA, to compare with the results when DMAEMA was used. The preparative conditions and results are shown in Table II. The amount of initiator and inhibitor were fixed at 0.10 g, respectively, and those of PVP and PVA were selected as 1.0 and 2.0 g, respectively. Normalized results of GPC measurement of the polymer are shown in Figure 2. It was evident that the inhibitor apparently affected the secondary nucleation. When PVP was used as the stabilizer [Fig. 2(a)], only one peak was found around 36 elution count when DAP was employed as the inhibitor in the aqueous phase. However, another low peak was also observed around 26 elution count when $NaNO_2$ was used, although the molar amount of $NaNO_2$ was much higher than that of DAP. In the case of HQ, the intensity of peak at the lower elution count became much higher. As shown in Table II, the peaks in the higher and lower elution count corresponded to the number-average molecular weights of the order of 10^4 and 10^5 g/mol, respectively. It was evident that the former corresponded to the polymer polymerized inside the droplets, and the latter was that formed in the secondary particles. That is, it can be concluded that no secondary nucleation occurred when DAP was used as the inhibitor, a few of the secondary particles formed when $NaNO_2$ was used. However, a large amount of the secondary particles

Table III Effect of Stabilizer and Inhibitor on the Secondary Nucleation in the Presence of DMAEMA

		Run No.					
		253	254	265	260	259	258
Preparative conditions	Continuous phase (g)						
	PVP	1.0	1.0	1.0	—	—	—
	PVA	—	—	—	2.0	2.0	2.0
	HQ	—	—	0.10	—	—	0.10
	$NaNO_2$	—	0.10	—	—	0.10	—
	NH_2—(C_6H_4)—NH_2	0.10	—	—	0.10	—	—
	Na_2SO_4			0.10			
	SLS			0.075			
	Water			225			
	Dispersion phase (g)						
	ADVN			0.10			
	St			17.55			
	DMAEMA[a]			0.45			
	HD			2.0			
Polymerization results	D_p (μm)[b]	5.71	4.95	5.35	6.07	5.63	6.32
	CV (%)	9.51	10.27	8.27	10.97	9.62	10.09
	Conversion (%)	63.2	86.5	48.8	90.3	100.0	67.0
	$M_n/10^4$ (g/mol)	2.40	1.65	2.35	1.69	0.837	2.71
		—[c]	45.33	—[c]	63.09	40.27	—[c]
	DMAEMA in polymer (mol %)	0.26	0.32	0.22	0.31	0.38	0.20
	Secondary particle Morphology	No One-hole	A lot Hollow	No One-hole	A lot One-hole	A lot Hollow	No One-hole

[a] DMAEMA/monomer in feed = 2.5 wt % = 1.67 mol %.
[b] D_p: diameter of particle after polymerization.
[c] The peak due to the secondary particles was not observed.

were observed in the case of HQ. On the other hand, when PVA was used as the stabilizer, no secondary nucleation occurred in the cases of DAP and $NaNO_2$, and a large amount of the secondary particles formed when HQ was used, the same as in the case of PVP. It can be said that DAP is most effective, and HQ is most inferior among three inhibitors for preventing the secondary nucleation in the aqueous phase in both cases of PVA and PVP. From the monomer conversion shown in Table II, it was known that the conversion was very high, nearly 100% when the secondary nucleation occurred. This result is consistent with the phenomenon that the polymerization rate of emulsion polymerization is much higher than that of bulk or solution polymerization, observed by many researchers. The typical OM and SEM micrographs of the polymer particles are shown in Figure 3. When DAP was used [Fig. 3(a) and (d), run 255], the particles with a large hole were obtained, where no secondary nucleation was observed. Because the phase separation between HD and polymer occurred as the polymerization proceeded, a hole was formed after HD was extracted by methanol in the purification of particles. When $NaNO_2$ was used [Fig. 3(b) and (e), run 256], the particles with a smaller hole were obtained. Figure 3(c) and (f) show the sample (run 257) when HQ was used, where a large amount of the secondary particles formed. Although no secondary particle was observed from OM micrograph due to its small size, it was apparent from Figure 3(f) that a lot of secondary particles formed and were adsorbed on the surface of the large particles. From Figure 3(c) it was known that HD located on the core of the particles, differently from Figure 3(a) and (b). Because the surface of the new particles that were adsorbed on the large particles was hydrophilic due to the adsorbed emulsifiers, the hydrophilicity of the surface forced the hydrophobic HD to locate in the inside of the particles.

When 2.5 wt % of DMAEMA based on the total monomer was added, however, different results

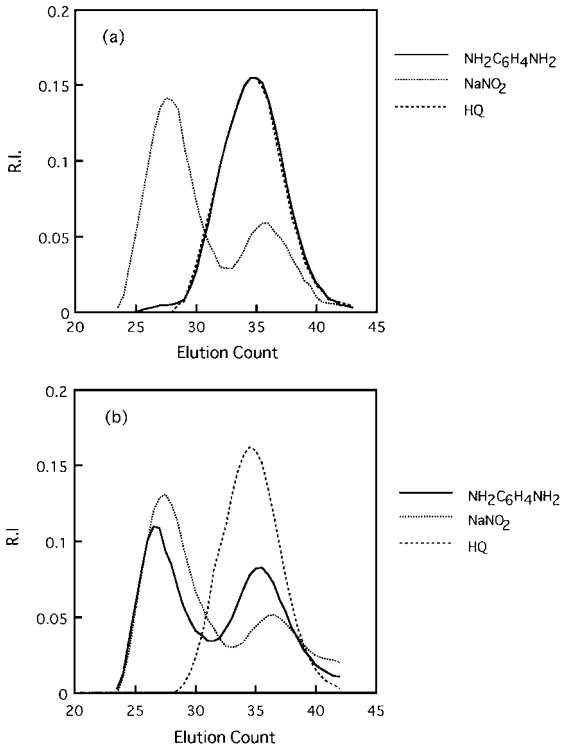

Figure 4 Normalized GPC results of polymer particles obtained in the presence of DMAEMA as a function of inhibitor types. Stabilizer: (a) PVP; (b) PVA.

