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One-Pot Synthesis of Linear-Hyperbranched Amphiphilic Block Copolymers Based on Polyglycerol Derivatives and Their Micelles

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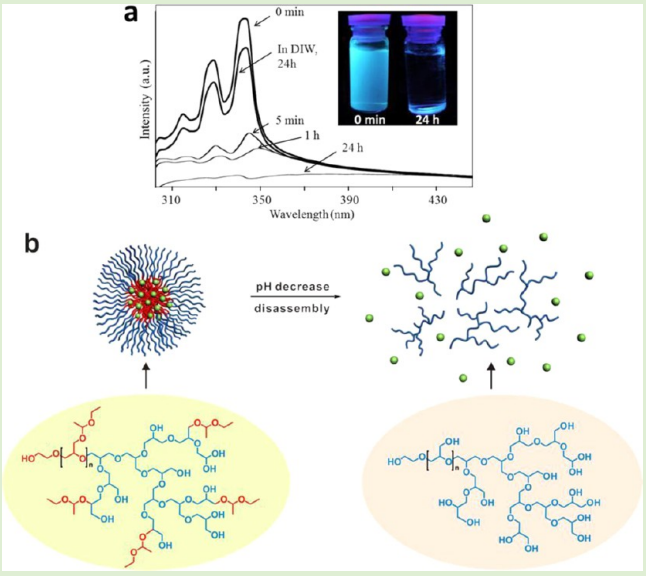
Supporting Information

ABSTRACT: This paper describes the one-pot synthesis of a polyglycidol (PG)-based polymer, poly(ethoxyethyl glycidyl ether) (PEEGE)-*b*-[*hyperbranched* polyglycerol (*hb*PG)-*co*-PEEGE]$_{x/y}$, its micelle formulation, and the ability to encapsulate a model therapeutic molecule. Amphiphilic block copolymers were prepared by the sequential addition of ethoxyethyl glycidyl ether (EEGE) to glycidol. The composition of the block copolymers varied from 62:38 to 92:8. Block copolymers with composition $x:y \geq 66:34$ were soluble only in organic solvents. Micelles were formulated by injection of deionized water into a tetrahydrofuran block copolymer solution with or without pyrene as a model hydrophobic molecule. The critical micelle concentration was 18.2−30.9 mg/L, and the micelle size was 100−250 nm. The pyrene-containing micelle rapidly collapsed on acidic exposure, allowing conversion of hydrophobic PEEGE to hydrophilic PG, thus, facilitating the release of the encapsulated pyrene. Cytotoxicity data showed high biocompatibility of PG-based block copolymers, suggesting their potential as a drug delivery carrier.



INTRODUCTION

Polymers with a branched architecture, such as star, block, and graft copolymers, hyperbranched (*hb*) polymers, and dendrimers, have gained increasing attention because of their unique three-dimensional architecture, which is useful for encapsulation of various molecules and nanosized objects.[1−5] In particular, hyperbranched polymers have advantages over dendrimers because of their variety of molecular designs and ease of preparation.[6−8]

Similar to its polyether analogue, poly(ethylene glycol) (PEG), polyglycerol (PG) is a promising candidate for application in drug delivery systems (DDSs) because of its biocompatibility, immunogenicity, and low toxicity.[9−11] Moreover, PG has advantages over PEG-based materials, such as oxidation stability,[12] protein resistance,[13,14] and facile access to various architectures. Since the first synthesis of PG by the ring-opening polymerization of glycidol (GL),[15] numerous reports have been published on the preparation of linear[16−20] and hyperbranched PG.[21] With its hydrophilic nature, PG has also been conjugated with hydrophobic segments, such as polystyrene,[22] polylactide,[23−25] polylactone,[26] poly(propylene oxide),[27] and protected PG,[28] in stimuli-responsive[29] and biomedical applications.[30]

The synthetic approach for a linear-hyperbranched "double hydrophilic" architecture based on PEG with PG was first reported by the Frey group in 2008.[31,32] This type of double hydrophilic copolymer is particularly promising in terms of enhancing biocompatibility, increasing water solubility, and, most importantly, in improving residue clearance after drug delivery. Therefore, the combination of PEG with PG to form a double hydrophilic drug carrier is gaining interest. For example, Kratz and co-workers reported acid-cleavable multifunctional prodrugs derived from dendritic PGs with a PEG shell.[33] Our group has also recently applied the PEG-*hb*-PG block copolymer to synthesize a novel DDS by using the anticancer drug doxorubicin (DOX) *via* an acid-labile hydrazone linkage.[34]

