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Novel polymeric micelles for hydrophobic drug delivery based on biodegradable poly(hexyl-substituted lactides)

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Abstract

Novel amphiphilic methoxy-poly(ethylene glycol)-poly(hexyl-substituted lactides) block copolymers were synthesized by ring-opening polymerization (ROP) of mono and dihexyl-substituted lactide (mHLA and diHLA) in bulk at 100 °C in the presence of tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) as catalyst and methoxy-poly(ethylene glycol) (MPEG) as initiator. MPEG-PmHLA and MPEG-PdiHLA copolymers of predictable molecular weights and narrow polydispersities were obtained, as shown by ^{1}H NMR and GPC. DSC experiments showed that the MPEG-PHLA block-copolymer presents a bulk microstructure containing MPEG domains segregated from the PHLA domains. Micelles were successfully prepared from these block copolymers, with sizes ranging from 30 to 80 nm. The critical micellar concentration (CMC) was found to decrease with the increasing number of hexyl groups on the polyester block (MPEG-PLA > MPEG-PmHLA > MPEG-PdiHLA) for copolymers of the same composition and molecular weight. The hydrophobicity of the micelle core in dependence of the number of hexyl groups along the PLA chain was evidenced by absorbance experiments with the incorporation of the dye Nile Red. These novel amphiphilic copolymers are interesting for micellar drug delivery and especially in regard to optimized hydrophobic drug loadings, as it was shown for griseofulvin as a model drug.

Keywords: Micelles; Drug delivery; Substituted poly(lactides); Poly(ethylene glycol); Biodegradable polymers; Biocompatible polymers; Hydrophobic drugs; Nile Red; Griseofulvin

1. Introduction

Due to their biocompatible and biodegradable properties, amphiphilic PEG-PLA or PEG-PLGA block-copolymer micelles have been extensively studied over the past few decades as drug carriers (Kataoka et al., 2001; Yasugi et al., 1999; Riley et al., 2001; Lin et al., 2003) and particularly recently for the delivery of anti-cancer drugs (Yoo and Park, 2001; Zhang et al., 2005). Such di-block copolymers can self-assemble in aqueous medium to form spherical micelles of about 50 nm with the core formed by the hydrophobic polylactide and the surrounding hydrophilic PEG shell. The latter stabilizes the surface in aqueous systems and ensures a long half-life in the blood compartment due to the reduced interaction with the biological components (Gref et al., 1995). Many hydrophobic drugs can be easily entrapped in the core of these micelles, but reported drug loadings are often low and need to be improved to be interesting for medical applications. In order to increase the hydrophobicity of the core-building polymer chemical modifications of PEG-poly(aspartic acid) and PEG-poly(aspartamides) by introducing acyl chains were initially reported by Yokoyama et al. (1998) and Kwon et al., respectively (Li and Kwon, 2000; Adams and Kwon, 2002). We recently described the potential of chemically modified PLAs in form of novel poly(hexyl-substituted lactides) PHLA as alternatives to standard PLA with regard to drug release, degradability and injectability (Trimaille et al., 2004, in press). The use of these hydrophobic alkyl-substituted PLA in combination with PEG is interesting for drug delivery due to their micelle size, drug loading and degradability. We describe here the synthesis and characterization of these novel amphiphilic block copolymers, as well as the preparation and properties of the micelles in regard to their encapsulation capacity of the dye Nile Red and griseofulvin (GF) as a hydrophobic model drug. The results are discussed and compared with standard

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PLA-PEG di-block copolymers of same molecular weights and composition.

2. Materials and methods

2.1. Materials

Heptaldehyde and 2-bromopropionyl bromide were purchased from Fluka (Buchs, Switzerland). D,L-Lactide from Purac Biochem (The Netherlands) was delivered under vacuum and directly transferred into a glove-box for storage. MPEG (M_n = 2000 g/mol) was kindly provided by BASF (Germany) and carefully dried and stored under vacuum before use. Tin(II) 2-ethylhexanoate ($Sn(Oct)_2$) and griseofulvin (GF) were purchased from Sigma (Buchs, Switzerland). Solvents were dried by standard methods and distilled prior to use. The mono- and di-hexyl-substituted lactides (mHLA and diHLA, respectively) were synthesised by the procedures described in a previous publication (Trimaille et al., 2004).

2.2. Polymer synthesis and characterization

Polymerizations were typically run with 1.0 g of monomer in bulk (mono and di hexyl-substituted lactide) or in toluene (D,L-lactide) in the presence of $Sn(Oct)_2$ as catalyst. MPEG (M_n = 2000 g/mol) was used as "macro" alcohol initiator with a molar ratio of $Sn(Oct)_2$/MPEG = 0.5.

