

Full Paper

Synthesis and Structural Analysis of Polyester Prodrugs of Norfloxacin

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Abstract: Two-, three- and four-arm, star-shaped poly(ϵ -caprolactone) and poly(*D,L*-lactide) homopolymers, and copolymers of ϵ -caprolactone with *D,L*-lactide were synthesized via ring-opening polymerization of cyclic esters in the presence of glycerol, pentaerythritol and poly(ethylene glycol) as initiators and stannous octoate as a catalyst. Thus obtained oligomers were successfully used in the synthesis of novel macromolecular prodrugs of norfloxacin. The structures of the polymers and prodrugs were elucidated by means of MALDI-TOF MS, NMR and IR studies.

Keywords: aliphatic polyesters, ring-opening polymerization, macromolecular prodrugs, prodrugs of norfloxacin.

Introduction

Pharmacy is one of the most important areas of application of polymers. They are used as active macromolecular pharmaceutical substances, blood substitutes, auxiliary materials and excipients, in production of macromolecular prodrugs, polymeric drug delivery systems, therapeutic systems, etc. The polymeric prodrugs, drug delivery systems and therapeutic systems exhibit unique pharmacokinetics, body distribution and pharmacological efficacy [1-12]. Biodegradable polymers like polylactide (PLA), poly(ϵ -caprolactone) (PCL) and copolymers of lactides (LA) and ϵ -caprolactone

(CL) are very often used as drug delivery systems. Aliphatic polyesters are usually prepared by ring-opening polymerization (ROP) of the corresponding cyclic monomers, that is *D,L*-LA, *L,L*-LA or CL. PLA and PCL can be efficiently obtained by ROP in the presence of ionic initiators as well as coordinative and enzymatic catalysts [13-28].

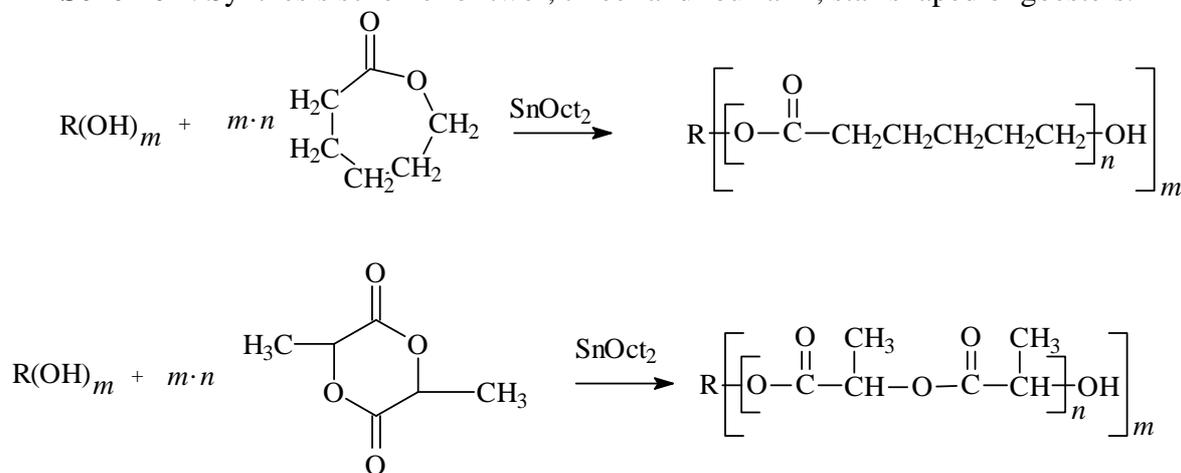
Fluoroquinolones are an important new class of synthetic oral antibacterial agents used against various infections. They work by killing bacteria or preventing their growth. The first discovered and clinically effective quinolone was norfloxacin, that is 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid [29]. Recently, the interaction of norfloxacin with DNA has been considered as useful in the anticancer drug design [30]. Preliminary efforts to prepare nanoparticles of poly(*D,L*-lactide-co-glycolide) loaded with adsorbed norfloxacin has already been reported [31]. The anticancer selectivity of norfloxacin is supposed to be improved by anchoring the drug using chemical linkage to biodegradable oligomers, which may transport the drug molecules more efficiently and more specifically. We go in the latter scientific direction.

In this paper, we describe the synthesis of a series of star-branched polyester prodrugs of norfloxacin. Chemical structures of the synthesized polymers have been confirmed by ¹H- and ¹³C-solution NMR as well as FT-IR spectroscopy. Absolute molecular weights of polymers have been determined using gel permeation chromatography (GPC), end-group analysis and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).

Results and Discussion

The homo- and copolymerisation reactions of CL and LA were carried out in the presence of initiators like glycerol (Gl), pentaerythritol (Pet) or poly(ethylene glycol) (PEG), and stannous octoate (SnOct₂) as catalyst. Reaction conditions, yields and average molecular weight of obtained polyesters are summarized in Table 1. Under these conditions, cyclic monomers underwent ROP and the low-molecular weight polyesters with chain-end hydroxyl groups were obtained. The synthesized PCL and PLA polymers, and the CL&LA copolymers had two-, three- and four-arm star shapes. A typical reaction scheme is presented in Scheme 1.

