BUTTERWORTH HEINEMANN

Polymer Vol. 36 No. 23, pp. 4497–4501, 1995

0032-3861/95/$10.00+0.00

Synthesis and properties of semi-interpenetrating polymer networks composed of β-chitin and poly(ethylene glycol) macromer

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(Received 2 February 1995)

Semi-interpenetrating polymer network (semi-IPN) hydrogel membranes composed of β-chitin and poly(ethylene glycol) (PEG) diacrylate macromer were synthesized and characterized for future biomedical application. PEG macromer/β-chitin dissolved in formic acid was cast to prepare films, followed by subsequent crosslinking with 2,2-dimethoxy-2-phenylacetophenone by u.v. irradiation. Photocrosslinked hydrogels exhibited relatively high equilibrium water content in the range of 60–81%. The crystallinity, thermal properties and mechanical properties of semi-IPN hydrogel membranes were studied. All the crosslinked membranes revealed a remarkable decrease in crystallinity. Their glass transition temperatures increased with increasing β-chitin content. The tensile strengths of semi-IPNs in the swollen state range between 1.35 and 2.41 MPa; these are the highest values reported to date for crosslinked hydrogels.

(Keywords: semi-IPN; β-chitin/PEG macromer; hydrogel)

INTRODUCTION

Biodegradable polymers have been used extensively in biomedical areas in the form of sutures, wound covering materials and artificial skin, and for the controlled release of drugs. As most of the polymers are synthetic materials, their biocompatibility and biodegradability are much more limited than those of natural polymers such as cellulose, chitin, chitosan and their derivatives. However, these naturally abundant materials also exhibit a limitation in their reactivity and processability. Many studies have attempted to overcome these shortcomings by chemical and physical alteration of natural polymers. Among these works, hydrogel types and interpenetrating polymer network (IPN) structures have been noted by several researchers in recent years[1–7].

Hydrogels are polymeric networks which retain a large quantity of water within their structures without dissolution. Sawhney *et al.*[8] synthesized bioerodible hydrogels based on photopolymerized poly(ethylene glycol) (PEG) macromer, which showed potential for use in macromolecular drug delivery. Even if this property in the water-swollen state gives these materials characteristics similar to those of natural tissues, a remarkable decrease of mechanical strength takes place in the swollen networks. One method to improve wet strength is to incorporate a hydrophobic component in the hydrogels. Klempner *et al.*[9] successfully incorporated hydrophobic low molecular weight linear polycaprolactone in the crosslinked poly(2-hydroxyethyl methacrylate). The resulting network showed improved mechanical properties in the swollen state, while high equilibrium water content and high permeability were maintained.

A semi-IPN is defined as a composition in which one or more polymers is crosslinked, linear or branched. Many hydrogels are generally formed from water-soluble polymers by crosslinking them, by radiation or chemical methods, or by polymerizing hydrophilic monomers in the presence of a crosslinker. Crosslinked polymers seem to be one of the candidates for improving the wet strength of materials. Vyavahare and Kahn[10] reported the preparation of a semi-IPN obtained from PEG, lysine and hydroxyethyl methacrylate. More recently, Yao *et al.*[11] reported on chitosan semi-IPN hydrogels crosslinked with glutaraldehyde and studied their swelling kinetics. Ramaraj and Radhakrishnan[12] studied swelling and release of bromothymol blue using an IPN based on gelatin and polyacrylamide. We have reported on the semi-IPN composed of β-chitin and PEG macromer[13].

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The β-chitin used in this study possesses excellent biocompatibility and mechanical properties, and has been used as a biomedical material. According to Kurita *et al.*[14,15], β-chitin has much higher reactivity and versatility than ordinary α-chitin, and thus can be used effectively as a novel type of material in biomedical fields. PEG is a water-soluble and non-toxic polymer which can be used to prepare acrylate-terminated macromer that could be crosslinked later[16]. There have been no reports to date on IPNs or semi-IPNs composed of chitin and PEG.

The objective of the present study is to report on the properties of semi-IPNs composed of β-chitin and PEG macromer. The resulting semi-IPNs are expected to show enhanced mechanical strength even at high equilibrium water content.

