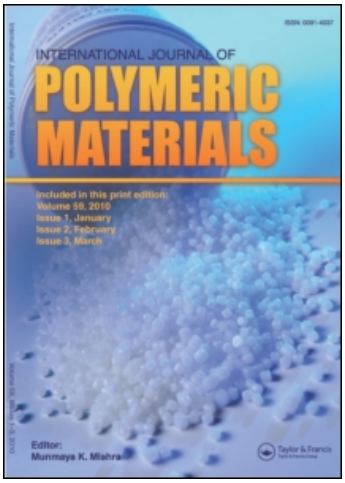


International Journal of Polymeric Materials
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713647664

Experimental Design in the Preparation of Modified HEMA-Based Superporous Hydrogels in an Aqueous Medium

Hossein Omidian[a]; Kinam Park[b]; Jose G. Rocca[c]
[a] College of Pharmacy, Nova Southeastern University, Fort Lauderdale, USA [b] Departments of Biomedical Engineering and Pharmaceutics, Purdue University, West Lafayette, USA [c] Solara Inc., Miami, USA

Online publication date: 21 July 2010

To cite this Article Omidian, Hossein , Park, Kinam and Rocca, Jose G.(2010) 'Experimental Design in the Preparation of Modified HEMA-Based Superporous Hydrogels in an Aqueous Medium', International Journal of Polymeric Materials, 59: 9, 693 — 709
To link to this Article: DOI: 10.1080/00914037.2010.483212
URL: http://dx.doi.org/10.1080/00914037.2010.483212

International Journal of Polymeric Materials, 59:693–709, 2010

ISSN: 0091-4037 print/1563-535X online
DOI: 10.1080/00914037.2010.483212

Taylor & Francis
Taylor & Francis Group

Experimental Design in the Preparation of Modified HEMA-Based Superporous Hydrogels in an Aqueous Medium

Hossein Omidian,[1] Kinam Park,[2] and Jose G. Rocca[3]

[1]College of Pharmacy, Nova Southeastern University, Fort Lauderdale, USA
[2]Departments of Biomedical Engineering and Pharmaceutics, Purdue University, West Lafayette, USA
[3]Solara Inc., Miami, USA

Due to a relatively large number of excipients and their concentrations, which can be used effectively in the preparation of superporous hydrogels, an experimental design based on the Taguchi matrix has proven to be a very valuable tool in screening and narrowing down the final formulation. In this study, the effect of starting materials, their concentrations as well as the starting reaction temperature, were examined in the preparation of superporous hydrogels based on hydroxyethyl methacrylate. A large number of possible formulations and conditions might lead to the production of a reasonable hydrogel network, but some formulations produce stronger or faster swelling superporous hydrogels than others. The final properties of the superporous hydrogels depend upon the events that occur during formation of the gel, including the presence of atmospheric oxygen, which is responsible for the inhibition period seen at the start of the reaction, and also including the change in temperature at which the reaction starts. These events can be largely affected by the choice of ingredients used in the reaction. For this study, eight variables were chosen, and their effects were examined using a Taguchi matrix. The parameters examined were the maximum temperature during the reaction, the time corresponding to the maximum temperature, and the reaction yield which is represented by the weight of the dry final SPH.

Keywords experimental design, gelation, inhibition period, poly (2-hydroxyethyl methacrylate), superporous hydrogels, synthesis

Received 4 January 2010; accepted 12 March 2010.
Address correspondence to Hossein Omidian, College of Pharmacy, Nova Southeastern University, 3200 S. University Drive, Fort Lauderdale, FL 33328, USA. E-mail: omidian@nova.edu

INTRODUCTION

Due to its biocompatibility and inertness, HEMA has been frequently used as an implantable material. PolyHEMA contact lens materials have been evaluated for the uptake and release of various drugs including cromolyn sodium, ketotifen fumarate, ketorolac tromethamine, dexamethasone sodium phosphate [1], and the anticancer drug 5-fluorouracil [2]. PolyHEMA hydrogels have also been examined as a release platform for ophthalmic drugs, to release alfuzosin [3], for protein delivery [4], protein separation [5], and ion removal from human plasma [6]. HEMA and its copolymers have also been studied for their potential to immobilize enzymes such as lipase [7], citrullus vulgaris urease [8], glucose oxidase [9], catalase, lysozyme, bovine serum albumin [10], and Jack bean urease [11]. As far as its synthesis is concerned, different porogens and techniques have been tried to generate porosity into the HEMA-based hydrogels. These include cyclohexane [12], dodecanol [13], and salt leaching utilizing sodium chloride or ammonium sulfate [14], cyclohexanol, dodecan-1-ol and saccharose [15,16].

Superporous hydrogels are hydrogels that swell to equilibrium within a few minutes in aqueous media. They were initially developed as a gastric retention device, and they are useful in applications where a large surface area and fast transfer of mass are beneficial [17]. Although many aspects of superporous hydrogels have been studied [18–24], thorough understanding of the synthetic issues would greatly help with the design of the new SPH formulations for more advanced applications. One of the main issues with the synthesis of PHEMA superporous hydrogels via porogens in an aqueous environment is to produce a homogeneous sample. A superporous hydrogel is a dispersion of air in solid. An SPH is considered ideal if air is distributed evenly throughout the solid matrix and the size of the air pockets are similar. In other words, air pockets should have a very narrow size distribution. In practice, due to various interfaces of air-air, air-liquid and air-solid, as well as a dynamic temperature change which brings about changes in matter state, pores of very different sizes and hence a defective SPH structure are achieved as shown in Figure 1 (right). A more hydrogel layer (a dispersion, which is poor in air) possesses better mechanical properties due to its high solid content. On the other hand, a more porous layer (a dispersion, which is rich in air) provides superior swelling kinetics at the expense of mechanical properties.