Scheme 1. Synthesis scheme for two-, three- and four-arm, star-shaped oligoesters.



$m = 2$ (for poly(ethylene glycol)), 3 (for glycerol), 4 (pentaerythritol)

Two-, three- and four-arm hydroxyl terminated oligomers were prepared using PEG, GI and Pet initiators, respectively. The respective reaction yields were in the 79-100, 50-100 and 44-62 % range. Thus, the polymerization yields were dependent on the type of the initiator. PEG was found to be more effective than GI and Pet. For the CL and LA homopolymers, the number-average molecular weights determined by GPC were in the range 5200-9600 and 4200–8400 Da, respectively, while for the LA&CL copolymer they were in the range 2900–3900 Da. PCL had higher molecular weights than PLA, and the homopolymers had higher molecular weights than the copolymers. In all cases, the polydispersity indexes were within 1.1–1.3 limits.

Table 1. Homopolymerization and copolymerization of CL and LA in the presence of various initiators and SnOct₂.

Monomer(s) /initiator/catalyst	M/I/Cat	Yield (%)	Phys. form	M_n^{GPC} (Da)	PD^{GPC}	M_n^{MS} (Da)	PD^{MS}	M_n^{th}	M_n^{arm}	cLA
CL/PEG/SnOct ₂	100:2:1	≈ 100	ss	5200	1.2	2500	1.2	6100	2600	-
CL/GI/SnOct ₂	150:1.5:1	≈ 100	ss	9600	1.3	-	-	11492	3200	-
CL/Pet/SnOct ₂	200:2:1	62	ss	5300	1.3	1900	1.1	7204	1300	-
LA/PEG/SnOct ₂	100:2:1	79	vl	4200	1.2	1400	1.1	6088	2100	-
LA/GI/SnOct ₂	150:1.5:1	65	vl	8400	1.3	-	-	9452	2800	-
LA/Pet/SnOct ₂	200:2:1	44	vl	5100	1.2	1600	1.2	6472	1300	-
LA&CL/PEG/SnOct ₂	50:50:2:1	92	vl	3900	1.2	-	-	3277	2000	37
LA&CL/GI/SnOct ₂	75:75:1.5:1	50	vl	2900	1.1	-	-	3205	1000	35
LA&CL/Pet/SnOct ₂	100:100:2:1	45	vl	3100	1.2	-	-	2690	800	44

Reaction conditions: temp. of 120°C, time – 48h

M_n^{GPC} - number-average molecular weight determined by GPC

PD^{GPC} - polydispersity (M_w/M_n) determined by GPC

M_n^{MS} - number-average molecular weight determined by MALDI-TOF

PD^{MS} - polydispersity (M_w/M_n) determined by MALDI-TOF

M_n^{th} - theoretical number-average molecular weight of polymer.

For homopolymers: $M_n^{th} = [M]/[I] \times M_{monomer} \times yield + M_{initiator}$.

For copolymers: $M_n^{th} = [M]/[I] \times M_{comonomer(LA)} \times yield \times cLA + [M]/[I] \times M_{comonomer(CL)} \times yield \times cCL + M_{initiator}$

M_n^{arm} - number-average molecular weight of arm of PCL or PLA, $M_n^{arm} = M_n^{GPC}/oligomer\ arm\ number$

cLA – content of the LA units in the copolymer (mol %), calculated from ¹H NMR on the basis of the intensity ratio of the main-chain [-C(O)CH(CH₃)O-] peak of PLA and the main-chain [-CH₂CH₂CH₂CH₂CH₂OC(O)-] peak of PCL