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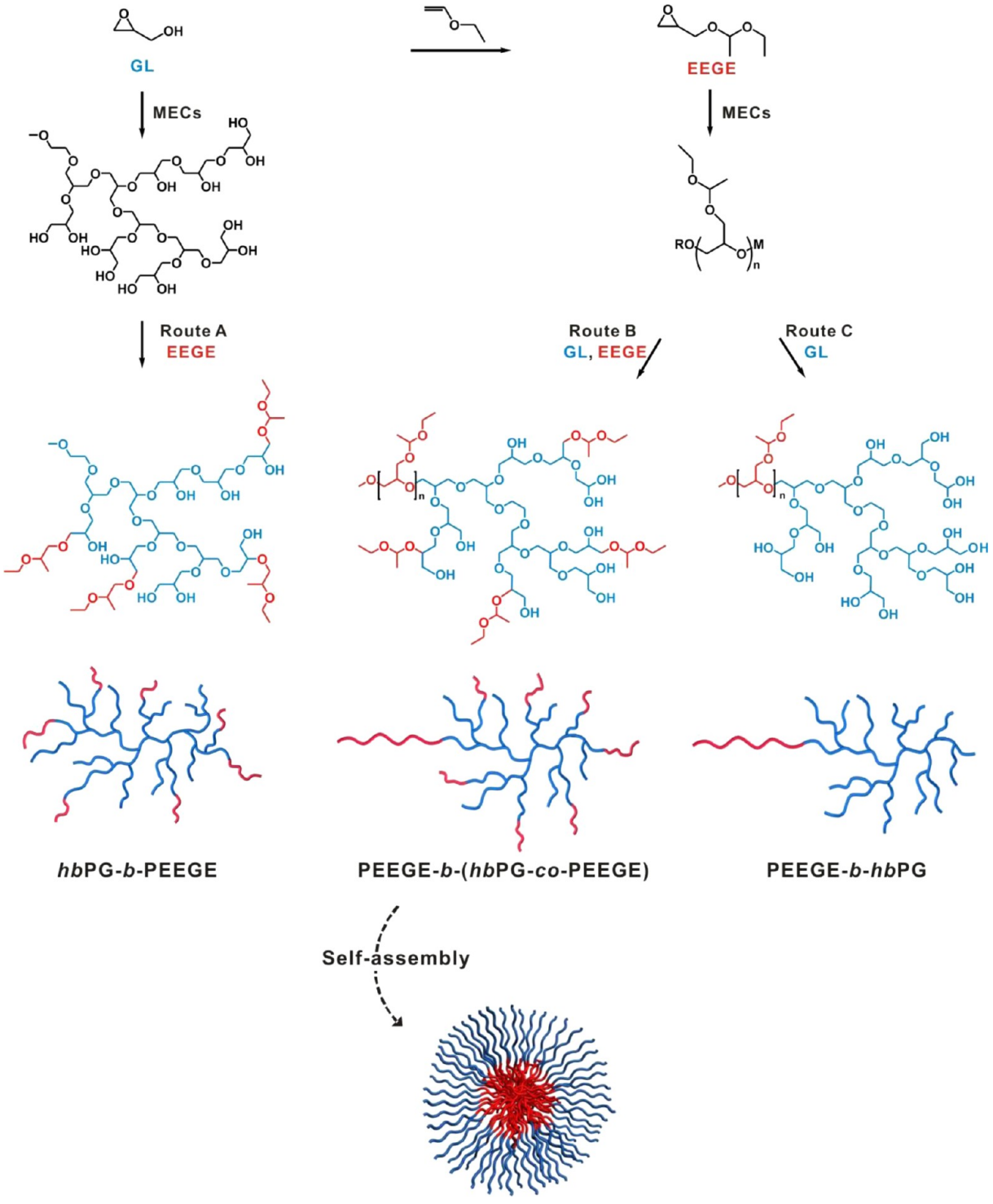

Figure 1. Synthetic pathways of PG-based polymers with different architectures prepared from GL and EEGE via three different synthetic routes.

The DOX-conjugated copolymer of PEG-*hb*-PG-DOX undergoes a spontaneous self-assembly process in an aqueous solution to create core−shell micellar aggregates, from which DOX is efficiently released on exposure to acidic conditions, resulting in remarkable cytotoxicity to HeLa cells.

Similar to linear PEG polymers, linear PG blocks have been reported by Spassky and co-workers using the protected monomer of GL, ethoxyethyl glycidyl ether (EEGE).[18] Following the polymerization of EEGE, the ethoxyethyl protecting group can be readily removed by acid-catalyzed hydrolysis with HCl, affording a linear PG with free hydroxyl groups in every repeating unit. These free hydroxyl groups afford initiation sites for the growth of other polymer blocks. Although there are several reports describing the synthesis of linear-hyperbranched polymers based on PG,[31] no study has exclusively detailed the systematic synthesis and characterization of linear-hyperbranched block copolymers of PG-based monomers with different architectures. In continuation of our investigations into the potential of PG-based polymers in biomedical applications, we report herein the one-pot synthesis

