Porous PolyHEMA Beads Prepared by Suspension Polymerization in Aqueous Medium

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SYNOPSIS

A study was made of the effect of the type of low-molecular-weight porogen on the properties of polyHEMA beads (sphericity, bead size, porosity, and morphology), prepared by radical suspension copolymerization of 2-hydroxyethyl methacrylate (HEMA) with ethylene dimethacrylate (EDMA) in aqueous dispersion. The porogen used was cyclohexanol, mixed with various alcohols, hydrocarbons, butyl acetate, or cyclohexanone. Spherical particles, with a size of hundreds of μm and a porosity of up to 68%, can be prepared using a mixture of cyclohexanol and 1-octanol in a volume ratio of 3 : 2. The tendency for the particles to agglomerate, observed in the presence of benzyl alcohol, 1-butanol, or cyclohexanone, can be a consequence of a change in the polymerization mechanism connected with the excessive solubility of these porogens, and thus also the initiator in water. © 1993 John Wiley & Sons, Inc.

INTRODUCTION

The preparation of spherical particles of poly(2-hydroxyethyl methacrylate) (polyHEMA) is a subject of great interest, especially in biomedical and pharmaceutical engineering. These particles are used as sorbents in various types of chromatography,[1,2] in hemoperfusion systems,[3,4] for embolization,[5-7] for controlled release of pharmaceuticals,[8] for immobilizing enzymes,[9,10] for encapsulation of mammalian cells,[11,12] and as immunoreagents.[13,14] They are prepared using various techniques: transfer of the HEMA monomer to a supercooled thermodynamically poor solvent, followed by irradiation,[3,15] emulsion polymerization,[10,16] or suspension polymerization.[17-19]

Some applications require the use of porous particles, which react rapidly in chemical modifications. For surgical applications, the particles must possess suitable properties in implantation (e.g., growth of a fibrous connecting tissue into the pores). Permanent porosity is obtained by adding to the polymerization mixture porogenic additives, which neither polymerize nor can be built in the polymer matrix. These materials must fulfil two more conditions: they must be soluble in the HEMA monomer and they must be immiscible with water. In general, low-molecular-weight porogens are used, which can be both solvents and nonsolvents for the growing polymer chains.[20] Macroporous, spherical polyHEMA particles have been prepared by suspension polymerization in the presence of the polymeric porogens, such as poly(methyl methacrylate) in toluene or poly(1,4-butanediol) in a concentrated NaCl solution, using magnesium hydroxide prepared *in situ* as a suspension stabilizer.[19] A disadvantage of systems using polymeric porogens lies in the difficulties connected with the removal of these substances from the final product.[21] Therefore, this work was carried out using low-molecular-weight porogens.

Porous polyHEMA particles of a spherical shape and a low level of crosslinking, prepared by suspension polymerization in water in the presence of a porogenic mixture of cyclohexanol and 1-dodecanol, have extensive applications in medicine as a suitable embolic material.[17] However, the preparation of these particles is accompanied by a number of problems. Although the product contains primarily spherical particles, these are often accompanied by irregular agglomerates that must be removed from

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the sample. The content of crosslinking agent cannot be increased in the synthesis if the particles in the swollen state are to retain the soft consistency essential for their implantation in the living organism. Consequently, a more suitable porogenic system than a mixture of cyclohexanol and 1-dodecanol was sought. However, the presence of cyclohexanol—a good solvent for polyHEMA—is essential if the particles are to be spherical. This work evaluates the addition of various poor solvents for polyHEMA to the polymerization mixture, in order to study their effect on the properties of the beads, especially their sphericity, size and porosity.

EXPERIMENTAL

Reagents

2-Hydroxyethyl methacrylate (HEMA; Léčiva Prague), poly(N-vinyl-2-pyrrolidone) K-90 (PVP, mol wt 360,000; Fluka), paraffin oil (Petrochema Dubová, Slovakia), and 1-dodecanol (Fluka) were used as supplied. All the other solvents, that is, cyclohexanol, benzyl alcohol, 1-butanol, xylene, cyclohexanone, 2-ethyl-1-hexanol, butyl acetate (all supplied by Lachema Brno, Czech Republic), and 1-octanol (Reachim, Russia) were distilled prior to use. Ethylene dimethacrylate (EDMA; Ugilor, France) was also distilled before use (b.p., 78°C/93 Pa). Azobis(isobutyronitrile) (AIBN; Fluka) was recrystallized twice from ethanol.

Suspension Polymerization Procedure[17]

The dispersed organic phase, consisting of 9.5 mL HEMA, 0.5 mL EDMA, 0.1 g AIBN, 15 mL of a mixture of a porogen and cyclohexanol (the ratios are given in Table I), and 75 mL of a 1% aqueous solution of PVP, was transferred into a 250 mL Büchi reactor and was purged with nitrogen for 10 min. The polymerization was allowed to proceed at 70°C for 8 h with continuous stirring (180 rpm). After cooling, the polymer was washed successively 10 times with water, 10 times with methanol, 3 times with acetone, and 3 times with ether. After drying (48 h, 21°C/66 Pa), the particles were fractionated on 100, 250, 315, 400, 600, 800, and 1000 μm sieves and the mean particle size $\bar{d}_w$ was calculated as the weighted arithmetic mean of the size fractions of the spherical particles. The fractions sometimes contain agglomerates, usually larger than 1000 μm, which were not included in the calculation. The percentage content of particles of irregular shape in the samples was found by evaluation of photographs out of at least 2000 particles.

