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Designing bioresorbable polyester matrices for controlled doxorubicin release in glioma therapy

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ABSTRACT

The influence of the chain microstructure on release process of doxorubicin from polymeric matrices was analyzed. Aliphatic polyester copolymers with optimal chain microstructure, i.e. poly(glycolide-co-L-lactide, 15/85) (PGLA) and poly(glycolide-co-ε-caprolactone, 10/90) (PGCA) were synthesized for long-term doxorubicin delivery systems. Various release profiles from PGLA and PGCA matrices were obtained. The investigations revealed the most steadily doxorubicin release from PGCA matrices with 5% (w/w) of drug content. Degradation of matrices with and without drug was monitored by means of NMR spectroscopy and confirmed stability of degradation process. From PGCA matrices the increase of released doxorubicin amount was observed during first 60 days. On the contrary in case of matrices obtained from PGLA the delay of doxorubicin release was observed during first 50 days, what was caused by interaction of drug molecules with polylactide chain of polymer matrix. The interaction between doxorubicin molecules and polylactide chains was confirmed by IR spectroscopy. This fact can be used for designing of delivery systems consisting of combination of matrices with different microstructure of copolymer chains in order to adjust concentration of released doxorubicin and stabilization of drug release process.

1. Introduction

One of the most specific type of tumors is brain cancer, among which glioblastoma multiform is the most malignant (Azizi and Miyamoto, 1998). A basic role in treatment of inoperable brain tumors plays fractional radiotherapy. This kind of therapy is applied in case of recurrence patients and causes side effects as demyelination or postradiation necrosis. Radiotherapy can be replaced by chemical brachytherapy where cytostatic drug is released from biodegradable polyester carrier implanted directly to brain tumor or postoperative brain site and characterizes degradation and absorption of the carrier in intended time. It is possible to implant the matrix composed of bioresorbable copolymer with cytostatic drug which is releasing to a surrounding tissue as a result of both diffusion and erosion of matrix. Conventional cancer chemotherapy without application of drug delivery system is limited, because blood–brain barrier (BBB) restricts the entry of high molecular drugs from systemic circulation into the brain (Huynh et al., 2006).

Commercial available matrix called Gliadel® is comprised of carmustine homogeneously distributed in a disk containing random copolymer 1,3-bis(p-phenoxycarboxy)propane and sebacic acid (PCPP–SA) in molar ratio of 20/80 and is currently used in the treatment of recurrent glioblastoma multiform. Lesniak et al. have been used biodegradable PCPP–SA for local delivery of doxorubicin for treatment of malignant brain tumors in rats. Doxorubicin, when delivered locally, is an effective therapeutic agent against experimental intracranial glioma (Lesniak et al., 2005). The biodegradable copolymer of D,L-lactide and glycolide was also used for local delivery of doxorubicin for malignant glioma. Sustained release of drug until day 34 and completely absorbtion after day 80 of implanted tetragonal sheets were observed (Manome et al., 2006).

Bioresorbable copolymers of glycolide with lactide and glycolide with ε-caprolactone are commonly used as drug delivery devices (Lupron Depot®, Atrigel®, Zoladex® LA, Parloder LAR®) (Plosker and Brodgen, 1994; Harish et al., 2000; Jonat et al., 2002; Ciccarelli et al., 1993). In many cases copolymers of glycolide, lactide and ε-caprolactone are synthesized with application of tin initiator, which neurotoxical properties were exhibited (Salanki et al., 2000; Schwach et al., 1997).

Abbreviations: PGLA, poly(glycolide-co-L-lactide); PGCA, poly(glycolide-co-ε-caprolactone).

