Microstructure of heterogeneous and homogeneous poly(2-hydroxyethyl methacrylate) hydrogels formed with and without pressurization

by

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INTRODUCTION

Hydrogels have been used for a variety of medical applications since 1960 (Wichterle and Lim, 1960). The wide range of applications is attributed both to their satisfactory performance when implanted in vivo and to the ability to fabricate the gel in various geometrical forms (Ratner and Hoffman, 1976).

The formulation used for polymerizing hydroxyethyl methacrylate (HEMA) in water to make poly(2-hydroxyethyl methacrylate) (P-HEMA) is very important in determining the structure of the hydrogel. If the monomer is polymerized in the presence of a good solvent such as ethylene glycol (EG) or water (content less than 40%), the resulting hydrogel is optically clear or transparent. This type of hydrogel is referred to as homogeneous or microporous and would be suitable for contact lenses or drug release systems. If the monomer is polymerized in the presence of a significant amount of nonsolvent, such as water (usually more than 40%), the resulting hydrogel is translucent or opaque because the polymer precipitates from the solution (Refojo and Yasuda, 1965). This type of hydrogel is referred to as heterogeneous

or macroporous and has true voids between the polymer units. This permits cellular ingrowth and this structure has been applied in wound dressing applications, for example.

Several studies have been performed to determine the microstructure of the hydrogel. Barvic et al. (1967) worked on the applicability of polymer-like sponges for biological use. They reported a mean size of polymer droplets of 2 to 5 micrometers (μm) which join together and form the network of the polymer channels of 40 to 80 μm in diameter. Sprincl et al. (1971, 1973) worked on controlling microstructure to develop a range of pore sizes leading to implant applications on a size scale of a few to a few tens of micrometers. Greer et al. (1978, 1979) developed the use of hydrogel composite materials and hydrogel coatings for prosthetic applications. Ronel et al. (1983) utilized macroporous hydrogels in an artificial pancreas with a pore size range of 1 to 18 μm. Grant (1990) studied the microstructure of P-HEMA polymerized by using different formulations of HEMA, water, EG, ethylene glycol dimethacrylate (EGDMA), and tetraethylene glycol dimethacrylate (TEGDMA) to characterize the organization of polymer subunits on a micrometer size scale. Migliaresi et al. (1981) provided physical characterization of microporous P-HEMA hydrogels (pores approximately 0.4 to 1.4 μm in size)

prepared using mixtures with different contents of HEMA, glycerol, poly(vinyl pyrrolidone) (PVP), and diacetin. Peppas et al. (1985) studied the outer and inner surfaces of homogeneous P-HEMA hydrogel films (40% water content). For formulations using HEMA as the monomer and water as the solvent, all of the above investigators found that the porosity in the resulting hydrogel increases with increasing water content, and that this was independent of the crosslinking agent used.

The difficulties of fabricating small prosthetic components from bulk hydrogel for use with or without mechanical support led to development of the pressurized polymerization technique. Pinchuk and Eckstein (1981) reported polymerization of HEMA under pressures ranging from 0 kPa to 700 kPa gage pressure. Their work revealed decreased bubble entrapment in the polymer lattice with increased pressure compared with non-pressurized polymerization samples.

In the present work, samples of homogeneous and heterogeneous gels were obtained by polymerizing HEMA monomer in the presence of water with and without pressure in order to investigate how this influences the microstructure of the hydrogel. The study includes specification of how the presence of pores is shifted to higher water contents due to

the pressurization compared with absence of pressurization. Optical properties, consistency of the hydrogel, and changes in porosity were compared for pressurized and non-pressurized polymerization examples.

LITERATURE REVIEW

P-HEMA Hydrogels

Background

The monomer, 2-hydroxyethyl methacrylate (HEMA), can be polymerized in the presence of a crosslinking agent in aqueous solvent, forming a soft rubbery polymer. This soft and rubbery consistency of P-HEMA hydrogel reduces physical irritation at polymer-tissue interfaces contributing in that way to its biocompatibility. Three physical properties of P-HEMA make it resemble soft living tissue: high water content, a soft and rubbery network, and low interfacial tension with other molecules. The P-HEMA structure permits a high water content uptake and is permeable to small molecules, thus allowing most solvents, initiators, and any other unwanted molecules to be expelled from the hydrogel network before implantation in a living system.

Polymerization kinetics

A three-dimensional polymeric network may be prepared by

1. bulk co-polymerization of the monomer with crosslinking agent;
2. crosslinking the polymer in solution; and

3. simultaneous copolymerization and crosslinking of a monomer with a crosslinking agent in solution.

The last method is preferable, since the polymerization can be achieved very quickly at near room temperature conditions, and the formation of gels can be readily obtained in a given shape since the starting materials are in liquid form. Volume contraction during polymerization manifests itself mainly in the first stage of polymerization when the main matrix is formed. As the network becomes more rigid, polymerization takes place within the primary matrix with practically no contraction (Wichterle and Chromecek, 1969).

The choice and concentration of the solvent during the polymerization determine the homogeneous or heterogeneous structure of the hydrogel produced. If water is used as the solvent, the concentration must be below a certain critical level to assure the production of an optically transparent, homogeneous hydrogel. When water exceeds this limit, opaque, heterogeneous, macroporous hydrogels are obtained.

The mechanism and reaction kinetics of the polymerization of HEMA have been established by Kopecek and Lim (1971). In homogeneous polymerization in an aqueous medium, the reaction order with respect to the concentration of the initiator is normal, i.e, 0.5. The reaction order with respect to the

monomer for a polymerization carried out in water is also 0.5 in the homogeneous region.

The above result can be explained in terms of the dependence of the propagation and termination rate on the thermodynamic properties of the medium. Dependence of reaction rate is given as the square root of the initiator concentration. The effect of the medium is negligible on initiation in homogeneous polymerization.

The reaction rate can be written as follows:

$$Rp = K[M]^{0.5}\ [I]^{0.5}$$

$$Kp = Kp'[M]^{x}$$

$$Kt = Kt'[M]^{y}$$

where Rp : rate of reaction

K : reaction constant

Kp : propagation rate constant

Kp': propagation constant (affected by physical properties)

Kt : termination rate constant

Kt' : termination rate constant (affected by physical properties)

[M] : monomer concentration

[I] : initiator concentration

and the rate of polymerization is therefore :

$$Rp = \frac{Ki^{0.5}\ Kp\ [I]^{0.5}\ [M]^{1+x-(y/2)}}{(Kt)^{0.5}}$$

where Ki is the initiation constant.

The relationship thus obtained satisfies the experimental data if the parameters x and y obey the equation $y - 2x = 1$. The dependence of the termination is more medium dependent than propagation dependent. A further consequence of this dependence of the termination rate on the concentration of the monomer is the comparatively large decrease in the termination constant with dilution of the mixture, which causes a relatively slight decrease in polymerization rate with decreasing concentration of the monomer (Kopecek and Lim, 1971).

In the heterogeneous region, the formal reaction order with respect to the monomer increases due to a decrease in the rate of termination.

Optical properties

The refractive index of swollen P-HEMA depends on the nature of the swelling agent and on the degree of swelling. To a good approximation it can be considered to be additive with respect to the refractive indexes of the two components

(hydrogel and solvent). When HEMA monomer is polymerized in the presence of a supercritical amount of a poor solvent such as water(60% - 90%), phase separation occurs and the gels become turbid as regions with different refractive indexes are formed (Refojo and Yasuda, 1965). In the course of polymerization, this process is manifested by the turbidity of the originally clear solution. The HEMA separates in the aqueous phase in the form of monomer droplets which join in the course of polymerization and become fixed, forming the spongy network of the heterogeneous hydrogel (Barvic et al., 1967). This phenomenon is called microsyneresis. The resulting polymer is opaque and has a macroporous structure (heterogeneous). When HEMA is polymerized in solution with a redox initiator (such as ammonium persulfate or sodium metabisulfite) in a homogeneous system, the polymerization medium must be a good solvent system for both the monomer and the polymer. A transparent and microporous gel is obtained (Refojo and Yasuda, 1965). The same result can be obtained using small amounts of water (less than 40%) as a solvent.

In 1966, Yasuda and collaborators reported that there is an indication that HEMA hydrogels are transparent with equilibrium water contents less than about 41%, and the hydrogels are opaque when the equilibrium water content is

higher than 54%. Gels that have an equilibrium water content between 41% and 54% are translucent and their turbidity increases with the water content (Figure 1).

In 1990, Grant prepared P-HEMA hydrogel by using different water/HEMA ratios. The samples prepared without any initiator and with ethylene glycol dimethacrylate (as a crosslinking agent) at a concentration between 0.1 and 7.0% resulted in hydrogels that were opaque. The samples prepared with 1 weight percent ammonium persulfate (as initiator) were opaque for formulations containing 90% and 70% water content, translucent for formulations between 60% and 40% water content, and transparent for water contents between 30% to 0%. The samples prepared with initiator and crosslinking agent were opaque for a water content in the range of 90% and 60%, and transparent for water contents of 50% or less. According to these results, and the results of Yasuda et al., 1966, the optical properties depend not only on the water content but also on the initiator and crosslinking concentrations.

