Microstructure of poly(hydroxyethyl methacrylate) hydrogels

by

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INTRODUCTION

Hydrogels have been used in medical applications for approximately three decades. Hydrogel means a soft, weak polymeric material which can usually imbibe more than 40 percent water by weight. The term was first used by Wichterle and Lim (1960) who synthesized and characterized poly(2-hydroxyethyl methacrylate) (P-HEMA) with an objective of developing a material with hydrophilic side groups for possible use in medical applications. P-HEMA is biocompatible. P-HEMA has been fabricated into coatings for use as a drug delivery matrix material, into nonporous membranes in artificial organs, into homogeneous gel embryo growth chambers, into transparent films in the form of contact lenses, and into porous sponges for use as artificial skin wound dressings.

The porosity of P-HEMA is a critical factor in determining its physical use and in predicting its permeabilities (Peppas et al., 1985). There are a lack of studies specifically designed to systematically characterize the pore structure of P-HEMA on a micrometer size scale. The present investigation was designed to characterize the presence and character of the network in P-HEMA for this size scale using principal polymerization techniques for widely used formulations. These techniques are based on the use of heat and the presence of polymerization initiators. Formulations that are used in the present work are based on the use of the following constituents: hydroxyethyl methacrylate (HEMA), the monomer; deionized water, a poor solvent

for the P-HEMA polymer; ethylene glycol dimethacrylate (EGDMA) or tetraethylene glycol dimethacrylate (TEGDMA), a crosslinking agent; ammonium persulfate or sodium metabisulfite, a polymerization initiator; and ethylene glycol (EG), a substance used in place of water to extend the P-HEMA formulation range for optical transparency.

The solutions containing one or more of the above constituents were either heat polymerized using a constant temperature bath at 60° or 65° C or using the heat from an exothermic reaction for certain constituents (under a pressure of 100 psi). The microstructural information was developed within a magnification range of 95 to 4000X using a scanning electron microscope.

LITERATURE REVIEW

P-HEMA Hydrogels

Background

P-HEMA is commonly obtained by polymerizing HEMA monomer in the presence of a crosslinking agent (free radical copolymerization) in an aqueous solution, forming a soft, rubbery polymer (Wichterle and Lim, 1960; Wichterle, 1971). The physical properties of P-HEMA closely resemble soft living tissue. This similarity to living soft tissue is based on three properties: high water content, soft and rubbery network, and low interfacial tension with other substances. The P-HEMA structure permits a high water content and permeability to small molecules, thus allowing initiator molecules, solvent molecules, and any other unwanted materials to be extracted from the hydrogel network before it is implanted into living systems. In vivo leaching of such molecules after implantation has been cited by Homsy (1970) as a material related cause of inflammation leading to the possible rejection of the implanted biomaterial. The soft and rubbery consistency of P-HEMA reduces physical irritation at polymer-tissue interfaces, and this contributes to its biocompatibility. Hydrogels also possess low interfacial free energy and work of adhesion. Ratner and Hoffman (1976) indicated that this low interfacial tension of hydrogels reduces the chance of the body rejecting the biomaterial.

Swelling properties

The swelling of P-HEMA is isotropic meaning that it swells equally in all dimensions. Water is a poor solvent for P-HEMA, and this poor solubility dictates its swelling properties. Bruck (1973) indicates that at room temperature, homogeneous P-HEMA absorbs a maximum of 40% water (by weight) regardless of the number of crosslinks within the network for a crosslinker content of 0 to 4 mole percent (Ratner and Miller, 1972). The amount of water present as a constituent during polymerization affects the optical transparency of the resulting gel (Refojo and Yasuda, 1965; Yasuda et al., 1966). No water or relatively low amounts of water in the formulation mixture leads to a tight microstructure and transparent hydrogels (homogeneous gels), intermediate amounts of water lead to the presence of microporosity on a micrometer size scale and translucent gels, and relatively high amounts of water lead to the presence of relatively high micoporosity and opaque (heterogeneous) gels. This is due to the separation of the polymer phase from the water during polymerization. Refojo and Yasuda (1965) and Gouda et al. (1970) determined that the water uptake of heterogeneous P-HEMA gels strongly depends upon the amount of water (polymer non-solvent) present during the polymerization reaction. Bruck (1973) determined that the swelling of P-HEMA hydrogels is influence by temperature and composition of the swelling agents also.

Transport properties

The permeability of hydrogels in aqueous systems is of great importance especially for contact lenses, controlled drug-delivery systems, synthetic wound

dressings, as well as newly developed embryo growth chambers (Pollard, 1987). 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 properties of ions (Hamilton et al., 1988; Murphy et al., 1988), neutral molecules such as amides, steroids (Zenter et al., 1979), sugars (Kim et al., 1980), and water (Yasuda et al., 1972; Wisniewski and Kim, 1980) have been studied and associated permeability models for hydrogels have been suggested.

Cell adhesion

Lyndon (1986) reviewed the importance of synthetic hydrogels in cell culture models for biomedical research. One of the best known examples of the use of synthetic hydrogels in cell culture was developed by Folkman and Moscona (1978) who reported that cellular metabolism and growth could be affected by coating tissue culture surfaces with increasing thicknesses of P-HEMA. Additional related cell culture studies with P-HEMA have been performed by Ben-Ze'ev (1983) and Raz and Ben-Ze'ev (1983). However, these results of Folkman and Moscona, Ben-Ze'ev, and Raz and Ben-Ze'ev have been shown to be anomalies associated with cell size distributions (Lyndon, 1986). Lyndon (1986) concluded that P-HEMA is completely non-adhesive for cells. The general nature of the above findings is of interest in using hydrogel coatings for drug release systems or for lenses since in either application cellular adhesion and development on surfaces should be minimal.

Microstructural features associated with wound dressing studies

The lack of a readily available biological material for use as a wound covering has led to the development of synthetic wound dressings. An ideal membrane for this purpose could be applied and left in place on an open wound as long as necessary (Pruitt and Silverstein, 1971). By comparison, temporary substitutes for wound coverage are used, but these must eventually be replaced by autographs as healed donor sites become available (Compton et al., 1989). Synthetic wound dressings are often provided with a textured under-surface for use next to the wound. This provides for adhesion, absorption of fluid, and transmission of water vapor. Ideally, a wound dressing should adhere tightly to the wound to prevent microbial invasion. This would require an ingrowth of tissue into the porous undersurface of the wound dressings. However, easy removal of the dressing is required in order to prevent pain to the patient and to prevent accidental removal of the regenerating epidermis or granulation tissue. Therefore, many investigators have developed wound dressings with degradable porous undersurfaces which would allow for tissue ingrowth, synthesizes of neodermal tissue, and the eventual degradation of the dressing surface for easy removal. The pore size is critical in encouraging an optimal amount of tissue ingrowth, as well as influencing vapor transmission rates.

Many polymers have been used in the construction of synthetic wound dressings (Chvapil, 1982) in the form of fibers, films, membranes, gels, sponges, and foams. These polymers have also been grafted with other materials to form composite wound dressings such as Biobrane (Zachary et al., 1982). Corkhill et al. (1989) and

Falanga (1988) provide detailed descriptions of the currently used natural and synthetic hydrogel wound dressing materials. Table 1 lists the major synthetic wound dressings, including those based on P-HEMA. Because of its properties, P-HEMA makes a desirable wound dressing, sometimes alone, but more often in the form of composites or laminates to increase the mechanical strength of the dressing. P-HEMA can be fabricated using a variety of polymerization techniques in order to create a wide range of wound dressings.

