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BIOCOMPATIBLE HYDROGELS: SYNTHESIS, SWELLING PROPERTY AND SOLVENT EFFECT ON GELATION

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ABSTRACT: Biocompatible hydrogels have an increasing interest in recent years. Poly (2-hydroxyethyl methacrylate, PHEMA) is widely studied with its biocompatible property. In this study, we have shown the gelation conditions to produce PHEMA hydrogels which have an excellent hydrogel property. Since dissolution forces by solvents are so important in gelation process, we studied the effect of solvent combination of acetone and water mixture in detail. As a result of investigation, the available acetone-water ratio limits were stated in order to obtain PHEMA hydrogels. The swelling property of PHEMA hydrogel was also shown. In our study, PHEMA samples imbibe water as much as five times of their own weight.
Key words: *Biocompatible, hydrogels, gelation, Poly (2-hydroxyethyl methacrylate)*

Biyouyumlu Hidrojeller: Sentezi ve Jelleşme Üzerinde Çözücü Etkisi

ÖZET: Son yıllarda biyouyumlu hidrojellere olan ilgi artmıştır. Bu çalışmada biyouyumlu bir materyal olan ve üstün hidrojel özellik gösteren poli hidroksietil metakrilat (PHEMA)'ın jel oluşum şartları araştırılmıştır. Jelleşme işleminde kullanılan çözücülerin çözme kuvvetleri oldukça etkindir. Bundan dolayı PHEMA eldesinde kullandığımız çözücü ortamı olan aseton-su karışım oranının jelleşme üzerine etkisi detaylı olarak araştırılmıştır. Araştırmanın sonucu olarak jelleşmeyi sağlayacak aseton-su karışım limitleri tespit edilmiştir. Hidrojeller su emme özelliği gösteren maddelerdir. Elde ettiğimiz PHEMA hidrojelinin su absorblama özelliği de incelenmiş ve hidrojel örneğinin kendi öz kütlesinin beş katı su emdiği gösterilmiştir.
Anahtar kelimeler: *Biyouyumlu, hidrojeller, jelleşme, Poli hidroksietil metakrilat*

1. INTRODUCTION

Hydrogels are physically or chemically cross-linked polymers that can imbibe large amount of water. In the polymer network, hydrophilic groups are present that are hydrated in aqueous medium so that a hydrogel structure is created. The term 'network' implies the cross-linked structure of polymers which avoid dissolution of polymers. Recently, researchers pay more attention on hydrogels because of their biocompatible properties. Additionally, hydrogels enable solute transport easily. The studies tend to in-situ hydrogel formation by photo-polymerization (Hill-West *et al.*, 1994) and by phase transition (Stile *et al.*, 1999; Jeong B, Choi YK *et al.*, 1999). The hydrogels exhibiting simple sol-gel transition are much more interesting and safe systems because there is no need to use chemicals where the sol phase is the flowing fluid and gel phase is the non-flowing part. Critical gel concentration (CGC) is the lowest concentration of polymer where gelation process starts. As it can be predicted, molecular weight of polymer and the CGC are inversely proportional. Dissolving forces of the solvent has a strong effect on gelation. The boundary of sol and gel phase can be determined by test-tube inverting experimental method (Jeong B, Lee DS *et al.*, 1999). Another way of determining sol-gel transition condition is falling ball method

(Yoshida *et al.*, 1998). The gelation occurs with various mechanisms that were reported in the literature (Guenet, 1992; Finch, 1983). Hydrogels have widespread application in different areas such as designing contact lenses, protein separation, cell-encapsulation matrices, control release of drugs and proteins (Peppas, 1986; Rosiak and Yoshii, 1999; Galaev and Mattiasson, 1999; Baldwin and Salzman, 1998; Gombotz and Pettit, 1995; Peppas *et al.*, 2000; Gehrke, 2000).

Crosslinking has to be present in a hydrogel, as mentioned above, in order to prevent dissolution of hydrophilic chain in aqueous medium. A great variety of methods to establish crosslinking has been used to prepare hydrogels. Basically, these methods can be divided into two categories: (1) chemical crosslinking, (2) physical crosslinking. Chemically crosslinked network structures can be obtained by crosslinking with aldehydes, addition reactions, condensation reactions, high energy irritation and using enzymes. Physical ones are by either ionic interactions or crystallization (Hennink and Nostrum, 2002).