Hydrogel-water interaction

The interfacial properties of hydrogels in contact with water are important in biomedical applications of hydrogels, such as blood compatibility, tissue compatibility, and cell

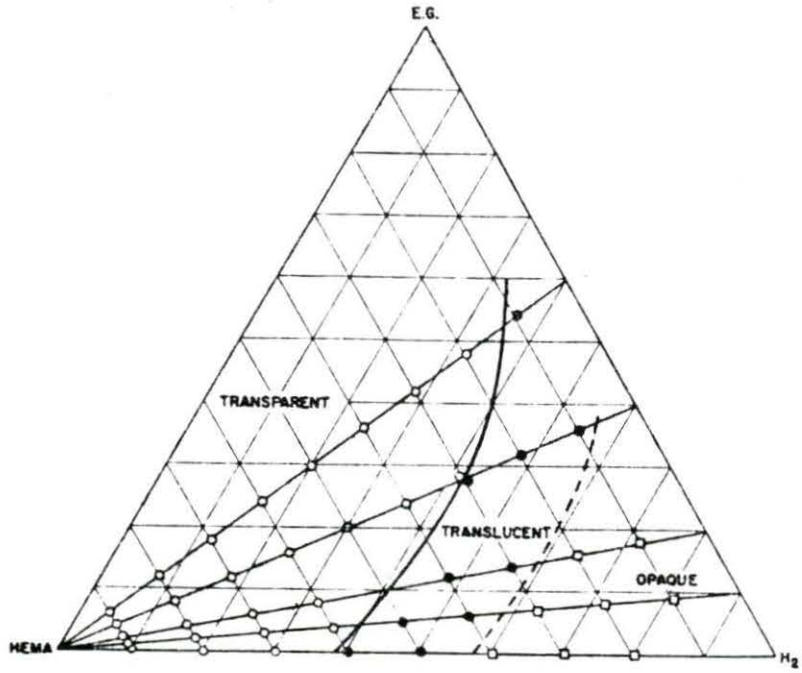


Figure 1. Transparency of HEMA hydrogels in HEMA-water-ethylene glycol system: (○) transparent gels; (●) translucent gels; (□) opaque gels (Yasuda et al., 1966)

adhesion. (Andrade et al., 1976). The nature or organization of water at the molecular level (water structure) is often extremely complex. The gross total water content of swollen hydrogels is most easily measured and reported (Ratner and Hoffman, 1976). Studies to date on the organization of water within hydrogel provide only a preliminary indication of water content. It should be noted that the organization and content of gel water will vary significantly with hydrogel composition in expected directions. Gels with higher water content will have lower fractions of bound and interfacial water (Figure 2). It is postulated that P-HEMA hydrogel has, in addition to its covalently linked network structure, a secondary structure stabilized by hydrophobic bonding. Hydrophobic interaction may induce P-HEMA molecules to assume compact conformations as far as the covalent crosslink will allow. In water, most of the hydrophobic portions of the chains tend to aggregate, avoiding contact with the solvent, while the water will hydrogen-bond the polar groups in the chains which accumulate preferentially on the periphery. Interactions of the hydrophobic portions of the polymer with each other, the so-called hydrophobic bonding, is probably a very important factor in holding together P-HEMA segments in an aqueous environment (Refojo, 1967a).

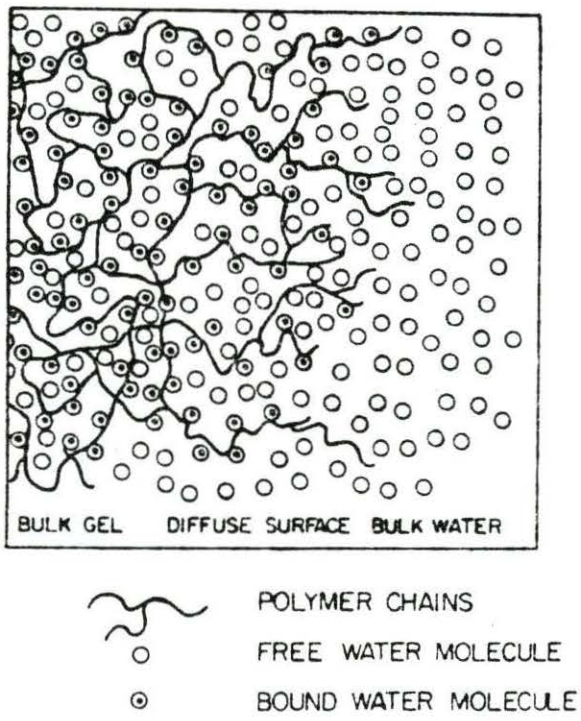


Figure 2. Schematic representation of the hydrogel-water interface. (Structured water is not shown in this diagram. Regions of structured water might be expected in the vicinity of the bound water molecules due to their strong, fixed dipoles) (Ratner, B. D., 1981)

Transport properties

The rate of transport of low molecular weight compounds through hydrogels is an important parameter for many applications. The rate of permeation of water under the influence of the hydrostatic pressure (Refojo, 1967b) was measured for methacrylic hydrogels prepared from various monomers and then compared with other hydrophilic gels. Rates of permeation and diffusion coefficients have been also measured (important for the long term contact lenses) (Kubin and Spacek, 1965) in hydrogels having various degrees of crosslinking with various initial water contents in the polymerization mixture. Investigations were also carried out to determine the diffusion rates for electrolytes such as sodium chloride (Yasuda et al., 1968) and potassium chloride and model organic low molecular weight compounds (Kubin and Spacek, 1965) for hydrogels of various compositions and structures. Oxygen, carbon dioxide, and body fluid components such as Na^+, Cl^-, and K^+ must be able to diffuse through a hydrogel medical device in order for the device to perform safely and effectively. Transport of ions (Hamilton et al., 1988; Murphy et al., 1988), sugars (Kim et al., 1980), water (Yasuda et al., 1972; Wisniewski and Kim, 1980), and steroids (Zentner et al., 1979) has been studied and

associated permeability models have been suggested.

Microstructure of P-HEMA Hydrogels

Numerous studies have been conducted to determine the microstructural features associated with the type of hydrogel (homogeneous and heterogeneous). Barvic et al. (1967) developed three types of sponge-like hydrogel polymers (heterogeneous) for potential biological use. They prepared an initial mixture containing monomer solution of 92.4 weight percent HEMA, 0.28 weight percent of ethylene glycol dimethacrylate (EGDMA), and 7.25 weight percent ethylene glycol (EG). The sponges were prepared using this mixture and increasing amounts of water (70%, 75%, and 80% water). Ammonium persulfate (10 weight percent) was used as initiator. The polymerization reaction was carried out at 65° C. Using optical microscopy, they demonstrated that the pore channel diameter in the polymers increased from 40 to 80 micrometers or more as the water content increased. Results of the specific channel size opening of the three samples reported ranged from 13 to 52 micrometers for the 70% water sample, 29 to 98 micrometers for the 75% water sample, and 144 micrometers and greater for the 80% water sample.

Sprincl et al. (1971), investigating the potential of P-HEMA hydrogels as implants, studied the porosity of heterogeneous gels using heat to polymerize the monomer. The monomer solution contained 2 weight percent of crosslinker ethylene glycol dimethacrylate (EGDMA) and 98 weight percent HEMA. This HEMA - EGDMA solution was mixed with specific amounts of water (50% to 90% by volume). Ammonium persulfate was used as initiator. The initiator content of 1 weight percent was added to the solution containing HEMA, EGDMA, and water. The mixture was purged with nitrogen gas, and then was polymerized at 60° C during a 10 hour period. The investigators, using optical microscopy, reported that the porosity of the hydrogels changed from microporous to macroporous for samples in which the water content was increased in comparison with that of the initial mixture (containing 50% water). Although specific pore sizes were not stated, the higher the water content, the higher the observed porosity. With relatively higher levels of porosity, the penetration of vessels and newly formed fibrous tissue was greater for implantation examples. When the water content was too high (greater than 80%), giant cells were observed. For clinical uses, a water percent more than 80% should not be used for making the hydrogel. Pore sizes must be at least 10

micrometers in diameter in order to allow cellular ingrowth.

Andrade et al. (1976), using radiation polymerization, obtained P-HEMA. Freeze-etched samples of bulk P-HEMA were observed by Scanning Electron Microscopy (SEM). A sample containing 54.4% HEMA, 7.5% EG, and 38.1% water was opaque and had pores less than 5 micrometers in diameter. Polymer samples prepared with 30% HEMA and 70% water, which were freeze fractured in liquid nitrogen, showed pores of about 10 micrometers in diameter. However, they stated that the freeze-fractured SEM sample preparation method tended to introduce microstructural distortions and artifacts.

Lee et al. (1978), working with homogeneous P-HEMA hydrogels, demonstrated that the pore size (of the order of angstroms in diameter) increases with a decrease in crosslinker concentration.

Radiation and chemical polymerization techniques to coat silicone rubber sheets or polyethylene terephtalate (Dacron^{R}) velour substrates with hydrogel have been developed (Greer et al., 1979). Their formulations contained HEMA (10-20%), EGDMA (0-3%), and n-vinyl pyrrolidone (NVP) (0-15%), together with water and methanol (25% methanol and 75% distilled water solvent by volume). The solutions were bubbled with nitrogen gas and were irradiated using Cobalt-60 radiation (a dose of

0.25 Mrad). The macrovoid size found for a bulk hydrogel with a HEMA content of 20% and EGDMA content of 1.5% was 20 to 50 micrometers in diameter. Microvoid sizes were less than 15 micrometers in diameter.

