

SYNTHESIS OF AMPHIPHILIC PEG-PCL-PEG TRIBLOCK COPOLYMERS

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ABSTRACT

A series of new triblock copolymers consisting of non-toxic, biocompatible and hydrophilic poly(ethylene glycol) (PEG) blocks and biodegradable, hydrophobic poly(ϵ -caprolactone) (PCL) block of the type (PEG-PCL-PEG) were successfully synthesized by a reaction of coupling. In this study, in order to obtain a variety of copolymers with different chemical and physical properties, PCL with a molecular mass M_w 2000 and PEG with M_w varied from 6000 to 15000 were used. Hexamethylene diisocyanate (HDI) was used as coupling agent. The PEG-PCL-PEG triblock copolymers were prepared by a two-step reaction. In the first step, hydroxyl-terminated PCL diol was functionalized by hexamethylene diisocyanate (HDI) to obtain an NCO-PCL oligomer. In the second step the obtained oligomer was additionally blocked with a HO-PEG oligomer. The obtained copolymers were isolated and their structures were characterized by FTIR, ^1H NMR spectroscopy and gel permeation chromatography (GPC).

Keywords: PCL, PEG, triblock copolymers, biocompatibility, biodegradable, reaction of coupling.

INTRODUCTION

The biodegradable polymers are suitable for many commercial products and medical applications, such as packaging, surgical implants, controlled release and drug delivery systems, but their use is still limited due to their high cost or their low performance [1-3].

The commonly used biocompatible polymers are aliphatic polyesters, such as poly(ϵ -caprolactone) (PCL), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their corresponding copolymers [4,5]. Special interest has been paid to their enzymatic biodegradation [6-9] and biomedical applications [10-12]. Therefore, the widely studied and applied block copolymer system of poly(ethylene glycol) (PEG) and poly(ϵ -caprolactone) (PCL) is of special interest, since PEG is biocompatible [13-15] whereas PCL is both biocompatible and biode-

gradable due to the enzymatic and/or pH dependant breakdown of ester bonds [16,17].

Poly(ethylene glycol) (PEG) is the most widely used biocompatible polymer for chemical and biological applications. PEG-containing amphiphilic copolymers may therefore be useful to modify the surface of biomedical polymer implants [18,19] and to design drug-delivery systems [20].

In the present study, PEG-PCL-PEG copolymers were successfully prepared by a two-step reaction. In the first step, HO PCL diol was functionalized by hexamethylene diisocyanate (HDI) to obtain NCO-end-capped telehelical oligomer (NCO-(PCL)). In the second step the obtained oligomer was additionally blocked with HO-PEG oligomers with different molecular masses. A series of copolymers was synthesized and characterized by FTIR, ^1H NMR spectroscopy and gel permeation chromatography (GPC).

EXPERIMENTAL

Materials

PCL diol ($M_w = 2000$, CAPA® 2205 (Solvay). The hydroxyl value is 56 mg KOH/g, and the water content is less than 0.02 %. Polycaprolactone (PCL) was dried under vacuum at 50°C for 24 h prior to use. Poly(ethylene glycol)'s having molecular masses 6000 (PEG 6000), 8000 (PEG 8000), 10000 (PEG 10000), 15000 (PEG 15000), obtained from Fluka were dried by azeotropic distillation with toluene under nitrogen atmosphere and used immediately. HDI (Aldrich) was distilled under nitrogen atmosphere N_2 , at 80-85°C. Toluene (Fluka) was dried 24 h over Na-K under dry N_2 and then distilled. Methylene chloride and hexane were dried over CaH_2 and then distilled under reduced pressure.

Synthesis

Functionalization of telehelic PCL diol with HDI, a typical procedure

The synthesis of NCO-terminated PCL prepolymer was performed in solution under N_2 atmosphere. HDI (1,62 ml) and dry toluene (10 ml) were placed into a 250 ml three necked flask at 60-65°C. Ten grams of PCL diol (5 mmol) dissolved in 20 ml dry toluene were added to the HDI slowly for a period of 60 min at 60-65°C. The ratio of NCO/OH was 2:1 (mol/mol). The reaction mixture was heated to 80-85°C and the reaction was continued until the NCO peak at 2281 cm⁻¹ has reached to a constant intensity. The synthesized PCL prepolymer was stored at 6°C in a desiccators.