cCL – content of the CL units in the copolymer (mol %): cCL = 100 – cLA

ss - sticky solid

vl - viscous liquid

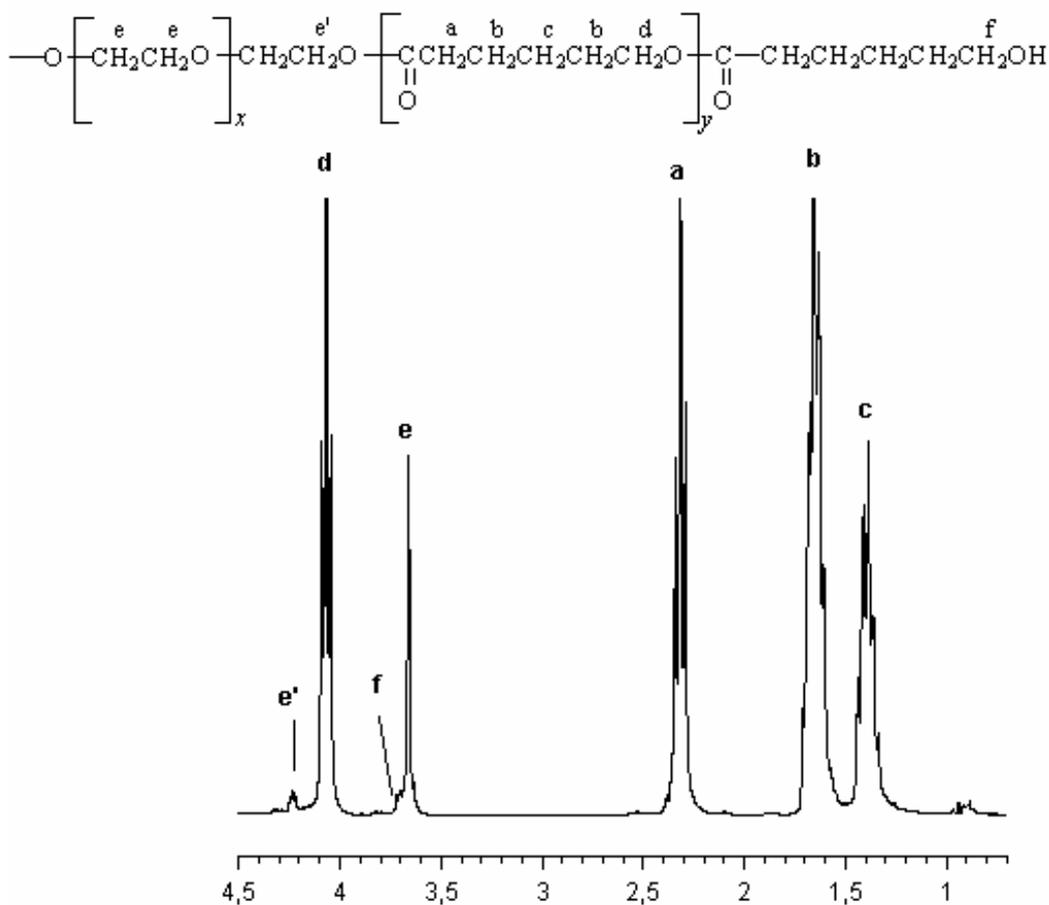
The chemical structures of the obtained polymers were confirmed by ¹H-, ¹³C-NMR and IR studies (Table 2). A typical ¹H-NMR spectrum of the two-armed PCL is shown in Figure 1.

Table 2. ^1H - and ^{13}C -NMR (CDCl_3 , δ , ppm) peak assignments and the main IR absorption bands (KBr , cm^{-1}) of the obtained polymers.

