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Synthesis and characterization of poly(ε-caprolactone-co-ethylene glycol) star-type amphiphilic copolymers by "click" chemistry and ring-opening polymerization

Temel Öztürk[a], Ali Kılıçlıoğlu[a], Bedrettin Savaş[b], and Baki Hazer[c,d]

[a]Department of Chemistry, Faculty of Arts and Sciences, Giresun University, Giresun, Turkey; [b]Kars Vocational School, Kafkas University, Kars, Turkey; [c]Department of Chemistry, Faculty of Arts and Sciences, Bülent Ecevit University, Zonguldak, Turkey; [d]Department of Aircraft Airframe Engine Maintenance, Kapadokya University, Ürgüp, Turkey

ABSTRACT

The synthesis of poly(ε-caprolactone-co-ethylene glycol) AAB star-type amphiphilic copolymers were carried out by use of a "click" chemistry reaction to block propargyl polyethylene glycol (propargyl-PEG) to terminally azide poly(ε-caprolactone) (PCL-N_3). For this purpose, propargyl-PEG was synthesized by the reaction of PEGs (3000 Da, 2000 Da, 1500 Da, and 1000 Da) and propargyl chloride. Terminally chloride poly(ε-caprolactone) (PCL-Cl) was carried out by means of ring-opening polymerization (ROP) of ε-caprolactone (CL) and 3-chloro-1,2-propanediol. Synthesis of PCL-N_3 was obtained by the chemical interaction of PCL-Cl and sodium azide. By reacting propargyl-PEG and PCL-N_3, the star-type amphiphilic copolymers were obtained. The characterization of products was accomplished by using multiple instruments including ^{1}H-NMR, FT-IR, GPC, TGA, contact angles, and elemental analysis techniques.

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"Click" chemistry; ring-opening polymerization; star-type amphiphilic copolymer; terminally azide poly(ε-caprolactone); propargyl polyethylene glycol

1. Introduction

Sharpless et al.[1] described "click" chemistry in 2001. After this time, "click" chemistry applications have been widely studied.[2–12] Ring-opening polymerization (ROP) technique was performed to a lot of monomers with many initiators and catalyst systems.[13–20] Poly(ε-caprolactone) (PCL) is a semi-crystalline biodegradable polyester with a low melting point and glass transition temperature and is also used for many copolymer synthesizes.[21–27] Copolymers, which have polyethylene glycol (PEG), are appealing substances for biomedical, industrial, and chemicals practices, as PEG has unparallel features such as superior ion absorbability, flexibility, hydrophilicity, and a superior grade of biocompatibility.[28–36] Copolymers including PEG and PCL unit has been verified to be a good transporter for hydrophobic drugs delivery.[37–39] PEG blocks are helpful for hydrophobic polymers to gain hydrophilicity.[40,41]

The drug release behavior of poly(ε-caprolactone-b-ethylene glycol) degradable copolymer in vitro was investigated by using 5-fluora-uracil as a model drug.[42] PEG-PCL hydrogels show superior gel strength.[43–45] Amphiphilic PCL-PEG polymer has a lot practices as micro- and nanoparticles or thermosensitive hydrogels.[46,47] Savic et al.[48,49] improved a few fluorescent poly(ethylene glycol-b-ε-caprolactone) copolymers that made possible visualization of interactions between micelles and cells by confocal microscopy.[50]

This paper demonstrates the synthesis of star-type amphiphilic copolymers of poly(ε-caprolactone-co-ethylene glycol) [poly(CL-co-EG)] using "click" chemistry. First, terminally chloride poly(ε-caprolactone) (PCL-Cl) was carried out means of by ring-opening polymerization (ROP) of ε-caprolactone (CL) and 3-chloro-1,2-propanediol. Synthesis of terminally azide poly(ε-caprolactone) ester (PCL-N_3) was obtained by the chemical interaction of PCL-Cl and sodium azide (NaN_3). By reacting propargyl-PEG and PCL-N_3, the star-type amphiphilic copolymers were obtained. Characterizations of the products are discussed in detail.