were observed. The effects of stabilizer and inhibitor on the formation of the secondary particles, monomer conversion, and the molar fraction of DMAEMA in polymer in the presence of DMAEMA are shown in Table III and Figure 4. It was found that DAP and HQ were effective for inhibiting the secondary nucleation when PVP was used as the stabilizer; however, only HQ can prevent the formation of the secondary particles when PVA was used. These results are very different from those when DMAEMA was not added. Although HQ is not effective for inhibiting the formation of the secondary particles in the absence of DMAEMA, no secondary nucleation occurred when DMAEMA was added. This is probably because that HQ was partitioned into aqueous phase more easily in the alkaline condition after DMAEMA was added by the following equations.

$$—N(CH_3)_2 + H_2O \rightarrow —NH(CH_3)_2^+ + OH^- \quad (1)$$

$$HO(C_6H_4)OH + OH^- \rightarrow HO(C_6H_4)O^- + H_2O \quad (2)$$

As a result, a much higher amount of HQ was partitioned in the aqueous phase to lead oligoradical, which diffused from the oil droplets, unreactive, so as to inhibit the secondary nucleation effectively in the aqueous phase, compared with the case without DMAEMA.

$NaNO_2$ effectively prevented the formation of the new particles when DMAEMA was not used, especially in the case of PVA. When PVP was used, a small amount of new particles formed. However, the secondary nucleation was enhanced when DMAEMA was added in both cases of PVA and PVP, as shown in Figure 4. The reason for this phenomenon was considered from the inhibition mechanism of $NaNO_2$, shown as follows:

$$NaNO_2 + H_2O \rightleftharpoons HNO_2 + NaOH \quad (3)$$

$$HNO_2 + P\cdot \rightarrow PH + \cdot NO_2 \quad (4)$$

$$\cdot NO_2 + \cdot P \rightarrow P—NO_2 \quad (5)$$

where P represents growing oligoradical. Because DMAEMA solution is basicity as shown by Eq. (1), the equilibrium of Eq. (3) will move to left side due to the increase of OH^- concentration. Then, the concentration of HNO_2 will decrease, and the secondary nucleation cannot be inhibited effectively.

In the case of DAP, more interesting phenomena were observed. No secondary nucleation occurred, irrespective of the addition of DMAEMA, when PVP was used as a stabilizer, as shown in Figures 2(a) and 4(a). This phenomenon also can be interpreted by the inhibition mechanism as follows.

$$NH_2(C_6H_4)NH_2 + P\cdot \rightarrow NH_2(C_6H_4)NH\cdot + PH \quad (6)$$

$$NH_2(C_6H_4)NH\cdot + P\cdot \rightarrow NH_2(C_6H_4)NH—P \quad (7)$$

On the other hand, DAP also shows basicity in the aqueous phase.

$$NH_2(C_6H_4)NH_2 + H_2O \rightleftharpoons NH_2(C_6H_4)NH_3^+ + OH^- \quad (8)$$

Thus, when using DMAEMA, the concentration of OH^- increased, and equilibrium of eq. (8) moved to the left side. As a result, the concentration of unionized $NH_2(C_6H_4)NH_2$ increased, compared with the case without adding DMAEMA. Therefore, the inhibition proceeded effectively, as indicated by eq. (6), although DMAEMA dissolved in the aqueous phase was higher, and the probabil-