EXPERIMENTAL

Materials

PEG ($M_n = 6000$) was purchased from Showa Chemicals Inc. and was dried by azeotropic distillation with benzene (Junsei Chemical Co. Ltd). Acryloyl chloride and photoinitiator, 2,2-dimethoxy-2-phenyl-acetophenone, were obtained from Aldrich and were used without further purification. n-Hexane and formic acid were purchased from Duksan Pharmaceutical Co. Ltd and Janssen Chimica, respectively. All other chemicals were reagent grade and were used as received. β-Chitin was prepared by Hackman's method[17] and its molecular weight was about 3×10^5, as determined by viscometry[18].

Synthesis of PEG macromer

Purified PEG (2×10^{-3} mol) was dissolved in 150 ml of benzene in a 500 ml round-bottomed flask and cooled to 0°C. Triethylamine (0.49 ml) and acryloyl chloride (0.57 ml) were added to the flask, and the reaction mixture was stirred for 3 h at 80°C. The reaction mixture was filtered to remove triethanolamine hydrochloride, then the macromer was obtained by pouring the filtrate into an excess of n-hexane. Finally, it was dried at 40°C under reduced pressure for a day.

Preparation of semi-IPN

Formic acid solutions (2.4% w/v) with various compositions (1/1, 1/2 and 1/3, w/w) of PEG macromer/β-chitin were prepared. Samples were denoted as PC1-1, PC1-2 and PC1-3, respectively. The solutions were bubbled for 30 min with nitrogen. 2,2-Dimethoxy-2-phenylacetophenone (0.3 g) dissolved in 1 ml of *N*-vinylpyrrolidone was added to the PEG macromer/β-chitin in the formic acid solutions. The solutions were poured into a circular glass mould and irradiated using a 450 W u.v. lamp (Ace Glass Co.) placed above the mould at a height of 20 cm for 10–20 min until gelation occurred. The mould was then kept under reduced pressure to evaporate the solvent. After 1 day, dry film was obtained and was washed with deionized water to remove unreacted PEG. Residual solvent residue and water were removed under high vacuum for 3 days.

Measurements

Fourier transform infra-red (*FT*i.r.) spectroscopy (Nicolet Model Magna IR 550) was used to confirm the structure of PEG macromer and semi-IPN. To measure the equilibrium water content (*EWC*), pre-weighed dry samples were immersed in distilled water. After the excess surface water was removed with filter paper, the weight of swollen samples was measured at various time intervals. The procedure was repeated until there was no further weight increase. *EWC* was determined according to the following equation:

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

where W_s and W_d represent the weight of swollen and dry samples, respectively. The crystallinity and melting endotherm of dry hydrogels were investigated by differential scanning calorimetry (d.s.c.) (Du Pont Instruments 910 DSC). All samples equilibrated at 20°C were sealed in aluminium pans and rescanned up to 100°C with a heating rate of 10°C min^{-1} under nitrogen flow. The melting characters of free water were estimated by d.s.c. in the temperature range of −20 to 30°C with a heating rate of 5°C min^{-1}. Dynamic mechanical thermal analysis (d.m.t.a.) (Polymer Laboratories Instruments) was employed to measure the glass transition temperature of hydrogels. The measurements were carried out in the temperature range of −50 to 40°C at 2 Hz with a heating rate of 2°C min^{-1}. The tensile strength of samples was determined (Toyo Baldwin UTM-400) with an extension rate of 10 mm min^{-1}.

RESULTS AND DISCUSSION

FT *i.r. analysis*

Figure 1 shows *FT*i.r. spectra of PEG (a), PEG macromer (b) and β-chitin/PEG macromer semi-IPN hydrogel (c). A new peak appears at 1730 cm^{-1} in PEG macromer (*Figure 1b*) that can be attributed to the formation of a carbonyl bond due to the reaction between acryloyl chloride and hydroxyl groups in PEG. Therefore, the –OH stretching vibration peak at 3400 cm^{-1} decreased markedly in the PEG macromer. Two peaks at 1609 and 1410 cm^{-1} indicate the presence of C=C bond. The peaks at 1660, 1560 and 1450 cm^{-1} in the spectrum of the semi-IPN hydrogel (*Figure 1c*) are

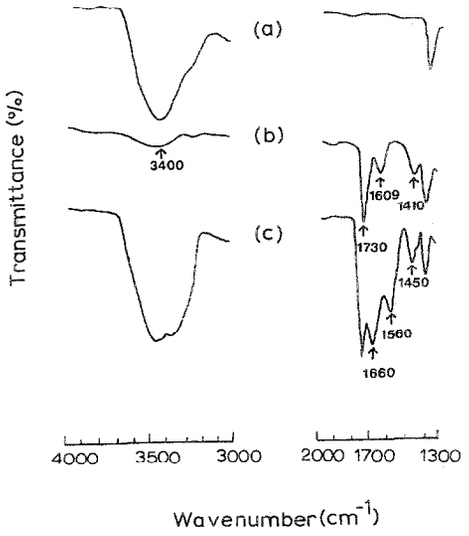

Figure 1 *FT*i.r. spectra of (a) PEG, (b) PEG macromer and (c) semi-IPN

assigned as amide I, II and III bands, respectively, in β-chitin. The peaks at 1609 and 1410 cm^{-1} disappeared after the photocrosslinking reaction.

