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Araştırma Makalesi / Research Article

Rapid Deswelling of PDMAEMA Hydrogel in Response to pH and Temperature Changes and Its Application in Controlled Drug Delivery

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Keywords
Hydrogel; Controlled drug delivery; Rapid response; Deswelling

Abstract

In this study, poly(2-dimethylamino)ethyl methacrylate (PDMAEMA) gels were prepared via in situ polymerization reaction. Synthesized hydrogel was characterized with FTIR spectroscopy and SEM. The pH- and temperature dependent swelling / deswelling behavior was investigated. The hydrogel showed highest value of swelling at pH 2. The rising temperature led to a decrease in swelling ratio due to the fact that hydrophobic interactions between polymer segments become dominant. Furthermore, it was observed that PDMAEMA hydrogel exhibited rapid deswelling rate in response to temperature and pH. The drug release profile of PDMAEMA hydrogel has been reported by using Ibuprofen as a model drug.

PDMAEMA Hidrojelinin pH ve Sıcaklık Değişimine Karşı Hızlı Büzülme Davranışı ve Kontrollü İlaç Salımında Uygulaması

Anahtar kelimeler
Hidrojel; Kontrollü ilaç salımı; Hızlı cevap; Büzülme

Özet

Bu çalışmada, poli(2-dimetilaminoetil metakrilat) (PDMAEMA) jeli, in *situ* polimerizasyon yöntemiyle sentezlenmiştir. Sentezlenen hidrojel, FTIR spektroskopisi ve taramalı elektron mikroskobu (SEM) ile karakterize edilmiştir. PDMAEMA jelinin, pH ve sıcaklığa bağlı şişme / büzülme davranışı incelenmiştir. Hidrojel pH 2'de en yüksek denge şişme oranına ulaşmıştır. Artan sıcaklık, polimerik zincirler arasında hidrofobik etkileşimlerin baskın hale gelmesi nedeniyle hidrojelin şişme oranında azalmaya yol açmıştır. Bundan başka hidrojelin sıcaklık ve pH duyarlı büzülme cevap hızının oldukça yüksek olduğu gözlenmiştir. İbuprofen ilacı model olarak kullanılarak PDMAEMA jelinin ilaç salım profili rapor edilmiştir.

1. Introduction

Hydrogels can keep the fluids in their structure by means of their three dimensional network structure and are insoluble in solvents due to their physical or chemical cross bands (Peppas and Mikos 1986). High water content and porous structure of hydrogels provide a biomimetic character to them and hence they are currently indispensable in many biomedical applications (Ratner and Hoffman 1976; Peppas and Langer 1994; Peppas *et.al* 2000).

Controlled releasing systems are generally polymer based drug carriers that can prevent frequent dosing due to the rapid decrease in blood drug level and decreased efficacy of the treatment and that provide a stable concentration of the bioactive materials of the drug in the blood and thus decrease the toxic or adverse effects. What is expected from the drug carriers that can provide a controlled release is an effective control in addition to sustainability of the blood level of the bioactive

depending on the exterior circumstances (Park, 2014; Patel *et. al* 2015; Bajaj and Desai 2006). Utilization of many natural or synthetic polymers as controlled drug carriers has been a common field of research currently. Especially depending on the environmental circumstances, intelligent gels with changeable volume phase transition properties are extremely attractive due to their controllability on the drug release profiles. Gels that contain functional groups such as -OH, -COOH, -$CONH_2$, -SO_3H in their chains are sensitive to some parameters such as temperature, pH and ionic strength of the surrounding swelling medium (Shrestha *et. al* 2015; Jiang *et. al* 2016; Jin *et. al* 2015; Mahdavinia and Etemadi 2015; Constantin *et. al* 2014). Since pH values of different body parts such as gastro-intestinal system, vagina and blood circulation differ from each other, pH sensitive gels have become an appropriate option for drug release with site specific. On the other hand, rapid swelling / shrinking responses of the hydrogels to be used in biomedical applications against environmental changes are important. Thus, since local pH changes may occur in the vital body and especially in diseases such as cancer, amount of the bioactive drug released from the drug carries may differ without any outsider interference (Yang *et. al*, 2016; Wang *et. al* 2014; Wang *et. al* 2015; Yang *et. al* 2015; Jia *et. al* 2014).