A reaction flask containing a stir bar was fitted with a septum, flame-dried under vacuum, and placed into a glove-box, where the monomer was filled in. In a typical procedure (for a targeted degree of polymerization [DP] of 15), 1.0 g monohexyl-substituted lactide (4.67 mmol) was heated until melting and 300 μL $Sn(Oct)_2$ from a stock solution (0.205 g/mL in dry THF) and 1.0 mL MPEG from a stock solution of 0.6 g/mL in dry THF (0.30 mmol) were added under argon atmosphere, and the mixture was heated to 100 °C, with the THF being rapidly removed from the flask. At the desired reaction time the reactions were stopped by adding 5 mL of non-dry THF, followed by precipitation in diethyl ether or hexane, solvents removal, and drying at 40 °C under vacuum. Polymerization conversions and DP were determined by ^{1}H NMR analysis, and molecular weights and polydispersities by gel permeation chromatography (GPC).

The ^{1}H NMR spectra were recorded in deuterated chloroform with a Bruker spectrometer (300 MHz). GPC was carried out on a Waters chromatography system mounted with Styragel HR 1–4 columns (Waters) and connected to a Waters 410 differential refractometer. THF was the continuous phase and polystyrenes of known molecular weights: 500, 2630, 5970, 9100, 37,900 and 96,400 g/mol (Tosoh Corporation) were used as calibration standards.

3. DSC measurements

Thermal analyses of the polymers were performed with a differential scanning calorimeter (SSC/5200, Seiko Instruments). Heating was done with a rate of 10 °C/min under nitrogen, and the temperature was calibrated with an indium standard.

4. Micelle preparation and characterization

4.1. Micelles with and without incorporated Nile Red

Twenty milligram purified copolymer were dissolved in 2 mL acetone. The solution was then added dropwise (1 droplet/3 s) into 4 mL milli-Q water under stirring. The acetone and a part of the water were removed under reduced pressure to reach a typical micelle concentration of 5.2 mg/L. The mean size of the micelles was determined by quasi-elastic light scattering (QELS) with a scattering angle of 90° at 25 °C using a Malvern Zetasizer 3000HS (UK), equipped with a He–Ne laser (633 nm).

4.1.1. Nile Red absorbance experiments on blank micelles

Twenty microliters of a stock solution of Nile Red (0.97 mg/mL in THF/acetone 1/2) were added to 1.5 mL of micelle solutions from each copolymer (MPEG-PLA, -PmHLA, -PdiHLA of same M_n and composition) of a given concentration of 2.1 mg/mL. For control a PEG solution (2.1 mg/mL H_2O) and pure water were also incubated with Nile Red. The solutions were equilibrated in the darkness overnight, and the THF and acetone evaporated. UV–visible spectra of each solution were recorded from 450–650 nm and corrected with the measurements of the corresponding control solutions prepared without Nile Red.

4.1.2. Critical micellar concentration (CMC) determination of blank micelles

Fluorescence measurements were performed with Nile Red to determine the CMC. Different dilutions were prepared from a 5 mg/mL stock solution of micelles to obtain samples of concentration ranging from 0.0001 to 1 mg/mL. Then 2 μL of a Nile Red stock solution in acetone (0.97 mg/mL) were added to 200 μL of each sample, and the acetone was evaporated. Fluorescence measurements were performed using a Safire (Tecan) microplate reader in a 96-well plate. Emission spectra were recorded from 560 to 750 nm using a λ_{exc} = 550 nm. The CMC was determined at the inflection point on the plots representing the maximum emission wavelength as a function of the copolymer concentration, as previously described by Coutinho et al. (2002).

4.2. Micelles with incorporated griseofulvin (GF)

Twenty milligram purified copolymer and different amounts of griseofulvin (GF) were dissolved in 2 mL acetone. The solution was then added dropwise (1 droplet/3 s) into 4 mL milli-Q water under stirring. The acetone and a part of the water were removed under reduced pressure to reach a typical micelle concentration of 5.2 mg/L. The mean size of the micelles was determined by quasi-elastic light scattering (QELS) with a scattering angle of 90° at 25 °C using a Malvern Zetasizer 3000HS (UK), equipped with a He–Ne laser (633 nm).