The SPH synthesis becomes more complicated as the reacting mixture needs to be polymerized in the presence of air. Using the inhibition period, a greater homogeneity is available by having sodium bicarbonate well-distributed within the reaction mixture. Even so, homogeneity is difficult to achieve with PHEMA SPHs, and the HEMA monomer can successfully be polymerized into a superporous hydrogel under well-designed conditions [25]. The existence of an inhibition period for a radical polymerization in the

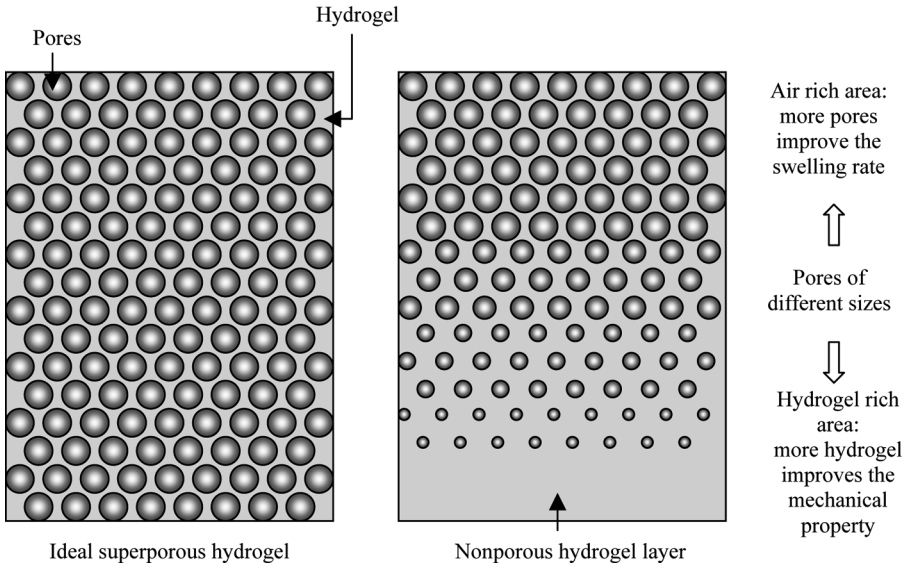


Figure 1: An ideal and defective superporous hydrogel.

presence of oxygen is well-known. Oxygen may participate in the reaction with the monomer (M) to form oxygen-containing residues such as ROO and ROOM. This reaction may compete with the addition of monomer to monomer, which generates normal polymer radicals, RM. Since the addition of monomer to the peroxy radical is much slower than the addition of monomer to a normal polymer radical, this step would be the rate-controlling step. As a result, an inhibition or induction period is often observed, which is followed by a normal polymerization. The normal polymerization is accompanied by a rapid increase in viscosity, slowing of oxygen diffusion inwards and a rise in temperature during gelation. The final properties of hydrogels prepared by radical chain polymerization are potentially dependent upon the events that occur during gel formation, particularly in the presence of atmospheric oxygen [26–30]. Omidian et al. used DSC to study the inhibition period during the gel formation of conventional acrylic-based hydrogel polymers [31]. They evaluated various schemes for the inhibition period and the final polymer properties, and found that the duration of the inhibition period and the exothermic feature can affect many features of the reaction. HEMA polymerization in a pure aqueous solution is a challenging one due to the limited solubility of the common peroxy sulfate initiators as well as the monomer itself. On the other hand, conducting the polymerization at a higher temperature complicates the foaming process, as it results in destabilization of the pores and changing their sizes.

Taguchi experimental design has been used in different disciplines to study, to screen and to optimize various parameters involved in the production

processes. For instance, the Taguchi matrix design has been used to optimize the weld line strength in injection-molded parts, to optimize the joint strength of ultrasonically welded thermoplastics, to optimize the bubble size in plastic parts formed by rotational molding, to optimize the surface quality of gas assist injection-molded composites, and in hydrogel preparation [32]. Omidian et al. demonstrated the use of the Taguchi matrix to examine the effect of several variables on the synthesis of superporous hydrogels based on acrylamide. Since the events during the hydrogel synthesis affect the final hydrogel properties to a lesser or a greater extent, the Taguchi method was used here to study as many factors as possible on the gelation features and synthesis of a 2-hydroxyethyl methacrylate (HEMA)-based superporous hydrogel formulation. Taguchi matrix designs are simple to use and cost-effective, and can cut the number of experiments to a minimum number possible, which can be very attractive in academia and industrial research.

EXPERIMENTAL

Materials

2-hydroxyethyl methacrylate (HEMA) (Sigma), polyethylene glycol diacrylate (PEGDA) (Aldrich), glacial acrylic acid (Aldrich), acetic acid (Mallinckrodt), propylene oxide-ethylene oxide-propylene oxide triblock copolymers (PEO-PPO-PEO) (Lutrol® F127, BASF), N, N, N′, N′-tetramethyl ethylenediamine (TMEDA) (Sigma), ammonium persulfate (APS) (Aldrich), sodium bicarbonate (SBC) (Mallinckrodt), and distilled water were used. All solutions were freshly made at room temperature before use.