2. Experimental

2.1. Materials

Tetrahydrofuran (THF), triethylamine (TEA), and polyethylene glycol (PEG) with 3000 Da, 2000 Da, 1500 Da, and 1000 Da were supplied by Merck Millipore. 3-Chloro-1,2-propanediol, toluene, copper(I) bromide (CuBr), NaN_3, N,N-dimethylformamide (DMF), 2,2′-bipyridyl (bpy), propargyl chloride, chloroform, and tin(II) 2-ethylhexanoate [$Sn(Oct)_2$], were bought from Sigma-Aldrich. ε-Caprolactone (CL) was received from Alfa Aesar. Diethyl ether was supplied by Carlo Erba Reagent. Methanol was bought from Merck (Germany). All the chemicals were used as supplied and used without further purification.

CONTACT Temel Öztürk temelozturk@msn.com, temel.ozturk@giresun.edu.tr Department of Chemistry, Faculty of Arts and Sciences, Giresun University, Giresun 28200, Turkey.
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Table 1. Synthesis of propargyl-PEG.

Code	PEG (g)	Propargyl chloride (g)	Triethylamine (mL)	Yield (g)	Conversion (wt%)
AK-1	10.059 (PEG-1000)	0.780	1.5	9.414	87.9
AK-2	10.001 (PEG-1500)	0.510	1.0	6.213	59.2
AK-3	10.073 (PEG-2000)	0.390	0.8	9.424	90.9
AK-4	10.006 (PEG-3000)	0.260	0.5	9.164	89.8

Reaction temperature: 25 °C, reaction time: 48 hours, chloroform: 20 mL.

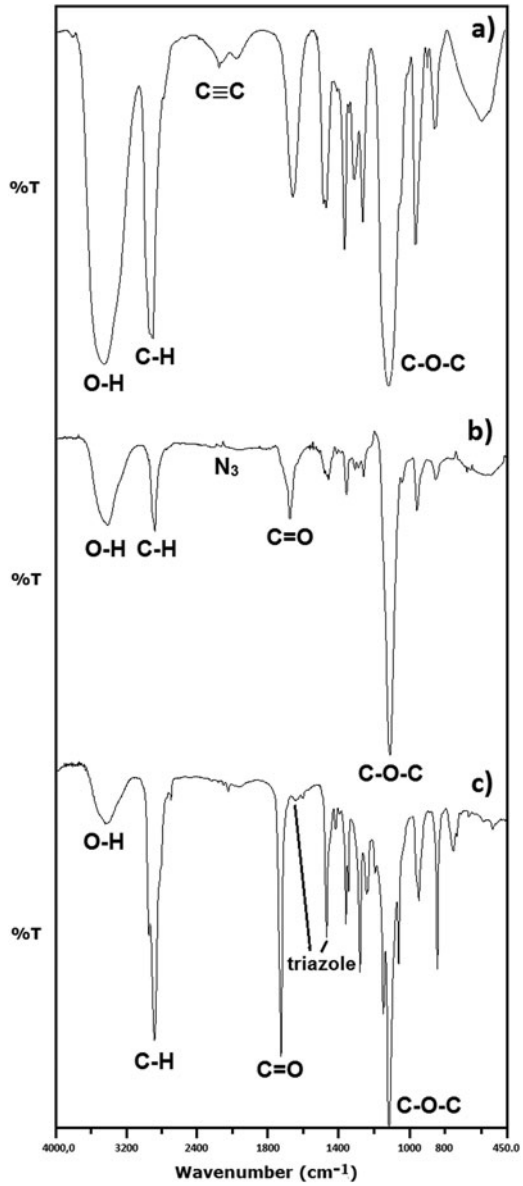


Figure 1. FT-IR spectrum of (a) propargyl-PEG; (b) PCL-N_3; (c) poly(CL-co-EG) star-type amphiphilic copolymers.