Determination of the Concentration of Organic Compounds in Water and Water in HEMA

The initial concentrations of HEMA, cyclohexanol, and porogens in the aqueous phase were determined by gas chromatography (Perkin-Elmer 8310 gas chromatograph, 15% GE XG-60 on Chromosorb W-AW HMDS, internal standard 1-propanol). The concentration of water in HEMA was determined by the two-component titration technique of Riedel-de Haën using Hydranal solvent (imidazole and sulfur dioxide in methanol) and Hydranal Titrant 5 (iodine in methanol).[22]

Scanning Electron Microscopy (SEM)

A JEOL JSM 35 microscope was used for these measurements. Particles were fixed to the substrate, using double-sided Scotch tape, and were uniformly coated with a gold layer with a thickness of approximately 10 nm. The inner particle structure was revealed by cutting them in half with a razor blade prior to their fixation on the substrate.

Water Regain

Water regain was measured as described elsewhere.[23]

RESULTS AND DISCUSSION

It has been observed[24] that, even if one of the monomers in a monomer mixture is highly water-soluble, copolymerization of the mixture can still be carried out in an aqueous dispersion. In this situation, the water-miscible monomer diffuses into the organic phase and undergoes copolymerization. The addition of certain water-immiscible solvents, which act as extraction agents, may promote this process. These solvents can also act as porogens. It can be assumed that HEMA will be more soluble in a properly selected porogenic system than in water, so that it essentially remains in the system.

Table I shows a list of porogens, practically all of which are poor solvents for polyHEMA. These porogens have been used in a mixture with cyclohexanol, which is a good solvent, in the synthesis of polyHEMA particles in aqueous dispersion. Porogens, such as benzyl alcohol, 1-butanol, xylene, paraffin oil, cyclohexanone, 2-ethyl-1-hexanol added to cyclohexanol, or to its mixture with 1-dodecanol,

Table I Synthesis and Characterization of PolyHEMA Particles

No.	Porogen[a] (mL)		Fraction (%) in Aqueous Phase[b]			Water Regain (g/g)	Particles		
			HEMA	CyOH	Other		Shape[c]		Size (μm)
1	CyOH/BOH	(9/6)	36	19	33[d]	0.55	a, i	(0)	—
2	CyOH/BuOH	(9/6)	39	19	31[e]	0.61	a	(0)	—
3	CyOH/XY/DOH	(9/3/3)	48	22	0[f] 0[g]	1.80	a, b	(30)	500
4	CyOH/PO/DOH	(9/3/3)	—	—	—	1.39	a, b	(14)	500
5	CyOH/Cyone	(9/6)	36	20	58[h]	0.56	a	(0)	—
6	CyOH/Cyone/DOH	(9/3/3)	47	24	35[h] 1.2[g]	1.53	a, b	(17)	500
7	CyOH/EHOH	(9/6)	37	15	0.4[i]	1.58	a, b	(15)	—
8	CyOH/EHOH/DOH	(9/3/3)	42	18	2.1[i] 0[g]	1.47	a, b	(30)	550
9	CyOH/DOH	(9/6)	44	19	0[g]	1.63	b	(82)	450
10	CyOH/BuOAc	(9/6)	34	18	1.3[j]	1.47	b	(84)	450
11	CyOH/BuOAc/DOH	(9/3/3)	39	19	3.1[j] 0[g]	1.69	a, b	(35)	500
12	OcOH	(15)	48	—	1.8[k]	1.17	i	(10)	650
13	CyOH/OcOH	(3/12)	45	19	0.2[k]	1.30	a, b, i	(12)	600
14	CyOH/OcOH	(6/9)	36	15	0.6[k]	1.40	a, b	(33)	550
15	CyOH/OcOH	(9/6)	39	16	0.2[k]	1.67	b	(98)	400
16	CyOH/OcOH	(12/3)	38	19	0.3[k]	1.46	b	(98)	350
17	CyOH	(15)	47	16	—	0.61	b	(98)	250
18	CyOH/OcOH/DOH	(9/3/3)	47	17	0[k] 0[g]	1.74	b	(80)	400

[a] (CyOH) cyclohexanol, (BOH) benzyl alcohol, (BuOH) 1-butanol, (XY) xylene, (DOH) 1-dodecanol, (PO) paraffin oil, (Cyone) cyclohexanone, (EHOH) 2-ethyl-1-hexanol, (BuOAc) butyl acetate, (OcOH) 1-octanol.
[b] Related to the total content of particular compounds in the polymerization mixture.
[c] (a) aggregates, (b) beads, (i) irregulars (in parenthesis percentage of beads as obtained by photographic analysis).
[d] BOH.
[e] BuOH.
[f] XY.
[g] DOH.
[h] Cyone.
[i] EHOH.
[j] BuOAc.
[k] OcOH.

have been found to be unsuitable for the preparation of spherical particles. The particles aggregate during the suspension polymerization and the product formed is often irregular in shape [Figs. 1(a,b)]. Particles with a predominantly spherical shape are formed only if mixtures of 1-octanol or butyl acetate or 1-dodecanol, containing at least 60 vol % cyclohexanol, are added to the polymerization mixture. Most regular spherical shapes were observed for samples No. 15 and 16 [Figs. 2(a,b)], where almost all the particles are spherical, that is, more than in the previously,[17] often-studied sample No. 9 (Table I). The distribution of bead sizes is usually within the range of 100–800 μm, with the most frequently found fraction lying in the range of 400–600 μm (e.g., 65 wt % in sample No. 10). This fraction, shown in Figure 2(b), can be used directly in biomedical applications.

