Hydrophilic sponges based on 2-hydroxyethyl methacrylate

Part VII: *Modulation of sponge characteristics by changes in reactivity and hydrophilicity of crosslinking agents*

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Despite previous unsuccessful attempts to use hydrated poly(2-hydroxyethyl methacrylate) sponges as implantable biomaterials, recently these materials became important as peripheral components in an artificial cornea of the core-and-skirt design. The low mechanical strength of sponges prompted this study on possible improvement of tensile properties by the use of a variety of crosslinking agents. Three vinylic (dimethacrylates) and two allylic compounds were used at different concentrations (0.1 to 2% (mol)) as crosslinking agents in the production of sponges. Their influence on the mechanical properties, porous morphology and swelling behavior of resulting sponges was evaluated. The onset of phase separation during polymerization was also measured by visible spectrophotometry. The results suggested an inherent heterogeneity of sponges, i.e. pores of non-uniform size and structural inhomogeneities. While the effects of changes in the nature and concentration of crosslinking agents on the equilibrium water content of sponges were ambiguous, some of the mechanical properties, such as toughness and elasticity, were improved by crosslinking with allylic agents. Scanning electron microscopic examination suggested that the mechanical effect is related to the variation of size of the polymer particles constituting the sponge structure, which was proved to be dependent upon the onset of phase separation during polymerization.

1. Introduction

Homogeneous, transparent poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogels have been extensively used as biomaterials in a variety of applications [1–4]. First produced at the same point in history [5], heterogeneous, opaque PHEMA hydrogel sponges, with a macroporous structure, raised less interest in the biomedical field. In spite of a relatively large number of experimental studies in animal models [6–21], their applications in humans have been limited until recently to the reconstructive surgery of breasts [11, 22, 23] and nasal cartilages [24], both now abandoned.

PHEMA sponges play an important role in an artificial cornea (keratoprosthesis) which was developed in our laboratories over recent years [25–32]. This device (dubbed ''Chirila keratoprosthesis'') consists of a porous annular skirt made from a PHEMA sponge, and a circular core of transparent PHEMA hydrogel, joined together via a sequential interpenetrating network (IPN). Our experiments *in vitro* and *in vivo* indicated that the sponges of appropriate pore size and morphology promoted the incorporation of host tissue into the prosthetic skirt through cellular invasion and growth [33–36]. This is a key feature of the keratoprosthesis, intended to prevent the expulsion of the prosthesis, which is the most frequent and devastating post-surgical complication. Being produced by polymerization of HEMA in a large excess of water, and consequently being the result of phase separation during polymerization [37], the PHEMA sponges display inherently poor mechanical strength. This may cause problems, as the threading of sutures through the prosthetic skirt at the completion of surgery can tear the sponge. To this end, continuous efforts have been made to improve the mechanical strength of PHEMA sponges, including the copolymerization of HEMA with 4-*t*-butyl-2-hydroxy-

cyclohexyl methacrylate (TBCM) [38] and the use of divinyl glycol (DVG) as a hydrophilic crosslinking agent [39], instead of the commonly used hydrophobic agent, ethylene dimethacrylate (EDMA). While the former attempt (TBCM) failed to provide stronger materials, the latter (DVG) resulted in sponges with improved elasticity. However, the DVG-crosslinked PHEMA sponges displayed an erratic swelling behavior and macroscopic inhomogeneities [40], which were attributed to a delayed gelation onset caused by the lower reactivity of DVG (an allylic monomer), as compared to EDMA (a vinylic monomer). In preventing these undersirable effects of DVG upon the porous structure, a more active initiating system, ammonium persulfate (APS) and N,N,N′,N′-tetramethylethylene diamine (TEMED), rather than APS and sodium metabisulfite (SMBS), proved more successful [39, 41].

Our previous studies [37, 40, 42] indicated unequivocally that the properties of PHEMA sponges, including their pore characteristics (size, morphology, contiguity), can be controlled by varying the amount of water in the initial monomer mixture. However, the modulation of mechanical properties appears to be a more complicated matter, as the attempts to upgrade these properties could be associated with the formation of an inappropriate porous structure [40]. It is worth mentioning that, in order to be useful as keratoprosthetic skirts, the PHEMA sponges must have pores sufficiently large (at least 10 to 20 μm) to accommodate the invading cells, and the pores should be interconnected throughout any whole piece of sponge regardless of its size [33–35, 37].

