Interpenetrating Network Hydrogels via Simultaneous "Click Chemistry" and Atom Transfer Radical Polymerization

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Received March 12, 2010; Revised Manuscript Received May 19, 2010

Simultaneous interpenetrating polymer networks (sIPNs) from concurrent copper(I)-catalyzed azide−alkyne cycloaddition "click chemistry" and atom transfer radical polymerization (ATRP) are described. Semi-sIPN of poly(ethylene glycol)/poly(2-hydroxyethyl methacrylate) (semi-PEG/PHEMA-sIPN) was first prepared via simultaneous "click chemistry" and ATRP from a mixture of poly(ethylene glycol)-diazide (N_3-PEG-N_3, M_n = 4000 g/mol), tetrakis(2-propynyloxymethyl)methane (TPOM), ethyl-2-bromobutyrate (EBB), CuBr, pentamethyldiethylenetriamine (PMDETA), and 2-hydroxyethyl methacrylate (HEMA) in dimethylformamide (DMF). Full sIPN of PEG/PHEMA (full-PEG/PHEMA-sIPN) was then prepared via simultaneous "click chemistry" and ATRP from a mixture of N_3-PEG-N_3 (M_n = 4000 g/mol), TPOM, EBB, CuBr, PMDETA, HEMA, and poly(ethylene glycol) diacrylate) (PEGDA, M_n = 575) in DMF. Both the semi- and full-sIPNs exhibit a fast gelation rate and high gel yield. The sIPNs also exhibit high swelling ratios and good mechanical and antifouling properties. The morphology and thermal behavior of the sIPNs were studied by scanning electron microscopy (SEM), thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC). These sIPNs could find applications as biomaterials for contact lenses, biomedical materials, artificial organs, and drug delivery systems.

1. Introduction

Interpenetrating polymer networks (IPNs), a kind of unique "alloy" of cross-linked polymers, can exhibit entirely new and sometimes surprising properties, such as tunable responsive properties, enhanced mechanical properties, and improved thermal stability.[1−3] Because of these unique properties, IPNs have found applications as biomedical materials.[3−7] Traditional synthesis of IPNs involves sequential polymerization of a mixture of monomer and cross-linking agents in a swollen network (sequential IPNs) or simultaneous one-step polymerization of two different monomer-cross-linking agent pairs with independent and noninterfering reaction mechanisms (sIPNs).[3,8] The preparation of sIPN is often accomplished by polymerizing one network via condensation polymerization, while the other by free radical polymerization. The preparation of sIPNs thus requires stringent conditions, such as functional group tolerance, mild reaction conditions, and good reaction yields.[1,9]

"Click chemistry" is a powerful technique for preparing macromolecules with complex architectures[10−15] and functional polymers for biomedical and pharmaceutical applications.[16] Recently, "click chemistry", especially copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC), has been widely used in the preparation of hydrogel networks because of its reaction specificity, quantitative yields, and good functional group tolerance.[17−19] Atom transfer radical polymerization (ATRP), on the other hand, provides a unique tool for preparing nearly monodispersed polymers with controlled molecular weight.[20−23] Hydrogels have also been prepared via ATRP of multifunctional, such as macromonomers,[24,25] methacryloyloxy poly(ethylene oxide) (PEO). Interestingly, ATRP not only shares a number of attractive features with CuAAC, such as good tolerance for a wide range of functional groups,[26] but also the same copper catalyst system.[27] Combined CuAAC and ATRP in one-pot synthesis has already been reported in the literature.[28−31] The influence of solvents, catalyst concentration, temperature, and various azido reagents on simultaneous copper(I)-catalyzed "click chemistry" and ATRP has been studied.[32] Simultaneous click reaction and ATRP in emulsion has also been reported.[33]

In this work, we demonstrate an alternative approach to the preparation of semi-sIPNs and full-sIPNs via the simultaneous reactions of "click chemistry" and ATRP. The interest in sIPN of poly(ethylene glycol) (PEG) arises from the fact that PEG is an uncharged, water-soluble, nontoxic, nonimmunogenic, and widely used biomedical material.[34−36] On the other hand, the choice of poly(2-hydroxyethyl methaycrylate) (PHEMA) as the other component of the IPNs arises from its hydrophilicity, nontoxic nature, and biocompatibility with a large number of existing biomedical and pharmaceutical applications.[37,38] Semi-PEG/PHEMA-sIPN was first prepared via simultaneous "click chemistry" and ATRP from a reaction mixture of poly(ethylene glycol)-diazide (N_3-PEG-N_3, M_n = 4000 g/mol), tetrakis(2-propynyloxymethyl)methane (TPOM), ethyl 2-bromobutyrate (EBB), CuBr, pentamethyldiethylenetriamine (PMDETA), and 2-hydroxyethyl methacrylate (HEMA) in DMF. Full-PEG/PHEMA-sIPN was also prepared via simultaneous "click chemistry" and ATRP from the same reaction mixture, except that the cross-linking agent, poly(ethylene glycol) diacrylate (PEGDA), was also used.

2. Experimental Section

2.1. Materials. The monomers, HEMA (97%) and PEGDA (M_n = 575 g/mol), were purchased from Acros Organic Co. of Geel, Belgium. The monomers were used after removal of the inhibitors in a ready-to-use disposable inhibitors-removal column. Propargyl bromide (80%),

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10.1021/bm100268t
Published on Web 06/02/2010

PEG (M_n = 4000 g/mol), and PMDETA (99%) were purchased from Aldrich Chemical Co. and were used as received. Sodium azide (99%), CuBr (99%), methane sulfonyl chloride, pentaerythritol, and bovine serum albumin (BSA) were purchased from Shanghai Chemical Reagent Plant.

