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Achieving Micelle Control through Core Crystallinity

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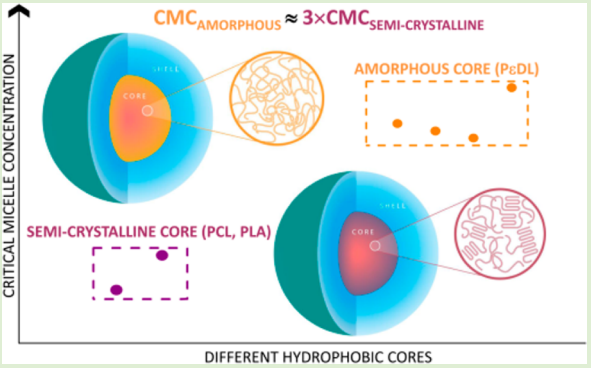
Supporting Information

ABSTRACT: We have designed a pathway for controlling the critical micelle concentration and micelle size of polyester-based systems. This was achieved by creating an array of different copolymers with semicrystalline or amorphous hydrophobic blocks. The hydrophobic block was constructed through ring-opening polymerization of ε-caprolactone, L-lactide, and ε-decalactone, either as homopolymers or random copolymers, using PEG as both the initiator and the hydrophilic block. Micelles formed with amorphous cores exhibited considerably higher critical micelle concentrations than those with semicrystalline cores. Micelles with amorphous cores also became larger in size with an increased molecular weight of the hydrophobic bock, in contrast to micelles with semicrystalline cores, which displayed the opposite behavior. Hence, core crystallinity was found to be a potent tool for tailoring micelle properties and thereby facilitating the optimization of drug delivery systems. The introduction of PEG-PεDL also proved to be a valuable asset in the tuning of micelle properties.



INTRODUCTION

Micelles are nanosized suprastructures of amphiphilic macromolecules that self-assemble in aqueous solutions into core−shell structures composed of hydrophobic cores stabilized by the hydrophilic coronas. The self-assembly occurs due to a phase separation induced by the incompatibility of the two blocks and acts to minimize the interaction of the hydrophobic block and the water molecules. The driving force for self-assembly is the lowering of surface tension.[1−3] The lipophilic environment formed in the micelle core is perfect for hydrophobic drug incorporation, and the hydrophobic interaction between a drug and the core is the primary mechanism of drug entrapment.[4] Drug release from micelles occurs through mechanisms such as diffusion[5] and core degradation.[6] The properties of the hydrophobic block (e.g., its composition and affinity to a drug) therefore control both drug entrapment and drug release.[7]

Numerous polymer combinations have been used in designing micelles for drug delivery applications. Poly(ethylene glycol) (PEG) is most frequently used as the stabilizing hydrophilic corona.[8] PEG is hydrophilic, biocompatible, and nontoxic. In addition, it has the ability to resist protein adhesion[9] and possesses "stealth properties". The term "stealth properties" refers to the ability of PEGylated micelles to avoid uptake by the reticuloendothelial system (RES) and thereby enables micelles to circulate in the blood for prolonged times. The hydrophobic component of the micelle is commonly composed of polyesters such as poly(ε-caprolactone) (PCL) and polylactide (PLA) because of their biocompatibility and biodegradability. PCL and PLA are commonly used for biomedical applications, for example, scaffolds for tissue engineering[10−12] and delivery systems.[13−15] Another polyester with promising properties for biomedical applications is PεDL.[16] This polymer can easily be prepared by conventional ring-opening polymerization of ε-DL, which is a naturally occurring monomer that can be obtained by fungal technology and is commercially available.[17] What makes it especially interesting is that the obtained polymer is amorphous.[16]

For micelles the critical micelle concentration (CMC) is an important property because it indicates both the polymer's ability to self-assemble in solution and the stability of the micelles once formed. The CMC is the concentration below which only single polymer chains exist and above which both micelles and single chains coexist.[2,18,19] For drug delivery applications, the CMC needs to be sufficiently low to withstand the severe dilution that accompanies intravenous injection[18] but at the same time be sufficiently high for the micelles to disassemble into single chains to facilitate polymer elimination from the body.[19] The ability to tailor the CMC is therefore imperative for the optimization of drug delivery systems. Another key characteristic is the micelle size. The size of a micelle determines its circulation time in the body and its distribution between organs.[20] Micelles smaller than 200 nm can avoid recognition by the RES, thereby eluding clearance from the body and prolonging their circulation times.[20,21] Small micelles will also accumulate in tumors because of the

