

Production of Highly Crosslinked Microspheres by the Precipitation Polymerization of 2-(Diethylamino)ethyl Methacrylate with Two or Three Functional Crosslinkers

Yeliz Tunc, Kezban Ulubayram

Department of Basic Pharmaceutical Sciences, Hacettepe University, Sıhhiye 06100, Ankara, Turkey

Received 7 January 2008; accepted 27 September 2008

DOI 10.1002/app.29390

Published online 2 January 2009 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Precipitation polymerizations of 2-(diethylamino)ethyl methacrylate were carried out with ethylene glycol dimethacrylate and then trimethylolpropane trimethacrylate in acetonitrile to produce monodisperse, highly crosslinked microspheres. Poly(diethylaminoethyl methacrylate-*co*-trimethylolpropane trimethacrylate) [poly (DEAEMA-*co*-TRIM)] microspheres, in the range of 1.2–2.7 μm , were obtained with a total monomer concentration of 1 vol % with respect to the solvent, and they kept their identity with several polymerization parameters. When the total monomer concentration was increased further, individual particles lost their identity and aggregated. Poly (DEAEMA-*co*-TRIM) particles with a total monomer concentration of 1 vol % had more discrete spherical forms with smoother surfaces, whereas in the poly(diethylaminoethyl methacrylate-*co*-ethylene glycol dimethacrylate)

system, sticky microspheres were obtained with a total monomer concentration of 2.1 vol %. Moreover, several polymerization parameters were investigated to control the physical properties of microspheres of poly(DEAEMA-*co*-TRIM) and to understand the nature of the precipitation polymerization. Thus, the average particle size increased from 2.3 to 2.7 μm with an increased azobisisobutyronitrile concentration and then decreased to about 1.2 μm as the polymerization temperature was increased. All the microspheres produced under different polymerization conditions were found to be monodisperse (polydispersity index <0.1) with a narrow size distribution. © 2009 Wiley Periodicals, Inc. *J Appl Polym Sci* 112: 532–540, 2009

Key words: copolymerization; crosslinking; microgels; radical polymerization

INTRODUCTION

Among polymeric materials, microspheres are an important group; they are characterized by their small size and volume, large specific surface area, uniform size, chemistry and morphology, and ability to form stable dispersions.¹ These materials are used in a wide range of medical and biochemical applications, including enzyme immobilization,² drug delivery systems,³ chromatographic separation,⁴ immunoassays, and medical diagnostics.^{5,6} All these applications depend on the size, monodispersity, morphology, and surface characteristics of the microspheres. Although large microspheres are used as cell culture carriers, smaller ones are used as drug carriers.¹ In addition to the other properties, the monodispersity of the microspheres is crucial in all applications to obtain reproducible results. Therefore, it is important to control their size and uniformity.

Polymeric microspheres can be prepared by different well-known heterogeneous polymerization methods such as emulsion polymerization, suspension polymerization, and dispersion polymerization. Emulsion polymerization produces particles that are 0.01–1 μm in diameter. This heterogeneous polymerization involves emulsification of a monomer in water by an emulsifier and initiation by a water or oil-soluble initiator. Because a large oil–water interfacial area is formed, a stabilizer (an ionic or nonionic surfactant or protective colloid) is required to prevent coagulation of the particles.⁷ Suspension polymerization is used to prepare large polymer beads with a wide range of diameters (5–1000 μm). In this method, water-soluble monomers may be polymerized with water in oil or the reverse, in which a concentrated aqueous monomer solution is polymerized in a non-polar medium.⁸ Surfactants are used to prevent coagulation as in emulsion polymerization. If the initial emulsion in the polymerization is polydisperse, then it will produce a broad particle size distribution and thus require a size classification step, which makes the method expensive and causes low reaction yields.⁹ Dispersion polymerization, used to prepare polymer microspheres in the range of 1–15 μm , is characterized by its initially homogeneous polymerization medium, in which the insoluble polymer is

Correspondence to: K. Ulubayram (ukezban@hacettepe.edu.tr).

Contract grant sponsor: Scientific Research Unit of Hacettepe University; contract grant number: BAB 06D07301001.

stabilized by the surfactants.⁸ However, it is difficult to obtain monodisperse, highly crosslinked microspheres by these conventional methods. Although the emulsion polymerization method can produce microspheres up to 1 μm in diameter, suspension polymerization provides a broad particle size distribution, and it is not possible to prepare highly crosslinked microspheres by dispersion polymerization.