Hydrogel Synthesis

In the SPH synthesis, the monomer is the building block of the final product, which is generally polymerized and crosslinked using a reduction-oxidation couple (e.g., TMEDA-APS) and a difunctional crosslinker (e.g., diacrylate), respectively. Water has dual function; it dilutes the heat of polymerization and acts as a dispersing and reacting medium for the solid foaming agent. The hydrogel becomes hydrogel foam when the foaming agent (bicarbonate) reacts with the foaming aid (an acid) in an aqueous medium. Since the generated foam is generally unstable, a foam stabilizer (e.g., Lutrol) is used in adequate concentration to stabilize the hydrogel foam. For this study, the monomer, crosslinker, water, foam stabilizer, acid, polymerization initiator, initiation catalyst and foaming agent were added sequentially to a test tube of dimensions approximately 25 mm outer diameter $\times$ 150 mm height. All volumes were based on the use of 800 μL of HEMA and 100 μL of 10 wt% F127. Followed by the addition

of HEMA, a 1:2 volume mixture of PEGDA/HEMA was placed into a test tube. To this solution, acrylic acid, acetic acid, 100 μL of 10% (w/v) aqueous Lutrol F 127 solution and distilled water were added under mild shaking. After some vigorous shaking of the complete mixture, an aqueous solution of TMEDA (40% v/v) was added under shaking and homogenized for 30 sec. This was followed by the addition of an aqueous solution of APS (20% w/v). Sodium bicarbonate was immediately added and carefully dispersed using a spatula. In order to increase the resolution on the T_{max} (maximum temperature due to the polymerization reaction) and t_{max} (time required to reach the maximum temperature) readouts, the reacting mixtures containing the initiator couple and the foaming agent were placed into the water bath set at either 35°C or 70°C. The temperature and the time were measured by placing a thermocouple directly into the reacting mixture. The reaction was monitored by noting changes in the readout of the thermocouple and noting the time at which changes took place. Time taken for each reaction to reach its maximum temperature, T_{max}, was recorded as the t_{max}. In cases where the t_{max} was extremely long, the foam produced by the reaction often dies down before gelation was complete. After the temperature of the reaction mixture (now a superporous hydrogel) had decreased by two degrees from its maximum temperature, the reaction vessel was removed from the water bath, and the superporous hydrogel was weighed. The superporous hydrogel was washed in distilled water by placing it into a bath full of distilled water and stirring. This washing process was repeated twice. After washing, the superporous hydrogel was removed, and dried in an oven at 60°C overnight.

Swelling Measurement

The dried superporous hydrogel (0.50 g) was placed into a beaker containing 50 mL of distilled water. After 30 min retention in the swelling medium, the swollen hydrogel was weighed again and the swelling was measured by dividing the hydrogel weight after and before the swelling.

Load-Deformation Measurement

In order to investigate the behavior of PHEMA superporous hydrogels under compression forces, a new sample was formulated based on the outcomes of this study, and tested using a Chatillon TCD-200 test stand, for its force-extension profile. In a test tube, HEMA (pure, 800 μl), PEGDA (pure, 15 μl), acetic acid (50 v/v%, aq, 30 μl), P127 (10 wt%, aq, 100 μl), were mixed at room temperature. TMEDA (40 v/v%, aq, 25 μl), distilled water (25 μl), and APS (20 wt%, aq, 50 μl) were added and mixed for 1.5 min. Sodium bicarbonate (170 mg) was thoroughly dispersed into the reacting mixture, and the

test tube was placed into the water bath at 65°C. The SPH was washed and dried as explained in the general synthetic procedure.

RESULTS AND DISCUSSION

General Observations

The amounts of crosslinker, comonomer, foaming aid, diluent, redox couple, foaming agent, and reaction temperature are listed in Table 1, along with overall reaction period and temperature changes brought about by each formulation. Table 2 shows the amount of hydrogel obtained from each experiment as well as other important observations for each preparation. The inhibition period is common to all of the experiments, but is not easily observable in some cases because there was a period at the beginning of each experiment, where the reaction mixture is both being warmed by the water bath and undergoing the inhibition period. It is, however, quite clear in other cases, and in experiments where the inhibition period is not clearly observable, it is easy to observe the rapid increase in temperature associated with "normal" polymerization. In certain experiments, the inhibition period was shorter than the time taken to warm the reaction mixture to the temperature of the water bath. In such cases, the inhibition period is measured as usual, but temperature points below the water bath temperature will also be used in the extrapolation. In some experiments, the inhibition period was very long and the experiment was abandoned. Since the inhibition period of each reaction is included in the total period of time to reach the maximum temperature, authors used the t_{max} as a better factor to explain each individual reaction.

Figure 2 shows that when for example the experiment 7 starts, the reaction mixture begins to warm up to 35°C. The inhibition period follows, and in this case, continues for about twelve minutes before "normal" polymerization begins. The maximum temperature is reached by about 16 min, and so the exothermic period is about 4 min. In general, time to reach the maximum temperature is a combination of the inhibition period, where no reaction has started, and the exothermic period, where reaction starts with its associated increase in reaction mixture temperature. Following the exothermic period, the temperature declined gradually to the temperature of the water bath. Two important data taken from this picture are T_{max} (maximum hydrogel temperature due to the exothermic reaction), and t_{max} (time to reach the maximum temperature), which has the two components of the inhibition and exothermic periods.

During a hydrogel synthesis in the presence of oxygen, oxygen itself acts like a comonomer and severely interferes with the polymerization reaction. If oxygen interaction is favored, weaker and lower molecular weight chains

Table 1: L-18 Taguchi matrix showing different factors at different levels and their corresponding effects.