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Table 1. Characterization of the Different Amphiphilic Copolymers in Terms of Composition and Molecular Weight Determined by SEC and ^{1}H NMR and the PDI Determined by SEC[a]

sample name	monomer	$M_{n,theoretical}$	M_n[a]	M_n[b]	PDI[b]	hydrophobic ratio[c]
PEG_{2k}-PCL_{1k}	CL	3000	2900	6200	1.2	0.5
PEG_{2k}-PCL_{2k}	CL	4000	3800	8200	1.4	1
PEG_{2k}-PCL_{3k}	CL	5000	4800	9900	1.5	1.5
PEG_{2k}-PCL_{4k}	CL	6000	6500	12000	1.2	2
PEG_{2k}-PεDL_{1k}	ε-DL	3000	3100	6200	1.1	0.5
PEG_{2k}-PεDL_{2k}	ε-DL	4000	4000	7400	1.1	1
PEG_{2k}-PεDL_{3k}	ε-DL	5000	4500	8600	1.1	1.5
PEG_{2k}-PεDL_{4k}	ε-DL	6000	6300	7400	1.1	2
PEG_{2k}-PLA_{2k}	LA	4000	4000	7500	1.2	1
PEG_{2k}-P$(CL/\varepsilon DL)_{2k}$	CL/ε-DL	4000	4200	6600	1.2	1
PEG_{2k}-P$(LA/\varepsilon DL)_{2k}$	LA/ε-DL	4000	4100	6300	1.1	1
PEG_{2k}-P$(CL/LA)_{2k}$	CL/LA	4000	3900	7400	1.2	1

[a]The molecular weights were calculated using ^{1}H NMR by integrating the methoxy peak of mPEG at 3.37 ppm and the peak for the repeating units of CL (at 4.06 ppm), ε-DL (at 0.86 ppm), and LA (at 5.17 ppm). [b]Determined by SEC using $CHCl_3$ as the eluent. [c]The hydrophobic ratio was defined as $M_{n,hydrophobic}/M_{n,hydrophilic}$, and $M_{n,hydrophilic}$ was held constant at 2000 (values obtained from ^{1}H NMR).

enhanced permeability and retention effect (EPR effect).[22] By controlling micelle size, the circulation time and distribution of these nanocarriers can be tailored.

The hydrophobic block of the amphiphile is known to play an important role in micelle formation;[3] therefore, the most straightforward method for modifying micelle characteristics, such as the CMC and micelle size, is to alter the hydrophobic block length or introduce different monomers into the core-forming block.[23−25] Increasing the molecular weight of the hydrophobic block while maintaining the hydrophilic block length will lead to desirable characteristics, such as lower CMCs. However, if the hydrophobic block is semicrystalline, then the molecular weight increase of the hydrophobic block will lead to an increase in core crystallinity and consequently a reduction in the drug loading capacity.[26] Due to the drug entrapment occurring only in amorphous parts of the core, micelles with amorphous cores should have an increased drug loading capacity compared to micelles with semicrystalline cores even though drug incorporation will lower the melting point of the crystalline domains and enable larger drug loading.

The tailoring of micelle characteristics has been focused on the development of different amphiphilic copolymers that induce specific micelle properties.[7,27,28] However, these modifications are only applicable to certain micelle systems, and the required procedures can be complicated and time-consuming. Our objective is therefore to design a pathway for controlling the critical micelle concentration and micelle size that is applicable to different polyester based systems. We hypothesize that by introducing ε-DL as a hydrophobic building block, the ability to obtain micelles with amorphous cores will be facilitated and, subsequently, that altering the crystallinity of the micelle core will induce a change in the self-assembly process. This will in turn affect the CMC and micelle size and thereby enable control over those properties. Although the impact of core crystallinity on micelle morphology has been extensively studied,[29−31] the influence of core crystallinity on CMC and micelle size has been neglected.

