Production of highly crosslinked hydrophilic polymer beads: effect of polymerization conditions on particle size and size distribution

Menemşe Kiremitçi and Hakan Çukurova
Chemical Engineering Department, Hacettepe University, Beytepe, Ankara, Turkey
(Received 4 June 1991; revised 17 September 1991; accepted 8 October 1991)

Highly crosslinked poly(2-hydroxyethylmethacrylate) (PHEMA) beads ($\sim 100\,\mu$m–2 mm in diameter) were prepared by the suspension polymerization of HEMA monomer in an aqueous medium consisting only of magnesium oxide (MgO) as suspension stabilizer and salting-out agent. The procedure is so simple and the particles have excellent spherical geometry and very narrow size distribution compared to PHEMA beads prepared by other techniques. The effect of various factors such as MgO concentration, stirring speed and monomer phase/aqueous phase ratio on the particle geometry, size and size distribution was investigated. It was shown that the amount of MgO in the dispersion medium is the most important parameter which affects the particle size and size distribution.

(Keywords: poly(2-hydroxyethylmethacrylate); crosslinking; suspension polymerization; hydrophilic polymer beads; ethyleneglycoldimethacrylate)

INTRODUCTION

Hydrophilic polymer microparticles are important in a variety of biomedical and biotechnological applications including endovascular embolization, controlled drug release systems, enzyme and cell immobilization and different types of chromatography[1–5]. A number of these applications require the preparation of crosslinked microparticles of known particle size, distribution and crosslinked structure. Among these particles, poly(2-hydroxyethylmethacrylate) (PHEMA) based particles have attracted attention recently due to their non-toxicity, non-irritability and biocompatibility with living tissues[6]. Such microparticles have been prepared by various techniques, however, suspension polymerization is the preferred method. Although suspension polymerization of hydrophobic monomers (e.g. methyl methacrylate, styrene, etc.) is relatively well studied, similar techniques applied to hydrophilic monomers are still in their infancy. The main reason for this is the high solubility of HEMA monomer in an aqueous medium. Preparation of beads in the organic phase has the disadvantage that the adsorbed chemicals are often difficult to remove after polymerization, since high purity is required for biomedical and biotechnological applications. Recently, different novel suspension polymerization techniques for the HEMA monomer have been reported by Horak *et al.*[1], Mueller *et al.*[7], Scranton *et al.*[8] and Jayakrishnan *et al.*[9,10].

In our earlier studies, we have reported the γ radiation polymerization of HEMA monomer is supercooled media[11]. Recently, Kiremitçi modified the suspension polymerization technique of Mueller *et al.* in order to prepare PHEMA beads for microcarrier-facilitated cell culture applications[12–14]. This study describes the effect of the polymerization conditions of this modified technique on particle size and size distribution.

MATERIALS AND METHODS

Chemicals

The basic monomer HEMA (Aldrich Chemical Co., Milwaukee, WI, USA) was used to prepare the hydrophilic PHEMA particles. The crosslinker, ethyleneglycoldimethacrylate (EGDMA) and the initiator, 2,2-azobisisobutyronitrile (AIBN) were purchased from Merck (Germany) and BDH (UK), respectively. Magnesium oxide (MgO) was obtained from BDH. All the chemicals were purified prior to use.

Suspension polymerization

Crosslinked PHEMA beads were prepared by the suspension polymerization technique of Mueller *et al.* with some modification. In this modified technique, polymerization was carried out in an aqueous phase containing MgO which was used as the stabilizing and salting-out agent. The pH of the suspension medium was kept constant at 10. A three-necked flask (500 ml) with a blade type stirrer was used as the polymerization reactor. The mixture containing the monomer (HEMA), crosslinker (EGDMA) and the initiator (AIBN) was added into the suspension medium. By taking into account the results of our preliminary experiments, EGDMA and AIBN concentrations were kept constant at 0.03 and 0.015 mol mol^{-1} HEMA, respectively. The mixture was maintained at 70°C for 3 h and then at 90°C for 1 h. By changing the stabilizer concentration, monomer phase/aqueous phase ratio and agitation speed, polymer beads of different size and size

0032-3861/92/153257–05

distribution were obtained. After cooling, the polymer beads were transferred into a dilute hydrochloric acid solution in order to remove the residual MgO. The microspheres were washed with water and ethanol, respectively, and then dried in a vacuum desiccator at room temperature.