Synthesis of PEG-PCL-PEG copolymers

ABA type triblock copolymers with different length of PEG block were synthesized from a carbamoyl derivate of telehelic PCL and HDI with molar ratio of PEG to the prepolymer 2:1 (mol/mol). Dry PEG (12 mmol) and 15 ml dry toluene were placed into a 250 ml three necked flask. The stirring was performed at 60°C under dry nitrogen atmosphere for 5 min to melt the PEG. PCL prepolymer (1,37 g) was dissolved beforehand in 10 ml dry toluene at room temperature with stirring. Then the obtained solution was added into the reaction vessel slowly dropwise with a dropping funnel at 60-65°C for over a period of 60 min. The reaction mixture was kept under stirring at 80°C. Samples have

been taken from the reaction kettle at every 60-120 min until a total disappearance of the NCO peak at 2281 cm⁻¹ in the FTIR spectra has been observed. The final product was isolated by dissolving the reaction mixture in methylene chloride, followed by precipitation in hexane at 0°C.

Analysis

Fourier transform infrared spectroscopy (FTIR)

The IR spectra (KBr pellets) were recorded on a Bruker-Vector 22 FTIR spectrometer at resolution of 1-2 cm⁻¹ accumulating 64 - 128 scans.

Nuclear magnetic resonance analysis (¹H NMR)

¹H NMR spectra (in CDCl₃ at 22°C) were recorded using a Bruker Avance DRX 250 at 250 MHz to characterize the chemical composition.

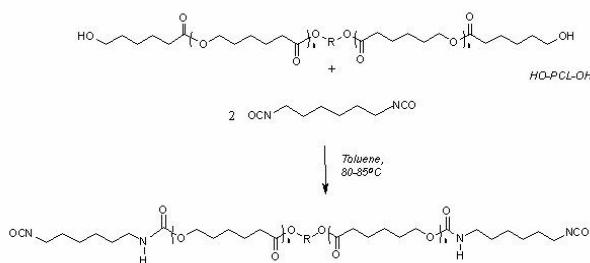
Gel permeation chromatography (GPC)

Molecular mass and molecular mass distribution of the PEG-PCL-PEG copolymers were determined by Gel permeation chromatography (GPC), using a Waters chromatography system. The analyses were performed on two PLGel columns with pore sizes of 500 Å, calibrated with poly(ethylene glycol) standards. Tetrahydrofuran (THF) was used as mobile phase with a flow rate of 0.5 ml/min at 45°C.

RESULTS AND DISCUSSION

Synthesis of NCO-terminated PCL prepolymer

The synthesis of NCO-terminated PCL prepolymer was carried out in solution at NCO/OH ratio of 2:1 (mol/mol) at 80-85°C in N_2 for a period of 60 min to avoid the side reactions of formation of alphanate and urea linkages (Scheme 1).



Scheme 1. Synthesis of an NCO-terminated polycaprolactone prepolymer.

Fourier transform infrared analysis of NCO-terminated PCL prepolymer

FTIR spectroscopy was used to characterize the structure of the obtained telehelic oligomers. It is of interest to determine the kinetics of the reaction of coupling and to confirm the required time for the exhaustion of the prepolymer in the course of the reaction. This could be done with success by following the quantitative changes of the absorption of the characteristic functional group as HO-PCL and NCO- of HDI with FTIR spectra in the region of 4000-500 cm⁻¹ during the reaction. In the prepolymer synthesis, the samples for FTIR spectra were collected every 60-120 min. In the course of the investigation it was confirmed that the signals of the urethane group increased and the HO- and NCO- signals decreased. At the end of the synthesis the absorbance of the polyol HO- groups approached zero, while the absorbance of the free isocyanate group was reduced to a constant value. This is a good evidence that almost all hydroxyl groups were consumed during the reaction (Fig. 1).

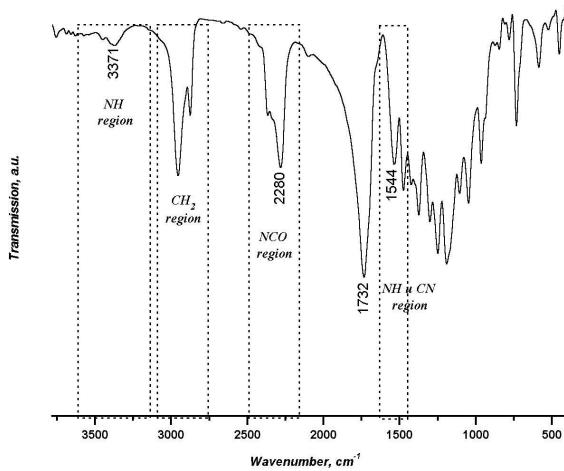


Fig. 1. FTIR spectrum of the NCO-terminated PCL prepolymer obtained at the 10th hour.

