

Monodisperse hydrophilic polymer microspheres having carboxylic acid groups prepared by distillation precipitation polymerization

Feng Bai, Xinlin Yang*, Rui Li, Bo Huang, Wenqiang Huang*

Key Laboratory of Functional Polymer Materials, The Ministry of Education, Institute of Polymer Chemistry, Nankai University, No. 94, Weijin Road, Tianjin 300071, PR China

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Abstract

Monodisperse hydrophilic polymer microspheres having carboxyl acid group with spherical shape in the range of 160 nm and 1.52 μm were prepared by distillation copolymerizations of (meth)acrylic acid with either ethyleneglycol dimethacrylate (EGDMA) or divinylbenzene (DVB) as crosslinker. Polymerization was carried out with 2,2'-azobisisobutyronitrile (AIBN) as initiator in neat acetonitrile without stirring. The polymer microspheres were formed and precipitated out from the reaction medium during the distillation of the solvent from the reaction system through an entropic precipitation polymerization manner. The effects of the crosslinker degree on the morphology and the loading capacity of the carboxylic acid group of the resultant polymer microspheres were investigated. The growth procedures of poly(DVB-co-AA) microspheres were traced by SEM characterization. The steric stabilization through the pendent chains and surface gel and the electrostatic repulsion from the carboxyl acid groups contribute to the formation of monodisperse polymer microspheres.

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Keywords: Distillation precipitation polymerization; Hydrophilic polymer microspheres; Formation mechanism

1. Introduction

Polymer materials have been utilized in a wide range of traditional applications, such as coatings, adhesives, inks, leather finishing and construction [1]. The wide range of commercial applications of polymer microspheres has encouraged active research in this field during last decade. The polymer microspheres with optimized characteristics, such as uniform size and shapes, functionality of the base polymer, morphology of the polymer particles, and degree of crosslinking, are being widely used as functional supports, chromatography separation, biomedical devices, coating additives, controlled release reservoirs, and in other areas [2–7].

The preparation methods of polymer microspheres have been studied for many years [8,9]. Dispersion and emulsion polymerizations are usually used for the synthesis of polymer microspheres, in which the surfactants in aqueous solution [10] and stabilizers in organic solution [9,11] are critical to stabilize the polymer phase and to avoid the aggregation of particles. Precipitation polymerization is unique to afford polymer microspheres with uniform size and shape which can lead to narrow dispersion, free of any added surfactant or stabilizer [12–16]. However, it was difficult to get monodisperse hydrophilic polymer microspheres with good spherical shape by precipitation polymerization [17].

Microspheres with various functional groups have many applications in many fields, such as solid carriers for the immobilization of biological substances such as enzymes, antibodies, etc. [18]. To date, work has been reported on the utilization of microspheres as microscopic markers for antigens or antibodies on the surface of the cells [19]. The

* Corresponding authors. Tel.: +86 22 23502023; fax: +86 22 23503510.

E-mail addresses: xlyang88@nankai.edu.cn (X. Yang), hwq60@nankai.edu.cn (W. Huang).

synthesis of microspheres with carboxylic acid, hydroxyl, and amino groups on the surface of the microspheres has been attempted by various methods, in which the functional groups were used to covalently bind antibodies and other proteins to the particles.

The polymer microspheres with uniform size are essential for drug delivery system (DDS) because the distribution of the microspheres in the body and the interaction with biological cells are greatly affected by the particle size [20]. Additionally, if monodisperse microspheres are available, the drug release kinetics can be manipulated, therefore making it easier to formulate more sophisticated intelligent DDS.

Polymer nanoparticles are being investigated extensively to improve the material properties of the polymer matrix [21,22]. In addition to their practical importance, such composites offer diverse scientific challenges, combining ideas from colloidal science, polymer physics and chemistry, as well as material science.

Amphiphilic copolymer containing carboxylic acid group with different architectures have been widely prepared for their utilization in emulsion polymerization and for the investigation of their unique rheological behavior [23–25]. Previously, monodisperse hydrophilic microspheres with functional groups such as aldehyde, imide, amide, etc. were obtained by a radiation precipitation polymerization, without stirring in the absence of any stabilizers or catalyst [26,27]. However, the irradiation technique needs a special γ -ray source of Co-60 and a special equipment to perform polymerization.

Recently, we reported the distillation precipitation polymerization as a novel technique to afford monodisperse poly(divinylbenzene) (polyDVB) [28] and poly(divinylbenzene-*co*-chloromethyl styrene) (poly(DVB-*co*-CMSt)) [29] microspheres in neat acetonitrile without any stirring. To date, few systematical studies have been investigated on the monodispersity and morphology of the hydrophilic polymer nano/micron-particles. In the present paper, monodisperse hydrophilic polymer microspheres with active carboxylic acid groups were prepared by distillation precipitation copolymerizations of either ethyleneglycol dimethacrylate (EGDMA) or divinylbenzene (DVB) as crosslinker and (meth)acrylic acid with 2,2'-azobisisobutyronitrile (AIBN) as initiator in neat acetonitrile without stirring and the loading capacity of the accessible carboxylic acid groups on the polymer microspheres was also determined. The objective of this study is to provide a valuable and effective guidance for the synthesis of monodisperse hydrophilic polymer microsphere, which may have wide application areas such as DDS and polymer nanocomposites.

2. Experimental part

2.1. Materials

Divinylbenzene-80 (DVB80, 80% divinylbenzene isomers) was supplied as technical grade by Shengli Technical Factory,

China, which was washed with 5% aqueous sodium hydroxide, water and then dried over anhydrous magnesium sulfate prior to use. Ethyleneglycol dimethacrylate (EGDMA) was chemical grade reagent from Heshibi Chemical Co., Shanghai, China and utilized without further purification. Methacrylic acid (MAA) and acrylic acid (AA) were purchased from Tianjin Chemical Reagent II Co. and purified by vacuum distillation. 2,2'-Azobisisobutyronitrile (AIBN) was analytical grade available from Chemical Factory of Nankai University, and was recrystallized from methanol. Acetonitrile (analytical grade, Tianjin Chemical Reagents II Co.) was dried over 4 Å molecular sieves and purified by distillation before use. The other reagents were of analytical grade and used without any further purification.