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Table 1. List of Polymers Synthesized in This Study

run	polymer	yield[a] (%)	M_n[b] (GPC)	M_w/M_n[b] (GPC)	M_n[c] (PEFGE, NMR)	M_n[c] (PG, NMR)	M_n[c] (total, NMR)	EEGE/GL feed	EEGE/GL composition[c]
1	PEEGE	64	4000	1.06	7950			100:0	100:0
2	*hb*PG	70	7200	1.37		8300		0:100	0:100
3	$hbPG_{72}$-*b*-$PEEGE_{28}$	54			2800	3600	6400	33:67	28:72
4	$PEEGE_{48}$-*b*-$hbPG_{52}$	57			7400	4100	11500	44:56	48:52
5	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{62/38}$	26			8700	2800	11500	66:34	62:38
6	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{66/34}$	50			12800	2500	15300	75:25	66:34
7	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{71/29}$	56			5200	900	6100	83:17	71:29
8	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{83/17}$	38			6900	600	7500	94:6	83:17
9	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{86/14}$	29			12700	900	13600	96:4	86:14
10	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{92/8}$	23			6300	300	6600	95:5	92:8

[a]Water-insoluble part. [b]Determined by GPC (NMP, PSt). [c]Determined by NMR (DMSO-d_6).

of PG-based polymers with different architectures by simply varying the sequence in which the monomers of GL (unprotected) and EEGE (protected) are used, in order to afford three types of PG-based polymers (Figure 1). This simple synthetic approach provided different architectures of PG-based polymers with varying aqueous solubility. Furthermore, we investigated their potential in the formation of stable micelles and in the encapsulation of a model hydrophobic drug.

EXPERIMENTAL SECTION

Materials. Methoxy ethanol (99.5%, Acros) was purified by vacuum distillation from CaH_2 prior to use. Deionized (DI) water was obtained using an Iwaki Glass ASK-2DS water system (0.8 μS/cm). EEGE was prepared according to the literature.[34,35] A phosphate buffer solution (PBS; pH = 5.0) was prepared by mixing NaH_2PO_4 (0.20 M, 92 mL) and Na_2HPO_4 (0.20 M, 8 mL) solution at 20 °C. Other reagents and solvents were used as provided.

Measurements. Fourier transform infrared spectra were measured using a Jasco IR-5500 spectrometer (Jasco Co., Ltd.) by transmittance absorption spectroscopy (KBr tablet method). ^{1}H NMR analysis was performed on a Bruker AC-400P spectrometer at 400 MHz. Deuterated dimethylsulfoxide (DMSO-d_6) was used as a solvent. Number- and weight-average molecular weights (M_n and M_w) were measured by gel permeation chromatography (GPC) on a Tosoh HLC-8120 GPC equipped with a consecutive polystyrene gel column (TSK-GEL GMHHR-M and GMHHR-N) at 40 °C eluted with *N*-methylpyrrolidone containing 0.01 mol/L lithium bromide at a flow rate of 1.0 mL/min calibrated by standard polystyrene samples. Fluorescence measurements were performed on a Jasco FP-6500 spectrometer using pyrene as the fluorescent probe, with an emission wavelength of 372 nm. The fluorescence intensities at an excitation wavelength of 336.4 and 339.6 nm were used to evaluate the critical micelle concentration (CMC) values. Transmission electron microscopy (TEM, JEM-2100, JEOL, Japan) was performed to investigate the morphology of the micelles. Size distribution analysis was performed using dynamic light scattering (DLS, BI-APD, Brookhaven Instrument, New York, U.S.A.).

Polymerization. Typical procedures for the synthesis of PEEGE-*b*-(hbPG-*co*-PEEGE): 0.108 g (1.41 mmol) of methoxyethanol and 0.217 g (1.29 mmol) of cesium hydroxide monohydrate were placed in a flask under nitrogen. The heterogeneous solution was stirred at 90 °C for 1.5 h, and the solvents were removed using a rotary evaporator. The opaque viscous liquid was heated at 90 °C and dried under reduced pressure for 2 h to give methoxyethoxy cesium (MECs) as a white powder. In a stream of nitrogen, 0.027 g (0.130 mmol) of MECs and 1.46 g (10.0 mmol) of EEGE were placed in a flask, and the polymerization was conducted at 60 °C for 48 h under nitrogen (at this moment, the conversion of EEGE was about 90%). Then, 0.370 g (5.00 mmol) of GL was added dropwise into this solution, and the post polymerization was allowed to proceed at 90 °C for 12 h. The polymerization was terminated by the addition of methanol/acetic acid, 0.1/0.08 mL (a slight excess compared with the initiator), and the solvents and unreacted monomers were removed at 100 °C for 12 h under reduced pressure. The resulting viscous liquid was dissolved in methanol and reprecipitated in distilled water. This was dried at 100 °C for 12 h under reduced pressure to give the title polymer as an opaque viscous liquid. The yields ranged from 23 to 56% (Table 1).