In this work, a series of PHEMA sponges were produced using different crosslinking agents which included 1,4-butanediol dimethacrylate (BDMA), 2,3-dihydroxybutanediol 1,4-dimethacrylate (BHDMA), 1,5-hexadiene (HD), and 1,5-hexadiene-3,4-diol (known better as divinyl glycol, DVG). Ethylene dimethacrylate (EDMA) has been widely studied as a crosslinking agent for PHEMA and was used here as a reference. Details on the structure of the crosslinking agents used in this study are given in Table I. The dimethacrylates BDMA, BHDMA and EDMA are vinylic, while HD and DVG are allylic difunctional compounds. The presence of hydroxyl groups in BHDMA and DVG imparts hydrophilicity. The aim of this study is to evaluate the relative contributions of the reactivity and hydrophilicity of the crosslinking agents to changes in the tensile properties, pore morphology and swelling behavior of PHEMA sponges.

2. Materials and methods

2.1. Materials

2-Hydroxyethyl methacrylate (HEMA) was supplied as Rocryl 400 by Rohm & Haas and was distilled prior to use (b.p. 68–70 °C/2 mm Hg). APS (BDH) and TEMED (Aldrich) were used together as initiators. EDMA and BDMA were supplied by Tokyo Kasei Kogyo, and HD and DVG by Aldrich. BHDMA was synthesized using a two–step method developed by us [43].

2.2. Polymerization

Five series of PHEMA sponges, corresponding to five crosslinking agents, were prepared following procedures described previously in detail [25, 26, 33, 37, 42]. In brief, to a solution of 20% (w/w) HEMA in water, a crosslinking agent, TEMED and APS were added, and the polymerization was carried out firstly at room temperature for 2 h and then completed at 50 °C for 20 h, either in polypropylene cylindrical molds (for microscopic examination), or between Teflon sheets separated by a silicon rubber gasket (for tensile measurements). Five different molar concentrations of each crosslinking agent were used in each series of sponges: 0.1; 0.15; 0.45; 1; and 2% (mol).

2.3. Spectrometry

The phase separation occurring during polymerization was monitored by the turbidity detected in a spectrophotomer (UV/VIS 918, GBC, USA) by recording time scans at a fixed wavelength (550 nm) and temperature (22 °C). Water was used as a reference. The scanning continued until the measured absorption became constant.

2.4. Equilibrium water content

Following polymerization, the sponge specimens were kept in deionized water for 2 weeks, with daily water exchanges. Prior to weighing, the hydrated samples were gently blotted with tissue paper. The specimens were then dried in an oven at 50 °C for 48 h. The equilibrium water content (EWC), as weight percentage, was calculated using Equation 1, where w_w and w_d are respectively the weight of a fully hydrated specimen and of the same specimen after drying.

TABLE I Crosslinking agents

	Vinylic	Allylic
Hydrophobic	$CH_2=C(CH_3)COOCH_2CH_2OOC(CH_3)C=CH_2$ *EDMA* $CH_2=C(CH_3)COO(CH_2)_4OOC(CH_3)C=CH_2$ *BDMA*	$CH_2=CH-CH_2CH_2-CH=CH_2$ *HD*
Hydrophilic	$CH_2=C(CH_3)COOCH_2CHCHCH_2OOC(CH_3)C=CH_2$ OHOH *BHDMA*	$CH_2=CH-CHCH-CH=CH_2$ OHOH *DVG*

$$EWC(\%) = 100(w_w - w_d)/w_w \quad (1)$$

The results are the average values of four measurements for each sponge.

2.5. Tensile properties

The sponge sheets were stamped with a cutting device into specimens of a dumb-bell shape according to ASTM D2116, which were then stored in distilled water. The tensile measurements were performed using a SINTECH® 200/M Material Testing Workstation (MTS Systems Corporation, USA) with a low capacity load cell (10 N). The cross-head speed was 0.5 mm/s and the working length of the central part was 13 mm. The energy to break, elongation at break, peak stress, and modulus were all measured for each specimen and given as averages of six measurements.

2.6. Scanning electron microscopy

Environmental scanning electron microscopy (ESEM) allows the examination of hydrated samples due to the fact that water vapors can be introduced into the sample chamber at a partial pressure large enough to avoid dehydration of samples, in conjunction with a short working distance which prevents spreading of the electron beam. We have pioneered the use of the ESEM for the study of morphology of the hydrophilic PHEMA sponges [33, 37]. The sponges can be observed in their native state, without prior treatments as required by conventional SEM (e.g. freeze-drying, critical point drying) which may cause the collapse of the porous structure of the samples.

