Synthesis, Properties, and Permeation of Solutes through Hydrogels Based on Poly(ethylene glycol)-*co*-poly(lactones) Diacrylate Macromers and Chitosan

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ABSTRACT: Triblock copolymers from poly(ethylene glycol) (PEG) and D,L-lactide or ε -caprolactone were synthesized to prepare semi-interpenetrating polymer networks (semi-IPNs) with chitosan by ultraviolet (UV) irradiation method. Then, the solute permeation through these semi-IPNs hydrogels were investigated. The structures of semi-IPNs were confirmed by Fourier transform infrared (FTIR) spectroscopy and wide-angle X-ray diffractometer (WAXD). The equilibrium water content (EWC) of these hydrogels was in the range of 67–75%. The crystallinity, thermal properties, and mechanical properties of semi-IPNs hydrogels were studied. All the hydrogels revealed a remarkable decrease in crystallinity as compared with the PEG macromer itself. The tensile strengths of semi-IPNs hydrogels in a dry state were rather high, but those of hydrogels in a wet state decreased drastically. The permeabilities of solutes of hydrogels followed the swelling behaviors and were regulated by solute size. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 73: 2151–2158, 1999

Key words: hydrogel; chitosan; PEG-co-PLA

INTRODUCTION

The class of biodegradable polymers is the most successful, important, and commercially used biomaterial in orthopedic surgery, drug control/release devices, coating materials for suture, vascular grafts, and surgical meshes to facilitate wound healing after dental extraction.^{1,2} As to the particular area of tailored ether–ester block copoly-

Contract grant sponsor: Korea Science and Engineering Foundation Grant; contract grant number: 95-0300-08-02-03. Journal of Applied Polymer Science, Vol. 73, 2151–2158 (1999) mers based on various lactones and poly(ethylene glycol) (PEG), many studies have been reported concerning their synthesis and characterization.³⁻⁵ Such types of triblock copolymers have been synthesized in bulk by a ring-opening polymerization mechanism without any added catalysts in order not to leave any toxic residues, like organometallic catalysts, in the final product. These polymers are hydroxy-terminated and can be used to prepare acrylates as end groups that undergo very rapid photopolymerization.

Chitin, chitosan, and their derivatives have become useful polysaccharides in the biomedical area because of its biocompatible, biodegradable, and nontoxic properties. In our previous articles, we reported on the preparation of semi-IPNs hy-

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drogels based on chitin and poly(ethylene glycol) macromer (PEGM)⁴ or PEG-co-poly(lactones) diacrylate macromers.⁵ The incorporation of chitin improved the mechanical properties of the swollen networks and preserved their biocompatibility. However, chitin has a problem on solubility because there are only a few strong acidic solvents to prepare solution, such as formic acid, which may irritate human tissues. However, chitosan, the deacetylated product of chitin, is dissolved in water by adding a small amount of acetic acid so that the hydrogel can be prepared under milder conditions. Therefore, it might be expected that chitosan would be a strong candidate for hydrogel preparation in a biomedical application. Moreover, they are degraded by lysozyme. Aliphatic polyether can also be degraded by hydrolysis in the human body. Therefore, semi-IPNs hydrogel composed of chitosan and polyether for a drug carrier has been investigated and developed. The semi-IPN is superior to chitosan hydrogel in reversible responsibility of swelling and deswelling in acid and alkali, respectively, and in flexibility of the semi-IPNs hydrogel.

In this article, we deal with the synthesis, characterization, and swelling behavior of semi-IPNs hydrogels. The solute permeation through swollen semi-IPNs hydrogels was investigated as well.