Swelling characteristics

Swelling kinetics of semi-IPN hydrogels are plotted in *Figure 2*. All hydrogels swelled rapidly and reached equilibrium within 20 min. In our previous studies[19], the *EWC* of β-chitin was around 48%. As PEG macromer was incorporated in the semi-IPN, the *EWC* of semi-IPN increased to 60–81% and increased with β-chitin content.

Since PC1-1 possesses rich crosslinkable end groups, the degree of crosslinking may be the highest among the samples, resulting in the lowest *EWC* for PC1-1. This behaviour is in general agreement with previous results for IPN hydrogels[10–13], which have shown that high crosslinking density leads to a low water content.

Figure 3 illustrates the free water melting thermograms of semi-IPN hydrogels. As a rule, d.s.c. is used to determine the amount of free water that is not bound by hydrogen bonding. The fraction of free water in the total water is approximately calculated as the ratio of the endothermic peak area between 0 and 10°C for water-swollen hydrogel to the melting endothermic heat of fusion (334 J g^{-1}) for pure water, as listed in *Table 1*. Bound water due to hydrogen bonding with the PEG chains is expressed as the difference between the total water and the free water. The endothermic peaks appearing at around 0–8°C, shown in *Figure 3*, were attributed to the presence of free water in the hydrogels. As can be seen in *Table 1*, the bound water contents of PC1-1 to PC1-3 range between 10 and 16% of the total water. However, the amount of free water increased with β-chitin content in the hydrogel. This indicates that the increase of *EWC* with β-chitin content is attributed mainly to the free water content in the hydrogel.

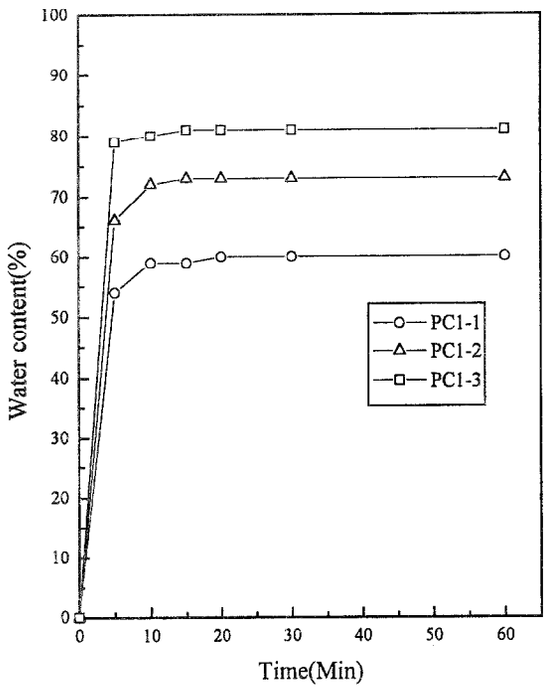

Figure 2 Swelling kinetics of semi-IPN

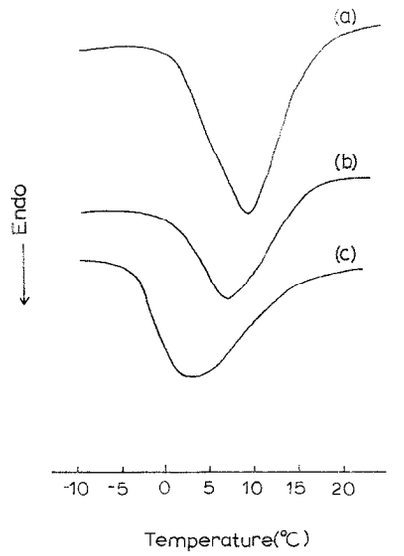

Figure 3 D.s.c. free water melting thermograms of water-swollen hydrogels: (a) PC1-1; (b) PC1-2; (c) PC1-3