2.2. Preparation of monodisperse hydrophilic polymer microspheres having active carboxylic acid groups

A typical procedure for the distillation precipitation copolymerization: EGDMA (0.80 mL, 0.84 g, 4.2 mmol), methacrylic acid (1.20 mL, 1.20 g, 14.1 mmol) (total loading of comonomers as 2.5 vol% of the reaction medium), AIBN (0.04 g, 0.24 mmol, 2 wt% relative to the comonomers) were dissolved in 80 mL of acetonitrile in a dried 100 mL two-necked flask, attached with a fractionating column, Liebig condenser, and a receiver. The flask was submerged in a heating mantle, and the reaction mixture was heated from ambient temperature to the boiling state within 20 min, and then the solvent began to distil. The initial homogeneous reaction mixture became milky white after boiling for 10 min. The reaction was ended after 40 mL of acetonitrile was distilled from the reaction system within 1.5 h. After the polymerization, the resultant poly(EGDMA-*co*-MAA) nano-microspheres were purified by repeated centrifugation, decanting, and re-suspension in ethanol or acetone with ultrasonic bath for three times.

The procedures for the other distillation precipitation copolymerizations were much similar as that for the typical one by either altering the concentration of EGDMA and MAA, or changing the crosslinker from EGDMA to DVB80, or altering AA from MAA as the comonomer to incorporate carboxylic group, while the total comonomer loading and AIBN initiator were kept at 2.5 vol% of the reaction medium and 2 wt% to the total comonomers, respectively. The particles were separated from the reaction system by either filtration of micrometer-size particles or centrifugation of nanometer-size particles after the reaction and washed successively three times each with ethanol and acetone. The reproducibility of the results was confirmed through several duplicate and triplicate experiments.

2.3. Growth procedures of the polymer microspheres

The growth procedures of the polymer microspheres with active carboxylic acid were traced by SEM observation of poly(DVB-*co*-MAA) (DVB/MAA = 1/4 as volume ratio in

the comonomer feed) as the sample. Polymerization was carried out in a 1200-mL two-necked flask containing 1000 mL of reaction mixture with 2.5 vol% of the total comonomer loading (relative to the reaction medium) and 2 wt% AIBN as initiator (comparing to the total comonomers). From the reaction system, 5-mL of reaction mixture was sampled each at different time and cooled immediately in liquid nitrogen to quit the polymerization. The polymer microspheres for SEM observation were separated from the reaction system by either filtration of micrometer-size particles or centrifugation of nanometer-size particles and washed successively three times each with ethanol, acetone and THF.

2.4. Measurement and characterization

The particle size and size distribution were determined by scanning electron microscopy (SEM) using a scanning electron microscope (Philips-XL-30). All of the SEM size data reflect the averages, about 100 particles each, which are calculated according to the following formula:

$$U = D_w/D_n \quad D_n = \frac{\sum_{i=1}^k n_i D_i}{\sum_{i=1}^k n_i} \quad D_w = \frac{\sum_{i=1}^k n_i D_i^4}{\sum_{i=1}^k n_i D_i^3}$$

where U is the polydispersity index, D_n is the number-average diameter, D_w is the weight-average diameter, N is the total number of the measured particles, and D_i is the particle diameters of the determined microspheres.

The loading capacity of the accessible carboxylic acid group on the polymer microspheres was determined by acid–base titration.

3. Results and discussion

The formation of polyDVB [28] and poly(DVB-co-CMSt) [29] was reported in our previous works by distillation precipitation polymerization. In both cases, the crosslinkers such as DVB and mono-vinyl comonomers used were styrenic and hydrophobic in nature.

Here, we intend to utilize this technique to prepare mono- or narrow disperse hydrophilic microspheres with active carboxylic acid groups. At first, AA was copolymerized with styrenic crosslinker DVB80. Then divinyl monomer, such as methacrylic monomer EGDMA or DVB as crosslinker was copolymerized with either MAA or AA having hydrogen bonding. All of these copolymerizations were carried out with AIBN as initiator in neat acetonitrile, which was a suitable solvent to afford styrenic polymer microspheres with uniform size and spherical shape by this technique in our previous papers [28,29]. In the presence of hydrophilic monomer either MAA or AA, it is expected to promote the formation of inter-chain hydrogen bonding between the carboxylic acid groups to reduce the polymer–solvent interactions during the distillation precipitation copolymerizations with either EGDMA or DVB as crosslinker in a suitable solvent.

3.1. Preparation of poly(DVB-co-AA)

A series of experiments were initially designed to investigate the effect of AA fraction on the formation of poly(DVB-co-AA) particles. The SEM micrographs of the poly(DVB-co-AA) microspheres with different AA fractions in the range of 0.20 and 0.95 are illustrated in Fig. 1. A few of second-initiated particles were observed when AA fraction in comonomer feed was lower than 0.60, which may be due to the different reactivity between DVB and AA during the radical polymerization and the different solubility of polyDVB and polyAA in acetonitrile media. The free radical copolymerization reactivity ratios are $r_1 = 0.26$, $r_2 = 1.18$ for M1 = styrene, M2 = *p*-divinylbenzene and $r_1 = 0.2$, $r_2 = 0.25$ for M1 = styrene, M2 = AA, respectively [30], which indicate that DVB has a much higher reactivity than AA. This means that DVB-co-AA copolymer formed at initial stage of the polymerization contains more DVB units than the monomer feed. On the other hand, the solubility parameters for polyDVB, polyAA and CH₃CN are 17.6, 16.9 and 24.3 MPa^{1/2}, respectively [31], which lead to the easier precipitation of oligomer of AA than that of DVB from the reaction system. With the copolymerization occurring with AA feed lower than 0.60, the surface of the initially formed poly(DVB-co-AA) microspheres cannot capture all the newly formed oligomers with more AA fragments in the later stage due to the too rapid precipitation of the oligomer from the reaction, which caused the second-initiated particles. Only microgel was obtained with AA fraction as high as 0.95 (Fig. 1 (A6)), which may be caused by the strong inter-particle hydrogen-bonding interaction and the gentle and soft surface due to the low crosslinking degree. The results demonstrated that all the poly(DVB-co-AA) microspheres had spherical shape with smooth surface.