EXPERIMENTAL

Materials

PEG $(M_n 6000)$ was purchased from Showa Chemical Inc. and purified by azeotropic distillation with benzene (Junsei Chemical Co., Ltd). D,L-lactide (Tokyo Kasei Organic Chemicals, Japan) was recrystallized from ethyl acetate (Junsei Chemical Co. Ltd). ε-Caprolactone (Tokyo Kasei, Japan) was purified by vacuum distillation over CaH₂. Acryloyl chloride and (4-benzoyl benzyl) trimethylammonium chloride as a photoinitiator were obtained from Aldrich and were used without further purification. Chitosan was purchased from Tokyo Kasei Organic Chemicals. The degree of deacetylation of chitosan was 0.76, and the viscosity-average molecular weight was 5×10^{5} . 1,2-Dichloromethane and anhydrous ethyl ether were supplied by Duksan Pharmaceutical Co. Ltd and J. T. Baker Inc., respectively. Theophylline (99% Aldrich Chem. Co.), vitamin B₁₂ (Sigma Chem. Co.), and bovine serum albumin (Sigma

Chem. Co.) were used as solutes in the permeation experiment through semi-IPNs hydrogels.

Synthesis of Semi-IPNs Hydrogels

PEG-co-poly(lactones) diacrylate macromers (PEGLM or PEGCM) were prepared according to the method described previously.⁵ 0.45 g of chitosan was dissolved in 28.6 mL of 0.33N acetic acid and mixed with PEG-co-poly(lactones) diacrylate macromers with different compositions. Then, (4-cenzoylbenzyl)trimethylammonium chloride (0.05M of PEGCM or PEGLM) was added with agitation. The mixture was poured into petri dishes and exposed to a 450-W ultraviolet (UV) lamp (Ace Glass Co.) placed above the mold at a height of 20 cm for 30 min with nitrogen gas blowing until gelation occurred. The samples were then dried completely under vacuum for 2 days. The composition of the samples used for synthesizing semi-IPNs is listed in Table I.

Characterization

The changes in chemical structure of block copolymers, PEGCM or PEGLM, and semi-IPNs were investigated by Fourier transform infrared spectroscopy (FTIR; Nicolet Model Magna IR 550 spectrometer). The crystalline characteristics of interpenetrating polymer networks (IPNs) were determined using wide-angle X-ray diffractometer (WAXD, Rigaku Denki). WAXD patterns were recorded by the reflection method with nickel-filtered CuK α radiation operated at 50 kV, 180 mA in the 2 θ scanning mode between 5 and 40°.

The equilibrium water content (EWC) was determined by weight measurement methods. The preweighed dry samples were immersed in distilled water. After the excess surface water was removed with filter paper, the weights of swollen samples were measured. The procedure was repeated until there was no further weight increase. EWC was determined according to the following equations.

EWC (%) =
$$[(W_s - W_d)/W_s] \times 100$$
 (1)

where W_s and W_d represent the weight of swollen and dry samples, respectively.

Differential scanning calorimetry (DSC; Perkin-Elmer DSC-7 instrument) were employed to investigate the crystallinity and melting endotherm of dry hydrogels at a heating rate of 10°C min⁻¹ under a nitrogen flow of 50 mL min⁻¹. The

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	Compc	osition							Ten	sile	Elongat	ion at
		PEGCM		Free	Bound				(kgf/d	m^2)	Break	(%)
Sample Code	Chitosan (Wt %)	(Wt %)	EWC ^e (%)	Water (%)	Water (%)	$\mathop{T_m}\limits_{(\circ \mathrm{C})}$	$\Delta H_f^{}({ m J}/{ m g})$	Crystallinity ^d (%)	Dry	Wet	Dry	Wet
PEGCM ^a	0	100				54	151	71				
$PEGLM^{a}$	0	100				56	154	70				
$C13^{b}$	25	75	70	40	30	53	63	29	21.5	10.1	1.2	8.2
C12	33	67	71	40	31	51	46	21	32.7	16.0	1.5	9.1
C11	50	50	76	45	31	49	29	14	41.4	20.1	3.2	17.7
$ m L13^{b}$	25	75	67	37	30	44	76	35	24.3	6.3	1.2	7.6
L12	33	67	68	38	30	43	68	31	27.2	10.9	1.3	9.8
L11	50	50	75	41	34	38	4	2	66.7	16.1	27.2	43.2
Chitosan	100	0										
a PEGCM a	nd PEGLM des	signate polv(ethv	lene glvcol)-c	o-polv(e-capro	lactone) diac	rvlate mac	romer and	polv(ethvlene_glvcol)-	co-polv(D.L-	lactide) dia	acrylate ma	cromer.
respectively.			- <u>()</u>									(
^b C and L n	epresent semi-Il	PNs of chitosan a	and PEGCM o	r PEGLM, re	spectively.							
EWC (%)	$= (W_s - W_d)/W$	$\frac{1}{8} \times 100.$										
a % Crystal.	$linity = \Delta H_{p} / \Delta F$	$H_f^{\prime} imes 100 \; (\Delta H_f^{\prime})$	of PEG : 219.	24 J/g).								