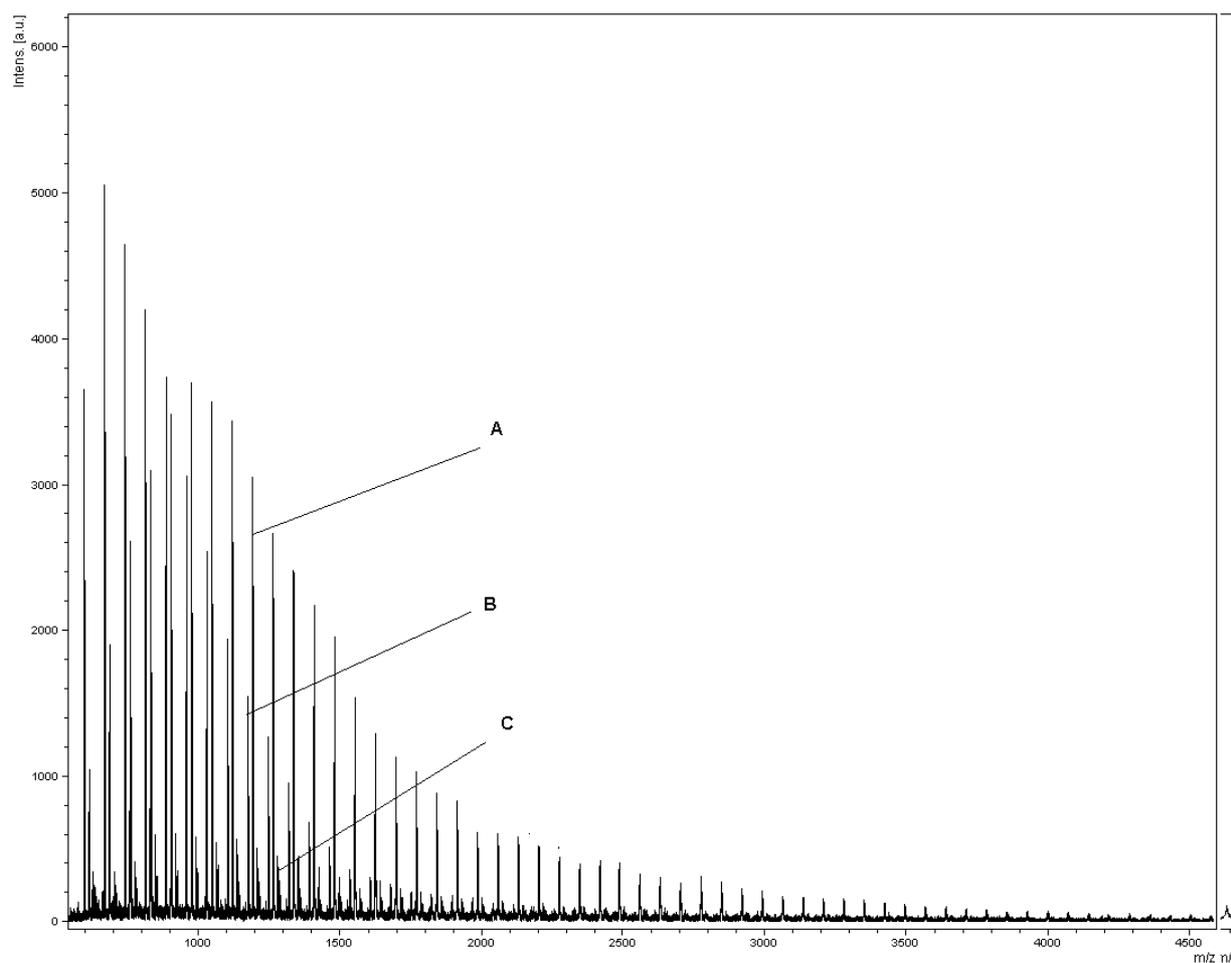
<p><i>PCL-PEG:</i></p> <p>$^1\text{H-NMR}$: 4.20 (2H, CL-OCH₂CH₂O-), 4.01 (2H, t, -CH₂CH₂OC(O)-), 3.70 (2H, t, -CH₂CH₂OH, end group), 3.66 (2H, t, -OCH₂CH₂O-), 2.24 (2H, t, -CH₂CH₂COO-), 1.58 (4H, m, -CH₂CH₂COO-), 1.33 (2H, m, -CH₂CH₂CH₂CH₂CH₂-)</p> <p>$^{13}\text{C-NMR}$: 173.1 (-C(O)O-), 70.1 (-OCH₂CH₂O-), 64.1 (CL-OCH₂CH₂O-), 63.7 (-CH₂CH₂OC(O)-), 33.6 (-CH₂CH₂COO-), 27.9 (-CH₂CH₂OC(O)-), 25.1 (-CH₂CH₂COO-), 24.1 (-CH₂CH₂CH₂CH₂CH₂-)</p> <p>FTIR: 2943 ($\nu_{\text{as}}\text{CH}_2$), 2862 ($\nu_{\text{s}}\text{CH}_2$), 1721 ($\nu\text{C=O}$), 1291 (C-O and C-C) 1240 ($\nu_{\text{as}}\text{COC}$), 1190 ($\nu\text{OC-O}$), 1170 ($\nu_{\text{s}}\text{COC}$), 1157 (C-O and C-C)</p>
<p><i>PCL-Gl:</i></p> <p>$^1\text{H-NMR}$: 5.24 (1H, p, =CH-O-), 4.28 (2H, d, -CH₂-O-), 4.04 (2H, t, -CH₂CH₂OC(O)-), 3.63 (2H, t, -CH₂CH₂OH, end group), 2.28 (2H, t, -CH₂CH₂COO-), 1.62 (4H, m, -CH₂CH₂COO-), 1.35 (2H, m, -CH₂CH₂CH₂CH₂CH₂-)</p> <p>$^{13}\text{C-NMR}$: 173.1 (-C(O)O-), 63.7 (-CH₂CH₂OC(O)-), 62.1 (-CH₂-O-), 33.6 (-CH₂CH₂COO-), 27.9 (-CH₂CH₂OC(O)-), 25.1 (-CH₂CH₂COO-), 24.1 (-CH₂CH₂CH₂CH₂CH₂-)</p> <p>FTIR: 2949 ($\nu_{\text{as}}\text{CH}_2$), 2865 ($\nu_{\text{s}}\text{CH}_2$), 1727 ($\nu\text{C=O}$), 1293 (C-O and C-C), 1240 ($\nu_{\text{as}}\text{COC}$), 1190 ($\nu\text{OC-O}$), 1170 ($\nu_{\text{s}}\text{COC}$)</p>
<p><i>PCL-Pet:</i></p> <p>$^1\text{H-NMR}$: 4.02 (2H, t, -CH₂CH₂OC(O)-), 3.60 (2H, t, -CH₂CH₂OH, end group), 2.25 (2H, t, -CH₂CH₂COO-), 1.59 (4H, m, -CH₂CH₂COO-), 1.34 (2H, m, -CH₂CH₂CH₂CH₂CH₂-)</p> <p>$^{13}\text{C-NMR}$: 173.1 (-C(O)O-), 63.7 (-CH₂CH₂OC(O)-), 63.4 (C-CH₂O-), 33.6 (-CH₂CH₂COO-), 33.3 (C-CH₂O-), 27.9 (-CH₂CH₂OC(O)-), 25.1 (-CH₂CH₂COO-), 24.1 (-CH₂CH₂CH₂CH₂CH₂-)</p> <p>FTIR: 2948 ($\nu_{\text{as}}\text{CH}_2$), 2864 ($\nu_{\text{s}}\text{CH}_2$), 1726 ($\nu\text{C=O}$), 1293 (C-O and C-C), 1238 ($\nu_{\text{as}}\text{COC}$), 1189 ($\nu\text{OC-O}$), 1169 ($\nu_{\text{s}}\text{COC}$)</p>