All the other polymers, PEEGE, *hb*PG, *hb*PG-*b*-PEEGE, and PEEGE-*b*-*hb*PG, were prepared by a similar MECs-initiated procedure, as described above. PEEGE was obtained in 64% yield as a brown transparent viscous liquid, and *hb*PG was obtained in 70% yield as yellow transparent viscous liquid.

Micelle Formulation Study. A polymer sample of 1.0 mg was dissolved in 1 mL of tetrahydrofuran (THF). A 10 μL pyrene solution in THF (5.2 mg/L) was added into the PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{86/14}$ solution, and the mixture was stirred for 30 min at ambient temperature. Then, 5 mL of DI water was injected into this solution via a syringe pump at a rate of 0.7 mL/min, and the resulting solution was dialyzed against DI water three times for 6 h each. The CMC values were determined by fluorescence measurements at wavelengths of 336.4 and 339.6 nm while varying the concentration of the polymer samples.[36−38]

Pyrene Release Experiments. Using PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{83/17}$, a pyrene-containing polymer micelle solution (polymer solution 350 μL, 10 μL of pyrene solution in THF (5.2 mg/L), diluted with 5 mL of DI water) was prepared according to the procedure described above. In this solution, 2.5 mL of PBS (pH = 5.8) was added, and the changes in excitation spectra were recorded.

Cytotoxicity Assay. HuCC-T1 human cholangiocarcinoma cells were purchased from the Health Science Research Resources Bank (Osaka, Japan). Cells were seeded into 96-well plates at a density of 5 × 10^4 cells per well and incubated for 24 h in 5% CO_2 at 37 °C. After removing the culture medium (with serum), the wells were washed with PBS. Each well was then replaced with 100 μL of fresh Roswell Park Memorial Institute (RPMI) 1640 media (without FBS) containing PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ (x/y = 66/34, 86/14, and 92/8) micelles. The cells were incubated for an additional 32 h; subsequently, 25 μL of MTT (3 mg/mL) was added to each well. After 4 h, 100 μL of an SDS−HCl solution (SDS 10% w/v, 0.01 M HCl) was added to each well, and absorbance was measured at 570 nm after 12 h (Infinite M200 Pro microplate reader, Tecan, Switzerland).

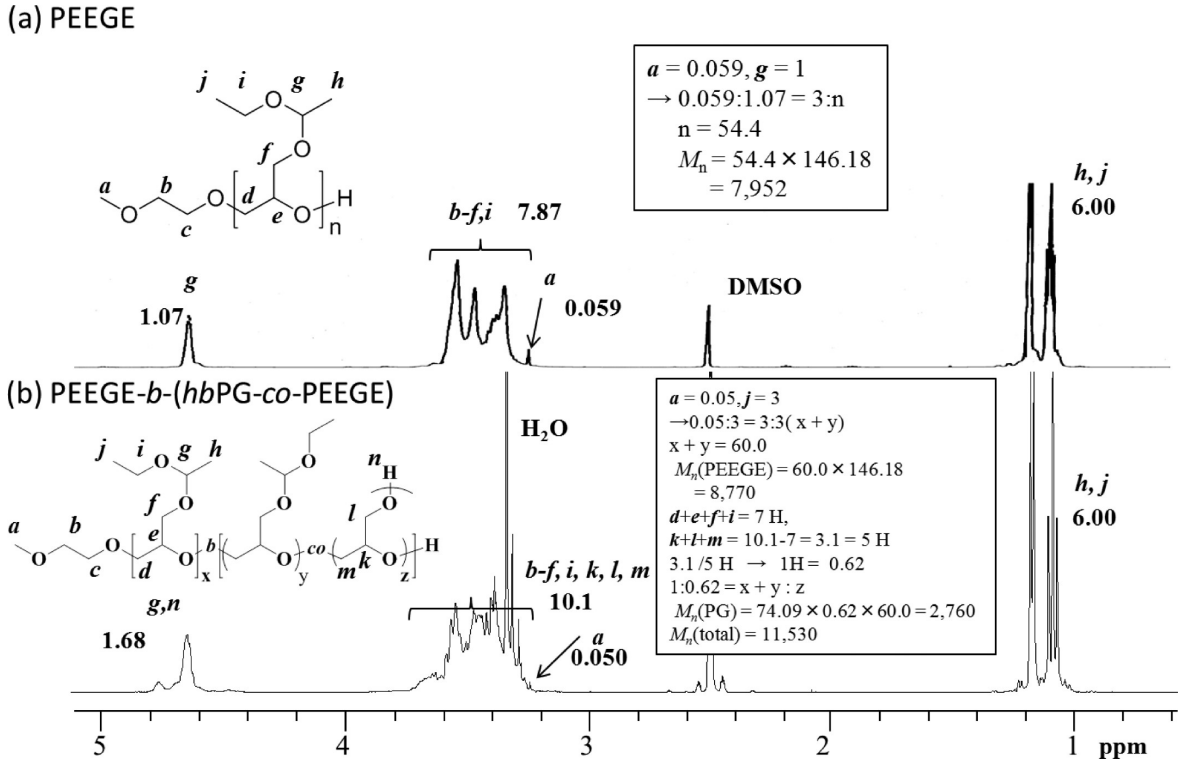

Figure 2. ^{1}H NMR (500 MHz) spectra of (a) PEEGE and (b) PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{62/38}$ in DMSO-d_6, with the calculation of the $M_{n(NMR)}$ of PEEGE, PG, and the block copolymers.