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In our work, polyester carriers of drugs were obtained from copolymers synthesized in presence of low-toxic zirconium initiator $Zr(acac)_4$ (Dobrzynski et al., 2001). Elaborated methods for analysis of biodegradable polyester materials microstructure and thus the possibility to control their structure, mechanical properties and degradation time were used in forming of resorbable polymer for controlled drug release systems (Li et al., 2005; Kryczka et al., 2002; Kasperczyk, 1999, 1996; Hu et al., 2007; Kasperczyk et al., 2006). The results of aliphatic polyesters degradation and influence of polymer chains microstructure on hydrolytic degradation (Jaworska et al., 2007; Kasperczyk, 1999; Kasperczyk et al., 2008a; Maciejowska et al., 2006) allow to design the bioresorbable controlled release systems and to control carrier degradation time as well as concentration of released drug. Copolymers of D,L-lactide and ε-caprolactone were used to obtain microspheres providing long-term constant release of steroids: progesterone and β-estradiol. The appropriate design of structure and composition of lactidyl monomeric units in copolymer chain allows to obtain microspheres that characterizes constant release of steroid until 70 days after rat administration (Buntner et al., 1998). The investigations on controlled release of nucleoside analogs: 5-fluorouracil (5-FU) and cladribine (2-chloro-2′-deoxyadenosine, 2-CDA) from 4 bioresorbable materials (copolymers of glycolide with D,L-lactide and D,L-lactide with ε-caprolactone) revealed constant release of cytostatic drug over 50 days (Kryczka et al., 2002). The release of cytostatic drug from biodegradable polymer implanted directly into cancer brain tissue is possible without any toxic reaction that was proved during observation of microspheres and polymer matrices degradation in rat brain tissue (Dobrzynski et al., 2006). Gliotic response on implanted microspheres was investigated. The results demonstrated proper tolerance of applied polymer carriers. Any pathological reactions in brain tissues as a result of the implanted polymers which could be caused by their chemical composition, structure and degradation products were not demonstrated.

Selection of doxorubicin as a cytostatic drug for controlled release directly to brain cancer tissue was based on radiobiological and clinical results and proved its efficiency in glioma cells damage (Lin et al., 2005). An immunoconjugate of doxorubicin and a tumor specific monoclonal antibody BR96-DOX was used in target chemotherapy in a human small-cell lung carcinoma intracerebral xenograft model in rats. The immunoconjugate was effective against intracerebral tumors. In the case of heterogeneous brain tumors, enhanced delivery of immunoconjugate with DOX significantly reduced tumor volumes (Muldoon and Neuwelt, 2003). The combination of pegylated-liposomal doxorubicin and topoisomerase I and II chemotherapeutic agent was used in the treatment of high-grade malignant brain tumors. The inhibition of tumor progression was occurred in half of patients, but the toxicity was high (Wagner et al., 2008). Free doxorubicin and liposomal doxorubicin were also used in therapy of brain tumors in rats (Zhou et al., 2002). The results suggest that the breakdown of tumor vasculature induced by stabilized long-circulating liposomes with DOX may arise from the perivascular accumulation of liposomes in tumor and cytotoxic effects on tumor vascular endothelium. However all of these liposomal systems are still high toxic after intravascular injection. In this work the method to obtain system for controlled, constant doxorubicin release from biodegradable carrier which may be implanted directly into brain tumor or postoperative brain site was shown. Biodegradable polyester matrices with specifically designed microstructure of polymer chain were used to obtain this effect. PGLA and PGCA were chosen to construction of matrices based on the hydrolytic degradation results of these polyester materials.

2. Materials and methods

2.1. Materials

Glycolide and L,L-lactide were purchased from Purac and purified by recrystallization from dry ethyl acetate and dried under vacuum at ambient temperature. ε-Caprolactone was supplied by Fluka and distilled under argon before use in copolymerization. Zirconium initiator $Zr(acac)_4$ was purchased from Sigma–Aldrich.

2.2. Synthesis of polyesters with different chains microstructure

Copolymerizations of glycolide with L,L-lactide and glycolide with ε-caprolactone were performed in bulk under argon at temperature (100–150 °C) in presence of zirconium initiator $Zr(acac)_4$ with molar ratio initiator to comonomers of 1/1000 for PGLA and 1/800 for PGCA. The resulting copolymers were washed with methanol to remove unreacted monomers and then dried under vacuum at 50 °C to constant weight (Dobrzynski et al., 2001, 2005).

2.3. Molecular weights measurements of obtained copolymers

GPC measurements were conducted for copolymers soluble in chloroform by using Spectra Physics SP 8800 chromatograph with Styragel columns in series (10^4, 10^3, 500 A) and Shoedex SE 61 refractive index detector. Chloroform was applied as mobile phase with flow rate 1 ml/min. Molecular weights were estimated according to polystyrene calibration curve using polystyrene standards (Polysciences).