The experimental conditions for the distillation precipitation copolymerizations of DVB and AA, size and size distribution of the resultant poly(DVB-co-AA) particles are summarized in Table 1. The particle size increased significantly with decreasing AA fraction and the maximum diameter of 1.52 μm was obtained with an AA fraction of 0.20. The narrow or monodisperse nano/micron-polymer microspheres were obtained with the polydispersity index (U) in the range of 1.012 and 1.080, which depended on the AA fraction in comonomer feed. Narrow disperse microspheres were obtained with AA fraction in the range of 0.20 and 0.40 and monodisperse nanoparticles were afforded with AA fraction higher than 0.60. The second-initiated effect resulted in the broader size dispersion with low fraction of AA in comonomer feed as discussed above. The narrowest poly(DVB-co-AA) particles with polydispersity index (PDI) of 1.012 and diameter of 0.46 μm were prepared at an AA fraction of 0.80.

3.2. Preparation of poly(EGDMA-co-MAA)

Crosslinked polymer networks afforded by free radical polymerization of ethyleneglycol dimethacrylate (EGDMA)

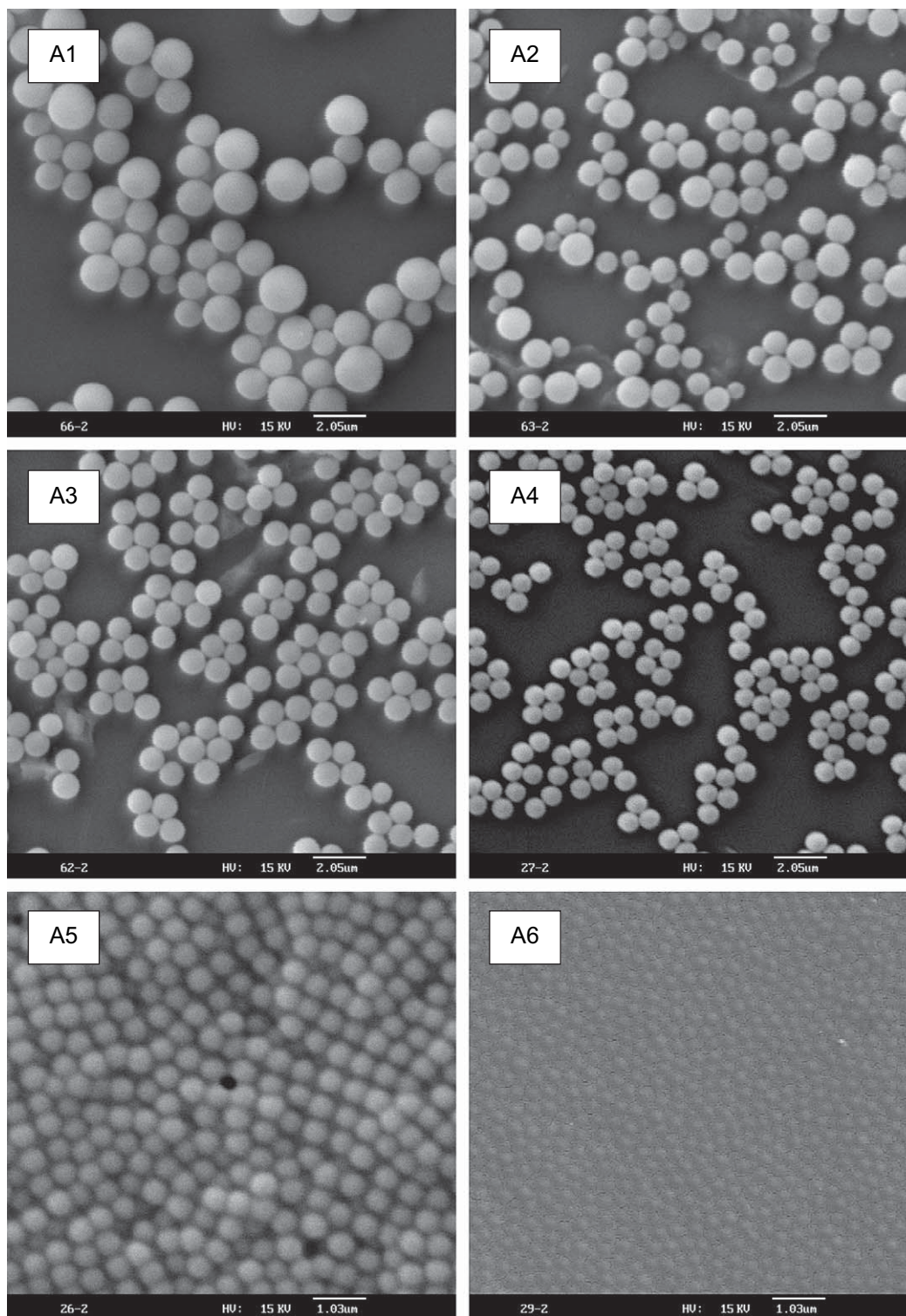


Fig. 1. The SEM images of poly(DVB-co-AA) nanoparticles with different AA fractions. A1: 0.20; A2: 0.40; A3: 0.60; A4: 0.80; A5: 0.90; A6: 0.95.

were found attractive as hydrogel matrices as they did swell in aqueous media to various extents depending on the crosslinking density [32,33]. All these investigations suggested that homogeneous hydrophilic and swellable materials were obtained with small amount of crosslinking agent and heterogeneous (nonswellable) glassy polymers were typically yielded by homopolymerizations of EGDMA.