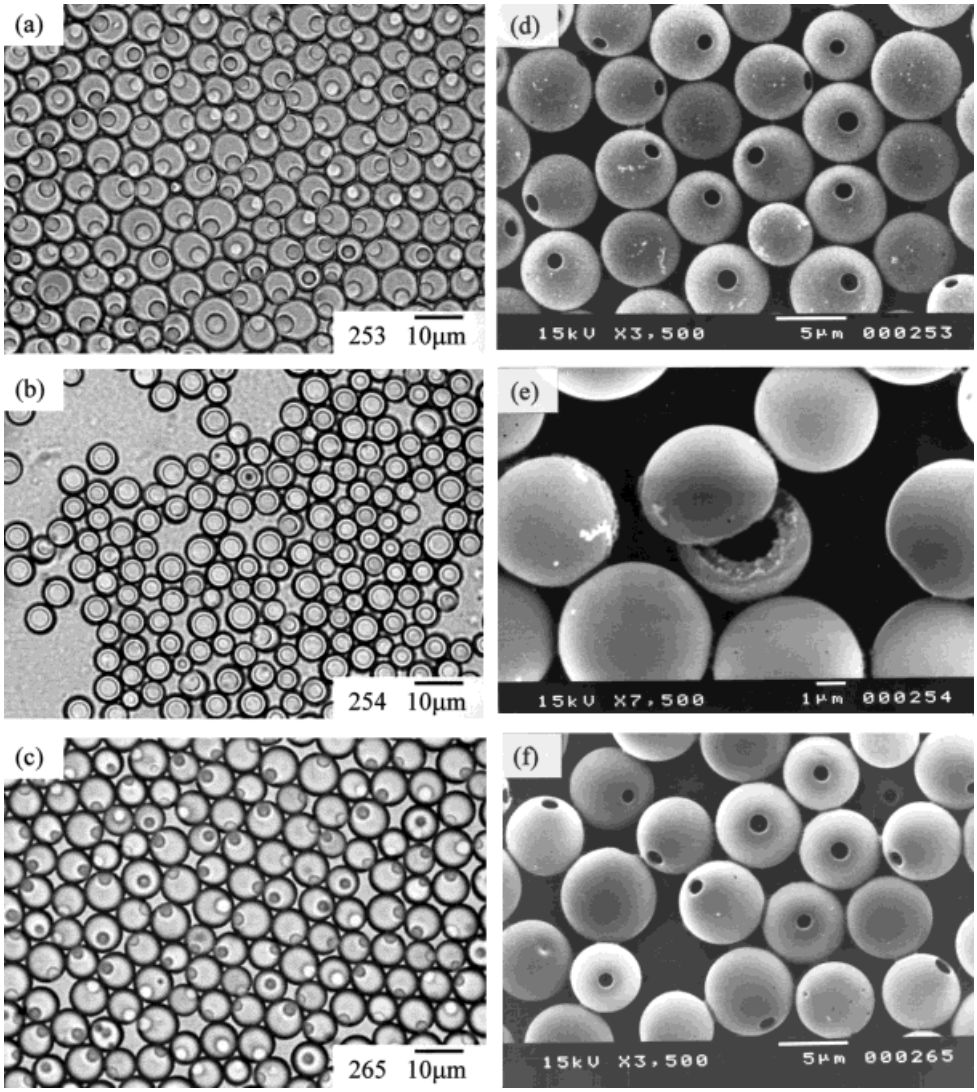

Figure 5 OM and SEM of polymer particles in the presence of DMAEMA as a function of inhibitor types. (a)–(c) OM; (d)–(f) SEM. Stabilizer: PVP. Inhibitor: (a),(d) DAP (run 253); (b),(e) $NaNO_2$ (run 254); (c),(f) HQ (run 265).

ity that the oligoradical containing DMAEMA units diffused into the aqueous phase became higher than that without containing DMAEMA units. When DMAEMA was not used, because the diffusion rate of the oligoradical without containing DMAEMA units was relatively lower, the secondary nucleation can be prevented effectively by DAP, although a part of DAP was ionized.

When PVA was used, however, the secondary nucleation was enhanced when DMAEMA was used [Fig. 4(b)], although no secondary nucleation occurred when DMAEMA was not added [Fig. 2(b)]. This is attributed to the interaction between PVA and DAP. Because there existed hydrogen bonding between DAP and PVA, DAP which dissolved in the aqueous phase was adsorbed on PVA. This retarded the reaction of DAP with the oligoradical, which escaped into the aqueous phase. When DMAEMA was not used, because the diffusion rate of the oligoradical without containing DMAEMA units was relatively lower, the secondary nucleation can be prevented effectively by DAP, even though a part of DAP was adsorbed on PVA. From the above results, it is clear that PVP is a more suitable stabilizer than PVA. In the following experiment, PVP was used as the stabilizer.

When DMAEMA was added, OM and SEMs of the polymer particles as a function of the types of inhibitors in the presence of PVP, are shown in Figure 5. It is very interesting that hollow parti-

Table IV Effect of Amount of ADVN on the Secondary Nucleation and Monomer Conversion When PVP Was Used as a Stabilizer

		Run No.								
		214	265	215	251	266	253	267	268	225
Preparative conditions	Continuous phase (g)									
	PVP					1.0				
	HQ	0.10	0.10	0.10	0.10	—	—	—	—	—
	NH_2—(C_6H_4)—NH_2	—	—	—	—	0.10	0.10	0.10	0.10	0.10
	Na_2SO_4					0.10				
	SLS					0.075				
	Water					225				
	Dispersion phase (g)									
	ADVN	0.05	0.10	0.20	0.30	0.05	0.10	0.20	0.30	0.60
	St					17.55				
	DMAEMA[a]					0.45				
	HD					2.0				
Polymerization results	D_p (μm)[b]	5.92	5.35	6.54	6.79	5.64	5.71	5.64	7.43	5.73
	CV (%)	9.62	8.27	10.33	9.23	8.33	9.51	8.33	15.83	9.15
	Conversion (%)	38.6	48.8	83.6	93.6	55.2	63.2	81.6	79.2	87.4
	$M_n/10^4$ (g/mol)	3.63	2.35	1.57	1.82	3.36	2.40	1.89	1.59	1.30
		—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
	DMAEMA in polymer (mol %)	0.41	0.22	0.17	0.22	0.24	0.26	0.13	0.23	0.43
	Secondary particle Morphology	No One-hole	No One-hole	A few One-hole	A few One-hole	No One-hole	No One-hole	A few One-hole	A few One-hole	Medium One-hole

[a] DMAEMA/monomer in feed = 2.5 wt % = 1.67 mol %.
[b] D_p: diameter of particle after polymerization.
[c] The peak due to the secondary particles was not observed, or was too low to be used for calculation of M_n of the secondary particles.

cles were obtained only when $NaNO_2$ was used as the inhibitor. This is because the interfacial tension between the polymer and aqueous phase containing $NaNO_2$ is lower than that between HD and the aqueous phase. Compared with the case without adding DMAEMA [Fig. 3(b)], the interfacial tension between polymer and aqueous phase will decrease due to the incorporation of the hydrophilic DMAEMA unit in the polymer. Therefore, HD was located in the center of the particle, and the hollow particle was obtained after HD was extracted. In the cases of other two inhibitors, however, the interfacial tension between polymer and aqueous phase is close to that between HD and the aqueous phase. HD protruded out of the particles, and the particle showed one-hole morphology after HD was extracted. The detailed discussion will be carried out in a next publication.