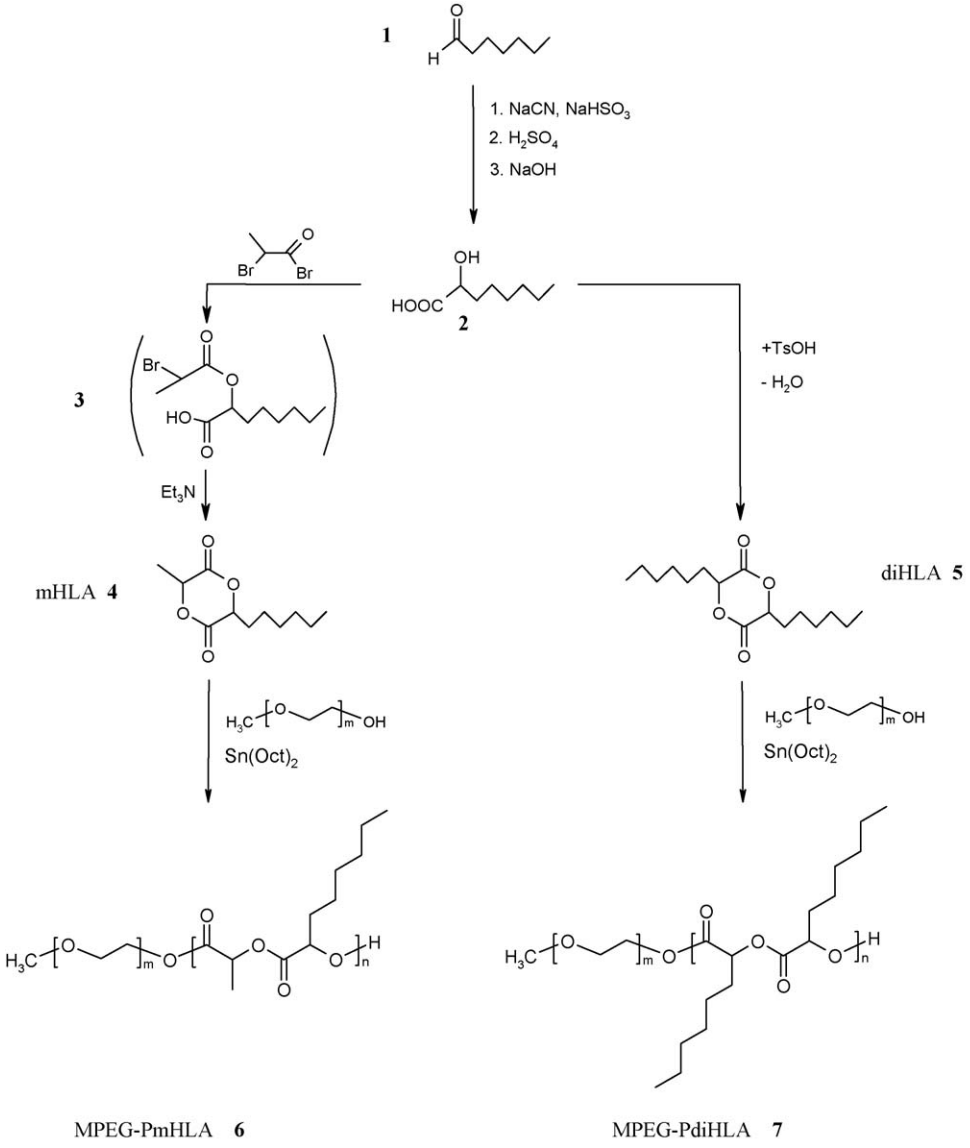
4.3. Measurements of griseofulvin incorporation with HPLC

The griseofulvin micellar solutions were prepared as described above and afterwards centrifuged at 6000G for 7 min to remove the non-entrapped GF. Then 100 μL of the micelle solution were dissolved in 900 μL acetonitrile to destroy the micellar structures and assay the encapsulated amount of GF. For the analyses a Waters HPLC system with a pump (Waters 600E controller), an autoinjector (Waters 717 plus autosampler), an UV detector (Waters 2487) and an integrator (Millenium software, Waters), and a Nucleosil 100–5 C18 column (Macherey-Nagel® Gmbh & Co., Düren, Germany) with 5 μm particle size, 250 mm length and 4 mm inner diameter was used. The mobile phase was a mixture of 45 mM potassium dihydrogen phosphate solution in Milli-Q water and acetonitrile (45% vol). Pyrophosphoric acid was used for maintaining a pH 3, and the solution was degassed with helium prior to use. The measurements were run with a flow rate of 1 mL/min. Standard solutions of GF in water/acetonitrile (1/9) of concentrations ranging from 2 to 18 μg/mL were prepared for calibration. The typical retention time of GF was 9.5 min monitored at 293 nm. It was verified that PEG-P(H)LA copolymers caused no interference at this wavelength.

5. Results and discussion

5.1. Synthesis and characterization of amphiphilic PEG-PHLA co-polymers and micelles

In our previous work we reported the synthesis and ring-opening polymerization (ROP) of alkyl-substituted lactide monomers for the design of novel functionalized polylactide materials (Trimaille et al., 2004). We particularly focused on the mono and di hexyl-substituted lactide (mHLA and diHLA, respectively), of which biodegradable polymers with interesting



Scheme 1. Synthesis of the mHLA **4** and diHLA **5** monomers, and MPEG-PmHLA **6** and MPEG-PdiHLA **7** from heptaldehyde.