2.2. Chemical Synthesis and Polymerization. *2.2.1. Synthesis of Poly(ethylene glycol)-diazide (N_3-PEG-N_3).* Poly(ethylene glycol)-diazide was prepared from PEG according to the method reported in the literature.[39] About 10 g (2.5 mmol) of PEG (M_n = 4000 g/mol) was dissolved in 50 mL of dry pyridine. The solution was cooled to 0 °C, and 0.98 g (12.5 mmol) of methanesulfonyl chloride dissolved in 10 mL of dry dichloromethane was added dropwise over 20 min. The mixture was allowed to return to room temperature and was stirred another 12 h. After removal of the solvent in a rotary evaporator, the residue was treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The solution was dried over $MgSO_4$ for 10 h. The organic solvent was removed by rotary evaporation. The product (8.9 g of pale powder) was precipitated by addition of an excess amount of diethyl ether. After that, a mixture of 8 g (2 mmol) of the as-prepared PEG and 0.65 g (10 mmol) of sodium azide in 50 mL of dry DMF was allowed to react at 85 °C for 24 h. The unreacted sodium azide was removed by passing the reaction mixture through an alumina column, and the filtrate was concentrated by rotary evaporation. The polymer was precipitated from the concentrated DMF solution by addition of diethyl ether and filtration. The product was studied by MALDI-TOF mass spectroscopy and ^{1}H NMR spectroscopy. The conversion efficiency of the hydroxyl groups into azide groups was about 93%. Yield: 90%; FTIR (cm^{-1}): $\nu_{(N=N)}$ = 2098.

2.2.2. Synthesis of Tetrakis(2-propynyloxymethyl)methane. About 2.4 g (0.017 mmol) of pentaerythritol was added into a solution of 15 g (0.264 mmol) of KOH in 30 mL of anhydrous DMF. After stirring at 5 °C for 30 min, 20 g (0.17 mmol) of propargyl bromide was slowly added over a period of 20 min. The color of the solution turned brown and the reaction mixture was stirring at 40 °C overnight. The reaction mixture was quenched with water and extracted thrice with 50 mL of ethyl ether. The organic layers were combined, washed with water, then with brine, and dried over Na_2SO_4. After removal of the ethyl ether by rotary evaporation, the adduct was further purified by passing it through a silica gel column, using mixed ethyl acetate/hexane (2/8 in volume ratio) as the eluent. An orange solid of about 3.57 g was obtained. Yield = 79%; ^{1}H NMR ($CDCl_3$, ppm): 4.13 (8H, -OCH_2), 3.55 (8H, C(CH_2)$_4$), and 2.43 (4H, CH); FTIR (cm^{-1}): $\nu_{(\equiv CH)}$ = 3299.

2.2.3. PEG-Based Network from "Click Chemistry". About 0.1 g (0.025 mmol) of poly(ethylene glycol)-diazide, 3.6 mg (0.0125 mmol) of tetrakis(2-propynyloxymethyl)methane, 8.7 mg (0.05 mmol) of PMDETA, and 1 mL of DMF were introduced into a small vial. After the mixture turned clear, the vial was degassed with argon for 20 min, and 7.2 mg (0.05 mmol) of CuBr was quickly added under ultrasonic agitation. The gelation point was reached in 1 min, and the reaction was allowed to continue for another 24 h at 60 °C. A uniform hydrogel was obtained upon removal from the vial. The gel was transferred to an EDTA (5%) solution to remove the copper ions and DMF. Finally, the gel was immersed into a large volume of pure deionized water to allow the water absorption.

2.2.4. PHEMA-co-PEGDA Network from Atom Transfer Radical Polymerization. A typical polymerization procedure was carried out as follow: 0.5 g (3.8 mmol) of HEMA, 0.54 g (0.95 mmol) of EGDA, 9.9 mg (0.057 mmol) of PMDETA, 11.1 mg (0.057 mmol) of EBB, and 1 mL of DMF was introduced into a dry and clean vial (molar ratio of [HEMA]/[EGDA]/[EBB]/[CuBr]/[PMDETA] = 66.7:16.6:1:1:1). The mixture was degassed with argon for 20 min, and then 8.2 mg (0.057 mmol) of CuBr was added into the vial. Gelation was reached in 45 min. After gelation, the reaction was allowed to proceed at 60 °C for another 24 h before being terminated via exposure to air. Finally, the copper catalyst and DMF were removed by immersing the gel into an excess volume of 5% EDTA solution.

2.2.5. Full- or Semi-sIPN via Simultaneous "Click Chemistry" and ATRP. 2.2.5.1. Preparation of Full-PEG/PHEMA-sIPN. A typical procedure for the preparation of full-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP was carried out as follows. About 0.5 g (3.8 mmol) of HEMA, 0.54 g (0.95 mmol) of EGDA, 18.5 mg (0.107 mmol) of PMDETA, 11.1 mg (0.057 mmol) of EBB, 0.3 g (0.075 mmol) of poly(ethylene glycol)-diazide, 10.8 mg (0.0375 mmol) of tetrakis(2-propynyloxymethyl)methane, and 1.5 mL of DMF were introduced into a 5 mL vial. The reaction mixture was purged with argon for 20 min and 15.4 mg (0.107 mmol) of CuBr was added quickly. The gelation of sIPN occurred in about 2 min. The mixture was kept at 60 °C for another 24 h to obtain a uniform solid sIPN hydrogel. The copper catalyst and DMF in the gel were removed in an excess volume of 5% EDTA solution and maximum water absorption was achieved by immersing the sIPN in deionized water.

2.2.5.2. Preparation of Semi-PEG/PHEMA-sIPN. To prepare the semi-sIPN, 0.74 g (5.7 mmol) of HEMA, 18.5 mg (0.107 mmol) of PMDETA, 15.4 mg (0.107 mmol) of CuBr, 11.1 mg (0.057 mmol) of EBB, 0.3 g (0.075 mmol) of poly(ethylene glycol)-diazide, 10.8 mg (0.0375 mmol) of tetrakis(2-propynyloxymethyl)methane, and 1.5 mL of DMF were introduced into a 5 mL vial (molar ratio of [HEMA]/[EbiB]/[CuBr]/[PMDETA] = 100:1:1:1). The reaction mixture was purged with argon for 20 min and sealed. The gelation of sIPN occurred in 2 min. The mixture was kept at 60 °C for a predetermined period of time to obtain the uniform solid sIPN hydrogel. The copper catalyst and DMF in the gel were also removed in 5% EDTA solution, and maximum water absorption was achieved by immersing the sIPN in deionized water.