PDMAEMA has been studied recently by investigators as a biocompatible and hydrophilic polymer (Wang *et. al* 2008a; Emileh *et. al* 2007; Zhang et. al 2006; Yang et. al 2014; Wang *et. al*, 2008b). In a previously reported study of ours, copolymer derivatives were prepared by MEMA monomer and “triple responsive” copolymers were reported (Taktak *et. al* 2015). Yanfeng *et. al* studied the swelling properties of the PDMAEMA gel that they synthesized by photopolymerization (Yanfeng and Min 2001). Tertiary amino groups in the PDMAEMA chain are protonated in low pH. Due to the repulsion between cationic quaternary amine groups, swelling capacity of the PDMAEMA gel demonstrates a dramatic increase in low pH.

Ibuprofen is a commonly used non-steroidal anti-inflammatory analgesic in human and animal health. Therefore it has been used in the symptomatic treatment of inflammation and pain in patients with rheumatoid arthritis and osteoarthritis (Sadecká *et. al* 2001). With sustainable controlled release of ibuprofen, frequency of drug treatment can be decreased and patient comfort is provided while prevention of gastric side effects can also be possible. Although the plasma concentration of orally administered ibuprofen reaches its maximal level in 2 hours, the drug ibuprofen has a very short half-life (2h) (Zhang *et. al* 2016, Varga *et. al* 2014; Zhang *et. al* 2016). Therefore, colon-targeted slow release has been a very attractive formulation for therapeutic effect and decreased gastric side effects.

In this present study, swelling kinetics and pH sensitive swelling characteristics of PDMAEMA gels was analyzed. Also, pH and heat sensitive shrinking behavior was established. On the other hand controlled release profile of ibuprofen drug from the PDMAEMA hydrogel was reported.

2. Material and Method

2-(dimethylamino) ethyl methacrylate monomer was purchased from Sigma-Aldrich and it was passed through a basic alumina column and the inhibitor it contained was removed. Other reactants and chemicals used in the preparation of buffered solutions were also purchased from Sigma–Aldrich. All chemicals were in analytic purity. Ibuprofen bioactive was provided by Abdi İbrahim İlaç Sanayi ve Tic A.S. (Abdi Ibrahim Pharmaceutical).

2.1. Hydrogel synthesis

Synthesis of the PDMAEMA hydrogel was performed using free radical polymerization method. Five ml of DMAEMA monomer was solved in pure water containing N,N'-methylene bisacrylamide (MBAAm) in 2% of the monomer mass and was mixed for 20 minutes under N_2 atmosphere. Ammonium persulphate (APS), used as the initiator was solved in water and was

transferred to the mixture by a cannula under N_2 atmosphere. Following a ten minutes of mixing, polymerization mixture was transferred into a cylindrical pipette mold with a diameter of 0.5 cm and made up of polyvinyl chloride and was kept for 24 hours in room temperature for completion of polymerization. Subsequently, hydrogels taken out of the mold were cut in 0.5 cm thick discs, washed and dried in a vacuum incubator at 50 °C.

2.2. Characterization

Dried gels were milled and brought into a form of thin powder and a functional group analysis was performed using a Perkin-Elmer M850 Model ATR-IR Spectrophotometer. Gels were kept in water for 24 hours to let them swell for SEM analysis and then they were dried under vacuum in Freeze Drier (Labconco CA) for 48 hours using freeze-drying procedure. For the examination of the morphological structure, gold plated gel samples were imaged at the JEOL, Ltd., JSM-6701F model SEM.

2.3. Swelling experiments

In order to study the swelling kinetics of the hydrogels, a gel sample with a previously determined mass by weighing was taken into a deionized water at room temperature. The gel which continued to swell was taken out of the water at predetermined time points and excess water was wiped out by a filter paper and then its mass was measured and recorded. The hydrogel swelling rate was calculated using these gravimetric measurement data and the Equation 1 defined below.

$$Swelling\ ratio = \frac{m_s}{m_d} \qquad (1)$$

In the equation, value m_s is the mass of the hydrogel after it comes to an equilibrium state and value m_d is the mass of the dry gel.