Furthermore, when DMAEMA was not added, the particle size and CV value were much smaller by using PVP than PVA. When DMAEMA was used, however, the difference was not as apparent. This is because the droplet size and its distribution are strongly affected by interfacial tension between oil phase and pore wall of the glass membrane.[24] When PVA was used and DMAEMA was not added, the interfacial tension was relatively larger, the droplet size and its distribution showed large values. This result suggested that DMAEMA and PVP can lower the interfacial tension between the oil phase and aqueous phase. As the results, the size became smaller and the size distribution, narrower.

DMAEMA fraction in the copolymer was in the range of 0.20–0.38 mol %; in other words, 12.0–23.0% of DMAEMA feed was incorporated into the composite microspheres. A large part of DMAEMA diffused out into the aqueous phase, then its polymerization was inhibited by the inhibitor. Therefore, the monomer conversion was not so high. When PVP was used, the monomer conversions were 63.2 and 48.8 wt %, respectively, for DAP and HQ. The conversion can be improved by varying the amount of the initiator and inhibitor, or by adding crosslinking agent in the oil phase, as described in following sections.

Effect of Amount of Initiator on the Secondary Nucleation and Monomer Conversion

It is understood that the amount of initiator plays a decisive role in the formation of the secondary particles, as well as monomer conversion, because

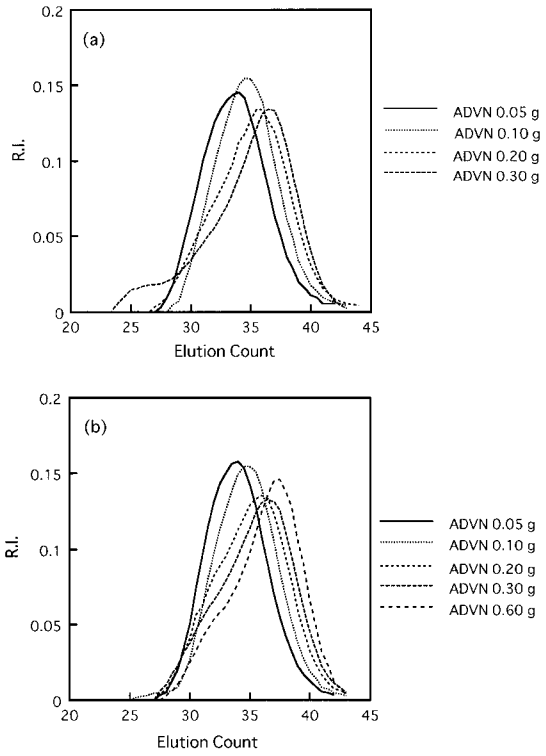

Figure 6 Normalized GPC results of polymer particles obtained in the presence of DMAEMA as a function of ADVN amount. Stabilizer: PVP. Inhibitor: (a) HQ; (b) DAP.

the amount of initiator controls the polymerization rate, and diffusion rate of the oligoradical into the aqueous phase. Therefore, the effect of the amount of ADVN was investigated. As described above, PVP is a more suitable stabilizer than PVA, and DAP and HQ are more effective inhibitor than $NaNO_2$, when DMAEMA was added. Therefore, the experiments were carried out with DAP and HQ in the presence of PVP. The amount of the inhibitor was fixed at 0.10 g. The results are summarized in Table IV, and the GPC data are shown in Figure 6. From Table IV and Figure 6(a), it was known that no secondary nucleation occurred when ADVN amount was lower (0.05, 0.1 g) in the presence of HQ. However, when ADVN amount was increased to 0.2 or 0.3 g, a weak shoulder was observed in the area of low elution count. That is, a small amount of the secondary particle formed. The intensity of shoulder became higher with the increase of the concentration of ADVN. That is, the fraction of the new particles increased as the amount of ADVN was raised. As shown in Table IV, the molecular weight decreased as the amount of ADVN increased, except the case of ADVN = 0.30 g. This result is consistent with the general phenomenon of bulk or solution polymerization. In the case of ADVN = 0.30 g, because a small amount of the new particles with high molecular weight formed, as a result, the average molecular weight became higher.

The monomer conversion increased as the amount of ADVN was raised. Although no secondary nucleation occurred when ADVN amount was lower, the monomer conversion was very low, only 38.6 and 48.8 wt %, respectively, for the cases of ADVN = 0.05 and 0.10 g. This is not a surprising result, because the initiator amount controls the polymerization rate.