Table 1
Characteristics of the copolymers obtained by ROP of the different lactides with MPEG 2000 g/mol as initiator

Name	Monomer	Time (h)	Lactide DP		Lactide	PEG/PHLA (wt.%)		M_n (g/mol)	M_w/M_n
			Target	Experiment	Conversion (%)	Feed	Experiment		
MPEG2-PLA3	D,L-LA	1	15	15	95	48/52	42/58	4800	1.18
MPEG2-PmHLA3	mHLA	1.5	15	13	94	38/62	39/61	5050	1.18
MPEG2-PmHLA5	mHLA	1.5	30	27	90	24/76	28/72	7100	1.17
MPEG2-PdiHLA3	diHLA	4	20	12	>90	26/74	38/62	4750	1.29

physical properties in comparison to standard PLA/PLGA could be obtained (Trimaille et al., in press). The novel PmHLA and PdiHLA homopolymers with their low glass transition temperatures are viscous at room temperature, and thus easily injectable polylactides in comparison to the solid PLA/PLGAs of same molecular weights, whereby the degradation and drug release are very similar. Here we present our studies on the potential of these hydrophobic polylactides in combination with hydrophilic PEG as novel amphiphilic block copolymers. The mono hexyl-substituted lactide (mHLA) synthesis is based on a "two step one pot" reaction of 2-hydroxyoctanoic acid **2**, easily synthesized in large scale from heptanal **1** with 2-bromopropionyl bromide leading to an intermediate ester **3**, which undergoes ring-closing after changing to basic reaction conditions with triethylamine (Scheme 1). The diHLA **5** was synthesized by the simple condensation reaction of the 2-hydroxyoctanoic acid **2** with *p*-toluenesulfonic acid in a Dean–Stark apparatus. The di-block MPEG-PmHLA **6** and MPEG-PdiHLA **7** copolymers were synthesized by ring-opening polymerization (ROP) of the mHLA **4** and diHLA **5**, respectively. The ROP were carried out in bulk at 100 °C using Methoxy-PEG-OH 2000 g/mol (DP ~45, referred as MPEG2) as an initiator and the FDA-approved tin-2-ethylhexanoate ($Sn(Oct)_2$) as catalyst with a molar ratio of $Sn(Oct)_2$/MPEG = 0.5. Both initiator and catalyst were used from stock solutions in THF, whereby the solvent was removed from the reaction flask in the beginning of the polymerization. Standard D,L-lactide was polymerized under the same reaction conditions.

The results of the ROP of the different MPEG-lactide copolymerizations are presented in Table 1. First, ROP was performed with a targeted DP of 15 for both mHLA and D,L-lactide. A polymerization time of 1 h appeared sufficient to reach a nearly complete conversion for D,L-lactide (95%). Since the conversion obtained for mHLA after the same polymerization time was a bit lower (84%), this is due to the steric hindrance of the hexyl side groups, the ROP of mHLA was performed for 1.5 h to give a comparable good conversion of 94%. A polymerization time of 1.5 h was also sufficient to reach an acceptable conversion of the mHLA for a targeted DP of 30 (90%). A prolonged time of 4 h was required to obtain a good conversion of >90% for the even more sterically hindered diHLA. In the following, the copolymers will be referred as MPEG*x*-P(H)LA*y* where *x* and *y* represent the M_n of the MPEG and P(H)LA blocks in kg/mol, respectively. For example the copolymer MPEG2-PHLA3 consists of a MPEG block with a M_n = 2000 g/mol and a PmHLA block of M_n = 3000 g/mol.

All copolymer molecular weights were close to those targeted, with narrow polydispersities (M_w/M_n ~1.15), indicating that the polymerizations were well controlled. The complete shift of the retention time peak observed by GPC analysis for MPEG-PmHLA compared to MPEG showed that the MPEG-macro-alcohol initiated the polymerization well (Fig. 1). As an example for the polymer characterization the ^{1}H NMR spectrum of the MPEG-PHLA copolymer after purification by precipitation in hexane is presented in Fig. 2. Both MPEG and lactide proton peaks could be clearly identified, and the composition of the copolymer could be determined from the peak integrals of the CH_2 protons of the PEG and the methine protons of the hexyl lactide. The block-copolymer compositions were close to those expected (see Table 1), confirming that the ROP were well controlled.

5.2. Analysis of the copolymer microstructure by DSC

DSC experiments were performed on MPEG-PHLA copolymers to elucidate the copolymer microstructure. The results are presented in Fig. 3 on the example of MPEG-PmHLA copolymers. As references, both the PmHLA5 and MPEG2, respec-

Fig. 1. GPC chromatograms of the MPEG2-PmHLA3 and MPEG2 polymers.

