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Potential Evaluation of PVA-Based Hydrogels for Biomedical Applications

Emel Tamahkar[1] and Bengi Ozkahraman[2]
[1] Hitit University, Department of Chemical Engineering, Corum, TURKEY
[2] Hitit University, Department of Polymer Engineering, Corum, TURKEY

ABSTRACT

Poly vinyl alcohol (PVA)-based hydrogels prepared using freeze/thawing treatment have become increasingly important biomaterials for biomedical applications having great properties such as biocompatibility, biodegradability and high water absorbency. In this study, PVA-based physically cross-linked hydrogels were prepared with and without the presence of poly ethylene glycol (PEG) freezing at -16 °C for 16 h and thawing at room temperature for 8 h. The focus of this work was to address the effect of the addition of PEG (Mw: 2000 or 5000) and the effect of the number of freezing/thawing cycles on swelling behaviour. The Scanning Electron Microscopy (SEM) measurements demonstrated the morphological characteristics of PVA-based hydrogels indicating the formation of the macroporosity fabricated during freeze/thawing process. From the swelling tests undertaken it w as apparent that all the hydrogels exhibited unique swelling characteristics having high swelling degree at all pH values such as pH 2.1, 5.5 and 7.4 representing the pH values of stomach, blood and dermis. Thus, the hydrogels synthesized in this study present important potential for biomedical applications.

Key Words:
Physically Cross-Linked Hydrogels; PVA-Based Hydrogels; Freeze/Thawing Treatment; PVA-PEG Hydrogels; Swelling Behavior.

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***Correspondence to**: Bengi Ozkahraman, Hitit University, Faculty of Engineering, Department of Polymer Engineering, Corum, Turkey*
Tel: +90 (364) 227-4533 (1227)
Fax: +90 (364) 227-4535
E-Mail: bengiozkahraman@hitit.edu.tr

INTRODUCTION

The hydrogels used, as crosslinked polymeric networks are prevalent in biomedical applications such as drug release systems, wound dressing materials, implants and dental applications since they have tunable chemical and morphological structures, high water uptake capacity and good chemical stability [1-5]. The hydrogels generally demonstrate good biocompatibility when used in contact with blood, body fluids and tissues [6, 7]. In order to prepare hydrogels, many techniques have been developed using physical methods, chemical methods in the presence of cross-linkers and radiation methods with electron beams or ultraviolet [8]. One of the useful methods for the preparation of physical hydrogel is low temperature gelation in aqueous solutions via freeze thawing [9-11]. The main benefit of the freeze/thawing method is the lack of necessity of the cross-linking agents and initiators in the synthesis of biomaterials. Thus the physically cross-linked hydrogels using freeze/thawing cycles attract a great deal of attention since they are biocompatible, non-toxic and non-carcinogenic biomaterials [12-15]. Poly vinyl alcohol (PVA) is one of the widely used polymers for the preparation of hydrogels. PVA based hydrogels have gained great importance as a biomaterial due to their permeability, high biocompatibility, high biodegradability and low toxicity [16-19]. Poly ethylene glycol (PEG) is a common hydrophilic and non-toxic biomaterial that is extensively utilized in food and pharmaceutics [20-22]. Therefore we have chosen PVA and PEG that are FDA-approved biodegradable polymers to prepare biocompatible hydrogels for biomedical applications.

In this study, we prepared PVA/PEG hydrogels via the freeze/thawing method using two different freeze-thawing cycles. The morphological structures of the hydrogels were introduced. The swelling behaviors of these hydrogels were investigated to evaluate the potential use of the hydrogels for biomedical applications. The swelling kinetic modeling of the hydrogels was also discussed in detail. The biodegradability of the resultant

hydrogels was investigated by calculating the weight loss after 15 days.

MATERIALS AND METHODS

Materials

Poly vinyl alcohol (PVA) (M_w: 145000) was purchased from Merck and poly ethylene glycol (PEG) (M_w: 2000 and M_w: 5000) were obtained from Sigma Chemical Co. Potassium chloride, sodium hydroxide, hydrochloric acid, potassium dihydrogen phosphate and sodium chloride were used for the preparation of buffer solutions and all were obtained from Merck Chemicals Ltd. The water used in the experiments was purified using a osmosis unit with a high-flow cellulose acetate membrane followed by organic/colloid removal and ion-exchange packed-bed system. The resulting purified water (deionized water) had a specific conductivity of 18 mS/cm. Buffer and sample solutions were filtered through 0.2-μm membrane.