EXP no.	PEGDA/HEMA (1/2) (μL)	Acrylic acid (μL)	Acetic acid (μL)	D.W (μL)	40% v/v TMEDA (μL)	20% w/v APS (μL)	SBC (mg)	Temperature (°C)	t_{max} (min.)	T_{max} (°C)
1	20	10	10	0	50	50	0	35	13.9*	36
2	50	50	10	200	100	100	150	35	17.9	44
3	100	100	10	500	200	200	300	35	4.1	53
4	100	10	50	0	100	100	300	35	16.1	37
5	20	50	50	200	200	200	0	35	8.8	49
6	50	100	50	500	50	50	150	35	29.6	38
7	100	50	100	0	50	200	150	35	19.1	46
8	20	100	100	200	100	50	300	35	10.9	35
9	50	10	100	500	200	100	0	35	13.5	37
10	20	100	10	0	200	100	150	70	2.0*	72
11	50	10	10	200	50	200	300	70	5.0	78
12	100	50	10	500	100	50	0	70	11.7	73
13	50	50	50	0	200	50	300	70	2.9*	68
14	100	100	50	200	50	100	0	70	3.3	76
15	20	10	50	500	100	200	150	70	4.7	73
16	50	100	100	0	100	200	0	70	3.7	88
17	100	10	100	200	200	50	150	70	5.0*	68
18	20	50	100	500	50	100	300	70	3.3	70

All volumes are based on the use of 800 μL HEMA and 100 μL of 10 wt% aqueous F127 solution. The temperature column displays the temperature of the water in the water bath that was used to give heat to the reaction. The T_{max} column shows the maximum temperature that was recorded in the reaction mixture. The t_{max} column gives the time that was required by each reaction to reach its maximum temperature due to exotherm.
*No gel was formed.

Table 2: Dry SPH weight and some important observations during the experimentation.

Expt.	SPH weight after synthesis, g	Dry SPH weight, g	Other observations
2	1.30	0.75	Porous, clear hydrogel formed. Had white, nonporous section at bottom. Pores in structure are large, but of variable size. Cracked during drying.
3	1.94	0.95	One of the larger SPHs made. Pores are quite, though not extremely, small and are present in a narrow range of sizes. The SPH is white. There is a nonporous section at the bottom of the sample that has caused cracking throughout the structure.
4	1.08	0.26	Small, porous hydrogel with clear, more porous top and white bottom. Pores are very large indeed and quite open at the top.
5	1.36	0.93	Colorless hydrogel with pattern on bottom that resembles a fingerprint.
6	1.53	0.56	Soft, sticky part-SPH/part-hydrogel product
7	1.22	0.60	Colorless SPH at top with large pores, and slightly white at the bottom of the sample.
8	1.57	0.44	Very weak, porous SPH that collapsed under its own weight to form a porous slime. Drying produced a flat SPH.
9	1.56	0.84	Two different sized samples were made. Both were clear hydrogels with ``fingerprint'' sections on the bottom.
11	1.46	0.54	Heterogeneous product consisting of SPH and hydrogel parts as well as large air pockets. The product is a mixture of colorless and white sections.
12	1.43	0.82	Clear hydrogel with fingerprint patterns on top and bottom. The edges are wrinkled, producing a flower-like effect.
14	1.23	0.84	Clear hydrogel with fingerprints on top and bottom. Circular perimeter, with no wrinkles in the edges.
15	1.49	0.78	Superporous hydrogels with hydrogel sections on the bottom. Very small pores that are evenly distributed, except for a large hole in the middle of the structures.
16	1.21	0.98	Clear hydrogel with fingerprints on top and bottom. Circular perimeter, with no wrinkles in the edges.
18	1.56	0.77	Superporous hydrogels with good homogeneity overall. The pores are of reasonable sizes, but are not the same size as each other, although they are not extremely different either. The bottom part is slightly nonporous, but far less than in most other cases. The SPH is somewhere between white and colorless in nature.

No gelation was observed for the reactions 1, 10, 13, and 17.

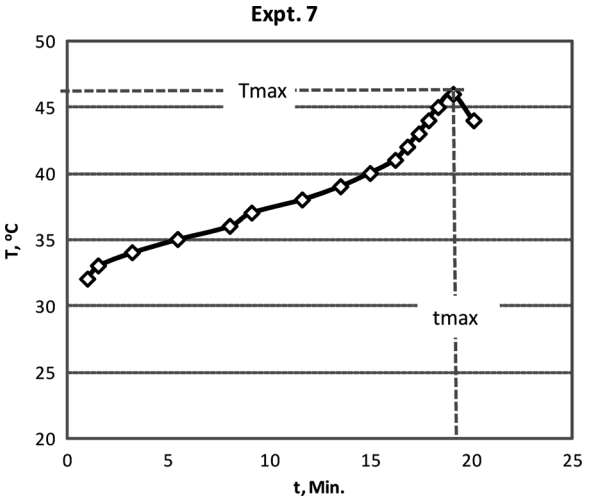
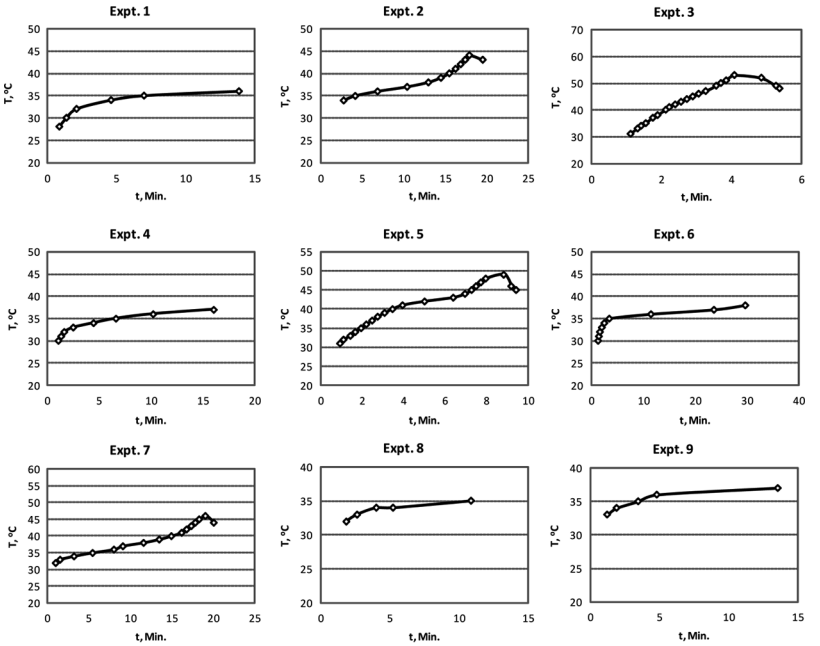