In addition, pH dependent swelling behavior of the PDMAEMA gels was studied. Solutions in different pH values were prepared as buffered solutions. Hydrogels were kept in the buffered solutions until they come to an equilibrium state and then the rate of swelling was calculated gravimetrically by the help of the Equation 1.

2.4. Shrinkage kinetics

Shrinking behavior which occurred with the effects of pH and temperature was kinetically evaluated. Gels were kept in deionized water for 24 hours and they were let to reach an equilibrium swelling status. For the temperature effect, swollen gels wiped with filter paper were weighed and they were taken in water baths of different temperatures (20-60 °C). Gels were taken out of the water bath and excess water of the gels were wiped out by a filter paper at predetermined time points and they were weighed. In order to evaluate the effect of pH change on the shrinking behavior, the gels that were reached to a balanced swelling rate were taken into buffered solutions with different pH and their masses were measured at different time points as described above. Water-holding capacity of the hydrogels was calculated with the Equation 2 described below.

$$[Water\ retention]_t = \left[\frac{m_t - m_d}{m_s}\right] x\ 100 \qquad (2)$$

2.5. Drug release studies

PDMAEMA gel disc was submerged in a capped bottle containing hexane solution with 2% ibuprofen and was kept for 24 hours at room temperature. Drug loaded gel discs were separated and were dried in a vacuum oven at 40 °C. The amount of the loaded drug was calculated by reading of the absorbance of the ibuprofen 2% solution prior to and after the adsorption at 280 wavelength (Ultraviolet (UV)-1800 spectrophotometer, Shimadzu).

In order to study the drug release kinetics, drug loaded PDMAEMA gel disk was kept in 100 ml phosphate buffered solution with a pH of 7,2 (intestinal pH) at 37 °C and the absorbance of the samples taken out of the solution at predetermined time points were measured and recorded.

3. Results and Discussion

3.1. Characterization of PDMAEMA hydrogel

The FTIR spectrum of the PDMAEMA hydrogel after drying and grinding is shown in Figure 1. The wide band at 3000-3600 cm^{-1} is originating from the O-H group due to its water content and from the stretch in the N-H groups of PDMAEMA. Asymmetrical and symmetrical stretching of the methyl groups in the hydrogel structure were observed as weak vibrations at a range of 2800-3000 cm^{-1}. The characteristic peak in a sharp structure of the C=O group belonging to the carboxylic acid group in the PDMAEMA structure occurred at 1720 cm^{-1}. Functional group analysis confirms the PDMAEMA hydrogel synthesis.