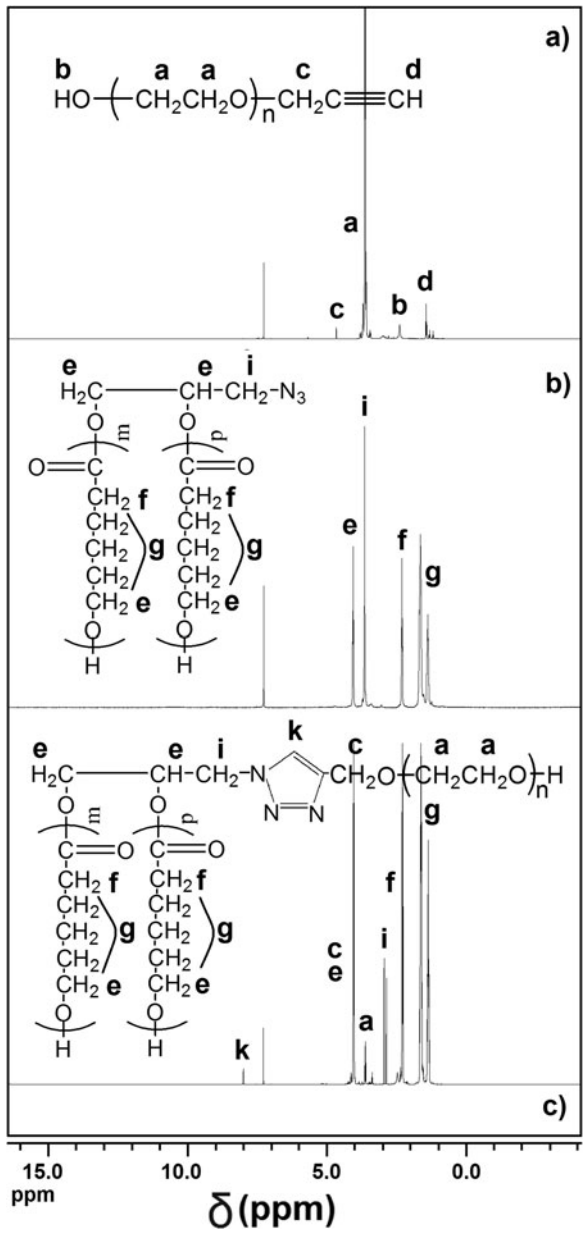


Figure 2. ^{1}H-NMR spectrum of (a) propargyl-PEG (AK-1 in Table 1); (b) PCL-N_3; (d) poly(CL-co-EG) star-type amphiphilic copolymers (AK-25 in Table 2).

2.2. Instrumentation

Mn, Mw, and dispersities were examined with Tosoh HLC-8320GPC gel permeation chromatography (GPC) instrument with THF mobile phase as the solvent 40 °C. ^{1}H–nuclear magnetic resonance (^{1}H–NMR) spectra of the products were detected using a Bruker Ultra Shield Plus, Ultra long hold time 400 MHz NMR instrument. Fourier transform infrared (FT-IR) spectra were detected using Perkin Elmer spectrum 100 model. The elemental analyses of the products were performed by a Costech ECS 4010. Thermal gravimetric/differential thermal analysis (TG/DTA) of the obtained polymers was carried out under nitrogen using a Seiko II Exstar 6000 TG/DTA to determine thermal degradation. A dried sample was heated from 30 to 900 °C at a rate of 10 °C min^{-1}. Contact angle measurements were obtained using a Nikon D3100 camera and AF-S DX Nikkor 18-55 mm objective.

2.3. Synthesis of propargyl polyethylene glycol (propargyl-PEG)

The similar procedure reported in the cited literature was followed for synthesis of propargyl-PEGs by using PEG.[51–53] Specified amounts of PEGs with 3000 Da, 2000 Da, 1500 Da, and 1000 Da (^{1}H–NMR: 3.6 ppm for –OCH_2 protons and 2.5 ppm for –OH protons for PEG wih 1500 Dalton) in a fixed 15 mL of chloroform was mixed with a certain amount of TEA as shown Table 1. The solution was transferred into a 200 mL flask with a nitrogen gas input. The flask was cooled down to below 0 °C and nitrogen was injected into the flask. To this solution certain amounts of propargyl chloride in 5 mL of chloroform was added via a dropping funnel over a duration of 60 minutes. The solution was mixed for 60 minutes below 0 °C. Afterwards, the contents were slowly warmed to 25 °C. After 48 hours, the solvent was partially evaporated and the residue precipitated in diethyl ether. The sample was kept in a refrigerator overnight. After decantation, the product was dried at 25 °C under vacuum for two days. Propargyl-PEG yield was defined gravimetrically. The FT-IR spectrum of propargyl-PEG in Figure 1(a) shows the signals at 3450 cm^{-1} for –OH groups, 2900 cm^{-1} for aliphatic –CH_2 groups, 2150 cm^{-1} for C≡C groups, and 1150 cm^{-1} for –COC groups. The ^{1}H–NMR spectrum of propargyl-PEG (Figure 2(a)) displayed peaks at 4.8 ppm for -OCH_2≡C protons, 3.6 ppm for –OCH_2 protons of PEG group, 2.5 ppm for –OH protons of PEG group, 1.5 ppm for -C≡CH protons.