Table 2. Solubility of Polymers Synthesized in This Study[a]

run	polymer	water	MeOH	EtOH	PrOH	THF	dioxane	DMF
1	PEEGE	−	++	++	++	++	++	++
2	*hb*PG	++	−	−	−	−	−	++
3	*hb*PG$_{72}$-*b*-PEEGE$_{28}$	++	−	−	−	−	−	++
4	PEEGE$_{48}$-*b*-*hb*PG$_{52}$	++	++	+	−	−	−	++
5	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{62/38}$	+	++	++	++	++	++	++
6	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{66/34}$	−	++	++	++	++	++	++
7	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{71/29}$	−	++	++	++	++	++	++
8	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{83/17}$	−	++	++	++	++	++	++
9	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{86/14}$	−	++	++	++	++	++	++
10	PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{92/8}$	−	++	++	++	++	++	++

[a]Polymer 10 mg/solvent 5 mL (++ soluble at room temperature; + soluble after heating; +− partially soluble; − insoluble).

Viable cells were expressed as a percent of control. Results were calculated as means with a standard deviation as an error range from three different experiments.

RESULTS AND DISCUSSION

Synthesis of Polymers. We designed and synthesized the linear and hyperbranched PG-based polymer with different architectures by exploiting the protected form of GL (i.e., EEGE) using different sequences during the polymerizations (Figure 1). Linear and hyperbranched polymers based on GL and EEGE were all prepared via the typical anionic ring-opening polymerization of GL and EEGE initiated with cesium alkoxide according to the literature.[31,36] As shown in Figure 1, using GL followed by EEGE provides discrete block copolymer structures of *hb*PG-*b*-PEEGE (route A), while an alternative sequence yields a different block copolymer of PEEGE-*b*-*hb*PG (route C). The combination of GL and EEGE allows access to linear and hyperbranched architectures, which can form micelles in selective solvents. Thus, we initially polymerized about 90% of EEGE and then fed GL to access the series of polymers denoted PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ (route B; subscripts *x* and *y* indicate the composition of the PEEGE and PG monomer units in the final products, respectively). Along with these copolymers, *hb*PG and PEEGE homopolymers were prepared for comparison. The results are summarized in Table 1.

The block copolymers were successfully prepared in moderate yields (23−57%) with M_n in the range 6100−15300, as determined by ^{1}H NMR spectroscopy. However, the molecular weights of these polymer samples could not be directly measured by our GPC system. Nevertheless, the M_n values of the respective homopolymer of PEEGE and *hb*PG determined by ^{1}H NMR showed similar values to those from GPC analysis; thus, we believe that the M_n data based on ^{1}H NMR can be a reliable measure for the composition of the synthesized copolymers. Figure 2 shows the ^{1}H NMR spectra of PEEGE (Table 1, run 1) and PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{62/38}$ (Table 1, run 5). The initiating ethoxy methoxy

