Synthesis and Characterization of Physical Crosslinking Systems Based on Cyclodextrin Inclusion/Host-Guest Complexation

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ABSTRACT: New supramolecular assemblies based on cyclodextrin and adamantane were prepared. Two methacrylate monomers bearing cyclodextrin and adamantane were synthesized, and copolymerized with poly(ethylene glycol) methyl ether methacrylate, (PEGMA, 300 g/mol), by free radical polymerization. Copolymers bearing pendent cyclodextrin and adamantane were characterized by NMR, FTIR, TGA, SEC, Differential scanning calorimetry (DSC), and UV-visible spectrophotometer. All copolymers showed two distinct glass transitions. The specific interaction between pendent adamantyl and cyclodextrin was examined by ^{1}H-NMR. The viscoelastic properties of supramolecular assemblies were investigated with frequency and temperature sweep experiments. The specific host-guest interaction between pendent adamantyl and cyclodextrin lead to large increases of the viscosity; and depending on the concentration of these groups, also to gel formation. © 2009 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 48: 581–592, 2010

KEYWORDS: adamantane; cyclodextrin; gel formation; gels; host-guest systems; physical crosslinking; radical polymerization; supramolecular assemblies

INTRODUCTION Cyclodextrins (CDs) have been extensively used for industrial applications in many fields from laundry soap to food and pharmaceuticals. They also have been investigated as building blocks for supramolecular chemistry because they can form complexes with a number of different molecules and polymers through host-guest interaction.[1,2] The most widely used CDs are α-CD, β-CD, and γ-CD, which respectively, consist of six, seven, or eight D-glucopyranose units. They possess truncated, cone-shaped hydrophobic cavities in which the narrow end has primary and the wide end secondary hydroxyl groups. Since the inner cavity does not have any hydroxyl groups,[3] it can bind a number of different hydrophobic moieties. The driving forces for complex formation are the expulsion of high energy water from the cyclodextrin cavity, the release of ring strain, van der Waals interaction, and hydrogen bonding.[4]

Several physical crosslinking systems have been reported utilizing CDs. Yui and coworkers[5] reported supramolecular hydrogels based on inclusion complexation between α-cyclodextrin and poly(ethylene glycol)-grafted dextran. α-Cyclodextrin threaded poly(ethylene glycol) (PEG) chains come together to form channel-type crystalline micro-domains. These crystalline microphases create physical junctions between dextran main chains. The sol–gel transition is based on physical threading-dethreading of α-CDs with the polymeric guests. The process is strongly affected by temperature changes, making gelation thermoreversible. The transition temperature can be varied by changing the solution concentrations, the PEG content in the graft polymer, and the stoichiometric ratio between guest and host molecules.

Yui and coworkers[3] used both ionic and hydrophobic interactions to obtain sol-gel systems with rapid phase transitions. They modified poly(ε-lysine) with β-CD to give biocompatible and biodegradable polymeric hosts (β-CDPL). The guest, 3-trimethylsilylpropionic acid (TPA), containing both hydrophobic and ionic groups, was chosen specifically to provide dual interactions with the polymeric host and each other. In this system, TPA is included into the CD cavity by host-guest interaction to create physical crosslinks through cooperative hydrophobic and ionic interactions. The system showed a very rapid phase transition with small change in temperature across the upper critical solution region. Because of the ionic character, these systems are profoundly affected by pH changes.

A variety of hydrophobic groups interact strongly with CDs. The interaction between adamantane and β-cyclodextrin was reported to be very strong compared to other bulky groups as studied by AFM.[6] In recent years, there have been a number of reports published utilizing these strong host-guest interactions.[7–10] Harada et al. reported a use of these host-guest interaction to obtain high molecular weight (M_n = 100,000) supramolecular polymers formed from a β-cyclodextrin dimer and a guest dimer having adamantyl groups linked by PEG.[11]

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Supramolecular hydrogels resulting from host/guest interaction or inclusion complexation obtained by cyclodextrin with various hydrophobic moieties and polymers has been investigated for biomedical application due to their possible potential in drug or cell deliveries.[12–15] The use of this specific interaction with guest molecules to design hydrogels sensitive to temperature, light, and pH has been reported.[16–19] Harada and coworkers[20] prepared a photoresponsive hydrogel system using different molecular recognition of a ternary mixture of dodecyl-modified poly(acrylic acid), α-cyclodextrin, 4,4′-azodibenzoic acid. Davis and coworkers[21,22] investigated biocompatible linear cyclodextrin polymers and several adamantane-terminated crosslinking agents for local gene delivery. These supramolecular systems were shown to be suitable for in vivo tissue repair applications.

Polymers consisting of poly(ethylene glycol)methyl ether methacrylate (PEGMA) have been investigated extensively for biomedical applications due to PEG biocompatibility and nonadhesive interactions to proteins.[23] These polymers also exhibit a lower critical solution temperature (LCST), which may be useful for nanotechnology and biotechnology applications.[24] Currently, several derivatives of PEGMA macromonomers with different molecular weights and chain ends such as methoxy or hydroxyl are commercially available. They have been copolymerized with a variety of monomers using several different methods including atom transfer radical polymerization,[25,26] reversible addition-fragmentation chain transfer (RAFT),[27,28] and conventional free radical methods.[29–31] Most of these copolymer systems have been studied for synergistic effects of two different units; for instance, to form pH and temperature sensitive copolymers.[27,24]

Here we report the synthesis of two novel monomers and their polymers bearing adamantane and cyclodextrin pendant groups, respectively. These monomers were copolymerized with PEGMA at three different compositions (5, 10, 15 mol % feed ratio) by conventional free radical polymerization techniques. The characterization of these copolymers has been done using NMR, FTIR, TGA, SEC, and Differential scanning calorimetry (DSC). In addition, the effect of the comonomers on the LSCT of PEGMA copolymers was also studied. Finally, the host-guest interactions between PEG and adamantane units with pendent cyclodextrin units were examined, and the viscoelastic properties of these new physical network forming systems were investigated with both frequency and temperature sweep rheology experiments.

EXPERIMENTAL

Materials

β-CD was purchased from TCI and used without purification. Poly(ethylene glycol) methyl ether methacrylate (PEGMA, 300 g/mol), *p*-toluenesulfonyl chloride (*p*-TsCl) and 1,6-hexanediamine (HDA), were purchased from Aldrich Chemical and used as received. Azobisisobutyronitrile (AIBN) was purchased from Aldrich Chemical, and recrystallized from methanol three times before use. 6-*o*-Monotosyl-6-deoxy-β-cyclodextrin (mono-6-OTs-β-CD) was synthesized based on a literature procedure.[32] 4-(1-Adamantyl)phenyl methacrylate (APM) was previously synthesized in our laboratory, and this procedure was followed to obtain APM as a white powder.[33]

6-(6-Aminohexyl)amino-6-deoxy-β-cyclodextrin (β-CD-HDA)

A 250 mL three-necked, round-bottom flask was charged with 5.0 g (3.8 mmol) of mono-6-OTs-β-CD and excess HDA (20 g, 172 mmol) in 25 mL of DMF. [34] The reaction was carried out overnight at 80 °C. After completion of the reaction, the mixture was allowed to cool down to room temperature and the product precipitated into excess acetone. After filtration, the product was dissolved in DMF and reprecipitated in acetone. After several reprecipitation cycles, the crude product was washed with diethyl ether and kept in vacuum oven at room temperature for 24 h. β-CD-HDA (2.3068 g) was obtained as white powder in 43% yield. ^{1}H-NMR (300 MHz, DMSO-d_6): 7.98, 5.75, 4.84, 4.49, 3.63, 3.4, 3.32, 3–3.1, 2.8–2.92, 2.64–2.74, 2.1, 1.35, 1.26 ppm. ^{13}C-NMR (300 MHz, DMSO-d_6): 102, 81.5, 73, 72.4, 72, 60, 49.5, 37, 29.5, 29, 26.5, 26.3 ppm.