Figure 2: Gelation thermogram, displaying t_{max} and T_{max} for the experiment 7.

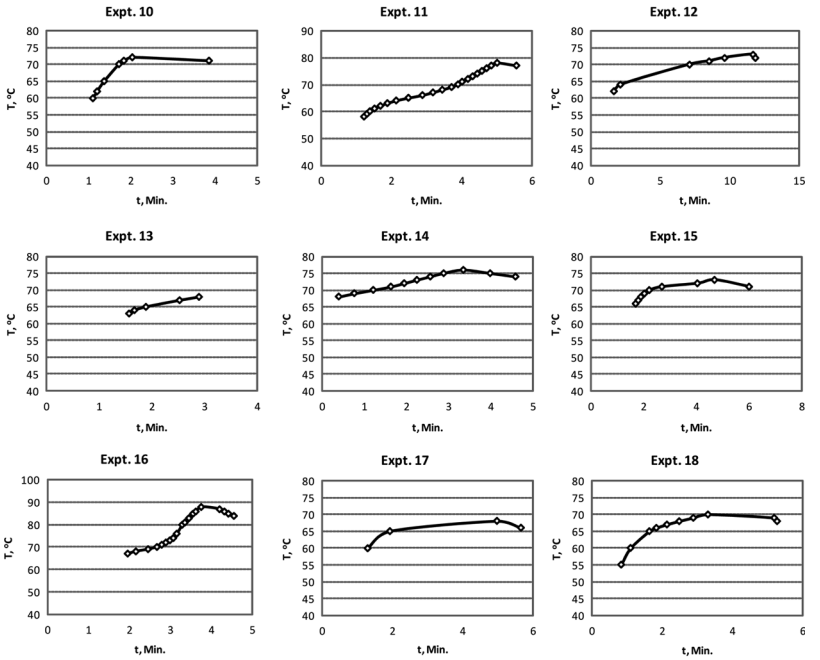
are then produced, which adversely affects the hydrogel properties. To reduce the oxygen interference, the inhibition component of the t_{max} should be minimized. With a few exceptions, a hydrogel synthesis would be unsuccessful when inhibition period lengthens or the peak temperature does not rise to a sensible extent.

Experiments 1–9 have been conducted at the low temperature of 35°C and their corresponding thermograms are compiled in Figure 3a. Despite the similar starting reaction temperature, the experiments 2, 3, 5, and 7 display a very different gelation behavior. These four experiments experience a noticeable peak temperature, which indicates more reaction has been happened for these experiments as opposed to the rest in the low temperature group. Despite the fact that experiments 10–18 were conducted at a higher temperature of 70°C (Figure 3b), the rate of temperature increase to the peak temperature is not linear for experiments 11 and 16. These two experiments display an inhibition period of 3.5 min and 2.5 min respectively. The exothermic period for these experiments was found to be 1.1 min and 0.5 min, respectively. Apparently, the combination of higher temperature reaction and some synthetic factors are responsible for this observation. For instance, no foaming agent and no water was used in the experiment 16, while both ingredients have been used in experiment 11 at reasonable concentrations.

On the other hand, different reactions showed different times to reach to their maximum temperature depending on their synthetic conditions. According to the t_{max} values in Table 1, reactions 3, 10, 11, 13, 14, 15, 16, 17, and 18 are categorized as short, while reactions 1, 2, 4, 5, 6, 7, 9, 12, and 18 can be categorized as long.



(a)



(b)

Figure 3: Gelation thermogram for experiments conducted at (a) 35°C, and (b) 70°C.