Fig. 2 shows the SEM images of the poly(EGDMA-co-MAA) microspheres with MAA fraction in the range of 0.20 and 0.95. The results demonstrated that all the resultant microspheres and microgels had spherical shape with smooth surface.

Table 2 summarizes the experimental conditions for the copolymerizations of EGDMA and MAA, size and size distribution of the resultant poly(EGDMA-co-MAA) nanoparticles.

Table 1
Reaction conditions for copolymerizations, size and size distribution of poly(DVB-*co*-AA) microspheres

Entry	Fraction of AA ^a	AIBN (g)	D_n (μm)	D_w (μm)	U
A1	0.20	0.04	1.41	1.52	1.08
A2	0.40	0.04	1.03	1.11	1.074
A3	0.60	0.04	0.98	0.99	1.014
A4	0.80	0.04	0.80	0.80	1.007
A5	0.90	0.04	0.46	0.46	1.012
A6	0.95	0.04	About 300 nm microgel		

Reaction conditions: the total comonomer loading of 2.5 vol% relative to the whole reaction medium in 80 mL of acetonitrile and initiator of 2 wt% relative to the total monomers.

^a Fraction of AA referred as: $V_{AA}/(V_{AA} + V_{DVB80})$.

All of the diameters of poly(EGDMA-*co*-MAA) were in the range of 164 and 310 nm. The minimum particles with diameter of 164 nm were obtained when MAA fraction in comonomer feed was as high as 0.90. Monodisperse microspheres with polydispersity index (U) around 1.025 were prepared with MAA fraction in the range of 0.60 and 0.95. Narrow

Table 2
Reaction conditions for copolymerizations, size and size distribution of poly(EGDMA-*co*-MAA) microspheres

Entry	Fraction of MAA ^a	AIBN (g)	D_n (nm)	D_w (nm)	U
M1	0.20	0.04	310	350	1.13
M2	0.40	0.04	263	276	1.051
M3	0.60	0.04	260	267	1.029
M4	0.80	0.04	204	210	1.026
M5	0.90	0.04	164	168	1.029
M6	0.95	0.04	187	191	1.022

Reaction conditions: the total comonomer loading of 2.5 vol% relative to the whole reaction medium in 80 mL of acetonitrile and initiator of 2 wt% relative to the total monomers.

^a Fraction of MAA referred as: $V_{MAA}/(V_{MAA} + V_{EGDMA})$.

disperse particles with diameter of 263 nm and the U of 1.051 were found at MAA fraction of 0.40. Polydisperse particles with diameter of 310 nm and the U of 1.13 were obtained at MAA fraction of 0.20 due to the significant formation of the second-initiated particles. In the other words, U increased with decreasing MAA fraction in the comonomer feed.

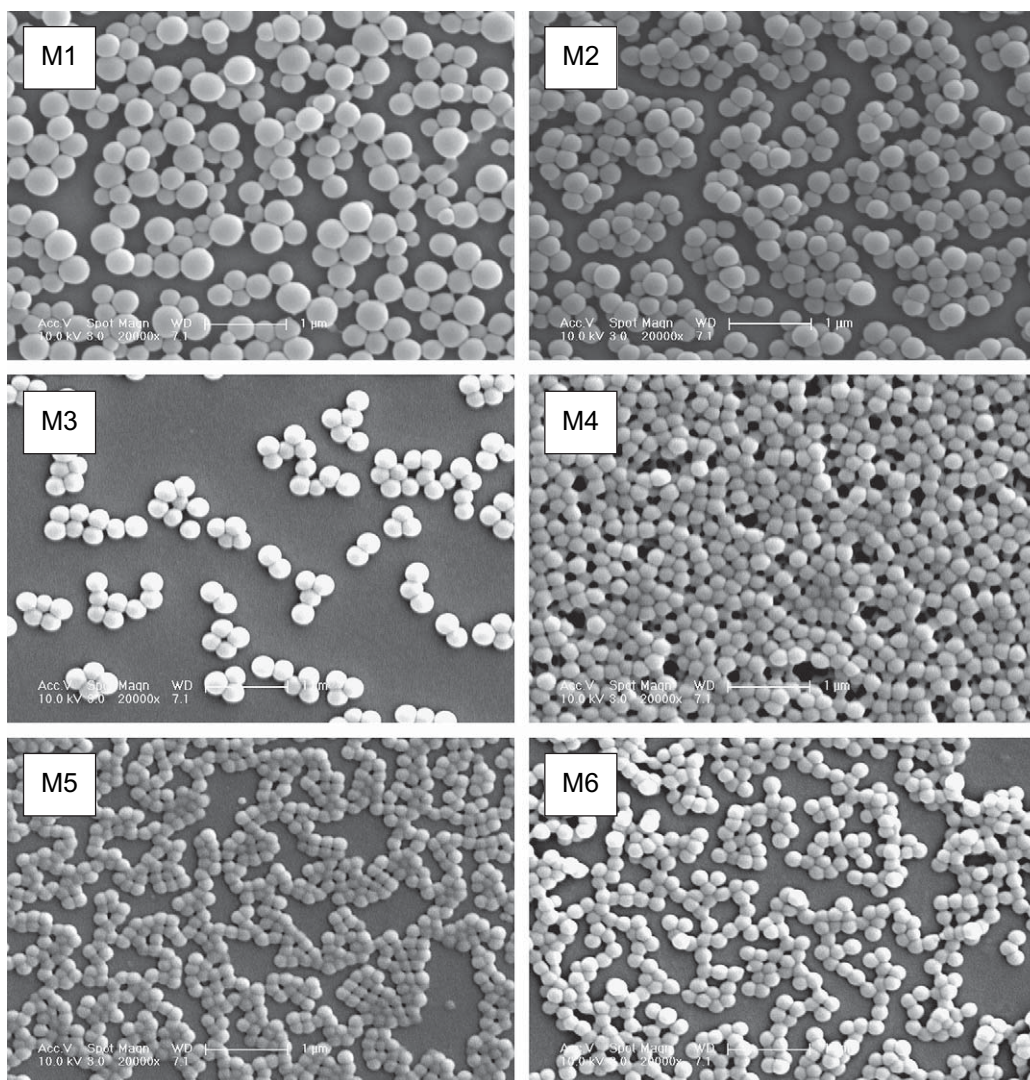


Fig. 2. The SEM images of poly(EGDMA-*co*-MAA) nanoparticles with different MAA fractions. M1: 0.20; M2: 0.40; M3: 0.60; M4: 0.80; M5: 0.90; M6: 0.95.