When DAP was used as the inhibitor, the similar result was observed. When 0.05 or 0.10 g of ADVN was used, no secondary particle formed, as shown in Figure 6(b). However, a shoulder was found when ADVN increased to above 0.2 g. That is, a small amount of the secondary particles formed. Therefore, it is an adequate amount to add ADVN between 0.1 and 0.2 g into the oil phase, in both HQ and DAP. When DAP was used, the molecular weight also decreased, and the monomer conversion showed an increasing trend as the amount of ADVN increased. Because the molecular weights of HQ and DAP are almost same, their efficiencies can be compared. It was found from Table IV that the monomer conversion was higher than the case of HQ when 0.10 g of ADVN was used, where no secondary nucleation occurred. Therefore, DAP is a more suitable inhibitor for the preparation of P(St-*co*-DMAEMA) composite particles.

From the Table IV, it was known that all of the particles showed one-hole morphology.

Effect of Amount of Inhibitor on the Secondary Nucleation and Monomer Conversion

Although no secondary nucleation occurred when ADVN amount was lower (0.05 and 0.10 g), the monomer conversion was very low, as shown in Table IV, especially in the case of HQ. Therefore, the amount of inhibitor was lowered by an attempt to increase the monomer conversion. The results were summarized in Table V, VI, Figure 7, and Figure 8.

In the case of HQ, the monomer conversion increased to 46.2 wt % from 38.6 wt % by decreasing HQ from 0.10 to 0.05 g, and increased further to 70.4 wt % by lowering HQ to 0.02 g when the ADVN amount was 0.05 g, as shown in Table V.

Table V Effect of Amount of HQ on the Secondary Nucleation and Monomer Conversion When PVP Was Used as a Stabilizer

		Run No.				
		214	276	278	265	250
Preparative conditions	Continuous phase (g)					
	PVP			1.0		
	HQ	0.10	0.05	0.02	0.10	0.05
	Na_2SO_4			0.10		
	SLS			0.075		
	Water			225		
	Dispersion phase (g)					
	ADVN	0.05	0.05	0.05	0.1	0.1
	St			17.55		
	DMAEMA[a]			0.45		
	HD			2.0		
Polymerization results	D_p (μm)[b]	5.92	5.04	4.96	5.35	6.30
	CV (%)	9.62	8.94	10.90	8.27	9.95
	Conversion (%)	38.6	46.2	70.4	48.8	66.6
	$M_n/10^4$ (g/mol)	3.63	3.49	3.52	2.35	2.95
		—[c]	—[c]	141.2	—[c]	—[c]
	DMAEMA in polymer (mol %)	0.41	0.24	0.27	0.22	0.15
	Secondary particle Morphology	No One-hole	No One-hole	Medium One-hole	No One-hole	A few One-hole

[a] DMAEMA/monomer in feed = 2.5 wt % = 1.67 mol %.
[b] D_p: diameter of particle after polymerization.
[c] The peak due to the secondary particles was not observed, or was too low to be used for calculation M_n of the secondary particles.

However, the secondary particles formed when HQ was decreased to 0.02 g, as shown in Figure 7(a). This implied that HQ amount should be more than 0.02 g. When the ADVN amount was 0.10 g, the monomer conversion increased to 66.6 wt % from 48.8 wt %, and no secondary nucleation occurred [Fig. 7(b)]. Therefore, HQ amount can be decreased as low as 0.05 g when ADVN amount was lower.

On the other hand, when DAP was used, as shown in Table VI, the monomer conversion increased to 71.4 from 55.2 wt % by lowering DAP from 0.10 to 0.02 g, when ADVN amount was 0.05 g. No secondary nucleation occurred even when DAP was decreased to 0.02 g, as shown in Figure 8(a). When ADVN amount was 0.10 g, the monomer conversion did not change, apparently even by lowering DAP from 0.10 to 0.05 g. However, a very low shoulder appeared when DAP amount was as lower as 0.05 g, as shown in Figure 8(b). Therefore, DAP can be lowered to 0.02 g when ADVN amount was 0.05 g, and can be decreased to 0.05 g when ADVN amount was 0.10 g.

Effect of Amount of DMAEMA on the Secondary Nucleation, Molar Fraction of DMAEMA, and Monomer Conversion

To know ADVN or DMAEMA was a main factor inducing the secondary nucleation, as well as the effect of DMAEMA on the molar fraction of DMAEMA in the particles and monomer conversion, the DMAEMA fraction in the monomer feed was varied from 2.5 to 30 wt %, when DAP was used as an inhibitor and PVP as a stabilizer. Both ADVN and DAP were fixed at 0.10 g. The results were summarized in Table VII, and the GPC measurement result is shown in Figure 9. The effect of DMAEMA feed amount on molar fraction of DMAEMA in the particles and monomer conversion is shown in Figure 10. From Figure 9, it was found that almost the same GPC curve was obtained, and no secondary nucleation occurred until DMAEMA was increased to 10 wt %. This result is also attributed to the inhibition mechanism and the special properties of DAP and DMAEMA, as shown in eq. (1), and eq. (6)–(8). Although the probability of secondary nucleation

Table VI Effect of Amount of NH_2—(C_6H_4)—NH_2 on the Secondary Nucleation and Monomer Conversion When PVP Was Used as a Stabilizer