A recent technique known as precipitation polymerization provides a one-step process to prepare highly crosslinked microspheres with the desired size distribution. Therefore, it has been more favored than the aforementioned polymerization systems. This method, developed by Li and Stöver,¹⁰ shows differences from the other methods because of the stabilization mechanism. In this technique, the particle formation mechanism is similar to dispersion polymerization. However, it does not require any stabilizer against particle coagulation as in the other heterogeneous polymerization methods. Here the stability of the particles formed by polymerization of the diluted monomer solutions is provided by the polymerization mechanism itself, not by added stabilizers. According to Li and Stöver, in the beginning stages of the polymerization, lightly crosslinked oligomeric radicals are formed and grow; in turn, microspheres are formed by their crosslinking. These microspheres do not aggregate because of the low monomer concentration (2–5 vol %). They grow further with the addition of oligomers and monomers that are present in the polymerization medium. Finally, stable particles are formed without any stabilizer with a high degree of crosslinking, which causes highly crosslinked and rigid surfaces.¹¹ The sizes and porosities of the microspheres depend on some polymerization parameters, such as the monomer and initiator concentrations, the polarity of the medium, and the polymerization temperature and time.¹²

In this study, for the first time, highly crosslinked, stable poly(diethylaminoethyl methacrylate-*co*-ethylene glycol dimethacrylate [poly(DEAEMA-*co*-EGDMA)]) and poly(diethylaminoethyl methacrylate-*co*-trimethylolpropane trimethacrylate) [poly(DEAEMA-*co*-TRIM)] microspheres were prepared by a single-step precipitation polymerization. We investigated the effects of the aforementioned reaction parameters on poly(DEAEMA-*co*-TRIM) microspheres to control the size and morphology of the particles.

EXPERIMENTAL

Materials

2-(Diethylamino)ethyl methacrylate (DEAEMA) and ethylene glycol dimethacrylate (EGDMA) were purchased from Aldrich (Steinheim, Germany) and purified by vacuum distillation before use to remove inhibitors. Trimethylolpropane trimethacrylate (TRIM)

TABLE I
Polymerization Compositions and Product Morphologies of the Copolymerization of DEAEMA and EGDMA^a

Sample code	Monomer composition (EGDMA/DEAEMA) ^b	Total monomer (vol %) ^c	Product type
1	1	6.2	Coagulum
2	1	3.1	Coagulum
3	1	2.1	Microspheres
4	2	4.6	Coagulum
5	2	3.1	Coagulum
6	2	2.3	Microspheres
7	4	5.1	Coagulum
8	4	3.8	Coagulum

^a Two weight percent AIBN with respect to the total amount of the monomers at 60°C for 24 h.

^b Molar ratio of the monomers.

^c Volume percentage of the monomers with respect to the solvent.

was supplied by Aldrich and purified with inhibitor remover replacement packing for hydroquinone and monomethyl hydroquinone (Aldrich). Azobisisobutyronitrile (AIBN) was obtained from Merck (Hohenbrunn, Germany) and used without further purification. Acetonitrile (high-performance-liquid-chromatography (HPLC) grade) and toluene (analytical grade) were supplied by Riedel (Seelze, Germany).

Precipitation polymerization of DEAEMA with EGDMA or TRIM

DEAEMA was copolymerized with TRIM or EGDMA in acetonitrile. In these systems, various total monomer concentrations and monomer compositions (crosslinker–monomer ratios; Tables I and II) were used to produce spherical polymer particles. To obtain microspheres with smooth spherical forms with the highest yield, several monomer concentrations were tested.

The general procedure for the precipitation polymerization of DEAEMA with crosslinkers (TRIM or EGDMA) was as follows. Known amounts of DEAEMA and crosslinkers (TRIM or EGDMA) were solvated in a large amount of acetonitrile, and then the initiator, AIBN (2 wt % with respect to the total amount of the monomers), was added. After 15 min of purging with N₂, the solution was sealed and then heated to 60°C for 24 h. After the polymerization was completed, the microspheres were washed with methanol and acetic acid (80 : 20) and acetonitrile; the polymeric particles were separated by filtration and then dried *in vacuo* at 50°C. The resultant product morphologies were examined with scanning electron microscopy (SEM), and then for the DEAEMA and TRIM system, a total monomer concentration of 1 vol % with respect to the solvent and an AIBN concentration of 2 wt % with respect to the

TABLE II
Polymerization Compositions and Product Morphologies
of the Copolymerization of DEAEMA and TRIM^a

Sample code	Monomer composition (TRIM/DEAEMA) ^b	Total monomer (vol %) ^c	Product type
9	1	4.2	Coagulum
10	1	2.8	Coagulum
11	1	2.1	Coagulum
12	1	1.4	Coagulum
13	1	1.0	Microspheres
14	1	0.69	Microspheres
15	2	4.5	Coagulum
16	2	3.4	Coagulum
17	2	2.2	Coagulum
18	2	1.1	Coagulum
19	2	0.84	Microspheres
20	2	0.42	Microspheres

^a Two weight percent AIBN with respect to the total amount of the monomers at 60°C for 24 h.

^b Molar ratio of the monomers.

