

Synthesis of biodegradable glycolide/L-lactide copolymers using iron compounds as initiators

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Abstract

The aim of this paper is to present a new method of copolymerization of glycolide with L-lactide with the use of low toxic iron compounds. The use of $\text{Fe}(\text{acac})_3$ and $\text{Fe}(\text{OEt})_3$ initiators enabled one to obtain copolymers with yields up to 100% and possessing good mechanical properties. The chain propagation process and the influence of the transesterification was examined.

On the basis of NMR examination and DSC thermograms, it was shown that the samples obtained at the temperature of 100 °C with the use of the initiators have quasi-segmental chain microstructure. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Polyglycolide and copolymers of glycolide with lactide belong to the renowned biodegradable materials widely used in medicine and pharmacy. They can be utilized to produce surgical fibers [1], devices for bone fracture internal fixation [2,3] as well as microspheres used in controlled drug release [4,5]. These copolymers are known as commercial materials (Dexon, Vicryl). Their synthesis is carried out generally with the use of tin compounds as initiators [6,7]. However, the complete elimination of highly toxic tin compounds from the polymers are practically impossible [8], which results in their slow penetration into patients' blood circulation systems. It is known that these compounds, even in trace amounts, are especially dangerous for small children and endanger proper functioning of tissues [9,10]. Several attempts were made to use less toxic initiators, mainly zinc chloride [11], zinc lactate [12] and calcium [13] and zirconium acetylacetonates [14,15]. So far only zinc chloride and zirconium acetylacetonate have allowed one to obtain copolymers of glycolide with lactide with high enough molecular masses to be used in production of surgical materials.

The use of iron compounds as initiators of biomedical materials synthesis is of particular interest because of the fact that iron is one of the elements found in natural

metabolic processes in human body. Complex iron compounds were found to be particularly low toxic [16].

Thus, several attempts to use these compounds as initiators in the polymerization of lactones were made. Kricheldorf et al. employed iron chloride for the copolymerization of glycolide with ϵ -caprolactone [17], as well as hematin, porphyrin iron complexes and iron (II) lactate as initiators in the polymerization of lactide [18,19]. Unfortunately, the obtained polylactide had relatively low molecular mass. Iron alkoxides [20] were also used for the polymerization of lactide.

This paper presents the results of research concerning copolymerization of glycolide with L-lactide with such initiators as iron(III) acetylacetonate, iron(III) ethanolate, iron(III) chloride and iron(II) lactate. Special attention has been paid to the influence of particular initiators on the transesterification process and its role in the formation of copolymer chain microstructure.

Some of our earlier papers concerned with lactide copolymerization with ϵ -caprolactone distinguished between the first and the second mode of transesterification [21,22]. Transesterification of the first mode takes place during intermolecular exchange of lactidyl (-LL-) and glycolidyl (-GG) units or their multiples. In the case of transesterification of the second mode lactidyl and glycolidyl groups undergo bond cleavage, which leads to the formation of GLG or LGL sequences, as well as GLLL, LGGGL ones and other sequences with odd numbers of lactyl (L) and glycolyl (G) units in microblocks.

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In the previous papers [15,23], the coefficient of transesterification of the second mode was introduced for glycolyl blocks as

$$T_{II\ LGL} = [LGL]/[LGL]_R \quad (1)$$

where [LGL] is the actual amount of sequences of the given type in copolymer, [LGL]_R is the amount of sequences of the given type calculated according to Bernoulian statistics:

$$[LGL]_R = k/(k + 1)^3 \quad (2)$$

where $k = [G]/[L]$

The coefficient of transesterification of the second mode of lactidyl blocks was introduced by analogy according to equations described in [15].

$$T_{II\ LGL} = [GLG]/[GLG]_R \quad (3)$$

where

$$[GLG]_R = k^2/(k + 1)^3 \quad (4)$$

According to Eqs. (1) and (2), the value of T_{II} is close to one when the contribution of glycolyl and lactyl units in the chain is close to Bernoulian statistics. The value of T_{II} is higher than one when longer alternative sequences of -GLGLGL- type are propagated in copolymers. Mechanical properties of chosen copolymers have also been examined and compared with properties of the copolymers obtained in the presence of Sn(oct.)₂.

2. Experimental

2.1. Monomers and initiators

Glycolide (Purac) and L-lactide (Purac) have been purified by recrystallization from dry ethyl acetate and dried in vacuum oven at room temperature. Iron(III) acetylacetonate (Fluka Chemica), iron(III) ethanolan (ABCR), iron(II) lactate (Fluka Chemika) iron(III) chloride (Fluka Chemika) and stannous 2-ethylhexanoate) (Sn(oct.)₂) (Sigma Chem. Co.) have been used without any purification.