Knoll (1980), using the method of Predecki (1974), prepared samples to coat silicone rubber by chemical polymerization. Silicone rubber substrates were boiled in xylene for 10 minutes to swell the sheets so that the monomer solution could enter the rubber and subsequently be polymerized. The sheets were then placed in a solution consisting of 10-20% HEMA, 0-2% EGDMA, and 5% ethanol by volume, with the balance to 100% being xylene. The polymerization time was 2 hours. The polymerization reaction was carried out in the temperature range of 118-135° C. The investigator reported microvoid sizes between 1-15 μm in diameter, and macrovoid sizes between 15-70 μm in diameter. He demonstrated that increasing the water content in the cosolvent mixture above 43% water resulted in forming a heterogeneous gel.

Migliaresi et al. (1981) prepared samples of P-HEMA by polymerizing HEMA in the presence of different types of solvents in order to obtain a wide range of physical properties. The free radical polymerization was accomplished

at 90° C during 1 hour using 99.4% by weight of HEMA, 0.5% by weight of ethylene glycol dimethacrylate (EGDMA) as crosslinking agent, and 0.1% by weight of benzoyl peroxide (BP) as initiator (for the HEMA-diacetin, poly(vinyl pyrrolidone), or glycerol series). An average pore radius, which was found from permeability measurements, varied from 3.82 to 14.64 angstroms, depending on the solvent used to make a particular polymer membrane sample.

The difficulties of fabricating small prosthesis components out of bulk hydrogel for use with or without mechanical support led to the development of the pressurized polymerization technique. In the presence of a quick reacting initiator system such as ammonium persulfate and sodium metabisulfite at atmospheric pressure, the heat of reaction of the free radical addition polymerization produces elevated temperatures. At these temperatures (70-90° C), the solubility of gases in the solvent is reduced; decreased solubility leads to bubble formation. Taking this into account, Pinchuk and Eckstein (1981) produced homopolymers of P-HEMA with no observable bubbles trapped in the lattice by performing the free radical initiated polymerization reaction under pressure (700 kPa). They used visual observations to evaluate the presence of the bubbles (best possible resolution

of about of 0.2 mm). Extension of this simple pressure method has proved useful for the construction of a variety of devices with different geometries (such as tubes with thin walls or contact lenses).

Ronel et al. (1983) reported the development of special macroporous membranes made of P-HEMA for potential use as an artificial pancreas. Samples were prepared by varying the water to HEMA ratios : 50:50, 55:45, 60:40, 70:30, and 75:25 (by volume). A constant crosslinker concentration of 0.12 percent EGDMA (by volume) and 0.25% of ammonium persulfate and 0.25% sodium metabisulfite (based on monomer weight) as redox initiators were added to each solution. The solution was degassed and polymerized at 10° C during an 18 hour period. The pore size found ranged from 1 to 18 micrometers. The pore size distribution showed no variation with change in water content of the solvent; however, the pore density increased with increasing water content. A water/HEMA ratio of 50:50 resulted in a nonporous membrane. In the 55:45 formulation, pores ranged between 5 and 10 micrometers (100X magnification). Scanning Electron Microscopy (SEM) surface analysis showed that the macroporous structure was nearly eliminated if the EGDMA concentration increased over 0.5% for a sample prepared with a water/HEMA ratio of 70:30 and for

values of EGDMA ranging between 0.02 and 3%. The investigators concluded that pore size and pore density were dependent on the water/HEMA ratio and on the amount of crosslinker.

Peppas et al. (1985) prepared homogeneous thin films by reacting HEMA monomer with EGDMA at concentrations of 0.005, 0.01, 0.0128, 0.025, and 0.05 mole EGDMA/mole HEMA in the presence of 0.5 weight percent benzoyl peroxide as initiator. Water was added to a level of 40% by weight of the initial mixture. This mixture was bubbled with nitrogen gas during a 2 hour period. The reaction took place at 60° C during a 12 hour period. The investigators produced a homogeneous gel type membrane of crosslinked P-HEMA. Also, a mesh size was calculated by applying a theoretical analysis from which the crosslinking density and the molecular weight between crosslinks are obtained. The mesh size reported ranged from 16.2 to 35.6 angstroms. They also reported an increase in the nonporous membrane mesh size as the crosslinker concentration decreased.

Grant (1990) studied the microstructure of P-HEMA by using formulations similar to that of Sprincl et al. (1971, 1973) and of Barvic et al. (1967). She reported that varying the water/HEMA ratio and using different concentrations of

crosslinker and initiator produce three different hydrogel structures. These were massive, bulk with pores, and extensive microporosity and channels. For samples prepared without initiator, tubular structures were prominent (pore openings and channels). A more dense structure was found at lower water contents. In samples prepared with initiator, but without any additional EGDMA, the microstructure changed from that containing spherical particles at high water content to a more dense and smooth P-HEMA as the water content decreased from 90% to 40%. For water contents of 0% to 30%, the polymer was transparent, and the hydrogel was a mass without obvious pores (viewed at 350X). An increase in water to a range of 40% to 70%, resulted in a translucent mass. It appeared as bulk hydrogel with pores ranging from 3 micrometers to 14 micrometers in diameter. As the water content increased from 70% to 90%, the pores increased in diameter, and channels appeared within the hydrogel strands with channels sizes ranging from 100 micrometers (80% water by volume) to 120 micrometers (90% water by volume) in diameter. Most of the samples showed a decrease in porosity as the water content decreased.

MATERIALS AND METHODS

The formulations used in this investigation correspond to that used by Sprincl et al. (1971) but with the difference that the crosslinker agent (EGDMA) was not used in the solution. The non-pressurized samples were prepared using a water/HEMA ratio of 90/10, 80/20, 70/30, 60/40, 50/50, 40/60, 30/70 percent (by volume) in the mixture (Table 1). The initiator concentration was kept constant at 1 weight percent.

Another set of samples (Table 2) was prepared using the same formulations mentioned which were polymerized under a moderate pressure of about 689 kPa. This technique was utilized by Pinchuk and Eckstein (1981) for several types of hydrogels. The microstructures for formulations of these two series, the non-pressurized and the pressurized, were compared in order to determine the effects of pressure on the porosity of the hydrogels.

Materials

The monomer was ophthalmic grade 2-hydroxyethyl methacrylate (HEMA) with a high purity of 99.5%. The monomer contained less than 0.15% EGDMA as an impurity and 200 ppm hydroquinone monoethyl ether as an inhibitor (MEHQ). The

Table 1. Formulations of the SI series samples (in volume percent) with 1 weight percent ammonium persulfate initiator

Sample #	% Water	% HEMA
SI1	90.0	10.0
SI2	80.0	20.0
SI3	70.0	30.0
SI4	60.0	40.0
SI5	50.0	50.0
SI6	40.0	60.0
SI7	30.0	70.0

Table 2. Formulations of the SIP series pressurized samples (in volume percent) with 1 weight percent ammonium persulfate initiator

Sample #	% Water	% HEMA
SIP1	90.0	10.0
SIP2	80.0	20.0
SIP3	70.0	30.0
SIP4	60.0	40.0
SIP5	50.0	50.0
SIP6	40.0	60.0
SIP7	30.0	70.0

monomer was obtained from Polysciences, Inc., Warrington, PA (Lot 401984). The initiator was ammonium persulfate (Lot 743791, Fisher Scientific, Fair Lawn, NJ). Type I deionized water was used as the solvent.

Polymerization Technique

For both series of samples, SI ("S" indicating the Sprincl method; "I" indicating that initiator was present) and SIP ("S" indicating the Sprincl method; "I" for the presence of initiator; and "P" for the pressurized polymerization case) are used for sample identification. HEMA and water were measured volumetrically for preparing the samples listed in Tables 1 and 2. The initiator, ammonium persulfate, was measured gravimetrically.

Fifty milliliters (ml) of each solution were prepared. Fifteen ml of each mixture were placed in individual test tubes (16 mm x 150 mm) while under a nitrogen environment (nitrogen gas inside a glove bag). Each solution was bubbled with nitrogen gas for 30 minutes to remove dissolved oxygen that otherwise would act as a reaction inhibitor.

For the SI samples, each mixture was placed into glass tubes with screw caps. The tube threads were wrapped with Teflon tape to prevent water from entering the tubes when they were placed in a water bath at constant temperature. Each

tube was positioned vertically in a temperature controlled stirred water bath. The polymerization reaction was carried out at 60° C during a 10 hour period. The temperature in the bath was kept constant by using a B. Braun Melsenger type 851253 temperature controller (B. Braun, West Germany).

In the case of the SIP samples, each solution was transferred to a 30 ml plastic syringe. Each sample was polymerized at 689 kPa (100 psi) and 60° C. The pressurizing rig was simply a lever resting on the plunger of the syringe with a sliding weight that could be set at different distances from the fulcrum (Pinchuk and Eckstein, 1981).

Critical Point Drying

The polymerized samples were removed from the tubes or syringes and were placed in a 50:50 ethanol/water (by volume) solution. The P-HEMA samples remained in this solution for 2 hours in order to permit unreacted monomer to diffuse out of the P-HEMA. Then the hydrogels were kept in deionized water. The water was changed twice a day for a period of seven days.