Preparation of PVA-based hydrogels

The PVA-based hydrogels were produced without the addition of the cross-linker agents by the freeze/thawing process. At first, PVA was dissolved in aqueous solution to prepare 5 % PVA solutions by using a magnetic stirrer for 2 h at 90 °C and then the solution was slowly cooled to room temperature. 0.5 % PEG solution was prepared using two different molecular weights of 2000 and 5000. The polymer feed ratios shown in Table 1. The two polymer solutions were mixed by a magnetic stirrer at room temperature for 2 h. The mixture was placed on the petri dish. The blend solution was directly kept frozen at -16 °C for 16 hours. Afterwards, the frozen hydrogels were thawed room temperature for 8 hours. This process of freezing/thawing was repeated for 2 and 4 times. The products were immersed in an excess amount of deionized water for one week to remove the residual unreacted monomers and then were dried in air during 4 days.

Equilibrium swelling experiments

The swelling behaviors of the dried hydrogels were observed at pH 7.4 (Phosphate Buffer Solution), pH 5.5 and pH 2.1 (KCI/HCl Buffer Solution) into 20 mL solution at room temperature for five days. The values of pHs of 2.1, 5.5 and 7.4 were chosen since they present the pH of the stomach, blood and dermis. The hydrogels were periodically weighed after removing the excess water on the surface with a filter paper. The swelling degree (SD) was calculated from the following equation:

$$\% SD = (W_t - W_i / W_i) \times 100 \quad (1)$$

Where W_t and W_i represent the weights of swollen and dried state of the samples, respectively.

Characterization Studies

The gels were characterized by Fourier Transform Infrared Spectrum (FTIR) between the range of 1000-3700 cm^{-1} by a Thermo Scientific/Nicolet 6700. The SEM images of hydrogels were taken by a JEOL JSM-7001F Scanning electron microscope. The samples were dried at room temperature before being analyzed. The samples were then sputtered with a thin layer of gold before SEM measurements.

RESULTS AND DISCUSSION

PVA-based hydrogels were synthesized via freeze/thawing treatment to obtain biocompatible, biodegradable and non-toxic biomaterials. PVA and PEG was selected due to their unique properties such as biodegradability and hydrophilicity. The polymer solutions were prepared and mixed to have blend polymer solution. After the freeze/thawing process, PVA-based hydrogels were fabricated with physically cross-linking method between the polymer chains (Figure 1).

Characterization of the hydrogels

The broad hydroxyl band typical for PVA appears at 3500 cm^{-1}. Also PVA showed the characteristic bands at 2942 cm^{-1} and 1907 cm^{-1} indicating C-H stretching and C-O stretching respectively. FTIR spectra analysis of PEG showed many typical peaks at 1096, 1146, 1287, 1349, 1556, 1772 and 2886 cm^{-1}. The FTIR spectra of the

Table 1. The feed compositions and the number of the freeze/thawing cycles for the preparation of the hydrogels.

Hydrogel	*PVA (%)*	*PEG 2000 (%)*	*PEG 5000 (%)*	*Number of Freeze/Thawing Cycles*
P-2	*5*			*2*
PP2-2	*5*		*0.5*	*2*
PP5-2	*5*	*0.5*		*2*
P-4	*5*			*4*
PP2-4	*5*	*0.5*		*4*
PP5-4	*5*		*0.5*	*4*

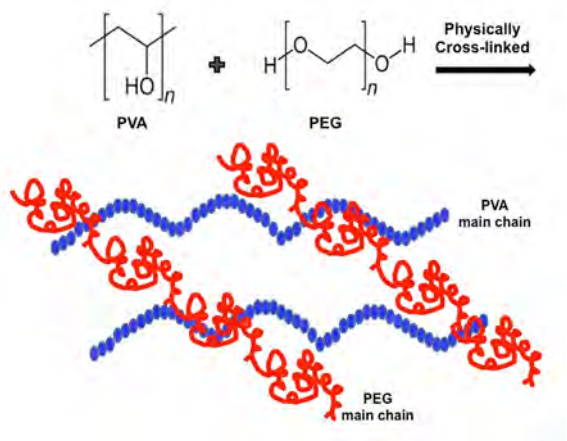

Figure 1. Schematic representation of synthesis of PVA/PEG hydrogels.