3.3. Preparation of poly(EGDMA-co-AA)

The SEM micrographs of poly(EGDMA-co-AA) copolymer microspheres with AA fractions in the range of 0.20 and 0.80 are shown in Fig. 3. The transition from hard and spherical particles with smooth surface to small-size microspheres is clearly visible in these images, which depended on the AA fraction in the comonomer feed. Microgels were formed at AA fractions higher than 0.90. Monodisperse microspheres were obtained at AA fractions ranging from 0.60 to 0.80 as shown in Fig. 3 (E4, E5). The U increased slightly when AA fraction decreased to 0.40 (Fig. 3 (E3)) and 0.20 (Fig. 3 (E2)), respectively. Decreasing the AA fraction further to 0.10 resulted in broadly disperse microspheres in the range of 180 and 740 nm. All of the poly(EGDMA-co-AA) microspheres occurred as multiplet particles and with some coagulum, especially in the case of the high AA fractions, which may be due to the strong inter-particle hydrogen-bonding interaction and soft surface of the polymer microspheres.

Table 3

Reaction conditions for copolymerizations, size and size distribution of poly(EGDMA-co-AA) microspheres

Entry	Fraction of AA ^a	AIBN (g)	D_n (nm)	D_w (nm)	U
E1	0.10	0.04	Polydisperse microspheres (180–740 nm)		
E2	0.20	0.04	590	640	1.071
E3	0.40	0.04	330	350	1.044
E4	0.60	0.04	180	190	1.029
E5	0.80	0.04	350	355	1.012

Reaction conditions: the total comonomer loading of 2.5 vol% relative to the whole reaction medium in 80 mL of acetonitrile and initiator of 2 wt% relative to the total monomers.

^a Fraction of AA referred as: $V_{AA}/(V_{AA} + V_{EGDMA})$.

Table 3 summarizes the experimental conditions for the copolymerizations of EGDMA and AA, the size and size distribution of the final poly(EGDMA-co-AA) particles. The diameter and the polydispersity of the particles had a tendency to increase with decreasing AA fraction.

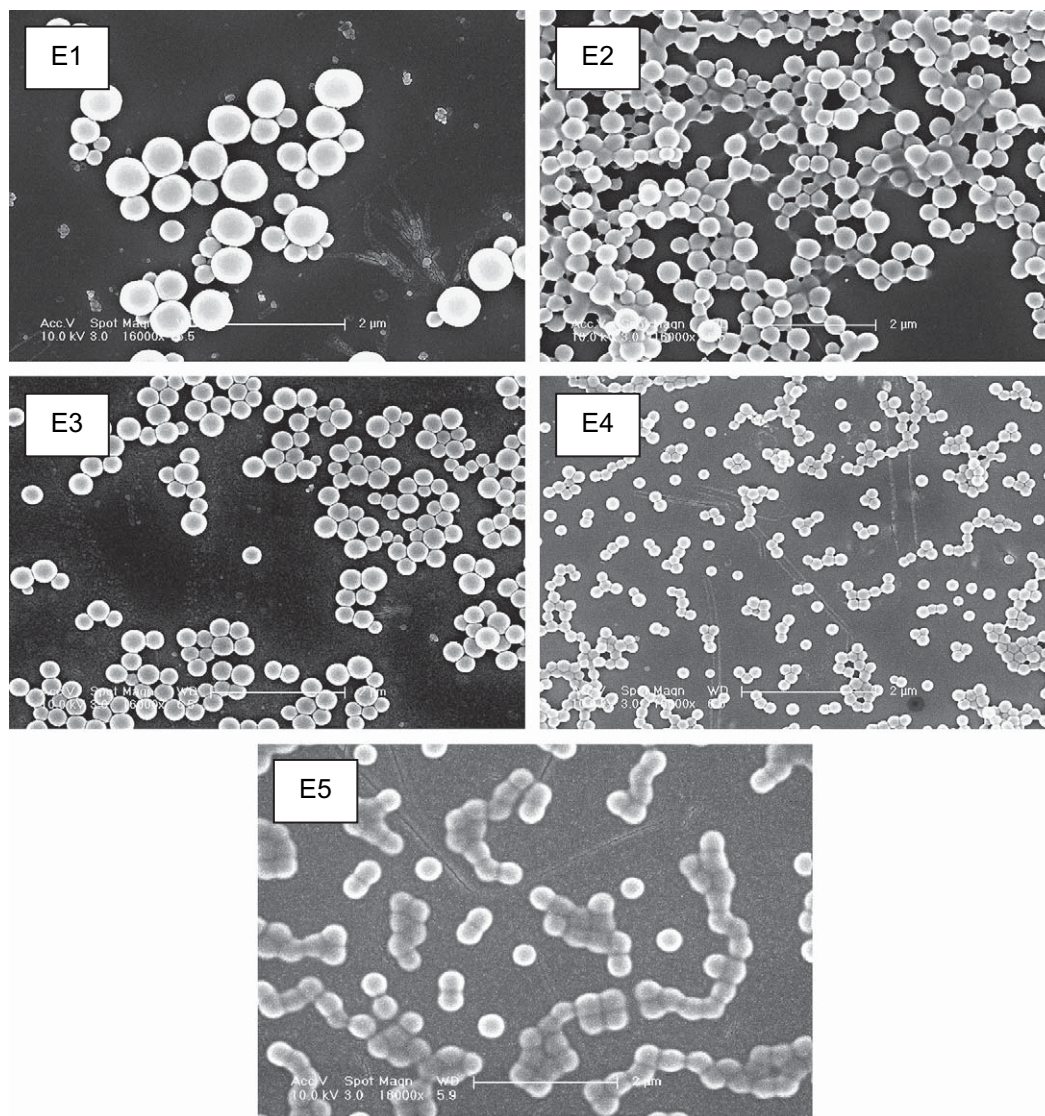


Fig. 3. The SEM images of poly(EGDMA-co-AA) nanoparticles with different AA fractions. E1: 0.10; E2: 0.20; E3: 0.40; E4: 0.60; E5: 0.80.