SYNTHESIS OF SOLUTES THROUGH HYDROGELS 2153

water state in the swollen hydrogels with different water content was also evaluated from the DSC analysis in the temperature range from -25to 25° C with a heating rate of 5° C min⁻¹. The endothermic peaks were used to determine the amount of free water in these hydrogels. The fraction of free water in total water was measured according to the following equation:

$$W_b(\%) = W_t - (W_f + W_{fb})$$

= $W_t - (Q_{endo}/Q_f) \times 100$ (2)

Here, W_t was the equilibrium water content (EWC) (%); W_b , the amount of the bound water (%); and W_f and W_{fb} , the amount of free water and the freezing bound water, respectively. Q_{endo} and Q_f were the heat of fusion of free water in semi-IPN hydrogel and that of the ice (79.7 cal/g), respectively.

Mechanical properties of semi-IPNs hydrogels were measured on a universal testing machine (UTM; Hounsfield 10KM) with a crosshead speed of 2 mm min⁻¹ under a 50-kg load cell. Reported values are the mean of five specimens and the deviation from the mean is within $\pm 5\%$.

In vitro Biodegradation

Semi-IPNs films with a thickness of 45–60 μ m were cut into small pieces (1 cm × 1 cm) and immersed into 1 mg/mL of phosphate buffer saline (PBS) lysozyme solution (pH 7.4) in a vial. The vial was stored in a constant temperature bath maintaining 37°C. After incubation, the film was repeatedly washed with ethanol and dried at 40°C under reduced pressure (10⁻² mmHg). A weight loss of the film was measured and plotted against time.

Partition of Solutes and Permeation Studies

The equilibrium partition coefficient of solutes between the hydrogel membrane and the surrounding solution as well as the permeation of solutes through semi-IPN hydrogels were carried out, as previously published.⁶ Solute permeation experiments were performed using three representative solutes with different molecular weights and hydrodynamic sizes. We used the theophylline (UV absorbance $\lambda_{max} = 274$ nm), vitamin B₁₂ (UV absorbance $\lambda_{max} = 361$ nm), and bovine serum albumin (UV absorbance $\lambda_{max} = 280$ nm) as nonionic solutes.



Wavenumber(cm⁻¹)

Figure 1 FTIR spectra of (a) PEG, (b) PEGC, (c) PEGCM, and (d) PEGCM-chitosan semi-IPNs.

RESULTS AND DISCUSSION

Structural Analysis

Figure 1 shows the FTIR spectra of (a) PEG, (b) PEGC, (c) PEGCM, and (d) semi-IPNs. The FTIR spectra of PEGL and PEGLM are very similar to those of PEGC and PEGCM and, therefore, are not shown here. Figure 1(b) shows the characteristic band of PEGC around 1735 cm⁻¹, which is due to the formation of ester bond by the ringopening reaction. Also, a broad peak appears at around 3400 cm^{-1} and indicates that the block copolymers of lactone and PEG are -OH-terminated. As shown in Figure 1(c), the reaction between acryloyl chloride and hydroxyl groups in the block copolymers leads to a decrease of the -OH stretching vibration peak appearing at around 3400 cm⁻¹. Absorption bands at 1652 and 1322 cm^{-1} due to amide I and amide III were observed in the infrared (IR) spectra of semi-IPNs [Fig. 1(d)]. It was noticed that in spite of disappearance of the amide II band at 1554 cm^{-1} , there still were stronger amide I and amide III bands, which are characteristic of chitin.⁷ The sharp band at 1383 cm⁻¹ has been assigned to the CH₃ symmetrical deformation mode.8 These may be due to the fact that the degree of deacetylation of chitosan is not so high that there are many amide groups present in the chitosan.