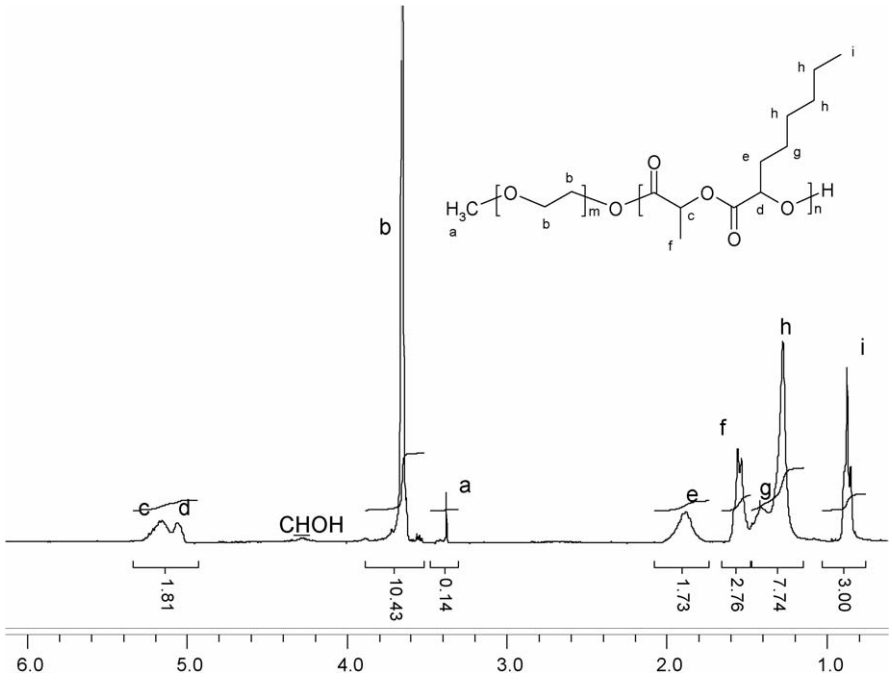


Fig. 2. ^{1}H NMR spectrum of MPEG2-PmHLA3 (300 MHz, $CDCl_3$).

tively, homopolymers were analyzed first. PmHLA5 is an amorphous polymer showing a low $T_g = -16\,^{\circ}C$, whereas MPEG2 is highly crystalline, showing a melting peak $T_m = 56\,^{\circ}C$. The DSC spectra of the MPEG-PHLA block-copolymers showed the characteristics of both homopolymers, demonstrating that the copolymer present a bulk microstructure containing MPEG domains segregated from PmHLA domains. However the shift of both melting and glass transition temperatures, compared to the homopolymers, show that there are also interactions between both polymer chains. This can be attributed to the covalent attachment of both polymer blocks, limiting the mobility of the MPEG- as well as the PmHLA-chains. With the increase of the chain length of the PmHLA segment in the block copolymer MPEG2-PmHLA5, the melting temperature derived from the PEG block shifted to lower values from $T_m = 56$ to $36\,^{\circ}C$, together with a decrease in the peak intensity. This demonstrates a less pronounced crystallinity in the PEG block of the copolymer. The glass transition temperatures of the copolymers ($T_g = -12.4$ and $-13\,^{\circ}C$) were slightly increased compared to the one of the PmHLA homopolymer ($T_g = -16.2\,^{\circ}C$), which probably is also due to a reduced mobility of the PmHLA segments, when covalently bound in the copolymer.

DSC analysis for the MPEG2-PdiHLA3 copolymer showed typically the same profile, as presented for MPEG-PmHLA, with a T_m of $38\,^{\circ}C$ and a T_g of $-42\,^{\circ}C$, whereby the T_g of the PdiHLA homopolymer of $M_n = 5600$ g/mol is $-47\,^{\circ}C$ (Trimaille et al., 2004).

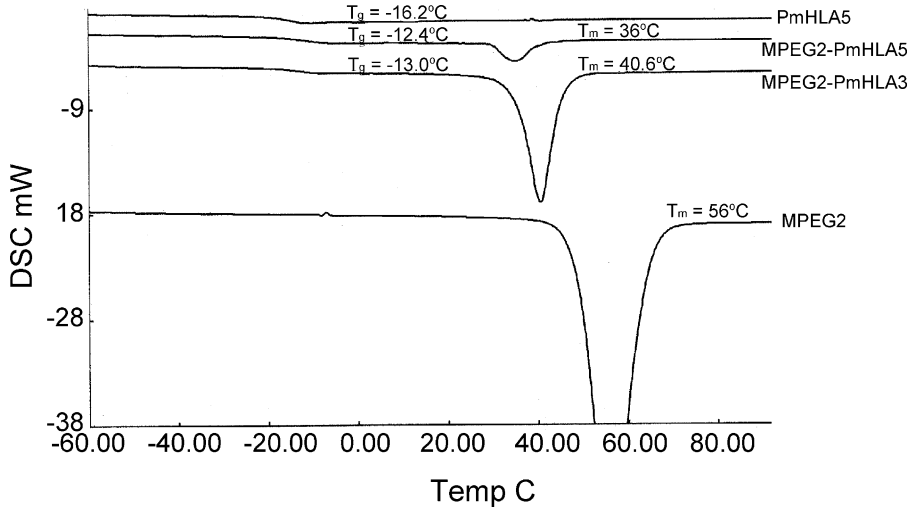


Fig. 3. DSC chromatograms of MPEG2 and PmHLA5 homo polymers, and MPEG2-PmHLA3 and MPEG2-PmHLA5 copolymers.