It is a great advantage for many biomedical applications that hydrogels are biodegradable which means that the cross-linked network structure of hydrogel decomposes by the time. In other words, labile bonds which were introduced in hydrogel structure can be broken enzymatically or chemically, in most cases by hydrolysis (Park, 1993). Control of the degradation kinetics, of course, has a great importance. That is, manipulating the parameters lets controlling degradation characteristics. However, degradability is not the only requirement for biomedical applications. Once the hydrogels are implanted, the gels have to have a good biocompatibility which means degradation products can be metabolized into harmless ones and/or have low toxicity (Park and Park, 1996; Smetana, 1993; Anderson and Langone, 1999; Anderson, 1994).

In this paper, we have shown the conditions for fabrication of PHEMA hydrogel. We discovered that the solvent mixture combination for free radical polymerization process is very important and should be within certain limits in order to obtain a gel structure. We also studied the swelling capacity of PHEMA hydrogel.

2. MATERIALS AND METHOD

2.1 Materials

2-Hydroxyethyl methacrylate (HEMA), ammonium persulfate (APS), Ethylene glycol dimethacrylate (EGDMA), rhodamine B, acetone chromasolv® Plus for HPLC ≥99.9% were obtained from Sigma-Aldrich and used as they are received. The water used in all experiments was deionized water with a resistivity of 18.2 mΩ, which was prepared by ultrapure water system (Millipore).

2.2. Synthesis of PHEMA hydrogels

PHEMA hydrogel was produced by radical polymerization method. 10 mmol HEMA monomer and 0.1 mmol EGDMA as a crosslinking agent were injected to a 10 ml acetone-water mixture (3 ml acetone+7 ml water) in 20 ml vial. For visualization, a trace amount of rhodamine B (dye) was added to the mixture. The mixture was stabilized by stirring with a magnetic stir bar for 10 min at room temperature. Then 0.1 mmol APS, a radical initiator, was dissolved in the mixture and the cover of the vial was tightly closed in order to prevent boiling of acetone. The vial was placed into a water bath which was previously heated to 75 ^{o}C. Within 30 min a gel was formed. The gelation was so strong that the stir bar could not spin around itself even the magnetic stirrer is on.

2.3. Swelling property of PHEMA hydrogel

Two pieces of PHEMA gel was placed in an oven and dried overnight at 75 ^{o}C. Dry PHEMA gel was weighted and recoded (W1). Dry gels were placed in water at room temperature. After 24 h, the excess water was filtered and the swollen gels were reweighted and recorded (W2).

2.4. Effect of solvent combination in gelation

In order to examine solvent effect on gelation, a series of experiments were done while keeping the monomer, cross-linker and initiator concentrations constant with various acetone/water ratios. Polymerization parameters are listed in Table 2. Polymerization procedure was the same of section 2.2. Shortly, HEMA and EGDMA were dissolved in the solvent mixture. Radical initiator (APS) was added to the mixture in a 20 ml vial. Cover of the reaction vial was closed tightly in order to prevent boiling of

acetone. The vial was placed into a water bath which was previously heated to 75 °C.

3. RESULTS AND DISCUSSION

2-Hydroxyethyl methacrylate (HEMA) is a biocompatible material that is widely used in producing hydrogels. We have chosen a free radical polymerization method to prepare PHEMA hydrogels. Ammonium persulfate (APS) homolytically dissociates in aqueous medium over 70 °C. Ethylene glycol dimethacrylate (EGDMA) is the crosslinking agent. In 15 minutes, gelation starts and almost completed in 45 minutes. The crosslinking agent, EGDMA, has a strong effect on gelation. The stir bar cannot spin, after a certain time, because of strong gelation. Hydrogels are the materials which cannot dissolve in water but absorb large amount of water. The data related with water absorption capacity of PHEMA, in our study, is given in Table 1.

Table 1: % Water absorption capacity of PHEMA gels. Samples A and B are small pieces taken from PHEMA gel.

Sample	Dry weight(g) W1	Wet weight (g) W2	Water swollen (g)	% Increase in weight
A	0.0825	0.4978	0.4153	% 603
B	0.2035	1.0612	0.8577	% 422

The absorption capacity of PHEMA gel is calculated by the formula:

% Absorption (in weight) = (W2-W1)/W1*100

Where W1 is the weight of dry PHEMA gel and W2 is the weight of water absorbed PHEMA gel. As shown in Figure 1, it is remarkable that PHEMA gel absorbs water as much as five times of its own weight.

The swelling ratio of PHEMA depends on crosslinking ratio and steroid solution swelling capacity of PHEMA is stated as %566 in Cooper et al. (2005) study. The swelling capacity of HEMA and acrylamide co-polymer differs between %513 and %988 (Işık, 2000).