^c Volume percentage of the monomers with respect to the solvent.

total amount of the monomers were chosen for further studies. For this system, DEAEMA (2 mmol) and TRIM (2 mmol) were solvated in 100 mL of acetonitrile, and then the initiator, AIBN (20.9 mg), was added. After 15 min of purging with N₂, the solution was sealed and then heated to 60°C. The effects of the polymerization time on the morphology and particle sizes of the samples were studied with samples taken at the end of 3, 6, 12, and 24 h. Furthermore, microspheres were prepared under different polymerization conditions. AIBN concentrations were increased from 2 wt % with respect to the total monomer and changed in steps of 3, 4, 5, and 6% to examine the effects on the particle size and morphology. The polarity of the medium was varied with the addition of up to 2.5 vol % toluene to the polymerization medium, and the reaction temperature was increased from 60 to 80°C to determine the effects on the microspheres.

Characterization

The mean diameter (*z* average) and polydispersity index (PDI; the width of the distributions) of the polymer particles in water were obtained with a Malvern Zetasizer Nano-ZS dynamic light scattering instrument (Malvern Instruments Ltd., Worcestershire, UK). Surface areas, pore volumes, and average pore diameters of the polymer particles in the dry state were measured with a Quantachrome Nova 2200e surface area and pore size analyzer (Quantachrome Instruments, Boynton Beach, FL). The microphotographs of the samples were obtained with SEM (model 6400, JEOL, Tokyo, Japan) after the samples were coated with gold. The chemical

structure was characterized with a high-power, solid-state, 300-MHz NMR spectrometer (Avance superconducting Fourier transform NMR spectrometer with a megahertz-wide board magnet, Bruker, Rheinstetten, Germany) running ¹³C cross-polarization/magic-angle spinning (CP-MAS) analysis at a spin rate of 5000 Hz with a scan number of 10,000. The Fourier transform infrared (FTIR) spectrum was obtained from a KBr disc of the sample with a PerkinElmer Spectrum BX FTIR system (Perkin Elmer, Shelton, CT) at a resolution of 2 cm⁻¹.

RESULTS AND DISCUSSION

Effect of the polymerization composition on the product morphology of the copolymerization of DEAEMA with TRIM or EGDMA

In this study, DEAEMA was copolymerized with different compositions of EGDMA and TRIM to obtain highly crosslinked microspheres. Studies of the physical nature of the products were carried out as a function of the monomer composition and total monomer concentration with respect to the solvent. In a copolymerization reaction, the most important parameters that affect the physical characteristics of the product are the crosslinker type and the concentration and volume of the solvent.¹³ Because at high crosslinker concentrations or high volumes of the solvent the initial spherical microgel particles form a macroporous polymer resin, they remain as a microgel powder or microspheres for lower concentrations.¹⁴ The previously mentioned transition of swellable microgel forms to microspheres requires a particular level of crosslinking and low solvency of the medium.¹⁵ It is well known that good solvency conditions and compatibility of a polymer with a solvent is related to the solubility parameter similarities. Although the solubility parameter of acetonitrile (the solvent used in this study) is 24.3 MPa^{1/2},¹⁶ the solubility parameters of poly(ethylene glycol dimethacrylate) and poly(trimethylolpropane trimethacrylate) [poly(TRIM)] were found to be 18.5 MPa^{1/2} by Bai et al.¹⁷ and 18.2 MPa^{1/2} by Rosenberg and Flodin.¹⁸ It can be seen from the solubility parameter values that acetonitrile is not a swelling solvent for these crosslinkers. Therefore, in our studies, the crosslinking level and solvency condition of the systems produced microspheres under the proper polymerization conditions.

Generally, a total monomer loading of 2–5 vol % with respect to the solvent produces nonaggregated microspheres by precipitation polymerization.¹⁹ In this study, the total monomer concentration was varied between 2.1 and 6.2 vol % in different monomer compositions in the polymerization of DEAEMA with EGDMA as the crosslinker and was found to have a profound effect on the product structure