Critical Point Drying (CPD) was utilized for preparing the samples for Scanning Electron Microscopy examination. Each sample was carefully divided at the middle to expose the interior of the specimen. A small sample, less than

one millimeter (mm) in thickness by 1 mm in length and by 1 mm in width, was obtained from each bulk specimen by carefully extracting a thin sample from the middle with a scalpel or a tweezer. Special care taken not to crush the subsample. Each subsample was sequenced through a series of acetone/water rinses (30, 50, 70, 80, 90, 95, 100, and 100% volume to volume ratio) for fifteen minutes in each rinse solution in order to replace the water in the hydrogel structure. A maximum of three subsamples at a time were then placed into the transfer boat of a E-300 Critical Point Drying apparatus (Polaron Instruments, Inc., Warrington, PA). The transfer boat was filled with 100% acetone to prevent drying of the samples. The acetone was replaced with liquid carbon dioxide during the CPD procedure. This was achieved by flushing the chamber of the apparatus for at least three minutes, but no more than five minutes, with liquid carbon dioxide. The flushing procedure was repeated one hour later to allow impregnation of the subsamples with liquid carbon dioxide. In order to assure that the conversion of the liquid CO_2 to gas was complete (without having to pass through a phase transformation), the temperature and pressure in the chamber were raised above 32° C and 1200 psi, respectively. This was attained by running hot water through the outer chamber shell.

After reaching conditions above the critical point, the hot water was shut off and the carbon dioxide gas which had formed was vented slowly to avoid recondensation.

Scanning Electron Microscopy

Each sample was mounted on a carbon stub by using double sided adhesive mounting tape. A Polaron thin film coating unit E-5100 was used to sputter coat the samples. Gold was deposited onto the samples for a period of two minutes using a gold deposition rate of 154 angstroms per minute. After coating, the samples were placed into petri dishes and stored in a desiccator (over Drierite^{R}).

A Jeol-JSM 840A SEM (Jeol USA Electron Optics, Peabody, MA) was used to characterize the microstructure of the specimens. The samples were observed using an accelerating voltage of 5 keV and a working distance of 15 mm. In this study, magnifications ranging from 350X to 18000X were utilized. Polaroid type 55 film (Polaroid Corporation, Cambridge, MA) was used for recording microstructural features.

Pore Size

The pore size was calculated by manually measuring the maximum diameter of the pore openings horizontally and vertically on the field of view of the SEM photographs.

An average pore size, based on length was calculated as:

$$D = \frac{\sum_i (N_i \; D_i)}{\sum_i N_i}$$

where:

D = average diameter of the pores (μm),

N_i = number of pores for a specific diameter category,

and D_i = diameter of the pores for the i^{th} category.

Any closed or open structure within spherical units or bulk hydrogel material was taken to be a pore opening or void. Microvoids were defined as being 10 micrometers or less in diameter and macrovoids were defined as being 11 to 50 micrometers in diameter after Knoll (1980). In these formulations, larger openings are also present at the high water content formulation cases. Thus, openings larger than 50 micrometers in diameter were designated as channels after Barvic et al. (1967). These channels appear to tunnel through a sample, whereas macrovoids and microvoids are localized.

RESULTS

The consistency and optical characteristics of the hydrogels are reported in Tables 3 and 4 for the SI series and SIP series samples, respectively. The SI series samples have little strength at 90% and 80% water contents. The samples are more compact and stronger when the water content of the formulations decreased below 60%. The gels are stiff and relatively strong for the 40% and 30% water content formulations. By comparison, because of the influence of pressure during their polymerization, the SIP series samples are more compact. These samples do not show the flaky consistency at high water contents seen for the SI series samples. They vary in flexibility, being relatively flexible at 30% HEMA and very stiff at 70% HEMA content.

Both series exhibited the same optical characteristics for a formulation. They were opaque for water contents between 90% and 60%. At a water content of 50%, both series were translucent. They became transparent when they were washed with 50:50 ethanol/water solution. For a water content of 40% or less, the material was transparent.

Table 3. Formulations and physical characteristics for the SI series samples

Sample #	% Water	% HEMA	Consistency of polymer	Optical properties
SIP1	90.0	10.0	Very soft	Opaque
SIP2	80.0	20.0	Soft	Opaque
SIP3	70.0	30.0	Flexible	Opaque
SIP4	60.0	40.0	Firm	Opaque
SIP5	50.0	50.0	Firm	Translucent-transparent
SIP6	40.0	60.0	Stiff	Transparent
SIP7	30.0	70.0	Very stiff	Transparent

Table 4. Formulations and physical characteristics for the SIP series samples

Sample #	% Water	% HEMA	Consistency of polymer	Optical properties
SI1	90.0	10.0	Flaky	Opaque
SI2	80.0	20.0	Flaky	Opaque
SI3	70.0	30.0	Flexible	Opaque
SI4	60.0	40.0	Flexible	Opaque
SI5	50.0	50.0	Firm	[a]Translucent-[b]transparent
SI6	40.0	60.0	Stiff	Transparent
SI7	30.0	70.0	Stiff	Transparent

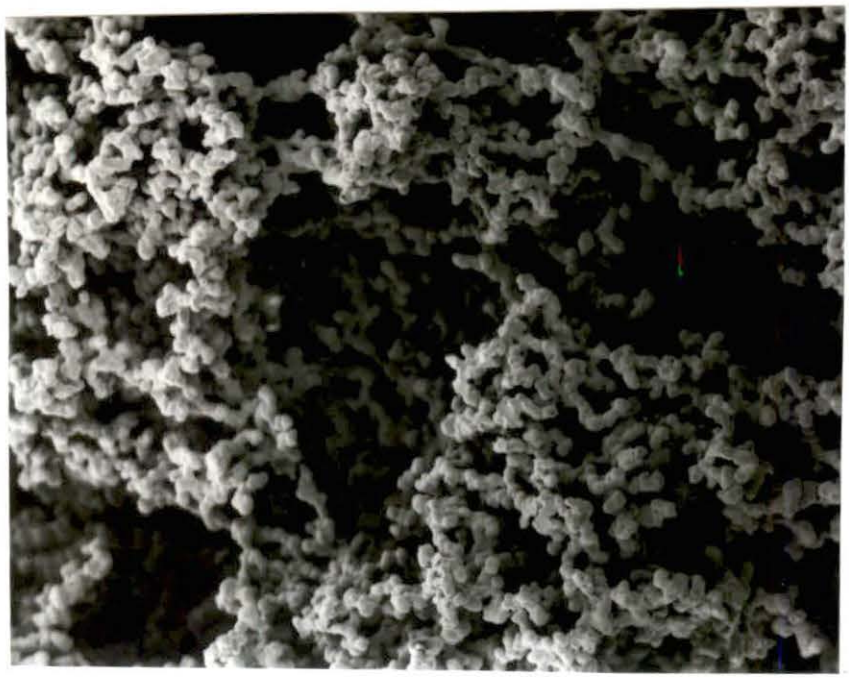
[a] Rind, or thin outer layer

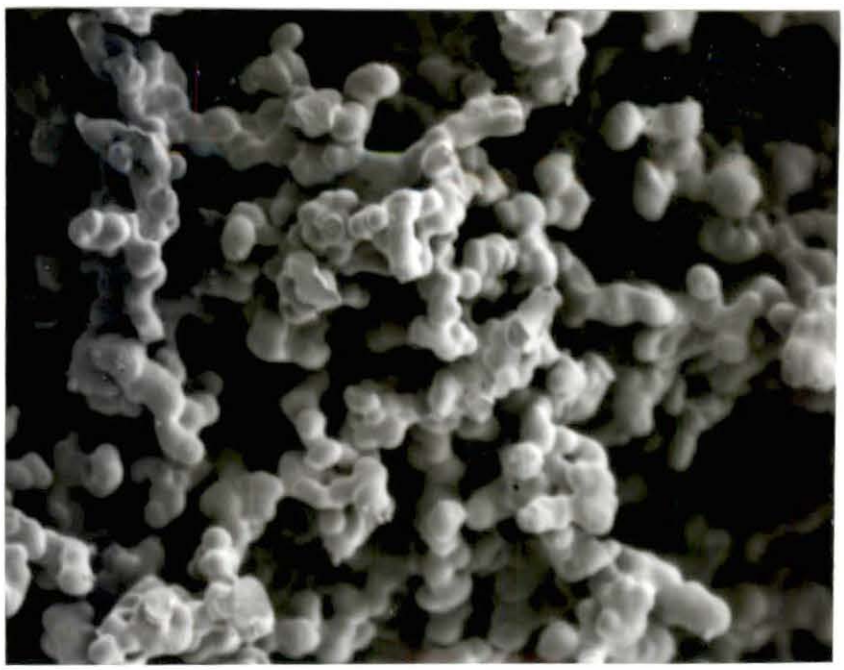
[b] Core where a sample was taken

The SEM results for the SI series show the presence of interconnected three dimensional pores and channels formed for high water content samples (90% and 80%). Examples are shown in Figures 3a, 3b, and 4, and observations are summarized in Table 5. For these high water content samples, SEM micrographs show a microstructure of stringers of spheres of hydrogels particles separated by macrovoids or channels. Table 5 shows the results of void size ranges obtained for the SI series samples. At a water content of 90%, the sample shows microvoids ranging from 0.5 to 8.6 μm (horizontally and vertically measured) in diameter (Figure 3a). Macrovoids present in the sample range from 14 to 29 μm in diameter. Decreasing the water content to 80% makes the sample less open. The maximum channel size (horizontal measurement) in Figure 3a is 220 μm. The maximum channel size (horizontal measurement) in Figure 4 is 143 μm. However, the void size range changes slightly with respect to the 90% water content sample. The polymer spheres are 3 to 45 μm in diameter in these figures. Decreasing the water content to 70% and to 60% produces a microstructure in which spherical forms are absent. The samples are now more filled in and pore sizes range from 0.1 to 1.3 μm for SI3, and 0.1 to 0.8 μm for SI4. Examples of this type of microstructure are shown in Figures 5a, 5b, 5c

Figure 3a. P-HEMA. Sample SI1 with 10% HEMA - 90% water and initiator, 5 keV, 350X