Solvent effect on gelation of HEMA: The solvent used in gelation process is acetone-water mixture. The effect of solvent combination is studied in detail according to Table 2.

We have done 11 gelation experimental trials while keeping amount of monomer HEMA, the cross-linker EGDMA and the initiator (APS) constant and varying acetone-water combination. The final states of G1-G10 are shown in Figure 2.

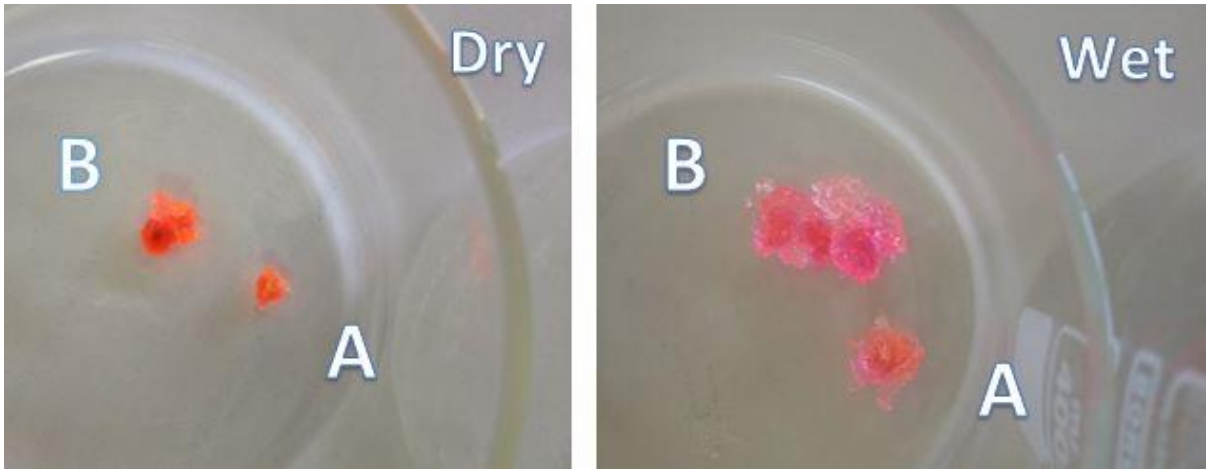

Figure 1. PHEMA hydrogel samples A and B (visualized by dye). Dry samples were immersed into water over night, and then filtered. The images of dry PHEMA gel (left) and water absorbed PHEMA gel (right).

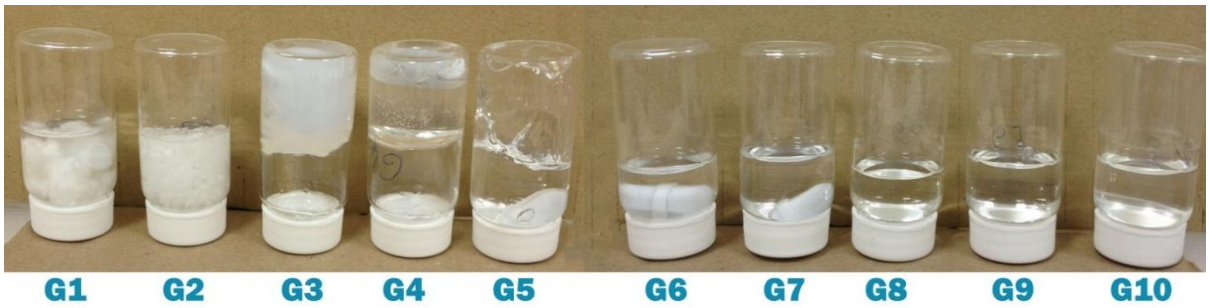

Figure 2. Polymerization products of PHEMA

Recipe code	HEMA (mmol)	EGDMA (mmol)	APS (mmol)	H_2O ml	Acetone ml	Observation
G1	10	0.1	0.2	10	0	Bulky polymer ppt in 5 min.
G2	10	0.1	0.2	9	1	Bulky polymer ppt in 5 min.
G3	10	0.1	0.2	8	2	Gel formation in 10 min.
G4	10	0.1	0.2	7	3	Gel formation in 30 min.
G5	10	0.1	0.2	6	4	Gel formation in 63 min.
G6	10	0.1	0.2	5	5	No gel formation
G7	10	0.1	0.2	4	6	No gel formation
G8	10	0.1	0.2	3	7	No gel formation
G9	10	0.1	0.2	2	8	No gel formation
G10	10	0.1	0.2	1	9	No gel formation
G11	10	0.1	0.2	0	10	No polymerization reaction