(1-Methacrylamidohexyl)amino-6-deoxy-β-cyclodextrin

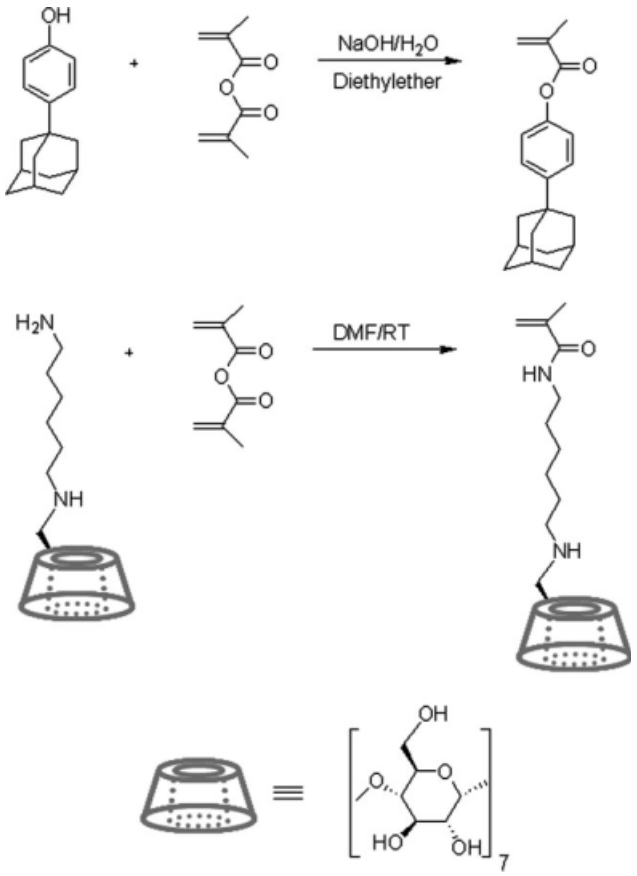
A 100 mL three-necked round-bottom flask was charged with methacrylic anhydride (MCD) (10 g, 64 mmol) and 20 mL of DMF. To this solution, β-CD-HDA (7.73 g, 6.3 mmol) in 20 mL of DMF was added dropwise under nitrogen atmosphere. The solution was stirred overnight. The product was precipitated into excess acetone. The solid powder was dissolved in DMF and reprecipitated into acetone several times. The final product was obtained as a white powder, which was dried in a vacuum oven at 70 °C overnight. The yield was quantitative. ^{1}H-NMR (300 MHz, DMSO-d_6): 5.7, 5.6, 5.3, 4.8, 4.5, 4.2, 3.2–3.7, 3, 2, 1.6–1.9, 1.37, 1.15 ppm. ^{13}C-NMR (300 MHz, DMSO-d_6): 167.9, 140.2, 119.1, 102, 81.7, 73, 72.4, 72, 60, 30.8, 28.9, 26.1, 25.9, 19.1 ppm.

Synthesis of Copolymer (PEGMA-*co*-MCD)

A typical copolymerization is given for (PEGMA-15-MCD). MCD (3.84 g, 2.9 mmol), PEGMA (4.9 g, 16 mmol), AIBN (0.079 g, 0.49 mmol), and 32 mL DMF were charged to a 50 mL three-necked, round-bottom flask. Nitrogen was bubbled through the solution for 15 min before heating at 45 °C for 24 h. The mixture was then precipitated into ethyl ether. After three reprecipitation cycles, the product was dried in a vacuum oven for 12 h at 40 °C. For further purification, the polymer was dissolved in deionized water, placed in Spectra Por dialysis tubing with a molecular cutoff of 12,000–14,000 and dialyzed against deionized water for 7 days. The final polymer was freeze-dried to obtain a fiber-like, slightly yellowish solid in ∼77% yield.

Synthesis of Copolymer (PEGMA-*co*-APM)

A typical copolymerization is given for (PEGMA-15-APM). APM (1.33 g, 4.5 mmol), PEGMA (7.65 g, 25.5 mmol), AIBN (0.098 g, 0.6 mmol), and 62 mL DMF were charged to a 100 mL three-necked, round-bottom flask, and bubbled with nitrogen for 15 min before heating. The reaction was carried out at 45 °C for 24 h, and the mixture was then precipitated into ethyl ether. After three reprecipitation cycles, the product was dried in a vacuum oven for 12 h at 40 °C. The



SCHEME 1 Synthesis of monomers.

copolymers were then dissolved in deionized water, placed in Spectra Por dialysis tubing with a molecular cutoff of 12,000–14,000, and dialyzed against deionized water for 7 days. The final polymers were freeze-dried to obtain the final products as transparent solids in about 55% yield. Only the copolymer with 5 mol % APM (PEGMA-5-APM) was sticky; all other were nonsticky materials.

Instrumental Analysis

NMR measurements were conducted on a Varian 300 MHz NMR using DMSO-d_6 and D_2O as solvents. FTIR spectra were obtained on a Nicholet 5DX using pressed KBr pellets. SEC was performed on a system using a HP 1037A RI detector with a constaMetric pump flowing THF at 100 mL/min through five American Polymer Standards separation columns with porosities ranging from 100 to 1,000,000 A. The SEC runs were calibrated using polystyrene standards. Copolymers were totally soluble in THF with no observed turbidity.

DSC experiments were performed on a TA Instruments 2920 using pierced-lid crimped aluminum pans at a ramp rate of 10.0 °C/min for both heating and cooling. Temperature and heat capacity were calibrated with indium and sapphire standards, respectively. Thermogravimetric analysis was conducted on a TA instrument 2960 at a heating rate of 10 °C/min under nitrogen.

The optical transmittances of polymer solutions were recorded as a function of temperature on a UV-visible spectrophotometer (Shimadzu, UV-1601PC). A 2.5 wt % solution of each polymer was prepared, and the samples were heated at 2 °C/min while transmittances were recorded. All polymers showed a sharp transition for the LCST, which was defined as the temperature on heating at which the solution gave almost no transmittance.

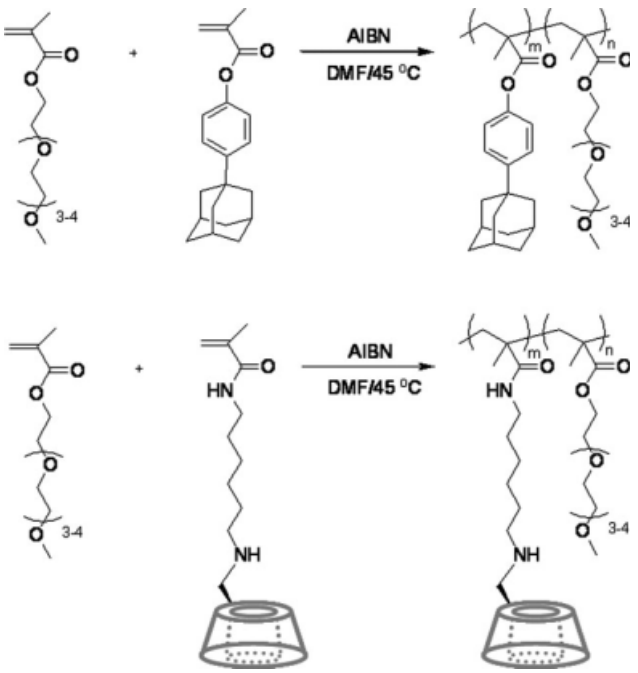
Rheological Measurements

Viscoelastic characterization was conducted with an Advanced Rheometerics Expansion System (ARES, Rheometrics) equipped with two 25 and 40 mm diameter parallel plates. A thin layer of low-viscosity silicone oil was applied to the air/sample interface to inhibit water loss. Frequency sweep experiments were conducted at two different temperatures (20 and 30 °C) to obtain complex viscosity, storage, and loss moduli over a wide range of frequencies. Temperature sweep experiments were conducted with a stress controlled rheometer (TA Instruments AR-G2) in a 40 mm double gap concentric cylinder system.