2.4. Synthesis of terminally chloride poly(ε-caprolactone) (PCL-cl) by ring-opening polymerization

20.26 g of CL (^{1}H–NMR: 4.0 ppm for –OCH_2 protons, 2.5 ppm for –CH_2CO protons, and 1.5 ppm for –CH_2 protons), 1.04 g of 3-chloro-1,2-propanediol, 20 mL of toluene and 2 drops of $Sn(Oct)_2$ (catalyst for ROP of CL) were put separately into a 200 mL flask followed by injecting nitrogen gas in the tube for five minutes. The flask was capped with a septum and immersed in an oil bath at 110 °C temperature for 24 hours. After ROP, the content was poured into excess diethyl ether to separate PCL-Cl. The product was kept in a refrigerator overnight. After decantation, the polymer was dried at room temperature under vacuum for two days. PCL-Cl yield was defined gravimetrically. The ^{1}H–NMR spectrum of PCL-Cl displayed peaks at 4.1 ppm for –OCH_2 protons of PCL segment, 3.8 ppm for –$ClCH_2$ protons, 2.3 ppm for –CH_2CO protons of PCL segment, 1.7 ppm for –OH protons of PCL segment, and 1.4 ppm for –CH_2 protons of PCL segment.

2.5. Synthesis of terminally azide poly(ε-caprolactone) (PCL-N_3)

13.03 g of PCL-Cl, 1.31 g of NaN_3, and 150 mL of DMF were placed in a 300 mL flask, were put separately into a 250 mL

Table 2. Synthesis of poly(ε-caprolactone-b-ethylene glycol) star-type amphiphilic block copolymers by "click" chemistry.

Code	Propargyl-PEG (g)	PCL-N_3 (g)	CuBr (g)	bpy (g)	Yield (g)	Conversion (wt %)	$M_{n,GPC}$ (g.mol^{-1})	M_w/M_n	Td (°C)
AK-25	5.088 (AK-1 in Table 1)	2.501	0.717	1.560	3.894	51.30	2,728	1.54	387
AK-47	5.162 (AK-2 in Table 1)	1.661	0.478	1.039	3.183	46.62	4,250	1.14	381
AK-52	5.097 (AK-3 in Table 1)	1.252	0.363	0.781	5.801	91.48	4,440	1.58	389
AK-57	5.132 (AK-4 in Table 1)	0.833	0.243	0.524	3.578	62.06	7,026	1.26	396

Polymerization temperature: room temperature, reaction time: 24 hours, chloroform: 30 mL.