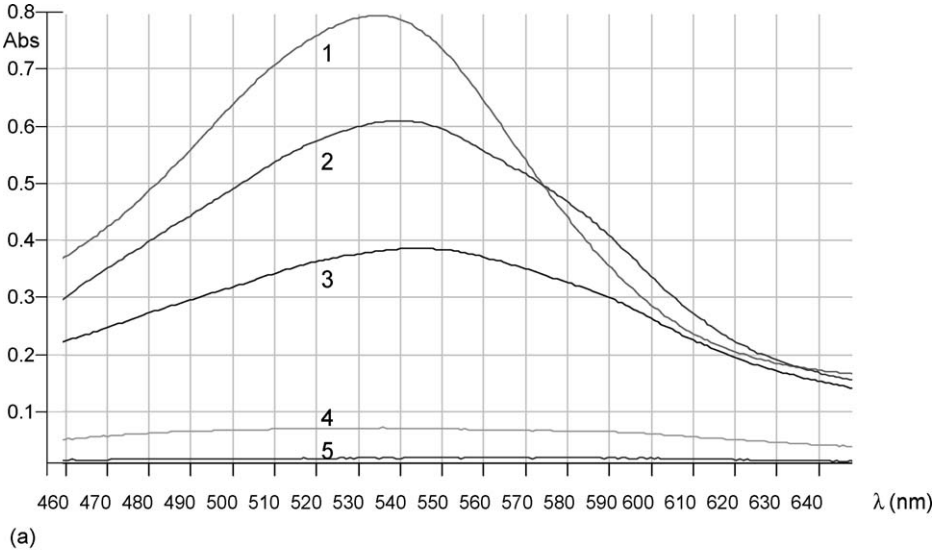
Table 2
Mean size (determined by quasi-elastic light scattering measurements, in triplicate) of the blank and GF-loaded micelles prepared from the different copolymers

Copolymer	Micelle mean size in nm (PI)[a]			
	0 mg/g GF[b]	10 mg/g GF[b]	30 mg/g GF[b]	40 mg/g GF[b]
MPEG2-PLA3	63.9 ± 1.2 (0.50)	70.0 ± 0.5 (0.53)	79.2 ± 0.1 (0.50)	19.3 ± 0.1 (0.10)
MPEG2-PmHLA3	77.4 ± 0.6 (0.60)	50.5 ± 0.1 (0.47)	30.4 ± 0.7 (0.30)	43.5 ± 1.1 (0.31)
MPEG2-PdiHLA3	29.1 ± 0.2 (0.26)	52.7 ± 0.4 (0.51)	32.5 ± 0.6 (0.33)	39.4 ± 0.4 (0.37)

[a] Determined by quasi-elastic light scattering (QELS) (polydispersity (μ_2/Γ^2)).
[b] Added amount of GF in milligram per gram of copolymer for micelle preparation.

5.3. Micelle preparation and characterization

The amphiphilic nature of the diblock copolymers, consisting of a hydrophobic P(H)LA and a hydrophilic PEG segment, provides the opportunity to form micelles in water with a PLA core and a PEG shell. MPEG2-PLA3, MPEG2-PmHLA3, MPEG2-PdiHLA3 copolymers, with the same molecular weight (∼5000 g/mol) and composition (PEG/PLA ∼40/60 in wt.%) were used for the micelle preparation. The "blank" polymeric micelles were prepared by a solvent evaporation method using acetone (see experimental part). The organic solvent was removed under reduced pressure after the micelle preparation. The mean size of the micelles was determined by QELS measurements at 90 °C, and the results are presented in Table 2 ("blank" micelles without griseofulvin are represented in the column "0 mg/g"). The smallest micelles were observed for the MPEG2-PdiHLA3 copolymer with 30 nm mean diameter compared to about 70 nm for the analogs MPEG2-PLA3 and MPEG2-PmHLA3. This can be explained by the higher hydrophobicity of the polylactide block with the increased number of hexyl groups along the chain, favouring a stronger shrinkage upon addition of the water as the non-solvent during the micelle preparation. The polydispersity index obtained by QELS was rather high (>0.2), but in fact a multimodal analysis showed



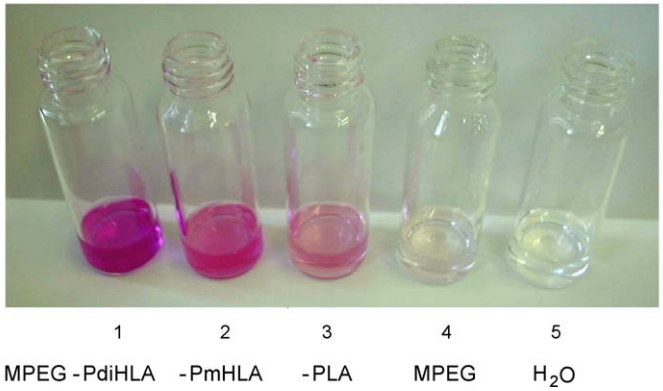


Fig. 4. Absorbance spectra (a) and photographs (b) of the Nile Red loaded solutions: (1) MPEG2-PdiHLA3 micelles (2.1 mg/mL); (2) MPEG2-PmHLA3; (3) MPEG2-PLA3; (4) PEG solution (2.1 mg polymer/mL); (5) pure water. Same amounts of Nile Red stock solution were added to each micelle or control solution.

the presence of few aggregates (400–700 nm) contributing to the increase in the polydispersity. These aggregates could be easily removed by filtration.