The completion of the reactions and their course is manifested by the determined ratio of the area of the characteristic peaks at 3371 cm⁻¹ which confirms the formation of N-H bonds (stretching vibrations), 3000 - 2800 cm⁻¹; CH stretching vibrations: antisymmetric and symmetric modes of methylene groups and 2281 cm⁻¹ (NCO asymmetric vibration). Also in the spectra is observed a new signal at 1544 cm⁻¹ that is attributed to

the overlapping of a signal for the N-H, N-C bands and NCO group. It is known that the N-H stretching vibration is sensitive to the specificity and magnitude of hydrogen bonding. The researchers have proved that the splitting of the bonded N-H band is related to different acceptors with which the N-H groups were hydrogen bonded [21, 22]. Because of multiple overlapping peaks in the region 3500-3200 cm⁻¹ it was necessary to use a deconvolution strategy which include of the peaks that form in a search for distribution patterns, best fits which the measured spectral bands. The curve-fitting simulations were performed using Origin software version 6. The N-H band was deconvoluted considering the peaks as Gaussian (Fig. 2a) with a number of iterations to get the best Gaussian peaks (Fig. 2b). A flat baseline was chosen in between 3500 and 3300 cm⁻¹ and the spectra were corrected by subtracting the baseline. The band at 3371 cm⁻¹ was assigned to N-H groups bonded with carbonyl (N-H···O=C) in the prepolymer (Fig. 3).

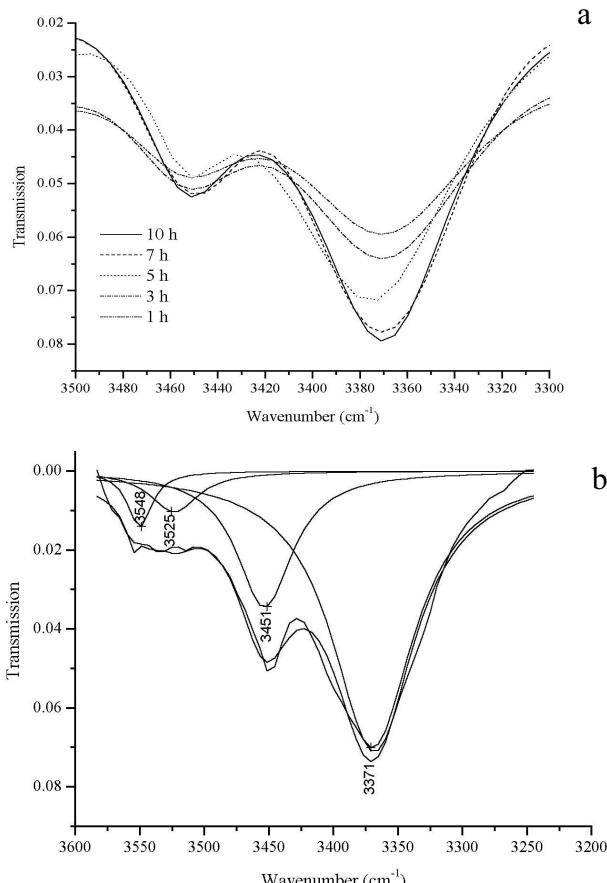


Fig. 2. (a) N-H zone of the FTIR spectra of NCO-terminated PCL prepolymer at different reaction time; (b) FTIR peak deconvolution of the N-H gange in the NCO-terminated PCL prepolymer obtained at the 5th hour.

As a result of the obtaining of areas for N-H, CH and NCO groups at 3371, 3000 - 2800 and 2281 cm^{-1} , respectively, after their deconvolution, we estimated the profile of the reaction with the time (Fig. 3), using a ratios of the following areas: $S_{\text{NH}}/S_{\text{CH}_2}$ and $S_{\text{NCO}}/S_{\text{CH}_2}$. The full completion of the reaction is obtained at the 10th hour.