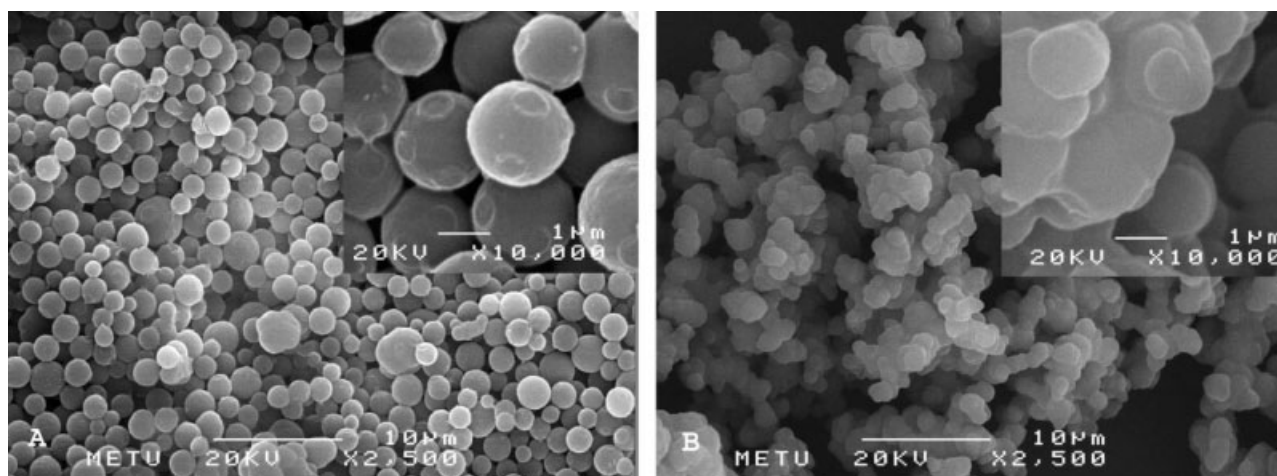


Figure 1 Poly(DEAEMA-*co*-EGDMA) obtained by precipitation polymerization with an AIBN concentration of 2 wt % in acetonitrile at 60°C: (A) microsphere structure of sample 3 and (B) coagulum form of sample 8.

(Table I). Results for the microsphere structure (sample 6) and coagulum structure (sample 8) of poly(DEAEMA-*co*-EGDMA) at total monomer concentrations of 2.3 and 3.8 are shown in Figure 1. SEM investigations of these samples showed that the microspheres [Fig. 1(A)] lost their identity and precipitated as coagulated microspheres [Fig. 1(B)] when the high crosslinker level crosslinked the opposing surfaces of the microspheres. When TRIM was used as the crosslinker, the monomer concentration was varied between 0.42 and 4.5 vol % in different monomer compositions (Table II). It was found that the total monomer concentration with respect to the volume of the solvent should be 1 vol % or lower for microsphere formation. At higher concentrations of the monomers, individual particles lost their identity and coagulated. Microspheres and coagulum structures of poly(DEAEMA-*co*-TRIM) at total monomer concentrations of 1 and 1.1 vol % are

shown in Figure 2, respectively. Although these monomer concentrations are close, the initial molar ratio of the crosslinker was higher in the system (sample 18) that gave coagulum. The system sensitivity is thought to come from the polymerization mechanism of the crosslinker, TRIM, which links three polymer chains. When one of the double bonds of TRIM is attached to a growing polymer chain, the other added double bond links to another molecule because of the compact tetrahedral structure with three double bonds of the TRIM molecule.²⁰

SEM investigations of poly(DEAEMA-*co*-TRIM) samples showed that the microspheres [Fig. 2(A)] had precipitated and formed coagulum [Fig. 2(B)] at a higher crosslinker concentration. Although the SEM microphotographs of these two samples are very similar, the physical appearance of the sample in Figure 2(B) showed the characteristics of coagulum formation. It was observed that poly(DEAEMA-

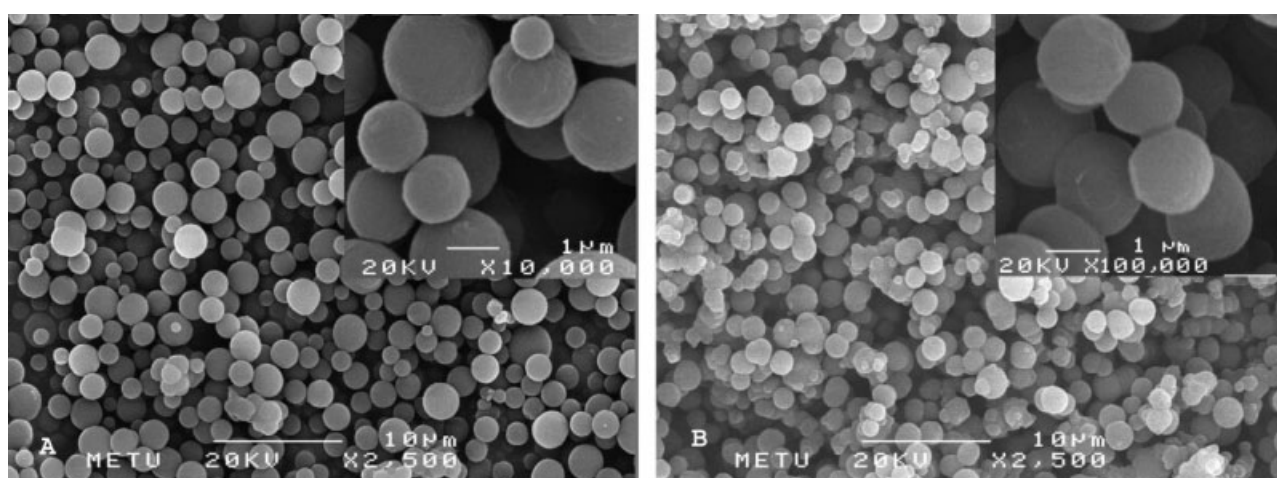


Figure 2 Poly(DEAEMA-*co*-TRIM) obtained by precipitation polymerization with an AIBN concentration of 2 wt % in acetonitrile at 60°C: (A) microsphere structure of sample 13 and (B) coagulum form of sample 18.