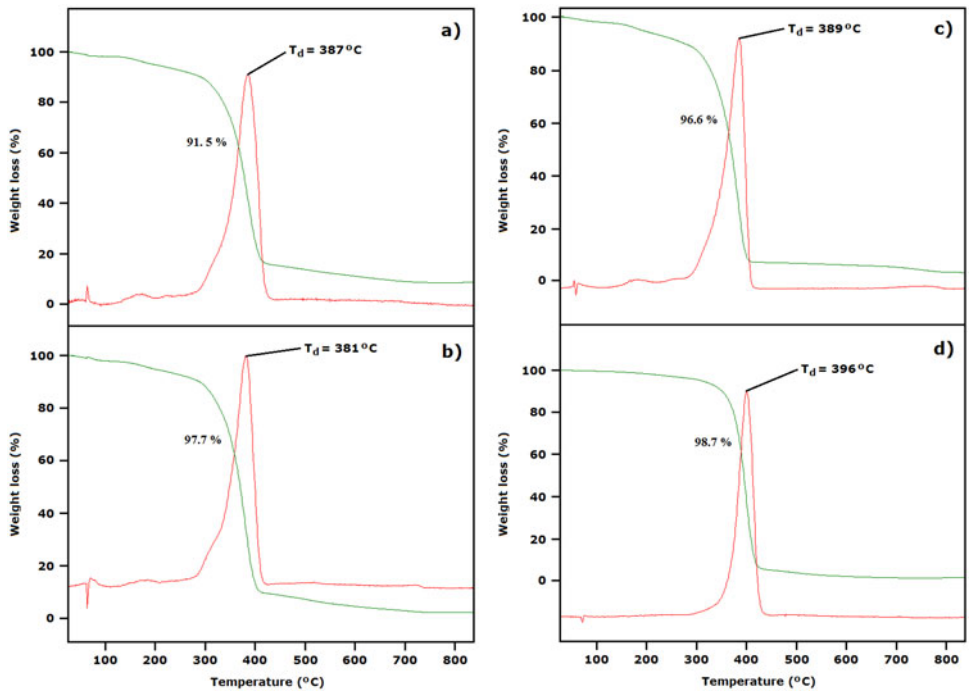
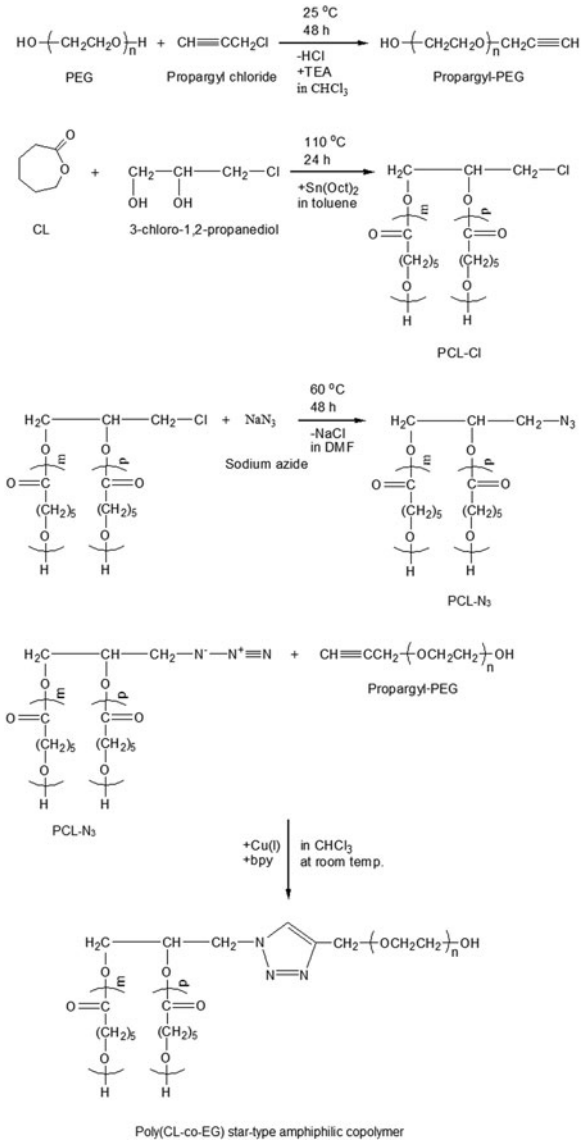


Figure 3. TGA curves of poly(CL-co-EG) star-type amphiphilic copolymer: (a) AK-25 in Table 2; (b) AK-47 in Table 2; (c) AK-52 in Table 2; (d) AK-57 in Table 2.

flask. The flask was immersed in an oil bath fixed at 60 °C on a magnetic stirplate, and nitrogen gas was introduced by injection with a needle. After 48 h, the contents were filtered. The solvent was evaporated. The residue was drained into excess diethyl ether to separate PCL-N_3. After decantation, the product was dried at 25 °C under vacuum for two days. PCL-N_3 yield was defined gravimetrically. The FT-IR spectrum of PCL-N_3 in Figure 1(b) shows the signals at 3400 cm^{-1} for –OH groups, 2850 cm^{-1} for aliphatic –CH_2 groups, 2100 cm^{-1} for N_3 groups, 1700 cm^{-1} for –C=O groups, and 1100 cm^{-1} for –COC groups. The ^{1}H–NMR spectrum of PCL-N_3 (Figure 2(b)) displayed peaks at 4.1 ppm for –OCH_2 protons of PCL segment, 3.6 ppm for –CH_2N_3 protons, 2.3 ppm for –CH_2CO protons of PCL segment, and 1.4 ppm for –CH_2 protons of PCL segment. The result of elemental analysis of PCL-N_3 shows 1.93 wt % N.