EXPERIMENTAL SECTION

Materials. L-Lactide (LA; Boehringer Ingelheim, France) was recrystallized twice from toluene, ε-caprolactone (CL, 97%, Sigma-Aldrich), and ε-decalactone (ε-DL, 99%, Sigma-Aldrich) were dried over CaH_2 and distilled under reduced pressure. Poly(ethylene glycol) monomethyl ether ($mPEG_{2k}$, Sigma-Aldrich) was dried under reduced pressure; stannous 2-ethylhexanoate ($Sn(Oct)_2$, 95%, Sigma-Aldrich) was dried over molecular sieves. HPLC-grade methanol (MeOH, Fisher Scientific), 1,6-diphenyl-1,3,5-hexatriene (DPH, 98%, Sigma-Aldrich), HPLC-grade chloroform (Fisher Scientific), and diethyl ether (99.8%, Sigma-Aldrich) were used without further purification.

Polymer Synthesis. All polymerizations were performed in bulk at 110 °C with 1 mol % of $Sn(Oct)_2$ as the catalyst and $mPEG_{2k}$ as the initiator. The reaction time varied depending on the chosen monomer and the hydrophobic block structure. LA and CL were reacted for 24 h, whereas ε-DL was reacted for 72 h. To ensure a high degree of transesterification, the random copolymers of CL/LA, CL/ε-DL, and LA/ε-DL were polymerized for 48 h.

Characterization. The chemical structure of the copolymers was determined and micelle formation was confirmed by ^{1}H NMR. $CDCl_3$ or D_2O was utilized as the solvent, and the spectra were referenced to the residual solvent peaks at δ = 7.26 or ∼4.8, respectively. The ^{1}H NMR spectra were obtained using a Bruker Avance 400 NMR spectrometer at 400 MHz. Before the acquisition, the NMR samples in D_2O were filtered using 0.45 μm Nylon syringe filters.

The number average molecular weights (M_n) and molecular weight distributions (polydispersity index, PDI) of the copolymers were obtained by size exclusion chromatography. A Verotech PL-GPC 50 Plus system was used with a PL-AS RT autosampler for PL-GPC, two Mixed-D columns (300 × 7.5 mm) from Varian, and a PL-RI detector. Chloroform was used as the mobile phase at 1 mL/min and 30 °C. The system was calibrated using polystyrene standards with narrow molecular weight distributions (580−400000). Toluene was used as the internal standard.

The thermal properties of the copolymers in bulk were analyzed by differential scanning calorimetry (DSC) using a Mettler Toledo DSC 820 module. A total of 4−8 mg of sample was placed in an aluminum cap (40 μL) and sealed with a lid. The atmosphere was kept inert during the experiment with a 50 mL/min nitrogen flow. The samples were heated at 10 °C/min to 200 °C, held at 200 °C for 10 min, cooled at 10 °C/min to −50 °C, held at −50 °C for 10 min, and finally heated at 10 °C/min to 200 °C. Runs were performed in triplicate, and the average value for each copolymer was reported. The melting enthalpies were taken from the last heating cycle in order to eliminate the impact of thermal history.

The critical micelle concentration (CMC) was measured for micelle solutions prepared by direct dissolution at different concentrations within the range of 0.001−25 mg/mL. To all of the solutions, 10 μL of 0.4 mM DPH (hydrophobic UV-probe) in MeOH was added per milliliter of solution.[32] UV−vis spectra were recorded on a UV-2401 UV−vis spectrophotometer.

Micelle solutions for size determination were prepared by the dissolution/evaporation method.[26] Typically, 50 mg of a copolymer

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was dissolved in 5 mL of acetone, and 0.6 mL of the polymer solution was added dropwise to 10 mL of deionized water under stirring. The acetone was allowed to evaporate overnight. Afterward, dynamic light scattering (DLS) measurements were performed using a Malvern Zetasizer Nano ZS at 25 °C. The size of the micelles was also measured after 4 weeks in aqueous solution to evaluate their stability. Before the measurements, all samples were filtered using 0.45 μm nylon syringe filters.