If the polyHEMA beads are to be used as implants coming into contact with the blood, it is necessary to know their behavior in water. Thus, their porous structure was characterized by their water regain (g H_2O/g dry material) (Table I). The water regain in the polymers prepared in the presence of cyclohexanol mixed with benzyl alcohol, 1-butanol, or cyclohexanone is equal to 0.55–0.60 g/g, corresponding to an equilibrium water content of 41–43%. Thus, these polymers have no permanent porosity but possess gel-type microporosity (swelling porosity). In the dry state, these particles are slightly

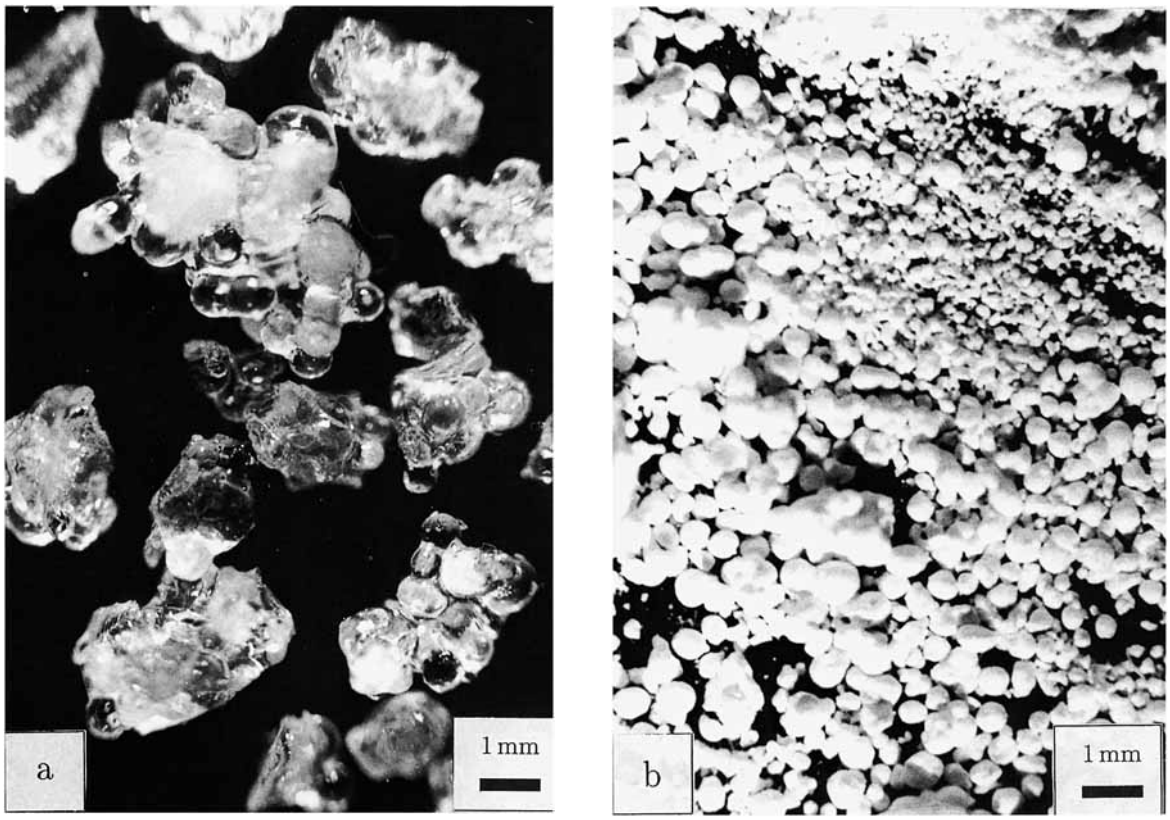

Figure 1 Photographs of polyHEMA particles; (a) sample No. 1 and (b) sample No. 4.

glassy in appearance [Fig. 1(a)]. Obviously, no phase separation occurs in glassy particles during the polymerization. In contrast, particles prepared with the addition of the other porogens to cyclohexanol behave differently. During the polymerization, phase separation occurs, and after extracting the porogen and drying, permanent pores or holes of various sizes are formed. These particles are characterized by water regain in the range 1.4–1.6 g/g, corresponding to the overall porosity of 63–67%. The swelling porosity is apparently accompanied by the permanent porosity. The structure of these particles is referred to as macroporous.

As particles prepared in the presence of cyclohexanol and 1-octanol seem to be useful in arterial embolization,[17] a study was made of the effect of the ratio of these two solvents on the properties of the particles produced. Figure 3 depicts the effect of this ratio on the particle size and the water regain value. As the 1-octanol content increases in the mixture, the mean particle size increases. The smallest glassy particles arise from the polymerization mixture without the poor solvent (1-octanol). However, it should be noted that particles with an almost exclusively spherical shape are formed only at a 1-octanol/cyclohexanol volume ratio of less than 2 : 3. It follows from Figure 3 that, at this ratio, the particles also have greater water regain (1.67 g/g) with a porosity of 68%.