2.2.6. Degree of Swelling of Full- and Semi-sIPNs. The degree of swelling of the sIPNs was measured as follow. Initially, the prepared sIPN was dried at 50 °C for more than 24 h, and the weight ($weight_{dry\ gel}$) was recorded when the sample reached a constant weight. Then it was immersed in deionized water for at least 24 h to allow the sIPN to become fully hydrated. When the weight of the swollen sIPN reached a stable value, it was again recorded ($weight_{swollen\ gel}$). The degree of swelling of hydrogels was calculated from the equation

$$\text{degree of swelling} = \{(\text{weight}_{\text{swollen gel}}/\text{weight}_{\text{dry gel}}) - 1\} \times 100\%$$

Each value was the average value from five measurements.

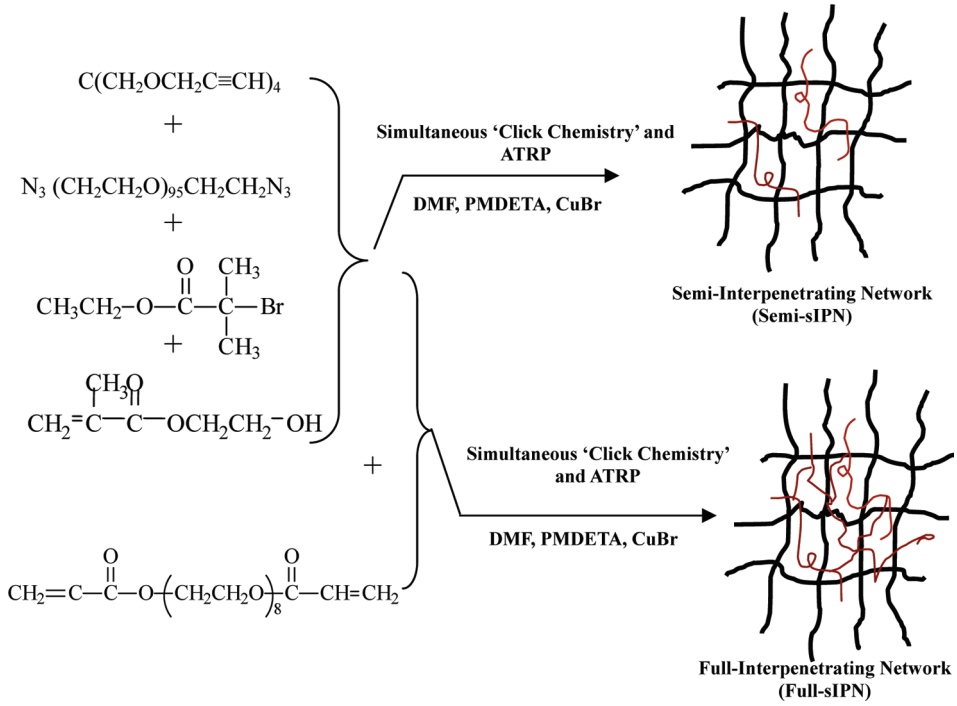
2.2.7. Antifouling Properties of the Full- and Semi-sIPNs. Bovine serum albumin (BSA) was diluted with a phosphate buffer solution (PBS, pH 7.4) to prepare the 1% (mg/mL) solution. Prior to the adsorption experiment, the hydrogels were equilibrated in PBS at the physiological pH of 7.4 for 48 h. The protein absorption of the sample was carried out by immersing the sample in the BSA solution at 25 °C for 24 h. After the absorption, the BSA concentration in the solution was determined by UV adsorption spectroscopy measurement at the wavelength of 280 nm. The absorbed amount of BSA (mg/g) was calculated from mass balance according to the following equation:

$$q_e = (C_0 - C_e) \cdot V/m$$

where q_e is the equilibrium absorption capacity, m (g) is the mass of fully swollen gel, V (mL) is the volume of BSA solution, and C_0 (mg/mL) and C_e (mg/mL) are the initial and equilibrium protein concentrations, respectively.

2.2.8. Characterization. The chemical structures of tetrakis(2-propynyloxymethyl)methane was characterized by ^{1}H NMR spectroscopy on a Bruker ARX 300 MHz spectrometer, using $CDCl_3$ as the solvent, in 1000 scans at a relaxation time of 2 s. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS) were recorded using a Bruker AutoFlex II apparatus. Fourier transform infrared (FT-IR) spectra were obtained from a MAGNA-IR 750 spectrometer (Nicolet Instrument Co.). The sample was dispersed in a KBr pellet. The swollen hydrogels were frozen rapidly at −80 °C and then dried in a freeze-dryer. The thermal stability of the full-PEG/

Scheme 1. Preparation of Semi-PEG/PHEMA-sIPN and Full-PEG/PHEMA-sIPN via Simultaneous "Click Chemistry" and Atom Transfer Radical Polymerization (ATRP)



PHEMA-sIPN, semi-PEG/PHEMA-sIPN, PEG-based network, and PHEMA-*co*-PPEGDA network were determined on a thermogravimetric analyzer (TA SDT Q-600). The DSC measurements were performed on a Pekin Elmer DSC7 calorimeter under a nitrogen atmosphere, at a heating rate of 10 °C/min. The absorption and transmittance spectra of the prepared hydrogels were measured on a Hitachi U-4100 UV−visible spectrophotometer. The hydrogel sample with a thickness of 0.5 cm was fixed on the inner wall of a quartz cell. The morphology of the sIPNs was studied on a scanning electron microscope (Hitachi X-650 SEM) at an accelerating voltage of 5−20 kV and an object distance of about 8 mm. Tensile testing was performed using an Instron Model 5844 tensile tester at room temperature. The extension speed was set to a constant stretching rate of 0.01 mm/s until the failure of the sample. The true stress and strain were calculated from the load and extension data recorded by the software Testworks.