The relatively poor mechanical properties of P-HEMA have presented some problems during use. Migliaresi et al. (1980) attempted to improve its mechanical strength by forming a P-HEMA/polybutadiene laminate material. The authors thermally grafted P-HEMA onto polybutadiene (PB) for potential use as a wound dressing. The presence of polybutadiene increases the tensile properties of the P-HEMA film, and PB inhibits water diffusion while it does not affect the oxygen permeability of the P-HEMA. The authors prepared the P-HEMA/PB film according to the following general method. From a 15 weight percentage solution of PB in toluene, a film of syndiotactic poly(1,2-butadiene) was cast on a polyester sheet. A mold was prepared by clamping two glass plates, separated by a silicone rubber gasket and two polyester sheets. A polyester sheet supported the cast PB film. The mold was filled with a 60 weight percent HEMA mixture (99.4% HEMA, 0.5% EGDMA, 0.1% 2-azobisisobutyronitrile) and 40 weight percent diacetine. The solution was polymerized at 90° C for one hour. SEM photos show very good

Table 1. Synthetic burn dressings (Quinn et al., 1985)

Type	Materials	Trade Name
Preformed films	Poly(vinyl chloride)	Clingfilm, Vitafilm, Stretch'n Seal
	P-HEMA and poly(ethylene glycol)-400	Hydron
	Polyurethane	Op-Site, Tegaderm
	Polytetrafluoroethylene	
	Polyacrylonitrile	
	Polyethylene	
	Polypropylene	
	Poly(lactic acid)	
	Polycaprolactone	PCL 700
Spray-on films	P-HEMA and polyethylene glycol	Hydron
	Poly(vinyl chloride) dissolved in ethyl acetate and propanone	
	2-Ethoxyethyl methacrylate dissolved in ethyl acetate	Nobecutane
	Poly-e-caprolactone in tetrahydrofuran	
Gels	Polypropylene and ethylene oxides	Pluronic F127
	Agar and polyacrylamide	Geliperm
	Hydrated poly(ethylene oxide)	Vigilon
Foams and Sponges	Poly(vinyl alcohol)	Ivalon
	Polysiloxane	Silastic Foam
	Polyurethane	Lyofoam, Synthaderm
	Polyesterurethane, polyetherurethane, and acrylic	
	Poly(vinyl alcohol) and formaldehyde	
Composites	Polyurethane foam and polypropylene film	Epigard
	Polydimethylsiloxane and nylon fabric	Biobrane
	Silicone rubber and nylon	IP-758
	Poly-e-caprolactone film and foam	
	Collagen and caprolactone	

adhesion between the resultant laminate. The authors attempted to use water instead of diacetine as a solvent, but after a few days of storing the laminate in distilled water, the layers separated. The laminate was reinforced using a polyethylene terephthalate net. This reinforced laminate net appears to have potential as a wound dressing based on animal studies, and further work is in progress (Corkhill et al., 1989).

In another relatively new form, P-HEMA is mixed with water-soluble organic solvents, plasticizers, and an antibacterial or other topical agent (Corkhill et al. 1989). This mixture is cured. A thin sheet of the resultant material shows good adherence to the skin (Korol, 1985).

Although a range of synthetic wound dressings has been developed and tried, many surgeons still prefer using conventional methods like paraffin gauze dressings (Bruin et al., 1990).

Porosity of P-HEMA Hydrogels

The formulation used to make P-HEMA is very important in determining the structure of the hydrogel. If the monomer is polymerized in the presence of a good solvent or a small amount of nonsolvent (such as water), 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. This type of hydrogel is

referred to as heterogeneous or macroporous. These heterogeneous hydrogels have true voids between the individual polymer chains. These permit cellular ingrowth and may be suitable for wound dressings, for example. The structure of P-HEMA is crucial in determining the specific biomedical application.

Heat polymerization studies

The major polymerization techniques used to make P-HEMA are heat, radiation, or chemical polymerization. These methods may not produce the same type of structure for a particular formulation. Also, a variety of structures can be developed using heat polymerization, for example, due to the different amounts of crosslinkers and initiators that might be used as constituents.

Barvic et al. (1967) developed sponge-like polymers for potential biological use, such as plastic and reconstructive surgery, using heat polymerization. They used an initial monomer solution of 92.47 weight percent HEMA, 0.28 weight percent EGDMA, and 7.25 weight percent ethylene glycol. Three types of sponges were prepared by increasing the amount of water from 70% to 75% to 80% water with 10 weight percent of initiator, ammonium persulfate. Polymerization was carried out at 65° C. They demonstrated that the pore channel diameters in the sponges increased from 40 to 80 micrometers or more as the water percent increased. Specific channel size openings of the three samples reported range 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. The Barvic method was used in this thesis for two levels of initiator concentration: 10% by weight of ammonium

persulfate and 1% by weight of ammonium persulfate.

Sprincl et al. (1971) investigated the porosity of heterogeneous P-HEMA hydrogels using heat polymerization and investigated the potential for using them as implants. The porosity was varied by changing the water content in the initial monomeric mixture. The monomer solution contained 2 weight percent of crosslinker (EGDMA) and 98 weight percent HEMA. This solution (50% to 10% by volume) was mixed with specific amounts of water (to provide water contents of 50% to 90% by volume). An initiator agent, ammonium persulfate, was added to all solutions (1 weight percent). The mixture was purged with nitrogen gas for thirty minutes and polymerized at 60° C for 10 hours. Using optical microscopy, the investigators discovered that by increasing the water content in the initial mixture, the porosity of the hydrogels changed from microporous to macroporous (having a spongy character). For clinical purposes, homogeneous gels have an equilibrium water content of 40 to 50% water and spongy gels have an equilibrium water content of 80% water. Although specific pore sizes were not stated, the higher the water content (that is, higher porosity), the greater the penetration of vessels and new-formed fibrous tissue. However, if the porosity was too high (greater than 80% water), giant multinuclear cells were observed. Pore sizes were at least 10 micrometers in diameter in order to permit cellular ingrowth. The Sprincl formulations were also used in this thesis, as well as a 40% water content sample.

Ronel et al. (1983) used low temperature polymerization to develop macroporous membranes for potential use as an artificial pancreas. Their results showed that the

pore size and pore density were dependent on the water to HEMA ratio and on the amount of crosslinker. Using a constant crosslinker concentration (0.12 weight percent EGDMA), the authors varied the water to HEMA ratios: 50:50, 55:45, 60:40, 70:30, and 75:25. Redox initiators (0.25% of ammonium persulfate and 0.25% sodium metabisulfite based on the weight of the monomer) were added to each solution. The solutions were degassed and polymerized at 10° C for 18 hours. The pore sizes ranged from 1 to 18 micrometers. Pore size distribution showed no systematic variation with water content; however, pore density increased with increasing water content. The authors also varied the crosslinker concentration from 0.02% to 3% concentration at a constant water to HEMA ratio of 70:30 with the same redox initiators. Pore sizes ranged from 1 to 18 micrometers; however, a crosslinker content over 0.5% nearly eliminated the macroporous structure.

Many studies have been performed using heat polymerization to develop homogeneous hydrogels. These studies are particularly important for contact lenses and controlled drug release systems.

Migliaresi et al. (1981) used heat polymerization to form P-HEMA. They used different types of solvents in order to obtain a wide range of physical properties for varied homogeneous hydrogel biomedical applications. A monomer solution composed of 99.4 weight percent HEMA, 0.5 weight percent EGDMA, and 0.1 weight percent initiator (benzoyl peroxide) was polymerized at 90° C for 1 hour. Diacetine, or poly(vinyl pyrrolidone), or glycerol was used as the solvent. The average pore radius (found from permeability measurements) varied from 3.82 to

14.64 angstroms, depending on the solvent used to make a particular polymer membrane sample.

Peppas et al. (1985) used heat to prepare homogeneous thin films by reacting HEMA monomer with EGDMA at crosslinking ratios 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 the initiator). The solvent, water, was added to a level of 40% by weight. The solutions were bubbled with nitrogen gas for at least 2 hours. Polymerization took place at 60° C for 12 hours. The investigators produced a homogeneous (nonporous) gel-type membrane of crosslinked P-HEMA. They also demonstrated an increase in the nonporous membrane mesh size as the crosslinker concentration decreased. Mesh size was determined by applying theoretical analyses from which the crosslinking density and the molecular weight between crosslinks are obtained. The models use these parameters to determine an equivalent number of repeating units between crosslinks and therefore establish a distance between crosslinks. The mesh size reported ranged from 14 to 36 angstroms. Lee et al. (1978) also demonstrated that the membrane pore size (of the order of several angstroms) of homogeneous P-HEMA hydrogels increases with a decrease in crosslinker concentration.

Radiation and chemical polymerization studies

In addition to heat polymerization, radiation and chemical polymerization techniques are used to develop P-HEMA hydrogels with a variety of structures.

Andrade et al. (1976) used radiation polymerization to obtain P-HEMA. Bulk P-HEMA was observed using freeze-etch SEM samples. A sample composed of 54.4% HEMA, 7.5% EG, and 38.1% water was opaque and had pores less than 5 micrometers in diameter. SEM photos of polymers formed from 30% HEMA and 70% water, which were freeze fractured in liquid nitrogen, showed pores about 10 micrometers in diameter. In general, the freeze-fracture SEM sample preparation method tends to introduce microstructural distortions and artifacts.

Greer et al. (1979) used radiation and chemical polymerization to coat silicone rubber sheets or polyethylene terephthalate (Dacron) velour substrates with hydrogel formulations containing HEMA (10-20%), EGDMA (0-3%), and NVP (n-vinyl pyrrolidone) (0-15%) together with water and methanol (a 25% methanol and 75% distilled water solvent). The solutions then were bubbled with nitrogen gas and irradiated using Cobalt-60 radiation (a dose of 0.25 Mrad). Pore sizes for the bulk hydrogel (20% HEMA and 1.5% EGDMA radiation polymerization technique) were 20-50 micrometers in diameter.