2.2. Copolymerization procedure

Copolymerization of glycolide with lactide has been performed in bulk at moderate temperatures in the range of 100–150 °C by a conventional method using a vacuum line for degassing and sealing of the ampoules. The copolymerization carried out with the use of Fe(OEt)₃ required higher temperature (150 °C) because of the low solubility of this compound at 100 °C.

When the copolymerization was carried out at 100 °C for the initial content of glycolide more than 50 mol%, the reaction mixture was initially heterogenic. The obtained copolymers have been ground and shaken with methyl alcohol in order to remove unreacted monomers and then dried in vacuum at 50 °C.

2.3. Measurements

The viscosity of the obtained copolymers has been determined in 1,1,1,3,3,3-hexafluoro 2-propanol (HFIP) at 25 °C using the Ubbelohde viscometer. The concentration of the solution was 2 g/dm³. Intrinsic viscosity has been calculated from measurements of relative viscosity on the basis of the single point method of Salomon and Ciuta [24]. The usefulness of such a method was demonstrated previously for this type of copolymers [25].

Average viscosity molecular weights for glycolide L-lactide copolymers have been calculated using Kenley's equation: $[\eta] = (1.67 \times 10^{-4})M_v^{0.794}$ [25].

The molecular weights and polydispersity indices of the copolymers which were soluble in chloroform have been determined by the liquid chromatography method using Waters ALC/GPC 3 m apparatus (polystyrene standards) and by gel permeation chromatography with the aid of a Spectra Physics SP 8800 chromatograph (chloroform was used as the eluent, flow rate = 1 mL/min, Styragel columns 104,103 and 500A Shoedex SE 61 detector).

The ¹H NMR spectra of the copolymers have been recorded at 300 MHz using Varian Unity Inova spectrometer and 5 mm sample tube. Dried DMSO-d₆ was used as solvent. The spectra have been obtained at 100 °C with 32 scans, 3.74 s acquisition time and 7 ms pulse width.

The ¹³C NMR spectra (75 MHz) have been acquired on Varian Unity Inova spectrometer using 5 mm sample tubes and dried DMSO-d₆ with measurement temperature 100 °C, 3000 scans, acquisition time 1.8 s, pulse width 9 ms and delay of 3 s between pulses.

The conversion of the reaction has been determined by NMR spectroscopy measurement and the yield by weighing washed and dried copolymers. The copolymer compositions, chain microstructure and transesterification processes have been defined by means of ¹H and ¹³C NMR spectroscopy measurements [14,15]. The ¹³C NMR and ¹H NMR peaks were assigned to different chain segments according to the method described previously in Ref. [23].

Thermal properties, such as glass transition temperatures and heats of crystallization or melting, have been studied by differential scanning calorimetry using a DSC Du Pont 1090B apparatus calibrated with gallium and indium (the heating rate –20 °C/min). The thermogravimetric measurements have been conducted with a Q-1500 MOM Budapest apparatus in nitrogen atmosphere at the heating rate of 10 °C/min.

2.4. Determination of mechanical properties

The following samples have been prepared for testing of mechanical properties:

Samples for compressive strength test. The material was melted in a closed cylindrical ampoule in argon atmosphere and then, after cooling, the casting cylinder was taken out and cut into smaller samples.

Table 1

Polymerization of glycolide and copolymerization of glycolide with L-lactide (polymerization in bulk, mole ratio of initiator to monomer -1.2×10^{-3} ; NG—feed mole fraction of glycolide (molar percentage), FG—contents of glycolide in copolymer (molar percentage), η_{inh} —inherent viscosity, M_v —viscosity-average molecular weight, *M_n —number-average molecular weight, D —molecular weight distribution, l_{GG} , l_{LL} —average length of glycolidyl or lactidyl blocks in copolymer chains, T_{II} [GLG]—yield of the second mode of transesterification (sequences GLG), T_{II} [LGL]—yield of the second mode of transesterification (sequences LGL))

No.	Initiator	N_G (%)	Temperature (°C)	Time (h)	Yield (%)	F_{GG} (%)	η_{inh} (dL/g)	M_v (*M_n) $\times 10^{-3}$	l_{GG}	l_{LL}	T_{II} [GLG]	T_{II} [LGL]
1A	Fe(acac) ₃	100	100	96	91	100	insoluble	> 40	–	0	–	–
1B	Fe(OEt) ₃	100	150	48	92	100	insoluble	> 40	–	0	–	–
1C	FeCl ₃	100	100	96	80	100	insoluble	> 40	–	0	–	–
2A	Fe(acac) ₃	80	100	120	96	80	2.1	140				
2B	Fe(OEt) ₃	80	150	72	94	82	1.5	90				
2C	FeCl ₃	80	100	120	90	84	0.7	35				
2D	Iron(II) lactate	80	100	120	70	100	0.6	25	0			
3A	Fe(acac) ₃	50	100	144	95	53	1.1	65	3.9	3.2	2.1	0.1
3B	Fe(OEt) ₃	50	150	144	96	53	1.3	77	3.7	3	2.7	0.2
3C	FeCl ₃	50	100	144	71	61	0.8	40	4.3	2.7	1.6	0.8
3D	Iron(II) lactate	50	100	144	60	80	0.4	15	5	1.3	0	0.1
4A	Fe(acac) ₃	15	100	144	92	18	1.4	[*] 61 $D = 2.2$				
4B	Fe(OEt) ₃	15	150	168	90	20	0.8	[*] 38 $D = 1.7$				
4C	FeCl ₃	15	100	144	62	32	0.5	[*] 18 $D = 1.5$				
4D	Iron(II) lactate	15	100	168	91	19	0.4	[*] 11 $D = 1.3$				