The morphology of the micelles was determined by scanning transmission electron microscopy (STEM) using a FE-SEM (Hitachi S-4800, Japan) equipped with a transmitted electron detector. The STEM samples were prepared by depositing a drop of a micelle solution onto a copper grid, and the water was subsequently allowed to evaporate. The micelle solutions for STEM were prepared by the dissolution/evaporation method using a 0.6 mg/mL polymer concentration.

RESULTS AND DISCUSSION

Micelles are an emerging class of self-assembled structures based on amphiphilic copolymers, aimed for controlled drug delivery applications.[1,19,33] The ability to tune their properties is therefore crucial. By using the crystallinity of the core-forming block as the main modifying parameter, we were able to tailor micelle properties such as the CMC and micelle size.

Characterization of Copolymers. *Polymer Synthesis.* A total of 12 different amphiphilic copolymers were synthesized to determine the influence of core crystallinity on micelle properties. PEG with a molecular weight of 2000 ($mPEG_{2k}$) was utilized as the hydrophilic block for all of the copolymers, while the hydrophobic blocks differed in molecular weight, chemical nature, and crystallinity.

The different ratios between the hydrophobic and hydrophilic blocks (hydrophobic ratios) were obtained by varying the total molecular weight of the copolymers from 3000 to 6000 (Table 1).

Copolymer synthesis was accomplished by ring-opening polymerization of the monomers using $mPEG_{2k}$ as the initiator and $Sn(Oct)_2$ as the catalyst. The monomers ε-DL, CL, and LA were chosen because they differ in both crystallinity and hydrophobicity. Copolymers with hydrophobic blocks containing homopolymers of ε-DL, CL, or LA were synthesized. In addition, three copolymers in which the hydrophobic blocks were copolymers of CL/ε-DL (PEG_{2k}-$P(CL/\varepsilon DL)_{2k}$), CL/LA ($PEG_{2k}$-$P(CL/LA)_{2k}$), and LA/$\varepsilon$DL ($PEG_{2k}$-$P(LA/\varepsilon DL)_{2k}$) were prepared; these three polymers were synthesized with a hydrophobic ratio of 1 and a total M_n of 4000. All of the polymerizations were stopped after full conversion. The copolymer composition was determined by ^1H NMR (Figure 1 and Supporting Information).

The molecular weights calculated from ^1H NMR were consistent with the theoretical M_n, whereas SEC overestimated the M_n (Table 1). This overestimation of M_n is consistent with previous observations for PLA and PCL in SEC experiments.[34] The decrease in M_n (as determined by SEC) from PEG_{2k}-$P\varepsilon DL_{3k}$ to PEG_{2k}-$P\varepsilon DL_{4k}$ is a result of the underestimation of PεDL in $CHCl_3$ SEC.[16] ^1H NMR spectra confirmed an approximate 50:50 molar ratio (mass ratio can be found in Supporting Information) between the two hydrophobic monomers in PEG_{2k}-$P(CL/LA)_{2k}$, PEG_{2k}-$P(LA/\varepsilon DL)_{2k}$, and PEG_{2k}-$P(CL/\varepsilon DL)_{2k}$. In addition, multiple peaks in the carbonyl region of their ^{13}C NMR spectra indicated that these hydrophobic blocks were random (Supporting Information).

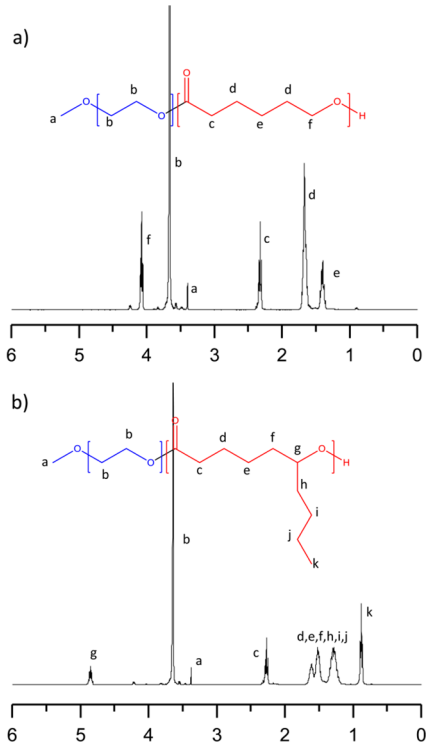

Figure 1. Structural characterization of (a) PEG_{2k}-PCL_{2k} and (b) PEG_{2k}-$P\varepsilon DL_{2k}$.