Determination of particle properties

The size and size distribution of PHEMA beads were determined by measuring the diameters of 150 particles under a microscope and evaluating these measurements by means of variance analyses. The surface and bulk structures of the PHEMA beads prepared were examined using a scanning electron microscope (model Leitz-AMR 1000 Raster Electronen Microscope, Germany). Optical micrographs of the beads were taken using a Nikon optical microscope. The swelling abilities of the PHEMA beads in water were determined by swelling experiments and were given as the equilibrium water content (EWC%) calculated from the weight of swollen and dry beads.

RESULTS AND DISCUSSION

As discussed in the literature, the preparation of large PHEMA particles in aqueous media is difficult due to the high solubility of HEMA[8–10]. Recently, Mueller *et al.* and Scranton *et al.* proposed a novel method to prepare crosslinked PHEMA microparticles by suspension polymerization carried out in a suspending phase of a gel-like precipitate of $Mg(OH)_2$. However, in this gel-like medium the control of polymerization parameters (such as stirring speed, uniform temperature distribution, etc.) is difficult and causes a number of undesired properties, i.e. particle agglomeration, a wide range particle size distribution, etc. In our previous studies, the effect of several metal oxides (calcium, aluminium, magnesium, etc.) on the solubility and stabilization of HEMA monomer droplets was investigated. It was found that only MgO can be used effectively as both the stabilizing and the salting-out agent in the aqueous-phase suspension polymerization of hydrophilic monomers. Therefore, in this study we attempted the suspension polymerization of HEMA monomer in MgO solution which was used as the dispersion medium.

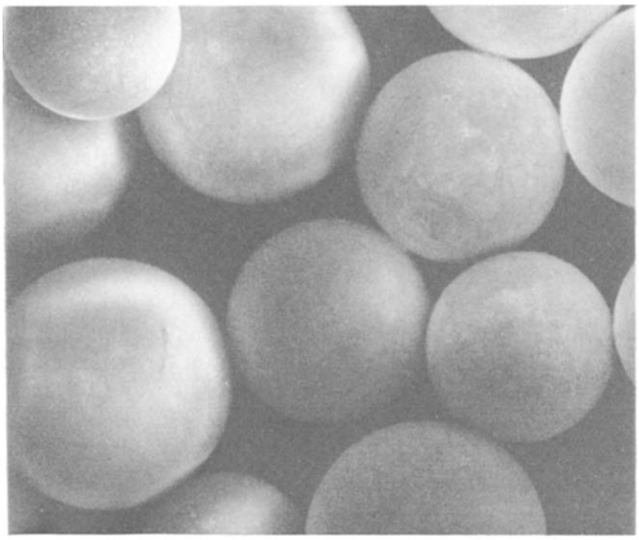

Figure 1 Scanning electron micrograph of PHEMA particles prepared using 0.015 g MgO ml^{-1} water at a stirring speed of 380 rotations min^{-1}

Table 1 Effect of MgO concentration on particle size distribution of PHEMA beads

MgO concentration (g ml^{-1} water)	Particle size range (μm)	Weight fraction (%)
0.005	1100–1900	83.5
0.010	600–850	78.5
0.015	540–740	78.2
0.020	320–480	74.0
0.025	280–450	71.0
0.050	65–170	100.0

Stirring speed: 380 rotations min^{-1}; monomer/water ratio: 1/10

The resultant beads have excellent spherical geometry and a very narrow size distribution. The scanning electron micrograph in *Figure 1* shows the geometry, size and size distrubition of PHEMA beads prepared in this study.