Samples for tensile strength tests. The samples were cut out from discs molded on a laboratory hydraulic press. Molding temperature depended on the kind of copolymer and varied from 150 to 190 °C. All samples were conditioned in the air at 23 °C for 4 days.

Compressive strength testing. Cylindrical samples (30 mm high) with diameter of 12 mm were tested at 20 °C using an Instron 2402 apparatus with the crosshead speed of 2 mm/min.

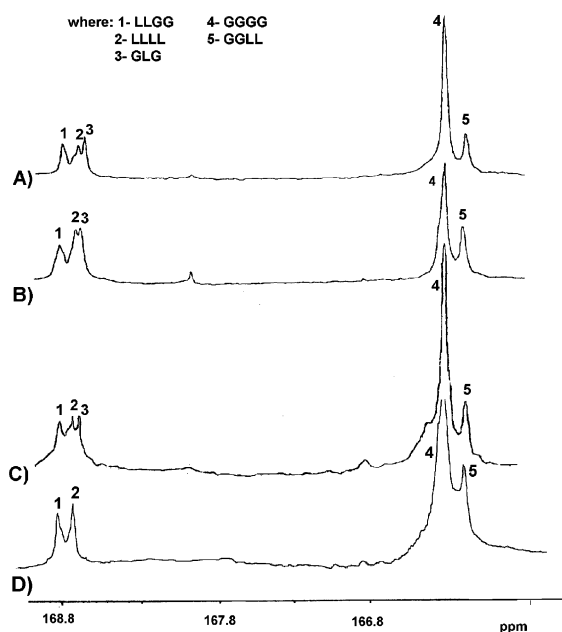


Fig. 1. ¹³C NMR spectra of poly(glycolide-co-L-lactide), 50 mol% of glycolide; (carbonyl region) (A) initiator Fe(acac)₃ (Table 1, pos. 3A), (B) initiator Fe(OEt)₃ (Table 1, pos. 3B), (C) initiator FeCl₃ (Table 1, pos. 3C), (D) initiator iron (II) lactate (Table 1, pos. 3D).

3. Results and discussion

3.1. Results

The results of homopolymerization of glycolide and its

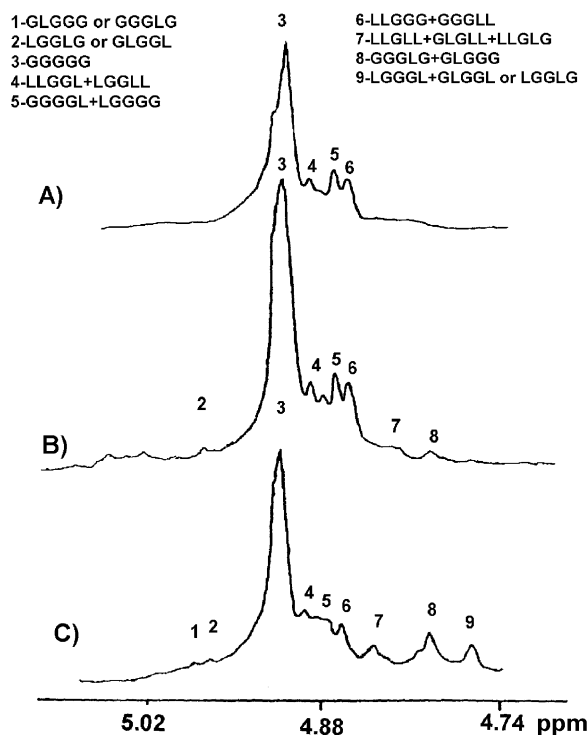


Fig. 2. ¹H NMR spectra of poly(glycolide-co-L-lactide), 50 mol% of glycolide; (region of glycolide methylene protons and lactide methine protons): (A) initiator Fe(acac)₃ (Table 1, pos. 3A), (B) initiator Fe(OEt)₃ (Table 1, pos. 3B), and (C) initiator FeCl₃ (Table 1, pos. 3C).