RESULTS AND DISCUSSION

The copolymers bearing cyclodextrin and adamantane pendent groups were synthesized by free radical polymerization as described in the experimental section. The general routes for the synthesis of monomers and polymers are given in Schemes 1 and 2.

Figure 1 shows a typical solution ^{13}C-NMR spectrum for a copolymer bearing APM moieties. P(PEGMA-*co*-15APM) was chosen as an example, and the homopolymer of PEGMA is given for comparison. All peaks are assigned based on the expected structures of the polymers. For PEGMA monomer,



SCHEME 2 General route for synthesis of copolymers.

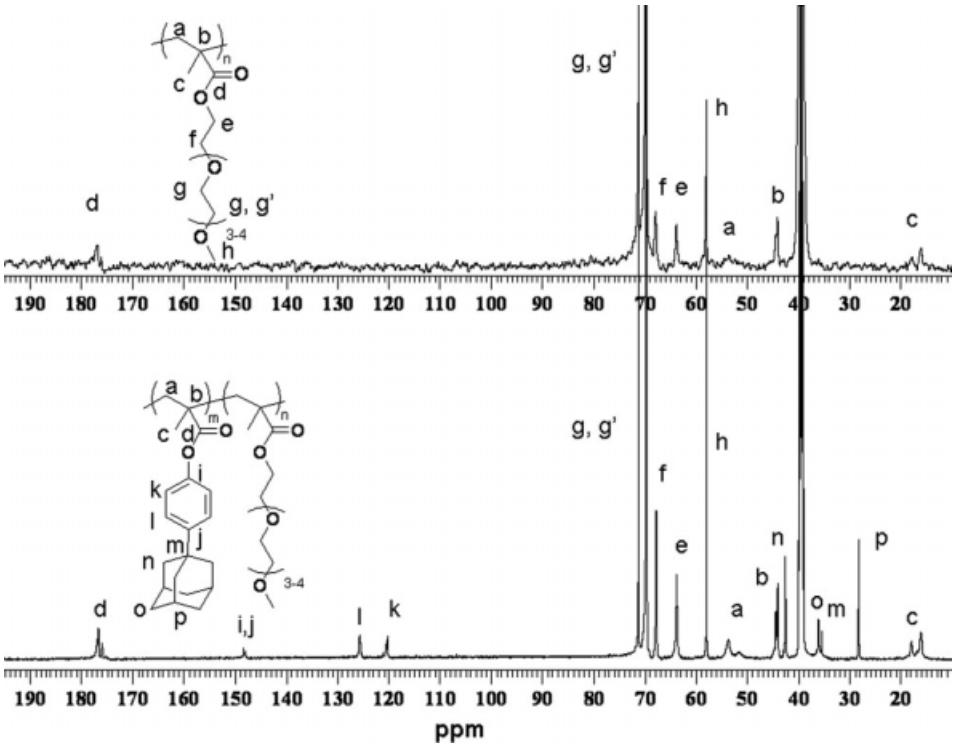


FIGURE 1 ^{13}C solution NMR of P(PEGMA) (top) and P(PEGMA-*co*-15APM) (bottom) in DMSO-d_6.

the double bond peaks appear at 135.9 and 125.4 ppm, and these are absent in the spectra of the homopolymer and copolymers. A broad new peak appears around 44.4 ppm, which is associated with the backbone carbons. In addition to PEGMA peaks, those associated with APM units are also observed for the copolymers. The aromatic peaks are located at 125.7 and 120.3 ppm, while the adamantyl peaks (labeled n, o, m, and p) appear at 42.8, 36.2, 35.4, and 28.2, respectively. The carbonyl peak of PEGMA monomer is around 166 ppm and shifts to 177 ppm in the homo- and copolymers.

The solution ^{1}H-NMR spectra of P(PEGMA) and P(PEGMA-*co*-15APM) are given in Figure 2. The double bond peaks of PEGMA at 5.64 and 6.03 ppm disappear upon polymerization, and the backbone peaks of the homopolymer appear around 1.4–1.9 ppm. The PEG proton chemical shift is observed at 3.5 ppm, whereas the methylene protons α and β to the ester groups give two distinct peaks at 4.2 and 3.7 ppm, respectively, for PEGMA; these two peaks shift slightly upfield upon polymerization. The methylene protons α to the ester group of PEGMA are at 4 ppm, whereas the methylene protons β to the ester group appear as a shoulder to PEG protons at around 3.6 ppm. In addition to all peaks associated with PEGMA units, new peaks are observed in the ^{1}H-NMR spectra of the copolymers due to APM units. The peaks at 7.02 and 7.4 ppm are attributed to the phenyl rings, whereas three peaks at 1.76, 1.88, and 2.08 ppm due to adamantyl hydrogens overlap the backbone peaks.

The copolymer series bearing MCD moieties was analyzed for copolymer composition by solution ^{13}C-NMR. The spectrum of P(PEGMA-*co*-15MCD) is given in Figure 3 as an example. All peaks are assigned based on the expected structure of the copolymers. Upon polymerization, the double bond peaks of MCD observed at 119.1 and 140.2 ppm disappear, whereas the carbonyl peak shifts from 167.9 to 175.8 ppm. The peaks associated with cyclodextrin units appear at 102.1, 81.4, 73–72, 59.8 ppm, whereas the peaks attributed to the alkyl spacer between the methacrylamide and cyclodextrin amine appear at 36.7, 28.8, and 25.6 ppm. The peaks ascribed to PEGMA units in the copolymer were assigned based on the ^{13}C-NMR spectrum of the homopolymer from Figure 1.

The solution ^{1}H NMR spectrum of P(PEGMA-*co*-15MCD) is given in Figure 4. The double bond peaks of PEGMA, which appear at 5.64 and 6.03 ppm are under the cyclodextrin peaks (2 and 3), whereas the double bond peaks of MCD appear at 5.32 ppm and as a shoulder on the cyclodextrin peaks (2 and 3) at 5.6 ppm. Upon polymerization, the double bond peaks disappear. The peaks associated with O(6)H, C(1)H, O(2)H, and O(3)H of cyclodextrin units appear at 4.50, 4.85, and 5.73 ppm, respectively. The other peaks attributed to cyclodextrin units are under the proton peaks of PEG units, and cannot be seen. The peaks associated with PEGMA units are assigned based on the ^{1}H spectrum of the homopolymer of P(PEGMA) (Fig. 2).