Figure 2 WAXD pattern of (a) PEGCM, (b) C13, (c) C12, (d) C11, and (e) chitosan.

Crystallinity of semi-IPNs, as well as PEGCM (or PEGLM), were characterized by a WAXD pattern, as shown in Figure 2. PEGCM exhibited sharp crystalline peaks at around $2\theta = 12.6, 18.1,$ and 23.3°. Chitosan gives somewhat broader patterns at around $2\theta = 9.6$ and 20° , indicating the lower crystallinity. It has been reported that the crystalline structure of chitin derivatives depends on the degree of deacetylation. Crystalline structure of shrimp chitosan is retained up to 70% of deacetylation degree. On further deacetylation, crystalline regions of chitosan become destructive and amorphous.9 The diffraction intensities of semi-IPNs are somewhat reduced compared to those of each chitosan and PEGCM. We admitted that the crystallinity of each polymer was strongly affected by the presence of the other component. The diffraction intensities of the semi-IPNs decreased with increasing content of the other component. Here, it should be noted that crystalline structure of semi-IPNs become amorphous when the ratio of PEGCM and chitosan is the same [Fig. 2(d)]. That is to say, the crystalline structure of PEGCM and chitosan is destroyed upon blending the two components by the same ratio.

Swelling Characteristics

Equilibrium water contents (EWCs) of semi-IPN hydrogels are listed in Table I. All the hydrogels swelled rapidly in water and reached an equilibrium within 30 min. However, their swelling kinetics couldn't be obtained because of so rapid a swelling process. The EWC of chitosan film is 50% by weight.¹⁰ As PEG macromer was incorporated in semi-IPN, EWC of semi-IPNs increased to 67-75% and increased with chitosan contents. This result agrees with our previous studies of PEGchitosan semi-IPNs.³ As the more chitosan content in blends and the less crosslinkable end group in the macromers, the hydrogels seem to possess a lower crosslinking degree and a higher EWC.⁵ Table I also listed the free water and bound water contents in swollen semi-IPN hydrogels, calculated according to the previous article.⁵ The amount of free water in hydrogels is usually found to be more than that of the total water $(EWC).^{11}$

Biodegradability

Figure 3 illustrates the biodegradation profile of semi-IPNs hydrogels at pH 7.4 in phosphate buffer saline (PBS) solution. All the hydrogels degraded in the PBS lysozyme solution result from enhanced susceptibility to lysozyme of semi-IPNs hydrogels, based on chitosan and hydrolysis of the ester linkage. The degradation of the hydrogel is a function of the crosslink density, as



Figure 3 Biodegradation profiles of semi-IPNs hydrogels in PBS lysozyme solution: (\bigcirc) C13, (\triangle) C11, (\square) L13, and (\bigcirc) L11.

well as the hydrolytic susceptibility of polyester. The more tightly crosslinked (L13 or C13) hydrogels thus degraded more slowly than hydrogels of a lower crosslinking density. Also, as the chitosan content in semi-IPNs hydrogels increases, the weight loss becomes greater. As seen from Figure 3, the weight loss of PEGLM–chitosan IPN hydrogels are somewhat greater than PEGCM–chitosan IPN hydrogels. This coincides with the work of Dawhney et al., in which the hydrolytic susceptibility of the ester linkages is in the following order: glycolidyl > lactoyl > ε -caprolactyl.¹²