Sponge buttons, crosslinked with different agents at a concentration of 1% (mol), were cut into square pieces (4×7 mm) and examined in an environmental scanning electron microscope (model E-3, Electroscan Corp., USA).

A chamber pressure between 400 and 500 Pa and a Peltier effect cooling stage operating between 5 °C and 7 °C were used in order to ensure that evaporation of water from the sponge is minimal. Removal of water from the interconnecting pores was achieved by gently blotting the sponge pieces with a tissue, followed by immersion in liquid nitrogen, a process that further reduces the evaporation of water from the sponge. The sample chamber was periodically flushed with water vapors to maintain a satisfactory partial pressure. Under these conditions, no dehydration of the samples occurred.

A working distance between 3 and 5 mm and an aperture of 50 μm were employed. An accelerating voltage of 15 kV was applied in order to minimize both heating effects and sample damage, which were observed at 30 kV and magnifications higher than 2000-fold.

3. Results and discussion

3.1. Phase separation

Absorption of visible radiation at 550 nm in each monomer mixture increased dramatically after a certain time from the beginning of polymerization, performed at 22 °C. This increase is caused by the onset of phase separation, as the mixture becomes turbid at that point in time. The sharp rise in absorption is followed, in a relatively short time, by a slower progress to a plateau which is established after approximately 40 to 45 min, when the material is beyond the gel point.

The time at which the absorption started to increase rapidly was considered the time of phase separation onset [44]. These values are given in Table II. In the sponges crosslinked with vinylic difunctional agents (EDMA, BDMA and BHDMA), the higher the concentration of agents, the faster phase separation occurs. At the same concentration, the hydrophobic BDMA promotes a faster phase separation than its hydrophilic homologue (BHDMA). This can be explained by the better miscibility of BHDMA with the aqueous polymerization medium, leading to a delayed phase separation as compared to the effect of the hydrophobic agents. However, at higher concentrations, all vinylic crosslinking agents reach a similar time for the onset of phase separation, likely due to the loss of efficiency. The low efficiency of crosslinking agents in dilute HEMA/water mixtures has been reported by other workers [45–47], and it may be caused by the predominance of the cyclization reactions in competition with the crosslinking reaction and by large differences between the free radical reactivity ratios of HEMA and crosslinking agents. This effect has been observed in our previous work on PHEMA sponges [37, 42].

The hydrophobic allylic agent HD induced, at low concentrations, a delay in phase separation as compared to the vinylic agents. The onset time for phase separation reaches a constant value at relatively low concentrations, which is significantly longer than that induced by the vinylic agents. This is an indication of the low crosslinking efficiency of the allylic agent, which may also be correlated to the lower free radical reactivity of allylic monomers as compared to the vinylic ones. The hydrophilic allylic agent DVG induced a rather erratic

TABLE II Onset of phase separation at 22 °C in the formation of PHEMA sponges as a function of nature and concentration of crosslinking agents

Crosslinking agent Concentration (% (mol))	EDMA	BDMA	BHDMA Onset times (min)	HD	DVG
0.10	4.7	3.6	4.3	4.9	5.0
0.15	3.7	2.6	4.2	4.8	4.2
0.45	2.1	2.1	3.8	3.8	4.1
1.0	1.8	1.6	1.8	3.8	7.1
2.0	1.6	1.4	1.4	3.8	6.9

range of phase separation onset times, generally longer than those induced by the previous crosslinking agents. This effect may be related to both its higher miscibility with the polymerization medium and its lower crosslinking efficiency and free radical reactivity. At the highest concentration used in this study, DVG induced an onset time almost 2 times longer than its hydrophobic homologue (HD) and about 5 times longer than that induced by the vinylic crosslinking agents. Our previous work [39] on the swelling behavior of DVG-crosslinked PHEMA sponges has shown an increased sol fraction at concentrations of DVG higher than 1% (mol), indicating a reduction in crosslinking efficiency and delayed phase separation.