2.6. Synthesis of poly(CL-co-EG) star-type amphiphilic copolymers by "click" chemistry

Poly(CL-co-EG) star-type amphiphilic copolymers was synthesized by "click" chemistry in this study. Specified amounts of propargyl-PEG, PCL-N_3, CuBr, bpy, and chloroform were put separately into a 250 mL Schlenk flask followed by injecting nitrogen gas in the tube for five minutes. The flask was put on a magnetic stirplate for 24 h at room temperature. After reaction, the flask contents were filtered. The solvent was partially removed by using a rotary evaporator. The mixture was drained into excess methanol to separate precipitated poly(CL-co-EG) star-type amphiphilic copolymer. The amphiphilic copolymer was dried at 25 °C under vacuum for two days. The conversion of the copolymer was defined gravimetrically. A small alumina column was used to remove the remaining copper catalyst from the copolymer. The FT-IR spectrum of poly(CL-co-EG) star-type amphiphilic copolymer in Figure 1(c) shows the signals at 3600 cm^{-1} for –OH, 2850 cm^{-1} for aliphatic –CH_2, 2100 cm^{-1} for N_3, 1700 cm^{-1} for –C=O, and 1100 cm^{-1} for –COC groups. Furthermore, the characteristic peaks of triazole group were observed at 1625 cm^{-1} and 1450 cm^{-1}. A typical ^{1}H–NMR spectrum of poly(CL-co-EG) star-type amphiphilic copolymers shown in Figure 2(c) displayed peaks at 8.0 ppm for aromatic –CH proton of triazole group,



Scheme 1. Reaction pathways in the synthesis of propargyl-PEG, PCL-Cl, PCL-N_3, and poly(CL-co-EG) star-type amphiphilic copolymers by "click" chemistry.

4.1 ppm for $-OCH_2$ protons of PCL group and for $-OCH_2$ protons linked triazole group, 3.6 ppm for $-OCH_2$ protons of PEG group, 3.0 ppm for $-NCH_2$ protons linked triazole group, 1.7 ppm for $-CH_2$ protons linked carbonyl group of PCL segment, and 1.4 ppm for $-CH_2$ protons of PCL segment. $M_{n,GPC}$ values of the star-type amphiphilic copolymers were between 2,728 g.mol^{-1} and 7,026 g.mol^{-1} as shown Table 2. Mw/Mn of the amphiphilic copolymers were between 1.14 and 1.54. Thermal analysis of the products was carried out by TGA. Thermogravimetric analysis has showed interesting properties of the copolymers indicating continuous weight loss starting from 290 °C to nearly 420 °C with a derivative at 387 °C (Figure 3(a)).

2.7. Preparation of polymer films

0.5 g of copolymer was dissolved in 10 mL chloroform. The solution was poured onto a lam and paper sealed over the lam. The solvent was evaporated. Then thin polymer film dried under vacuum at room temperature for 48 h. The same procedure was repeated for all samples.[54]

3. Results and discussion

3.1. Synthesis of propargyl-PEG

Propargyl-PEG was synthesized by reacting PEG and propargyl chloride. The gravimetric conversion obtained from the weight of propargyl-PEG was between 91 wt% and 59 wt% as shown in Table 1. Scheme 1 (first line) shows the reaction pathway for propargyl-PEG.

3.2. Synthesis of PCL-cl by ring-opening polymerization

PCL-Cl was synthesized by reacting CL and 3-chloro-1,2-propanediol. The second line in Scheme 1 (second line) shows the reaction pathway for PCL-Cl. The yield was 18.01 g. The gravimetric conversion obtained from the weight of PCL-CL was 85.6 wt%.

3.3. Synthesis of PCL-N_3

Scheme 1 (third line) shows the reaction pathway for PCL-N_3. The yield was 10.68 g. The gravimetric conversion obtained from the weight of PCL-N_3 was 74.6 wt%. The theoretical wt % N result of PCL-N_3 was 1.75 wt% N which was calculated by using $M_{n,GPC}$ value (2,395 g.mol^{-1}).