2.4. Melting and glass-transition temperatures measurements of obtained copolymers

Differential scanning calorimeter (DSC) measurements were performed with PerkinElmer DSC 6 instruments in temperature range between −70 and +230 °C with heating rate 10 °C/min.

2.5. Comonomers composition and chains structure measurements of obtained copolymers

Composition and structure of polymer materials were analyzed by proton nuclear magnetic resonance spectroscopy using BRUKER AVANCE II Ultra Shield Plus (600 MHz) spectrometer. Dried dimethylsulfoxide-d6 (DMSO) was used as a solvent and tetramethylsilane (TMS) was applied as internal standard. The spectra were obtained at 80 °C with 32 scans, 3.74 s acquisition time and 7 μs pulse width.

2.6. Characteristics of polyester chains

According to the integral intensity of signals in ^{1}H NMR spectra for PGLA (methylene protons region of glycolidyl units) and PGCA (methylene proton region of glycolidyl units and ε-methylene proton region of ε-oxycaproyl units) the following parameters were calculated according to precise algorithms: the experimental average lengths of blocks: glycolidyl (l^e_{GG}), lactidyl (l^e_{LL}), ε-oxycaproyl (l^e_{Cap}), degree of randomness (R) and transesterification coefficient of the second mode (T_{II}) (Kasperczyk, 1996; Kasperczyk, 1999; Dobrzynski et al., 2005).

2.7. Formation of implantable doxorubicin delivery system

Matrices containing 5% (w/w) or 10% (w/w) of doxorubicin were obtained via dissolution of copolymers (0.3 g) in dichloromethane (2 ml) and drug in 1,1,1,3,3,3-hexafluor-2-propanol (1 ml). Solutions were mixed, put into desiccator and next were cast by means

Table 1
T_m: melting temperature, T_g: glass-transition temperature, M_n: number average molecular weight, D: polydispersity, l^e: experimental average length of blocks, R: degree of randomness, T_{II}: transesterification of the second mode, k: ratio of comonomeric units in copolymer chain.

Type of copolymer	T_m (°C)	T_g (°C)	M_n (kDa)	D	k	l^e	R	T_{II}
PGLA	158	58	119	2.1	[GG]/[LL] = 15/85	$l^e_{GG} = 1.373$ $l^e_{LL} = 6.998$	0.507	0.15
PGCA	54	−60	91	2.1	[GG]/[C] = 10/90	$l^e_{GG} = 0.541 l^e_{Cap} = 6.672$	1.07	1.14

of a standard cast device. The matrices were dried at ambient temperature and under vacuum for 14 days. Then the matrices were placed into aCFS for the purpose of elimination of drug molecules from the matrix surface, shaked for 1–2 min and dried again under vacuum.

2.8. Preparation of artificial cereobrospinal fluid solution (aCFS)

aCFS was made by combination of two solutions in a 1:1 ratio. First solutions contains: 8.66 g NaCl, 0.224 g KCl, 0.156 g $CaCl_2$, 0.163 g $MgCl_2 \cdot 6H_2O$ in 500 ml pyrogen-free, sterile water. Second solution contains: 0.214 g $Na_2HPO_4 \cdot 7H_2O$, 0.027 g $NaH_2PO_4 \cdot H_2O$ in 500 ml pyrogen-free, sterile water. Sterilization was made by gamma-irradiation with dose of 25 kGy.

2.9. Investigation of doxorubicin release from matrices

About 30 mg of polymer matrix with cytostatic drug were placed in ampoules with 2 ml of aCFS, which was replaced every 4 days. Incubation was conducted at 37 °C during 476 days. Absorbance level of doxorubicin released from polymer carriers was analyzed by means of UV–vis spectroscopy at wavelength $\lambda = 482$ nm. 3 Samples of matrices with the same chain microstructure were analyzed parallel in one experiment. Experiment was repeated two times.