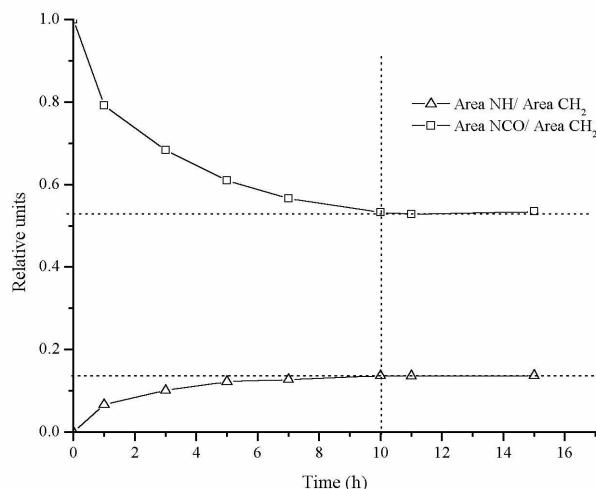
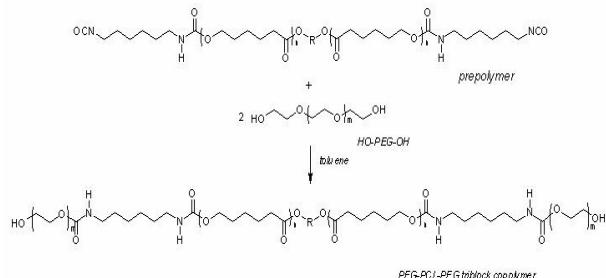


Fig. 3. Changes of the intensity with the time of the peaks which characterize NCO- and NH- groups.

Synthesis of PEG-PCL-PEG triblock copolymers by reaction of coupling

The reaction of coupling to produce PEG-PCL-PEG triblock copolymers proceed according Scheme 2. The molecular masses of PEG were varied from 6000 to 15000. The reaction between the OH-groups from PEG and the terminate NCO-groups from the prepolymer is accomplished in a toluene (homogeneous) solution with NCO/OH ratio of 1:2 (mol/mol). To avoid the side reaction of formation of alternating copolymers with regular alternating A and B units, the toluene solution of the diisocyanate-end-capped PCL prepolymer was added to the toluene solution of PEG for a period of about 60 min.

The structure of triblock copolymers is confirmed by FTIR and ¹H NMR spectra. The FTIR spectra of all copolymers show similar bands and signals (Fig. 4). The absorption band at 1116 cm^{-1} is attributed to the characteristic C-O-C stretching vibration of the repeated $-\text{OCH}_2\text{CH}_2-$ units of the polyethylene glycol backbone. A weak C=O stretching band at 1739 cm^{-1} determines the presence of $-\text{C}(\text{O})\text{OCH}_2-$ ester bonds in the repeated



Scheme 2. Preparation of PEG-PCL-PEG amphiphilic triblock copolymers.

units of the polycaprolactone. There is no absorption in the 2270-2285 cm^{-1} range, which indicates that the NCO-groups of the hexamethylene diisocyanate have disappeared completely. The weak absorption band at 1540 cm^{-1} (N-H bending vibrations) confirms the formation of an urethane group in the copolymers.

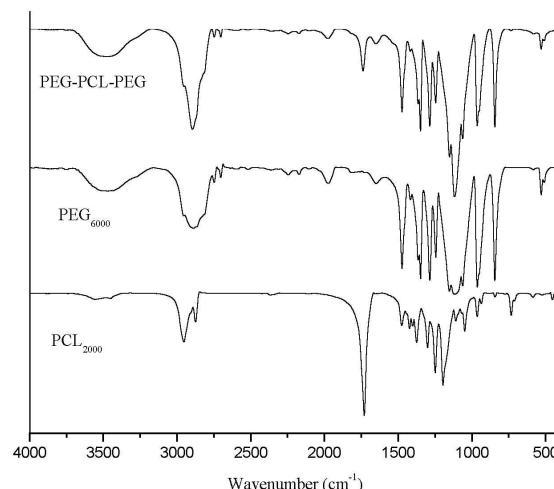


Fig. 4. FTIR spectra of the PEG-PCL-PEG triblock copolymers, PEG_{6000} and PCL_{2000} .

The ¹H NMR spectra also confirm the obtaining of PEG-PCL-PEG triblock copolymers (Fig. 5). The appearance of strong signals due to the α -, β -, γ -, δ - and ϵ -methylene protons to the carbonyl group of the PCL side chain was detected at 2.31 ppm, 1.64 ppm, 1.38 ppm and 4.05 ppm, respectively. A broad singlet signal of the poly(ethylene glycol) backbone at 3.63 ppm is also observed. The signals at 4.93 ppm and 3.13 ppm are attributed to the NH and CH_2-NH protons in the urethane group. The signal at 4.17 ppm is attributed to the $-\text{NH}-\text{C}(\text{O})\text{O}-\text{CH}_2-$ protons.