3.4. Synthesis of the star-type amphiphilic copolymer by "click" chemistry

Scheme 1 (fourth line and fifth line) shows the reaction pathway for poly(CL-co-EG) star-type amphiphilic copolymer. The observed characteristic peak at 8.0 ppm for aromatic –CH proton of triazole group in the ^{1}H–NMR spectrum was an evidence that the copolymer was obtained. Furthermore, the observed peaks of triazole group at 1625 cm^{-1} and 1450 cm^{-1} in FT-IR spectrum was the other further evidence that the copolymer was synthesized. Mw/Mn values of the copolymers were relatively low. Increases in the molecular weights of the copolymers as compared with the molecular weights of the reactants is consistent with the formation of star-type amphiphilic copolymer. The maximum yield of the star-type amphiphilic copolymer was obtained by using propargyl-PEG (AK-3 in Table 1). The minimum yield of the star-type amphiphilic copolymer was obtained by using propargyl-PEG (AK-2 in Table 1). Decomposition temperatures (Td) of the copolymers are shown in Table 2. In the case of poly(CL-co-EG) star-type amphiphilic copolymer, PCL and PEG units have not the individual Td as shown in Figure 3.

The hydrophilic character of the copolymers was explored by the water drops on the polymer films. 2 cm ×2 cm thick sections were taken from the 0.1 mm films of the copolymers. 1 drop of deionized water was dripped on the polymer and after 10 seconds, 20 seconds, 40 seconds, 60 seconds, and 80 seconds its photos were taken from a fixed point with a professional camera. The angle measurement was done with a goniometer on the captured images. Figure 4 shows the photographs of the water drops on the star-type copolymer

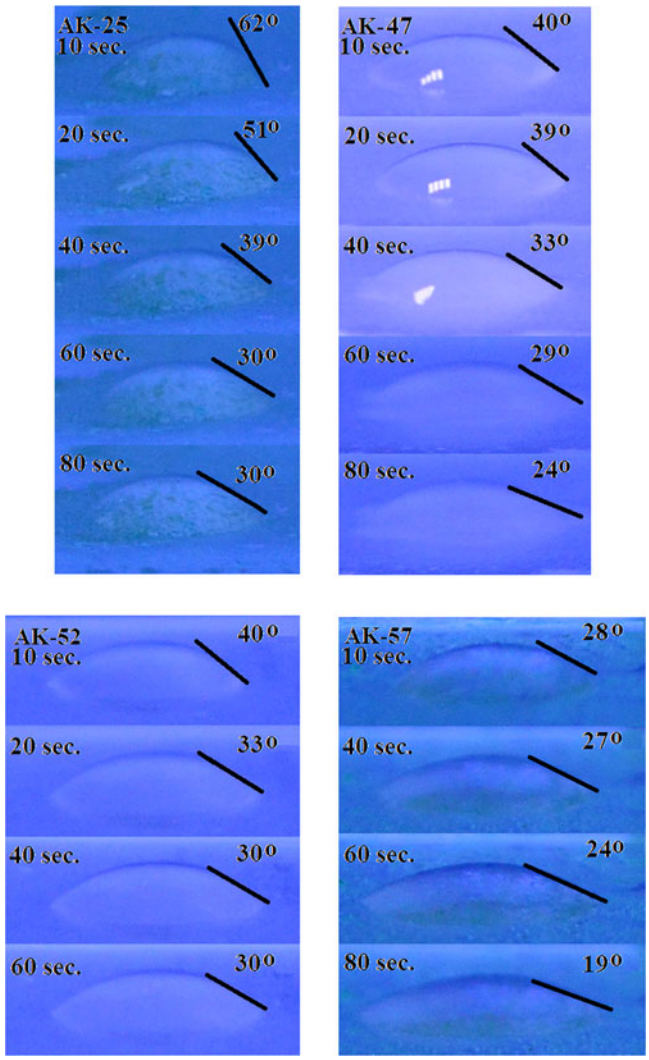


Figure 4. Photographs of the water drops on the star-type amphiphilic copolymer films (AK-25 in Table 2; AK-47 in Table 2; AK-52 in Table 2; AK-57 in Table 2).

films. Less than 90° contact angles for the star-type copolymers indicates the increase in hydrophilicity, while PCL have more than 90° contact angles due to hydrophobic nature.[54–56] As the time increases, the propagation velocity of the water droplets increases as well.

4. Conclusions

The "click" chemistry synthesis of poly(CL-co-EG) star-type amphiphilic copolymer from PCL and PEG was achieved. The amphiphilic copolymers were acquired in high yield and high molecular weight. It was demonstrated that the contact angle decreases due to increasing PEG content. The proposed method for the synthesis of copolymer is simple and efficient. This study can provide new, well-characterized materials with wide application potential through the synergistic combination of crystalline PCL and hydrophilic PEG.

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