Samples prepared by chemical polymerization (Knoll, 1980), using the method of Predecki (1974), were also studied. Silicone rubber substrate materials were boiled in xylene for 10 minutes to swell the sheets so that the monomer solution could enter the rubber for subsequent polymerization. Then the sheets were placed in a particular solution (containing monomer) consisting of 10-25% HEMA, 0-2% EGDMA, and 5% ethanol with the balance as xylene for 2 hours. The polymerization reaction then was completed in the range of 118-135° C (just below

the boiling point of the solution). The investigators determined that the microstructure of the hydrogel in the interpenetrating network (i. e., the hydrogel within silicone rubber) system is more porous than that of the radiation initiated polymerization system.

Knoll (1980) investigated methods for the formation of bulk hydrogel and the chemical and radiation grafting of hydrogels onto different substrates (Dacron and Silastic) using the methods of Greer et al. (1979). Knoll used a wide variety of formulations based on mixtures of HEMA, EGDMA, methanol and distilled water. Samples prepared with 54 to 58% distilled water in the cosolvent mixture had a Feret diameter (Fischmeister, 1968) (Feret diameter is equal to the diameter of a circle with the same circumference as the average figure observed on a line scan basis) of 1 to 30 micrometers. Also, a finely divided substructure was seen in the homogeneous polymer networks of a size range of 0.3 to 0.8 micrometers in diameter. Knoll demonstrated that increasing the water in the cosolvent mixture above 43% water resulted in heterogeneous gels.

MATERIALS AND METHODS

Several formulation methods were used to determine the effects of crosslinker, initiator, and the water to HEMA ratio on the pore or channel structure of P-HEMA hydrogels. Samples developed using the method of Sprincl et al. (1973) are listed in Tables 2 and 3. The monomer used in these studies contains 0.1% EGDMA as an impurity. The samples listed in Table 2 were prepared using a is a modification of the Sprincl method in that no initiator was used, while the sample series in Table 3 were prepared using 1% by weight ammonium persulfate. Samples for these two series were compared in order to determine the effects of the initiator on the microstructure of the hydrogels. Samples using another Sprincl et al. (1971) procedure also were studied, and the sample series developed is listed in Table 4. In this case, there is a solution of 98 weight percent HEMA and 2 weight percent crosslinker (EGDMA) added to the water solution in varying volume percent ratios. Also, there is 1 weight percent initiator (ammonium persulfate) added to each solution. Microstructural information developed for this series was compared to the series in Table 3 in order to determine what effect the crosslinker had on the microstructure of P-HEMA hydrogels. Samples representative of the method developed by Barvic et al. (1967) were incorporated into this study also. The two series listed in Table 5 were prepared. One series had the 10 weight percent initiator (which is what Barvic used) added to each solution, while the second series

Table 2. Formulations of the S series (S = Sprincl) samples (in volume percent); no initiator added

Sample #	% Water	% HEMA	% EGDMA added
S1	95.0	4.9	0.1
S22	95.0	5.0	---
S2	90.0	9.8	0.2
S21	90.0	10.0	---
S3	85.0	14.5	0.5
S20	85.0	15.0	---
S4	80.0	19.0	1.0
S19	80.0	20.0	---
S6	75.0	24.0	1.0
S5	75.0	25.0	---
S7	70.0	29.0	1.0
S18	70.0	30.0	---
S9	60.0	37.0	3.0
S8	60.0	40.0	---
S10	50.0	48.0	2.0
S17	50.0	50.0	---
S16	40.0	60.0	---
S11	38.0	60.0	2.0
S12	33.0	60.0	7.0
S15	30.0	70.0	---
S13	20.0	80.0	---
S14	10.0	90.0	---

Table 3. Formulations of the SI series (S = Sprincl; I = initiator present) samples (in volume percent) with 1 weight percent of ammonium persulfate initiator added to each solution

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
SI8	20.0	80.0
SI9	10.0	90.0
SI10	0.0	100.0

Table 4. Formulations of the SX series (S = Sprincl; X = crosslinker added) samples; 1 weight percent ammonium persulfate initiator added to each solution

Sample #	Water, volume percent	HEMA (as 98 weight percent HEMA + 2 weight percent EGDMA), volume percent
SX1	90.0	10.0
SX2	80.0	20.0
SX3	70.0	30.0
SX4	60.0	40.0
SX5	50.0	50.0
SX6	40.0	60.0

Table 5. Formulations based on the Barvic series samples (in weight percent)

Sample #[a]	% Water	% HEMA	% EGDMA	% EG	% $(NH_4)_2S_2O_8$
B110	63.6	27.7	0.08	2.2	6.4
B210	68.2	23.1	0.07	1.8	6.8
B310	72.7	18.5	0.06	1.4	7.3
B1	69.3	27.7	0.08	2.2	0.7
B2	74.3	23.1	0.07	1.6	0.7
B3	79.2	18.5	0.06	1.4	0.8

[a]Note: The B110, B210, and B310 samples have 10% initiator, $(NH_4)_2S_2O_8$; the B1, B2, and B3 samples have 1% initiator, $(NH_4)_2S_2O_8$. This description is based on Barvic et al. (1967). They mixed either 70, 75, or 80% by weight of the 10% ammonium persulfate solution with 30, 25, or 20% by weight of the monomer solution, respectively. The monomer solution was 92.47% by weight HEMA, 0.28% by weight EGDMA, and 7.25% by weight EG. In the above table, the percent water and the percent initiator are listed separately.

had only 1 weight percent initiator in each solution. This provided samples for comparison with the Sprincl et al. method. Therefore, the effect of initiator on microstructure could be examined for a relatively low and a relatively high level of initiator content.

A pressure polymerization technique was also used to determine the effect of pressure on the resulting microstructure (Pinchuk and Eckstein, 1981; Pollard, 1987).

Materials

The monomer, poly(2-hydroxyethyl methacrylate), P-HEMA, was obtained from Polysciences, Inc., Warrington, PA (ophthalmic grade, Lot 82459). It was used as supplied, containing an impurity level of 0.1% EGDMA. Note that the Tables report the formulations without the 0.1 % EGDMA added. The crosslinker, tetraethylene glycol dimethacrylate (TEGDMA), was also obtained from Polysciences, Inc. (Lot 18976). The crosslinker, ethylene glycol dimethacrylate (EGDMA), was obtained from Monomer-Polymer and Dajac Laboratories, Inc., Trevose, PA (Lot 1-2-14). Ethylene glycol (EG) was obtain from Fisher Scientific, Fair Lawn, NJ (Lot 864180). Type I deionized water was used as the solvent. The initiators, ammonium persulfate (Lot 743791) and sodium metabisulfite (Lot 745412), were obtained from Fisher Scientific.

Polymerization Procedure

For the S series and the SI series samples (Tables 2 and 3) volumetric measurements were used to make the samples using HEMA, EGDMA, and deionized water. The ammonium persulfate was measured gravimetrically for the SI

series samples. For the SX series samples (Table 4), HEMA and EGDMA were weighed and combined (98 weight percent HEMA and 2 weight percent EGDMA). Then volumetric measurements were used to make up the HEMA/EGDMA and deionized water solutions, while the ammonium persulfate was measured gravimetrically. For the Barvic samples (Table 5), all the components (deionized water, HEMA, EGDMA, EG, and ammonium persulfate) were measured gravimetrically. For samples based on the Pollard (1987) method, all the components were measured by volume except the two initiators which were measured by weight.

Fifty milliliters (ml) of each formulation were prepared (except for the Pollard method). Ten ml of each solution were placed in individual glass screw cap tubes (16mm x 150mm) that had been previously flushed with nitrogen. The tube threads were wrapped with Teflon tape. In an inert nitrogen atmosphere (nitrogen gas inside a glove bag), each solution was bubbled with nitrogen for 30 minutes to remove dissolved oxygen. After 30 minutes, each tube was sealed and placed upside down in a water bath at 60° C for 10 hours for the S, SI, and SX series samples, while the Barvic series samples were placed in a 65° C water bath until the polymerization process was completed. If a solution failed to polymerize, the process was repeated using 10 ml of the previously prepared solution.

For the Pollard method (after Lee et al., 1978), three stock solutions were prepared. Solution A was a mixture of 10 ml P-HEMA, 0.1 ml TEGDMA, 3.0 ml EG, and 2.0 ml deionized water. Solution B was 1.0 ml ammonium persulfate (40 g

per 100 ml deionized water). Solution C was 1.0 ml of sodium metabisulfite (15 g per 100 ml deionized water). Each solution was purged with nitrogen for 30 minutes before use. Then a mixture of 1.51 ml of solution A, 0.1 ml of solution B, and 0.1 ml of solution C was made in a syringe, and the liquid was pressure polymerized within the syringe at 100 psi for 1 hour.

