European Journal of Medicinal Chemistry 46 (2011) 3047–3051

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Preparation and characterization of polyester- and poly (ester-carbonate)-paclitaxel conjugates

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ARTICLE INFO

Article history:
Received 25 February 2011
Received in revised form
13 April 2011
Accepted 14 April 2011
Available online 22 April 2011

Keywords:
Paclitaxel
Macromolecular conjugates
Polyesters
Control release

ABSTRACT

The polyester- and poly(ester-carbonate)-paclitaxel conjugates with low molecular weight were synthesized using dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) as catalysts. Polymeric matrices were obtained by ring-opening polymerization of ε-caprolactone (CL), *rac*-lactide (*rac*-LA), L-lactide (LLA) and trimethylene carbonate (TMC). The macromolecular conjugates were characterized by using spectroscopic techniques, such as ^{1}H, ^{13}C NMR and FTIR. The degree of degradation of polyester- and poly(ester-carbonate)-paclitaxel conjugates was tested in vitro under different conditions. The preliminary results of drug release were discussed.

1. Introduction

Paclitaxel (PACL) is a natural product with antitumor activity (Fig. 1). Taxol (paclitaxel) is obtained via a semi-synthetic process from *Taxus baccata*. PACL is one of the most common anticancer drugs used for chemotherapy. It is antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions.

PACL is usually used to treat patients with lung, ovarian, breast, head and neck cancer. However some problems such as allergic reactions, heart and blood vessel effects, infections due to low white blood cell count, hair loss, joint and muscle pain, irritation at the injection site, low red blood cell count, mouth or lip sores, numbness, tingling, or burning in the hands and/or feet, stomach upset and diarrhea, decrease in urine output and/or swelling of the hands, face, or feet, have limited its use [1–3]. Therefore, polymeric conjugates have been extensively studied and proved as promising delivery systems to augment therapeutic efficacy of chemotherapeutic agents in the treatment of cancer. Macromolecular conjugates of paclitaxel, such as poly(ethylene glycol) PEG [4], poly(L-glutamic acid) (PG) [5], monomethoxy-poly(ethylene glycol)-b-poly(lactide) (MPEG-PLA) [6], recently attracted more and more attention.

Poly(lactide) (PLA), poly(D,L-lactide-co-glycolide) (PLGA), and poly(caprolactone) (PCL) are biodegradable polymers, which are used most often in the literature of drug delivery [7–15]. Aliphatic polyesters are attractive, because they undergo hydrolysis to produce compounds which can be metabolized in vivo and in the environment [16]. Aliphatic polyesters are commonly prepared by two different routes: polycondensation and the ring-opening polymerization (ROP). The ROP of cyclic esters is initiated/catalyzed by metal complexes, organic compounds, or enzymes, to yield high molecular weight in excellent conversion and purity [16–21]. The most common catalysts are metal (Sn, Zn and Al) coordinating compounds, which are useful due to their selectivity and efficacy. On the other hand, for pharmaceutical applications metal residues are undesirable considering their toxicity.

Recently, we found that natural amino acids and creatinine are satisfactory initiators for ROP of cyclic esters [13,22].

The aim of the present study is to synthesize polyester-paclitaxel and poly(ester-carbonate)-paclitaxel conjugates of different molecular weights and to characterize their physicochemical properties. We hope that the obtained macromolecular conjugates are good potential candidates as implant drug delivery systems.