3. Results and Discussion

3.1. Preparation of Interpenetrating Polymer Networks (sIPNs) from Simultaneous "Click Chemistry" and Atom Transfer Radical Polymerization (ATRP). Full- and semi-sIPNs were prepared from the simultaneous reactions of (i) "click chemistry" of N_3-PEG-N_3 (M_n = 4000 g/mol) and TPOM to generate the network with 1,2,3-triazole linkage and (ii) ATRP of HEMA, or PEGDA and HEMA, to form the respective semi- and full-sIPNs (Scheme 1). Figure 1 shows the optical images of the pristine PEG network from "click chemistry", PHEMA-*co*-PPEGDA network from ATRP, semi-PEG/PHEMA-sIPN, and full-PEG/PHEMA-sIPN, respectively.

The gelation effect is very important in the investigation of sIPN formation from simultaneous ATRP and "click chemistry". Because "click chemistry" and ATRP share the same catalyst system, the concentration of Cu(I) catalyst plays an important role in the gelation effect. Simultaneous ATRP and "click chemistry" with varying concentration of Cu(I) catalyst were carried out to obtain the optimal gelation effect. Figure 2 shows the dependence of gelation time on the molar ratio of CuBr/azide groups of the pristine PEG network from "click chemistry" and semi-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP. The increase in the amount of Cu(I) catalyst can reduce the gelation time. By increasing the concentration of CuBr from 20 to 100% (relative to the mole concentration of azido and alkynyl groups), the respective gelation time decreases from about 38 to 2 min and about 42 to 2 min. A similar observation has been reported.[40,41] The fact that, in the presence of limited Cu(I) catalysts, the gelation time of PEG-based network is shorter than that of the semi-PEG/PHEMA-

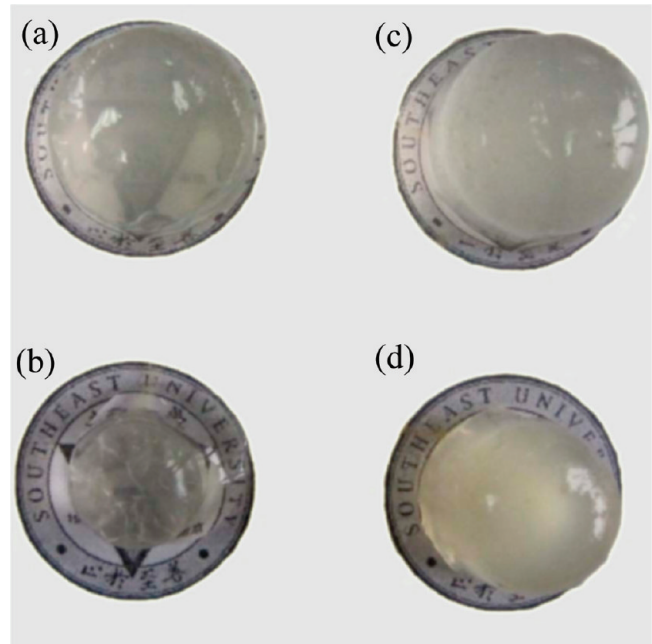


Figure 1. Photographs of (a) the PEG-based network from "click chemistry", (b) the PHEMA-*co*-PPEGDA network from ATRP, (c) semi-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP, and (d) full-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP.

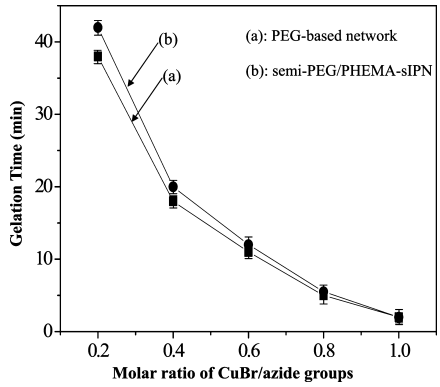


Figure 2. Dependence of gelation rate on the molar ratio of CuBr/azide groups: (a) the PEG-based network from "click chemistry" with molar ratio of [azido]/[alkynyl] = 1:1 in 1.5 mL of DMF at 60 °C and (b) semi-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP with molar ratio of [azido]/[alkynyl]/[HEMA]/[EBB] = 1:1:100:1 in 1.5 mL of DMF at 60 °C.

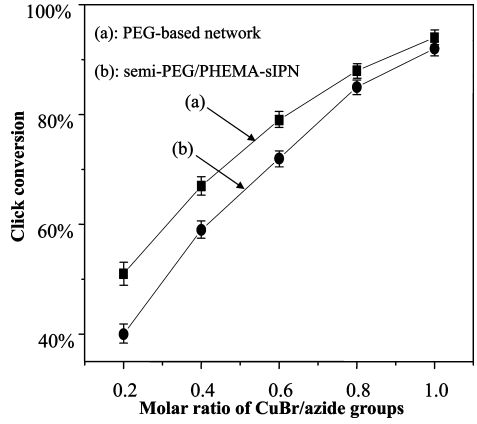


Figure 3. Dependence of the hydrogel yields on the molar ratio of CuBr/azide groups of (a) the PEG-based network from "click chemistry" with a molar ratio of [azido]/[alkynyl] = 1:1 in 1.5 mL of DMF at 60 °C for 24 h and (b) the semi-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP with molar ratio of [azido]/[alkynyl]/[HEMA]/[EBB] = 1:1:100:1 in 1.5 mL of DMF at 60 °C for 24 h.

sIPN suggests that a part of Cu(I) catalysts is used to initiate the ATRP process, thus, reducing the catalyst concentration for the "click chemistry".