Critical Point Drying

After the polymerization process was completed, the hydrogels were removed from the tubes or syringes and were placed in glass jars in a solution of ethanol and water (50:50 volume percent). The hydrogels remained in these solutions for 2 hours to remove any unreacted monomer. After the 2 hour wash, the hydrogels were stored separately in clean glass jars filled with deionized water until the samples could be dried for subsequent SEM studies. An additional series was prepared and washed in ethanol and water over a 2 day period. These were compared with the samples which recerived shorter washes to determine if there had been complete removal of initiator residues prior to SEM examination. A small sample, less than one millimeter in thickness, was obtained from each bulk hydrogel specimen by pulling the bulk hydrogel apart and carefully extracting a thin sample using a scalpel or a tweezers. Care was taken to avoid crushing the subsample. Each subsample was then rinsed in a series of acetone/deionized water solutions (30, 50, 70, 80, 90, 95, 100, 100% volume to volume ratio) for fifteen minutes in each in order to replace the water in the hydrogel structure. A maximum number of three samples was placed into the transfer boat of the E3000 critical point dryer (Polaran

Instruments, Inc., Warrington, PA). The transfer boat then was filled with 100% acetone to prevent drying of the samples. Liquid carbon dioxide was used to fill the critical point drying apparatus chamber and to flush out the acetone . The flushing action was continued for at least three minutes, but not more than five minutes. After flushing, the samples were allowed to remain in the critical point dryer for one hour to allow for impregnation of the samples with liquid carbon dioxide. After one hour, the chamber was flushed again for three to five minutes. Hot water was then passed through the chamber shell in order to raise the liquid carbon dioxide in the apparatus above its critical point. For a pressure reading above 1200 psi and a temperature in the chamber above 32° C, the conversion of the liquid carbon dioxide to a gas is complete (without having to pass through a phase transformation boundary). The hot water was shut off and the carbon dioxide gas was vented slowly to avoid re-condensation. The samples were removed from the critical point dryer, placed into vials (15mm x 45mm), and stored in a desiccator (over Drierite^{R}) for future SEM studies.

Subsample Preparation

The subsamples were tipped out of the vials onto double stick adhesive tape that was placed on top of a one-half inch diameter carbon cylinder surface. The samples were pressed down carefully at the corners (without distorting the central regions of the samples) in order to fix them to the tape. They were sputtered coated using an E5100 sputter coater (Polaron Instruments, Inc.). Gold was deposited onto the samples for two minutes with a gold deposition rate of 154 angstroms/minute. The

maximum number of samples coated at any time was five. After coating, the samples were placed into petri dishes and stored in a desiccator (over Drierite^{R}).

SEM

A JSM 840A SEM was utilized to characterize the morphology of the samples. The SEM was operated at an accelerating voltage between 5 to 10 keV using a working distance of 15 mm. Magnifications used in this study range from 95X to 4000X. SEM photos were taken using Polaroid (Polaroid Corporation, Cambridge, MA) type 55 film.

Pore and Channel Structures

The pore structures were determined from the SEM photos at the 120X, 350X, or 1000X magnifications. The pore densities are reported as pores per square centimeter (pores/cm^2). The densities were determined by counting the number of pores within a one centimeter by one centimeter square at 12 locations on an SEM photo at 120X or at 350X magnification. The average was converted to pores/cm^2 based on the magnification factor. The pore sizes were determined by measuring the diameter of the pore openings in one-half of the field of view of either a 120X or a 350X magnification SEM photo, and then doubling the results. The channels were characterized the same way as the pore openings. Note, a pore opening is defined as any closed or open structure within spherical units or bulk hydrogel material, while a channel is defined as an opening within clusters of hydrogel. Typically, pores are less than 25 micrometers in diameter, and channels are generally larger than 25 micrometers (up to approximately 100 micrometers in diameter).

RESULTS

The following microstructure features for selected SEM images are representative for the samples of Tables 2-5. For each method used, a description of the overall appearance of the samples is given. Also tables are provided that list the pore density, pore size, channel size, and particle size for each sample studied, as appropriate.

Under the influence of heat, the samples of Table 6 will polymerize without initiator present. However, the polymer formation is not efficient or uniform. The polymer forms as tubular strands and piles up leaving space between the strands. The polymerized material (wet condition) is opaque (white). An example of the general appearance for the entire compositional interval of 100% HEMA to 5% HEMA and 95% water is shown in Figure 1 (sample S17). The strands are approximately 1 to 4 micrometers in diameter in this field of view.

By comparison with the S series, the SI and SX series (Tables 7 and 8, respectively) polymerized in the presence of an initiator which provides free radicals for joining the mers (units) together to make up the polymer. The resultant microstructure of the polymer is of three general forms, depending on the specific composition interval of water and HEMA. These are massive, bulk with pores, and extensive microporosity and channels. For water contents of 0 to 30%, the polymer is transparent (wet condition) with the hydrogel as a mass without obvious pores. An

Table 6. Formulations, appearance, and optical properties for the S series samples; no initiator added

Sample #	% Water	% HEMA	% EGDMA	Appearance of polymer	Optical property
S1	95.0	4.9	0.1	flaky	opaque
S22	95.0	5.0	---	flaky	opaque
S2	90.0	9.8	0.2	flaky	opaque
S21	90.0	10.0	---	flaky	opaque
S3	85.0	14.5	0.5	bulky, rubbery	opaque
S20	85.0	15.0	---	bulky, rubbery	opaque
S4	80.0	19.0	1.0	bulky, rubbery	opaque
S19	80.0	20.0	---	bulky, rubbery	opaque
S6	75.0	24.0	1.0	bulky, stiff	opaque
S5	75.0	24.0	---	bulky, stiff	opaque
S7	70.0	29.0	1.0	bulky, stiff	opaque
S18	70.0	30.0	---	bulky, stiff	opaque
S9	60.0	37.0	3.0	bulky, stiff	opaque
S8	60.0	40.0	---	bulky, stiff	opaque
S10	50.0	48.0	2.0	bulky, stiff	opaque
S17	50.0	50.0	---	bulky, stiff	opaque
S16	40.0	60.0	---	bulky, stiff	opaque
S11	38.0	60.0	2.0	bulky, very stiff	opaque
S12	33.0	60.0	7.0	bulky, very stiff	opaque
S15	30.0	70.0	---	bulky, very stiff	opaque
S13	20.0	80.0	---	bulky, very stiff	opaque
S14	10.0	90.0	---	bulky, very stiff	opaque

Figure 1. P-HEMA. Sample S17 with 50% water - 50% HEMA and no initiator added. 350X

Table 7. Formulations, appearance, and optical properties for the SI series samples; 1 weight percent ammonium persulfate initiator added to each solution

Sample #	% Water	% HEMA	Appearance of polymer	Optical property
SI1	90.0	10.0	very soft	opaque
SI2	80.0	20.0	soft	opaque
SI3	70.0	30.0	flexible	opaque
SI4	60.0	40.0	flexible	translucent
SI5	50.0	50.0	firm	translucent
SI6	40.0	60.0	firm	translucent-transparent
SI7	30.0	70.0	stiff	transparent
SI8	20.0	80.0	very stiff	transparent
SI9	10.0	90.0	very stiff	transparent
SI10	0.0	100.0	very stiff	transparent

Table 8. Formulations, appearance, and optical properties for the SX series samples; 1 weight percent ammonium persulfate initiator added to each solution

Sample #	Water, volume percent	HEMA (as 98 weight percent HEMA + 2 weight percent EGDMA), volume percent	Appearance of polymer	Optical property
SX1	90.0	10.0	flexible	opaque
SX2	80.0	20.0	firm	opaque
SX3	70.0	30.0	firm	opaque
SX4	60.0	40.0	firm	opaque
SX5	50.0	50.0	stiff	transparent
SX6	40.0	60.0	very stiff	transparent

example is shown in Figure 2 (sample SI8). For water contents of 40 to 70%, the second major structure type is seen (Figures 3 to 6). The material in this case is translucent and appears as bulk hydrogel containing pores ranging from 3 micrometers (Figure 3; sample SI6) to 14 micrometers (Figure 6; sample SI3) in association with increasing water content. As the water content increased for the samples of Figures 3 to 6 which had a relatively low crosslinker content (0.1% EGDMA), the pores increased in diameter. The effect of increasing crosslinker content can be seen in a representative comparison of Figure 4 and Figure 7. The SX series has 2% EGDMA (crosslinker) compared with the 0.1% EGDMA contents of the SI series. The presence of 2% EGDMA tightens up the HEMA structure, and so the sample in Figure 7 (sample SX5) is nonporous in comparison with the sample in Figure 4 (sample SI5) of the same water content. Samples SX6 to SX4 are nonporous, whereas the porosity appears at relatively higher water contents in samples SX3 to SX1, compared with the SI6 to SI3 samples of Figures 3 to 6. The third microstructural form is seen in samples with water contents of about 70% and above. The material is stringers of spheres of hydrogel (relatively larger at lower water contents in this range) with the pores and channels increasing in dimension as the water content increases and less hydrogel is available for polymerization. This material is opaque, as the light scatters off the large number of surfaces of hydrogel. Figure 8 (sample SX2) and Figure 9 (sample SI1) represent this third class of organization of the polymer. The spheres in Figure 8 are about 1 micrometer in diameter (2% EGDMA example), and the spheres in Figure 9 are about 4