3.4. The loading capacity of accessible carboxylic acid groups on the polymer microspheres

The surface modification of (M)AA leading to poly(DVB-*co*-AA), poly(EGDMA-*co*-MAA), and poly(EGDMA-*co*-AA) microspheres was proven by FT-IR spectra as shown in Fig. 4. All of the copolymer particles with (M)AA as comonomer had a strong and broad peak at 3400 cm^{-1} due to the vibration of hydroxyl stretching of the carboxylic acid group and the intensity increased significantly (not shown in detail in the present paper) with increasing (M)AA fraction in the copolymer (decreasing the crosslinking degree). At the same time, there was a strong peak at 1680 cm^{-1} corresponding to the stretching vibration of the carbonyl group of the carboxylic acid. These results demonstrated that the carboxylic acid groups were successfully incorporated into the copolymer microspheres by distillation precipitation polymerization.

The relationship between the loading capacity of the accessible carboxylic acid groups and the initial (M)AA fractions in the comonomer feedings for these polymer microspheres is illustrated in Fig. 5.

The results indicated that the carboxylic acid loading in the final poly(DVB-*co*-AA) particles was much lower than the AA fraction in comonomer feed, especially with AA fraction lower than 0.90. Such results may originate from the higher reactivity of DVB crosslinker compared to that of AA during the distillation precipitation polymerization with radical initiator. In other words, more DVB was incorporated into the inner layer than the outer layer of the resultant poly(DVB-*co*-AA) microspheres. With increasing AA fraction in the polymer particles, the fraction of the outer layer increased as the particle size decreased significantly from $1.41\text{ }\mu\text{m}$ at AA fraction of 0.20 to 300 nm at AA fraction of 0.95 (in comonomer feed). The functional groups (hydroxyl and mercapto groups) both on the surface and in the soft gel layer of the polymer microspheres were highly accessible with good reactivity in our previous results [6,34]. However, the outer

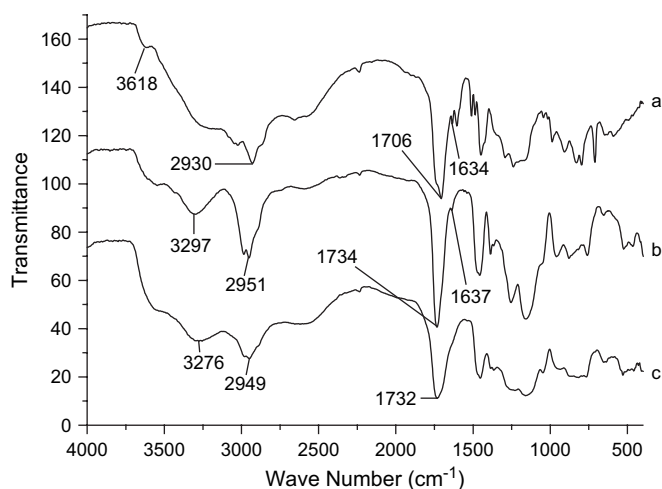


Fig. 4. FT-IR spectra of polymer microspheres with active carboxylic acid group. a: poly(DVB-*co*-AA) (DVB/AA = 60/40); b: poly(EGDMA-*co*-MAA) (EGDMA/MAA = 60/40); c: poly(EGDMA-*co*-AA) (EGDMA/AA = 60/40).

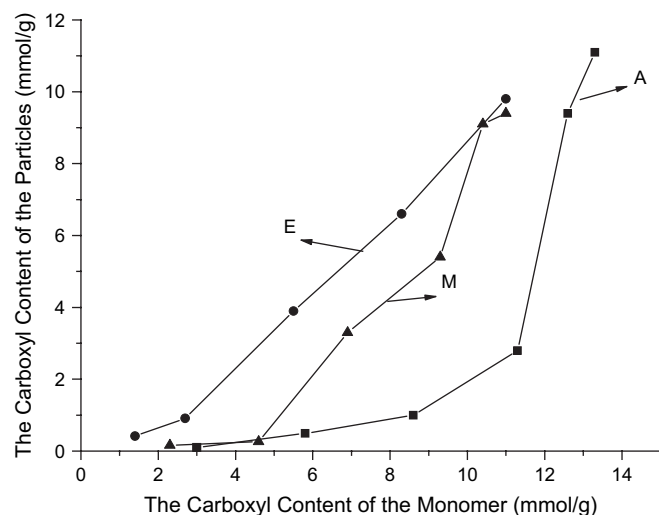


Fig. 5. The relationship between loading capacity of the accessible carboxylic acid group and (M)AA fraction in the comonomer feed for polymer microspheres: (A) poly(DVB-*co*-AA); (M) poly(EGDMA-*co*-MAA); (E) poly(EGDMA-*co*-AA).

gel layer is difficult to be swollen in water media during the titration due to the hydrophobic nature of DVB component with increasing DVB in the final polymer particles, which leads to the much low loading capacity of carboxylic acid group especially in the case of DVB feed higher than 0.80. Therefore, the loading capacity of the accessible carboxylic acid groups was low (2.8 mmol/g) with AA fraction of 0.80 in comonomer feed, while it increased promptly to 9.4 mmol/g with AA fraction of 0.90 in comonomer feed.