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doi:10.1016/j.ejmech.2011.04.046

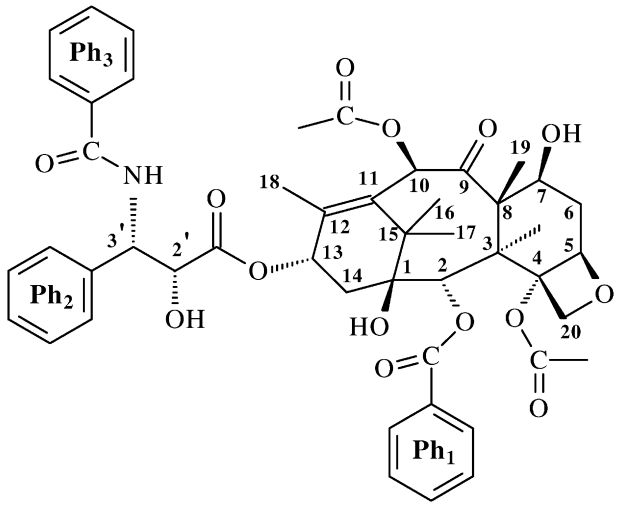


Fig. 1. Structure of paclitaxel.

2. Experimental

2.1. Chemicals

(3*S*)-*cis*-3,6-Dimethyl-1,4-dioxane-2,5-dione (L-lactide, 98%, LLA) was purchased from Aldrich and recrystallized from ethyl acetate for several times. 3,6-Dimethyl-1,4-dioxane-2,5-dione, (*rac*-lactide, 98%, *rac*-LA) (Aldrich) was crystallized from a mixture of dry toluene with hexane and dried at room temperature under vacuum. ε-Caprolactone (2-Oxepanone, CL, 99%) was purchased from Aldrich. Before use, it was dried and distilled over CaH_2 at reduced pressure. Paclitaxel (97%), from semi-synthetic (from *Taxus* sp., PACL) (Aldrich), creatinine (anhydrous, 99%, CE) (Aldrich), diethyl carbonate (DEC, 98%) (Aldrich), propane-1,3-diol (PD, 98%) (Aldrich), stannous octoate ($SnOct_2$, tin (II) 2-ethylhexanoate, 95%) (Aldrich), dicyclohexylcarbodiimide (DDC) (Aldrich 99%), dimethylaminopyridine (DMAP) (Aldrich 99%), ethanol (99.8%) (Aldrich), dichloromethane (POCh Poland) and methanol (POCh), were used as received.

2.2. Synthesis of trimethylene carbonate

Trimethylene carbonate (TMC) was synthesized in the reaction of equimolar quantities of DEC and PD in the presence of $SnOct_2$ as catalyst at 160 °C during 8 h. Then, ethanol and unreacted substances were evaporated under reduced pressure. TMC was produce by depolymerization of the polycarbonate. Then the monomer was crystallized from a mixture of dry benzene/tetrahydrofuran (1:4) and dried at 30 °C under vacuum [23].

2.3. Synthesis of polyesters and poly(ester-carbonate)s

Homo- and copolymerization of cyclic esters and TMC were carried out in the same way. Monomers (CL, *rac*-LA, LLA, TMC) and CE were placed in 10 mL glass ampoules under an argon atmosphere. The reaction vessels were then left standing at the required temperature in a thermostated oil bath for the appropriate time (Table 1). After desired time the ampoule was opened and methylene chloride was added in order to dissolve the products. Then, the obtained solutions were washed with methanol and dilute hydrochloric acid (5% aqueous solution) under vigorous stirring. The latter operation was repeated three times. The isolated polymer was dried in vacuum for 3 days.