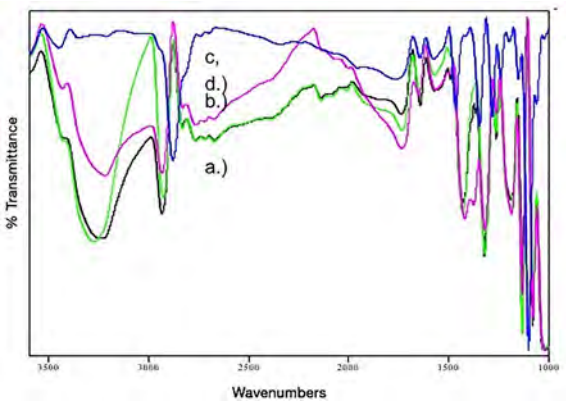

Figure 2. FTIR spectra of a.) PEG, b.)P-4, c.) PP2-4 and d.) PP5-4.

hydrogels of P-4, PP2-4, PP5-4 and PEG were shown in Figure 2. The O-H stretching band in the IR spectra of the all hydrogels which is the most characteristic peak of alcohols appears at 3355 cm^{-1} indicating hydroxyl groups. The band that was shifted to the higher wave number clearly indicates the presence of the formation of hydrogen bonds between the polymer chains. The sharp peaks at 1080 cm^{-1} which are due to ether groups of PEG appear in the FTIR spectra of all the hydrogels having PEG content.

Figure 3 shows SEM images of the hydrogels prepared in this study having different contents of PEG and two different freeze/thawing cycles. All the hydrogels introduced a porous structure indicating the formation of gelation during freeze/thawing cycles. The macroporosity of the biomaterials enable the swelling of the hydrogels facilitating the transport of the water molecules by decreasing the

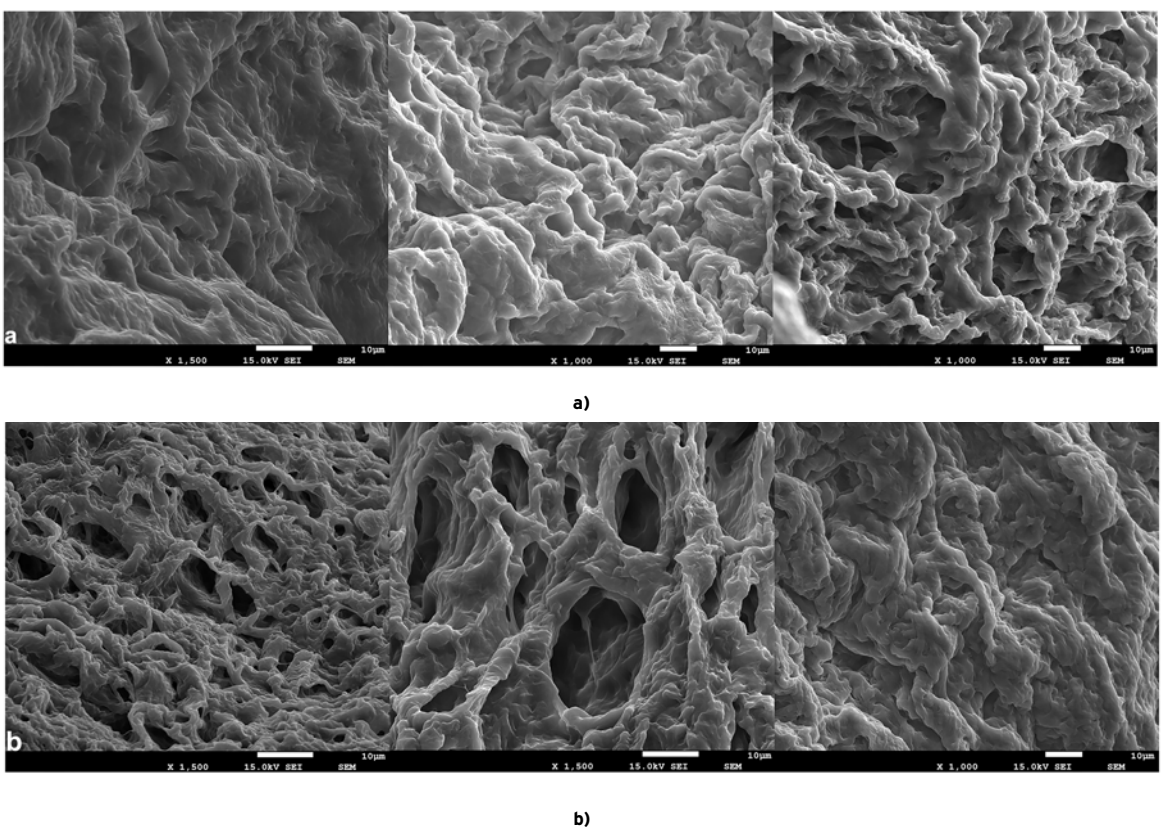

Figure 3. SEM images of the hydrogels; a) SEM images of P2, PP2-2, PP5-2 hydrogels and b) SEM images of P4, PP2-4, PP5-4 hydrogels

diffusion resistances at all of the pH values studied.