Figure 2. P-HEMA. Sample SI8 with 20% water - 80% HEMA and initiator. Small needle shaped crystals are present due to incomplete initiator removal after polymerization. 1000X

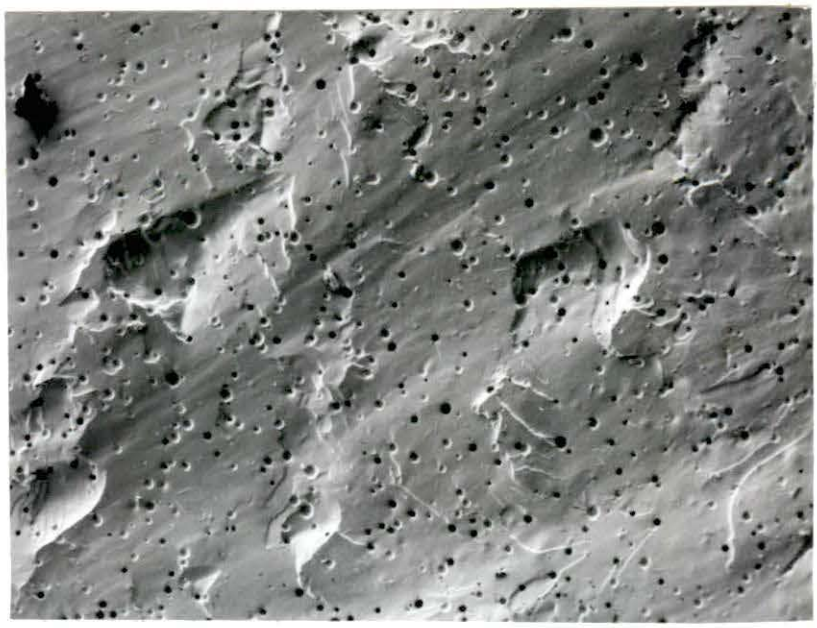

Figure 3. P-HEMA. Sample SI6 with 40% water - 60% HEMA and initiator. 350X

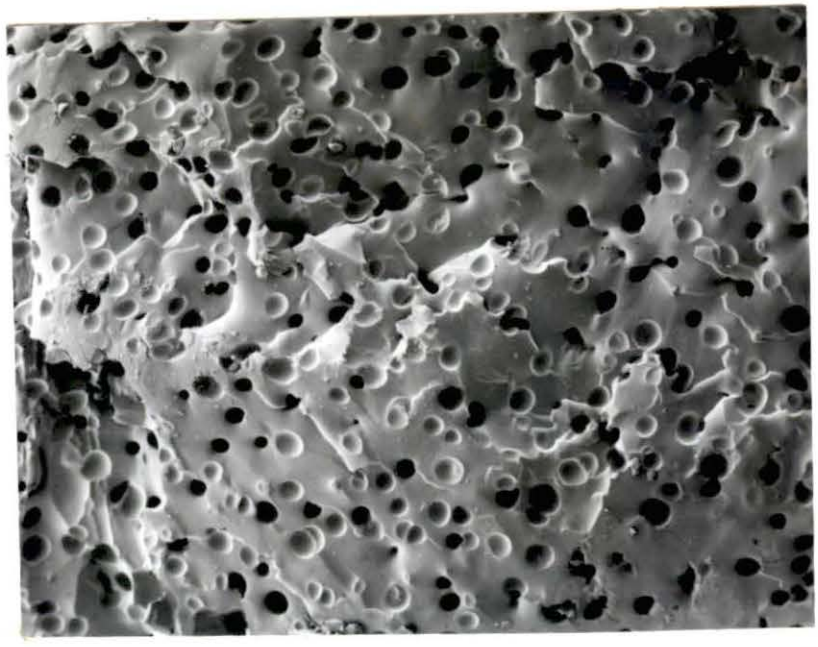

Figure 4. P-HEMA. Sample SI5 with 50% water - 50% HEMA and initiator. 350X

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

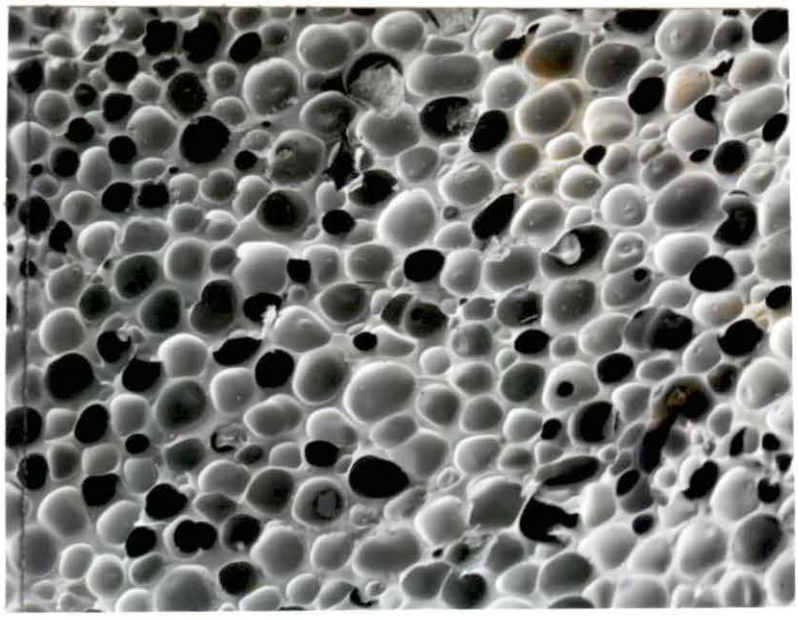

Figure 6. P-HEMA. Sample SI3 with 70% water - 30% HEMA and initiator. 350X

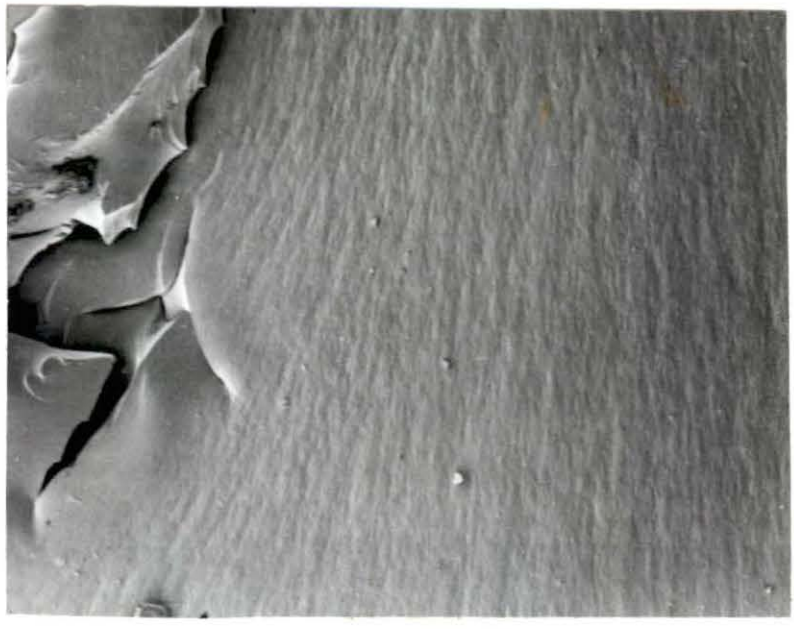

Figure 7. P-HEMA. Sample SX5 with 50% water - 50% HEMA and initiator. EGDMA content is 2%, compared with 0.1% for samples of Figures 2 to 6. 350X