PCL: ^{1}H NMR ($CDCl_3$, δ, ppm): 1.38 (2H, m, J = 8.0, 7.2 Hz, $-OCH_2CH_2C\mathbf{H_2}CH_2CH_2C(O)O-$), 1.63 (4H, m, $-OCH_2C\mathbf{H_2}CH_2C\mathbf{H_2}CH_2C(O)O-$), 2.29 (2H, t, J = 7.3 Hz, $-OCH_2CH_2CH_2CH_2C\mathbf{H_2}C(O)O-$), 3.73 (2H, t, J = 3.1 Hz, $-C\mathbf{H_2}OH$, end group), 4.04 (2H, t, J = 6.7 Hz, $-OC\mathbf{H_2}CH_2CH_2CH_2CH_2C(O)O-$); ^{13}C NMR ($CDCl_3$, δ, ppm): 24.9 ($-OCH_2CH_2\mathbf{C}H_2CH_2CH_2C(O)O-$), 25.8 ($-OCH_2CH_2CH_2\mathbf{C}H_2CH_2C(O)O-$), 28.4 ($-OCH_2\mathbf{C}H_2CH_2CH_2CH_2C(O)O-$), 33.8 ($-OCH_2CH_2CH_2CH_2\mathbf{C}H_2C(O)O-$), 63.9 ($-\mathbf{C}H_2C(O)OH$, end group), 64.5 ($-O\mathbf{C}H_2CH_2CH_2CH_2CH_2C(O)O-$), 173.8 ($-OCH_2CH_2CH_2CH_2CH_2\mathbf{C}(O)O-$); FTIR (KBr, cm^{-1}): 2944 ($\nu_{as}CH_2$), 2867 ($\nu_{as}CH_3$), 1722 (νC=O), 1244 (νC–O).

PLA: ^{1}H NMR ($CDCl_3$, δ, ppm): 5.17 (1H, q, J = 6.7 Hz, $-\mathbf{C}H(CH_3)-$), 4.36 (1H, q, J = 7.3, 6.7 Hz, $-C\mathbf{H}(CH_3)OH$, end group), 1.58 (3H, d, $-C\mathbf{H_3}$); ^{13}C NMR ($CDCl_3$, δ, ppm): 169.9 ($-\mathbf{C}(O)O-$), 69.4 ($-\mathbf{C}H(CH_3)-$), 16.9 ($-\mathbf{C}H_3$); FTIR (KBr, cm^{-1}): 2999 ($\nu_{as}CH_3$), 2949 (ν_sCH_3), 2884 (νCH), 1761 (νC=O), 1454 ($\delta_{as}CH_3$), 1346–1389 (δ_sCH_3), 1365–1370 (δ_1CH + δ_sCH_3), 1315–1300 (δ_2CH), 1270 (δCH + νCOC), 1215–1185 (ν_{as}COC + $r_{as}CH_3$), 1131 ($r_{as}CH_3$), 1100–1090 (ν_sCOC), 1045 (νC–CH_3), 960–950 (rCH_3 + νCC), 875–860 (νC–COO), 760–740 (δC=O), 715–695 (γC=O), 515 (δ_1C–CH_3 + δCCO), 415 (δCCO), 350 (δ_2C–CH_3 + δCOC), 300–295 (δCOC + δ_2C–CH_3), 240 (τCC).

2.4. Synthesis of macromolecular conjugates of paclitaxel

A 0.1 g quantity of homopolymer or copolymer and 25 mg of paclitaxel were dissolved in 50 mL anhydrous methylene chloride.

Table 1
Synthesis of polyesters and poly(ester-carbonate)s.

Code	Monomer I	Monomer II	$M_I/M_{II}/I$	Yield (%)	M_n[a] (Da)	PD[a]	M_n[b] (Da)	PD[b]	TMC[c] (% mol)	η_{inh}[d] (dL/g)	η_{inh}[e] (dL/g)
PCL	ε-CL	–	50:1	81	4400	1.1	3200	1.1	–	0.06	0.05
PLA-1	LLA	–	50:1	62	4000	1.2	2800	1.2	–	0.12	0.07
PLA-2	*rac*-LA	–	50:1	57	3900	1.2	2700	1.1	–	0.15	0.09
COP-1	ε-CL	TMC	25:25:1	60	2900	1.2	–	–	36	0.06	0.06
COP-2	ε-CL	TMC	30:20:1	67	3200	1.2	–	–	26	0.08	0.07
COP-3	ε-CL	TMC	40:10:1	72	3700	1.2	–	–	18	0.09	0.07
COP-4	LLA	TMC	25:25:1	43	2400	1.1	–	–	44	0.11	0.10
COP-5	LLA	TMC	30:20:1	54	2900	1.2	–	–	38	0.15	0.14
COP-6	LLA	TMC	40:10:1	58	3600	1.2	–	–	28	0.18	0.16
COP-7	*rac*-LA	TMC	25:25:1	39	2300	1.1	–	–	39	0.12	0.10
COP-8	*rac*-LA	TMC	30:20:1	55	3200	1.2	–	–	31	0.20	0.18
COP-9	*rac*-LA	TMC	40:10:1	61	3400	1.2	–	–	25	0.22	0.19