The loading capacity of the accessible carboxylic acid group in the resultant poly(EGDMA-*co*-AA) and poly(EGDMA-*co*-MAA) microspheres was near the (M)AA fraction in comonomer feed, especially with (M)AA fraction higher than 0.50. These results demonstrated that the reactivity of EGDMA crosslinker is near that of (M)AA during the distillation precipitation polymerization with radical initiator. The polar and better swellable nature of EGDMA crosslinker in water may result in the higher capacity of the accessible carboxylic acid group in the polymer microspheres with EGDMA as crosslinker than that with DVB as crosslinker, especially with crosslinker degree in the range of 0.20 and 0.40. On the other hand, the polymer microspheres with EGDMA as crosslinker was some hydrophobic to be swollen in a less extent with crosslinker higher than 0.50, which led to the much lower loading capacity of the accessible carboxylic acid group determined by titration.

All the results demonstrated that the loading capacity of the accessible carboxylic acid groups increased significantly with enhancing (M)AA fraction of comonomer feeding (lower the crosslinking degree). High loading capacity with 9.0 mmol/g carboxylic acid group can be obtained with a crosslinking degree of 0.10 for all the polymer microspheres with either DVB or EGDMA as crosslinker. Such high loading capacity polymer microspheres may have wide applications, such as DDS, polymer composites, supports for the immobilization of biological substances and catalysts.

3.5. The growth mechanism of the polymer microspheres with active carboxylic acid

The initial homogenous reaction mixture became milky white after boiling for 10–30 min depending on the cross-linking degree and the comonomer used, which indicated the formation of nuclei of the copolymer. Then the polymer microspheres were formed by the capture of the oligomer species during distilling solvent from the reaction system. As a sample, the growth processes of poly(DVB-*co*-MAA) (DVB/MAA = 1/4 as volume ratio in comonomer feed) microspheres were traced with SEM observation as shown in Fig. 6.

The SEM images of poly(DVB-*co*-MAA) microspheres at different reaction times showed that the polymer particles had spherical shape and smooth surfaces during all the procedures of the distillation precipitation polymerization. The size and size distribution of the polymer microspheres are summarized in Table 4. The results indicated that the polymer microspheres grew significantly from 162 nm at the beginning of the reaction to 436 nm of the final polymer microspheres, while the polydispersity index (U) remained monodispersity of around 1.010 without any second-initiated particles. In other words, no new particles were formed during the further polymerization to enlarge the particle size after the formation of nuclei. All the particles grew stably and simultaneously with the amount of DVB and AA comonomer consumed through the capture of the oligomers from the reaction system during the reaction.

Table 4

Reaction conditions for copolymerizations, size and size distribution of poly(DVB-*co*-MAA) microspheres at different reaction times^a

Entry	Volume of acetonitrile ^b	D_n (nm)	D_w (nm)	U
1	20	162	166	1.026
2	50	200	204	1.019
3	100	263	266	1.010
4	150	296	300	1.013
5	200	334	337	1.009
6	300	358	363	1.015
7	400	413	417	1.010
8	500	436	439	1.007

Reaction conditions: the total comonomer loading of 25 mL (2.5 vol% relative to the whole reaction medium in 1000 mL of acetonitrile) and initiator of AIBN 0.50 g (2 wt% relative to the total comonomers).

^a Five-milliliter reaction mixture was sampled from the reaction system each at different time and cooled immediately in liquid nitrogen to quit the polymerization.

^b The volume of acetonitrile referred as the distilled volume of acetonitrile out of the reaction system at each sampled point.

The experimental results of poly(EGDMA-*co*-AA) (EGDMA/AA = 1/1) showed that the growth procedures were much similar as those of poly(DVB-*co*-MAA) (the detail results not shown here), in which the size increased from 132 nm for the particles at distilling of 100 mL acetonitrile was distilled off the system to 195 nm of the final particles and the size distribution kept at monodispersity with U around 1.030.

The reaction system was kept at distillation state which was essential to get the monodisperse polymer microspheres for