The curve in Figure 3, which relates the dependence of water regain to the 1-octanol content in the mixture with cyclohexanol, shows a maximum, which also corresponds to a change in the morphological structure of the particles. Figures 4–7 depict the scanning electron micrographs of the surface and interior of the beads prepared in the presence of various amounts of cyclohexanol and 1-octanol. It is observed that the interior of the bead contains large microspheres (0.5–3 μm) formed by phase separation inside the bead or agglomerates of microspheres. The largest microspheres (2–3 μm) are observed in sample No. 15 [Fig. 6(c)], the smallest (0.5–1 μm) in sample No. 16 [Fig. 7(c)], and the medium-sized microspheres (1–2 μm) in samples No. 12 [Fig. 4(c)] and No. 14 [Fig. 5(b)]. Large pores (up to about 10 μm) are formed between the microspheres. While samples No. 12 [Fig. 4(a–c)] and No. 13 exhibit common features on the surface and inside the beads, from sample Nos. 15 and 16, the surface and bulk of the beads are different. The size

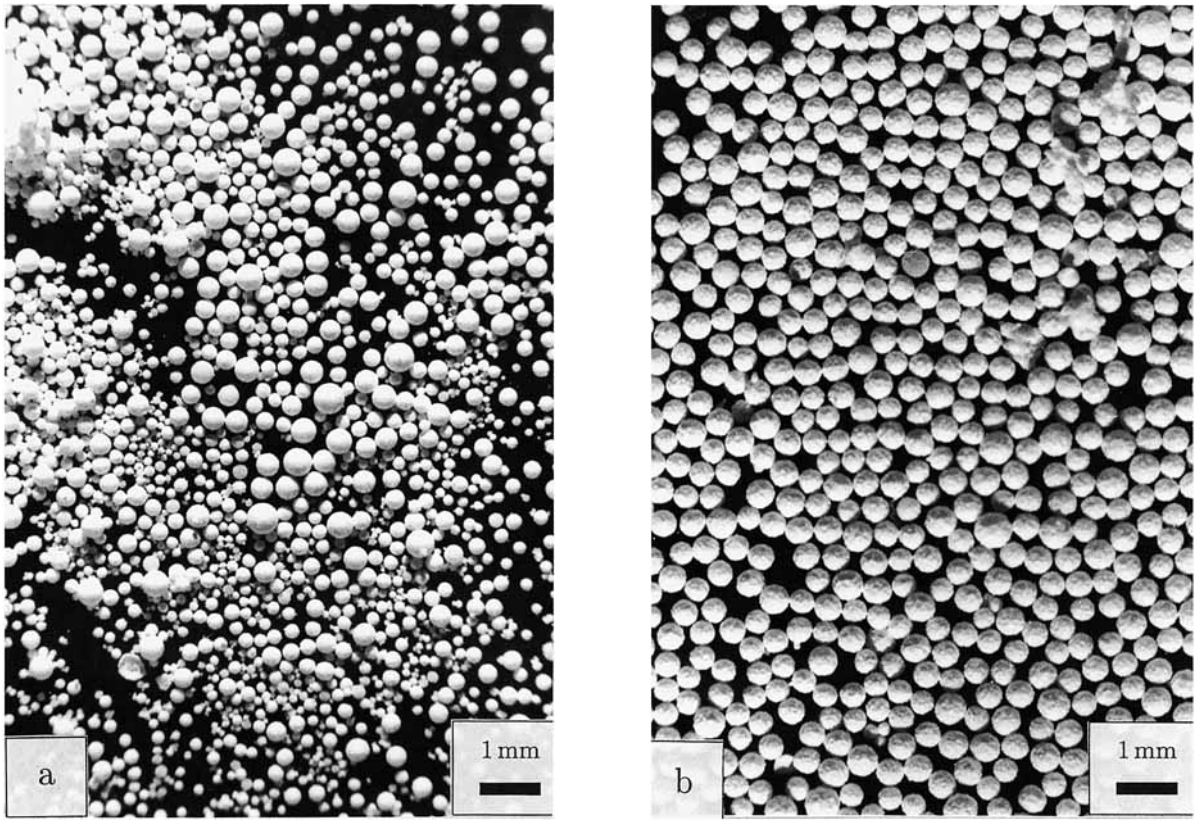

Figure 2 Photographs of polyHEMA particles; (a) sample No. 16 and (b) sample No. 15. Size fraction 400–600 μm.