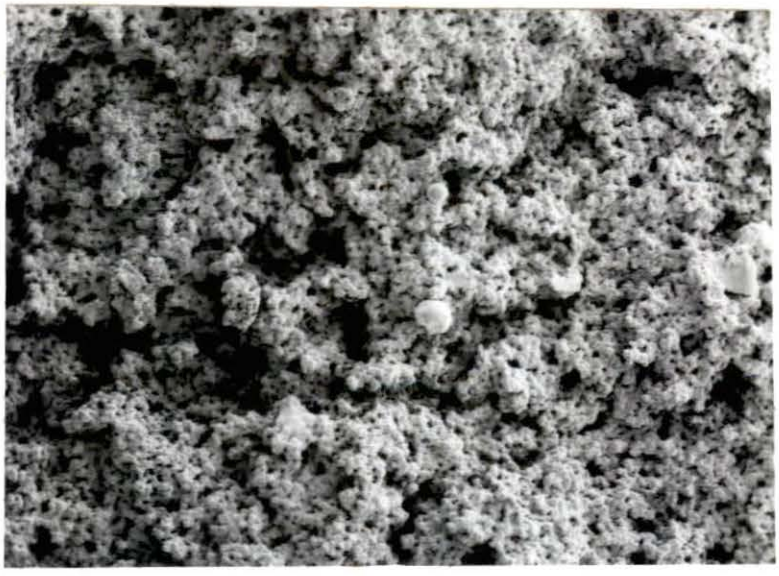

Figure 8. P-HEMA. Sample SX2 with 80% water - 20% HEMA and initiator. 350X

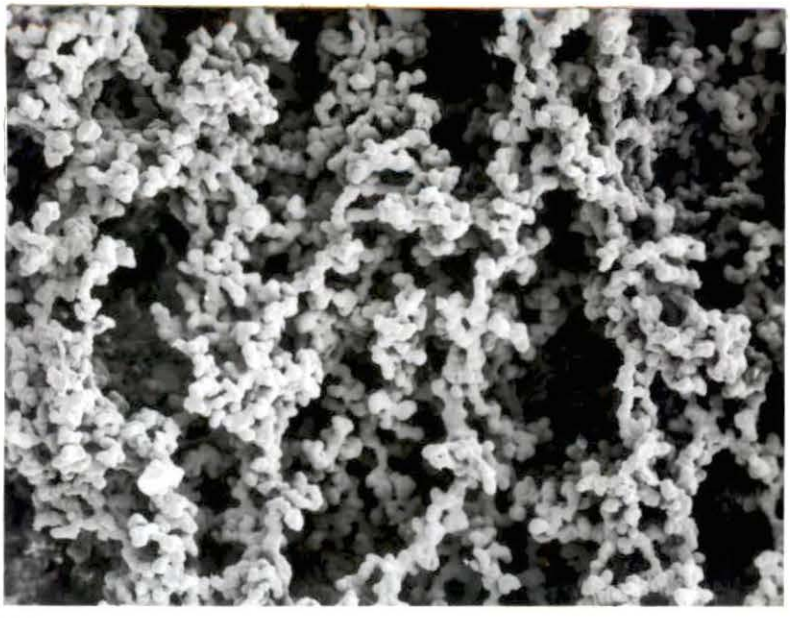

Figure 9. P-HEMA. Sample SI1 with 90% water - 10% HEMA and initiator. 350X

micrometers in diameter (0.1% EGDMA example). For the same level of crosslinker, as water increases the sphere sizes decrease and the structure becomes more open. For higher crosslinker content (2% compared with 0.1% samples), the relative sizes of spheres are smaller, but a similar trend of sphere size and degree of openness of the structure with increasing water content is seen to occur for the SX series compared to the SI series for water contents above about 70%. Channels and pores are seen in Figures 8 and 9.

To show the effect of initiator content on microstructure, the samples prepared by the Barvic method (Table 9) can be compared in two groups: B1, 2, and 3 for the 1% initiator content and B110, 210, and 310 for the 10% initiator content. Also, three different levels of water content are used for the two series. Figures 10 to 12 correspond to the 10% initiator content with water increasing from 64% (Figure 10; sample B110) to 73% (Figure 12; Sample B310). Spheres are present, and decrease in size as water content increases (channel size increases as water content increases). A higher magnification view of the channels and pores and spheres of Figure 11 (sample B210) is shown in Figure 13 (sample B210). For the lower initiator content series of samples, the same general trend is seen for sizes of spheres, and channel openings. Figure 14 (sample B1) is an example which can be compared with Figure 11 (sample B210) at comparable water levels to show the relatively smaller size of spheres at the lower initiator content (Figure 14) compared to the larger size at the higher initiator content (Figure 11). The higher magnification view of Figure 14 is seen in Figure 15 (sample B1), and this can be compared with Figure 13 (sample

Table 9. Formulations, appearance, and optical properties for the Barvic sample series

Sample #[a]	Water, weight percent	HEMA, weight percent	EGDMA, weight percent	EG, weight percent	$(NH_4)_2S_2O_8$, weight percent	Appearance of polymer	Optical property
B110	63.6	27.7	0.08	2.2	6.4	firm	opaque
B210	68.2	23.1	0.07	1.8	6.8	flexible	opaque
B310	72.7	18.5	0.06	1.4	7.3	flexible	opaque
B1	69.3	27.7	0.08	2.2	0.7	flexible	opaque
B2	74.3	23.1	0.07	1.6	0.7	flexible	opaque
B3	79.2	18.5	0.06	1.4	0.8	soft	opaque

[a]Note: the B110, 210, and 310 samples have 10% initiator, $(NH_4)_2S_2O_8$; the B1, B2, and B3 samples have 1% initiator, $(NH_4)_2S_2O_8$. This description is based on Barvic, et al. (1967). They mixed either 70, 75, and 80% by weight of the 10% ammonium persulfate solution with 30, 25, or 20% by weight of the monomer solution, respectively. The monomer solution was 92.47% by weight HEMA, 0.28% by weight EGDMA, and 7.25% by weight EG. In the above table, the percent water and the percent initiator are listed separately.