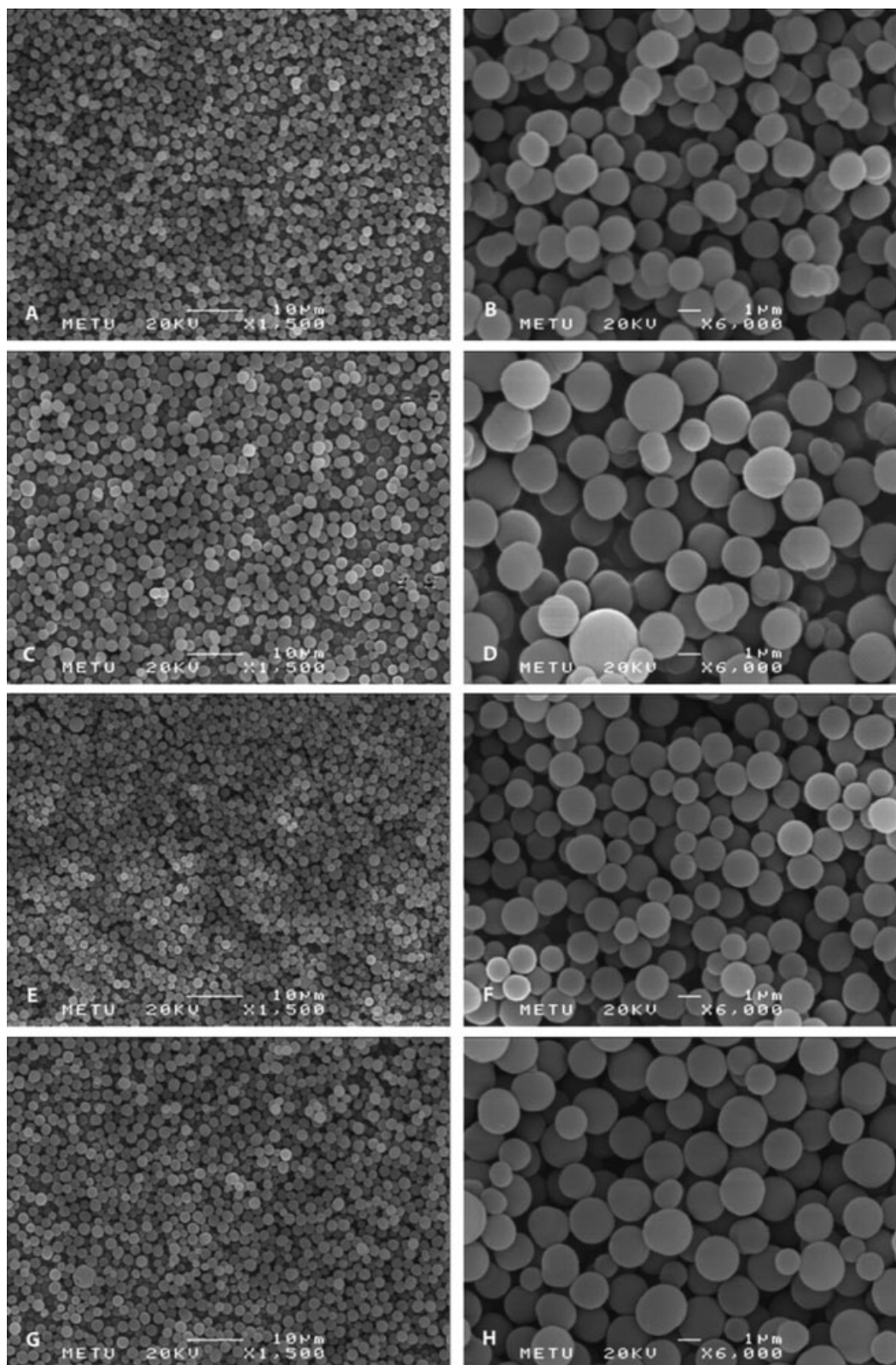


Figure 3 SEM micrographs of microspheres at different polymerization times: (A) 3 ($\times 1500$), (B) 3 ($\times 6000$), (C) 6 ($\times 1500$), (D) 6 ($\times 6000$), (E) 12 ($\times 1500$), (F) 12 ($\times 6000$), (G) 24 ($\times 1500$), and (H) 24 h ($\times 6000$). Poly(DEAEMA-co-TRIM) microspheres were produced with a total monomer concentration of 1 vol % and an AIBN concentration of 2 wt % in acetonitrile at 60°C.