PHEMA particles were produced by a simultaneous copolymerization/crosslinking reaction of HEMA with EGDMA which used as the crosslinking agent. The mechanism involved was found from the solid state ^{13}C n.m.r. spectra of the particles[15]. The results of our previous studies reveal that the initial concentration of initiator (AIBN) and the crosslinking ratio are important parameters which affect particle formation and these parameters are related to each other. As the AIBN concentration increases, a higher concentration of PHEMA chains is obtained and thus the amount of crosslinker may be insufficient to crosslink all the polymer chains. Therefore in this study the EGDMA and AIBN concentrations were kept constant at 0.03 mol EGDMA mol^{-1} HEMA and 0.015 mol AIBN mol^{-1} HEMA, respectively.

It was known that, in the case of suspension polymerization, particle size and size distributions are dependent on the rotations per minute of the agitator, the concentration of the suspending agents and the reactor design. Furthermore, interfacial tension, changes in the organic phase as the reaction proceeds, and density changes of the organic phase during reaction significantly affect particle size and size distribution. Therefore, in this study the effects of MgO concentration, stirring speed and monomer/aqueous phase ratio on the particle size and size distribution were investigated.

The results showed that variation of the amount of MgO present in the dispersion medium affects the particle size greatly. A lower concentration of MgO caused large sized spheres. An increase in concentration up to a certain level led to a decrease in the bead size. The optical micrographs in *Figure 2* clearly show the effect of MgO on particle size and distribution. At high MgO concentrations, the separation of small size PHEMA particles from the suspending phase is difficult. However, in all cases the size distribution was narrow when compared with particles prepared by other techniques[8]. *Figure 2f* shows the particles prepared in NaCl and $Mg(OH)_2$ media according to the method used by others. By changing the amount of MgO it would be possible to adjust the particle size over the range of 65–1900 μm (*Table 1*).

The other interesting result is the formation of porous spherical beads at lower MgO concentrations. This may