I – initiator (CE).
Reaction conditions: time – 72 h, temp. – 140 °C.
[a] Determined by GPC.
[b] Determined by MALDI-TOF.
[c] TMC units content in copolymer chain.
[d] Determined by viscosity method (before degradation).
[e] Determined by viscosity method (after 8 weeks).

DCC (10 mg) and DMAP (5 mg) were added at room temperature. The reaction was continued under stirring for 24 h. The precipitate was filtered out and the filtrate was washed with hydrochloric acid (5% aqueous solution) and methanol [6]. The conjugates isolated from the solution's organic phase were kept under vacuum at room temperature for 48 h.

PACL: ^{1}H NMR (DMSO, δ, ppm): 0.97, 1.46, 1.74, 2.07, 2.18, 3.57, 3.97, 4.54, 4.86, 5.37, 6.24, 7.36, 7.45, 7.47, 7.59, 7.66, 7.84, 7.92, 8.84; ^{13}C NMR (DMSO, δ, ppm): 20.3, 26.0, 57.0, 69.2, 73.2, 76.4, 79.9, 83.2, 127.0, 127.9, 128.3, 129.2, 129.6, 133.0, 134.1, 138.9, 165.9, 168.4, 172.3, 202.0; FTIR (KBr, cm^{-1}): 2933 (ν_sCH$_3$), 1728 (νC=O), 1647 (νNH), 1371, 1246, 1178, 1071, 709 (finger print);

2.5. Characterizations

The polymerization products and macromolecular conjugates of PACL were characterized by means of ^{1}H and ^{13}C NMR (Varian 300 MHz) at room temperature, with $CDCl_3$ or DMSO as solvent and TMS as internal reference. The FTIR spectra were recorded from KBr pellets (Spectrum 1000, Perkin–Elmer). Relative molecular mass and molecular mass distributions were determined by MALDI-TOF MS and GPC techniques. The MALDI-TOF spectra were measured in the linear mode on a Kompact MALDI 4 Kratos analytical spectrometer using a nitrogen gas laser with 2-[(4-hydroxyphenyl) diazenyl] benzoic acid (HABA) as a matrix. GPC measurements were made at 25 °C in the tetrahydrofuran solution using Shimadzu C-R4 Chromatopac apparatus. The molecular weights were calibrated with polystyrene standards. Polymers viscosity were measured in *N*,*N*-dimethylformamide (at 30 °C) using an Ubbelohde viscometer (on Stabinger Viscometer SVM 3000).

2.6. Paclitaxel released from macromolecular conjugates

Dried macromolecular conjugate (0.05 g) was poured into aqueous buffered solution (25 mL, pH 1 or 7) at 37 °C for 3 or 8 weeks. The mixture was stirred. When the process time was completed, water was removed under reduced pressure. Then, 25 mL of ethanol was added to the flask and the mixture was stirred for 2 h. Next, the sample was removed and filtered. The amount of paclitaxel released was analyzed using a UV spectrophotometer (UV-1202 Shimadzu) at the λ_{max} value of 229 nm. The quantity of released drug was determined from the calibration curve obtained previously under the same conditions.

Degradation was evaluated by the η_{inh} of polymers decrease.

3. Results and discussions

Recently, a progressive interest has arisen for preparation of paclitaxel prodrugs. It is commonly known that the 2′- and 7-hydroxyl groups of paclitaxel are suitable for its structure modification [6].