The introduction of ATRP into the "click chemistry" might affect the molecular structure of the PEG network and the efficiency of CuAAC. Thus, the CuAAC efficiency of pristine PEG network and semi-PEG/PHEMA-sIPN were studied. The CuAAC efficiency can be calculated from the residual of azide/acetylene groups. According to the method reported,[17] postgel "click chemistry" of the azide-functionalized chromophores (3-azido-7-hydroxycoumarin) was performed, followed by UV absorption analysis to determine the amount of the unreated alkyne groups in the gels. Figure 3 shows the dependence of CuAAC efficiency on the CuBr/azide molar ratio of pristine PEG network prepared with an [azido]/[alkynyl] molar ratio of 1:1 in 1.5 mL of DMF at 60 °C for 24 h, and of semi-PEG/PHEMA-sIPN prepared with an [azido]/[alkynyl]/[HEMA]/[EBB] molar ratio of 1:1:100:1 in 1.5 mL of DMF at 60 °C for 24 h. Thus, the CuAAC efficiency is enhanced by the increase in catalyst concentration. The CuAAC efficiency of semi-PEG/PHEMA-sIPN is lower than that of the pristine PEG-based network, especially when a low concentration of CuBr is used. This result is consistent with the fact that introduction of ATRP reduces the amount of Cu(I) for CuAAC and dilutes the concentration of the azide and alkyl groups. Although the side reaction between the azide groups and vinyl monomers can proceed at a finite rate,[42] this side reaction is much slower than the reaction involving "click chemistry". Thus, the effect of the side reaction between the azide and the vinyl groups is negligible. In Figure 3, the increase in concentration of CuBr leads to an increase in CuAAC efficiency of both the pristine PEG network and semi-PEG/PHEMA-sIPN. At the CuBr/azide ratio of about 0.2, the CuAAC efficiency of pristine PEG network is about 50%, which is higher than that (40%) of semi-PEG/PHEMA-sIPN. When the CuBr/azide ratio is increased to 1.0, the CuAAC efficiency in semi-PEG/PHEMA-sIPN reaches 92%, which is comparable to that (94%) of the pristine PEG network. These results indicate that sufficient catalyst concentration in the reaction mixture is critical to both "click chemistry" and ATRP in a one-pot synthesis. An additional increase in the amount of CuBr will not improve the CuAAC efficiency remarkable but will lead to a poor control of ATRP. Thus, in this study, the molar ratio of [CuBr]/[azido]/[alkynyl] is fixed at 1:1:1.

Semi-PEG/PHEMA-sIPN was prepared via simultaneous "click chemistry" and ATRP from a reaction mixture of N_3-PEG-N_3 (M_n = 4000 g/mol), TPOM, EBB, CuBr, PMDETA, and HEMA in DMF. The PEG gel fraction of semi-PEG/PHEMA-sIPN was obtained from a control experiment with the same reaction conditions as that for the preparation of semi-PEG/PHEMA-sIPN, albeit in the absence of EBB. The gel fraction of semi-PEG/PHEMA-sIPN was obtained from the relation: gel fraction = $\text{mass}_{\text{dried gel}}/\text{mass}_{\text{polymer precursors}}$. The data in Table 1 show that the PEG gel fraction of semi-PEG/PHEMA-sIPN was about 90%, which was slightly lower than that (94%) of the pristine PEG-based network. The conversion of PHEMA was calculated from the expression of $[\text{mass}_{\text{dried gel of semi-PEG/PHEMA-IPN}} - \text{mass}_{\text{dried gel of control experiment}}]/\text{mass}_{\text{HEMA}}$. The data in Table 1 also show that at the reaction time of 12 h, the conversion of HEMA is about 0.43. With the increase in reaction time from 12 to 24 h, the gel fraction of PEG remains unchanged, while the conversion of HEMA increases from 0.43 to 0.59. Part of the Cu(I) catalyst forms the Cu(I) acetylide complex with alkyne for "click chemistry", and the remaining part reacts with EBB to generate the radicals and Cu(II) for ATRP.[22,43] In fact, the rate of "click chemistry" was very fast. A 90% click conversion can be achieved in 5 min.[32] Thus, in the first few minutes, "click chemistry" was the predominant reaction. In a control experiment for the preparation of semi-PEG/PHEMA-sIPN, the reaction was stopped at 3 min when the gel point was reached, and the unreacted molecules were extracted from the hydrogel. FTIR studies show that the hydrogel is composed mainly of a PEG-based network and no PHEMA polymer was found in hydrogel. When the gel point of PEG was reached and most of the click reactions had been completed, the polymerization became dominated by ATRP of HEMA. At this stage, polymerization may be considered as the ATRP of HEMA in a PEG-based network.

Full-PEG/PHEMA-sIPNs were also prepared via simultaneous "click chemistry" and ATRP from a reaction mixture of N_3-PEG-N_3 (M_n = 4000 g/mol), TPOM, EBB, CuBr, PMDETA, HEMA, PEGDA (M_n = 575), and DMF. The PEG gel fraction of full-PEG/PHEMA-sIPN was obtained from a controlled experiment carried out under the same reaction condition as that used for the preparation of full-PEG/PHEMA-sIPN, albeit in the absence of EBB. The gelation was reached in 2 min and a PEG gel fraction of about 88% in full-PEG/PHEMA-sIPN

Table 1. Characterization of the Interpenetrating Networks

sample	gel fraction	swelling degree[f] (%)	max. stress[f] (kPa)	max. extension to break[f] (%)
PEG-based network	0.94	1570 ± 110	630 ± 17	800 ± 59
PHEMA-*co*-PPEGDA network	0.77	120 ± 10	60 ± 5	20 ± 3
semi-PEG/PHEMA-sIPN1[a]	0.90/0.43[e]	1330 ± 90	920 ± 30	480 ± 29
semi-PEG/PHEMA-sIPN2[b]	0.90/0.59	1230 ± 95	960 ± 28	650 ± 33
full-PEG/PHEMA-sIPN1[c]	0.88/0.60	870 ± 70	1430 ± 36	600 ± 25
full-PEG/PHEMA-sIPN2[d]	0.88/0.64	1090 ± 85	1480 ± 41	760 ± 41