Thermal Properties. Differences in the thermal properties of the synthesized copolymers resulted primarily from differences in the crystallinity of the hydrophobic blocks. The polymers containing ε-DL[16] or two different monomers had an amorphous hydrophobic block, whereas the PEG-PCL copolymers and PEG_{2k}-PLA_{2k} exhibited a semicrystalline hydrophobic block (Figure 2 and Supporting Information).

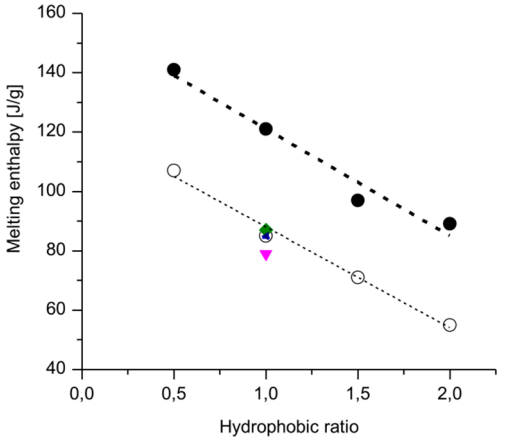

Figure 2. Melting enthalpies of PEG-PCL copolymers (●) and PEG-PεDL copolymers (○) with increasing hydrophobic ratios. The triangles and rectangles represent PEG_{2k}-PLA_{2k} and the copolymers with two different monomers in the hydrophobic block, respectively. The hydrophobic ratio was defined as $M_{n,hydrophobic}/M_{n,hydrophilic}$ and $M_{n,hydrophilic}$ was held constant at 2000 (values obtained from ^1H NMR). The melting enthalpies observed for PEG-PεDL copolymers arise only from the PEG block while for the semicrystalline copolymers, the reported enthalpy is the combined melting enthalpy of the hydrophilic and hydrophobic block.

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The amorphicity of PεDL is due to the racemic orientation of the butyl side group, which prevents PεDL from arranging and packing itself sufficiently tight to permit crystallization.[16] The amorphicity of the PEG-PεDL polymers and the copolymers with a hydrophobic block constituted of two different monomers (random structure) meant that the melting enthalpy arose only from PEG crystallization.

One of the advantages of having an amorphous core is the increase in accessible volume relative to that of a semicrystalline core; this increased volume should lead to increased drug loading capacity.[26] The differences between amorphous and semicrystalline structures regarding diffusion[35] and degradation behavior[36−38] also permit the tailoring of drug release properties by choosing one over the other.

The melting enthalpies decreased with increased hydrophobic ratios for both PEG-PCL and PEG-PεDL copolymers. The explanation for this observation is 2-fold. First, the increase in molecular weight leads to a decrease in chain mobility. This decrease in mobility rendered chain organization and crystallization more difficult, thereby lowering the melting enthalpy. Second, the crystallization process is influenced by the hydrophobic ratio. The ratio between PEG and PCL determined which of the blocks crystallized first and thus affected the crystallization of the other block.[39] Moreover, for PEG-PεDL copolymers, the amorphicity of the hydrophobic block influenced the ability of the PEG block to crystallize.