Table 1 Water contents of semi-IPN hydrogels

Polymer code	Total water (%)	Free water (%)	Bound water (%)
PC1-1	60	51	9
PC1-2	73	57	16
PC1-3	81	70	11

Thermal properties

The d.s.c. thermograms in *Figure 4* exhibit the melting endotherms of PEG macromer (a) and crosslinked semi-IPNs (b–d). PEG macromer shows a sharp melting endothermic peak at 63°C, while weak and broad melting peaks of PEG macromer segments in the semi-IPN, caused by crosslinking reaction and IPN formation, appeared between 52 and 54°C. Meanwhile, the melting temperature (T_m) of chitin was not detected due to the rigid-rod backbone chain of chitin. In fact, it

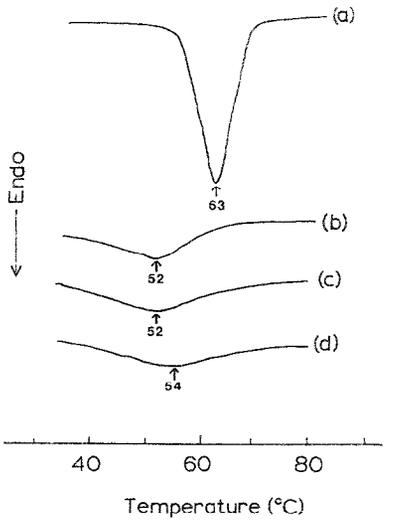

Figure 4 D.s.c. melting thermograms of PEG macromer (a) and semi-IPN hydrogels: (b) PC1-1; (c) PC1-2 and (d) PC1-3

Table 2 Thermal properties, crystallinities and mechanical properties of PEG macromer and semi-IPN hydrogels

Sample	T_g (°C)	T_m (°C)	ΔH_f (J g^{-1})	Crystallinity (%)	*EWC* (%)	Tensile strengths (MPa)	
						Dry	Wet
PEGM	−53	63	195	88	–	–	–
PC1-1	18	52	24	11	60	21.8	1.35
PC1-2	21	52	10	5	73	33.1	2.12
PC1-3	20	54	<10	<5	81	35.0	2.41
α-Chitin	236[a]	–	–	–	20	–	–
β-Chitin	170[b]	–	–	–	48	–	–

[a] From ref. 21
[b] From ref. 19

degraded before melting, which is typical for many polysaccharides.

Table 2 summarizes the thermal properties, crystallinities and mechanical properties of PEG macromer (PEGM) and semi-IPN hydrogels. The heat of fusion (ΔH_f) at T_m was measured through d.s.c. analysis as shown in *Figure 4*. The crystallinity of PEG chains in the semi-IPN was estimated from the following equation: crystallinity (%) $= (\Delta H_f / \Delta H_f^\circ) \times 100$, where ΔH_f° ($= 219.24$ J g^{-1}) and ΔH_f are the heat of fusion for 100% crystalline PEG and observed samples, respectively. It is clear that as the samples are further crosslinked, the crystallinity (%) decreases in semi-IPN systems. The areas of the melting endotherms in semi-IPNs were markedly reduced after crosslinking. In other words, as photocrosslinking takes place in the blend, the degree of crystallinity and reorientation of the PEG macromer in semi-IPN hydrogels decrease compared with the PEG macromer itself (see *Table 2*). Consequently, the T_m of PEG macromer in the semi-IPNs shifted to lower temperatures and the melting peaks became smaller.

In general, the glass transition temperature (T_g) of crosslinked polymers is difficult to observe using ordinary d.s.c. technique. The T_g of β-chitin, however, was measured[19] to be around 170°C. We employed the more sensitive techniques of d.m.t.a. to determine the T_g of semi-IPN hydrogels. *Figure 5* exhibits the mechanical damping, loss tan δ, of PEG segments in semi-IPN hydrogels. Loss tan δ maximum values were taken to be the T_gs of PEG macromer segments in semi-IPNs. D.m.t.a. analysis (*Figure 5*) showed that the T_gs in semi-IPNs were much higher than that of PEG macromer and nearly shifted up to room temperature. The tan δ maximum value of PC1-2 became about 3°C higher than that of PC1-1. As the β-chitin content increases in the semi-IPNs, crosslinked network chains become stiffer, resulting in the restriction of relaxation in the main chain leading to higher T_g. No significant difference in the tan δ curve of PC1-3, irrespective of increasing β-chitin content, is observed. The T_g of PEG macromer segments in the semi-IPNs may also be related to their degree of crosslinking. As PC1-3 had the lowest degree of crosslinking among the semi-IPNs because it contained the smallest portion of PEG macromers, PC1-3 did not show an increase in T_g but rather a decrease.