[a] Molar feed ratio of [HEMA]/[EBB]/[CuBr]/[PMDETA]:/[N_3-PEG-N_3]/[TPOM] = 100:1:1:1:0.5:0.25. The reaction was carried out at 60 °C, and the reaction time was fixed at 12 h. [b] Molar feed ratio of [HEMA]/[EBB]/[CuBr]/[PMDETA]/[N_3-PEG-N_3]/[TPOM] = 100:1:1:1:0.5:0.25. The reaction was carried out at 60 °C, and the reaction time was fixed at 24 h. [c] Molar feed ratio of [HEMA]/[EGDA]/[EBB]/[CuBr]/[PMDETA]/[N_3-PEG-N_3]/[TPOM] = 66.7:16.6:1:1:1:0.5:0.25. The reaction was carried out at 60 °C, and the reaction time was fixed at 12 h. [d] Molar feed ratio of [HEMA]/[EGDA]/[EBB]/[CuBr]/[PMDETA]/[N_3-PEG-N_3]/[TPOM] = 66.7:16.6:1:1:1:0.5:0.25. The reaction was carried out at 60 °C, and the reaction time was fixed at 24 h. [e] PEG and PHEMA gel fractions. [f] The value is the average of five measurements.

was obtained (gel fraction = $\text{mass}_{\text{dried gel}}/\text{mass}_{\text{polymer precursors}}$). To study the formation of PHEMA/PEGDA networks in simultaneous "click chemistry" and ATRP, another controlled experiment under the same reaction condition as that used for the preparation of full-PEG/PHEMA-PEGDA-sIPN, except using PEG (M_n = 4000 g/mol) instead of N_3-PEG-N_3, was carried out. In the controlled experiment of ATRP of PEGDA and HEMA, the gelation was achieved at a reaction time of about 45 min. The polymerization rate of PEGDA was relatively slow[25] and the living character of polymerization was maintained in the first 20 min. In the process of simultaneous "click chemistry" and ATRP, gelation commenced in about 2 min. Prior to gelation, the ATRP process proceeds in a controlled manner. However, as the reaction proceeds, the concentration of radical may start to increase. The increase in concentration of radicals can be attributed partially to the release of Cu(I) from the Cu(I) acetylide complex due to the completion of "click chemistry" and partially to the reduction in radical deactivation because of the decrease in mobility of the Cu(I) and Cu(II) species arising from the increase in system viscosity. The increase in radical concentration results in a high ATRP rate and promotes the formation of PEGDA and PHEMA networks. Thus, in the full-PEG/PHEMA-sIPN, the networks of PEG and PEG/PHEMA were generated sequentially. The gel fraction of PHEMA was calculated from the equation [$\text{mass}_{\text{dried gel of full-PEG/PHEMA-IPN}} - \text{mass}_{\text{dried gel of control experiment}}$]/$\text{mass}_{\text{HEMA}}$. The data in Table 1 show that as the polymerization time is increased from 12 to 24 h, the PHEMA fraction increases correspondingly from 0.60 to 0.64.

3.2. Physical Properties of the sIPNs. All the sIPNs prepared exhibit a high degree of swelling. The data in Table 1 shows that the degrees of swelling of the prepared semi- and full-sIPN are 1230 and 1090%, respectively. They are higher than that of the PHEMA-*co*-PPEGDA network (120%) but lower than that of PEG-based network (1570%). The ability of the polymer chains to relax fully has allowed the formation of bigger pores and cavities, as well as given rise to a higher degree of water adsorption by the pristine PEG networks from "click chemistry". For full-PEG/PHEMA-sIPN, the PEG network and PHEMA-*co*-PPEGDA network are entangled, restricting the full stretching of the network lattice and resulting in a lower degree of water adsorption. For semi-PEG/PHEMA-sIPN, the hydrophilic PHEMA can stretch freely within the network lattice. The extension of PEG chains is also much easier than those of full-PEG/PHEMA-sIPN. Thus, the degree of swelling of semi-PEG/PHEMA-sIPN is approaching that of the PEG network.

Both full- and semi-sIPNs exhibit improved mechanical properties over those of the PEG network from "click chemistry" and PHEMA-*co*-PPEGDA network from ATRP (Table 1). The entanglement of networks by low molecular weight segments between the cross-linking points (M_c) and mesh size have significantly increased the tensile stress of sIPNs. The maximum extension to break (MEB) of sIPNs, however, is slightly lower

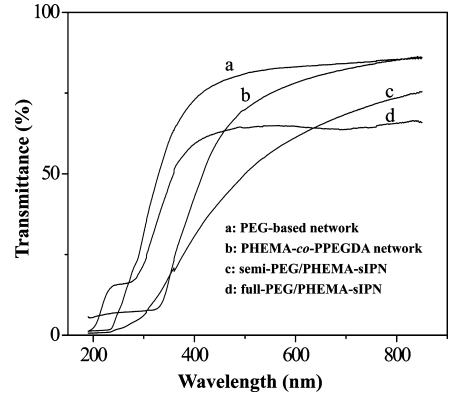


Figure 4. UV−visible transmittance spectra of (a) the PEG-based network from "click chemistry", (b) PHEMA-*co*-PPEGDA network from ATRP, (c) semi-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP, and (d) full-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP. PEGDA = poly(ethylene glycol) diacrylate.

than that of the pristine PEG network from "click chemistry". The MEB of the pristine PEG network is about 800%, while the MEB's of full-PEG/PHEMA-sIPN and semi-PEG/PHEMA-sIPN are about 760 and 650%, respectively. The decrease in MEB can be attributed to the relatively lower gel fraction (gel yield) of full- and semi-sIPN in comparison to that of the PEG-based network (Table 1). A higher gel yield means fewer disfigurements in the network, leading to a higher tensile stress.