The melting enthalpies of the copolymers with two different monomers in the hydrophobic block were similar to that of PEG-PεDL copolymer with the same hydrophobic ratio of 1 (Figure 2, triangular and rectangular dots), which further confirmed the amorphous nature of these hydrophobic blocks. The DSC experiments were conducted on the bulk material. It should therefore be noted that the thermal properties of the copolymers might be altered when their respective micelles are formed in solution. For example, in solution, the PEG blocks will not crystallize; they will instead dissolve in the specific solvent. DSC measurements on PEG-PCL copolymers performed in the micelle state have previously shown that crystallization of the core does occur,[40] and ^{13}C CP-MAS NMR has also been used to determine the crystallinity of PLLA microspheres.[41] Hence, the given melting enthalpies should be considered as indicative of the hydrophobic cores ability to crystallize rather than giving an exact value of the crystallinity in the micelle state. The degree of crystallinity was not calculated because of the complex nature of copolymer crystallization, which depends on factors such as the compositions of the blocks and their molecular weights.[39]

Micelle Preparation and Characterization. *Self-Assembly Behavior.* The self-assembly of the copolymers, both the previously made and the newly introduced, in water was confirmed by ^1H NMR. Copolymer spectra were taken in D_2O (selective for the PEG block) and $CDCl_3$ (mutual solvent; Figure 3 and Supporting Information). The spectrum of PEG_{2k}-$P\varepsilon DL_{2k}$ in $CHCl_3$ (Figure 3a) exhibited peaks for both the PEG and PεDL block. By contrast, the D_2O spectrum (Figure 3b) exhibited only PEG peaks. As expected, these data verified that the copolymers self-assembled into micelles with the PEG blocks acting as the shells shielding the hydrophobic cores.[42] In addition, the morphology of PEG_{2k}-$P\varepsilon DL_{2k}$ and PEG_{2k}-PCL_{2k} micelles was determined (Supporting Information).

Critical Micelle Concentration. The CMC is an important property of a micelle solution that indicates a polymer's ability to self-assemble and the stability of its micelles once formed.[2,18]

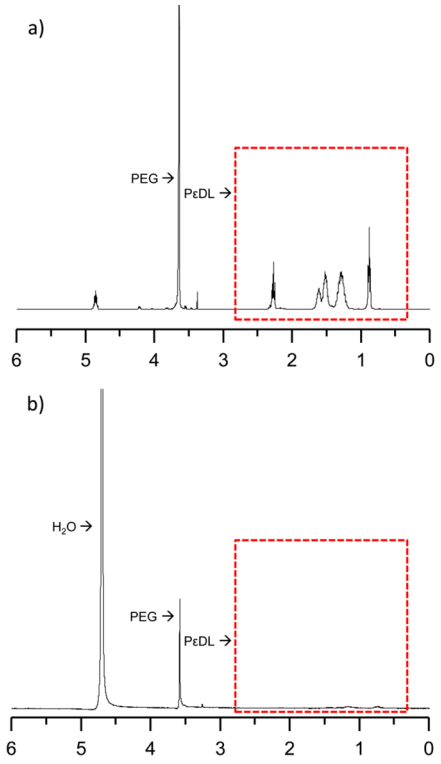

Figure 3. Evidence of the self-assembly of PEG_{2k}-$P\varepsilon DL_{2k}$. ^1H NMR in (a) $CDCl_3$ and (b) D_2O.

The CMCs of both PEG-PεDL and PEG-PCL copolymers decreased with increased hydrophobic ratios (Figure 4). The CMC decrease is a result of an increase of surface tension that occurs with increased hydrophobic ratios and means that the driving force (lowering of surface tension) for self-assembly is increased as well.[43,44]

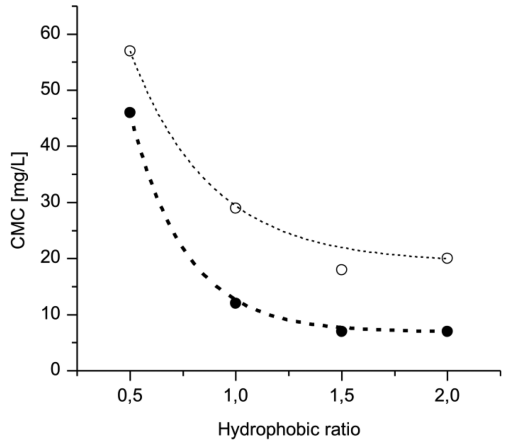

Figure 4. Decrease of CMC with increased hydrophobic ratios of PEG-PCL (●) and PEG-PεDL copolymers (○). The hydrophobic ratio was defined as $M_{n,hydrophobic}/M_{n,hydrophilic}$, and $M_{n,hydrophilic}$ was held constant at 2000 (values obtained from ^1H NMR).