Equilibrium swelling experiments

In order to evaluate the swelling behavior of the hydrogels prepared with PEG and using two different freeze/thawing cycles, equilibrium swelling tests were performed at different pH values. In general, the swelling degrees of all the hydrogels increased with time and reached a saturation value within five days. In Figure 4, 5 and 6, the results of swelling degrees of the hydrogels were obtained at pH 2.1, 5.5 and 7.4 respectively. The increasing order of swelling degrees of the hydrogels were PP5-2>PP5-4>PP2-2>P-2>PP2-4>P-4 for all the pH values. The highest swelling degree was achieved with PP5-2 hydrogels having PEG (Mn: 5000) and after 5 days it reached the maximum value at 430 % at pH 2.1, 407 % at pH 5.5 and around 320 % at pH 7.4. The swelling properties of PP5-4 were similar to PP5-2. PP2-2 hydrogels demonstrate similar swelling behavior with PP5-2 hydrogels. This may be explained with the dominant effect of PEG on swelling capacity. The swelling degree of PP2-2 was higher than that of P-2 since the presence of PEG results in a more hydrophilic structure [23, 24]. PP2-4 exhibited less swelling degree than the swelling degrees of the other hydrogels except P-4 which has no PEG content since more physical cross linking occur with higher number of freeze/thawing cycles thus resulting a more rigid structure [20, 25, 26]. Increased freezing/thawing cycles cause high cross-linked gel due to the more crystal formation. The results herein indicated that the highest swelling degrees of all the hydrogels were achieved at pH 2.1 (431%) and the lowest swelling degrees of all the hydrogels were obtained at pH 7.4 (337%). These results indicated quite comparable manner with the hydrogels reported in the literaure [27-29].

Modeling of the swelling kinetics

To evaluate the mechanism of the swelling characteristics of the hydrogels, Fick diffusion model (2) was used.

$$M_t/M_{eq}=kt^n \quad (2)$$

where M_t and M_{eq} are the amount of the swollen weight at time t and at equilibium respectively, k is the Fick constant and n is the number indicative of the type of diffusion. For Fickian diffusion, n is reported close to 0.5 or over 0.5 in many research articles [30-33]. When the water molecules penetration is less than the penetration rate of the polymer chains, n is generally below 0.5. This situation is named as Pseudo-Fickian (or Less-Fickian). All the results demonstrate that swelling of the hydrogels was in conformity with pseudo-fickian diffusion model.

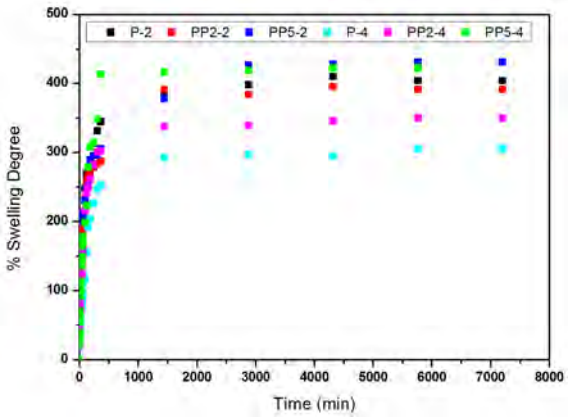

Figure 4. Swelling kinetics of PVA-based hydrogels in pH 2.1.

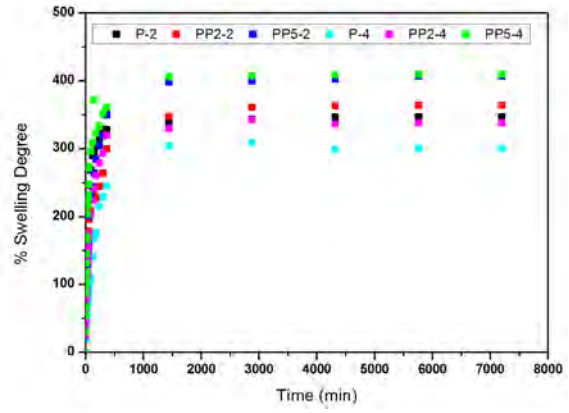

Figure 5. Swelling kinetics of PVA-based hydrogels in pH 5.5.