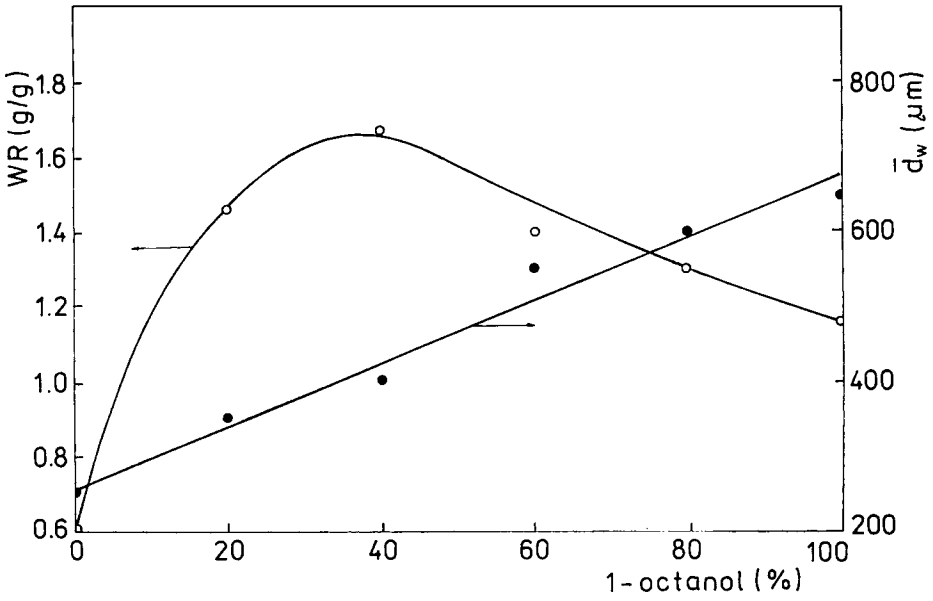

Figure 3 Dependence of mean particle size ($\bar{d}_w$) and water regain (WR) on the content of 1-octanol in mixtures of 1-octanol/cyclohexanol used as porogen in the suspension polymerization of HEMA.

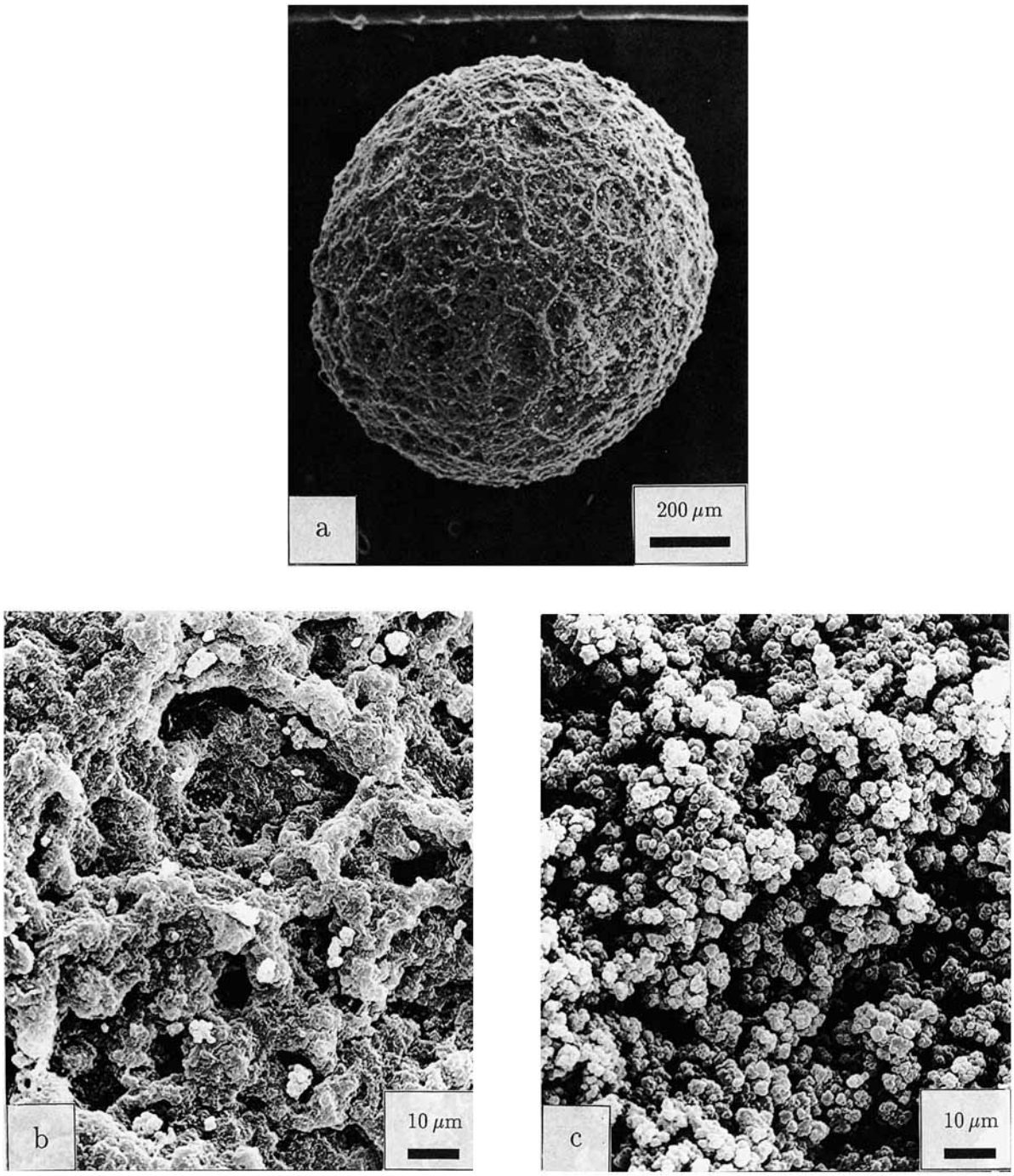

Figure 4 SEM of sample No. 12; (a) surface, (b) surface, and (c) interior.

of the pores on the surface of the beads in sample No. 12 [Fig. 4(a,b)] corresponds to the size of the pores inside the beads [Fig. 4(c)]. This is also true for sample No. 13. Thus, these beads do not have a clear shell of compactly arranged microspheres on their surface, in contrast to samples No. 14 to 16 (Figs. 5–7), where the surface is wrinkled. The surface of sample No. 16 contains ridges of approximately the same width and height, with dimensions of about 10 μm [Fig. 7(a,b)], while the interior contains smaller heterogeneities [Fig. 7(c)]. Sample No. 14 contains microspheres (1–2 μm) joined together to form agglomerates [Fig. 5(a,b)]. As the content of cyclohexanol increases in the mixture

with 1-octanol, the surface of the beads becomes more compact and smoother; simultaneously, the interior contains smaller pores than in samples prepared with high 1-octanol contents.