Figure 3b. P-HEMA. Sample SI1 with 20% HEMA - 90% water and initiator, 5 keV, 1000X





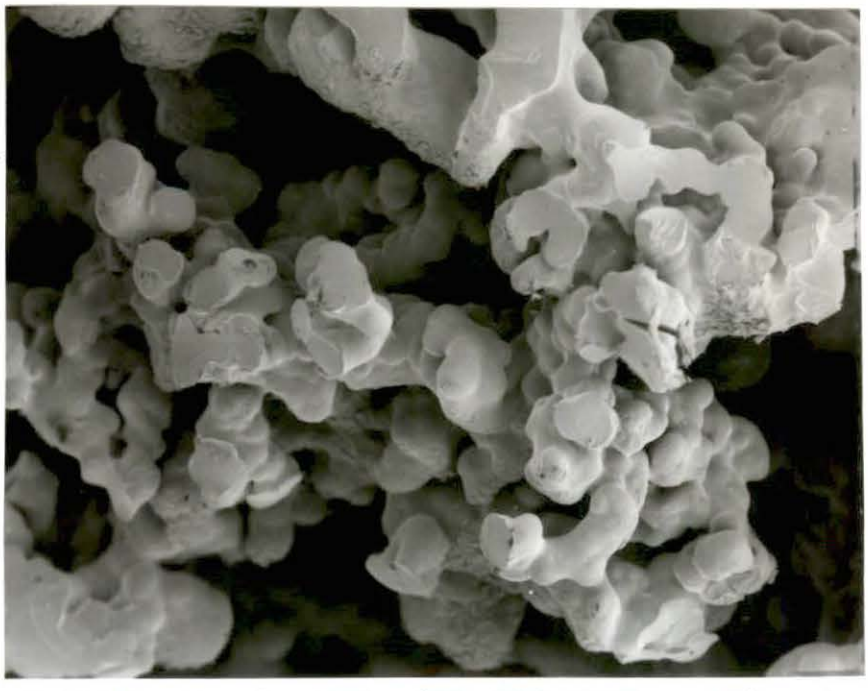


Figure 4. P-HEMA. Sample SI2 with 20% HEMA - 80% water and initiator, 5 keV, 350X

Table 5. Void size range, mean and standard deviation for the SI series samples

Sample (Figure)	Magnification		Void size range(μm) micro	Void size range(μm) macro		Void size (μm) micro	Void size (μm) macro	Void size (μm) overall
SI1	350X	[a]H	1.4-8.6	14-29	[b]M(N)	4(56)	19(38)	10(94)
(3a,b)					[c]SD	2.8	4.8	8.0
		[d]V	1.4-8.6	14-29		5(68)	20(20)	8(88)
						2.3	4.8	7.2
	1000X		0.5-10	15-20		2(30)	17(3)	3(33)
						2.7	2.9	5.0
			0.5-10	15-20		4(30)	16(7)	6(37)
						4.2	2.1	7.2
SI2	350X		1.4-10	14-34		5(17)	20(11)	11(28)
(4)						2.4	6.4	8.9
			1.4-5.7	14-29		4(10)	18(7)	10(17)
						1.9	7.0	8.8

[a]H= horizontal measurement

[b]M(N)= arithmetic mean(number of observations)

[c]SD= standard deviation

[d]V= vertical measurement

Table 5. (continued)

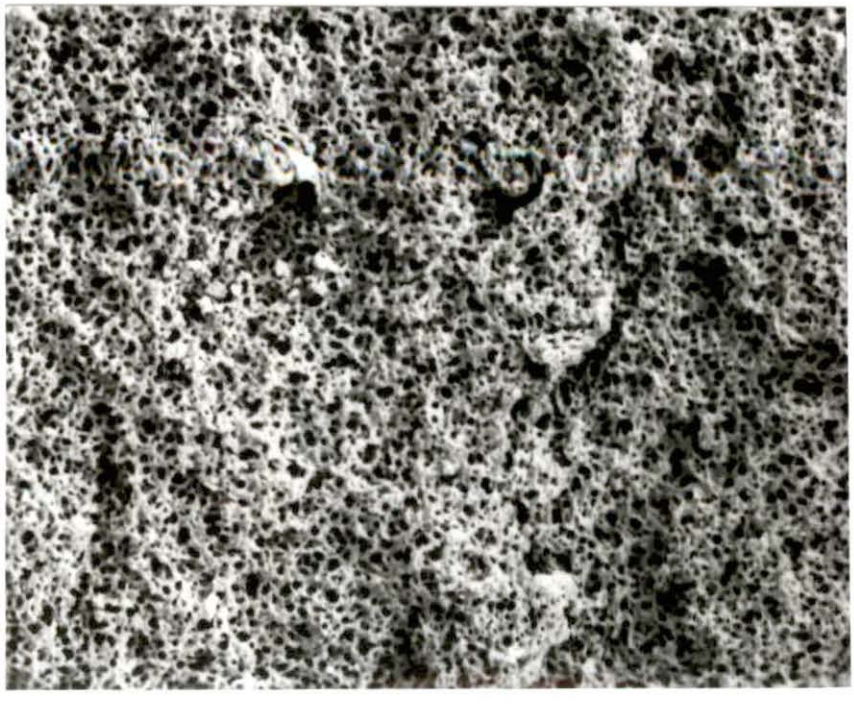
Sample (Figure)	Magnif-ication	Void size range (μm) micro	macro	Void size (μm) micro	macro	overall
SI3	3000X	0.2-1.2	-	0.3(426)	-	0.3(426)
(5b,c)				0.2	-	0.2
		0.2-1.3	-	0.2(370)	-	0.2(370)
				0.2	-	0.2
	18000X	0.1-0.7	-	0.3(34)	-	0.3(34)
				0.1	-	0.1
		0.1-0.8	-	0.3(39)	-	0.3(39)
				0.2	-	0.2
SI4	4000X	0.1-0.5	-	0.2(130)	-	0.2(130)
(6b)				0.1	-	0.1
		0.1-0.8	-	0.3(68)	-	0.3(68)
				0.2	-	0.2
SI5	350X	1.4-8.6	-	5(68)	-	5(68)
(7)				2.3	-	2.3
		1.4-8.6	-	5(50)	-	5(50)

Table 5. (continued)

Sample (Figure)	Magnif-ication	Void size range(μm) micro	macro	Void size (μm) micro	macro	overall
SI6	350X	1.4-7.1	-	5(29)	-	5(68)
(8)				1.6	-	1.6
		1.4-7.1	-	4(29)	-	4(29)
				1.8	-	1.8

Figure 5a. P-HEMA. Sample SI3 with 30% HEMA - 70% water and initiator, 5 keV, 350X

Figure 5b. P-HEMA. Sample SI3 with 30% HEMA - 70% water and initiator, 5 keV, 3000X



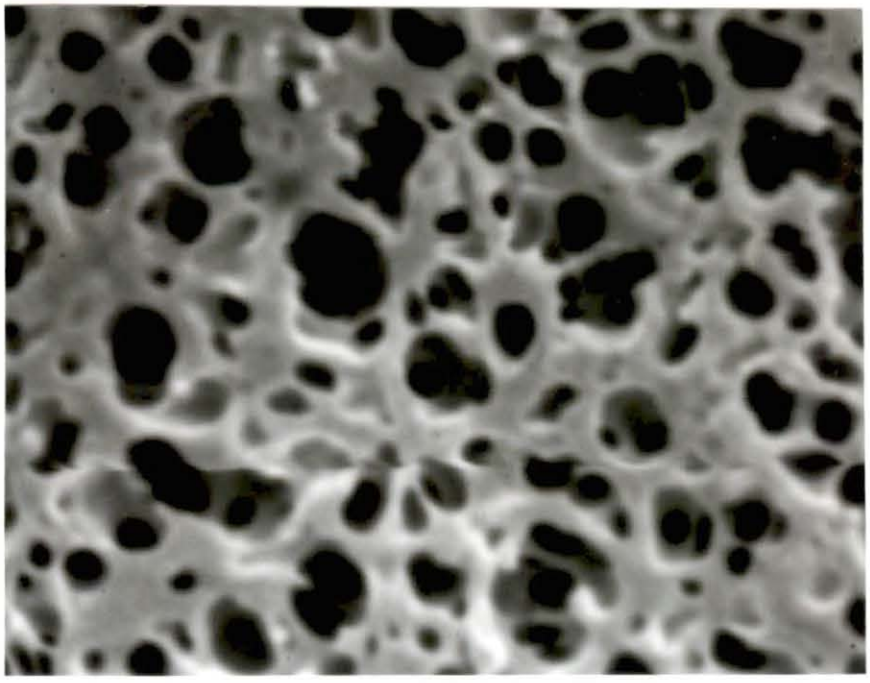


Figure 5c. P-HEMA. Sample SI3 with 30% HEMA - 70% water and initiator, 5 keV, 18000X

and 6a, 6b, where net-type, or reticular structure is observed. Figures 7 and 8 show an example of porosity porosity produced by gas trapped in the samples (SI5 and SI6). In these samples, spherical openings are observed which differ greatly from the voids found in the samples with higher water contents. Figure 8 shows detail of the presence of gas still trapped in the sample; the voids form a dome-like shape. The results of the current investigation show microvoid sizes ranging from 1.4 to 8.6 micrometers for the SI5 sample and 1.4 to 7.1 micrometers in diameter for the SI6 sample. Furthermore, the surface surrounding the openings is very smooth with no smaller microporosity seen even at a higher magnification of 4000X (a level at which 0.1 micrometer diameter pores could be recognized, if present).