Figure 10. P-HEMA. Barvic method sample B110 with 10% initiator. 350X

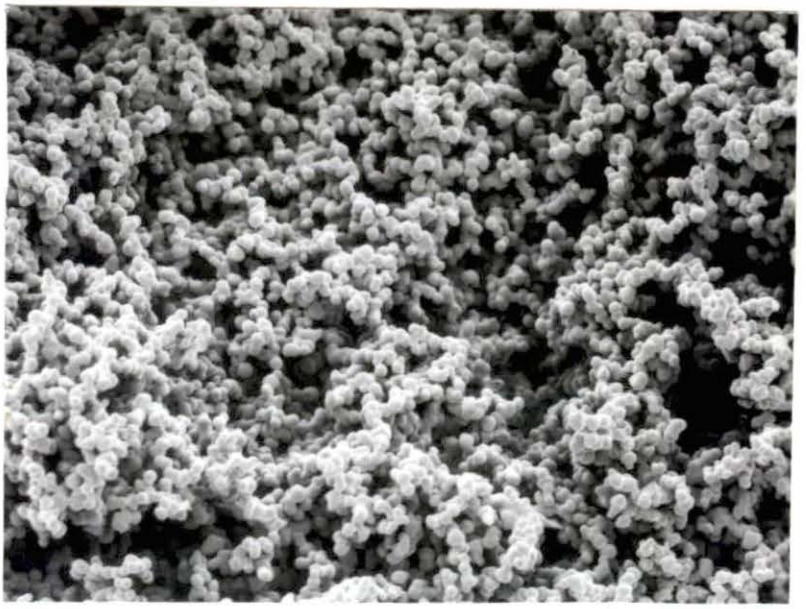

Figure 11. P-HEMA. Barvic method sample B210 with 10% initiator. 350X

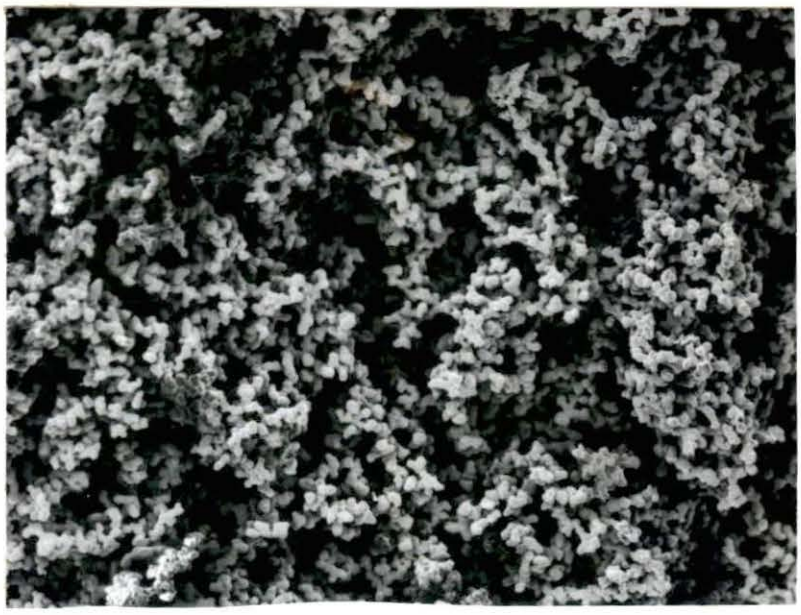

Figure 12. P-HEMA. Barvic method sample B310 with 10% initiator. 350X

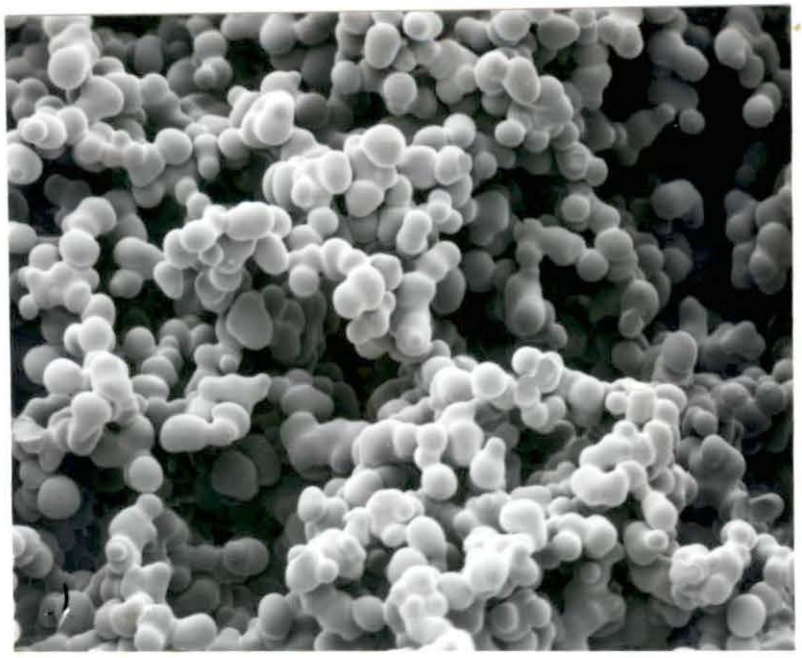

Figure 13. P-HEMA. Barvic method sample B210 with 10% initiator. 1000X

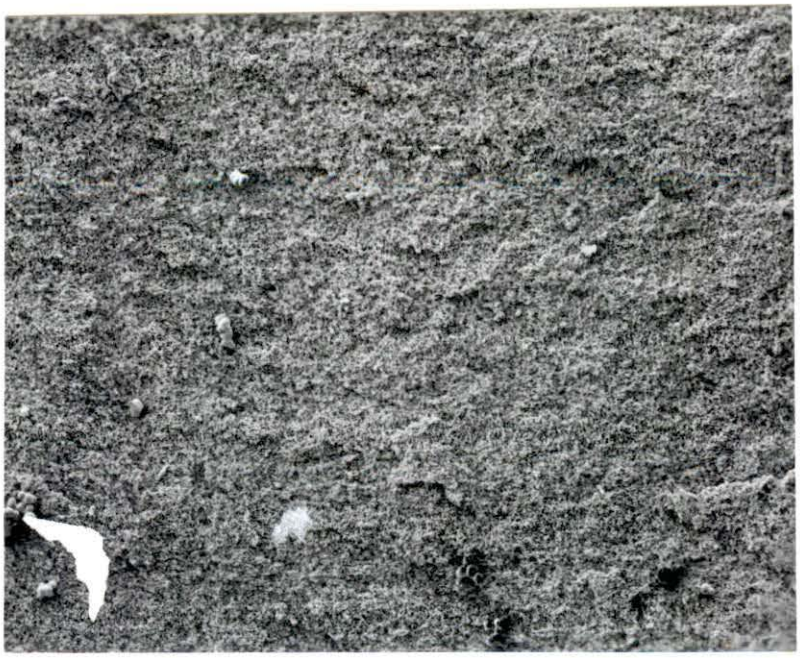

Figure 14. P-HEMA. Barvic method sample B1 with 1% initiator. 350X

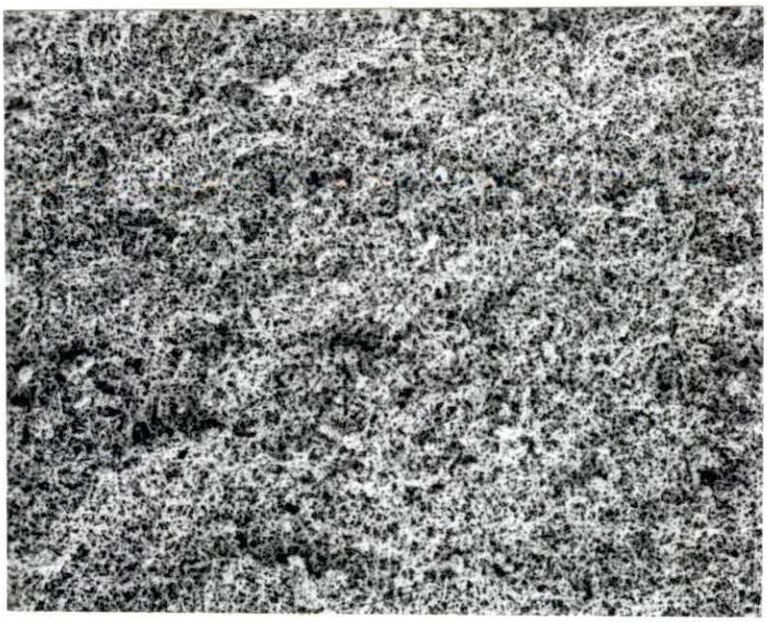

Figure 15. P-HEMA. Barvic method sample B1 with 1% initiator. 1000X

B210) to show that the channel size of the lower initiator content sample is smaller than that for the higher initiator content sample (at comparable levels of water content).

Two other examples are of general interest. Figure 16 shows the effect of replacing water with ethylene glycol in a formulation. This replacement tends to extend the homogeneous structural field to somewhat higher water contents, depending on the amount of EG used. For the cases where water is completely replaced by EG, the hydrogel would be homogeneous. Figure 16 represents a homogeneous structure (transparent) for an embryo growth chamber (Pollard, 1987). The sample contains a small amount (of the order of 0.52% by volume) of a crosslinker, TEGDMA. Figure 17 represents an example where the TEGDMA content is much greater, (approximately 8.6% by volume), and this apparently results in the formation of two basic structures, a compact and an open structure as seen in the same low magnification field of view.

Additional details of measurements for the various fields of view of the S, SI, SX, and Barvic samples are listed in Tables 10-13. The trends described above can be developed by these tabulated values using sample comparisons based on relative water content, the absence of presence of initiator (and level of concentration of initiator), as well as relative crosslinker contents.

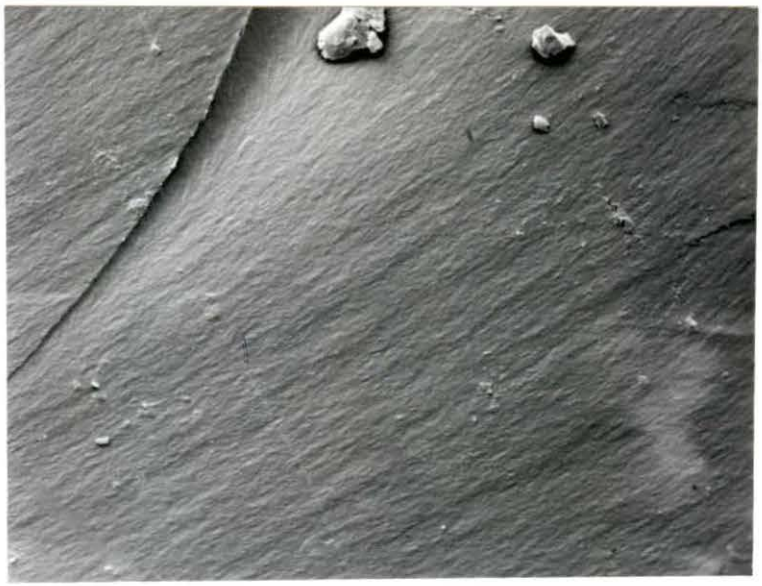

Figure 16. P-HEMA. Pollard method sample with 0.58% TEGDMA. 1000X

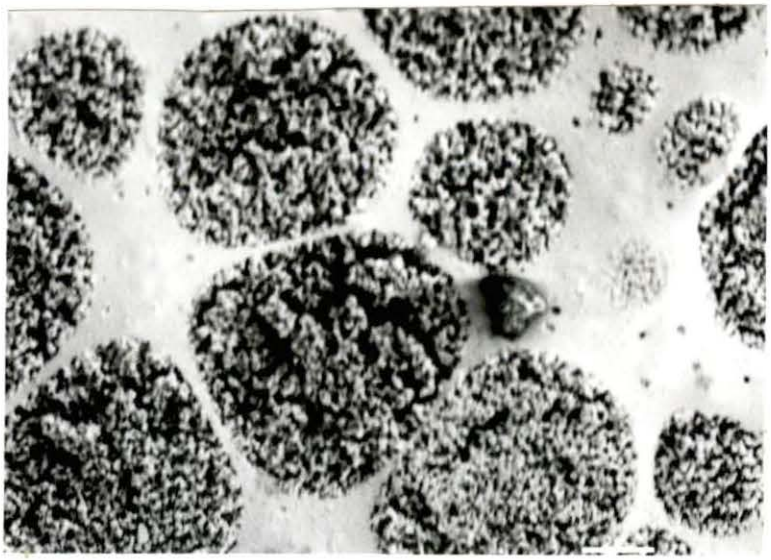

Figure 17. P-HEMA. Lee et al. (1978) method sample with 8.6% TEGDMA. 95X

Table 10. Pore densities, pore sizes, channel sizes, and hydrogel particle sizes of S series samples