3.2. Swelling behavior

The equilibrium water contents of the sponges are given in Table III. As shown in our previous studies [39, 40, 42], the water uptake in PHEMA sponges displays an erratic dependence upon the quantitative variation of crosslinking agents, and the present results confirm this behavior. As the syneretic sponges are the result of a fast phase separation followed by network gelation, and the process is sensitive to variations in the amount and reactivity of any component in the polymerization mixture, the anomalous hydration behavior can be explained by the existence of pores of a non-uniform size, and of macroscopic inhomogeneities induced by the differences in the free radical reactivity ratios of HEMA and crosslinking agents.

3.3. Tensile properties

The results of tensile measurements are shown in Table IV. Some anomalous values and a relatively large scatter of results for the same concentration of a crosslinking agent reflect the intrinsic inhomogeneity of the samples and non-uniformity of their internal morphology. Their low strength, and problems associated with the clamping of these loose materials in the grips of the instrument can also contribute to the quality of results. However, the occasional high values may have a natural cause specific to a particular crosslinking agent at a critical concentration. To check this hypothesis, more measurements over

TABLE III Equilibrium water content of PHEMA sponges crosslinked with various crosslinking agents at different concentrations

Crosslinking agent	EDMA	BDMA	BHDMA	HD	DVG
Concentration (%(mol))	Equlibrium water content (%(wt))				
0.10	74.05 ± 0.24	69.89 ± 0.41	69.94 ± 0.56	71.72 ± 0.44	70.08 ± 0.73
0.15	74.46 ± 0.37	74.95 ± 0.45	73.44 ± 0.83	74.83 ± 0.68	73.95 ± 0.86
0.45	73.46 ± 1.19	68.95 ± 0.68	73.31 ± 0.31	72.26 ± 0.92	73.25 ± 0.83
1.0	77.2 ± 0.89	72.88 ± 0.82	75.06 ± 0.97	77.44 ± 1.77	75.27 ± 0.21
2.0	76.6 ± 0.34	74.75 ± 0.73	74.1 ± 1.58	75.12 ± 1.53	72.13 ± 0.30

TABLE IV Tensile properties of sponges

Crosslinking agent	Concentration (%(mol))	Energy to break (mJ)	Elongation at break[b] (%)	Peak stress[c] (kPa)	Modulus[d] (kPa)
EDMA	0.1	10.37	798	15.6	2.72
	0.15	5.55	644	12.3	4.52
	0.45	4.12	348	14.1	6.03
	1	4.54	272	18.8	6.94
	2	3.01	176	19.5	11.31
BDMA	0.1	5.52	696	11.1	3.78
	0.15	4.78	696	11.5	4.16
	0.45	4.26	316	14.8	5.58
	1	3.44	194	18.0	9.34
	2	3.05	185	14.1	8.11
BHDMA	0.1	7.12	680	14.9	4.34
	0.15	13.31	501	27.7	5.48
	0.45	5.29	450	12.7	4.23
	1	3.99	349	14.5	5.16
	2	3.60	159	22.4	14.21
HD	0.1	10.61	813	18.1	5.71
	0.15	14.60	738	25.8	4.79
	0.45	9.37	616	21.7	4.95
	1	8.31	754	12.9	4.40
	2	6.05	738	12.6	4.27
DVG	0.1	10.50	806	18.3	3.19
	0.15	8.58	853	15.4	4.56
	0.45	13.77	723	23.3	4.82
	1	9.69	797	19.1	6.10
	2	9.01	902	15.2	4.87

Standard deviations (±) were 0.5 to 1.98[a], 13 to 132[b], 1.2 to 3.7[c], and 0.37 to 2.53[d], respectively.

much narrower concentration intervals should be performed, but this was beyond the purpose of our study.

Although the proportional limit, the elastic limit and the break point were difficult to distinguish in many samples, this should not be regarded as a proof for a Hookean behavior up to the failure. For small strains and for short periods of time, the systems are probably linear, but longer duration will induce creep (at constant stress) or stress relaxation (at constant strain), resulting in irrecoverable deformation and anomalous values of some measurements. The peak stress values (Table IV), representing the ultimate strength, were largely insensitive to changes in the nature and concentration of the crosslinking agents, all being very low and in the same range (10 to 30 kPa) for all samples. However, one can say that the DVG-crosslinked sponges are slightly stronger. While in each of EDMA and BDMA series there is a vague indication of an increase of strength with the concentration of crosslinking agent, in the case of BHDMA and of allylic crosslinking agents the results are erratic. This may reflect the less reactive nature of these crosslinking agents, as their effective concentration, i.e. the actual number of crosslink points, can be much lower than the nominal concentration, i.e. the amount of added agent.