TABLE III
Particle Diameter, PDI, and Yield Values of
Poly(DEAEMA-*co*-TRIM)^a Microspheres at Different
Polymerization Times

Polymerization time (h)	Particle diameter (μm)	PDI	Microsphere yield (%)
3	1.99	0.013	4.8
6	2.01	0.065	40
12	2.25	0.084	75
24	2.28	0.092	87

^a Obtained by precipitation polymerization with a total monomer concentration of 1 vol % and an AIBN concentration of 2 wt % in acetonitrile at 60°C.

co-TRIM) at a total monomer concentration of 1 vol % had more discrete spherical particles with smoother surfaces in comparison with the sticky microspheres of poly(DEAEMA-*co*-EGDMA). Therefore, poly(DEAEMA-*co*-TRIM) microspheres were chosen for studying the system parameters that control the physical properties of microspheres in precipitation polymerization.

Effect of the polymerization time

Figure 3 shows SEM micrographs of poly(DEAEMA-*co*-TRIM) microspheres prepared with a total monomer concentration of 1 vol % and an AIBN concentration of 2 wt % in acetonitrile at 60°C with different polymerization times (3, 6, 12, and 24 h). The particle sizes and PDI values of the different time products were measured with dynamic light scattering (Table III). It is remarkable that polymeric microspheres with smooth and clean surfaces were obtained in all stages of the polymerization [Fig. 3(A–H)]. Their average size was 1.99 μm at the first stage of 3 h of the polymerization [Fig. 3(A,B)]. Then, they grew further to 2.28 μm until the end of 24 h [Fig. 3(G,H)]. Although the PDI value of the microspheres was found to be 0.013 at 3 h, it increased with the polymerization time, reaching 0.092 at the end of 24 h. The higher uniformity of the microspheres at the initial stages versus that of the microspheres at the final stage can also be observed from the microphotographs. However, the microspheres of all the stages were monodisperse, with PDI values lower than 0.1 according to International Standard ISO13321.²¹

The yield of microspheres (the percentage of the product obtained as microspheres) was measured gravimetrically. The yield varied from 4.8 to 87 with increasing polymerization times (Table III). The maximum yield of 87 was obtained at 24 h. The increase in the yield with the polymerization time was found to be the same as that in solution or dispersion polymerization.

Effect of the initiator concentration

We studied the effect of the initiator concentration on the average diameters of microspheres by increasing the concentration of AIBN from 2 to 6 wt % with respect to the total amount of the monomers. The increase in the initiator concentration led to a rise in the average particle size from 2.3 to 2.7 μm (Fig. 4). Similar results were reported by Li et al.²² This rise can be attributed to an increase in the number of free radicals. A higher number of free radicals results in an increase in the concentration of growing oligomeric radicals, the crosslinking density, and the conversion. Therefore, a higher concentration of the initiator enhances the integration processes between the oligomeric radicals, and larger particles are formed.

Effect of the polarity of the medium

The polarity of the medium is another important parameter for controlling the morphology and size of the microspheres. When a proper solvent is used, the polymer being formed remains solvated up to high conversions of the monomer into the polymer.¹³ On the other hand, a nonsolvent causes early phase separation, and the microspheres grow by capturing oligomers and monomers.¹⁹ If the polarity of the medium is changed to provide phase separation during later stages of the reaction, then the solvent remaining in the particles may cause an increase in the porosity. The maximum swelling of poly(TRIM) was observed in toluene in a bed swelling test by Rosenberg and Flodin.¹⁸ Therefore, in our system, the polarity of the medium was changed by the addition of up to 2.5 vol % toluene as a cosolvent to the reaction medium. A higher toluene volume (>2.5%) caused microsphere aggregation because of the combination of later phase separation

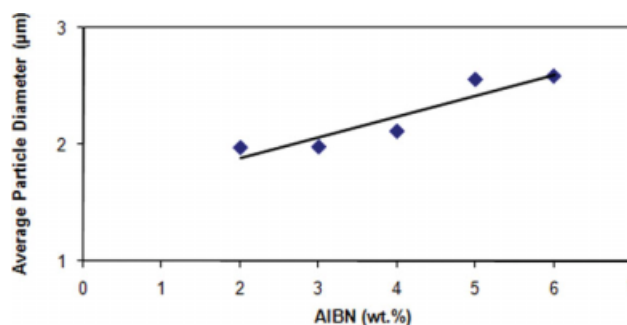


Figure 4 Effect of the initiator concentration on the particle size. The AIBN concentration was changed from 2 to 6 wt % with respect to the total amount of the monomers. Poly(DEAEMA-*co*-TRIM) microspheres were prepared with a total monomer concentration of 1 vol % in acetonitrile at 60°C for 24 h. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE IV
Effects of Toluene on the Properties of Poly(DEAEMA-*co*-TRIM) Microspheres