The optical properties of the as-prepared sIPNs were studied. Figure 4 shows the transmittance of pristine PEG network from "click chemistry", PHEMA-*co*-PPEGDA network from ATRP, semi-PEG/PHEMA-sIPN and full-PEG/PHEMA-sIPN, respectively. In the ultraviolet range, the transmittances of full-PEG/PHEMA-sIPN and PEG-based network are higher than those of the semi-PEG/PHEMA-sIPN and PHEMA-*co*-PPEGDA network. At the wavelength of 280 nm, the respective transmittances of the PEG-based network and full-PEG/PHEMA-sIPN are 23 and 20%, which are higher than that of semi-PEG/PHEMA-sIPN (3%) and that of PHEMA-*co*-PPEGDA network. In the visible region, both the full-PEG/PHEMA-sIPN and PEG-based network exhibit relatively constant transmittances of about 63 and 79%, respectively, while the transmittance of the semi-PEG/PHEMA-sIPN increases with the increase in wavelength. At 400 nm, the transmittance of semi-PEG/PHEMA-sIPN is only 28%. However, the transmittance increases dramatically to 75% at 800 nm.

The morphology of sIPNs was also studied. Figure 5a,b shows the cross-sectional scanning electron microscopy (SEM) images of the freeze-dried samples of PHEMA-*co*-PPEGDA network from ATRP, PEG-based network from "click chemistry", semi-PEG/PHEMA-sIPN, and full-PEG/PHEMA-sIPN, respectively. The PHEMA-*co*-PPEGDA network (Figure 5a) has a homoge-

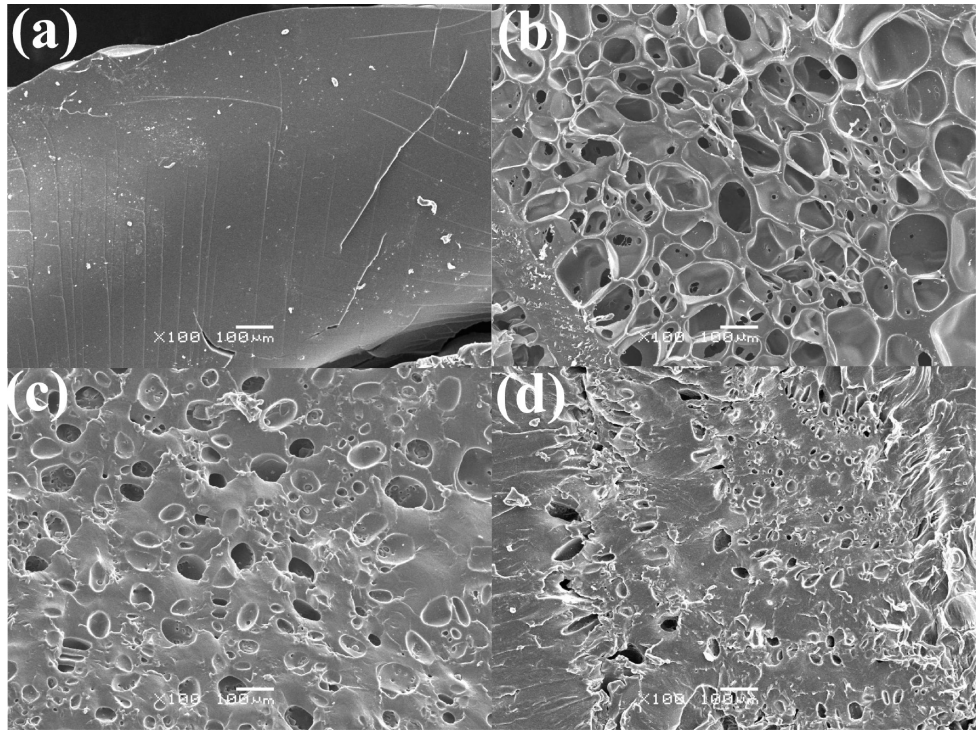


Figure 5. SEM images (cross-section view) of (a) the PHEMA-*co*-PPEGDA network from ATRP, (b) PEG-based network from "click chemistry", (c) semi-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP, and (d) full-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP.

neous and dense morphology, while the PEG-based network (Figure 5b) is highly porous with pore sizes ranging from 90 to 150 μm. The morphology of semi-PEG/PHEMA-sIPN (Figure 5c) and full-PEG/PHEMA-sIPN (Figure 5d) is similar to that of the PEG-based network, and the pore sizes are in the range of 60−90 μm. The SEM results are thus consistent with the swelling results, that is, the more porous the structure, the higher the degree of swelling.

3.3. Thermal Properties. The thermal stability is very important for materials aiming for biomedical applications. For the thermally unstable biomaterials, thermal treatment during the process of manufacturing and long-term usage at 37 °C can lead to degradation of their mechanical properties and alteration of their cytotoxicity and biocompatibility.[44] Thus, the thermal properties of sIPNs were also studied. Figure 6 shows the thermogravimetric analysis (TGA) results of the pristine PEG network from "click chemistry" (curve a), semi-PEG/PHEMA-sIPN (curve b), full-PEG/PHEMA-sIPN (curve c), and the PHEMA-*co*-PPEGDA network from ATRP (curve d). The weight loss of semi-PEG/PHEMA-sIPN and full-PEG/PHEMA-sIPN commences at the temperature of about 290 °C, which is lower than that (350 °C) of the pristine PEG network but is higher than that (250 °C) of the PHEMA-*co*-PPEGDA network. The network from ATRP consists of a dense cluster of multiple acrylate groups within a weakly cross-linked matrix.[45] Thus, the introduction of easily decomposable composition (network or linear polymer from ATRP) reduces the thermal stability of semi- and full-PEG/PHEMA-sIPNs.