By comparison, the results obtained for the SIP series show that at about 40 percent water content, the presence of pores is shifted to higher water contents due to the effect of pressurization restricting the expansion of the hydrogel (Table 6). Data in Table 6 indicate a significant decrease in microvoid size at a water content of 40% (SIP4, Figure 12b), with 0.1 micrometer compared to 0.8 micrometer found in the SI4 sample. Another important effect of pressurizing the samples during their polymerization is the absence of pores

Figure 6a. P-HEMA. Sample SI4 with 40% HEMA - 60% water and initiator, 5 keV, 350X

Figure 6b. P-HEMA. Sample SI4 with 40% HEMA - 60% water and initiator, 5 keV, 4000X

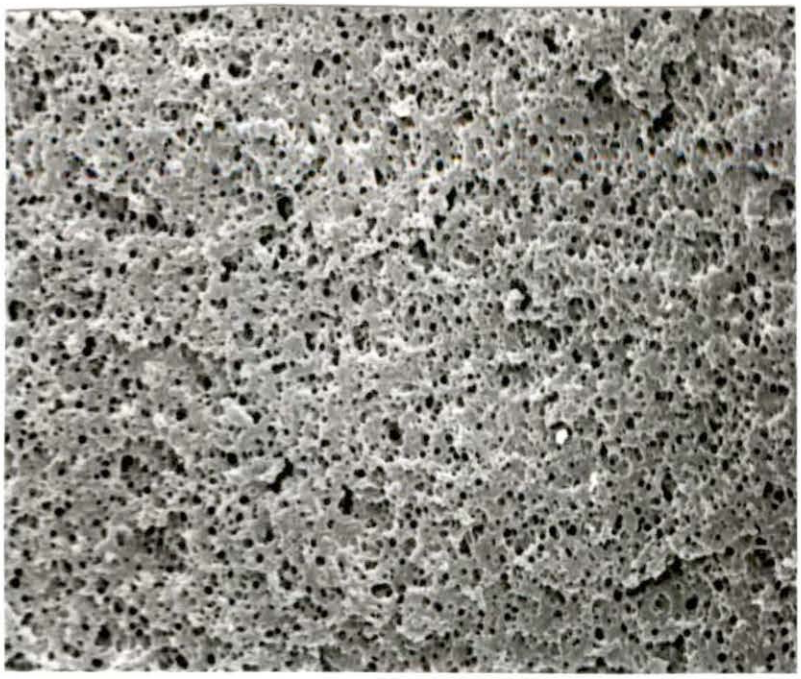
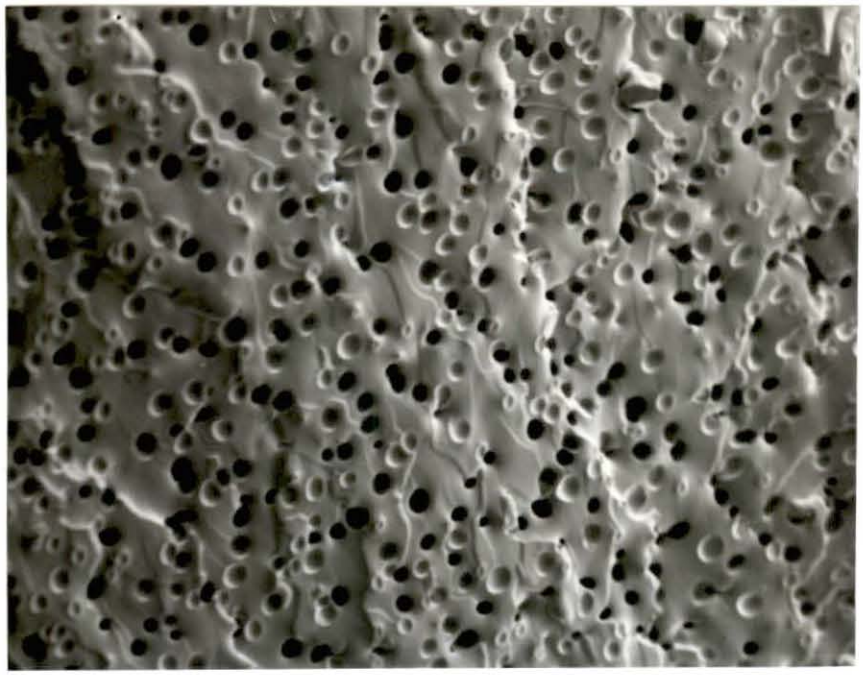


Figure 7. P-HEMA. Sample SI5 with 50% HEMA - 50% water and initiator, 5 kev, 350X

Figure 8. P-HEMA. Sample SI6 with 60% HEMA - 40% water and initiator, 5 keV, 350X



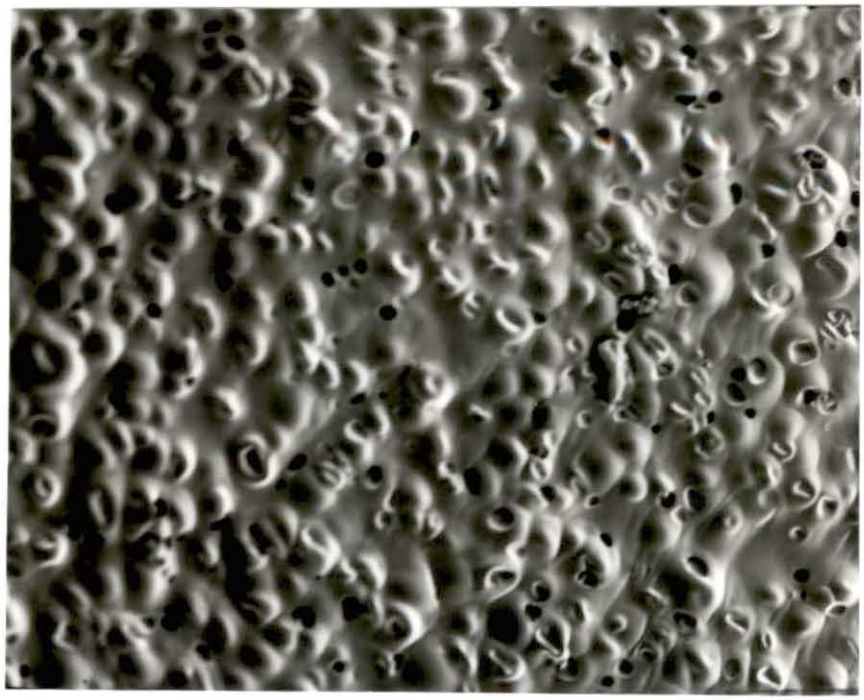


Table 6. Void size range, mean and standard deviation for the SIP series samples

Sample (Figure)	Magnif-ication		Void size range (μm) micro	Void size range (μm) macro		Void size (μm) micro	Void size (μm) macro	Void size (μm) overall
SIP1	350X	[a]H	1.4-10	17-43	[b]M(N)	3(92)	28(22)	8(121)
(9)					[c]SD	2.5	9.7	10.7
		[d]V	1.4-7.1	11-49		4(32)	23(20)	11(52)
						2.7	12.4	12.3
SIP2	350X		2.9-8.6	20-34		4(64)	26(14)	8(78)
(10a,b)						2.0	5.5	8.8
			1.4-8.6	14-46		6(68)	23(18)	9(86)
						2.9	11.4	9.2
	1000X		1-4	12-22		2(26)	17(2)	3(28)
						1.0	7.1	4.4
			1-4	12-15		2(28)	14(5)	4(33)
						1.1	1.3	4.8

[a]H= horizontal measurement

[b]M(N)= arithmetic mean(number of observations)

[c]SD= standard deviation

[d]V= vertical measurement

Table 6. (continued)

Sample (Figure)	Magnif-ication	Void size range (μm) micro	macro	Void size (μm) micro	macro	overall
SIP3	4000X	0.3-0.6	-	0.4(238)	-	0.4(238)
(11b,c)				0.1	-	0.1
		0.3-0.5	-	0.3(216)	-	0.3(216)
				0.1	-	0.1
	18000X	0.1-0.7	-	0.3(29)	-	0.3(29)
				0.2	-	0.2
		0.1-0.4	-	0.2(32)	-	0.2(32)
				0.1	-	0.1
SIP4	4000X	0.1	-	0.1(16)	-	0.1(16)
(12b)				-	-	-
		0.1	-	0.1(16)	-	0.1(16)
				-	-	-

caused by trapped gas at water contents of 50% or below. This is different compared with the results obtained for the SI series samples for the same range of water contents. The micrographs show details of the microstructure obtained at several water/HEMA ratios. Figure 9 shows a field of view for a sample containing 90% water. Here a macroporous structure can be seen with macrovoids as large as 49 μm in diameter (Figure 9). The main features of the structure are linked to the formation of spheres, which form continuous chains that are separated by macrovoids or channels. The spheres are as large as 8 μm in diameter. This is similar to that seen for the SI1 sample. The channels in the figures have a maximum size of 56 μm (Figures 10a and 10b; SIP2 sample) and 85 μm in diameter (Figure 9; SIP1 sample). The spheres, unlike the ones observed in SI1 sample micrograph, are more agglomerated. More spheres are joined together as subunits to form the network. The hydrogel is less open compared with the sample with a similar composition but which was formed using no pressure during the polymerization (sample SI1). For the water content of 80% (Figures 10a and 10b), the microstructure is similar to that seen in SIP1 (Figure 9) with the difference being that this sample is more agglomerated. There is a decrease in maximum channel sizes in these views from 85 μm