Cosolvent toluene (vol %)	Surface area (m ² /g)	Pore volume (cm ³ /g)	Average pore diameter (nm)
0	4.97	0.0100	42.80
2.5	2.37	0.0108	76.92

with further polymerization in the medium. The effect of the cosolvent, toluene, on the porosity of the microspheres was analyzed with measurements using nitrogen adsorption (Brunauer–Emmett–Teller (BET) method), and the results are given in Table IV.

The poly(DEAEMA-*co*-TRIM) microspheres had a very low surface area (4.97 m²/g). Rosenberg and Flodin²⁰ studied the solution polymerization of TRIM with monomer concentrations of 5–60%. They observed that the large pores collapsed at monomer concentrations below 15% upon drying. They also indicated that it was difficult to prepare macroporous poly(TRIM) when the solubility parameter difference of the polymer and medium was greater than 2 MPa^{1/2}. Therefore, the low surface area of poly(DEAEMA-*co*-TRIM) microspheres was thought to come from the collapse of the large pores because of the low concentration of TRIM and low solvency of the medium in our system. The addition of 2.5 vol % toluene to the polymerization medium had no dramatic effect on the surface area and did not change the total pore volume. For a given pore volume, the surface area decreased with increasing pore size. It was reported by Li and Stöver¹⁹ that the total pore volume and the surface area of polydivinylbenzene microspheres prepared by precipitation polymerization increased with increasing toluene volume in the polymerization medium. However, this behavior was not observed in our study because we could not increase the volume fraction of the toluene beyond 2.5 vol % on account of the aggregation problem.

Effect of the polymerization temperature

The polymerization temperature, which determines the radical formation rate, is an important parameter influencing the physical properties of the final product. Figure 5 shows that as the polymerization temperature was increased from 60 to 80°C, with the other parameters kept fixed, the resultant microsphere diameters decreased from 2.3 to 1.2 μm. Similar behavior was also reported by Macková and Horák¹² for poly(*N*-isopropylacrylamide) microspheres prepared by precipitation polymerization. This result can be explained as follows. Increasing the polymerization temperature results in a higher decomposition rate of the initiator, which increases

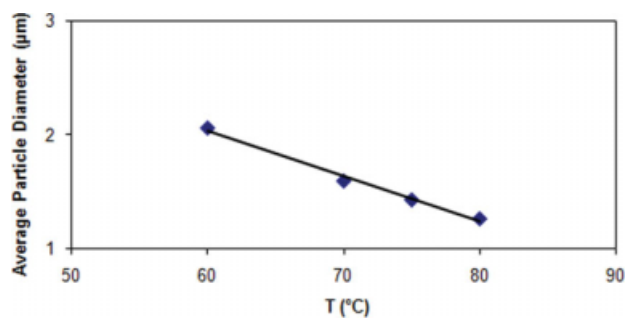


Figure 5 Effect of the polymerization temperature on the particle size. Poly(DEAEMA-*co*-TRIM) microspheres were obtained at different polymerization temperatures with a total monomer concentration of 1 vol % and an AIBN concentration of 2 wt % in acetonitrile for 24 h. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

the number of free radicals and microspheres. The increase in the number of microspheres reduces their size. On the other hand, if the rate of polymerization is slow, the conversion of a large amount of the monomers results in the growth of nuclei to larger sizes.²³

Characterization of the poly(DEAEMA-*co*-TRIM) microspheres

¹³C-NMR CP-MAS and FTIR studies were conducted to investigate the chemical characterization of the poly(DEAEMA-*co*-TRIM) microspheres prepared with a total monomer concentration of 1 vol %.

The ¹³C-NMR CP-MAS spectrum of a sample is given in Figure 6. In the spectrum, the carbonyl carbons C3 and C12 can be seen at 168 ppm. The region

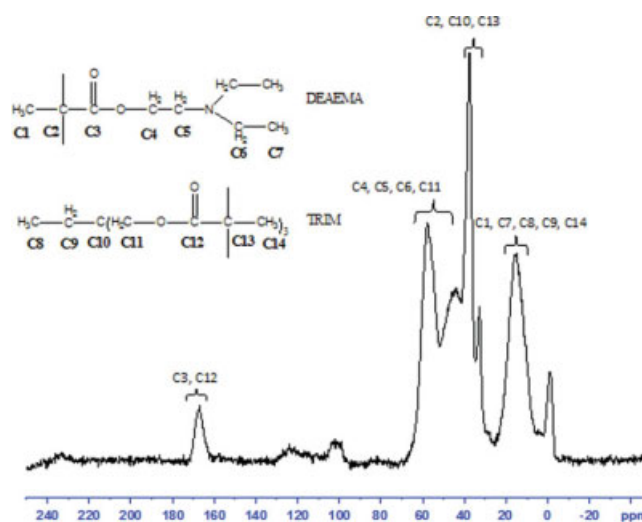


Figure 6 ¹³C-NMR CP-MAS spectrum of poly(DEAEMA-*co*-TRIM) microspheres prepared with a total monomer concentration of 1 vol % and an AIBN concentration of 2 wt % in acetonitrile for 24 h. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