The results measured for energy to break, representing the toughness of materials, were more conclusive, especially when analyzed in correlation with the values for elongation at break (Table IV). In each series of vinylic crosslinking agents, there is a clear trend of decrease of toughness as the concentration of the agent increases, which correlates well with the marked decrease of elongation in the same series. The higher the crosslink density, the lower the elasticity, and the fracture of materials occurs earlier, therefore requiring less work per unit volume. In the two series of allylic crosslinking agents, both energy to break and elongation are relatively constant and much higher than vinyl-crosslinked sponges. Again, this invariance can be attributed to the narrower range of effective concentrations of these crosslinking agents. The very high elongation can also be explained by the lower reactivity and crosslinking efficiency of allylic agents. First, less crosslink points leads to higher elasticity. Second, as shown in the next section, the spheres (droplets) constituting the porous structure of sponges were larger when allylic agents were used for crosslinking, due to a delayed phase separation (Table II). Larger polymer spheres means more extended connectivity between them, therefore higher elasticity.

In the series of sponges crosslinked with vinylic compounds, the modulus of elasticity (Table IV), which is a measure for stiffness, showed an expected [39] increase with the concentration of crosslinking agents. The moduli of sponges crosslinked with allylic compounds were, however, relatively constant over the concentration range investigated and only slightly lower.

3.4. Porous structure

In order to investigate the correlation between the size of spheroidal droplets of polymer present in the sponges and the nature of crosslinking agents, selected samples were examined by ESEM. Fig. 1 shows sponge specimens crosslinked with BDMA (a), BHDMA (b), HD (c) and DVG (d) at a concentration of 1% (mol). Rather than investigating the arbitrary nature of pore size, observation of the sponge morphology based on the individual size of polymer droplets is more appropriate. By correlating the droplet size with the phase separation onset of the four crosslinking agents, an insight of the effect of hydrophilic nature and reactivity of crosslinking agents can be achieved. As shown in Fig. 1, the droplet size follows the order DVG > HD $\sim$ BHDMA > BDMA. Table II shows that the time taken for the onset of phase separation follows the same order at the same concentration of crosslinking agents. This indicates that the longer it takes for phase separation to occur, the larger the size of resulting polymer droplets.

The hydrophilic crosslinking agents BHDMA and DVG, which caused a more delayed onset of phase separation than their hydrophobic homologues BDMA and HD, led to larger spheres, as they allowed longer time for the growth of polymer droplets. The delay in phase separation of sponges containing hydrophilic crosslinking agents may be attributed to increased solubility of the propagating polymer chains, i.e. a larger critical molecular weight (MW_{cr}) for phase separation.

The droplet size of allylic–crosslinked sponges is also significantly larger than that of sponges crosslinked with their methacrylate counterparts. This difference is due to delayed phase separation caused by lower participation of allylic crosslinking agents in the propagating soluble polymer chain. The contribution of crosslinking agents in propagating polymer chains is important, as the number of polymerization sites on the chain is directly affected by their involvement. For example, the incorporation of the first crosslinking point will double the number of propagating sites from one to two, and the involvement of further crosslinking agents will increase the propagation even further. The sooner a crosslinking agent participates in the propagating chain, the faster such a chain will grow. In the case of the reactive methacrylates, a polymer chain will reach the MW_{cr} for phase separation sooner than in the case of allylic compounds. As a result, the methacrylate crosslinking agents (BDMA, BHDMA) induced smaller polymer droplets as compared to the allylic crosslinking agents (HD, DVG).

The effect of droplet size on the mechanical strength, however, has not been fully elucidated, and requires further investigation to determine the optimum droplet size and distribution, before correlating sponge morphology to mechanical strength.