Sample #	Pore density (x 10^5 pores/cm^2)	Pore size (microns)	Maximum channel size (microns)	Particle size (microns)
S1	69	0.01-2	29	---
S22	2.2	0.01-7	130	---
S2	38	0.01-2	63	---
S21	2.18	0.01-7	124	---
S3	36	6-9	81	3.0
S20	1.31	0.01-2	200	---
S4	12.2	0.01-7	133	---
S19	0.835	0.01-2	160	---
S6	16.8	1-14	86	---
S5	8.2	2-25	200	---
S7	16.6	0.6-6.0	84	---
S18	0.435	3-6	150	---
S9	16.6	2-7	14	---
S8	0.40	3-25	75	---
S10	10.7	1-25	108	---
S17	0.435	0.01-25	125	---
S16	0.145	0.01-25	120	---
S11	10	0.01-6	20	---
S12	10	0.01-4	57	---
S15	0.140	0.01-25	166	---
S13	0.346	0.01-7	46	---
S14	0.30	0.01-7	66	---

Table 11. Pore densities, pore sizes, channel sizes, and hydrogel particle sizes for SI series samples

Sample #	Pore density (x 10^5 pores/cm^2)	Pore size (microns)	Maximum channel size (microns)	Particle size (microns)
SI1	3.05	0.01-2	120	3-8
SI2	2.813	0.01-2	100	8-55
SI3	4.21	3-25; maj. 10-15	---	---
SI4	1.07	4-20; maj. 7-11	---	---
SI5	4.06	3-9; maj. 3-6	---	---
SI6	3.67	0.01-3	---	---
SI7	---	---	---	---
SI8	---	---	---	---
SI9	---	---	---	---
SI10	---	---	---	---

Table 12. Pore densities, pore sizes, channel sizes, and hydrogel particle sizes for SX series samples

Sample #	Pore density (x 10^5 pores/cm^2)	Pore size (microns)	Maximum channel size (microns)	Particle size (microns)
SX1	71	0.01-1.5	---	---
SX2	90	0.01-2.0	20	0-2.0
SX3	50	0.01-4.0	3	0-4.0
SX4	---	0.01-0.17	---	---
SX5	---	---	---	---
SX6	---	---	---	---

Table 13. Pore densities, pore sizes, channel sizes, and hydrogel particle sizes for Barvic series samples

Sample #	Pore density (x 10^5 pores/cm^2)	Pore size (microns)	Maximum channel size (microns)	Particle size (microns)
B110	4.32	0.01-5.7	42	3.5-10
B210	12.2	0.01-14	50	3.0-5.5
B310	12.2	0.01-7.0	57	2.0-4.0
B1	3.36	0.25-1.6	---	---
B2	15.9	0.01-4.3	60	1.5-4.0
B3	19.6	0.01-8.6	43	1.0-4.0

DISCUSSION

Varying the water to HEMA ratio and using different concentrations of crosslinker(s) and initiator(s) will produce different hydrogel structures.

Optical Transparency Changes

The S series samples were the only samples prepared without an initiator, and all the samples were opaque and bulky or flaky in appearance. Tubular structures were prominent and they established the pore openings and channels. They also coalesced to form a more dense structure at the lower water contents.

The SI series samples were prepared with an initiator but without any additional EGDMA compared with the S series. Spherical particles were prominent at the 90% and 80% water concentrations. They combined to form chains at 90% water content while at the 80% water content they were larger in size and had combined into groups instead of chains. The samples above 70% water were opaque. The structure of the samples changed between the 80% and 70% water content level. The structure now formed was dense and smooth with pore openings that decreased in diameter with decreasing water content. From 60% to 40% water content, the samples were translucent to almost transparent near the 40% water content level. Below 40% water, all the samples were transparent. These optical phenomena are in general agreement with Sprincl et al. (1973) who stated the homogeneous gels (transparent) occurred below 50% water, microporous gels (translucent) at more than

50% water but less than 70% water, and macroporous gels (opaque) at greater than 70% water (in the initial mixture). Yasuda et al. (1966) stated similar findings. The observations of these earlier investigators were developed by light microscopy (with its low depth of field).

The SX series samples were prepared with an initiator and a crosslinker. Spherical particles again were formed, and their size increased with the decreasing water content. Chain formation was again prominent at the higher water content. Pores and channels were formed as a result of the particles combining in strands or in clusters. Above 60% water content, the samples were opaque while the 50% water content sample was translucent and below 50% water content, the samples were transparent. The additional crosslinker content appeared to extend the range of homogeneous gels to higher water contents, compared with that of the SI series.

The B110, B210, and B310 samples were developed using the same method as described by Barvic et al. (1967). The results on the B samples are in agreement with the results obtained from the Barvic paper. However, the microstructural detail developed by Barvic and coworkers was very limited as their samples were characterized using optical microscopy for features at a relatively high magnification. The samples consisted of spherical particles that combined together into a chain structure. Openings among the chains increased as the water content increased while the particle size decreased as the water content increased. The microstructural features for the B1, B2, and B3 samples also followed this pattern.

Samples above 85% water content may have dissolved partially during the acetone/water rinses of the critical point drying procedure. Therefore, characterization of features for the very high water content samples may be affected.

Porosity

The majority of the samples showed a decrease in porosity as the water content decreased (or as the HEMA content increased) and as the crosslinker concentration (EGDMA) increased.

For the SX series samples, the porosity was greatest at the 80% water content (SX2) then it decreased with decreasing water content. SX1 at the 90% water content dissolved into a sticky substance so these measurements were omitted.

To summarize: a decrease in water content caused a decrease in porosity.

Pore Size

Larger pore sizes are found in the SI samples compared to those found in the SX series samples. For example at 70% water, SI3 had a pore size range of 3 to 25 micrometers while SX3 had a pore size range of less than 4.0 micrometers.

The water to HEMA ratio has been shown to influence porosity, but what effect does it have on pore sizes? Barvic et al. (1967) demonstrated that an increase in the water concentration from 70 to 80% does increase the pore size and channel size. The pore size of the SI series increased with increased water content.

When comparing samples prepared by the Barvic method, one can conclude that a 10 weight percent initiator content allowed larger pores to form compared with samples formed using 1% weight percent initiator content solution.

Channels

The channels appeared to increase in size with an increase water content for the SI series samples. Also the Barvic samples, B110 to B310, were found to show an increase in channel size as the water content increased. This is in agreement with Barvic et al. (1967).

CONCLUSION

This study characterized the pore and channel structures of P-HEMA that were developed using a variety of formulation methods that included varying the amount of deionized water and HEMA in solutions with and without crosslinkers and initiators. These solutions were heat polymerized. The accurate characterization of the pore structure is critical since it is the structure of the hydrogel that will determine the specific biomedical application such as wound dressings, artificial organs, drug release systems, or contact lenses.

From this study, it was concluded that the water to HEMA ratio, and to a lesser extent, the crosslinker and initiator concentrations play important roles in determining the resulting structure of the hydrogel. The following primary changes were seen as formulations were adjusted:

1. Porosity increased as the water content increased.
2. Porosity decreased as the crosslinker content increased.
3. From applying the Barvic method, a 10 weight percent initiator solution produced bigger pore openings than a 1 weight percent initiator solution.
4. Pore size increased as the water content increased.
5. Channel size increased as the water content increased.
6. The particle size increased with decreasing water content.
7. Hydrogels prepared without an initiator were opaque due to the presence of an open microstructure.
8. Hydrogels prepared with an initiator and/or crosslinker showed an optical change from opaque to transparent as the amount of water in the formulations was increased.

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