2.10. Degradation investigation of matrices with and without cytostatic drug

Matrices of PGCA with 5% (w/w) of doxorubicin content were chosen for degradation study. Matrices with and without drug were placed in aCSF. Polymer discs with doxorubicin ($d = 1.2$ cm) were incubated at 37 °C and simultaneously shaked. The medium was replaced every 4 days. Every two weeks, the matrices were dissolved in dimethylsulfoxide-d6 to study changes in polymer chain structure by means of H-1 NMR. Degradation of PGCA matrices was analyzed during 126 days. Degradation study of matrices without drug was performed in the same way.

2.11. Investigation of doxorubicin release from combination of matrices with different microstructure

The investigation of doxorubicin release from combination of PGLA and PGCA matrices was conducted according to the procedure described in Section 2.9.

3. Results and discussion

PGLA and PGCA copolymers with specific designed chains microstructure where chosen to obtain matrices with doxorubicin (Dobrzynski et al., 2001, 2005; Li et al., 2005). Copolymers were chosen on the basis of previous results of in vitro degradation studies on these kind of polymers (Jaworska et al., 2007; Kasperczyk et al., 2008a; Maciejowska et al., 2006). Theoretically, PGLA degrades faster than PGCA with low content of glycolidyl units in copolymer chain (about 10 mol%). Moreover, presence of specific sequences in copolymer chain enables its stable, slow degradation what was confirmed by means of NMR spectroscopy and ESI-MS mass spectrometry (Kasperczyk et al., 2008b). The parameters used to

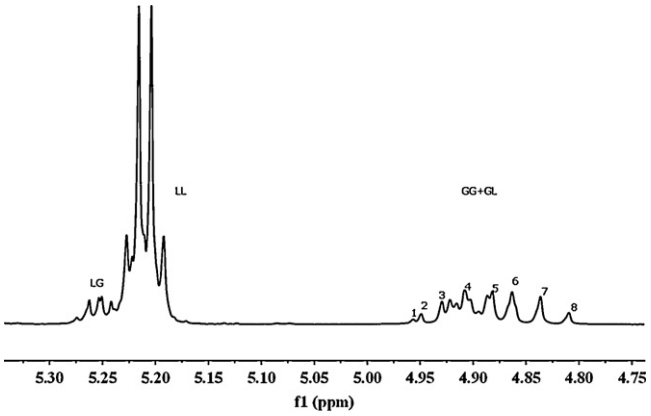

Fig. 1. ^{1}H NMR spectrum (600 MHz, DMSO-d6) of PGLA, methine proton range of lactydyl units [5.15–5.28 ppm] and methylene proton region of glycolidyl units [4.80–4.96]. LL, LG, GL and GG—diad comonomeric sequences, (1) GLGGG or GGGLG, (2) LGGLG or GLGGL, (3) GGGGGG, (4) LLGGL + LGGLL, (5) GGGGL + LGGGG, (6) LLGGG + GGGLL, (7) LLGLL + GLGLL + LLGLG + GLGLG, and (8) GGGLG or GLGGG pentad comonomeric sequences.

characterize the obtained polymer materials: melting temperature (T_m), glass transition temperature (T_g), molecular weights and polydispersity (GPC) as well as the parameters characterizing the polyester chains microstructure (NMR) were shown in Table 1. In the case of PGLA the appropriate comonomer sequences were assigned to spectral lines in methylene protons region of glycolidyl units and methine protons region of lactidyl units (Fig. 1). In the case of PGCA the appropriate comonomer sequences were assigned to spectral lines in methylene protons region of glycolidyl ε-oxycaproyl units (Fig. 2). According to equations shown in previous papers (Kasperczyk, 1996, 1999; Dobrzynski et al., 2005; Li et al., 2005) and spectral lines intensity, the parameters characterizing the copolymers chains microstructure: experimental average