		Run No.				
		266	277	279	253	269
Preparative conditions	Continuous phase (g)					
	PVP			1.0		
	NH_2—(C_6H_4)—NH_2	0.10	0.05	0.02	0.10	0.05
	Na_2SO_4			0.10		
	SLS			0.075		
	Water			225		
	Dispersion phase (g)					
	ADVN	0.05	0.05	0.05	0.10	0.10
	St			17.55		
	DMAEMA[a]			0.45		
	HD			2.0		
Polymerization results	D_p (μm)[b]	5.64	4.75	5.02	5.71	5.82
	CV (%)	8.33	8.72	9.30	9.51	9.96
	Conversion (%)	55.2	49.4	71.4	63.2	60.5
	$M_n/10^4$ (g/mol)[c]	3.36	3.49	4.74	2.40	3.92
	DMAEMA in polymer (mol %)	0.24	0.30	0.25	0.26	0.17
	Secondary particle	No	No	No	No	No
	Morphology	One-hole	One-hole	One-hole	One-hole	One-hole

[a] DMAEMA/monomer in feed = 2.5 wt % = 1.67 mol %.
[b] D_p: diameter of particle after polymerization.
[c] The peak due to the secondary particles was not observed.

became higher due to the increase of DMAEMA partitioned in the aqueous phase, unionized DAP increased, and almost all of DAP was used effectively to prevent the secondary nucleation. As described before, however, a small increase in ADVN amount led to the formation of the secondary particles. Therefore, it can be concluded that the escape of ADVN or oligoradical containing ADVN segment into the aqueous phase was the main factor responsible for the secondary nucleation when DAP was used as an inhibitor. The solubility of ADVN in the aqueous phase is higher than that of BPO, which was used in our previous studies. Therefore, it was easier to escape into the aqueous phase to react with the monomer dissolved in the aqueous phase to form the secondary particles. After DMAEMA was increased to above 20 wt %, a small amount of secondary particle formed. In the case of 30 wt % of DMAEMA, the secondary nucleation became more enhanced.

From Figure 10, it was known that the molar fraction of DMAEMA in the particle increased with increase of DMAEMA fraction in the feed. When DMAEMA fraction in the feed was raised to 10 wt % where no secondary particle formed, DMAEMA fraction in the particle attained to 1.35

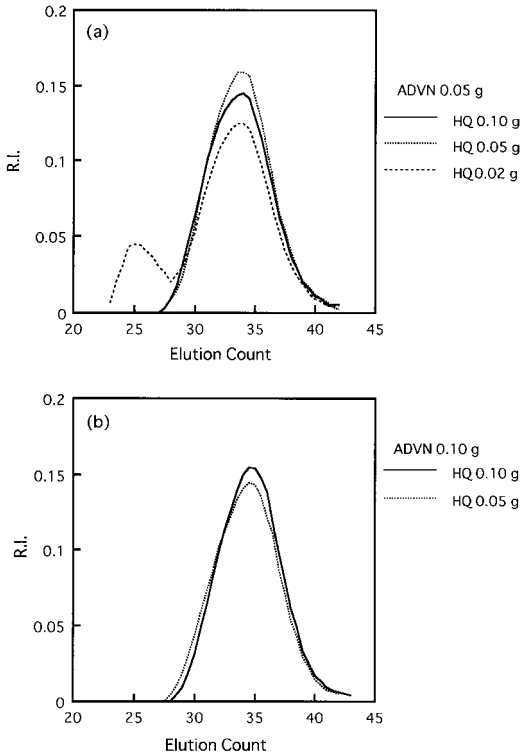

Figure 7 Normalized GPC results of polymer particles obtained in the presence of DMAEMA as a function of HQ amount. Stabilizer: PVP.

Table VII Effect of Amount of DMAEMA on the Secondary Nucleation, Monomer Conversion, Incorporation of DMAEMA When PVP Was Used as a Stabilizer and NH_2—(C_6H_4)—NH_2 as a Inhibitor

		Run No.						
		253	270	271	272	273	274	275
Preparative conditions	Continuous phase (g)							
	PVP				1.0			
	NH_2—(C_6H_4)—NH_2				0.10			
	Na_2SO_4				0.10			
	SLS				0.075			
	Water				225			
	Dispersion phase (g)							
	ADVN				0.10			
	St	17.55	17.28	16.92	16.56	16.2	14.4	12.6
	DMAEMA	0.45	0.72	1.08	1.44	1.8	3.6	5.4
	HD				2.0			
	DMAEMA/Mono. (wt %)	2.5	4.0	6.0	8.0	10.0	20.0	30.0
	DMAEMA/Mono. (mol %)	1.67	2.69	4.06	5.45	6.86	14.21	22.11
Polymerization results	D_p (μm)[a]	5.71	6.00	5.40	6.43	5.52	6.52	—
	CV (%)	9.51	9.20	8.84	10.07	11.04	10.48	—
	Conversion (%)	63.2	62.2	46.2	43.5	42.7	33.7	69.4
	$M_n/10^4$ (g/mol)	2.40	2.60	2.50	2.47	2.46	1.98	2.48
		—[b]	—[b]	—[b]	—[b]	—[b]	81.27	—[b]
	DMAEMA in polymer (mol %)	0.25	0.52	0.81	1.13	1.35	2.21	2.62
	Secondary particle Morphology	No One-hole	No One-hole	No One-hole	No One-hole	No One-hole	A few One-hole	Medium Agglomeration

[a] D_p: diameter of particle after polymerization.
[b] The peak due to the secondary particles was not observed, or was too low to be used for calculation of M_n of the secondary particles.