The purpose of our work was to obtain the polyester and poly(ester-carbonate) conjugates of PACL. Polymers were synthesized by ring-opening polymerization (ROP) of CL, LLA, *rac*-LA and TMC using CE as a catalyst (Scheme 1).

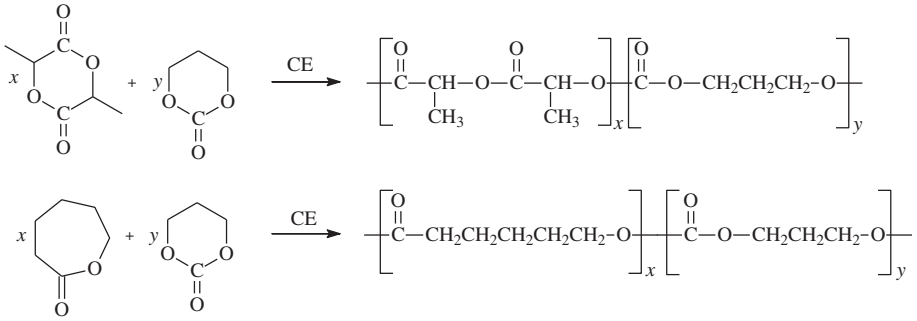
The first test of LLA polymerization in the presence of CE was described by Wang [24]. The results of the ROP of LLA, *rac*-LA and CL in the presence of CE and glycols (ethylene glycol, diethylene glycol or 1,4-butanediol) were already published by us [13]. The paper is a continuation of our earlier investigations.

The polymerization reactions of CL, LLA and *rac*-LA in the presence of CE were carried out at 140 °C for 72 h (Table 1). The chemical structures of the obtained homopolymers were confirmed by ^{13}C, ^{1}H NMR and IR studies (Experimental part). The spectroscopic data are in agreement with what was reported in the literature. The respective reaction yields were in the 81 (PCL), 62 (PLA-1) and 57% (PLA-2) range. For the homopolymers, the number-average molecular weights (M_n) determined by GPC were in the range 3900–4400 Da. The polydispersity indexes (*PD*) were within 1.1–1.2 limits. The M_n of homopolymers determined using MALDI-TOF MS were in the 2700–3200 Da ranges.

The copolymers were prepared under similar conditions. Melt polymerization was performed at 140 °C for 72 h under an argon atmosphere. The molar ratio of CL (LLA, *rac*-LA):TMC:CE was 25:25:1, 30:20:1, or 40:10:1. The results of these melt polymerization runs are summarized in Table 1. The chemical structure of the resulting precipitated copolymers was characterized by ^{1}H NMR and ^{13}C NMR.