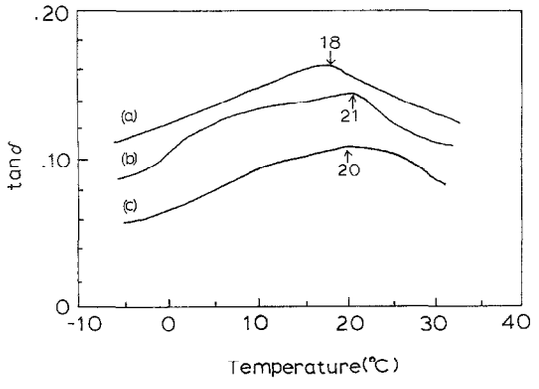

Figure 5 D.m.t.a. thermograms of semi-IPNs: (a) PC1-1; (b) PC1-2; (c) PC1-3

Mechanical properties

The mechanical strength of semi-IPN hydrogels is also shown in *Table 2*. The tensile strength of semi-IPN hydrogels in both the dry and wet states increases with β-chitin content. In the dry state, the mechanical strength of the semi-IPN hydrogels turned out to be relatively strong. In addition, their mechanical strength was retained even in the highly swollen state. As might be expected, the lower amount of crosslinkable end groups led to higher *EWC*. However, regardless of increasing *EWC*, the tensile strength of semi-IPNs in the dry and wet states was still enhanced. Our results contradict the general proportional relationship between tensile strength and crosslinking density.

Suto and Yoshinaka[20] studied the effect of crosslinking density on the water swelling ratio and tensile properties of hydroxypropyl cellulose (HPC) solid films crosslinked with glutaraldehyde and glyoxal. They reported that decreasing the concentration of crosslinking agent contributed to an increase in swelling and a decrease in tensile strength. However, our finding that the tensile strength of semi-IPN hydrogels is retained, even in the highly swollen state, was unprecedented and could not be explained only by the degree of crosslinking. Vyavahare and Kohn[10] have reported that a membrane obtained from poly(PEG–lysine–hydroxyethyl methacrylate) showed a tensile strength of 1.09 MPa at an *EWC* of 78%. They suggested that the phenomenon might be related to microstructural features. That is, during crosslinking, chains of polyacrylate or polymethacrylate are being formed that are most probably intertwined with the original chains of the PEG–lysine copolymer backbones. Therefore, it is clear that the semi-IPN structure contributed to the retention of mechanical strength even in the swollen state.

Note that PC1-3 showed a tensile strength of 2.41 MPa

at an *EWC* of 81%. Our β-chitin/PEG macromer semi-IPN ranks among the strongest and most highly swollen hydrogels reported to date. We conclude that the stiff β-chitin chain, exhibiting strong intramolecular hydrogen bonding, formed a network structure with the flexible and hydrophilic PEG, resulting in much stronger and more highly swollen hydrogels. The hydrolytic degradation kinetics of semi-IPN hydrogel membranes with bioerodible linkage is under investigation.

CONCLUSIONS

To prepare a polymeric biomedical material, semi-IPN hydrogels composed of β-chitin and PEG diacrylate macromer were synthesized by u.v. irradiation and their properties were studied. Hydrophilic PEG diacrylate macromer segments were crosslinked and formed a network structure with β-chitin. All hydrogels exhibited relatively high *EWC* in the range of 60–81%. As estimated by d.s.c. analysis, bound water contents in the semi-IPN hydrogels are in the range of 10–16%, while free water contents in semi-IPN increases from 51 to 70% with β-chitin content. Upon crosslinking, the degree of crystallinity of PEG macromer chains in the semi-IPNs decreased remarkably because of the reduced reorientation of the PEG macromer and β-chitin. Meanwhile, their glass transition temperature and mechanical strength were much higher with increasing β-chitin content. The tensile strength in the swollen state ranged from 1.35 to 2.41 MPa. In particular, PC1-3 showed the highest tensile strength of 2.41 MPa at an *EWC* of 81%; it is known to be the strongest and most highly swollen hydrogel reported to date.

ACKNOWLEDGEMENT

The authors wish to acknowledge the Ministry of Education Research Fund for Advanced Materials in 1995.

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