The molecular weights, M_w and M_n, and polydispersity as estimated by SEC are given in Table 1. The copolymer compositions are calculated by the total area ratios of the specific peaks using ^{1}H-NMR and are also given in Table 1. The compositions of copolymers bearing APM were calculated from the area ratios of protons in the phenyl-rings (assigned as *k*, and *l*) and PEGMA protons α to the ester group (assigned as *e*), using the equation $m/n = (A_1/4)/(A_2/2)$,

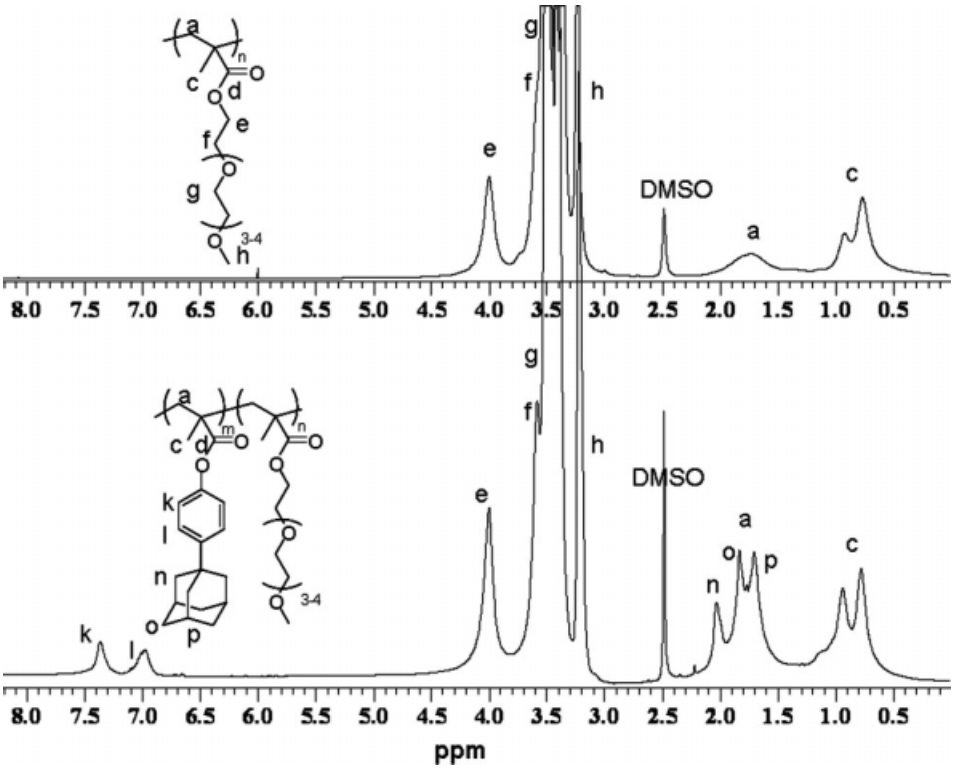


FIGURE 2 ^{1}H solution NMR of P(PEGMA) (top) and P(PEGMA-*co*-15APM) (bottom) in DMSO-d_6.

where A_1 and A_2 are the total area under (k + l) and e, respectively. The composition of copolymers bearing MCD was calculated from the area ratios of C_1H protons of cyclodextrin to PEGMA protons α to the ester group (assigned as e), using the equation, $m/n = (A_1/7)/(A_2/2)$, where A_1 and A_2 are the total area under C_1H and e, respectively.

The polymers were further characterized by FTIR, and the FTIR spectra of P(PEGMA-*co*-10APM) and P(PEGMA-*co*-10MCD) are given as examples of each series of copolymers (Fig. 5). Since each spectrum is dominated by PEGMA units (90 mol % in each copolymer), the FTIR spectra of the homopolymer of PEGMA and the PEGMA monomer are also given for comparison. The band observed at 1640 cm^{-1} belonging to the double bond of the monomer disappears in the homo- and copolymers, which indicates that no residual monomer is present.[35] The band associated with stretching of the ester carbonyl group at 1720 cm^{-1} for PEGMA shifts to 1731 cm^{-1} in the polymers. The peak observed around

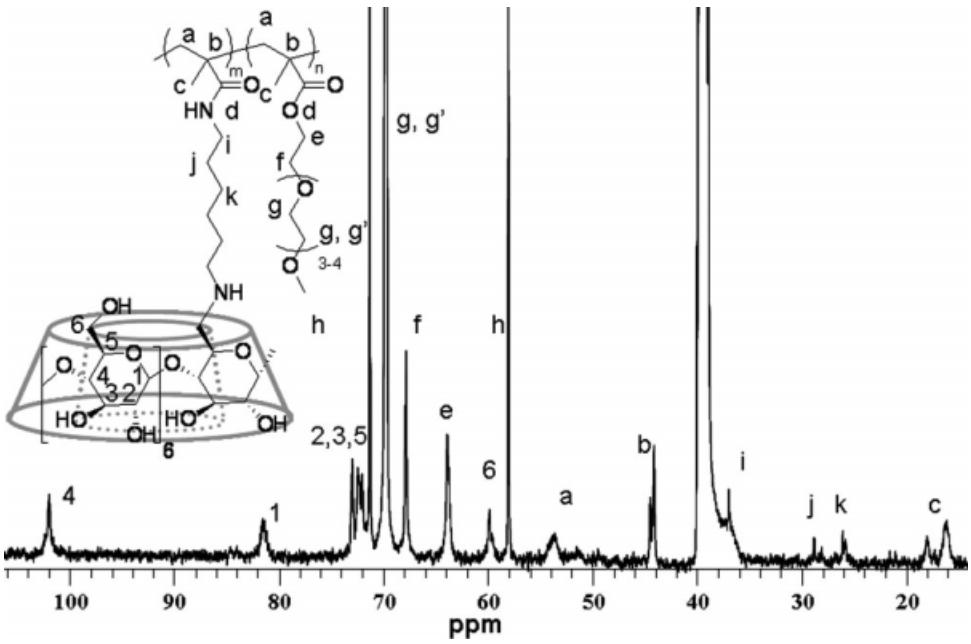


FIGURE 3 ^{13}C solution NMR of P(PEGMA-*co*-15MCD) in DMSO-d_6.

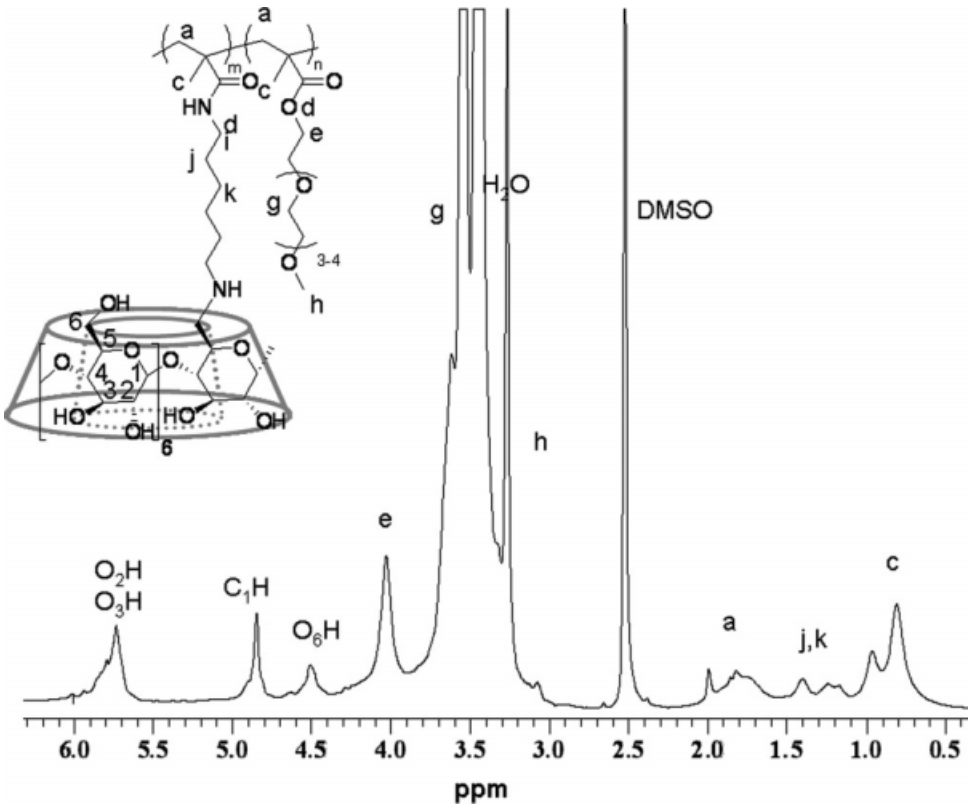


FIGURE 4 ^{1}H solution NMR of P(PEGMA-*co*-15MCD) in DMSO-d_6.