The signals observed in ^{1}H NMR spectra of CL/TMC copolymers can be attributed to the following units: 4.21 [−C**H**$_2$CH$_2$CH$_2$OC(O)O−], 4.12 [−C**H**$_2$CH$_2$CH$_2$CH$_2$CH$_2$C(O)O−], 4.03 [−CH$_2$CH$_2$C**H**$_2$OC(O)O−CL], 3.61 [HOC**H**$_2$−], 2.29 [−CH$_2$CH$_2$CH$_2$CH$_2$C**H**$_2$C(O)O−], 2.00 [−CH$_2$C**H**$_2$CH$_2$OC(O)O−], 1.63 [−CH$_2$C**H**$_2$CH$_2$C**H**$_2$CH$_2$C(O)O−], 1.38 [−CH$_2$CH$_2$C**H**$_2$CH$_2$CH$_2$C(O)O−] ppm. In ^{13}C NMR spectra of CL/TMC copolymers, the main signals characteristic for repeating and terminal units appear at δ = 173.5 [−**C**(O)−, CL**CL**CL], 173.3 [−**C**(O)−, CL**CL**TM] 155.2 [−**C**(O)−, CL**TMC**CL], 155.0 [−**C**(O)−, TMC**TMC**CL], 154.9 [−**C**(O)−, TMC**TMC**TM] 67.8 [TMC−**C**H$_2$CH$_2$CH$_2$CH$_2$CH$_2$C(O)O−], 64.1 [−**C**H$_2$CH$_2$CH$_2$CH$_2$CH$_2$C(O)O−, −**C**H$_2$CH$_2$**C**H$_2$OC(O)O−], 61.2 [−OCH$_2$**C**H$_2$CH$_2$O−], 60.5 [−**C**H$_2$CH$_2$**C**H$_2$OC(O)O−CL], 34.0 [−CH$_2$CH$_2$CH$_2$CH$_2$**C**H$_2$C(O)O−], 28.3 [−CH$_2$**C**H$_2$CH$_2$CH$_2$CH$_2$C(O)O−], 28.0 [−CH$_2$**C**H$_2$CH$_2$OC(O)O−CL], 25.2 [−CH$_2$CH$_2$CH$_2$**C**H$_2$CH$_2$C(O)O−], 24.4 [−CH$_2$CH$_2$**C**H$_2$CH$_2$CH$_2$C(O)O−] ppm (the Supplementary material).

The chemical structure of the LA/TMC copolymers obtained was characterized by ^{1}H NMR. For all products, peaks appeared at 5.14 [−C**H**(CH$_3$)COO−], 4.26 [HOC**H**(CH$_3$)COO−], 4.21 [−C**H**$_2$CH$_2$C**H**$_2$OC(O)O−], 3.61 [HOC**H**$_2$−], 1.98 [−CH$_2$C**H**$_2$CH$_2$OC(O)O−], 1.46 [−CH(C**H**$_3$)COO−] ppm. In ^{13}C NMR spectra of LA/TMC copolymers, the signals characteristic appear at 169.7 [−COO−, TMC−**LA**−TMC and LA−**LA**−LA], 154.6 [−COO−, TMC−**TMC**−LA], 154.0 [−**C**(O)−, TMC**TMC**TM] 71.4 [−**C**H(CH$_3$)COO−TMC], 69.0



Scheme 1. Synthesis of poly(ester-carbonate)s.

Table 2
Synthesis of macromolecular conjugates of PACL.

Code	Composition	Drug content[a]	pH 7	pH 7	pH 1	pH 1
			% Released after 3 weeks	% Released after 8 weeks	% Released after 3 weeks	% Released after 8 weeks
CON-1	PCL–PACL	2.6	18	43	–	–
CON-2	PLA-1–PACL	3.6	24	65	–	–
CON-3	PLA-2–PACL	3.7	27	72	–	–
CON-4	COP-3–PACL	2.9	8	17	11	23
CON-5	COP-6–PACL	3.4	15	29	18	41
CON-6	COP-9–PACL	3.6	14	26	9	38

Reaction conditions: room temperature, time – 24 h, argon atmosphere.
[a] PACL units content in macromolecular conjugates (%mol), determined by 1H NMR.

[–**C**H(CH_3)COO–], 61.5 [–**C**$H_2$$CH_2$**C**$H_2$OC(O)O–], 58.4 [LA–**C**$H_2$$CH_2$-**C**$H_2$OC(O)O–, –HO**C**$H_2$$CH_2$$CH_2$O–], 31.4 [–$CH_2$**C**$H_2$$CH_2$OC(O)O–], 16.5 [–**C**H($CH_3$)COO–] ppm (the Supplementary material).

The M_n of the synthesized copolymers were relatively low in the range of 2900–3700, 2400–3600 and 2300–3400 g/mol, for CL/TMC, LLA/TMC and *rac*-LA/TMC copolymers respectively.