Table 2: Polymerization parameters of PHEMA

In G1 and G2, the polymerization was so fast that a white polymer precipitated in 5 minutes. This is not a gel formation but cross-linked polymer precipitation. From trial G1 to G10, water content in the solvent decreases while acetone content increases as shown in Table 2. The polymerization product, PHEMA, is insoluble in water but soluble in acetone. The combination G3, G4 and G5 are the only suitable solvent combination to produce PHEMA hydrogels. G5 has more acetone content than G4 and G4 has more than G3. This means dissolution forces in G5 is higher than G4 and G4 is higher than G3. As a result of this, gelation in G5 starts to form later than G4 and gelation in G4 does than G3 (gelation time for G3, G4 and G5 are 10 min, 30 min and 63 min, respectively). Gel structure in G5 is less

dense than G4 and G3. This also supports that when acetone content is more, gelation hardly occurs. When acetone to water ratio equal to or greater than 1, there is no more gelation (from G6 to G10). The polymerization reaction still continues in G6-G10. In G11, there was no

polymerization reaction because the radical initiator APS does not dissolve in pure acetone.

In order to understand acetone-water content effect on polymer solubility more clearly, we have added G6 dropwise into certain amount of water by a pasteur pipette. By doing this, water content in the polymer solution (of G6) increases and a gel like adhesive polymer is seen clearly as shown in Figure 3.

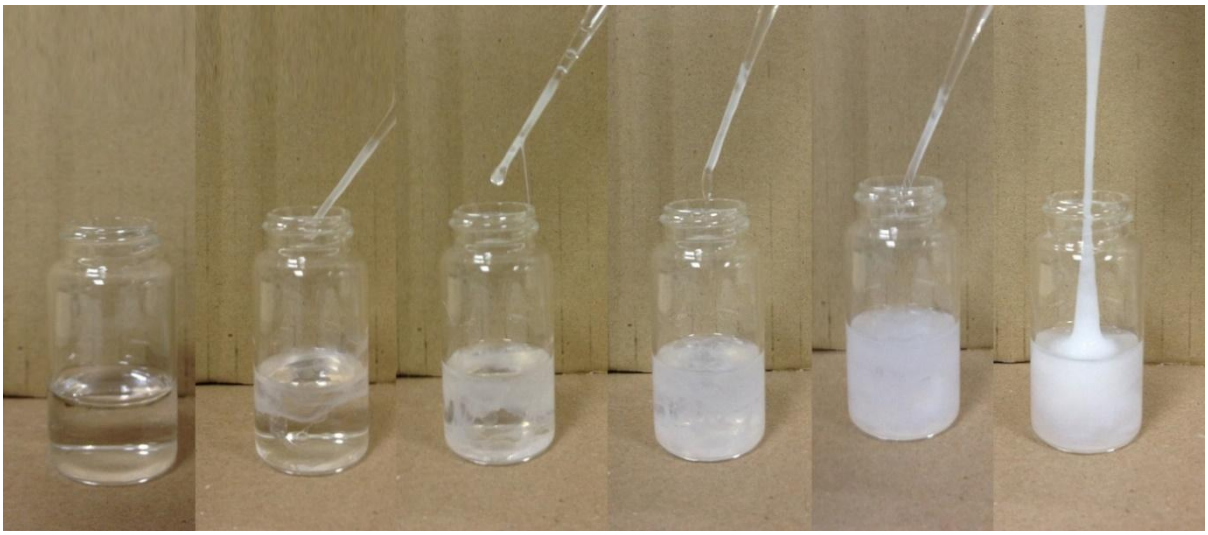

Figure 3. Dropwise addition of G6 to water

4. CONCLUSION

In this work biocompatible PHEMA hydrogel was successfully synthesized via radical polymerization method. Hydrogel property of PHEMA is visually shown and water imbibed by PHEMA hydrogel is recorded as five times of its original weight. We stated suitable acetone-water solvent mixture ratio for gelation conditions. The acetone/water (v/v) should be less than 1 and greater than 0.25 for gelation process. If acetone/water (v/v) equal to or greater than 1, no gelation occurs. In this case the product is in sol phase. If acetone/water (v/v) is less than 0.25, a crosslinked precipitation of bulky polymer is obtained which is not a gel structure. The hydrogels synthesized and examined in this study can be further developed and modified by using cleavable bond containing crosslinker instead of EGDMA for drug and enzyme delivery systems.

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