1133 cm^{-1} is due to C—O—C stretching of ester and ether groups of PEGMA. The FTIR spectrum of P(PEGMA-*co*-10MCD) shows a broad distinct peak around 3384 cm^{-1} associated with the hydroxyl groups of pendant CD, and this peak is not observed for the PEGMA monomer, the homopolymer of PEGMA and P(PEGMA-*co*-10APM).

DSC thermograms of selected copolymers are given in Figure 6. DSC curves of all copolymers have two distinct T_g transitions, and no observed side chain crystallinity probably due to the PEG side chains not being long enough to form ordered structures. Observation of two T_g's is generally an indication of separate microphases. Similar transitions were observed for various copolymer systems consisting of PEGMA and *n*-butyl methacrylate.[36] The PEGMA polymers have a limiting T_g corresponding to the glass transition temperature of PEG chains around −59 °C,[37] and the T_g of P(PEGMA300) previously was given as −57 °C.[38] The T_g1 values, given in Table 2, are slightly higher than the T_g value reported for PEG. However, T_g2 values of P(PEGMA-*co*-APM) are much lower compared with the homopolymer of APM synthesized in our laboratory with a reported T_g of 253 °C.[39] Therefore, the two glass transitions are not due to completely phase separated blocks but to essentially random copolymers with microdomains of pendent PEG groups. The glass transitions of this series of copolymers continuously increase with increasing APM ratio from 5 to 15 mol %. The T_g values for the copolymer series having MCD units are more or less in the same range of the APM series. The glass transition temperatures of the copolymers are given in Table 2.

TABLE 1 M_n, M_w, PDI, Compositions, and Yield of Copolymers

Sample	Feed (mol %)[a]	Mol %[b]	M_n[c]	M_w[c]	PDI[c]	Yield %
P(PEGMA-*co*-5APM)	5	6	20,600	128,000	6.2	75
P(PEGMA-*co*-10APM)	10	8	18,200	127,000	7	80
P(PEGMA-*co*-15APM)	15	17	55,100	278,000	5	55
P(PEGMA-*co*-5MCD)	5	2	42,300	165,000	3.8	74
P(PEGMA-*co*-10MCD)	10	3.4	21,700	50,000	2.3	76
P(PEGMA-*co*-15MCD)	15	10.2	52,800	287,000	5.4	77

[a] Comonomer feed mol %.
[b] Copolymer compositions estimated by ^{1}H NMR.
[c] Estimated by SEC.

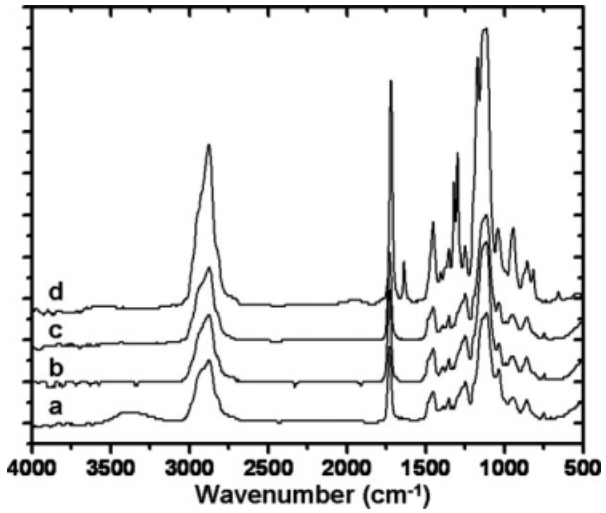


FIGURE 5 FTIR spectra of (a) P(PEGMA-*co*-10MCD), (b) P(PEGMA-*co*-10APM), (c) P(PEGMA), and (d) PEGMA.

Thermal stabilities of the copolymers were analyzed by TGA. Figure 7 shows TGA thermograms of two copolymers of each series with a heating rate of 10 °C/min in N_2. The copolymers with MCD exhibit a two-step degradation process. The onset of thermal decomposition of P(PEGMA-15MCD) is much lower compared with other copolymers perhaps due to the thermal degradation of pendant cyclodextrin units at lower temperatures. Similar behavior was observed for the copolymers having the highest feed ratio of MCD. The temperature at 10 wt % loss for this polymer is 250 °C. The copolymers with 5 mol % APM and MCD give almost the same thermograms. The onset of the thermal degradation for the P(PEGMA-*co*-5MCD) is somewhat earlier because of the less stable cyclodextrin pendant units. However, it is not as pronounced as the onset of the thermal decomposition of the copolymer with 15 mol % MCD. The temperature at 10 wt % loss for P(PEGMA-*co*-15APM) and P(PEGMA-*co*-5APM) are 290 and 280 °C, respectively. These values are in the same range as the homopolymer of PEGMA.[40] The slight increases may be due to incorporated APM units, which have been reported to enhance thermal stabilities in copolymers.

TABLE 2 T_g1 and T_g2 Values of Copolymers

Sample	T_g1	T_g2
P(PEGMA-*co*-5APM)	−51.84	51.81
P(PEGMA-*co*-10APM)	−54.62	54.34
P(PEGMA-*co*-15APM)	−48.49	59.27
P(PEGMA-*co*-5MCD)	−54.53	61.89
P(PEGMA-*co*-10MCD)	−53.52	55.77
P(PEGMA-*co*-15MCD)	−48.59	58.46

The thermosensitive behaviors of solution of the copolymers and the homopolymer of PEGMA were investigated using a UV-visible spectrophotometer. The copolymer composition has a great effect on LCST behavior of the polymers, since the hydorphobicity-hydrophilicity balance changes with composition. In general, hydrophobic comonomers decrease the LCST, whereas hydrophilic comonomers increase it.[27] It was expected that the copolymers with hydrophobic APM moieties and hydrophilic MCD would show different thermoresponsive behavior. The effect of these hydrophobic or hydrophilic comonomers on LCST of P(PEGMA) is summarized in Figure 8. All polymers showed a sharp transition at the cloud point. The LCST of the homopolymer of PEGMA was 63 °C, which is close to the LCST of 3 wt % solution of P(PEGMA) reported of 60.8 °C.[38] As expected, the cloud point continuously decreases with increasing content of the hydrophobic APM units in the copolymers. The decrease is as high as 14 °C for the copolymer with 17 mol % APM. On the other hand, there are slight increases of observed cloud points with increasing MCD ratio in copolymers.

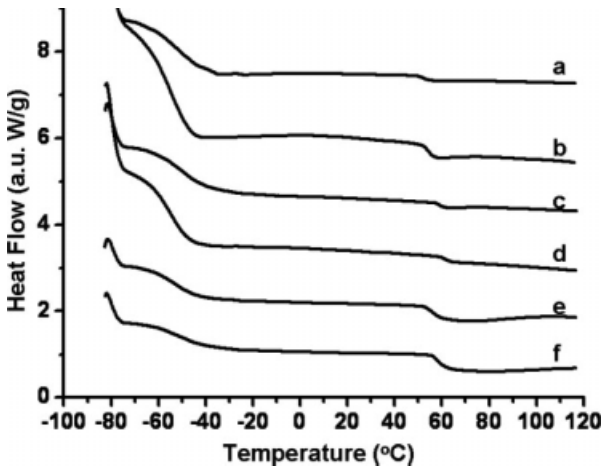


FIGURE 6 DSC thermograms of copolymers (a) P(PEGMA-*co*-5APM), (b) P(PEGMA-*co*-10APM), (c) P(PEGMA-*co*-15APM), (d) P(PEGMA-*co*-5MCD), (e) P(PEGMA-*co*-10MCD), (f) P(PEGMA-*co*-15MCD).