With this set of 18 experiments, a variety of gelation features was observed as shown in Tables 1 and 2. Some experiments, such as 16, show a very short t_{max}, while experiments such as 12 display a very long t_{max}. A broad range of temperature rises was also observed as well, as seen with experiments 16 and 12, which have high and low temperature rises, respectively. Generally, for the experiments performed at 35°C (Figure 3a), the formulations with the most redox initiator produced the fastest and steepest reaction profiles, with shorter t_{max}, but greater temperature rises. For the experiments performed at 70°C (Figure 3b), the concentration of APS seems to have an effect on the speed of the reaction, but the TMEDA concentration does not. This probably boiled off rather quickly anyway. The concentration of HEMA and PEGDA in the mixture seemed important, and it seems that those experiments made with larger amounts of these had faster reaction profiles. Also, the inclusion of larger amounts of water in the formulation seems to increase the length of the t_{max}, as can be seen by comparing experiments 12, 15 and 18 with experiments 9, 10, 11, 13, 14, 16 and 17. Clearly, experiments performed without the addition of sodium bicarbonate (1, 5, 9, 12, 14, and 16) could not produce superporous hydrogels, because this is the foaming agent. Thus, in all cases where sodium bicarbonate was used, a superporous hydrogel was formed. The exception is experiment 1, which did not produce a hydrogel or a superporous hydrogel. The reason for this was probably the low concentrations of all reagents. Experiments where acrylic or acetic acid concentrations were high resulted in greater pore sizes, and generally produced superporous hydrogels, except in cases where no sodium bicarbonate was available for foaming. In comparing experiments 3, 4 and 7, it seems that a lower concentration of water (i.e., higher monomer concentration) allows larger pores to form. Lower TMEDA concentration also seems to have the effect of increasing pore size. Experiments 8 and 6 have low crosslinker and initiator concentration and so they have collapsed pores. Their very long t_{max} explain this, because such a long t_{max} means that pores form and have the chance to collapse well before gelation is complete. Besides, the strength of the hydrogel was probably low due to low crosslinker concentration. At low temperatures, a low concentration of crosslinker tends to produce samples with low strength, and so poor samples, generally, not superporous hydrogels. At higher temperatures, two superporous hydrogels were produced using formulations with low crosslinker concentration. Comparing experiments conducted at high and low temperatures, it is clear that the t_{max} periods are generally shorter for higher temperature reactions. This makes sense because increased temperature generally does increase the speed of a reaction. The temperature rise is, in general, smaller for higher temperature experiments as well. As far as the SPH homogeneity is concerned, the SPH prepared in experiment 18 was found to be the most desirable one as it swelled in the swelling medium homogeneously to a

reasonable size. The swelling homogeneity can be translated to homogeneous pore structure of the SPH. Most SPHs produced in this study displayed an undesirable anisotropic swelling, which indicates that the SPHs had heterogeneous porous structure.

Evaluation of Variables and Parameters

The effect of the concentration of each ingredient on the t_{max} and the T_{max} values can be seen in Figure 4. To obtain these data, the magnitude of the effect was considered negative and positive at the lowest and at the highest concentration, respectively. For instance, the magnitude of the effects corresponded to all experiments conducted at 35°C was assigned negative, while those performed at the temperature of 70°C were assigned positive. The negative and the positive effects were added up and the net effect was obtained over the temperature range studied, i.e., 35–70°C. The effect of each variable on the t_{max} and T_{max} values are shown as gray and black bars, respectively. In qualitative terms, increased concentrations of the redox couple and crosslinker have the effect of shortening the t_{max} periods, as well as increasing the temperature rise during gelation.

Effect of Initiator Concentration

In general, at higher concentrations of the redox couple initiator, the t_{max} periods are shorter and a greater temperature rise is observed. A greater concentration of the redox couple results in a greater concentration of initiator radicals. Above a certain concentration, there is a great enough concentration of initiator radicals to overcome the effect of oxygen in the solution, thus shortening the inhibition period. At greater initiator concentrations, the gelation reaction occurs faster and so the exothermic period is shorter.

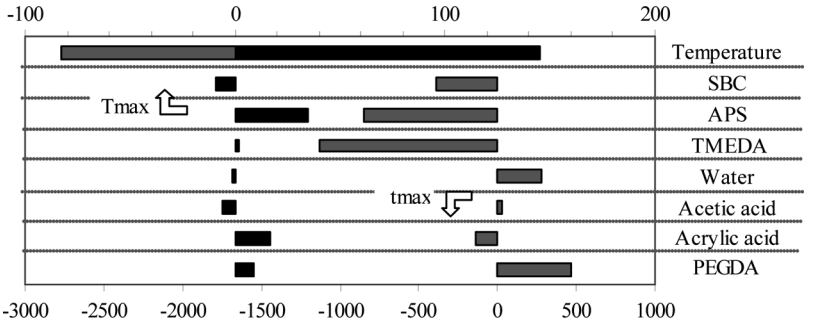


Figure 4: Effect of the variables on t_{max} and T_{max}.

Effect of Water Concentration

High dilution of the formulation with water results in greater inclusion of molecular oxygen and a lower effective monomer concentration in the reaction mixture. Increased molecular oxygen leads to an increased incidence of undesirable reactions as noted, thus increasing the t_{max} period. Decreased monomer concentration results in reduced collision of monomer units, producing a similar effect.

Effect of Acid Addition

Large concentrations of either acrylic or acetic acid were important because these acids interact with sodium bicarbonate for the foaming reaction. In experiments where the acid concentration was high and sodium bicarbonate was present, a superporous hydrogel was made.

Although the incorporation of acrylic acid into the formulation would have an effect on the polymer produced and the incorporation of both acids would be expected to have an effect on the t_{max} periods, it seems that these effects were insignificant in comparison to the other effects observed. In two cases (experiments 3 and 8), it is clear that the addition of a large amount of acrylic acid produces weak superporous hydrogels.

Effect of Crosslinker Concentration

Theoretically, the crosslinker can shorten the t_{max} periods by increasing the reaction viscosity due to crosslinks between the polymer chains.

Effect of Reaction Temperature

Increased temperature of the water bath resulted in a faster overall reaction, i.e., shorter t_{max}. The increased temperature potentially increases the rate of collision between monomers and between monomers and initiator radicals.

Effect on the t_{max}

Water dilution had the effect of increasing the t_{max}. Increased TMEDA and APS concentrations promoted the gelation process.

Effect on the Maximum Temperature

Examination of Table 1 shows that the highest temperatures resulted from the use of larger amounts of TMEDA and APS. At greater temperatures, APS became far more important than TMEDA.

Effect on Porosity

The greatest effect on porosity was the inclusion of sodium bicarbonate. Without SBC, the results of experiments were not superporous hydrogels. Larger amounts of acid—either acetic or acrylic—result in very porous superporous hydrogels.