A heterogeneous, macroporous polymer structure is obtained when phase separation occurs during the crosslinking polymerization in the presence of porogens. Phase separation depends on the following main factors[22]: the molar volumes of the individual components, the initial solvent and crosslinking agent concentrations, the polymerization conversion, and the interaction parameters of the components. In polymer samples No. 12–17, the first three factors remain constant; however, the fourth factor, the solvent–polymer interaction parameter, is variable. This parameter is affected by the changes in the thermodynamic quality of the porogenic mixture as the ratio between the contents of cyclohexanol (good solvent) and 1-octanol (poor solvent) varies.[25] If the thermodynamic quality of the mixture is good, and the degree of crosslinking is low, then phase separation does not occur (sample No. 17). However, phase separation already occurs in sample No. 16, prepared in the presence of cyclohexanol and 1-octanol in a volume ratio of 4 : 1, and small microspheres are formed. If the thermodynamic quality of the porogenic mixture deteriorates even more, phase separation occurs at much lower polymerization conversion than in the previous case and microspheres (or their aggregates), preferentially solvated by the monomer, then grow to larger dimensions (sample No. 12).

Simultaneously, the effect of water, a poor solvent for polyHEMA, on the interaction parameter cannot be excluded. However, the concentration of water dissolved in the organic phase is low and was found by titration to be between 2% (sample No. 12) and 2.8% by weight (sample No. 17). It can be assumed that this amount cannot substantially influence the thermodynamic quality of the porogenic mixture.

The shape of the droplets in the radical suspension copolymerization of HEMA with EDMA in the aqueous disperse phase is certainly affected by the solubilities of HEMA, the porogens, and cyclohexanol in water. The concentrations of these substances in the aqueous phase were determined by gas chromatography of model mixtures, containing all the components in the same ratio as in the polymerization mixture. Table I shows the percentage contents of HEMA, cyclohexanol, and porogens that passed from the organic phase to the aqueous phase, related to the overall contents of these individual substances in the polymerization mixture. If HEMA alone is added to water, 81 wt % of it is dissolved.

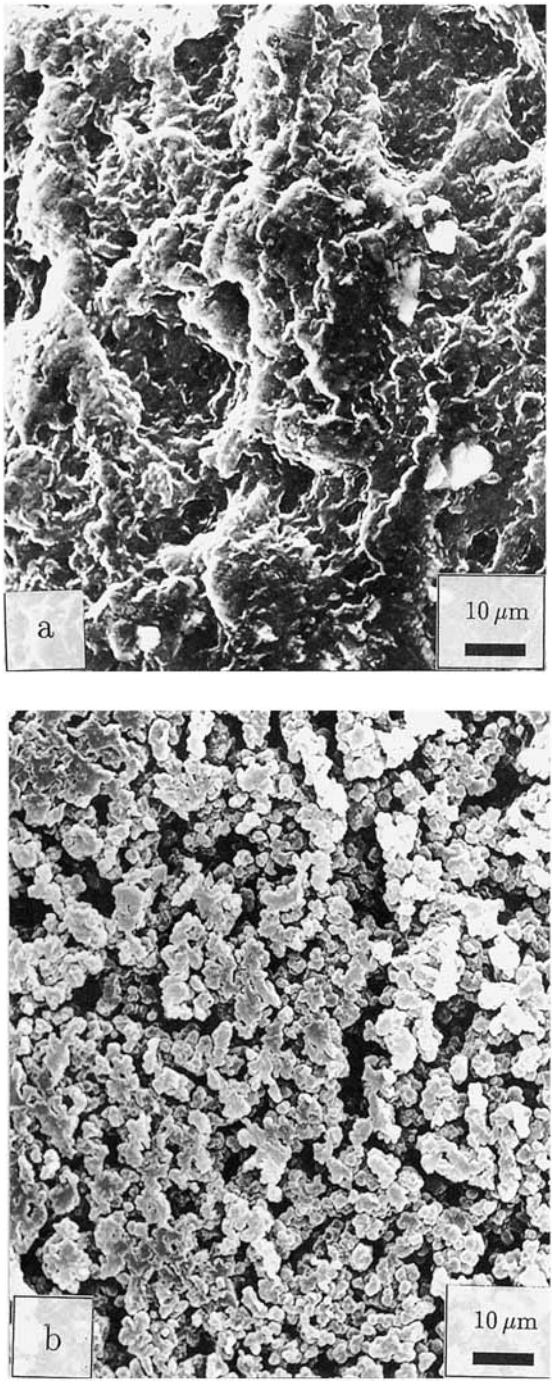

Figure 5 SEM of sample No. 14; (a) surface and (b) interior.