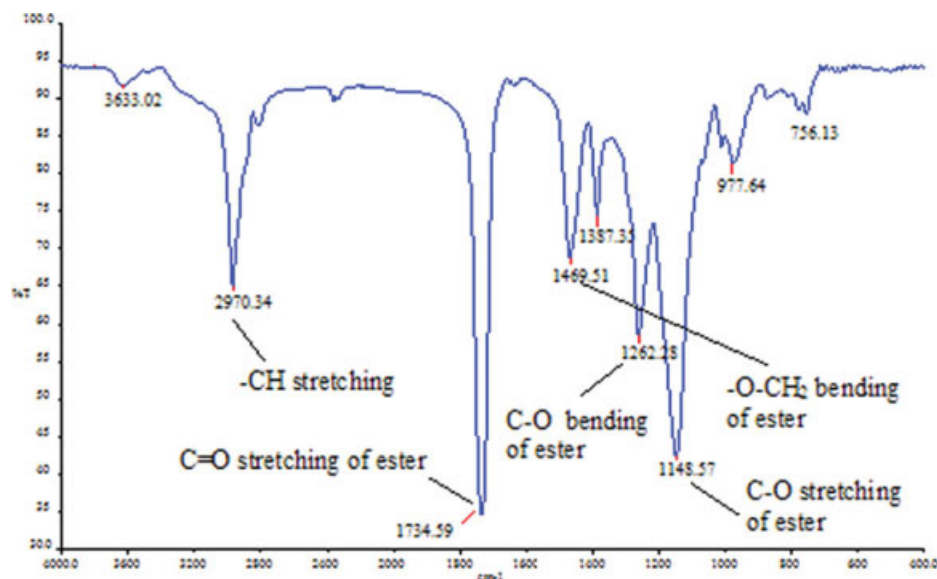


Figure 7 FTIR spectrum of poly(DEAEMA-co-TRIM) microspheres prepared with a total monomer concentration of 1 vol % and an AIBN concentration of 2 wt % in acetonitrile for 24 h. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

between 30 and 70 ppm can be characterized as C2, C4, C5, C6, C10, C11, and C13. Another region in the spectrum between 10 and 30 ppm is attributed to C1, C7, C8, C9, and C14 carbons. This spectrum is in accordance with the spectra of the polymers obtained from DEAEMA and TRIM in previous studies.^{24,25}

In the FTIR spectrum (Fig. 7), the peak assignments are as follows. The band in the range between 2980 and 2840 cm^{-1} represents the C—H stretching of aliphatic groups. The ester groups in the structure represent the C=O stretching band at 1734 cm^{-1} , the —O—CH₂ bending band at 1469 cm^{-1} , the C—O bending band at 1262 cm^{-1} , and the C—O stretching band at 1148 cm^{-1} .

CONCLUSIONS

Highly crosslinked poly(DEAEMA-co-EGDMA) and monodisperse poly(DEAEMA-co-TRIM) microspheres with clean and smooth surfaces were produced by precipitation polymerization for the first time. Under various conditions, the sizes of the microspheres remained in the range of 1.2–2.7 μm with a maximum yield of 87% poly(DEAEMA-co-TRIM).

We observed that large numbers of parameters affect the final properties of polymers. The total monomer concentration and monomer–crosslinker ratio are crucial factors for producing discrete microspheres. Only a 0.4% change in the total monomer concentration determines the formation of coagulum or microspheres. This system sensitivity is thought to come from the crosslinker, TRIM, which effec-

tively links three polymer chains. Despite the system sensitivity, all the microspheres produced under different polymerization conditions were monodisperse. Furthermore, several polymerization parameters such as the polymerization time, initiator concentration, polarity of the medium, and polymerization temperature control the physical properties of microspheres of poly(DEAEMA-co-TRIM). As an increase in the AIBN concentration was observed to increase the average particle size, an increase in the polymerization temperature reduces the average particle size.

The authors thank S. Ali Tuncel and his group at the Department of Chemical Engineering of Hacettepe University for the porosity measurements. They also thank Göktug Günkaya of Atomika Co. for the particle size analysis and Ayse Aksoy for the NMR study.

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