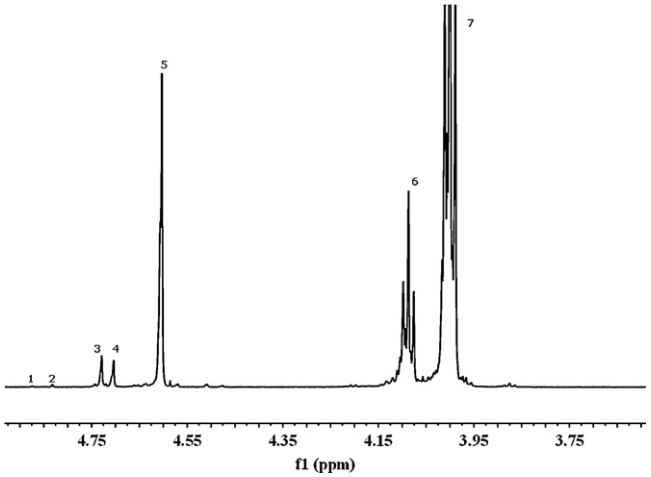

Fig. 2. ^{1}H NMR spectrum (600 MHz, DMSO-d6) of PGCA, methylene protons region of glycolidyl units—GG [4.60–4.88 ppm] and methylene proton region of ε-oxycaproyl units—GG [3.95–4.10 ppm]: (1) 4.88 ppm [GGGGGG], (2) 4.83 ppm [GGGGCap], (3) 4.73 ppm [CapGGGG + CapGGGCap], (4) 4.70 ppm [CapGGCap], (5) 4.60 ppm [CapGCap], (6) 4.09 ppm [GCap], and (7) 4.00 ppm [CapCap].

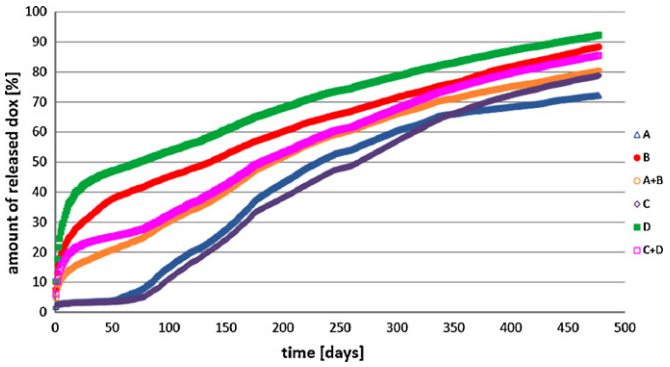

Fig. 3. Cumulative release of doxorubicin from copolymer matrices: (A) PGLA 5% of doxorubicin; (B) PGCA 5% of doxorubicin; (C) PGLA 10% of doxorubicin; (D) PGCA 10% of doxorubicin; (A + B) combination of A and B matrices; (C + D) combination of C and D matrices.

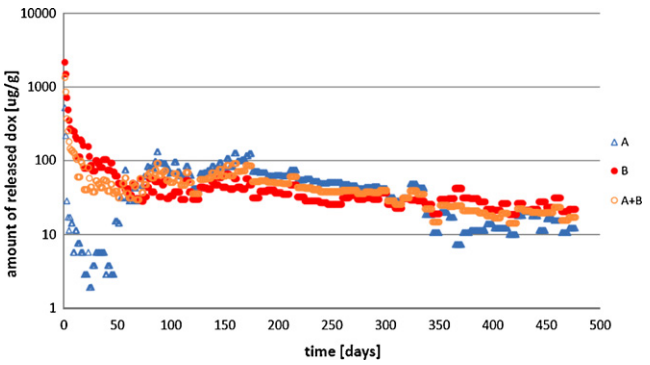

Fig. 4. Daily dose of released doxorubicin from copolymer matrices: (A) PGLA 5% of doxorubicin; (B) PGCA 5% of doxorubicin; (A + B) combination of A and B matrices.

lengths of blocks (l^{e}_{GG}, l^{e}_{LL}, l^{e}_{Cap}), degree of randomness R, transesterification of the second mode (T_{II}) were determined. The obtained copolymers were used to prepare matrices with uniform cytostatic drug.

The drug release profile is dependent on the shape of the matrix, particularly in the case of large-sized matrix, in which faster internal degradation and degradation induced morphological may be present (Li, 1999). The main restriction in local chemotherapy is small size of implantation site. The shape of matrices was connected with improvement of implantation manner. Therefore in our case cylindrical shape of matrices 1.2 cm in diameter was chosen to avoid sharp edge of matrix. The thickness of matrices 0.5 mm decreases possibility of faster internal degradation of matrix and also ensures with flexibility of such devices. Discs up to 0.5 mm in thickness could be easily rolled up and put directly through a small hole to postoperative site.