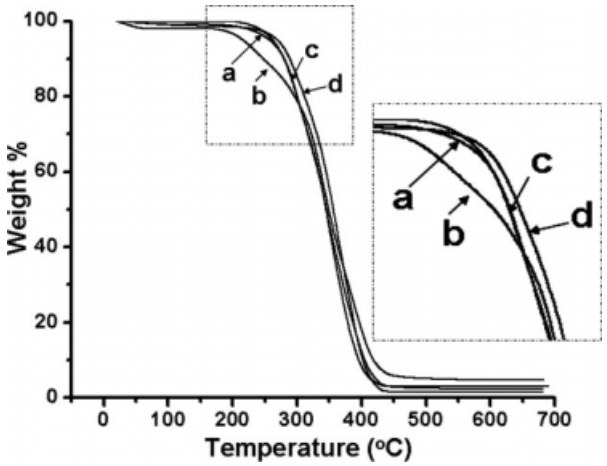


FIGURE 7 TGA thermograms of copolymers (a) P(PEGMA-*co*-5MCD), (b) P(PEGMA-*co*-15MCD), (c) P(PEGMA-*co*-5APM), (d) P(PEGMA-*co*-15APM) in N_2.

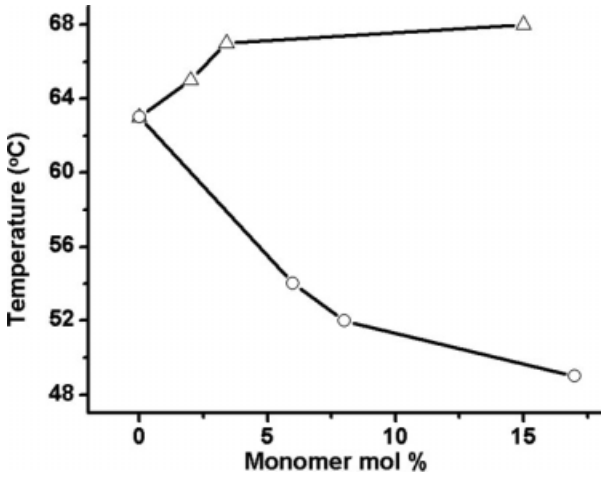


FIGURE 8 Cloud point versus mol % of comonomers determined by ^{1}H-NMR in copolymers bearing MCD (△) and APM (○).

The copolymers having APM moieties are expected to show amphiphilic properties due to combined hydrophobic and hydrophilic segments. To explore the amphiphilic character of the copolymer, ^{1}H-NMR was used and the spectrum of P(PEGMA-*co*-15APM) is given for two different solvents, DMSO-d_6 and D_2O (Fig. 9). DMSO-d_6 is a good solvent for the copolymers, and with it, the adamantyl peaks can be easily identified, plus there are two separate peaks associated with the aromatic group of APM. On the other hand, the peaks of the adamantyl groups totally disappear in D_2O or they may not be observed because of overlap with the backbone peaks. The spectrum has very broad peaks with no distinct separation for the aromatic groups of APM consistent with hydrophobic association. The spectral changes due to solvent differences indicate structural rearrangement, and perhaps pendent group association, of the amphiphilic polymer in D_2O. Similar observation has been reported for the amphiphilic block copolymer of PEG with hydrophobic poly-(β-benzyl L-aspartate) and poly [*N*-{*o*-(4-phenyl-4,5-dihydro-1,3-oxazol-2-yl)phenyl}maleimide].[41,42] In D_2O, the hydrophobic groups tend to aggregate and may form a micelle-like structure. Mobility decreases in micelle structures, and would cause broadening of the APM peaks, as can easily be seen for the peaks associated with the aromatic groups, and disappearance of peaks associated with adamantane.

It is generally accepted that, unlike neat α-cyclodextrin, which has been reported to form polyrotaxane type complexes with PEG, neat β-cyclodextrin cannot form such stable complexes with PEG.[43–45] However, Ripmeester and coworkers[46] did report stable binding between PEG and neat β-cyclodextrin, and this complexation was further investigated by Cosgrove and coworkers[47] In both cases, complexation of linear PEG with free β-cyclodextrin was investigated. Here, on the other hand, the mobilities of PEG and β-cyclodextrin units are restricted by the main polymer chain. Therefore, the binding and interactions of these groups would be expected to be different. Considering expected compositions of copolymers with adamantane and PEG units, three possibilities should be considered: (1) PEG units of the polymers can form stable complexes with cyclodextrin; (2) PEG units do not form stable complexes but inhibit interactions of adamantyl moieties with

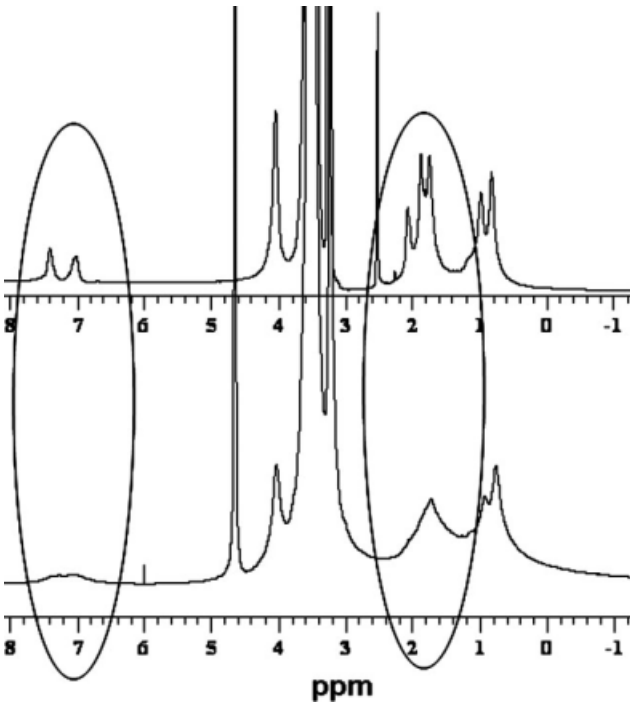


FIGURE 9 ^{1}H-NMR analysis of P(PEGMA-*co*-15APM) in D_2O (bottom) and DMSO-d_6 (top).

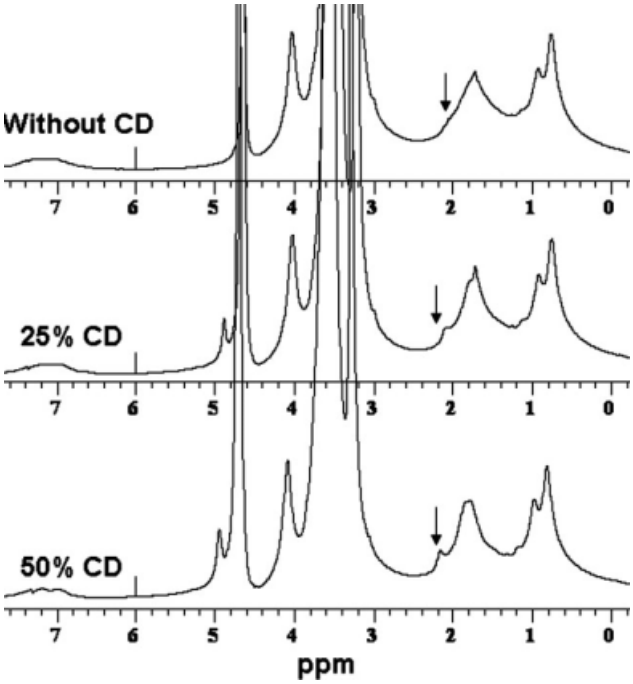


FIGURE 10 ^{1}H-NMR analysis of inclusion complex formation between P(PEGMA-*co*-10APM) with various concentration of free cyclodextrin.