However, the aqueous phase contains far less of the dissolved monomer if porogen, or a mixture of porogens, is added to HEMA. Then only 34–48 wt % HEMA is dissolved (Table I). As the fraction values in Table I may be accompanied by an experimental error of up to 10%, it is apparent that various com-

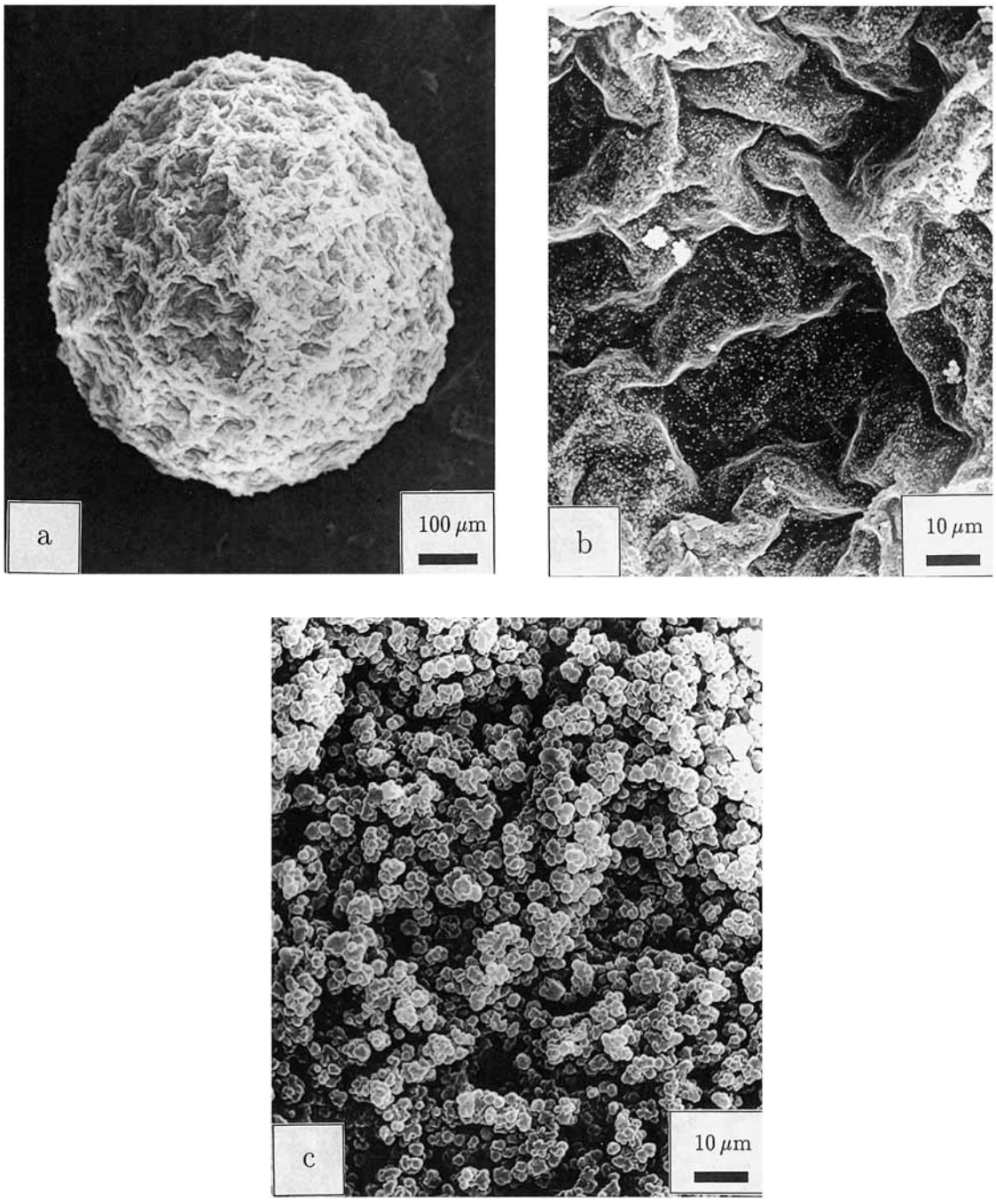

Figure 6 SEM of sample No. 15; (a) surface, (b) surface, and (c) interior.

binations of good and poor solvents do not greatly affect the solubility of HEMA in the aqueous phase.

It should be noted in this connection that, while the concentration of cyclohexanol in water, which is not greatly affected by the addition of porogen, is relatively high and usually equals 15–20 wt %, 1-dodecanol is practically insoluble in water. The results indicate that an optimal concentration of the porogen dissolved in water can be important if spherical particles are to be formed. This concentration would then permit an optimal rate of transfer of the monomer from the aqueous disperse phase to the polymerizing monomeric droplets. If the organic phase contains both cyclohexanol and higher alco-