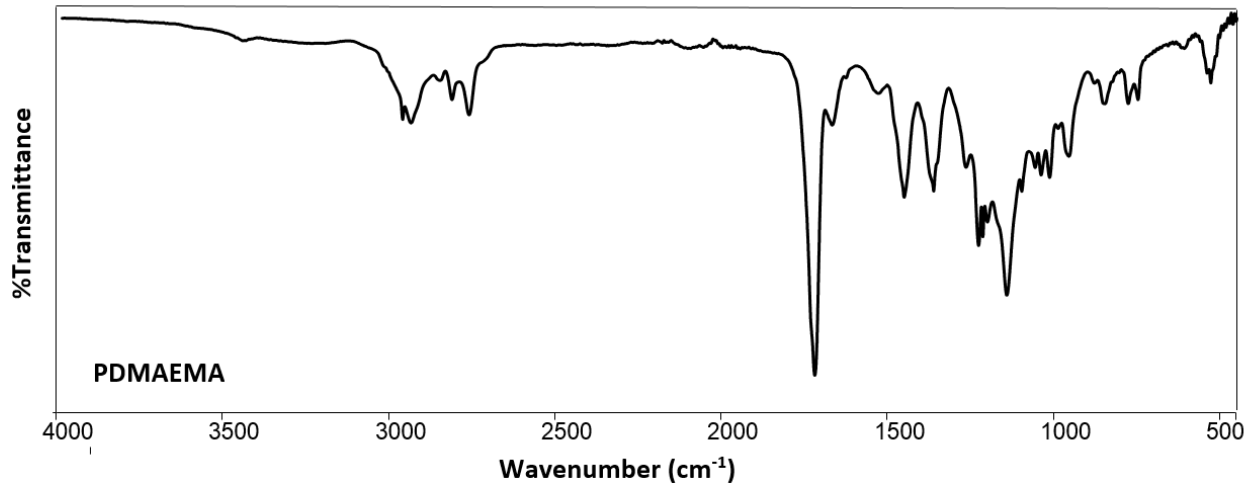

Figure 1. ATR-FTIR spectra of the PDMAEMA hydrogel

SEM images enlightening its morphological structure of the PDMAEMA hydrogel, taken after drying with "freeze drying" method are demonstrated in Figure 2. As seen, homogeneously distributed and uniformly seen open pores are present in the hydrogel. These open pores facilitate the fluid flow into the gel and play role in the achievement of the PDMAEMA gel in a high grade swelling capacity.

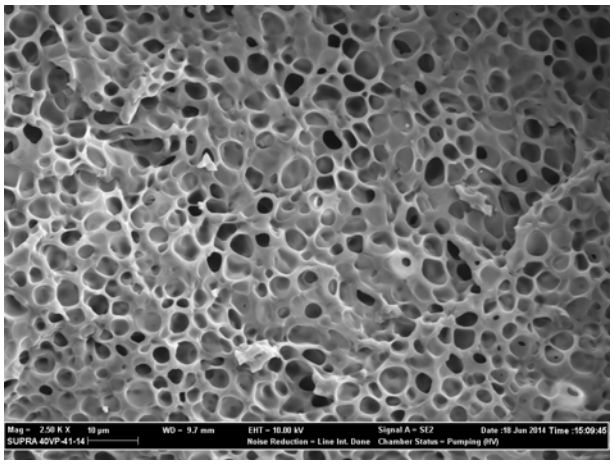

Figure 2. SEM images of PDMAEMA hydrogel

3.2. Swelling studies

Graph of swelling kinetics of the PDMAEMA hydrogel is demonstrated in Figure 3. Hydrogel demonstrated a quite high swelling ratio. Water-binding capacity of PDMAEMA is high since it is a highly hydrophilic polymer. Uniformly open pores in the morphological structure play an active role in the diffusion of water molecules into the gel matrix. Swelling ratio reached its maximal in a short time such as 6 hours.

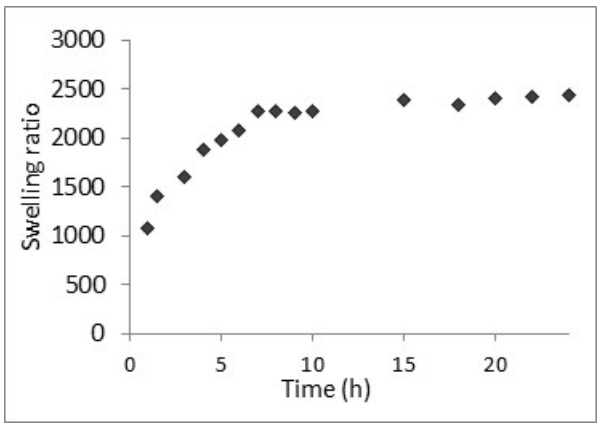

Figure 3. Swelling kinetics of PDMAEMA hydrogel

The pH-dependent swelling behavior is seen in Figure 4. According to this, a high swelling rate is observed at low pH, while swelling rate is substantially decreased with an increase in the pH. Tertiary amine side-groups in the PDMAEMA polymer chains have a transient cationic charge by protonating in acidic pH. Polymer chains move away from each other due to the electrostatic repulsion between the polymeric chains carrying the quaternary amine groups. Consequently, this increases the gel volume and thus the swelling rate of the gel. Due to deprotonation which occurs completely at pH higher than 8 electrostatic repulsion disappears and swelling ratio is decreased substantially. This results similar to those achieved by Yanfeng and Min (Yanfeng and Min 2001).