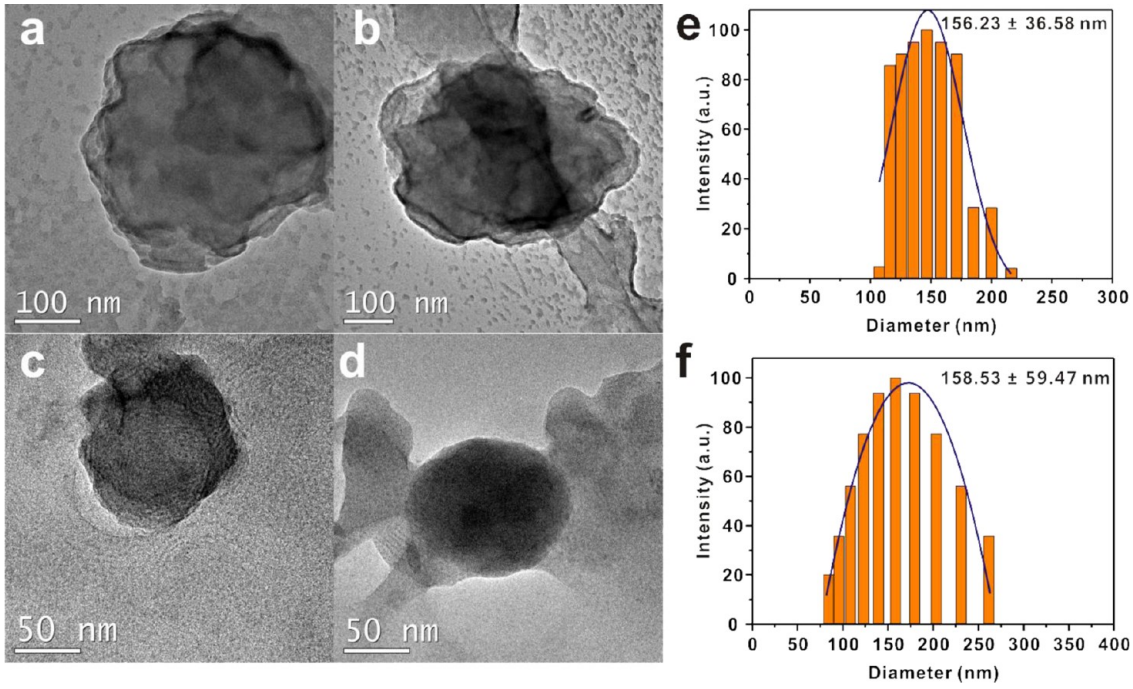

Figure 3. (a–d) TEM images of PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$-based micelles after dialysis against DI water for 5 days. (e,f) Distribution of the diameter of micelles determined by DLS. (a, b, and e) PEEGE/PG = 66:34, (c, d, and f) PEEGE/PG = 92:8.

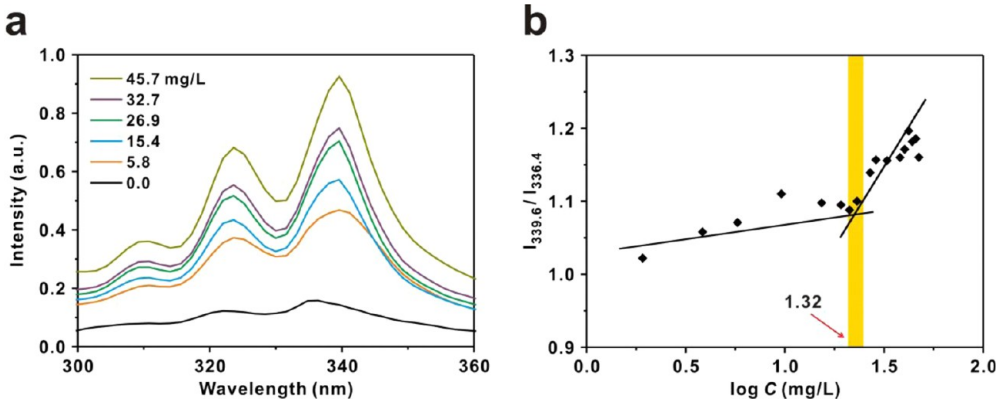

Figure 4. (a) Excitation spectra of pyrene in the presence of PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{86/14}$ at a concentration of 0–45.7 mg/L in water and (b) the relationship between $I_{339.6}/I_{336.4}$ and log C (mg/L).

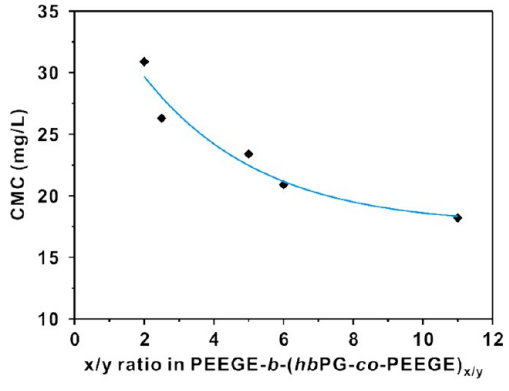

Figure 5. Relationship of CMC values with respect to the ratio of PEEGE and PG block (x/y) in PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ copolymers.

($CH_3OCH_2CH_2O-$) group can be detected as proton *a*, and this integration value is compared with proton *g* in EEGE to show the degree of polymerization of EEGE to be 60.0. After subsequent polymerization with a mixture of monomers, GL and EEGE, it is evident from the ^{1}H NMR spectrum of the block copolymer (Figure 2b) that the residual EEGE was copolymerized with GL in the second stage of the polymerization. Therefore, the accurate expression of the block copolymer is PEEGE$_{54}$-*b*-(*hb*PG$_{38}$-*co*-PEEGE$_6$) for the block copolymer obtained in Table 1, run 5 (PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{62/38}$). By controlling the feed ratio of the monomers (EEGE/GL) from 33:67 to 95:5, the composition of EEGE and GL in the final product could be varied from 28:72 to 92:8. Samples of this type with different amphiphilicity were used for the micelle formulation study.