The obtained matrices were placed into artificial cerebrospinal fluid solution (aCFS) and the processes of cytostatic drug release and matrices degradation were analyzed. At the same time the degradation process of polymer carrier without cytostatic drug was monitored.

The influence of polymer carrier microstructure on controlled doxorubicin release to aCFS was determined. In case of matrix obtained from PGLA delay of doxorubicin release was observed. The release process was very slow until about 50 days, what is visible in cumulative diagram (Fig. 3A) and daily dose diagram (Fig. 4A). Just after 50 days of experiments the increase of released doxorubicin concentration was observed as a result of progressive matrix degradation. Comparison of the obtained results with data concerned on copolymeric carrier degradation was surprising, because other result was expected—slower doxorubicin release from PGCA matrix and faster from PGLA matrix, because PGCA with only 10% of glycolidyl units content undergoes much slower degradation than PGLA. Slow decrease of doxorubicin release after burst effect was observed in case of matrices obtained from PGCA (Figs. 3B and 4B). Doxorubicin release from PGCA in initial phase of experiments can be explained as a result of cytostatic drug diffusion through matrix containing 90% of ε-oxycaproyl units, what was observed repeatedly (Buntner et al., 1998). However, the release delay in case of PGLA matrix suggests presence of strong interactions between cytostatic drug molecule and polymer matrix.

In order to confirm the presence of these interactions infrared spectroscopy was used. The FTIR spectra recorded for pure doxorubicin, pure PGLA and mixture of them prove that after mixing PGLA with doxorubicin the broadening and shifts of bands in the region of 3800–3200 cm^{-1} are observed (Fig. 5A spectra 1–3). That region of FTIR spectra is characteristic for the hydroxyl group stretching vibrations. Positions of appearing bands, below 3600 cm^{-1}, suggest that both in drug and in mixture of drug with copolymer, the hydroxyl groups occur as association form. However changes in shape of the spectra in that region indicate that after mixing is followed by change in hydrogen bonds distribution. It could be explained by forming of hydrogen bonds between hydroxyl groups

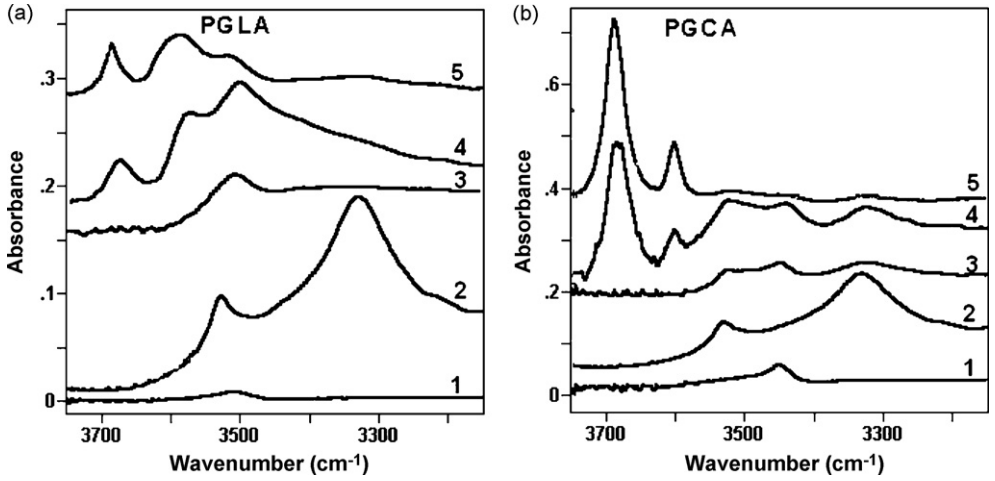

Fig. 5. FTIR spectra of PGLA (A) and PGCA (B) matrixes with doxorubicin: (1) matrix as a film obtained from dichloromethane solution after evaporating of solvent, (2) DOX in potassium bromide pellet, (3) mixture of matrix with doxorubicin as a film obtained from dichloromethane solution after evaporating of solvent, and (4) mixture of matrix with doxorubicin as a solution in dichloromethane in 0.10 mm cell, 5–10 times dissolved the (4) solution in 1.10 mm cell.