Correlation Between the T_{max} and Reaction Yield

For the most part, except experiments 9 and 11, there is a good correlation between these two factors. Although data are not very supportive for low temperature reactions, the trends for the T_{max} and the reaction yield is in good agreement for high temperature reaction, in particular for experiments 12, 14, 15, 16 and 18. Generally speaking, the T_{max} can be used as a good indicator of the reaction yield, especially when the hydrogel is prepared at higher temperature. This fact is shown in Figure 5.

Based on the results of this investigation, experiment 18 had the optimum PHEMA formulation. From formulation perspective, this SPH was prepared using the lowest concentrations of the crosslinker and the reductant, but at the highest concentrations of acetic acid, water, the SBC and at the higher temperature set up. The good pore homogeneity of this SPH can be accounted for in terms of the concentration of the key ingredients used in its synthesis. High foaming agent (bicarbonate) and foaming aid (acetic acid) concentration can generate as much CO_2 gas as possible in the HEMA hydrophobic medium containing water at its highest concentration. Moreover, due to the lipophilic nature of the HEMA environment, the rate of foaming is expected to be slow. On the other hand, the lowest TMEDA concentration used in this experiment could slow down the exothermic reaction. As a result, a SPH with a desirable porous structure was

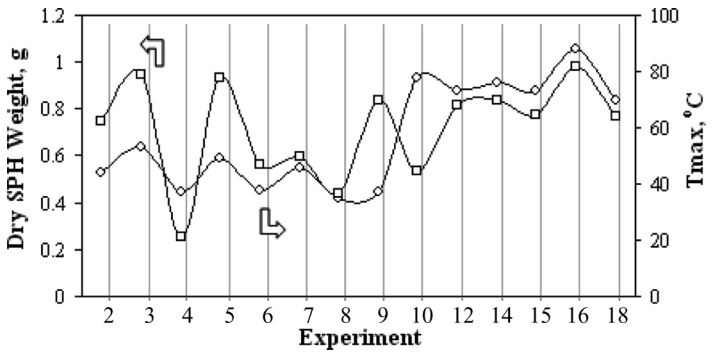


Figure 5: Correlation between the yield of each experiment (dry SPH weight) and the corresponding T_{max}.

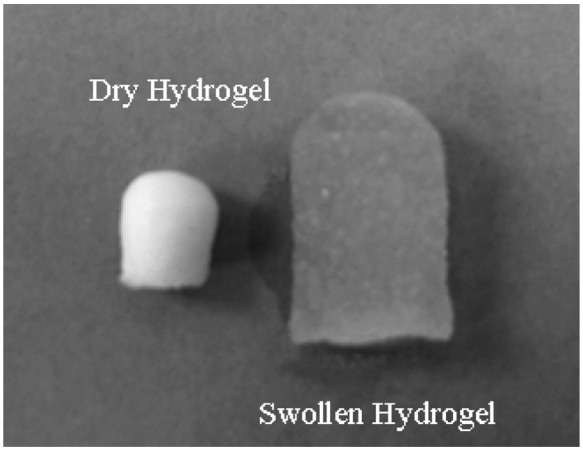


Figure 6: Swelling property of the optimized SPH formulation.

achieved under the conditions that the foaming and the polymerization processes were somehow synchronized, i.e., under slow rate of foaming and slow rate of polymerization reaction. For future investigations, the PHEMA formulation can be further optimized by using variables that have closer values to those used in experiment 18. The inhibition and exothermic period for formulation are both of intermediate length, leading to a better level of homogeneity than some other formulations. Figures 6 and 7, respectively, show the swelling and the mechanical property of the SPH, in which its formulation was designed based on the results of this study. Due to a low swelling ratio of about 13.5 g/g, the SPH is strong, withstanding 5.5 N/cm^2 (55 kPa) before breaking. The point at which the curve becomes greater than zero is the point at which the pressure gauge makes contact with the SPH.

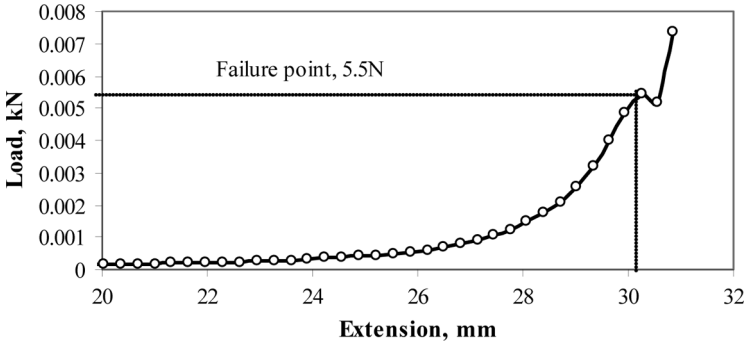


Figure 7: Mechanical property of the optimized SPH formulation.