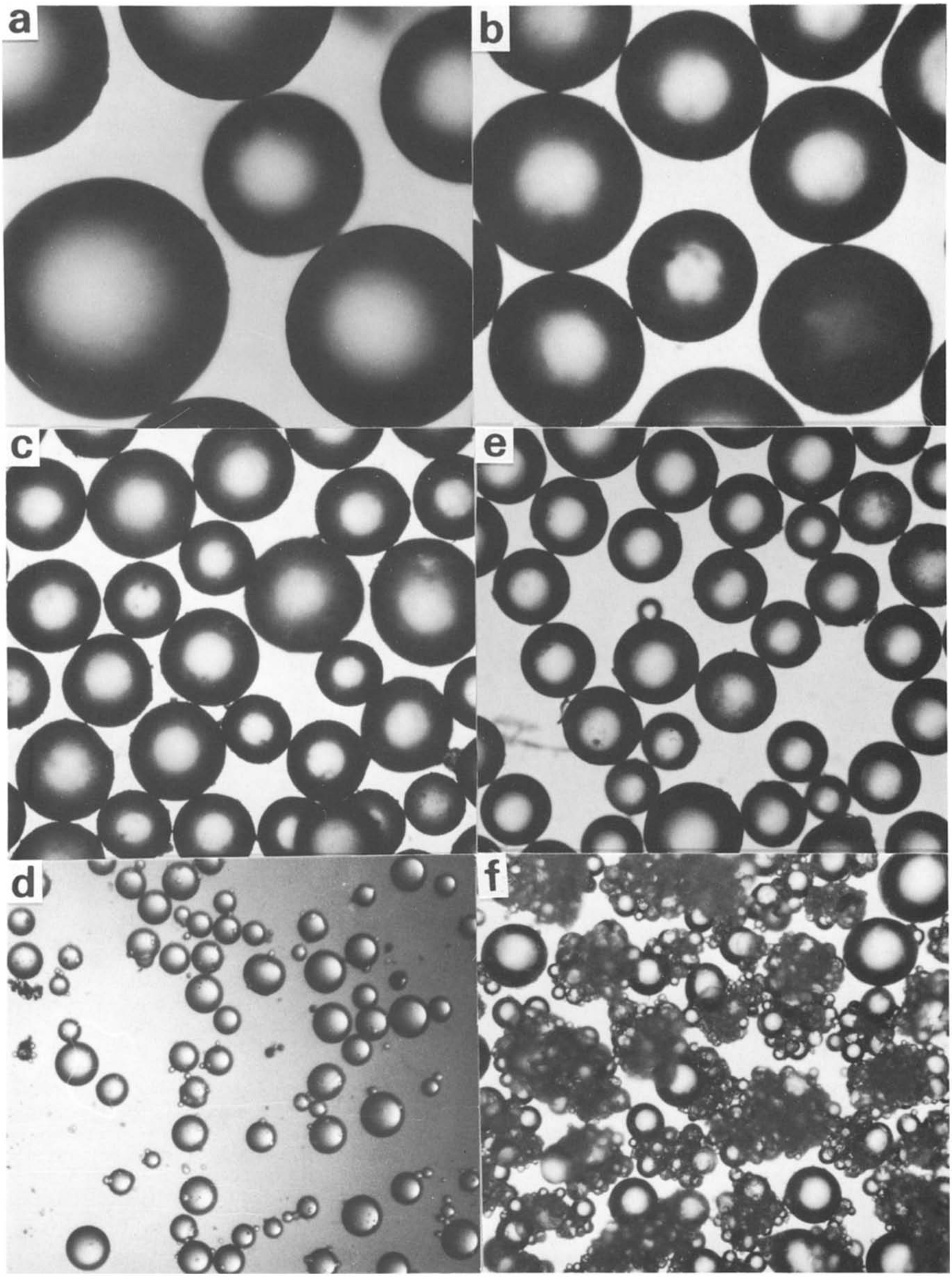

Figure 2 Optical micrographs of PHEMA particles showing the effect of MgO concentration on particle size and size distribution. (All the micrographs were taken without applying screen analysis.) MgO concentrations (g ml^{-1} water): (a) 0.005; (b) 0.015; (c) 0.025; (d) 0.040; (e) 0.050; (f) PHEMA particles prepared by other techniques