<p><i>PLA-PEG:</i></p> <p>$^1\text{H-NMR}$: 5.17 (1H, q, -CH(CH₃)-), 4.36 (1H, q, -CH(CH₃)OH, end group), 4.25 (2H, LA-OCH₂CH₂O-), 3.61 (2H, t, -OCH₂CH₂O-), 1.58 (3H, d, -CH₃)</p> <p>$^{13}\text{C-NMR}$: 169.8 (-C(O)O-), 69.2 (-CH(CH₃)-), 16.8 (-CH₃).</p> <p>FTIR: 2997 ($\nu_{\text{as}}\text{CH}_3$), 2947 ($\nu_{\text{s}}\text{CH}_3$), 2882 ($\nu\text{CH}$), 1760 ($\nu\text{C=O}$), 1452 ($\delta_{\text{as}}\text{CH}_3$), 1348-1388 ($\delta_{\text{s}}\text{CH}_3$), 1368-1360 ($\delta_1\text{CH}+\delta_{\text{s}}\text{CH}_3$), 1315-1300 ($\delta_2\text{CH}$), 1270 ($\delta\text{CH} + \nu\text{COC}$), 1215-1185 ($\nu_{\text{as}}\text{COC} + r_{\text{as}}\text{CH}_3$), 1130 ($r_{\text{as}}\text{CH}_3$), 1100-1090 ($\nu_{\text{s}}\text{COC}$), 1045 ($\nu\text{C-CH}_3$), 960-950 ($r\text{CH}_3 + \nu\text{CC}$), 875-860 ($\nu\text{C-COO}$), 760-740 ($\delta\text{C=O}$), 715-695 ($\gamma\text{C=O}$), 515 ($\delta_1\text{C-CH}_3 + \delta\text{CCO}$), 415 ($\delta\text{CCO}$), 350 ($\delta_2\text{C-CH}_3 + \delta\text{COC}$), 300-295 ($\delta\text{COC} + \delta_2\text{C-CH}_3$), 240 ($\tau\text{CC}$)</p>
<p><i>PLA-Gl:</i></p> <p>$^1\text{H-NMR}$: 5.24(1H, p, =CH-O-), 5.16 (1H, q, -CH(CH₃)-), 4.35 (1H, q, -CH(CH₃)OH, end group), 4.27 (2H, d, -CH₂-O-), 1.59 (3H, d, -CH₃)</p> <p>$^{13}\text{C-NMR}$: 169.7 (-C(O)O-), 69.1 (-CH(CH₃)-), 62.1 (-CH₂-O-), 16.7 (-CH₃)</p> <p>FTIR: 2997 ($\nu_{\text{as}}\text{CH}_3$), 2947 ($\nu_{\text{s}}\text{CH}_3$), 2882 ($\nu\text{CH}$), 1760 ($\nu\text{C=O}$), 1452 ($\delta_{\text{as}}\text{CH}_3$), 1348-1388 ($\delta_{\text{s}}\text{CH}_3$), 1368-1360 ($\delta_1\text{CH}+\delta_{\text{s}}\text{CH}_3$), 1315-1300 ($\delta_2\text{CH}$), 1270 ($\delta\text{CH} + \nu\text{COC}$), 1215-1185 ($\nu_{\text{as}}\text{COC} + r_{\text{as}}\text{CH}_3$), 1130 ($r_{\text{as}}\text{CH}_3$), 1100-1090 ($\nu_{\text{s}}\text{COC}$), 1045 ($\nu\text{C-CH}_3$), 960-950 ($r\text{CH}_3 + \nu\text{CC}$), 875-860 ($\nu\text{C-COO}$), 760-740 ($\delta\text{C=O}$), 715-695 ($\gamma\text{C=O}$), 515 ($\delta_1\text{C-CH}_3 + \delta\text{CCO}$), 415 ($\delta\text{CCO}$), 350 ($\delta_2\text{C-CH}_3 + \delta\text{COC}$), 300-295 ($\delta\text{COC} + \delta_2\text{C-CH}_3$), 240 ($\tau\text{CC}$)</p>