In order to further characterize the properties of the micelles formed from these novel PHLA-based amphiphilic copolymers, compared to those prepared from the standard MPEG-PLA, Nile Red probe incorporation experiments were performed. The maximum absorption wavelength of this dye is strongly influenced by its hydrophobic environment, as reported by Davis and Hetzer (1966). Nile Red solution was added to each micelle solution (2.1 mg/mL), and the mixtures were slowly agitated for 24 h. The micelle solutions turned quickly reddish as a result of the diffusion of the Nile Red into the core of the micelles (Fig. 4b; sample 1: MPEG2-PdiHLA3, sample 2: MPEG2-PmHLA3 and sample 3: MPEG2-PLA3), whereas control solutions with pure PEG (sample 4) and pure water (sample 5) remained uncoloured. In Fig. 4a the recorded UV–visible spectra of the different samples are shown. The maximum wavelength absorption is shifting from 545 nm (sample 3: MPEG2-PLA3) to 540 nm (sample 2: MPEG2-PmHLA3) and 535 nm (sample 1: MPEG2-PdiHLA3), respectively, indicating clearly that the hydrophobicity of the micelle core is increasing with the increasing density of hexyl groups along the PLA chain. At the same time the Nile Red absorbance was higher for the polymers with higher numbers of hexyl groups (from samples 3 to 1), proving that higher amounts of the hydrophobic Nile Red molecules were incorporated in the micelle core. The quasi absence of absorbance observed for the sample made of pure PEG (sample 4) confirmed that the Nile Red has no affinity for the hydrophilic PEG block, and is only to observe in combination with the core-centered hydrophobic P(H)LA block.

Critical micellar concentrations (CMC) were determined using Nile Red as a fluorescent probe. Based on the fact that this molecule is quasi insoluble in water and solubilizes itself only into the hydrophobic region of the micelles, an intensified fluorescence can be observed as soon as micelles are formed, as shown in Fig. 5a. Here the maximum fluorescence intensity (I_{max}) is presented as a function of the polymer concentration. The CMC could be precisely determined at the inflection point of the plot of the maximum emission wavelength (λ_{max}) as a function of the polymer concentration (Fig. 5b), a method developed by Coutinho et al. (2002). As expected, the CMC determined for MPEG2-PmHLA3 and MPEG2-PdiHLA3 was slightly lower with 8.5 and 8 mg/L, respectively, in comparison to the analog MPEG2-PLA3 with 10 mg/L, due to the increased hydrophobicity of the P(m/di)HLA3 segment. These low CMC values envision the use of these novel micelles as drug carriers in very diluted conditions.

The increased hydrophobic character of the micelle core of the hexyl-substituted PLA in comparison to standard PLA can especially be of interest for improved hydrophobic drug loadings. For this purpose the incorporation of griseofulvin (GF) in these novel micelles was investigated. The procedure to prepare the GF-loaded micelles was the same as described for the blank ones, except that GF was dissolved together with the copolymer in the acetone phase prior to addition into the water phase. After the evaporation of acetone the non-entrapped and water