CONCLUSIONS

HEMA monomer has so far been polymerized in many different ways for different applications. The HEMA polymerization in water and in the presence of ionic or very hydrophilic components is very challenging as HEMA is not a pure hydrophilic reactive monomer. This feature adversely affects the efficiency of the foaming process in which a water-soluble porogen such as sodium bicarbonate is used. Since a successful synthesis of a superporous hydrogel is dictated by a good balance between the chemical gelling and physical foaming processes, more knowledge about these processes will greatly help with a better design and formulation of superporous hydrogels. For this reason, the influence of starting materials and reaction temperature on the gelling and foaming properties of the HEMA-based hydrogels was evaluated using an L-18 Taguchi matrix. Among the variables studied, the redox initiator couple and the reaction temperature had the most significant effects upon the gelation properties. However, the inclusion of sodium bicarbonate was shown to be of utmost importance in producing a foaming effect. The homogeneous distribution of sodium bicarbonate was also of great importance. The most suitably homogeneous hydrogel was of intermediate length in terms of the t_{max} period, allowing for even distribution of SBC and quick gelation, before the foam is collapsed. It was also found that there is a good correlation between the yield of each reaction and the maximum temperature they can reach during their synthesis. This is obviously valid with the hydrogels prepared at higher temperatures. The load-deformation characteristics of a typical HEMA-based SPH were also investigated. PHEMA was shown to be a strong SPH, able to withstand a large amount of stress before breaks under a compressive force.

REFERENCES

[1] Karlgard, C. C. S., Wong, N. S., Jones, L. W., and Moresoli, C. *International Journal of Pharmaceutics* **257**, 141 (2003).

[2] Jeyanthi, R., Nagarajan, B., and Rao, K. P. *Journal of Pharmacy and Pharmacology* **43**, 60 (1991).

[3] Mohapatra, R., Ray, D., Swain, A. K., Pal, T. K., and Sahoo, P. K. *Journal of Applied Polymer Science* **108**, 380 (2008).

[4] Chung, J. T., Vlugt-Wensink, K. D. F., Hennink, W. E., and Zhang, Z. *International Journal of Pharmaceutics* **288**, 51 (2005).

[5] Unsal, E., Durdu, A., Elmas, B., Tuncel, M., and Tuncel, A. *Analytical and Bioanalytical Chemistry* **383**, 930 (2005).

[6] Asr, S., Uzun, L., Turkmen, D., Say, R., and Denizli, A. *Separation Science and Technology* **40**, 3167 (2005).

[7] Basri, M., Samsudin, S., Bin Ahmad, M., Razak, C. N. A., and Salleh, A. B. *Applied Biochemistry and Biotechnology* **81**, 205 (1999).

[8] Hamdy, S., El-Sigeny, S., and Abou Taleb, M. *Journal of Macromolecular Science Part A-Pure and Applied Chemistry* **45**, 982 (2008).

[9] Brahim, S., Narinesingh, D., and Guiseppi-Elie, A. *Journal of Molecular Catalysis B-Enzymatic* **18**, 69 (2002).

[10] Denizli, A., Yavuz, H., and Arica, Y. *Colloids and Surfaces A-Physicochemical and Engineering Aspects* **174**, 307 (2000).

[11] Ayhan, F., Ayhan, H., Piskin, E., Tanyolac, A. *Bioresource Technology* **81**, 131 (2002).

[12] Gomez, C. G., Igarzabal, C. I. A., and Strumia, M. C. *Polymer* **45**, 6189 (2004).

[13] Vianna-Soares, C. D., Kim, C. J., and Borenstein, M. R. *Journal of Porous Materials* **10**, 123 (2003).

[14] Horak, D., Hlidkova, H., Hradil, J., Lapcikova, M., and Slouf, M. *Polymer* **49**, 2046 (2008).

[15] Hradil, J., and Horak, D. *Reactive & Functional Polymers* **62**, 1 (2005).

[16] Kroupova, J., Horak, D., Pachernik, J., Dvorak, P., and Slouf, M. *Journal of Biomedical Materials Research Part B-Applied Biomaterials* **76B**, 315 (2006).

[17] Chen, J., Park, H., and Park, K. *Abstracts of Papers of the American Chemical Society* **216**, 68 (1998).

[18] Chen, J., Park, H., and Park, K. *Journal of Biomedical Materials Research* **44**, 53 (1999).

[19] Gemeinhart, R. A., Park, H., and Park, K. *Polymers for Advanced Technologies* **11**, 617 (2000).

[20] Hwang, S. J., Park, H., and Park, K. *Critical Reviews in Therapeutic Drug Carrier Systems* **15**, 243 (1998).

[21] Chen, J., and Park, K. *Journal of Controlled Release* **65**, 73 (2000).

[22] Gemeinhart, R. A., Park, H., and Park, K. *Journal of Biomedical Materials Research* **55**, 54 (2001).

[23] Gemeinhart, R. A. Chen, J., Park, H., and Park, K. *Journal of biomaterials Science-Polymer Edition* **11**, 1371 (2000).

[24] Dorkoosh, F. A., Brussee, J., Verhoef, J. C., Borchard, G., Rafiee-Tehrani, M., and Junginger, H. E. *Polymer* **41**, 8213 (2000).

[25] Park, K., and Park, H. US Patent 5,750,585. (1988).

[26] Flory, P. J. (1953). *Principles of Polymer Chemistry*, Vol. 168., Cornell University Press, Ithaca, NY.

[27] Bamford, C. H., Barb, W. G., Jenkins, A. D., and Onyon, P. E. (1958). *The Kinetics of Vinyl Polymerization by Radical Mechanisms*, Butterworth Scientific Publications, London.

[28] Bevington, J. C. (1989). *Comprehensive Polymer Science*, Pergamon Press, Oxford.

[29] Omidian, H., Hashemi, S. A., Sammes, P. G., and Meldrum, I. G. *Polymer* **39**, 3459 (1998).

[30] Brandrup, J., and Immergut, E. H. (1989). *Polymer Handbook,* 3rd ed., Wiley, New York.

[31] Omidian, H., and Zohuriaan-Mehr, M. J. *Polymer* **43**, 269 (2002).

[32] Omidian, H., and Park, K. *Journal of Bioactive and Compatible Polymers* **17**, 433 (2002).