Table 2. Cont.

<p><u>PLA-Pet:</u></p> <p><u>¹H-NMR:</u> 5.17 (1H, q, -CH(CH₃-), 4.36 (1H, q, -CH(CH₃)OH, end group), 1.60 (3H, d, -CH₃)</p> <p><u>¹³C-NMR:</u> 169.6 (-C(O)O-), 69.1 (-CH(CH₃-), 63.5 (C-CH₂O-), 33.4 (C-CH₂O-), 16.7 (-CH₃)</p> <p><u>FTIR:</u> 2998 (ν_{as}CH₃), 2947 (ν_sCH₃), 2883 (νCH), 1760 (νC=O), 1453 (δ_{as}CH₃), 1348-1388 (δ_sCH₃), 1368-1360 (δ₁CH+δ_sCH₃), 1315-1300 (δ₂CH), 1270 (δCH + νCOC), 1215-1185 (ν_{as}COC + r_{as}CH₃), 1132 (r_{as}CH₃), 1100-1090 (ν_sCOC), 1046 (νC-CH₃), 960-950 (rCH₃ + νCC), 875-860 (νC-COO), 760-740 (δC=O), 715-695 (γC=O), 516 (δ₁C-CH₃ + δCCO), 415 (δCCO), 351 (δ₂C-CH₃ + δCOC), 300-295 (δCOC + δ₂C-CH₃), 242 (τCC)</p>
<p><u>Copolymers of LA and CL:</u></p> <p><u>¹H-NMR:</u> 5.15 (1H, q, -CH(CH₃-), 4.27 (1H, q, -CH(CH₃)OH, end group), 4.11 (2H, t, -CH₂CH₂OC(O)-LA), 4.03 (2H, t, -CH₂CH₂OC(O)-), 3.67 (2H, t, -CH₂CH₂OH, end group), 2.37 (2H, t, LA-CH₂CH₂CH₂CH₂COO-), 2.29 (2H, t, -CH₂CH₂COO-), 1.63 (4H, m, -CH₂CH₂COO-), 1.59 (3H, d, -CH₃), 1.34 (2H, m, -CH₂CH₂CH₂CH₂CH₂-), and peaks of Gl, Pet and PEG</p>

Figure 1. ¹H-NMR spectrum of the two-armed PCL (in CDCl₃).

The MALDI-TOF mass spectra of obtained oligomers confirmed that the main product was star-shaped oligoester terminated with hydroxyl group. The mass spectra also revealed a small fraction (presumably below 5 wt %) of cyclic oligolactones. Figure 2 shows typical MALDI-TOF spectra of the polymeric products.

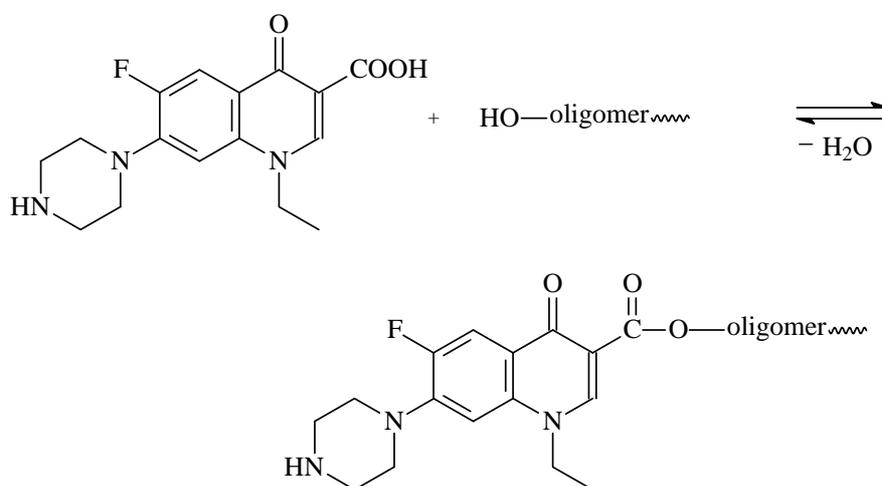
Figure 2. MALDI-TOF spectrum of PLA synthesized in the presence of Pet and SnOct₂.

The MALDI-TOF spectra of PLA comprise three series of peaks. The main series of prominent peaks (A) corresponds to the PLA molecules terminated with a hydroxyl group (residual mass: 41 Da, Na⁺ adduct), the second series of smaller peaks (B) also corresponds to the PLA molecules terminated with a hydroxyl group (residual mass: 57 Da, K⁺ adduct) and the third series of low-intensity peaks (C) corresponds to cyclic molecules (residual mass: 23 Da, Na⁺ adduct). Populations of PLA chains with both even and odd numbers of LA monomer units (m.u.) can be observed. The presence of the odd number of LA m.u. indicates that under the reaction conditions the polymer chain undergoes intermolecular transesterification, leading to the exchange of segments. This is a typical phenomenon for the polymerization of lactides [14]

In the MALDI-TOF spectra of PCL there are also three series of peaks. The most dominant one is characterized by a mass increment of 114 Da, which is equal to the mass of the repeating PCL unit. This series has been assigned to PCL terminated with a hydroxyl group (residual mass: 41 Da, Na⁺ adduct) (A). The second series of peaks also corresponds to PCL terminated with a hydroxyl group (residual mass: 57 Da, K⁺ adduct) (B). In addition, the PCL mass spectrum contains a series of minor peaks corresponding to cyclic molecules (residual mass: 23 Da, Na⁺ adduct) (C). The average molecular weights determined using MALDI-TOF MS were in the 1900–2500 and 1400–1600 Da ranges for PCL and PLA, respectively.