Thermal Characterization

Table I also listed the melting temperature (T_m) , heat of fusion, and crystallinities of PEG segments in PEG macromers and dry IPNs hydrogels. PEGCM (or PEGLM) reveals a sharp melting transition at 54°C, whereas crosslinked hydrogels exhibit a broader melting endothermic peak around 42-53°C. They can be explained by the fact that the crosslinking reaction may prevent PEG segments from melting with a sharp transition.³ The melting temperature T_m of chitosan was not detected due to the rigid backbone chain of chitosan.³ Crystallinities of PEG segment in semi-IPNs were calculated from the ratio of heat of fusion (ΔH_f) at T_m for the polymer sample and corresponding 100% crystalline polymer. as follows:

Crystallinity (%) =
$$\Delta H_f / \Delta H_f^0 \times 100$$
 (3)

where ΔH_f^O (=219.24 J/g)⁴ and ΔH_f are the heat of fusion for 100% crystalline PEG and PEG segments in hydrogels, respectively. The area of melting endothermic peaks of crosslinked decreased, attributed to the decrease in crystallinity. This phenomenon is a typical feature of a crosslinked polymer.

Mechanical Properties

Table I summarizes the mechanical properties of semi-IPNs hydrogels in dry and swollen state. Mechanical properties of hydrogels are a very important factor in biomedical fields. We have reported that semi-IPN hydrogels containing chitin or chitosan enhanced the mechanical properties.^{3–5} However, some problems remained; although the tensile strength of semi-IPNs hydrogel in dry state is high, they suddenly lose their mechanical strength in wet state. It is generally

Table II Characteristics of Permeating Solutes

Solute	Molecular Weight	Hydrodynamic Radius (Å)	Ionization
Theophylline	180	3.5	рКа : 8.77
Vitamin B ₁₂	1355	8.5	neutral
BSA	65,000	36.1	neutral

expected that crosslinking degree in network plays a major role in enhancing the tensile strength of IPNs hydrogels. However, as can be seen in Table I, the tensile strengths of semi-IPNs hydrogels increased from 21.5 to 66.7 with increasing chitosan content. These results indicated that the tensile strength of these hydrogels were controlled not by the crosslinking degree that affected the changes in EWC but also by the chitosan content as a reinforcing agent.⁵

Permeation of Solutes Through Semi-IPNs Hydrogels

Solute permeation experiments were conducted using three representative solutes with different molecular weights and hydrodynamic sizes. Characteristics of used solutes are listed in Table II. The partition coefficients (K_d) were defined as the ratio of solute concentration in hydrogel membrane to that in surrounding solution and expressed as

$$K_d = \frac{C_m}{C_s} = \frac{V_{\rm sol}(C_i - C_t)}{V_m C_t} \tag{4}$$

Here, C_m is the concentration of the solute in the hydrogel membrane, C_s is the concentration in the solution, C_i is the initial concentration of surrounding solution, C_t is the concentration after hydrogels have reached an equilibrium state, and $V_{\rm sol}$ and V_m are the volume of the surrounding solution and the hydrogel membrane, respectively.¹³ The permeability coefficients were calculated with the following equation¹⁴:

$$\ln\left(1 - \frac{2C_t}{C_0}\right) = -\frac{2A}{V\delta}Pt \tag{5}$$

Here, C_t is the solute concentration in the receptor cell at time t, C_0 is the solute concentration in the donor cell at initial state, A is the surface area, V is the volume of each cell, δ is the membrane thickness, and P is the permeability coeffi-