The co-monomers composition had influenced on the molecular weight of the copolymer: the higher CL content in the co-monomer feed results in a higher molecular weight of the copolymer formed (Table 1). Copolymer compositions were determined from the ^{1}H NMR spectra by taking the ratio of the peak areas corresponding to the TMC (–CH_2C**H**$_2$$CH_2$OC(O)O–) protons at $\delta = 2.00$ ppm and the CL (–$CH_2$$CH_2$$CH_2$$CH_2$C**H**$_2$C(O)O–) protons at $\delta = 2.30$ ppm. The CL content in the copolymer of CL and TMC exceeded the CL feed ratio for copolymers (amounts to 64–82 mol%). As it is common knowledge, carbon dioxide is sometimes eliminated during ROP of TMC and, hence, that some ether linkages are formed in the polycarbonate. It was found that no elimination of carbon dioxide was detected in our experiments, because no peak at 3.4 ppm, which can be assigned to –CH_2OCH_2–, is present.

The η_{inh} of CL/TMC copolymers increase only from 0.06 to 0.09 dL/g with an increase CL content in the copolymer chain.

Similar to the results obtained from the copolymerization of LLA or *rac*-LA with TMC, increasing the LA content in the co-monomer feed from 25:25:1 to 40:10:1 increased M_n of the copolymer formed. For example, When the LLA/TMC/CE ratio was 25:25:1, the M_n (from GPC) was 2400 g/mol. However, when the LLA/TMC/CE ratio was 40:10:1, the M_n (from GPC) was 3600 g/mol. Similarly, the M_n of COP-7 is smaller about 30% than M_n of COP-9.

The composition of the LA/TMC copolymers was determined from the integrations of the bands at 4.2 ppm for TMC and at 4.9–5.2 ppm for LLA (or *rac*-LA). It should be noted that each LA molecule contains two lactyl units. As indicated in Table 1, the LA content in the copolymer of LA and TMC exceeded the LA feed ratio for copolymers (amounts to 56–75 mol%). The intrinsic viscosities of LA/TMC copolymers lie between 0.11 and 0.22 dL/g.

The macromolecular conjugates were obtained from the reactions of homopolymers (PCL, PLA-1, PLA-2) and copolymers (COP-3, COP-6, COP-9) with PACL (Table 2) (Scheme 2).

The chemical structures of the prepared macromolecular conjugates of PACL were confirmed by ^{1}H and ^{13}C NMR studies. Typical proton NMR spectrum of the reaction product of PCL with PACL is shown in Fig. 2. All the conjugate spectra have revealed characteristic peaks of PACL, indicating successful preparation of the macromolecular conjugates of PACL.

The PACL content in macromolecular conjugates was calculated by ^{1}H NMR. The signal intensity of the two hydrogen on the phenyl ring of paclitaxel (7.92 ppm) and the signal intensity of the C**H**$_2$COO (for PCL and CL/TMC copolymers) or C**H**(CH_3)COO (for PLA and LA/TMC copolymers) has been compared. The drug content in the macromolecular conjugates amounts to 2.6–3.7 mol%.

$$\text{HO—R—COOH} + \text{HO—PACL} \xrightarrow[\text{DDC}]{\text{DMAP}} \text{HO—R—COO—PACL}$$

Scheme 2. Synthesis of macromolecular conjugates of PACL.

The kinetic rates of PACL release from macromolecular conjugates at pH 7 or 1 are shown in Table 2.

It was found that the rate of PACL release from obtained macromolecular conjugates depends on the structure of the polymer. The **CON-2** (PLA) and **CON-3** (PLA) conjugates released PACL faster compared to the **CON-1** (PCL) conjugates. The percentage of released PACL after 8 weeks incubation was about 43% from **CON-1**, 65% from **CON-2** and 72% from **CON-3** at pH 7.