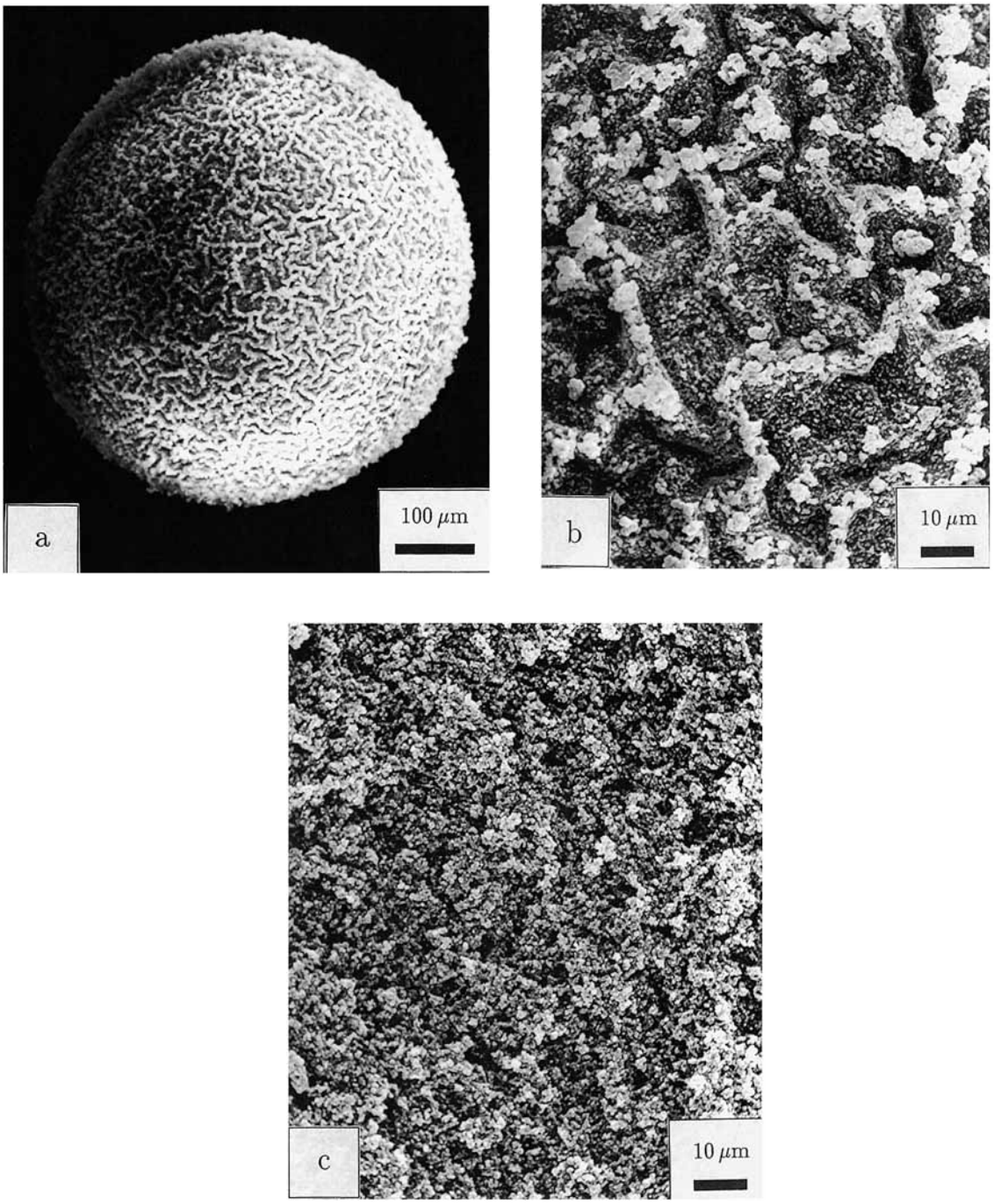

Figure 7 SEM of sample No. 16; (a) surface, (b) surface, and (c) interior.

hols (1-octanol, 1-dodecanol) or butyl acetate, with limited solubility in water, then predominantly regular spherical particles are formed. In contrast, porogens, such as 1-butanol, benzyl alcohol, and cyclohexanone, which are readily soluble in water, when combined with cyclohexanol lead to the formation of the agglomerated polymerization product. The formation of aggregates may be connected with a change in the mechanism of the polymerization as a consequence of increased solubility of the initiator in the aqueous phase if the porogen concentration in this phase is high. The participation of solution precipitation copolymerization in this phase could then increase. In addition, in the presence of

benzyl alcohol and cyclohexanone in the aqueous phase, the transfer of polymer radicals also cannot be excluded and could affect the growth reaction.

CONCLUSIONS

Free radical suspension polymerization in aqueous dispersion can be employed to prepare porous, relatively low, crosslinked polyHEMA particles of spherical shape. The process uses a combination of porogen with low solubility in water (poor solvent for polyHEMA) and cyclohexanol (good solvent) to prevent the dissolution of the monomer and the initiator in water, thus hindering the occurrence of solution precipitation copolymerization. Of the whole range of porogens added to cyclohexanol in the organic phase, 1-octanol was found to be the most useful in a volume ratio of 2 : 3. The polyHEMA particles formed using this mixture have a regular spherical shape, low tendency to agglomeration, size of the order of hundreds of μm, and high porosity. Their properties are better than those of particles synthesized in the presence of the, thus far, commonly used mixture of cyclohexanol and 1-dodecanol. The heterogeneous porous structure of the beads could be advantageous in applications, such as arterial embolization, immobilization of cells and enzymes, and controlled release of pharmaceuticals. They may also enhance the accessibility of the hydroxy groups of polyHEMA beads to reagents in chemical modifications.

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