Higher CMCs were obtained for the PEG-PεDL micelles with amorphous cores than for PEG-PCL micelles with semicrystalline cores (Figure 4). There are two contributing reasons explaining this behavior. The most probable reason is the differences in core crystallinity; where the crystallization process itself may have acted as an additional driving force for

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self-assembly.[45] Consequently, the PEG-PCL copolymers will have a higher total driving force for self-assembly, resulting in lower CMC compared with that of the amorphous PEG-PεDL copolymers. The other reason is that the ε-DL side group may disrupt the self-assembly process. The PEG-PεDL copolymers form micelles only when the hydrophobic effect overcame the bulky structure, resulting in higher CMCs than those for the PEG-PCL copolymers.

To support our assertion that the CMC differences resulted primarily from differences in core crystallinity and not from the differences in structure, micelle solutions of the copolymers with random hydrophobic blocks (PEG_{2k}-$P(CL/\varepsilon DL)_{2k}$, PEG_{2k}-$P(CL/LA)_{2k}$, and PEG_{2k}-$P(LA/\varepsilon DL)_{2k}$), as well as PEG_{2k}-PLA_{2k} were characterized.

All of the micelles with amorphous cores had significantly higher CMCs than those with semicrystalline cores (Figure 5)

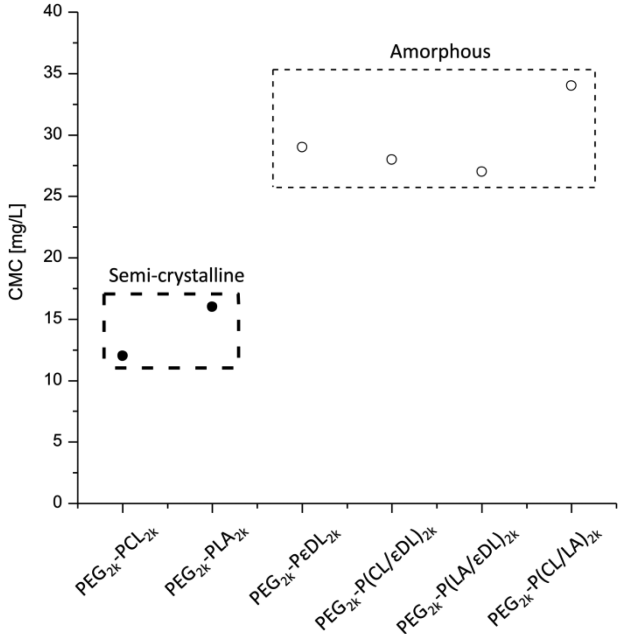

Figure 5. Difference in CMCs between the micelles with semicrystalline cores (●) and those with amorphous cores (○). All of the copolymers had a hydrophobic ratio of 1 and a $M_{n,hydrophilic}$ of 2000 (values obtained from ^{1}H NMR).

and thereby confirmed our hypothesis. These results indicate that the crystallinity of the core plays a larger role during micelle self-assembly than chemical structure. Moreover, PεDL is more hydrophobic than PCL, and it should therefore give rise to lower CMC because of increased surface tension.[2] However, the opposite trend was observed. This observation suggests that the crystallinity of the core has a larger influence on self-assembly than the cores hydrophobicity.[1,3]

Micelle Size. The size of the micelles determines the circulation time and distribution of the particles in the body.[20−22] PEG-PεDL micelles increased in size with increasing hydrophobic ratio (Figure 6). As the M_n of the hydrophobic block increased, the core volume increased, resulting in larger micelles. By contrast, the PEG-PCL micelles decreased in size as the hydrophobic ratio increased (Figure 6). These observations are most likely results of the changes in core crystallinity and hence the core's ability to pack tightly in the crystalline regions, which influences the core size and thereby the micelle size.