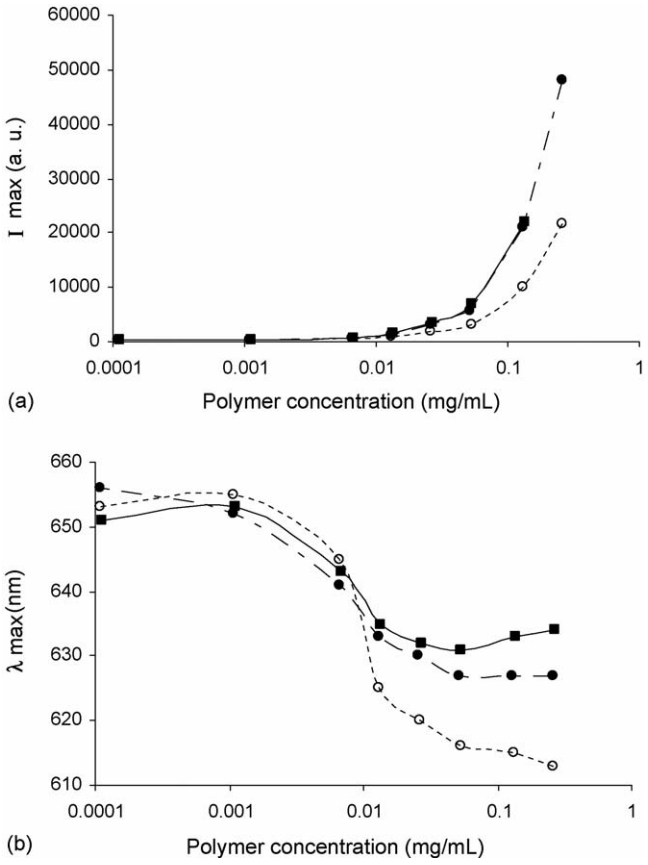


Fig. 5. Plot of the fluorescence emission intensity (a) of the Nile Red vs. copolymer concentration for MPEG2-PLA3 (◯), MPEG2-PmHLA3 (●) and MPEG2-PdiHLA3 (■) micelles and (b) the maximum emission wavelength.

insoluble GF was easily removed by centrifugation. Independent of the amounts of GF added, the mean size of the micelles was always comprised in the range of 30–80 nm. The amount of incorporated GF in the different micelles was assessed by HPLC analysis after destroying the micelles by solubilization in acetonitrile. The levels of incorporated GF were significantly higher and more efficient in the micelles of the novel hexyl-substituted PLAs with the more hydrophobic core (Fig. 6). Especially in the case of the addition of lower amounts, as for example

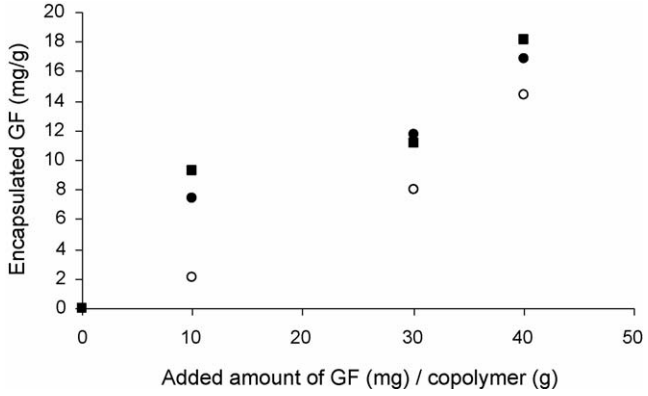


Fig. 6. Loading of micelles with griseofulvin (mg/g polymer) as a function of the griseofulvin added amount (mg/g polymer) for MPEG2-PLA3 (◯), MPEG2-PmHLA3 (●) and MPEG2-PdiHLA3 (■).

10 mg GF addition per 1 g polymeric micelles in the preparation solution, the drug loading was increased from 2.1 mg GF/g in MPEG2-PLA3-micelles (21% incorporation) to 7.5 mg/g in MPEG2-PmHLA3-micelles (75%), and 9.3 mg/g in MPEG2-PdiHLA3 micelles (93%), which resembles an increase of four and five times, respectively. This increased efficiency of nearly complete drug encapsulation is especially advantageous when considering the incorporation of expensive hydrophobic drugs. Higher amounts of GF in the preparation solution lead in general to higher amounts of GF incorporation, still with higher amounts incorporated in the more hydrophobic hexyl-substituted lactide micelles. By increasing the drug addition from 10 to 40 mg/g polymeric micelles, the drug loading was increased from 2.1 mg GF/g to 14.4 mg GF in MPEG2-PLA3 micelles, from 7.5 mg/g to 16.9 mg GF in MPEG2-PmHLA3 micelles, and from 9.3 mg/g to 18.2 mg GF in MPEG2-PdiHLA3 micelles. Eventually drug loading amounts and efficiency could be further improved by optimizing the novel polymeric micelles related to the molecular weights of the hexyl-substituted PLA and PEG chains.

6. Conclusion

We reported the synthesis and characterization of novel amphiphilic MPEG-PHLA di-block copolymers by ROP of hexyl-substituted lactides using a methoxy-terminated PEG as initiator in the presence of $Sn(Oct)_2$ as a catalyst with predictable molecular weights and narrow distributions. The physical properties of the copolymers were determined by DSC, showing the presence of amorphous and crystalline domains deriving from both homopolymer segments. Micelles of sizes between 30 and 80 nm were successfully prepared from these new amphiphilic copolymers. UV–visible light experiments with Nile Red proved the increased hydrophobic character of the micelle core when increasing the number of hexyl side groups along the polyester chain. Higher amounts of Nile Red could be incorporated into the more hydrophobic micelle cores of the novel hexyl-substituted polylactides. The low CMC (8–8.5 mg/L) for the micelles based on the mono and di hexyl-substituted polylactide allow to envision the use of these micelles as drug carriers in diluted conditions. With the increased hydrophobicity of the inner micelle core in comparison to standard MPEG-PLA micelles higher loadings of hydrophobic drugs are favoured, which was also shown by the incorporation of griseofulvin. It is to point out that the MPEG-PHLA composition and the molecular weights of the two segments in the copolymers can be easily fine tuned for further optimized properties of these micellar drug delivery systems.

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