Micelle Formulation and Dye Encapsulation. To form micelles in selective solvents, we next assessed the solubility of the polymers (Table 2). As expected, PEEGE was insoluble in water but soluble in organic solvents. On the other hand, *hb*PG

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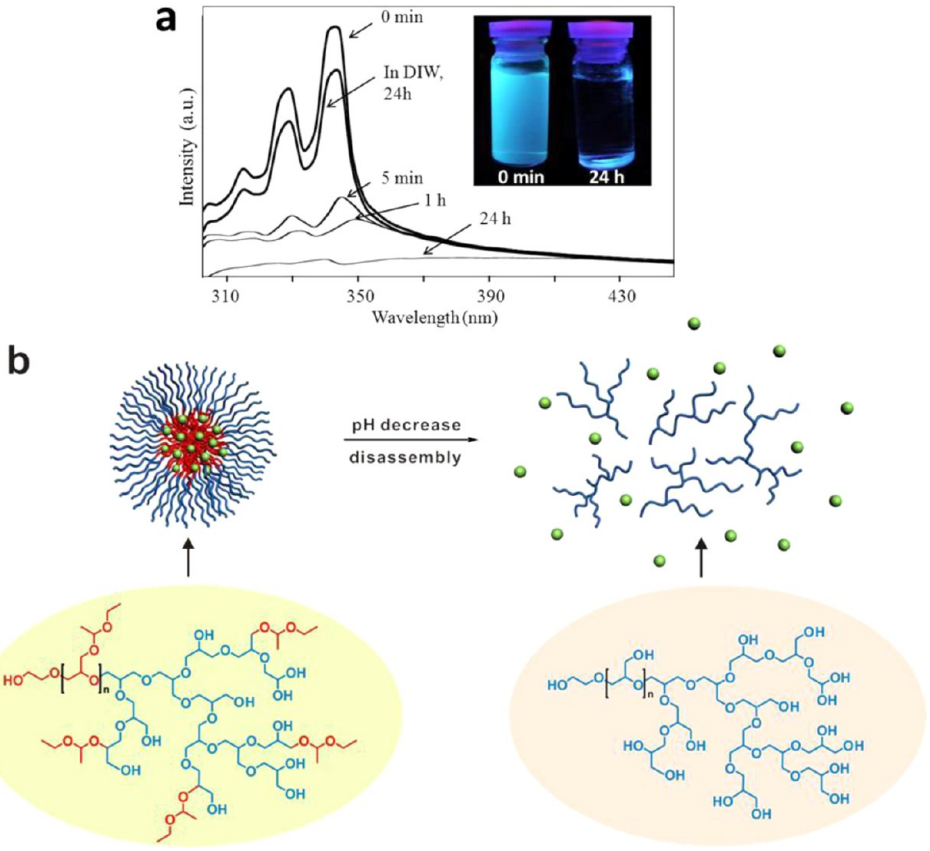

Figure 6. (a) Excitation spectrum changes of the pyrene-containing polymer micelle based on PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{83/17}$ at a concentration of 65.3 mg/L with and without PBS (pH = 5.8). Inset shows the solution before (left) and 24 h after (right) PBS treatment (pH 5.8). (b) Illustration of disassembly of the pyrene-containing polymer micelle under acidic conditions.

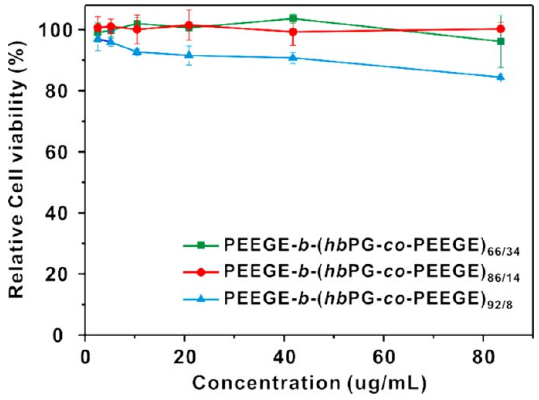

Figure 7. MTT-based cell viability of PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ micelles (square, 66/34; circle, 86/14; and triangle, 92/8).

was insoluble in methanol and many other organic solvents and was soluble only in water and DMF. *hb*PG$_{72}$-*b*-PEEGE$_{28}$ showed similar solubility to *hb*PG because of the excessive number of hydrophilic PG segments. PEEGE$_{48}$-*b*-*hb*PG$_{52}$ also showed a similar solubility to *hb*PG, but greater solubility in organic solvents, such as alcohols, because of the decreased hydrophilicity of the polymer. For PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ samples, all polymers except PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{62/38}$, which exhibited marginal solubility in water, showed good solubility only in organic solvents.