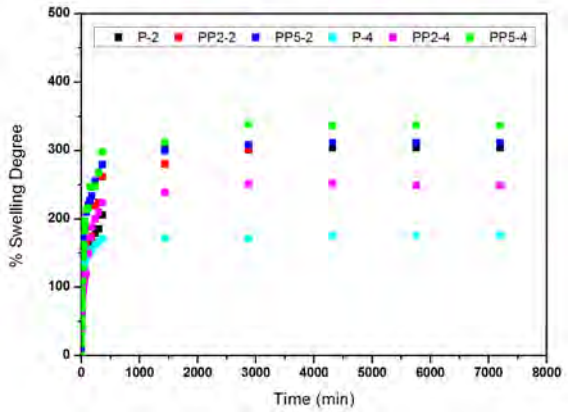

Figure 6. Swelling kinetics of PVA-based hydrogels in pH 7.4.

It was reported that n value is linearly dependent with the affinity of the polymer chains and the water molecules [34]. At all pH values, n values of the hydrogels having PEG (Mn: 5000) namely, PP5-2 and PP5-4 were higher than that of the other hydrogels (Table 2). Thus it was determined that the presence of PEG resulted in high n values.

Table 2. Swelling kinetic parameters of PVA-based hydrogels at different pHs.

Hydrogel	pH 7.4		pH 5.5		pH 2.1	
	n	k	n	k	n	k
P-2	0.170	0.286	0.152	0.357	0.142	0.321
PP2-2	0.190	0.250	0.166	0.291	0.146	0.311
PP5-2	0.193	0.231	0.186	0.270	0.181	0.278
P-4	0.178	0.252	0.175	0.253	0.50	0.498
PP2-4	0.183	0.261	0.172	0.288	0.130	0.373
PP5-4	0.199	0.223	0.170	0.308	0.176	0.283

Stability of the hydrogels

All the hydrogels were placed in aqueous solutions at different pHs for 15 days to determine the stability of the prepared hydrogels [35]. The samples were weighed every day for the first five days and fifteenth day. Table 3 shows the percantage of the weight losses for the hydrogels for the duration of the study. It was clearly seen that the least stable hydrogels were determined as hydrogels having PEG (M_w: 5000) and independent from the number of freeze/thawing cycle for all pHs providing more biodegradable biomaterial. The addition of PEG having higher molecular weight results in an increased biodegradability. The most stable hydrogels were determined as the hydrogels having PEG (M_w: 2000) at four cycles of freeze/thawing for all pHs possesing the higher cross-linked hydrogels [36].

Table 3. Stability of the hydrogels at different pHs.

pH 7.4			
Hydrogels	Initial dry weight (g)	Highest swollen weight (g)	Weight loss (%)
P-2	0.070	0.35	10.00
PP2-2	0.074	0.35	13.50
PP5-2	0.090	0.48	60.00
P-4	0.074	0.29	4.60
PP2-4	0.11	0.15	4.20
PP5-4	0.084	0.43	66.00
pH 5.5			
Hydrogels	Initial dry weight (g)	Highest swollen weight (g)	Weight loss (%)
P-2	0.084	0.37	2.30
PP2-2	0.088	0.36	11.30
PP5-2	0.099	0.41	51.80
P-4	0.090	0.36	0.00
PP2-4	0.105	0.46	6.50
PP5-4	0.098	0.40	63.50
pH 2.1			
Hydrogels	Initial dry weight (g)	Highest swollen weight (g)	Weight loss (%)
P-2	0.082	0.33	28.70
PP2-2	0.097	0.40	31.20
PP5-2	0.10	0.41	53.20
P-4	0.091	0.25	7.60
PP2-4	0.91	0.32	3.50
PP5-4	0.092	0.40	63.80

CONCLUSIONS

PVA-based physically cross-linked hydrogels were successfully produced at different number of freeze/thawing cycles and using different PEGs (M_w: 2000 and M_w: 5000). The results of the study show that:

1. The swelling properties of the hydrogels were evaluated and the highest swelling degree was achieved with PP5-2 hydrogels having PEG (M_w: 5000) and after 7 days it reached the maximum value at 430 % at pH 2.1, 407 % at pH 5.5 and around 320 % at pH 7.4.
2. All the hydrogels exhibited approximately the same swelling capacities at all pH values due to the presence of the weak ionized groups of the PVA-based hydrogels.
3. The swelling of all of the hydrogels was in conformity with pseudo-fickian diffusion model.
4. It was determined that biomaterials having better biodegradability were obtained with the addition of PEG (M_w: 5000).
5. The hydrogels prepared with four freeze/thawing cycles exhibited higher stability at all pHs.

Based on the data of this study, all the hydrogels produced in this study present significant potential having high macroporosity, high swelling capacity and biodegradability for biomedical applications such as wound dressing, drug delivery and implants.

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