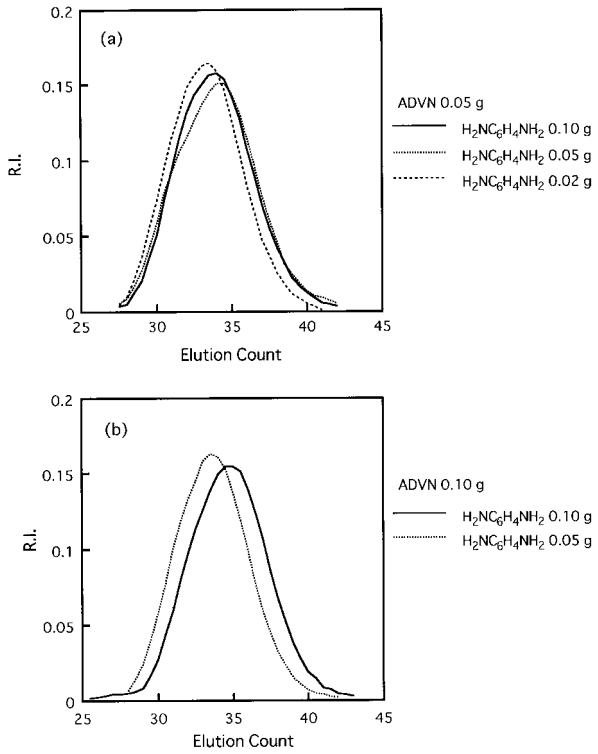

Figure 8 Normalized GPC results of polymer particles obtained in the presence of DMAEMA as a function of DAP amount. Stabilizer: PVP.

mol %. The monomer conversion decreased with increase of DMAEMA in the feed, except the case of 30 wt % of DMAEMA. This is because a higher part of DMAEMA diffused into the aqueous phase as the polymerization proceeded and the further polymerization was inhibited by the inhibitor in the aqueous phase. Furthermore, as DMAEMA diffused into aqueous phase, the solubility of ST in the aqueous phase also became higher. As a result, the monomer conversion became lower. In

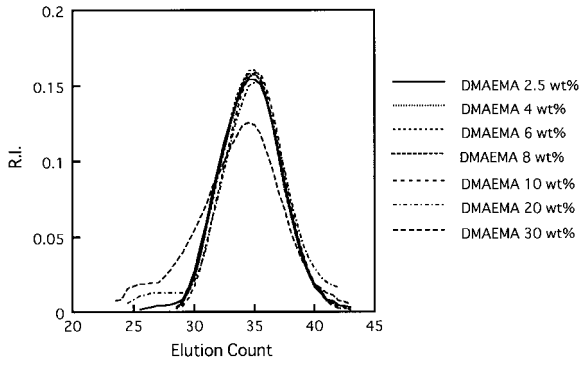

Figure 9 Normalized GPC results of polymer particles obtained in the presence of DMAEMA as a function of feed fraction of DMAEMA. Stabilizer: PVP. Inhibitor: DAP.

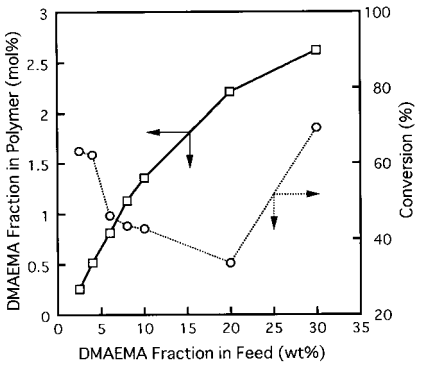

Figure 10 Effect of DMAEMA feed fraction on molar fraction of DMAEMA in the particles and monomer conversion Stabilizer: PVP. Inhibitor: DAP.

the case of 30 wt % of DMAEMA, the solution polymerization also occurred, together with the emulsion polymerization, because a large amount of monomer dissolved in the aqueous phase. As a result, a large agglomeration formed, leading to the increase of the monomer conversion.

Crosslinked Particle

As described above, a one-hole particle was always obtained when HQ or DAP was used as the inhibitor, because of the phase separation between polymer and HD. To obtain a spherical particle, the crosslinking agent DVB was added into the oil phase when PVP and DAP were used as the stabilizer and inhibitor, respectively. Both of ADVN and DAP were fixed at 0.10 g. The results were shown in Table VIII. After DVB was added, the spherical particles were obtained, irrespective of the amount of DMAEMA and DVB. The typical OM and SEMs of the polymer particles were shown in Figure 11 (run 282). As shown in Figure 11(a), although the phase separation between HD and polymer occurred, HD was squeezed out of the particles because the elasticity of the crosslinked polymer became lower. This phenomenon is consistent with that observed by Sheu et al.[25,26] They studied about the phase separation between PST of the seed particle and PST polymerized at the seeded polymerization. When the seed particle was not crosslinked, the spherical particle was obtained because St can permeate into the network of the seed particle and polymerized in the inside of the network, no phase separation occurred. However, when the seed particle was crosslinked, the dumbbell-like particle was obtained. This is because PST polymerized in the

Table VIII Effect of Crosslinking Agent on the Secondary Nucleation, Monomer Conversion, and Morphology When PVP Was Used as a Stabilizer and NH_2—(C_6H_4)—NH_2 as a Inhibitor