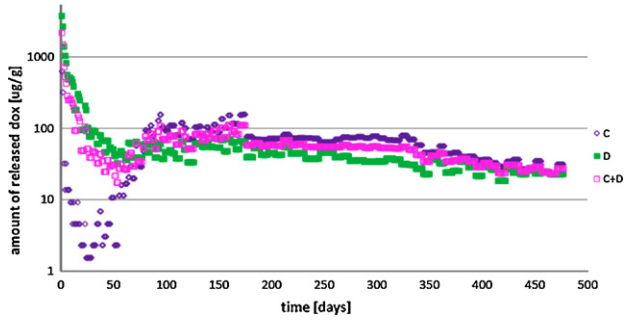

Fig. 6. Daily dose of released doxorubicin from copolymer matrices: (C) PGLA 10% of doxorubicin, (D) PGCA 10% of doxorubicin; (C + D) combination of C and D matrices.

present in doxorubicin and carbonyl groups of copolymer. The band due to free hydroxyl groups appears just in diluted solutions (in our case in dichloromethane) at about 3700 cm^{-1} (Fig. 5A spectra 4 and 5), although bands due to bonded hydroxyl group are still observed.

On the contrary, in the case of PGCA matrix, the FTIR spectrum of the mixture is a sum of PGCA and doxorubicin FTIR spectra in that region (Fig. 5B spectra 1–3). It indicates that no interactions between the copolymer and doxorubicin take place. Dilution of that mixture in dichloromethane causes only the break of hydrogen bonds present in doxorubicin and appearing free hydroxyl groups at about 3700 cm^{-1}. Intensity of this band increases with following dilution of the solution (Fig. 5B spectra 4 and 5).

The influence of drug amount in polymeric carrier was also analyzed. In comparison to matrices with 5% (w/w) of cytostatic content, the amount of released doxorubicin (calculated as % of released drug) from PGLA matrices with 10% (w/w) of drug content did not change during first 50 days (Figs. 3C and 6C), which was caused by interaction of doxorubicin hydroxyl group with polylactide carbonyl group. However, the amount of released doxorubicin was higher in case of matrices obtained from PGCA with 10% (w/w) of drug content than for matrices with 5% (w/w) of doxorubicin content during first 50 days of the experiment (Figs. 3D and 6D). After 476 days of doxorubicin release from polyester carriers, the percentage amount of released doxorubicin from both PGLA and PGCA matrices containing 10% (w/w) of cytostatic drug content were higher than from matrices with 5% (w/w) of drug content. It resulted from looseness of matrix structure caused by twice higher amount of cytostatic drug molecules that allowed the process of doxorubicin molecules diffusion from matrix to occur or increase. Daily dose diagrams for 5% (w/w) and 10% (w/w) of cytostatic drug content clearly prove the observed delay of doxorubicin release during first 50 days from PGLA (Figs. 4A and 6C). In case of PGLA matrix with 5% (w/w) of doxorubicin content (Fig. 4A) after delay stage, the increase of released drug amount to level of 80–100 μg/g and stable release in this range from 60 to 180 days of experiment was observed. Next, slow decrease of released drug amount from 70 to 10 μg/g was registered. In case of PGCA matrix with 5% (w/w) of doxorubicin content (Fig. 4B) burst effect followed by fast decrease of released drug amount to level of about 40 μg/g was observed during first 60 days. Next, slow decrease of released drug amount from 40 to 25 μg/g was registered. In case of 10% (w/w) of doxorubicin content in polymeric matrices similar release profiles were observed. In case of PGLA matrix (Fig. 6C) after delay stage, increase of released drug amount to level of 90–110 μg/g and release in this range from 80 to 180 days were observed. Next, between 180 and 330 days of experiment, stable release about 70 μg/g of doxorubicin was noticed, afterwards slow decrease of released drug amount from 70 to 30 μg/g was registered. In case of PGCA matrix (Fig. 6D) burst effect followed by fast decrease of released drug amount to level of about 50 μg/g was observed during