The macromolecular prodrugs were obtained (Scheme 2) from the reactions of the two-, three- and four-arm, star-shaped PCL and PLA homopolymers, and the CL&LA copolymers with norfloxacin (NOR).

Scheme 2. Synthesis of the polyester prodrugs of norfloxacin.



The chemical structures of the macromolecular prodrugs were confirmed by ¹H- and ¹³C-NMR, and by IR studies. Typical proton NMR spectra of pure NOR and of the reaction products of the two-armed hydroxyl terminated PCL with NOR are shown in Figures 3 and 4, respectively. All the prodrug spectra have revealed characteristic peaks of norfloxacin, indicating successful preparation of the polymer-NOR conjugate.

Figure 3. ¹H-NMR spectrum of NOR (in DMSO).

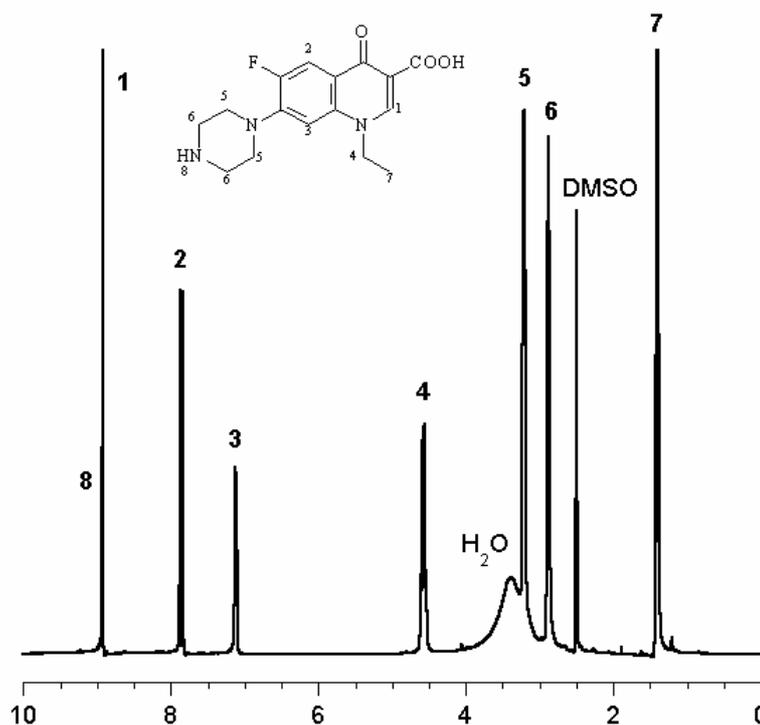
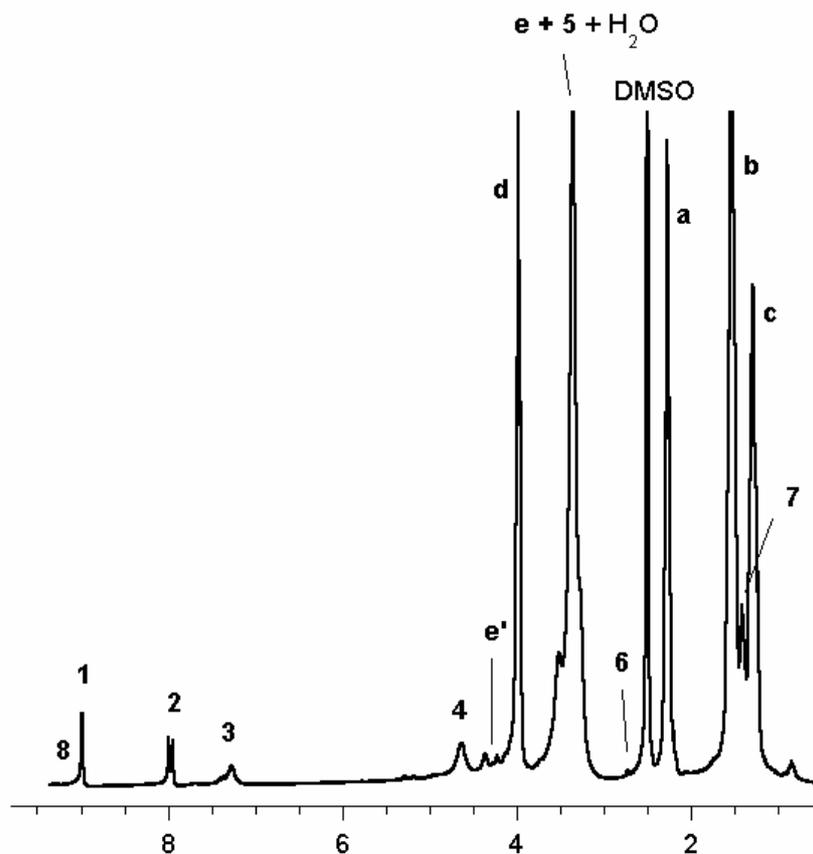


Figure 4. $^1\text{H-NMR}$ spectrum of the prodrug PCL(PEG)-NOR (in DMSO).