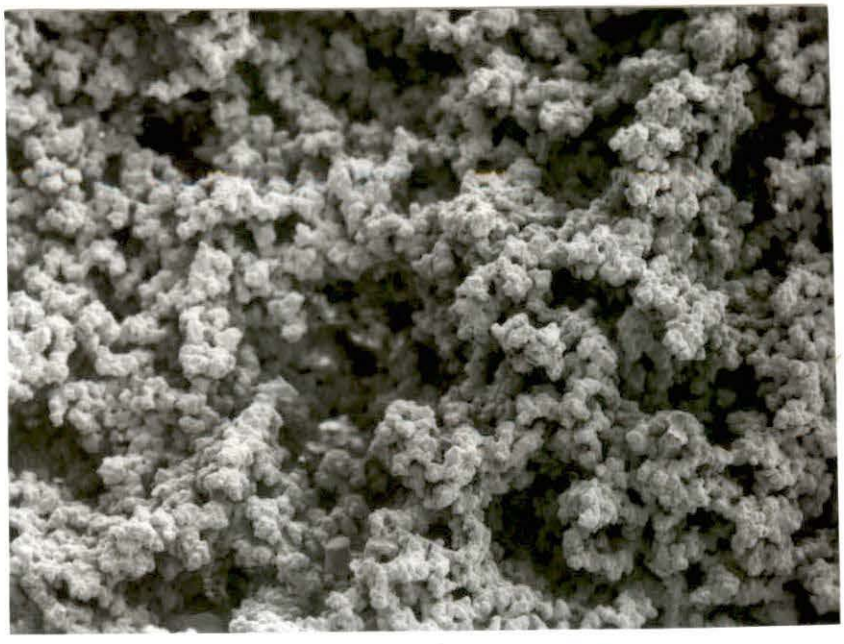
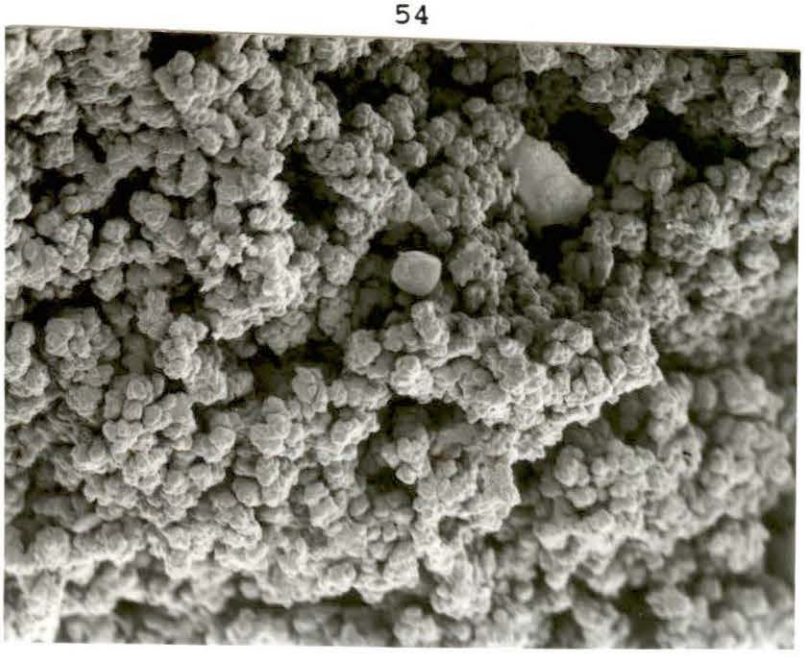


Figure 9. P-HEMA. Sample SIP1 with 10% HEMA - 90% water and initiator (689 kPa (100 psi)), 5 keV, 350X

Figure 10a. P-HEMA. Sample SIP2 with 20% HEMA - 80% water and initiator (689 kPa (100 psi)), 5 keV, 350X

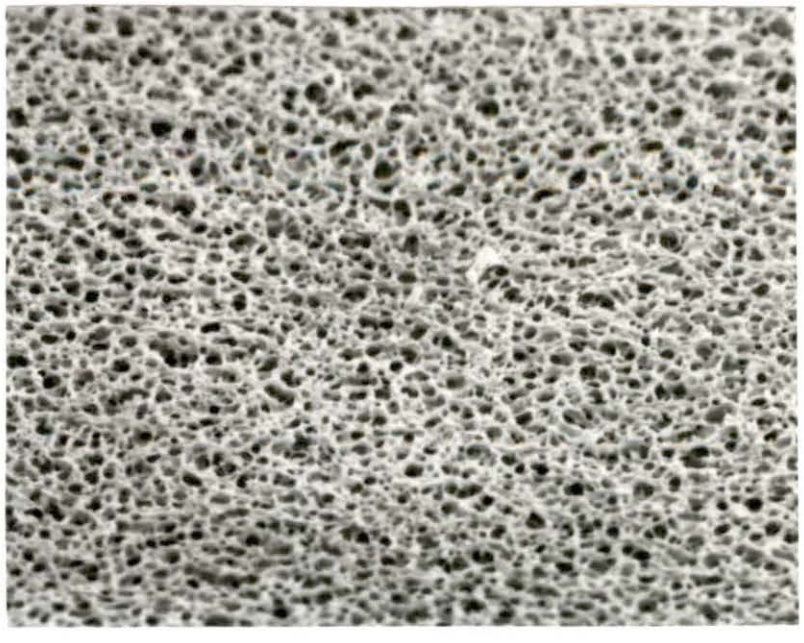
Figure 10b. P-HEMA. Sample SIP2 with 20% HEMA - 80% water and initiator (689 kPa (100 psi)), 5 keV, 1000X



(SIP1) to 56 μm (SIP2), and an increase in the particle size up to 10 μm at 80% water content due to the higher HEMA content. The microvoids found range from 1 μm (Figure 10b) to 8.6 μm (Figure 10a). Macrovoids range from 12 μm (Figure 10b) to 46 μm in diameter (Figure 10a). Increasing the HEMA content up to 30% (Figures 11a, 11b, and 11c) produces another type of microstructure. In this case, the structure is net-like. At this composition, the spheres are not apparent. A continuous network of hydrogel is formed and more monomer is available to fill in the voids. The microstructure is formed by microvoids ranging from 0.1 to 0.7 μm in diameter (Figure 11c). Macrovoids are no longer present at this composition. This type of microstructure is similar to that found in SI3 sample (Figures 5a, 5b, and 5c). The last sample where a porosity was found (while increasing the relative amount of HEMA to water in a formulation) corresponds to a formulation of 40% HEMA (Figures 12a and 12b; SIP4). Figure 12b shows a uniform microporous structure with microvoids of 0.1 μm in diameter. By comparison with SI4 (Figure 6b), the sample SIP4 (Figure 12b) shows the effect that increasing pressurization has in decreasing the void size. At higher HEMA contents for samples SIP5, SIP6 (Figure 13), and SIP7, porosity is no longer present. The surfaces of these samples are very

Figure 11a. P-HEMA. Sample SIP3 with 30% HEMA - 70% water and initiator (689 kPa (100 psi)), 5 keV, 350X

Figure 11b. P-HEMA. Sample SIP3 with 30% HEMA - 70% water and initiator (689 kPa (100 psi)), 5 keV, 4000X



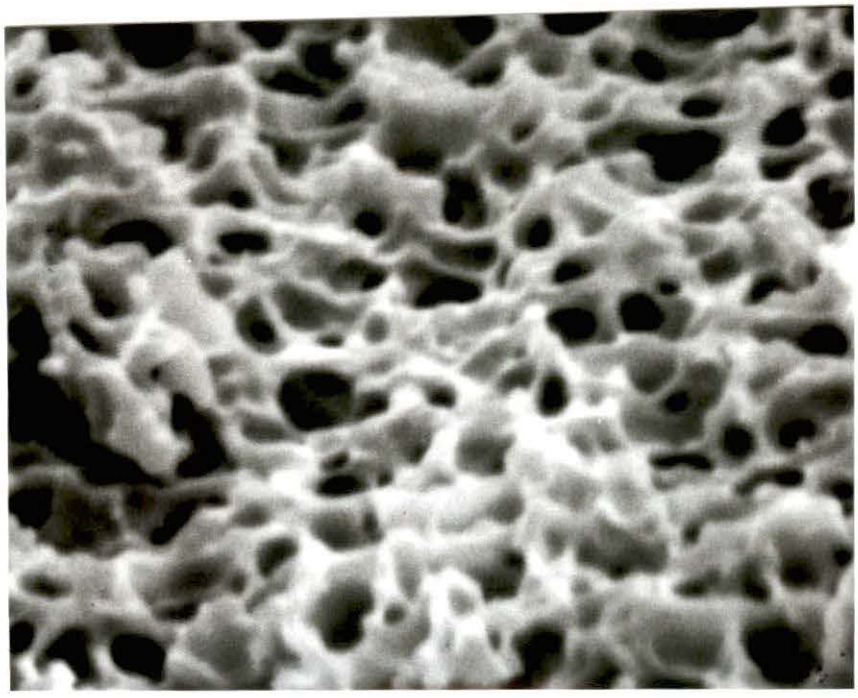


Figure 11c. P-HEMA. Sample SIP3 with 30% HEMA - 70% water and initiator (689 kPa (100 psi)), 5 keV, 18000X

Figure 12a. P-HEMA. Sample SIP4 with 40% HEMA - 60% water and initiator (689 kPa (100 psi)), 5 keV, 350X