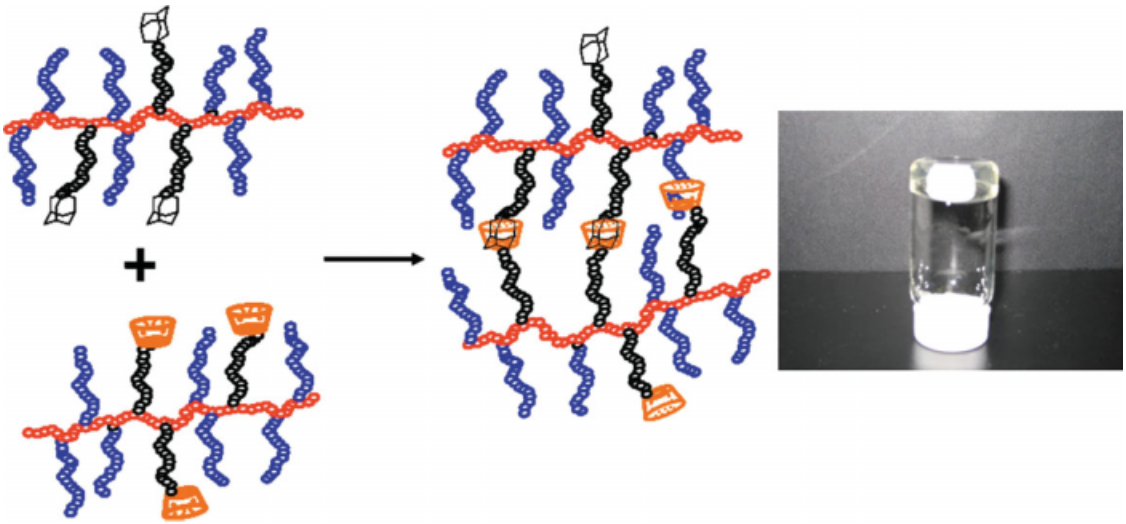


FIGURE 11 Photograph and the schematic representation of gel formation as a result of inclusion complexation between adamantyl and cyclodextrin pendent groups of copolymers.

cyclodextrin; and (3) only adamantane and cyclodextrin groups form stable complexes. Another important factor, which will influence the host-guest interaction between adamantyl and cyclodextrin groups, may be the inter- and intramolecular self-association of bulky adamantyl moieties, which may lead to inhibition of the host-guest complex formation between adamantyl groups and CDs.

^{1}H-NMR analysis has been extensively used to probe inclusion formation in similar complexes.[48–50] The formation of inclusion complexes between free cyclodextrin and adamantyl moieties of P(PEGMA-*co*-10APM) was investigated here using ^{1}H-NMR. Figure 10 shows variation of the ^{1}H proton NMR spectra with increasing free CDs in solution (25% CD: 0.015 mmol CD and 0.25 g polymer in 2 mL D_2O; 50% CD: 0.03 mmol CD and 0.25 g polymer in 2 mL D_2O). The top spectrum is ^{1}H-NMR spectrum of P(PEGMA-*co*-10APM) given for comparison. The shifts of specific peaks in the polymer spectrum result from the inclusion complexation between adamantyl moieties and PEG units with added cyclodextrin. Chemical shifts of adamantane moieties in ^{1}H-NMR with various concentrations of cyclodextrin can also be used to obtain the association constant, K_a. Due to hydrophobicity of adamantane moiety and its size, which perfectly matches the cavity of β-cyclodextrin, the specific interaction of adamantane and cyclodextrin has been shown to be very strong with an association constant between 10^4 and 10^5 M^{-1} depending on the nature of the systems.[51,52] The assosication constant of complex between P(PEGMA-*co*-10APM) with neat β-cyclodextrin was determined, using Benesi-Hildebrand plots, to be 1.9×10^4 M^{-1}.

The downfield shift indicates that there is indeed host-guest complex formation between pendant adamantane and cyclodextrin and confirm that self-association of the amphiphilic polymer does not inhibit this specific complexation between two groups. In fact, the interaction between these two groups is so strong that the association of hydrophobic adamantyl moieties may be disturbed upon addition of the cyclodextrin. Figure 11 shows a schematic representation and photograph of the gel formation. This gel was obtained with the 30 wt % of the P(PEGMA-*co*-15APM)/P(PEGMA-*co*-15MCD) mixture. Initially, both solutions of 30 wt % of P(PEGMA-*co*-15APM) and 30 wt % of P(PEGMA-*co*-15MCD) were prepared; these solutions were viscous liquids at these concentration. After mixing, gel formation occurs rapidly, and is demonstrated by the test tube inversion method as shown in the photograph.

To investigate viscoelastic properties of supramolecular assemblies, four 1:1 aqueous solution mixtures were prepared: P(PEGMA-*co*-15APM)/P(PEGMA-*co*-15MCD), P(PEGMA-*co*-10APM)/P(PEGMA-*co*-10MCD), P(PEGMA-*co*-5APM)/P(PEGMA-*co*-5MCD). Each pair was mixed together to explore the effect of increasing associative group contents on viscosity. An aqueous solution of P(PEGMA)/P(PEGMA-*co*-10MCD) was used as the control to probe the interaction between PEG units of P(PEGMA) and the pendent CDs groups of P(PEGMA-*co*-10MCD). For consistency, all samples were prepared as 10 wt % solutions in water, and the complex viscosity, storage, and loss moduli as a function of angular frequency were determined in frequency sweep measurements. The viscosities were measured for two different temperatures, 20 and 30 °C.

The complex viscosities of the mixtures of viscous liquids as a function of angular frequency are given Figure 12. The complex viscosities are almost independent of frequency for all four samples for both temperatures. The viscosity values are dramatically higher for those samples with higher ratios of associative groups in the copolymers. The 1:1 mixture of P(PEGMA-*co*-15APM)/P(PEGMA-*co*-15MCD) and P(PEGMA-*co*-10APM)/P(PEGMA-*co*-10MCD) show the highest viscosities, which indicates that the solution properties of P(PEGMA) are tunable by changing the associating comonomer contents. It is worth noting that the temperature dependence of viscosity is stronger for the samples with higher comonomer loading. Therefore, it