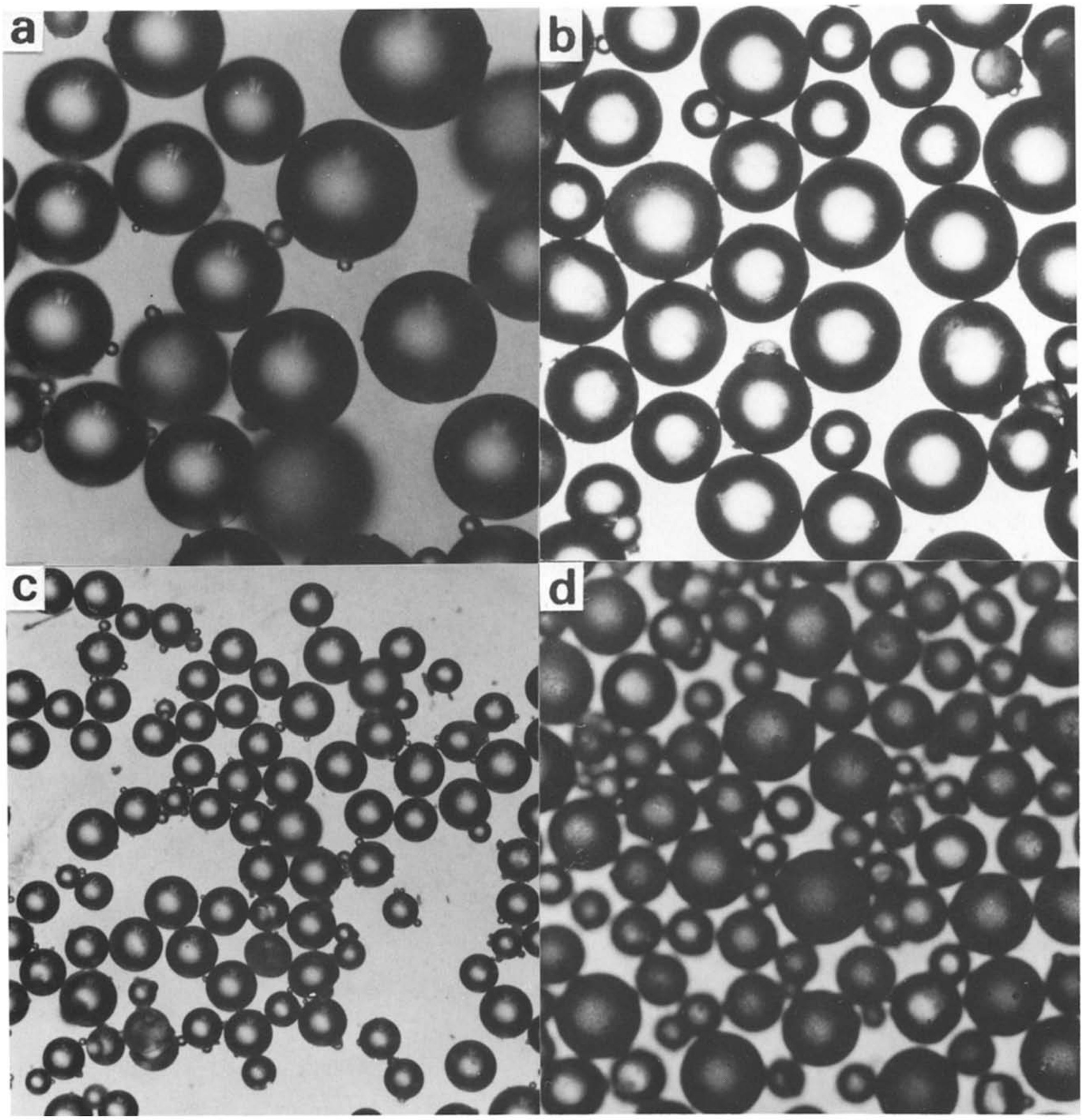

Figure 3 Optical micrographs of PHEMA particles showing the effect of stirrer type and stirring speed on the particle shape, size and size distribution: (a) blade type stirrer, 500 rotations min^{-1}; (b) blade type stirrer, 590 rotations min^{-1}; (c) blade type stirrer, 780 rotations min^{-1}; (d) anchor type stirrer, 590 rotations min^{-1}

be explained by the higher water diffusion to the droplets of HEMA at lower MgO concentrations. At low MgO concentrations, the surface is highly porous, however, increasing concentration decreases surface porosity and leads to the smooth structure. Swelling experiments have indicated that, while the EWC value is ~43% for the particles prepared by 0.005 g MgO ml^{-1} water, it is ~21% for particles prepared at higher MgO concentrations. This result is extremely important since porosity is an important requirement for the chemical modification of PHEMA structures.

The other parameter which affects the particle size is stirring speed. As expected an increase in stirring speed from 380 to 780 rotations min^{-1} the same conditions causes smaller sized beads to form (100–850 μm) (*Figure 3*). *Table 2* gives the particle size distribution for different stirring speeds in the dispersed phase. In addition, the effect of stirrer type on the particle geometry was investigated by using various types of stirrers. As can be seen from *Figure 3*, the anchor type stirrer causes distortion of the particles.

A change in concentration of the HEMA monomer also influences the particle size and distribution. *Table 3* gives the effect of monomer phase/aqueous phase ratios on the size distribution of particles. Increase in monomer concentration increases particle size but the particle shape is not as good. This may be explained by the viscosity changes in the reaction medium.