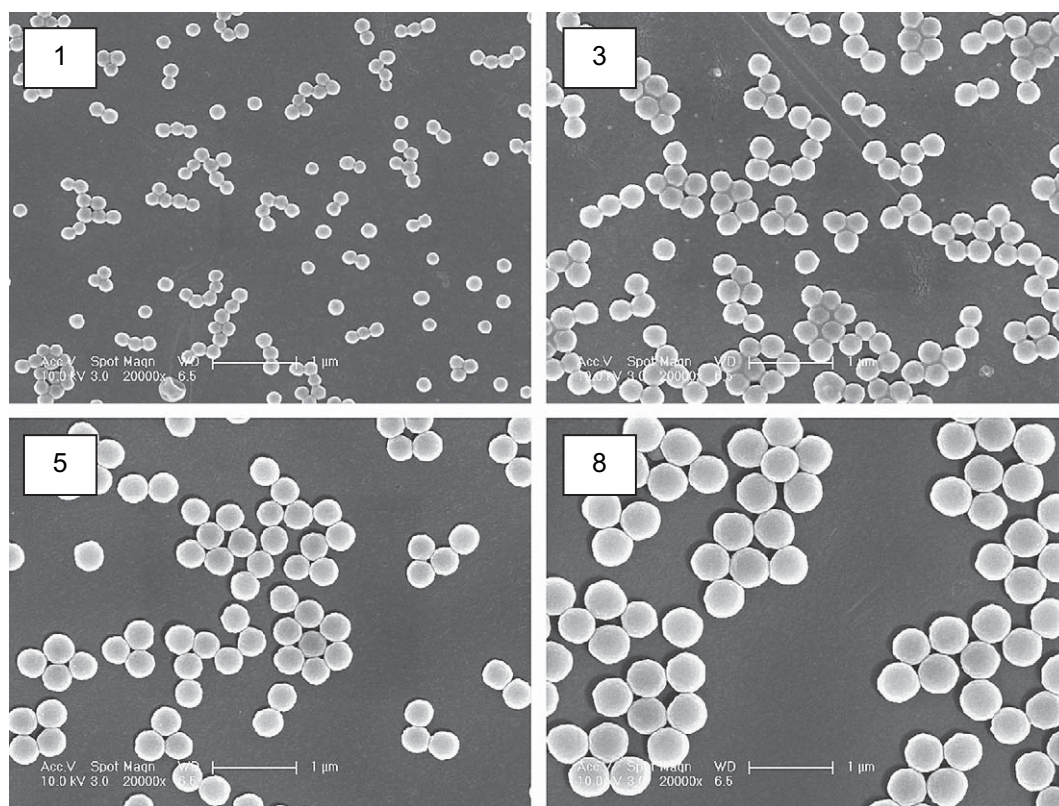


Fig. 6. The SEM images of poly(DVB-*co*-MAA) microspheres while distilling different volumes of acetonitrile during the distillation precipitation polymerization. V1: 20 mL; V3: 100 mL; V5: 200 mL; V8: 500 mL.

the distillation precipitation polymerization. Otherwise, the reaction system would bump or aggregation of the polymer would occur. In other words, the polymer microspheres were formed and precipitated out from the reaction system with the simultaneous distillation of the solvent from the reaction system for the distillation precipitation polymerization.

All the results demonstrated that the solvent–polymer system had a remarkable effect on the particle formation during the distillation precipitation polymerizations. Apparently, acetonitrile is a suitable solvent for the moderate polar comonomers, such as the comonomers of DVB and MAA, comonomers MAA and EGDMA, to afford the monodisperse polymer microspheres with a much wide range of crosslinking degree. While the polarity of the comonomers increased further, such as the comonomers of EGDMA and AA, the polydispersity of the resultant particles tend to increase.

Distillation precipitation polymerization is highly sensitive to the subtle changes in the reaction system and its nature is quite complicated especially in the presence of a high polar comonomer having hydrogen bonding (AA or MAA). The hydrogen bonding between carboxylic acid units played an essential role during the distillation precipitation polymerization, which can partly replace the covalent crosslinkers to aid the desolvation of the copolymer. A slightly crosslinked outer surface was suggested as steric stabilizing layer in the presence of a solvent better than θ solvents to prevent the aggregation of the colloidal gels [35,36]. In general precipitation polymerization and distillation precipitation polymerization, the microparticles were sterically stabilized by the pendent chains and surface gels [28,29,36]. After introducing AA or MAA as comonomer, the microparticles would be co-stabilized by electrostatic and steric effects. The amphiphilic copolymers with active carboxylic acid group were reported as stabilizer for emulsifier polymerization [24,25]. Therefore, narrow- or monodisperse polymer microspheres can be afforded in a wider range of reaction conditions than those in the systems involving less polar comonomers in the absence of hydrogen bonding [12–17,28,29]. During the present distillation-precipitation copolymerizations, an increase in the feed of either DVB or EGDMA crosslinker led to less PAA or PMAA fragment in the resultant polymer network. The formation of polymer microspheres was contributed to the electrostatic stabilization through the interchain hydrogen bonding between the carboxylic acid units at low crosslinking degree and the steric stabilization through the pendent chains and surface gels at high crosslinking degree. These driving forces caused the desolvation during the growth processes and resulted in the collapse of the network. In other words, the formation of monodisperse polymer microspheres occurred through an entropic distillation precipitation manner, in which the soluble oligomeric species reacted with the pendent vinyl groups on the surface of existing particles to enlarge the size of the microspheres. The essential role of the residual vinyl group on the polymer microspheres for the further growth of the particles has been studied in detail during the precipitation polymerization of DVB [37]. The interchain hydrogen bonding between the carboxylic acid in the copolymers did promote

the formation of monodisperse microspheres, which was confirmed by the polymerizations carried out at crosslinking degree as low as 5 vol% (Entry A6 and M6) relative to the total comonomers. This was confirmed further only by the formation of second-initiated particles during the second-stage polymerization of a two-stage polymerization process, in which poly(DVB-co-AA) (1/9) was prepared during the first-stage reaction with complete removal of all the residual comonomers and only DVB was added during the second-stage polymerization. In this case, the residual double bonds on the polymer microspheres were too few to efficiently capture the oligomers and monomer from the reaction medium during the second-stage polymerization. On the other hand, the absence of hydrogen-bonding interaction between the poly-(DVB-co-AA) and newly formed DVB oligomers disabled the capture of the DVB oligomers for poly(DVB-co-MAA) particles. Furthermore, the solvency of the continuous phase should be below θ condition for the polymer to cause phase separation by the crosslinking network and results in monodisperse microspheres.

4. Conclusion

A simple and effective synthesis of highly hydrophilic monodisperse polymer microspheres with active carboxyl acid groups in the range of 160 nm and 1.52 μm by distillation precipitation copolymerizations of (meth)acrylic acid with either DVB or EGDMA as crosslinking agent in neat acetonitrile without stirring was demonstrated. The solvent–polymer system had a significant effect on the particle formation during the distillation precipitation polymerization. The loading capacity of the accessible carboxylic acid groups increased significantly with increasing (M)AA fraction in the comonomer feed and high loading capacity as 9.0 mmol/g can be obtained with the crosslinker fraction in the comonomer feed lower than 0.10. The growth mechanism for monodisperse polymer microspheres occurred by an entropic distillation precipitation polymerization through the crosslinking effect from the crosslinking agent, such as either EGDMA or DVB, and the interchain hydrogen bonding of the carboxyl acid groups. Both the steric stabilization from the pendent chains and surface gel layer, and the electrostatic repulsion from the carboxyl acid groups prevent the particle coagulating to result in mono- or narrow disperse polymer microspheres with active carboxyl acid groups. The studies on the scope of such polymer microspheres, including the extension to the preparation of the other hydrophilic polymer particles by distillation precipitation polymerization and the applications of such hydrophilic particles in DDS, polymer nanocomposites and bioseparation are in systematical progress.

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