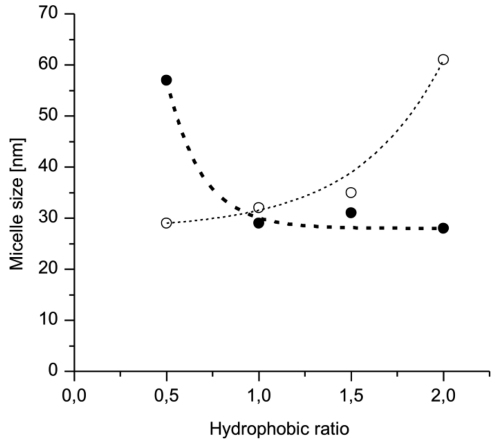

Figure 6. The trends in micelle size observed for semicrystalline PEG-PCL (●) and amorphous PEG-PεDL (○) micelles as the hydrophobic ratio was increased. The hydrophobic ratio was defined as $M_{n,hydrophobic}/M_{n,hydrophilic}$, and the $M_{n,hydrophilic}$ was held constant at 2000 (values obtained from ^{1}H NMR).

The drug loading capacity is directly influenced by the size of the micelle core and increases with increasing core size.[46] The overall micelle size differences were solely due to a change in core size because the PEG block was kept constant. This fact implies that when the hydrophobic ratio is increased, the drug loading capacity should increase for the PEG-PεDL copolymers and decrease for PEG-PCL copolymers.

Micelles with semicrystalline cores and those with amorphous cores exhibited distinctly different trends in size as a function of the hydrophobic ratio (Figure 6). However, no discernible difference was observed between the semicrystalline and amorphous micelles when the hydrophobic ratio was held constant (Table 2).

Table 2. Micelle Size of the Copolymers with the Hydrophobic Ratio of 1 and a $M_{n,hydrophilic}$ of 2000 (Values Obtained from ^{1}H NMR)

sample name	size[a] (nm)	PDI (nm)	hydrophobic ratio	crystallinity of core
PEG_{2k}-PCL_{2k}	29	0.2	1	semicrystalline
PEG_{2k}-PLA_{2k}	57	0.6	1	semicrystalline
PEG_{2k}-PεDL_{2k}	27	0.2	1	amorphous
PEG2k-$P(CL/\varepsilon DL)_{2k}$	41	0.3	1	amorphous
PEG_{2k}-$P(LA/\varepsilon DL)_{2k}$	24	0.2	1	amorphous
PEG_{2k}-$P(LA/CL)_{2k}$	27	0.2	1	amorphous

[a] z-Average value.

In conclusion, the clear trends observed for PEG-PCL and PEG-PεDL copolymers demonstrated that the crystallinity of the micelle core influenced the size of the micelles. No clear relationship between the core hydrophobicity and micelle size existed.

Micelle Stability. The shelf life of the micelles was determined by measuring the size of the micelles after 4 weeks in aqueous solution at room temperature. No change in micelle size was observed, which indicated that the micelle solutions were stable (Supporting Information).

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CONCLUSIONS

We successfully controlled the critical micelle concentration and micelle size of polyester based systems solely by modifying the core crystallinity, thereby establishing this as a strategy for tailoring of the CMC and micelle size. The alteration of the core crystallinity was simplified by the use of the amorphous PεDL as the hydrophobic block, which as amphiphiles with PEG formed micelles with tailorable CMCs and sizes.

We demonstrated that micelles with amorphous cores (PEG-PεDL and the copolymers with random hydrophobic blocks) have higher CMCs than those with semicrystalline cores (PEG-PCL and PEG-PLA). Additionally, the variation in micelle size clearly revealed the difference between micelles with semicrystalline and amorphous cores. For the amorphous PEG-PεDL copolymers, an increase in the molecular weight of the hydrophobic block led to an increase in micelle size; conversely, the semicrystalline PEG-PCL copolymers exhibited the opposite trend.

The ability to tailor the CMC and micelle size simply by altering the micelle core crystallinity is a step toward optimizing drug delivery systems.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for the copolymers and a table of the exact melting enthalpies and of the micelle stability, as well as the STEM micrographs. 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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