The differential scanning calorimetry (DSC) thermograms of sIPNs were investigated in the temperature range of 0 to 200 °C. The results are shown in Figure 7. There were two transitions in the DSC curves of semi-PEG/PHEMA-sIPN and full-PEG/PHEMA-sIPN. The first weak endothermic peak appeared at around 50 °C is associated with the melting temperature (T_m) of the PEG network, which is comparable to that (55 °C) of

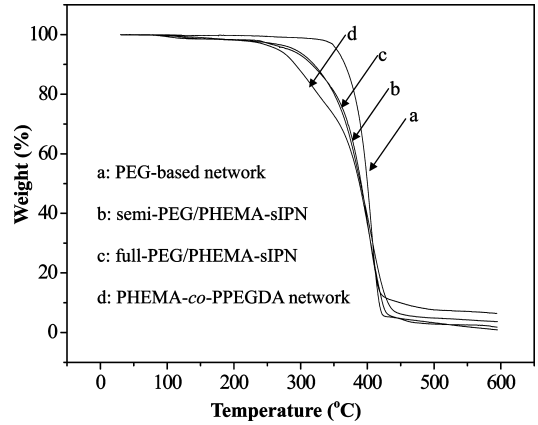


Figure 6. Thermogravimetric analysis (TGA) of (a) the PEG-based network from "click chemistry", (b) semi-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP, (c) full-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP, and (d) PHEMA-*co*-PPEGDA network from ATRP.

the pristine PEG-based network. The second endothermic peak at around 88 °C is attributable to the glass transition temperature (T_g) of PHEMA and the PHEMA-*co*-PEGDA network. The DSC results are thus consistent with the structures of semi-PEG/PHEMA-sIPN and full-PEG/PHEMA-sIPN prepared by simultaneous ATRP and "click chemistry".

3.4. Antifouling Property of the sIPNs. For application as biomaterials, such as soft contact lenses, the ability to resist protein adsorption (or the antifouling property) is very important. The antifouling properties of pristine PEG network, PHEMA-*co*-PPEGDA network, full- and semi-PEG/PHEMA-sIPNs against the plasma protein, BSA, were studied. Figure 8 shows the amount of absorbed protein on the hydrogel samples after equilibrating in 1% (mg/mL) PBS of BSA at the physiological pH of 7.4 for 48 h. The PHEMA-*co*-PPEGDA network exhibits a higher BSA absorption (11.3 mg/g^{-1}) than the pristine PEG

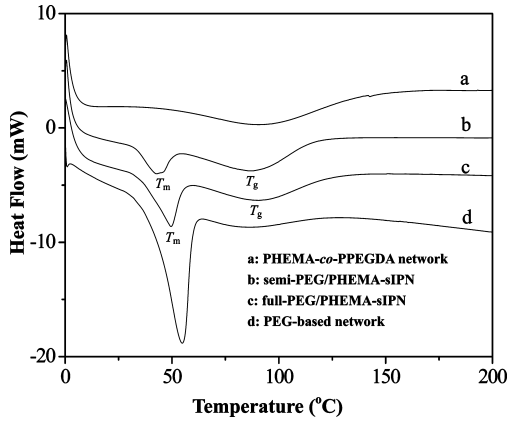


Figure 7. Differential scanning calorimetry (DSC) of (a) the PHEMA-*co*-PPEGDA network from ATRP, (b) semi-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP, (c) full-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP, and (d) PEG-based network from "click chemistry".

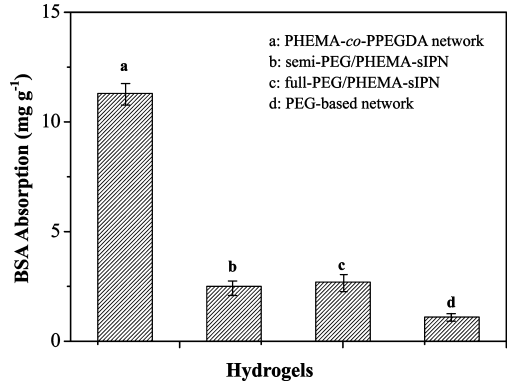


Figure 8. Protein absorption by (a) the PHEMA-*co*-PPEGDA network from ATRP, (b) semi-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP, (c) full-PEG/PHEMA-sIPN via simultaneous "click chemistry" and ATRP, and (d) PEG-based network from "click chemistry" after equilibration in 1% (mg/mL) PBS solution of BSA at the physiological pH of 7.4 for 48 h.

network (1.0 mg/g), semi-PEG/PHEMA-sIPN (2.5 mg/g), and full-PEG/PHEMA-sIPN (2.6 mg/g). PEG is well-known for its unique physiological behavior in suppressing the level of protein absorption.[46,47] The good antifouling properties of pristine PEG network is attributable to the Lewis base component of the PEG molecules. Thus, the introduction of PEG network into semi-PEG/PHEMA-sIPN and full-PEG/PHEMA-sIPN has impacted the sIPNs with good antifouling properties.

4. Conclusions

Simultaneous interpenetrating polymer networks (sIPNs) have been prepared via concurrent "click chemistry" and ATRP. Thus, semi-PEG/PHEMA-sIPN or full-PEG/PHEMA-sIPN were prepared from a reaction mixture of N_3-PEG-N_3, TPOM, EBB, CuBr, PMDETA, and HEMA (or HEMA and PEGDA) in DMF. The approach of simultaneous "click chemistry" and ATRP is effective in IPN formation and exhibits several advantages, including high gel yield, fast gelation rate, mild reaction conditions, and high chemoselectivity. The so-prepared semi- or full-sIPNs also exhibit good and tunable physical and mechanical properties, such as a high degree of swelling, good mechanical properties, and good thermal stability, as well as good antifouling properties. The so-prepared semi-PEG/PHEMA-sIPN and full-PEG/PHEMA-sIPN are, thus, potentially useful as biomedical materials and vehicles for drug delivery. The synthesis method also provides a versatile platform for preparing other functional semi- or full-sIPNs by using different monomers and different azide/acetylene functional polymer pairs.

Acknowledgment. This work was supported by the National Natural Science Foundation of China Grant 20804009 and the Key Project of Chinese Ministry of Education Grant 108062. This work was also supported by the Program for New Century Excellent Talents in University Grant NCET-08-0117 and the Southeast University Foundation Grants 400741012 and 4007041023.

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BM100268T