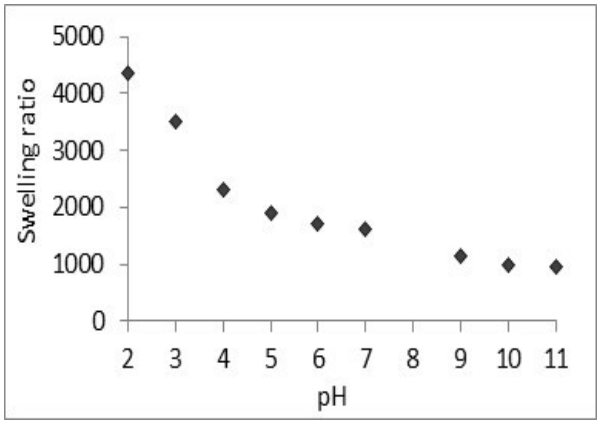

Figure 4. pH sensitive swelling behaviors of PDMAEMA hydrogel

3.3. Shrinking studies

In order to understand the kinetics of the temperature sensitive shrinking behavior, swollen gels that were reached an equilibrium of swelling at 20 °C were taken into deionized water at different temperatures. Then, the amount of water that was lost in time was determined gravimetrically. As seen in Figure 5a, shrinking ratio of the hydrogel changes considerably according to the temperature. Water loss in two hours at a temperature of 30 °C was 62%, while hydrogel lost 90% of water at 60 °C.

This phenomena is related with the LCST value of the polymer. Since hydrogel gains a hydrophobic character at temperatures higher than the LCST value, it undergoes a phase separation. Therefore, water molecules can easily be removed from the hydrogel network that starts shrinking. It is possible to determine the LCST value with swelling / shrinkage behavior. For this reason, water binding capacity of the hydrogel at different temperatures was calculated and was recorded as a graph by temperature. The temperature at which hydrogel releases the half of the water that it had absorbed was defined as the "lower critical solution temperature (LCST)" value. According to the Figure 5b, the LCST value of the PDMAEMA hydrogel is around 45 °C (Guan *et. al* 2015).

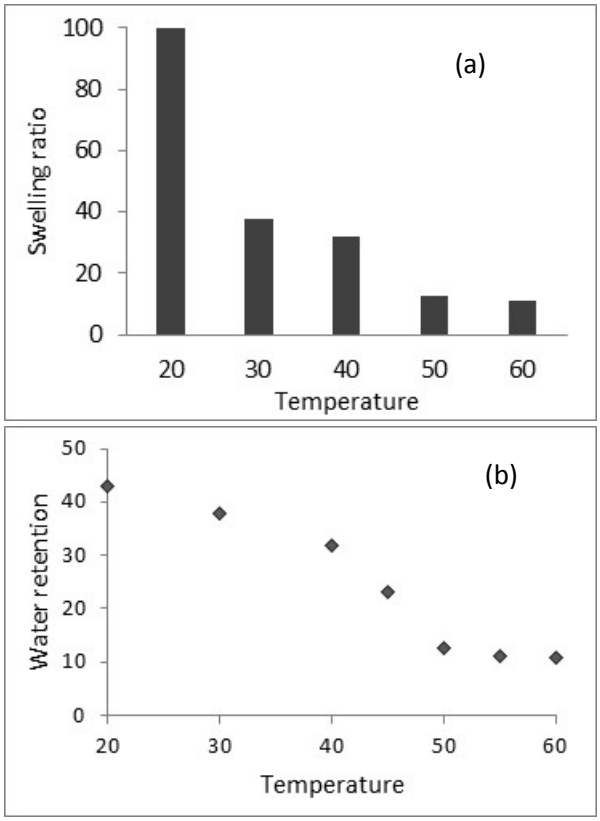

Figure 5. Temperature sensitive swelling behaviors of PDMAEMA hydrogel

On the other hand, the pH sensitive shrinking behavior was studied by gravimetrically of the water loss with time by passaging the swollen hydrogel which had reached its maximal equilibrium swelling rate in a buffered solution with a pH of 2 into a solvent with a pH of 8. As seen in the Figure 6, hydrogel lost water at a rate of 85% in 2 minutes at pH 8 solution. This behavior occurs due to a decreased solubility of PDMAEMA chains at high pH and thus development of a dominance of polymer-

to-polymer interaction instead of polymer-to-water interaction and shrinkage of the hydrogel network. In conclusion, the response rate of the PDMAEMA gel to the pH change is quite higher than its response rate to temperature change. The capacity of a rapid response to temperature and pH changes of the PDMAEMA gel might be associated with its easy water desorption due to its multiporous morphology and thus demonstration of an easy shrinkage behavior.