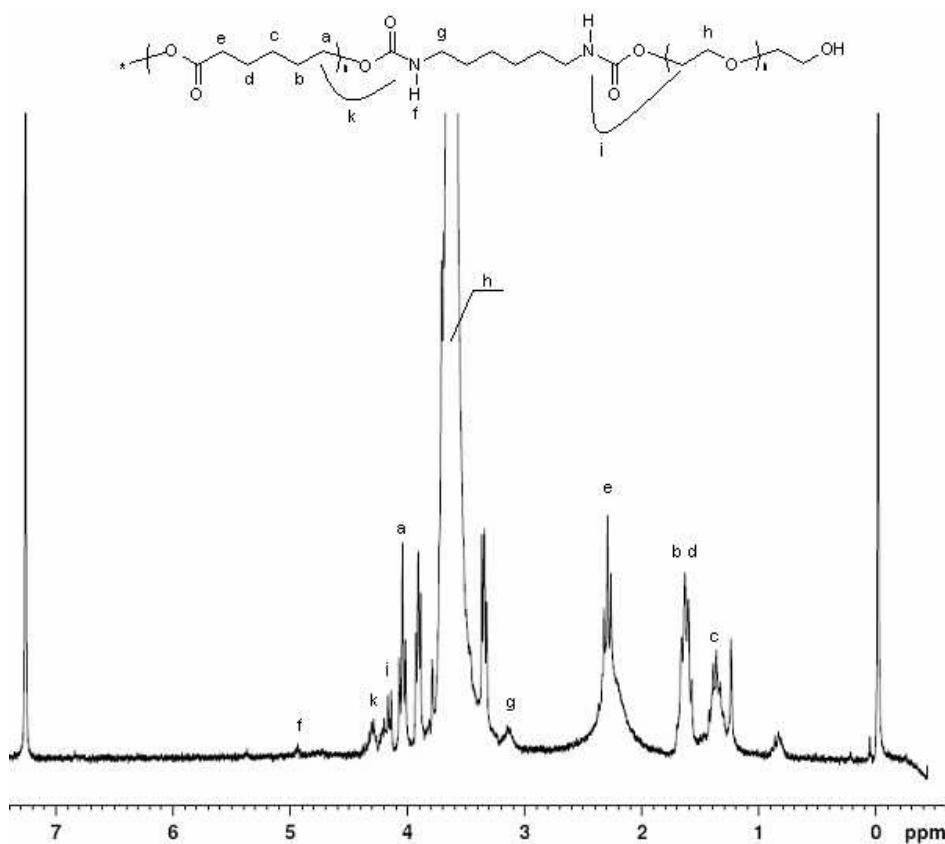


Fig. 5. ^1H NMR spectrum of the PEG-PCL-PEG (PEG₁₅₀₀₀) triblock copolymer in CDCl_3 .

The M_n values of the PEG-PCL-PEG triblock copolymers and the PEG/PCL block ratio were estimated from ^1H NMR spectrum (Fig. 5) and GPC analysis (Table 1). Additionally, the molecular masses evaluated from the NMR PEG/PCL ratio and by GPC were in satisfactory agreement. The M_n of the triblock copolymers and the PEG/PCL ratio were calculated from the ^1H NMR spectra:

$$I_D/I_A = 2[4(Y-1)]/4 \quad (1)$$

$$I_E/I_A = 4X/4 \quad (2)$$

$$M_{n(\text{PEG})} = 2(44Y+17) \quad (3)$$

$$M_{n(\text{PCL})} = 2(114X) \quad (4)$$

$$M_{(\text{PEG-PCL-PEG})} = M_{n(\text{PEG})} + M_{n(\text{PCL})} = 2(44Y+17)+2(114X) \quad (5)$$

where I_A , I_D and I_E are the integral intensities of the peaks at 4.93, 3.63 and 4.05 ppm, respectively, in the ^1H NMR spectrum of PEG-PCL-PEG. $2X$ and Y are the respective block numbers of PCL and PEG. In all cases, the GPC analysis showed monomodal, relatively narrow molecular mass distributions (Table 1).

CONCLUSIONS

The diisocyanate-end-capped prepolymer was prepared by a coupling reaction between hydroxyl and isocyanate groups in the polycaprolactone and the hexamethylene diisocyanate, respectively. Hexamethylene diisocyanate was selected as a coupling agent because of its low cost, high reactivity and the low toxicity of the biodegradable products of its urethane derivate.

The NCO PCL prepolymer was used for the preparation of PEG-PCL-PEG PCL- copolymers, by the reaction of coupling. The synthesized polymers are expected to be biologically non-toxic and biocompatible on the basis of the literature data and can have potential applications in the field of delivery systems for bioactive agents [23].

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