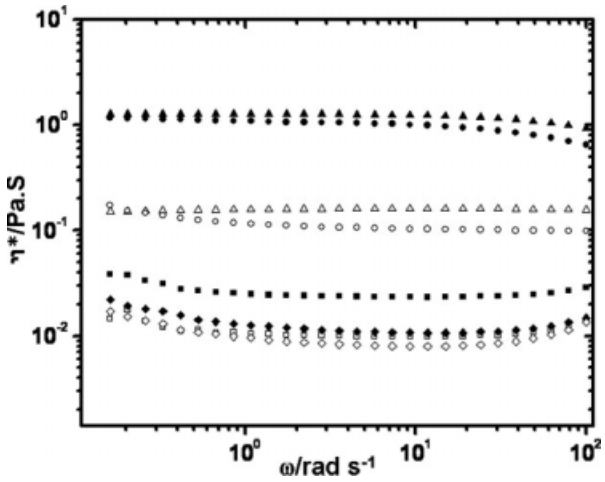


FIGURE 12 Angular frequency dependence on complex viscosity for the mixture of 10 wt % P(PEGMA-*co*-5APM)/P(PEGMA-*co*-5MCD) (■, □), P(PEGMA-*co*-10APM)/P(PEGMA-*co*-10MCD) (▲, △), P(PEGMA-*co*-15APM)/P(PEGMA-*co*-15MCD) (●, ○), and P(PEGMA)/P(PEGMA-*co*-10MCD) (◆, ◇) at 20 (filled symbols) and 30 °C (open symbols).

can be concluded that the decrease in viscosity with temperature must be related with the supramolecular inclusion association of adamantyl and cyclodextrin groups rather than the interaction between PEG units with CDs. Another interesting finding is the fact that the viscosity increases for the samples bearing 5 mol % associative groups to 10 mol % associative groups is significant, whereas there is no further increase for the mixture of the copolymer bearing 15 mol % associative groups. P(PEGMA-*co*-15APM) possesses more hydrophobic groups, which enhance micelle formation and hydrophobic associations, and then may limit or decrease the inclusion complexation once the adamantyl group reaches a certain upper concentration.

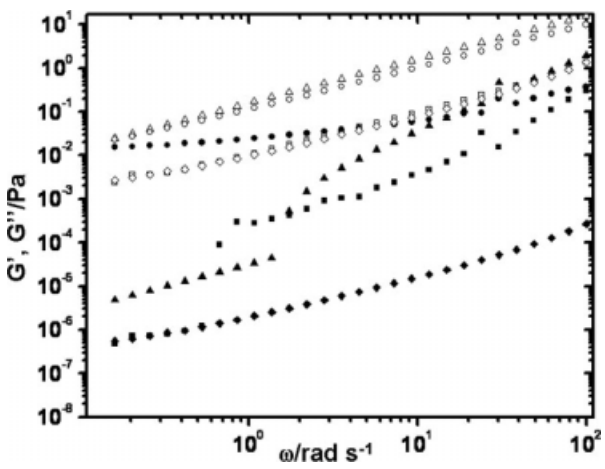


FIGURE 13 Frequency dependence on storage (filled symbols). and loss moduli (open symbols) for the mixture of 10 wt % P(PEGMA-*co*-5APM)/P(PEGMA-*co*-5MCD) (■, □), P(PEGMA-*co*-10APM)/P(PEGMA-*co*-10MCD) (▲, △), P(PEGMA-*co*-15APM)/P(PEGMA-*co*-15MCD) (●, ○), and P(PEGMA)/P(PEGMA-*co*-10MCD) (◆, ◇) at 30 °C.

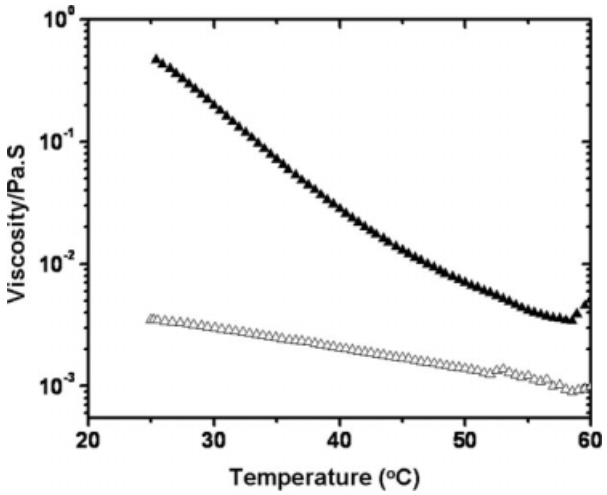


FIGURE 14 Viscosity dependence on temperature for the mixture of P(PEGMA-*co*-10APM)/P(PEGMA-*co*-10MCD) (▲) and P(PEGMA-*co*-10MCD) (△) alone.

The storage modulus, G', and the loss modulus, G'', of the four samples in 10 wt % solutions are given in Figure 13. The values of both G' and G'' increase with increasing associative groups in the copolymer compositions, and the magnitudes of G'' is higher than that of G' for all sample, which means viscous flow dominates elastic response over the range of angular frequencies monitored. However, at low frequency, G'' is almost equal to G' for the samples bearing the highest associative groups, P(PEGMA-*co*-15APM)/P(PEGMA-*co*-15MCD), and the difference between G'' and G' increases with angular frequency. The data at Figure 13 indicates that P(PEGMA-*co*-15APM)/P(PEGMA-*co*-15MCD) is at the gel boundry, and the inclusion complexes are dissociated as viscous flow dominates the elastic response with increasing angular frequency. This observation is not surprising considering adamantyl/cyclodextrin inclusion complexation is in dynamic equilibrium, and the fast exchange between free and complexed adamantyl moieties may not maintain long-range connectivity.[48] The data indicates that both G' and G'' are frequency dependent, and that they increase with increasing applied frequency. Similar observations were reported for G' and G'' of cyclodextrin and adamantyl-grafted chitosan, and the decrease of G' and G'' with decreasing frequency was explained by network relaxation as a result of breaking and reforming of the crosslink points.[45]

Temperature effects on host-guest complex formation were further investigated for the 5 wt % aqueous solution of P(PEGMA-*co*-10APM)/P(PEGMA-*co*-10MCD) via temperature sweep measurement. The variation in viscosity as a function of temperature is given in Figure 14. The viscosity change of the 5 wt % aqueous solution of P(PEGMA-*co*-10MCD) with temperature is also included in the same plot for comparison. As expected, the initial viscosity is significantly higher for the P(PEGMA-*co*-10APM)/P(PEGMA-*co*-10MCD) mixture

due to host-guest inclusion complexation between adamantyl and cyclodextrin pendent groups. However, the viscosity constantly and drastically decreases with increasing temperature since the inclusion complexation is enthalpy driven. That is, temperature increases leads to decreases in the number of inclusion complexes, which in turn result in lower apparent molecular weight and decreased viscosity.[8,53,54] This may result in a thermoreversible gel system such as has been reported by Hennick et al. for a star-shaped eight-arm PEG which was end-modified with β-cyclodextrin and cholesterol moieties. The storage (G') and loss moduli (G'') of the hydrogel system formed by the mixture of β-cyclodextrin end-capped PEG and cholesterol end-capped PEG decreased with increasing temperature from 4 to 37 °C and reverted back to original values with cooling.[55] Another important factor, which leads to decreased viscosity may be increasing phase separation with temperature; this may explain the slight decrease of the viscosity seen even for P(PEGMA-*co*-10MCD).

CONCLUSIONS

Methacrylate monomers bearing cyclodextrin and adamantane pendent groups were synthesized and copolymerized with PEGMA by free radical polymerization. Both ^{13}C and ^{1}H solution NMR showed peaks associated with adamantyl and cyclodextrin units besides PEGMA units. Although micelle formation (hydrophobic interaction of adamantyl groups) was observed for the copolymer bearing APM moieties examined by ^{1}H-NMR, these associations did not inhibit the host-guest complex formation between pendent adamantyls with free CD. The viscoelastic properties of supramolecular assemblies were investigated with frequency and temperature sweep experiments. It was shown that PEG units did not form stable complexes with pendent CD groups, while the specific host-guest interaction between pendent adamantyl and cyclodextrin moieties lead to large increases in viscosity: It has thus been shown that the viscosity of these systems is tunable by varying the concentration of these groups in water-soluble copolymers.

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