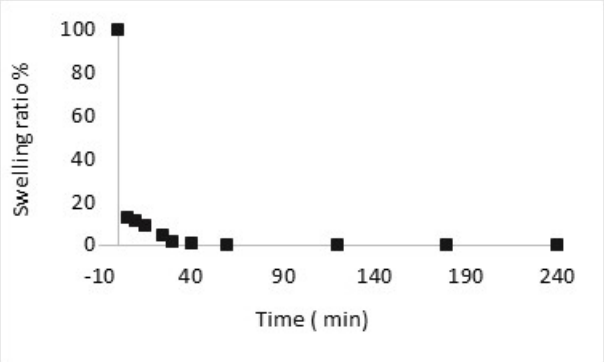

Figure 6. Deswelling kinetics for PDMAEMA hydrogel after a pH jump from 2 to 8 at 20 °C

3.4. Drug loading and release studies

The encapsulation of ibuprofen into the PDMAEMA gel matrix was realized using immersing method. As seen in Figure 7, the loading capacity of PDMAEMA gel was increased with increase of the initial concentration of Ibuprofen.

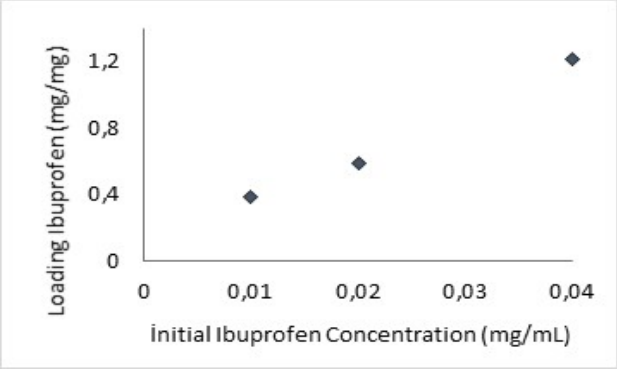

Figure 7. Loading capacity with different initial Ibuprofen concentrations.

The drug loading capacity could reach 1.2 mg mg^{-1} at the initial ibuprofen concentration of 0.04 mg ml^{-1}. Such a high loading capacity of gel was attributed to higher porosity of gel matrix that have a large surface area. The release profile of drug from

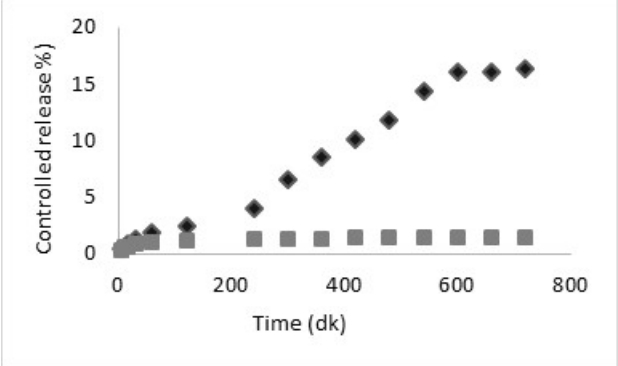

Figure 8. Ibuprofen release from PDMAEMA gel at different pH.

PDMAEMA gel was studied at acidic (pH 1.2) and neutral (pH 7.4) solution conditions and results were given in Figure 8. The release rate of Ibuprofen was found to be a highly pH-dependent. The released amount of Ibuprofen was about 1.46% at pH 1.2, while nearly %16 of Ibuprofen was released at pH 7.4. The reason for the lower drug release in acidic medium is poor solubility of Ibuprofen at lower pH. On the other hand, H-bonding interaction under neutral conditions led to slower release rate of drug from PDMAEMA gel. It should be noted no burst release was observed. This pH-dependent slower sustained release profile is promising for colon targeted drug delivery.

4. Conclusion

The results indicated that PDMAEMA hydrogels had higher swelling ratio and rapid swelling/deswelling properties. Such rapid response hydrogels have potential applications in biomedical field. Furthermore, in vitro release studies of hydrogels showed slower release rate could be controlled by changing the pH. Therefore, PDMAEMA hydrogels have been considered to be a promising drug carrier PDMAEMA hydrogel could promising candidate as colon targeted drug carrier.

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