We have found that macromolecular conjugates containing TMC units slowly released PACL compared to the PCL or PLA conjugates. The percentage of released PACL after 3 weeks incubation was about 18% from **CON-1**, 24% from **CON-2**, 27% from **CON-3**, 8% from **CON-4**, 15% from **CON-5** and 14% from **CON-6** at pH 7, for respectively. The result seems logical, because it is known that polycarbonate is relatively resistant on the hydrolysis.

The results suggest a higher stability of obtained macromolecular conjugates of PACL to chemical hydrolysis at pH 7 than 1. The amount of released drug within 8 weeks was about 23% from **CON-4**, 41% from **CON-5** and 38% from **CON-6** at pH 1. However, 17% PACL was released from **CON-4**, 29% from **CON-5** and 26% from **CON-6** at pH 7.

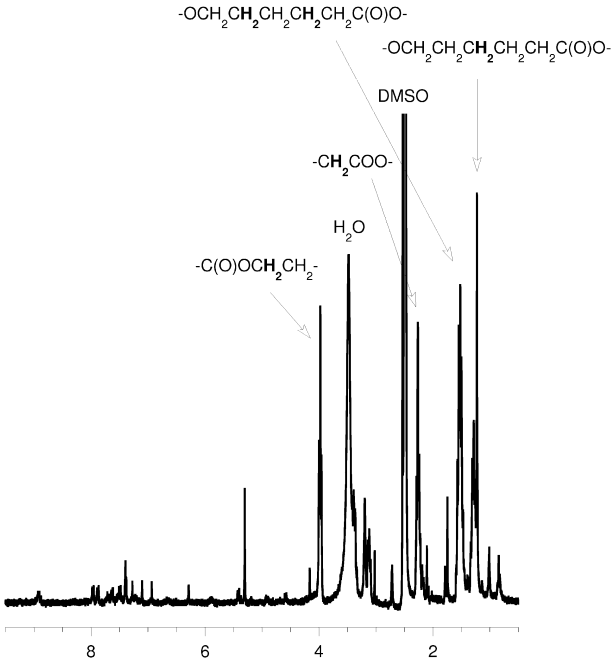


Fig. 2. The ^{1}H NMR spectrum of the PCL–PACL conjugate (in DMSO-d_6).

Summing up, PACL release depends upon the kind of the polymer matrix (ability to biodegradation) as well as pH for the media. To prove our hypothesis additional experiments were carried out. Tests of the degradation of homo- and copolymers were conducted in the buffer of pH 7 at 37 °C. The results of intrinsic viscosity of original and hydrolytic degraded polymers are shown in Table 1. The degradation process is rather slow, if it is compared with the rate of PACL release. This fact is due to the hydrophobic character of the obtained polyesters and poly (carbonate-ester)s, which determines that they are not soluble in water solutions, and also because the low area of the polymer exposed to the hydrolysis solution. The results suggested that the hydrolytic degradation rate of the homo- and copolymers depended upon the CL, LA or TMC content in polymer chain. The η_{inh} of homopolymers changed from 17 to 42% within 8 weeks. However, the η_{inh} of copolymers changed from 0 to 14% after 8 weeks incubation. This showed that the LA units were earlier degraded before TMC and CL units due to its higher hydrophilicity and faster degradation.

In conclusion we can state that the rates of PACL release and the biodegradation of macromolecular conjugates depends on the chemical composition. Our preliminary studies showed that the PACL could be released from the prepared macromolecular conjugates, but detail kinetic studies still remain to be done.

4. Conclusions

In this work the production of macromolecular conjugates made from PCL, PLA or copolymers of CL, LA and TMC was evaluated. The release rates of the PACL were shown to be directly dependent on the nature of polymers. The obtained results demonstrate that the homo- and copolymers of CL, LA, *rac*-LA and TMC are interesting materials for the controlled release of PACL. They are good potential candidates to be applied as implantation drug delivery carriers.

Acknowledgments

The work was supported by the research program (Project MNiSW-0451/B/H03/2010/39, N N209 045139) of the Committee of Scientific Research in Poland.

Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2011.04.046.

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