Solutes	Semi-IPNs Hydrogels	P^{a} (cm ² /s)	K .b	$D^{\rm c}$ (cm ² /s)
Solutes	Hydrogets	1 (CIII 75)	\mathbf{n}_{d}	D (CIII 75)
Theophylline	C13	$3.10 imes10^{-5}$	1.37	$2.26 imes 10^{-5}$
Theophylline	C11	$5.02 imes10^{-5}$	1.88	$2.67 imes10^{-5}$
Theophylline	L13	$3.26 imes10^{-5}$	1.43	$2.28 imes10^{-5}$
Theophylline	L11	$5.59 imes10^{-5}$	2.04	$2.74 imes10^{-5}$
Vitamin B ₁₂	C13	$5.58 imes10^{-6}$	0.91	$0.61 imes10^{-5}$
Vitamin B_{12}	C11	$1.19 imes10^{-5}$	0.82	$1.45 imes10^{-5}$
Vitamin B_{12}	L13	$5.61 imes10^{-6}$	0.97	$0.58 imes10^{-5}$
Vitamin B_{12}	L11	$1.28 imes10^{-5}$	0.85	$1.51 imes10^{-5}$
BSA	C13	$1.58 imes10^{-11}$	1.89	$8.34 imes10^{-12}$
BSA	C11	$0.95 imes10^{-6}$	0.27	$0.35 imes10^{-5}$
BSA	L13	$1.74 imes10^{-11}$	1.98	$8.79 imes10^{-12}$
BSA	L11	$1.03 imes10^{-6}$	0.34	$0.31 imes10^{-5}$

Table III The Permeation Studies of Various Solutes Through Semi-IPNs Hydrogels at 25°C

^a P is the permeability coefficient.

^b K_d is the partition coefficient.

 ^{c}D is the diffusion coefficient.

cient. The diffusion coefficients (D) of each solute in the hydrogel membrane was evaluated by

$$D = \frac{P}{K_d} \tag{6}$$

where K_d is the partition coefficient of the hydrogel membrane, and P is the permeability coefficient, respectively.¹⁵ In eqs. (4), (5), and (6), the values of P, K_d , and D for three solutes through semi-IPNs hydrogels were calculated and are listed in Table III. The permeation of solutes through semi-IPNs hydrogels was in accordance with the swelling behaviors of the semi-IPNs hydrogels. As shown in Table I, the degree of swelling became larger with increasing chitosan contents. Therefore, higher swelling in semi-IPNs increases the free volume, which the solutes permeate more freely. The size of solute was an important factor in determining the diffusion as well as permeation. The hydrodynamic sizes of three solutes are in the range from 3.5 to 36.1 Å, as seen in Table II. Theophylline, having the smallest molecular size of 3.5 Å, showed the most rapid diffusion through hydrogel. The diffusion of vitamin B_{12} (hydrodynamic radius = 8.5 Å) is faster than that of BSA (hydrodynamic radius = 36.1 Å). The free volume caused by hydration may allow the pathway of solutes, through which the larger molecules were excluded in the permeation. Permeabilities of solutes through semi-IPNs hydrogels exhibited a similar tendency with diffusion

coefficients. These results are clearly indicative of the fact that the solute diffusion is much affected by the solute size between solutes and membranes.

Figure 4 shows the relative permeation of the mixture of theophylline, vitamin B_{12} , and BSA using L11 hydrogels. These results demonstrated that these hydrogels are capable of selective permeation with different molecular weight and size. However, further study is needed to verify the interaction, which affects and determines the partition coefficients of solutes within the swollen hydrogels.

CONCLUSIONS

Semi-IPNs hydrogels composed of PEGCM (or PEGLM) and chitosan were prepared by the UV



Figure 4 Relative amount of permeated (\bigcirc) theophylline, (\triangle) vitamin B₁₂, and (\square) BSA through L11 hydrogel.

irradiation method, and the solute permeation through these hydrogel membranes was investigated. FTIR spectroscopy and WAXD patterns confirmed the structure of semi-IPNs. All hydrogels exhibited a high EWC in the range of 67– 75%. The hydrogels show higher EWC with less a degree of crosslinking and more chitosan content. Mechanical strength of semi-IPNs hydrogels depended upon the crosslinking degree of network and chitosan content. The permeation of solutes increased according to higher swelling in semi-IPNs hydrogel. Smaller solutes and higher swelling of IPN hydrogel produced a higher diffusion coefficient. Changing the molecular composition in semi-IPNs could selectively control the permeated amount of solute.

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