On the basis of solubility tests, the micelles were prepared by dissolving PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ in THF, followed by the slow addition of excess amounts of DI water with a subsequent dialysis process. The morphology of the micelles was investigated by TEM, as shown in Figure 3. In general, according to TEM images, the micelles were spherical ranging from 100 to 250 nm (Figure 3). With increasing hydrophobicity of the PEEGE segment, the size and the shape of the micelles became smaller and more spherical. The size of the micelles formed from the PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{92/8}$ sample was around 100 nm, according to TEM observations, but a broad distribution with an average diameter of 158 nm was observed in the DLS analysis, with occasional identification of large-sized aggregates. The relatively large size and broad size distribution of the micelles may possibly have two origins. First, the PEEGE segment has insufficient hydrophobicity because its main backbone PG is essentially hydrophilic in nature, and thus, the block copolymer is insufficiently amphiphilic to form a rigid stable micelle structure in water, compared with typical amphiphilic diblock copolymers such as PG-*b*-polystyrene and PG-*b*-polylactide. Second, the nondiscrete architecture of the PEEGE block with respect to PG prevents clear phase separation behavior during the micelle assembly.

For the investigation of model hydrophobic therapeutics, we used pyrene during the formation of the micelles. Figure 4a depicts the excitation spectra of pyrene in the presence of PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{86/14}$ at a concentration of 0−45.7 mg/L in water. With an increase in the concentration of the polymer sample, the intensity of the excitation spectra clearly increases, and the excitation band at 336.4 nm is shifted to 339.6 nm, indicating the incorporation of pyrene into the

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hydrophobic interior formed by the polymer micelle.[37,38] The fluorescence intensity ratio at 339.6 nm against 336.4 nm ($I_{339.6}/I_{336.4}$) is plotted with varying polymer concentration in Figure 4b, in which a clear crossover point can be observed at 1.32 for PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{86/14}$ in log *C*, corresponding to a CMC of 20.9 mg/L. Interestingly, we found that increasing the hydrophobic segment of PEEGE from 66/34 to 92/8 effectively decreased CMC values from 30.9 to 18.2 mg/L (Figure 5). This observation can be attributed to the increased hydrophobicity efficiently enhancing the segregation of the polymer block.

pH-Responsive Features. The pH-responsive nature of DDSs has been extensively investigated as an effective way of treating cancer cells. Recently, biocompatible PG-based polymeric micelles have been investigated as promising drug carriers with low toxicity for effective DDSs. In this study, we could tune the hydrophobicity of the PEEGE block to the hydrophilic PG block via simple acid-catalyzed deprotection of the ethoxyethyl group to afford a hydrophilic PG block copolymer. Once pyrene was loaded into the core of the micelles of PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{83/17}$, pH-adjusted PBS buffer (pH 5.8) was slowly added into the solution. As depicted in Figure 6, the fluorescence of pyrene dramatically decreased after 5 min of PBS injection, with a shift in the excitation peak from 339.6 to 336.4 nm. The corresponding image shows the pyrene-containing PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{83/17}$ solution in water and in PBS after 24 h, where the fluorescence of pyrene is only observed from the top of the vial because of the collapse of the amphiphilic block copolymer to exclusively hydrophilic PG-based block copolymers.

Finally, we investigated the potential of PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ block copolymers as a drug carrier from cytotoxicity studies. In vitro cytotoxicity of PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{66/34}$, PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{86/14}$, and PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{92/8}$ was investigated by a cell viability assay using a HuCC-T1 human cholangiocarcinoma cell line, as shown in Figure 7. PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ micelles show no cytotoxicity to cholangiocarcinoma cells. It is evident that the amphiphilic block copolymer of PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ is highly biocompatible and nontoxic. The stability of micelles in serum was found to be highly dependent on the fraction of the hydrophobic core segment within the polymer of PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{x/y}$ (x/y = 66/34, 86/14, and 92/8), such that the lower fraction samples like PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{66/34}$ and PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{86/14}$ become quite unstable, whereas the PEEGE-*b*-(*hb*PG-*co*-PEEGE)$_{92/8}$ with a more hydrophobic core block can hold the integrity of the micelles upon serum addition during the experiments.

CONCLUSIONS

In this study, we report the rapid one-pot synthesis of a PG-based block copolymer, PEEGE-*b*-(*hb*PG-*co*-PEEGE), and a micelle formulation−deformation study in DI water. The amphiphilic block copolymer was prepared by the sequential addition of EEGE with GL, and the composition of the block copolymers was successfully varied by adjusting the feed of the two monomers. The CMC was determined by the authentic fluorescence study, and the size of the micelle was measured by TEM and DLS analyses. The pyrene-containing micelle rapidly collapsed on exposure to acidic conditions, resulting in an all hydrophilic PG-based block copolymer. These results indicate that this type of biocompatible PG-based copolymer would be advantageous over conventional amphiphilic block copolymers for DDS applications because of the facile and potentially perfect removal of the polymeric residues after the drug release.

ASSOCIATED CONTENT

Supporting Information

Additional TEM image of PG micelles and additional fluorescence excitation spectra of all PG-based polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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