		Run No.				
		253	280	281	273	282
Preparative conditions	Continuous phase (g)					
	PVP			1.0		
	NH_2—(C_6H_4)—NH_2			0.10		
	Na_2SO_4			0.10		
	SLS			0.075		
	Water			225		
	Dispersion phase (g)					
	ADVN			0.10		
	St	17.55	16.65	15.75	16.2	15.3
	DMAEMA	0.45	0.45	0.45	1.8	1.8
	DVB	0	0.9	1.8	0	0.9
	HD			2.0		
	DMAEMA/Mono. (wt %)	2.5	2.5	2.5	10.0	10.0
	DMAEMA/Mono. (mol %)	1.67	1.69	1.70	6.86	6.93
Polymerization results	D_p (μm)[a]	5.71	7.12	6.99	5.52	6.85
	CV (%)	9.51	9.68	10.43	11.04	10.46
	Conversion (%)	63.2	97.2	100.0	42.7	88.8
	DMAEMA in polymer (mol %)	0.25	—[b]	—[b]	1.35	—[b]
	Secondary particle	No	No	No	No	No
	Morphology	One-hole	Spherical	Spherical	One-hole	Spherical

[a] D_p: diameter of particle after polymerization.
[b] ^{1}H-NMR was not carried out because crosslinked polymer did not dissolve in the $CDCl_3$.

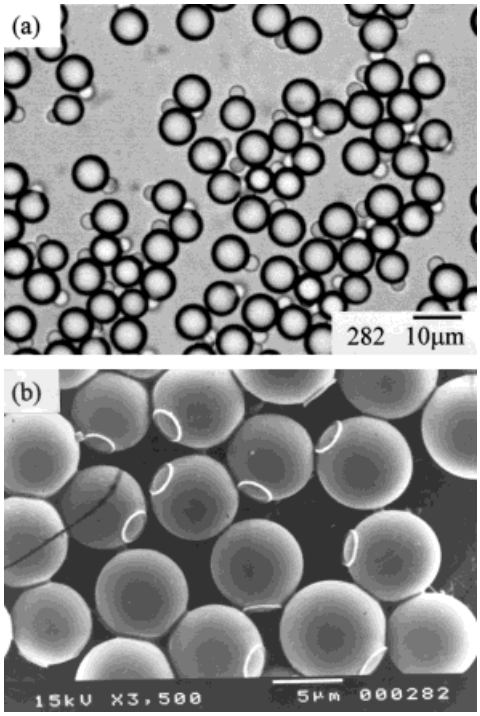

Figure 11 Typical OM and SEM of crosslinked spherical particles without a hole (run 282). (a) OM; (b) SEM.

second stage was not able to stay in the network of the seed particle due to the decrease of the elasticity of the seed polymer, and polymerized on the surface of the seed particle. Another interesting phenomenon was that the monomer conversion was remarkably improved by adding DVB. When DMAEMA fraction in the feed was 2.5 wt %, the monomer conversion increased to 97.2 wt % and 100.0 wt % by adding 5.0 wt % and 10.0 wt % of DVB, respectively. When DMAEMA fraction was 10.0 wt %, the monomer conversion increased to 88.8 wt % from 42.7 wt % by varying DVB from 0 to 5.0 wt %. This is because that the copolymerization between St and DMAEMA proceeded rapidly due to crosslinking by DVB, more than the diffusion of DMAEMA into the aqueous phase. The similar phenomenon was observed in a previous study of copolymerization of PST and poly(2-hydroxyethyl methacrylate) (PHEMA).[27] Further more, it was found that the particle size also increased by adding DVB. This is because the monomer conversion significantly increased, the particle did contract apparently even after it was dried.

Concluding the above results, PVP was a most suitable stabilizer, and DAP was the best inhibitor among three inhibitors studied in this study for the preparation of P(ST-DMAEMA) composite particles. An adequate amount of ADVN was between 0.1–0.2 g (/18 g monomer). The DMAEMA fraction in the feed can be as high as 10 wt %, although the monomer conversion was lower. However, adding crosslinking agent can remarkably increase monomer conversion. Hollow particle was obtained only when $NaNO_2$ was used. In other cases, a one-hole particle was found in all of other cases. However, this hole can be removed by adding a crosslinking agent in the oil phase. The DMAEMA fraction incorporated in the copolymer was not so high, because a large part of DMAEMA was partitioned in the aqueous phase. This problem was expected to be overcome by adding organic solvent into the aqueous phase to lower the solubility of DMAEMA in the medium.

CONCLUSION

The monodispersed P(ST-*co*-DMAEMA) composite particles can be prepared by employing the SPG emulsification technique followed by a polymerization process. The secondary nucleation was successfully prevented by using DAP or HQ as the inhibitor in the aqueous phase when PVP was used as the stabilizer. When PVA was used as the stabilizer, the secondary nucleation can be effectively suppressed only by the addition of HQ. The fraction of DMAEMA in the particle can be increased by increasing the amount of DMAEMA fraction in the feed, and no secondary nucleation occurred even by increasing DMAEMA fraction in the feed to 10 wt %. However, a little increase in the ADVN amount induced the secondary nucleation. This result suggested that ADVN was a main factor responsible for the secondary nucleation more than DMAEMA, due to its relatively high solubility in the aqueous phase. Therefore, it is necessary to control the ADVN amount below a critical level. The monomer conversion increased by raising the ADVN amount and lowering the inhibitor amount in the feed. Adding a crosslinking agent can raise the monomer conversion. It also was found that the morphology of the particle also was affected by the type of the inhibitor. The hollow particle was obtained only when $NaNO_2$ was used. In other cases, one-hole particles were always observed. The hole can be eliminated by adding crosslinking agent in the oil phase.

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