Figure 12b. P-HEMA. Sample SIP4 with 40% HEMA - 60% water and initiator (689 kPa (100 psi)), 5 keV, 4000X

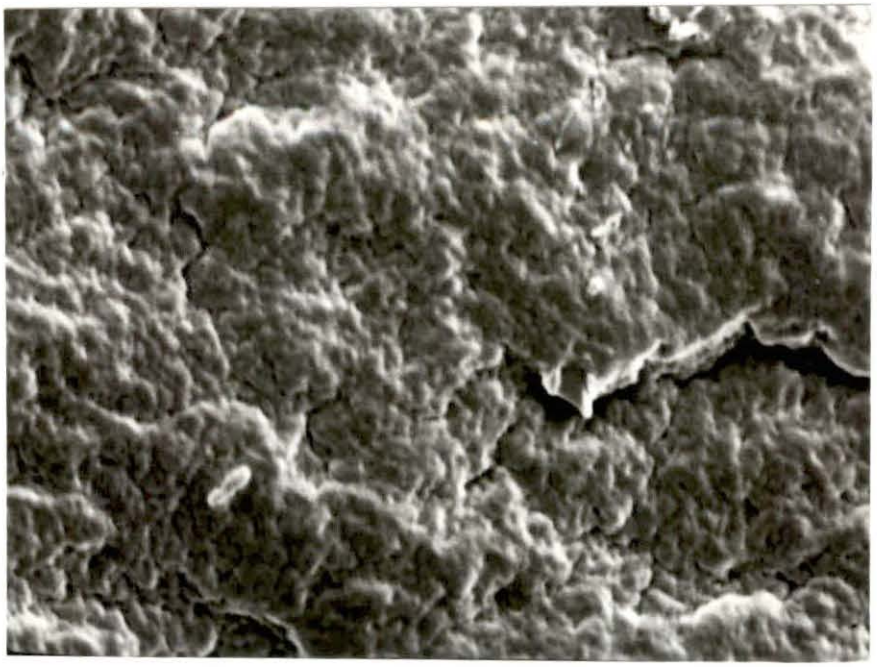


Figure 13. P-HEMA. Sample SIP6 with 60% HEMA - 40% water and initiator (689 kPa (100 psi)), 5 keV, 350X

smooth. This absence of porosity results in the high transparency of the samples representative of these compositions (50 to 70% HEMA).

Tables 5 and 6 summarize the results of void sizes obtained for both series of samples related to formulation. These data indicate that microvoid or macrovoid diameters are in general similar for both horizontal and vertical measurement comparisons. This indicates that most of the structures are not distorted in a significant way either in association with the mounting procedure or with the polymerization. The SI series data of Table 5 indicate that the average diameters of the voids decrease with increasing the amounts of HEMA to water for the group comparison of sizes for samples SI1 and SI2 [the first group] and SI3 and SI4 [the second group] (except samples SI5 and SI6 where results seem to be influenced by trapped gas). The results for the SIP series samples of Table 6 show a consistent decrease in average diameter of the voids (micro, macro, and overall) as the HEMA to water ratio increases for the group comparisons of sizes for samples SIP1 and SIP2 [the first group] and SIP3 and SIP4 [the second group]. In both Tables 5 and 6, the macrovoids are no longer present for formulations with above 20% HEMA content.

DISCUSSION

For both series of formulations (SI and SIP), the porosity of the HEMA hydrogels is governed by the ratio of water to HEMA monomer. At certain water contents, porosity is present, and porosity then increases as water content increases among formulations. An important finding is the influence of pressure on the suppression of the channels for comparable water content comparisons of pressurized and non-pressurized samples as the formulation water contents decrease.

Changes in Optical Properties

The concentration of water present during the polymerization determines if the homogeneous or the heterogeneous structure is produced. When the water concentration is below the critical level (40% by volume or lower), the production of an optically transparent, homogeneous hydrogel is ensured. On the other hand, when the water content exceeds this limit of 40%, opaque, heterogeneous, macroporous hydrogels are obtained.

The hydrogels of both series become opaque for a water content ranging between 90% and 60% by volume. They are

translucent at a 50% water content, and transparent at 40% or lower water contents. For the samples with the highest water content (90% and 80%), the phenomenon of microsyneresis was observed. The lack of porosity seen at lower water contents (40% or lower) resulted in transparent samples.

The optical characteristics found in this investigation (for both series) are in general agreement with the non-pressurized sample observations of Yasuda et. al. (1966). They stated that when more than 40% water is used in the polymerization mixture, hydrogels become translucent to opaque, and a lower water content makes the hydrogels transparent (Figure 1). Sprincl et. al. (1973) reported similar results.

Microstructure

The SI series samples exhibited microstructures similar to that found by Grant (1990). In this series, spherical particles are prominent for formulations with 90% or 80% water contents. They combine to form chains separated by macrovoids and channels at 90% water concentration. At 80% water content, the spheres are larger in diameter and have combined into groups instead of chains. When the water content is decreased to 70%, spheres are absent, and the

structure becomes more compact. The sample becomes microporous as the hydrogel P-HEMA builds-up between and among the spherical subunits, resulting in a low degree of porosity. The results obtained for SI5 and SI6 are influenced by the presence of gas trapped in the solution. The gas leaves the sample due to the 60° C temperature used during the polymerization as well as the exothermic nature of the polymerization reaction. This release of the gas within the sample causes spherical void openings within the polymer whereas irregular voids are found in the non-pressurized samples SI1, SI2, SI3, and SI4 with relatively lower water contents.

By comparison, the SIP series samples show a macroporous structure at 90% and 80% water contents which is similar to that found in the SI series. Spheres covalently link to form the polymer structure, and the spheres are separated by voids. There is a significant sphere shape difference between the SI and SIP samples. Spheres agglomerate more in the SIP cases (particles have coalesced, forming the network). Refojo (1967a) reports that hydrophobic interactions may cause P-HEMA molecules to assume compact conformations to the extent that covalent crosslinks will occur. In water, most of the hydrophobic portions of the

chains tend to aggregate as these sites avoid contact with the solvent. In the case of the SIP samples, the pressure applied during the polymerization seems to increase this hydrophobic interaction not only because more particles are aggregated to form the polymer network but also because the separations between the networks decrease.

Pinchuk and Eckstein (1981) stated that the initiation of the polymerization reaction is not significantly altered by varying the pressure. However, in this investigation (on a microscopic scale) a significant variation in the microstructures for pressurized samples compared to similar formulation non-pressurized samples provides evidence that the kinetics are affected, especially in samples with a relatively higher water percentage (80% and 90%). These samples present a less open structure compared with SI series samples with the same water contents. Furthermore, these samples (SIP1 and SIP2) show agglomerated spheres instead of the stringers found in the non-pressurized case. This is an indication that the reaction occurred faster in samples polymerized under pressure.

The samples with lower water contents (70% to 30% by volume) show similar structures to those obtained in the SI series, with the difference being that pores caused by

trapped gas were not observed, compared with SI5 and SI6 non-pressurized samples.

Porosity

In both series, the porosity is greatest at the relatively high 80-90% water contents. This is because less monomer is available to react to form the P-HEMA hydrogel material. An increase in monomer concentration reduces the void and channel sizes. The porosity decreases with decreasing water contents for the formulations studied. In summary, a decrease in water content causes a decrease in porosity for both the SI and the SIP series of formulations.

Pore Size

Larger channels or voids are found in the SI series samples compared with those found in the SIP series samples for comparable formulations. In both series, macrovoids are only present in the formulations with 80% or 90% water contents. The pressurization seems to act predominantly on the channels. For pressurized samples, the void features are less than 50 micrometers in diameter for the formulations studied.

CONCLUSIONS

By raising the content of water in the HEMA monomer-water mixture, it is possible to pass continuously from a homogeneous bulk polymer to a heterogeneous polymer with three-dimensional voids. In agreement with theoretical arguments outlined by Kopecek and Lim (1971), the phase separation depends mainly on the water content. When phase separation takes place during polymerization, the resulting polymer has a microporous structure as seen for a size scale of the order of micrometers or fractions of micrometers. A porous structure arises by coalescing the water-phase droplets into interconnected chains as initially described by Wichterle and Lim (1960).

The use of pressure during the polymerization of HEMA apparently did not influence the degree of transparency of the hydrogels formed compared with the similar non-pressurized hydrogel formulations in any significant way as judged by visual observation. For both series, the P-HEMA hydrogels were opaque at water contents of 60% and higher, translucent at a water content of 50%, and transparent for water contents of 40% or less.

The pressurization did influence the type of microstructure present compared with microstructure for non-pressurized samples on a micrometer size scale of the hydrogels as follows:

1. the porosity formed by trapped gas was eliminated for formulations with 50% water or greater,
2. the void sizes decreased significantly; for example, at 60% water content, a microporous structure was obtained with occasional 0.1 μm size microvoids compared to the non-pressurized case where the voids were common and were 0.2 μm in diameter on the average and,
3. the particle sizes decreased for samples with a relatively higher water content.

This study demonstrated that the use of pressure during the polymerization of HEMA monomer in the presence of water as the solvent shifts the presence of porosity in the hydrogels to higher water content formulations compared to similar formulations in the absence of the application of pressure during polymerization. Also, in the non-pressurized case, entrapped gas voids are apparent and sizes differ as a function of water content (40-50% water). They are relatively

larger at higher water contents. Spherically shaped gas voids are not apparent in the pressurized polymerization cases (for the 40-50% water content cases).

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