4. Conclusions

While the ultimate strength of hydrated PHEMA sponges for biomedical use is almost insensitive to changes in the reactivity and/or concentration of the crosslinking agents employed in this study, the sponges crosslinked with allylic compounds (HD, DVG) are tougher and more elastic than those crosslinked with vinylic compounds (EDMA, BDMA, BHDMA). The influence of crosslinking agents on mechanical characteristics and porous morphology appears intrinsically related to the mechanism of sponge formation, i.e. phase

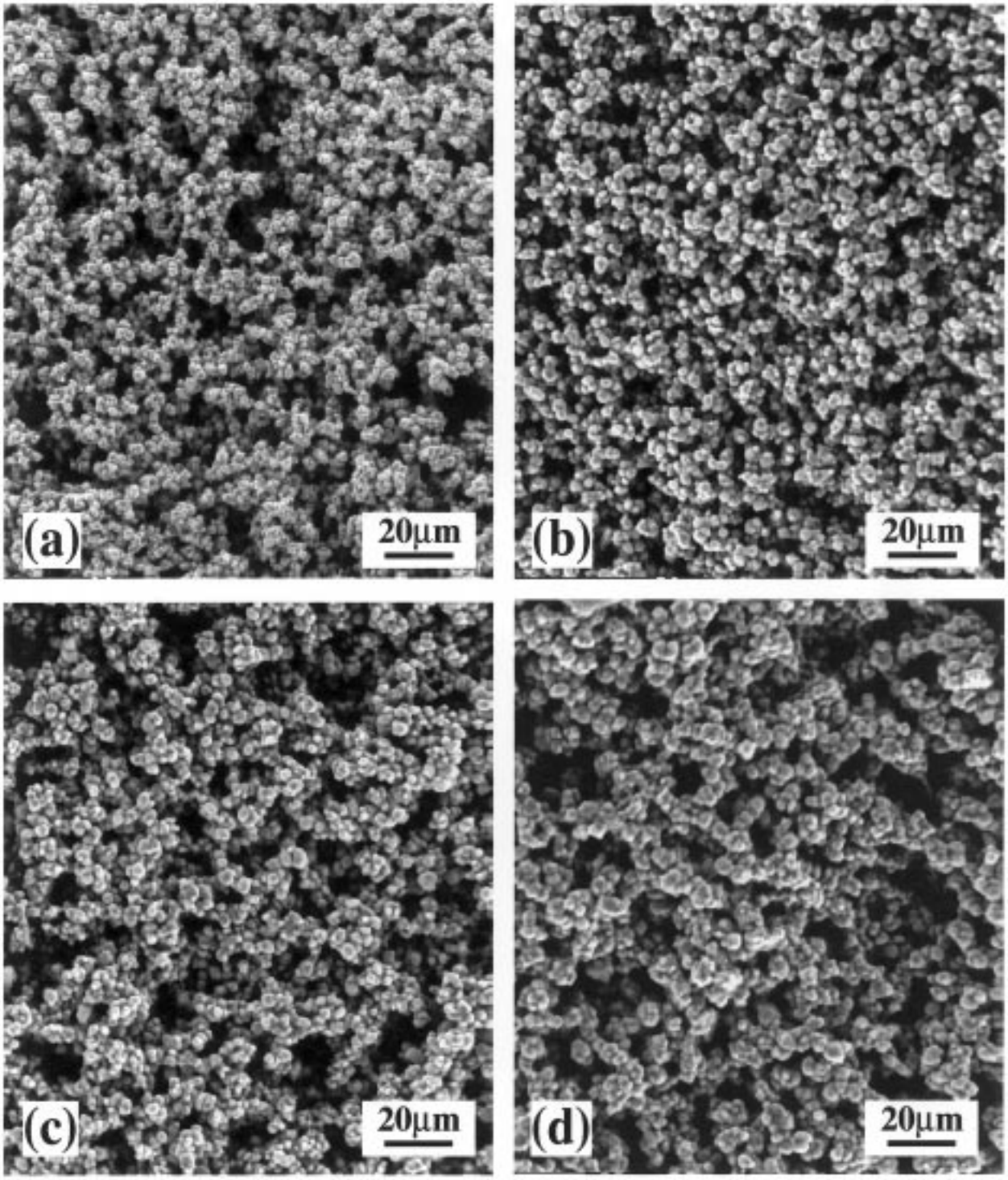

Figure 1 ESEM photographs of PHEMA sponges crosslinked with (a) BDMA, (b) BHDMA, (c) HD, (d) DVG. Concentration: 1% (mol).

separation and subsequent network gelation, which dictates ultimately the size of the polymer spheres constituting the sponge. However, the use of different crosslinking agents as a method of modulating the sponge characteristics is limited in its scope: these materials are so weak that it is unlikely that any crosslinking agent can eventually induce a significant enhancement of their strength.

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