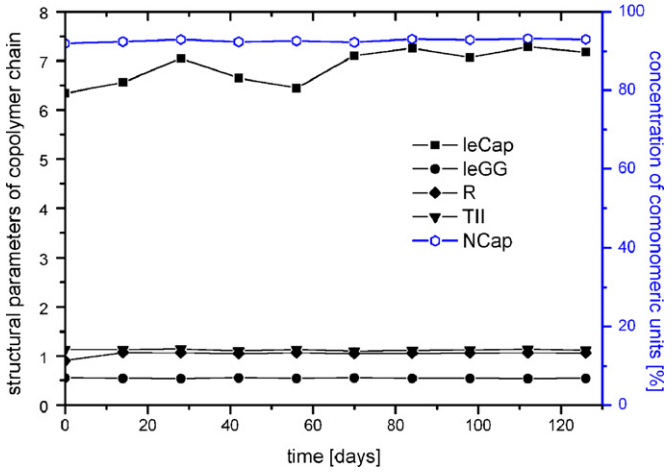

Fig. 7. Changes of ε-oxycaproyl units N_{Cap} concentration in copolymer chain, averages lengths of glycolidyl l^e_{GG} and caproyl l^e_{Cap} blocks, degree of randomness R and transesterification coefficient T during degradation, matrices with 5% of doxorubicin content.

first 60 days. Next, stable, slow decrease of released drug amount to 25 μg/g was registered. The comparison of doxorubicin release profiles from degradable polymer matrices showed that doxorubicin was released in the most stable way from PGCA with 5% (w/w) of drug content.

The degradation process studies of PGCA matrices with and without 5% of doxorubicin content confirmed slow, stable degradation, because only insignificant changes of parameters values characterizing copolymer chain: concentration of comonomeric units (N_{GG} and N_{Cap}), average lengths of glycolidyl (l^e_{GG}), and ε-oxycaproyl (l^e_{Cap}) blocks, degree of randomness (R) and transesterification coefficient of the second mode (T_{II}) were observed (Fig. 7). For example, the concentration of glycolidyl units (N_{GG}) decreased insignificantly from 8% to 7% after 126 days, what confirms the resistance of alternate sequences [CapGCap] to degradation, that was presented in our previous papers (Li et al., 2005; Kasperczyk et al., 2008b; Kasperczyk, 1999).

The observed influence of matrices microstructure on doxorubicin release profile as well as release delay from PGLA matrices in the beginning stage can be useful for modification of released drug concentration. The system of doxorubicin release composed of matrices with different microstructure was designed. Doxorubicin release from system composed of 50% of PGLA matrices and 50% of PGCA matrices were examined. Cumulative curves and daily dose of released doxorubicin from this system were shown in Figs. 3, 4 and 6. Doxorubicin was released more evenly from combination of polyester matrices with different copolymer chain microstructure especially during first 50 days (Figs. 4 and 6). High level of doxorubicin released in first 60 days from PGCA matrices was balanced by low-level release from PGLA matrices and in consequence more evenly release of doxorubicin was observed from 15 day.

4. Conclusions

The influence of the chain microstructure on release process of doxorubicin from polymeric matrices was found. Various release profiles from PGLA and PGCA matrices were obtained. The investigations showed the most steadily doxorubicin release from PGCA matrices with 5% (w/w) of drug content. Degradation study of these matrices with drug and without drug determined by means of NMR spectroscopy confirmed stability of degradation process. In the case of PGCA matrices, during first 60 days of release process,

the increase of released doxorubicin amount was observed. On the contrary in the case of matrices obtained from PGLA the inhibition of doxorubicin release was observed during first 50 days, what was caused by interaction of drug molecules with polymer chains matrix as a result of intermolecular hydrogen bonds formation between hydroxyl group of doxorubicin and carbonyl group of polylactide. This fact can be used for designing of delivery systems consisting of combination of matrices with different microstructure of copolymer chains in order to adjust concentration of released doxorubicin and stabilization of drug release process.

Acknowledgments

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