Table 2 Effect of stirring speed on particle size distribution of PHEMA beads

Particle size range (μm)	Weight fraction (%)			
	Stirring speed (rotations min^{-1})			
	380	500	590	780
100–150	–	–	7.9	18.0
150–200	–	–	10.5	40.5
200–250	–	–	13.1	27.0
250–300	–	12.2	34.4	12.0
300–350	–	14.0	15.9	2.5
350–400	–	33.7	13.2	–
400–450	–	33.0	5.0	–
450–500	–	7.1	–	–
550–600	6.2	–	–	–
600–650	17.2	–	–	–
650–700	19.8	–	–	–
700–750	32.3	–	–	–
750–800	17.8	–	–	–
800–850	6.7	–	–	–

MgO: 0.015 g ml^{-1} water; monomer phase/aqueous phase: 1/10

Table 3 Effect of monomer phase/aqueous phase ratio on particle size distribution of PHEMA beads

Particle size range (μm)	Weight fraction (%)	
	Monomer phase/aqueous phase	
	1/5	1/10
550–600	–	6.2
600–650	–	17.2
650–700	–	19.8
700–750	–	32.3
750–800	–	17.8
800–850	–	6.7
850–900	5.0	–
900–950	12.5	–
950–1050	32.5	–
1050–1150	37.5	–
1150–1300	12.5	–

MgO: 0.015 ml^{-1} water; stirring speed: 380 rotations min^{-1}

The studies also showed that polymerization is sensitive to the applied temperature. The finite heat transfer coefficient between the organic and aqueous phase causes complications in the preparation of beads in a narrow size distribution.

CONCLUSIONS

The main goal of this study is the preparation of crosslinked PHEMA particles which have a very narrow size distribution and excellent spherical shape. This is achieved by the stabilizing effect of MgO in the dispersed phase. The effects of a number of parameters, such as MgO concentration, stirring speed and monomer phase/aqueous phase ratio on the particle size, size distribution, geometry and porosity were investigated. The results show that particle size distribution and porosity mainly depend on the MgO concentration.

ACKNOWLEDGEMENT

This study was supported by grant no. TBAG-1052 from the Turkish Scientific and Research Council (TÜBİTAK).

REFERENCES

1 Horak, D., Svec, F., Kalal, J., Gumargalieva, K., Adamyan, A., Skuba, N., Titova, M. and Trostenyuk, N. *Biomaterials* 1986, **7**, 188

2 Robert, C. C. R., Buri, P. A. and Peppas, N. A. *J. Control. Rel.* 1987, **5**, 151

3 Dawson, R. M., Broughton, R. L., Stevenson, W. T. K. and Sefton, M. V. *Biomaterials* 1987, **8**, 360

4 Kamei, S., Okubu, M. and Matsumoto, T. *J. Appl. Polym. Sci.* 1987, **34**, 1439

5 Kahovec, J. and Coupek, J. *Reactive Polym.* 1988, **8**, 105

6 Andrade, J. D. (Ed.) 'Hydrogels For Medical and Related Applications', American Chemical Society, Washington DC, 1976

7 Mueller, K. F., Heiber, S. J. and Plankl, W. L. *US Pat. 4 224 427*, 1980

8 Scranton, A. B., Mikos, A. G., Scranton, L. C. and Peppas, N. A. *J. Appl. Polym. Sci.* 1980, **40**, 997

9 Jayakrishnan, A. and Thanoo, B. C. *J. Biomed. Mater. Res.* 1990, **24**, 913

10 Jayakrishnan, A., Sunny, M. C. and Thanoo, B. C. *Polymer* 1990, **31**, 1339

11 Denizli, A., Kiremitçi, M. and Pişkin, E. *Biomaterials* 1988, **9**, 257

12 Kiremitçi, M. *PhD Thesis* Hacettepe University, Ankara, 1988

13 Kiremitçi, M., Özilgen, M. and Pişkin, E. *Enzyme and Microbiol Technol.* 1989, **12**, 830

14 Kiremitçi, M., Gürhan, I. and Pişkin, E. *Biotechnol. Appl. Biochem.* 1991, **14**, 170

15 Kiremitçi, M. and Özkar, S. *Int. Polym. J.* in press