This work focused at the synthetic aspects of the NOR prodrugs. Kinetics of the NOR release from those polymers is still under study and will be presented in the next paper.

Conclusions

The two-, three- and four-arm, star-shaped poly(ϵ -caprolactone) and poly(*D,L*-lactide) homopolymers, and the copolymers of ϵ -caprolactone with *D,L*-lactide have been successfully used for the preparation of novel drug delivery systems of norfloxacin. The synthesis of those prodrugs was done in two steps. First, the ring-opening homo- or copolymerization of ϵ -caprolactone and *D,L*-lactide in the presence of initiators (poly(ethylene glycol), pentaerythritol or glycerol) and SnOct_2 as a catalyst was carried out. In the second step, the reaction of the polymer or copolymer with norfloxacin was performed. Our method of the synthesis is simple and effective. Thus obtained polyester prodrugs of norfloxacin are good potential candidates to be applied as drug delivery carriers. The latter application requires subsequent careful *in vitro* and *in vivo* examinations.

Experimental

General

ϵ -Caprolactone (CL) (2-Oxepanone, Aldrich 99%) was dried and distilled before use over CaH_2 at reduced pressure. 3,6-Dimethyl-1,4-dioxane-2,5-dione (*D,L*-LA) (rac-lactide, Aldrich 98%) was

crystallized from a mixture of dry toluene with hexane and dried under vacuum. Poly(ethylene glycol) (PEG) ($M_n = 400$, Serva Feinbiochemica), pentaerythritol (Pet) (Aldrich 99%), glycerol (Gl) (Aldrich 99%) and norfloxacin (NOR) (Aldrich 99%) were exhaustively dried under vacuum prior use. Stannous octoate SnOct_2 (tin (II) 2-ethylhexanoate, Aldrich 95%), dichloromethane and anhydrous methanol were used as received.

Polymerization procedure

Monomers (CL, LA), initiators (PEG, Pet, Gl) and the SnOct_2 catalyst were placed in a 10 mL glass ampule under nitrogen atmosphere. The reaction vessel was then kept standing in a thermostated oil bath at 120 °C over 48 h (Table 1). When the reaction time was completed, the cold reaction product was dissolved in CH_2Cl_2 , precipitated from cold methanol with diluted hydrochloric acid (to wash out the catalyst residue) and dried under vacuum for 72h.

Prodrugs synthesis

The prodrugs were prepared under nitrogen atmosphere at room temperature immediately before use. The polyesters were dissolved in CH_2Cl_2 (1g/50mL) and this solution was placed in a 150 mL three-necked flask equipped with a stirrer and addition funnel. A solution of NOR in CH_2Cl_2 (2g/50mL) was placed in the funnel and added dropwise into the reactor, while the reaction mixture was vigorously stirred. After the addition procedure was completed, the reaction mixture was left stirring for an additional 8 h, then it was washed with dilute hydrochloric acid and water. The washing was continued to fully remove any unreacted drug. The prodrugs isolated from the solution (organic phase) were kept under vacuum at room temperature for no more than one week.

Measurements

The polymerization products were characterized by means of ^1H - and ^{13}C -NMR (Varian 300 MHz), and FTIR spectroscopy (Spectrum 1000, Perkin Elmer). The NMR spectra were recorded in CDCl_3 or DMSO-d_6 . The IR spectra were recorded from KBr pellets. 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.

Norfloxacin:

^1H -NMR (CDCl_3 , ppm): 1.61, 3.14, 3.31, 4.33, 6.84, 8.07, 8.69, 8.73; (DMSO, ppm): 1.40, 2.88, 3.21, 4.56, 7.13, 7.87, 8.93, 9.03; ^{13}C -NMR (CDCl_3 , ppm): 14.7, 46.1, 49.9, 51.3, 103.9, 108.6, 113.2, 137.3, 147.3, 152.1, 155.5, 167.5, 177.3; FTIR (cm^{-1}): 3470 (νOH), 1710 (νCO), 1624 ($\nu\text{C}=\text{C}$ i $\text{C}=\text{N}$),

1452 (δCH_2 i ωCH_2), 1194 (δCH , γCH i $\nu\text{C-O}$), 1102 (benzene + pyridine ring breathing), 801 ($\nu\text{C-N}$ i δCH_2);

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Sample availability: Contact the authors.