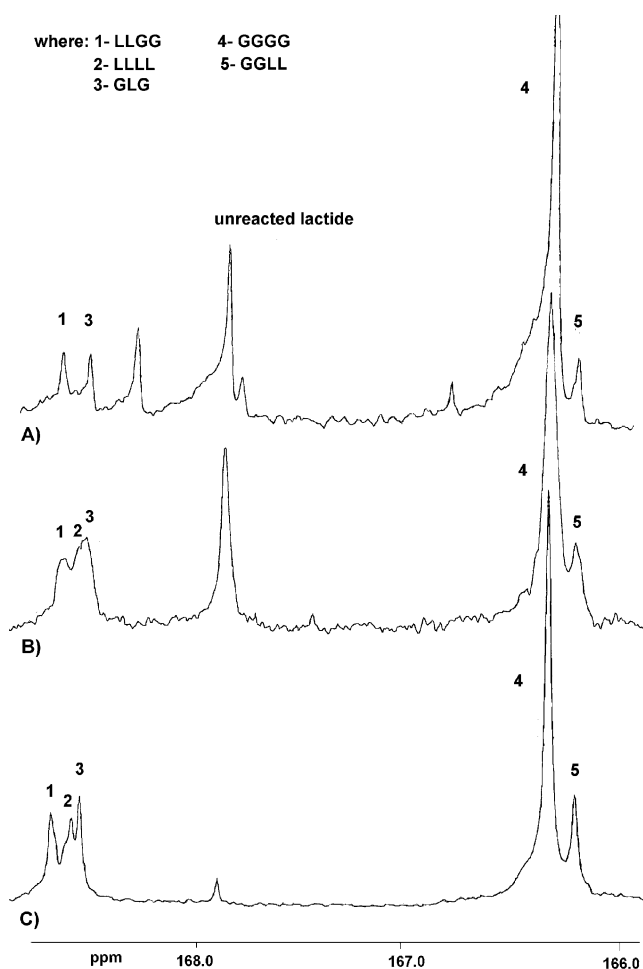


Fig. 3. ^{13}C NMR spectra of poly (glycolide-*co*-L-lactide) (carbonyl region) obtained at different conversion with using $\text{Fe}(\text{acac})_3$ as initiator: (A) conversion 35% (Table 2, pos. 1A), (B) conversion 70% (Table 2, pos. 1C), and (C) conversion 89% (Table 2, pos. 1E).

copolymerization with L-lactide in the presence of various initiators are presented in Table 1. Polyglycolide of high molecular weight has been obtained. Its insolubility in HFIP at room temperature (polyglycolide with $M_v < 40,000D$ is soluble in such a solvent in identical conditions [26]) as well as its DSC thermogram (Figs. 6 and 7) characteristic for high molecular weight polyglycolide [27] support this fact.

Molecular weights of the copolymers obtained in the presence of $\text{Fe}(\text{acac})_3$ and $\text{Fe}(\text{OEt})_3$ are similar to the molecular weights of the copolymers obtained with $\text{Sn}(\text{oct.})_2$ [28]. However, they are higher than the ones obtained with the use of salt type compounds (FeCl_3 , iron lactate). The rate of yield is also lower when iron salts are used, which is connected with the forming of fraction of oligomer soluble in methyl alcohol as one of the reaction products. The presence of -GLG- sequences formed in the process of the second mode transesterification of lactidyl segments by active glycolidyl chain ends is observed in ^{13}C NMR spectra of the obtained copolymers (Fig. 1). On

the other hand, the phenomenon does not occur in the copolymerization process carried out in the presence of iron lactate (Fig. 1D).

The observation of ^1H NMR spectra shows the presence of sequences of -LGL- type (Fig. 2). They form as a result of second mode transesterification of glycolidyl segments by active lactidyl chain ends. The yield of these sequences is quite high only in the case of copolymers achieved in the presence of FeCl_3 (Fig. 2C). Thus, the transesterification coefficient $T_{II}[\text{GLG}]$ is higher than the coefficient $T_{II}[\text{LGL}]$. Table 1 presents respective coefficients of the second mode transesterification. One can notice the lack of correlation between the lengths of microblocks and the coefficients T_{II} , which is due to the fact that the average lengths of microblocks depend not only on the extent of transesterification, but also on the reactivity of particular comonomers in the presence of a given initiator.

3.2. Investigation of copolymerization process

In order to explain the process of formation of the final microstructure of the obtained copolymer, the processes of copolymerization and chain propagation have been examined on the basis of equimolar copolymerization at the temperatures of 100 and 150 °C.

In the case of copolymerization carried out in the presence of $\text{Fe}(\text{acac})_3$, mainly glycolide addition to the growing chain of

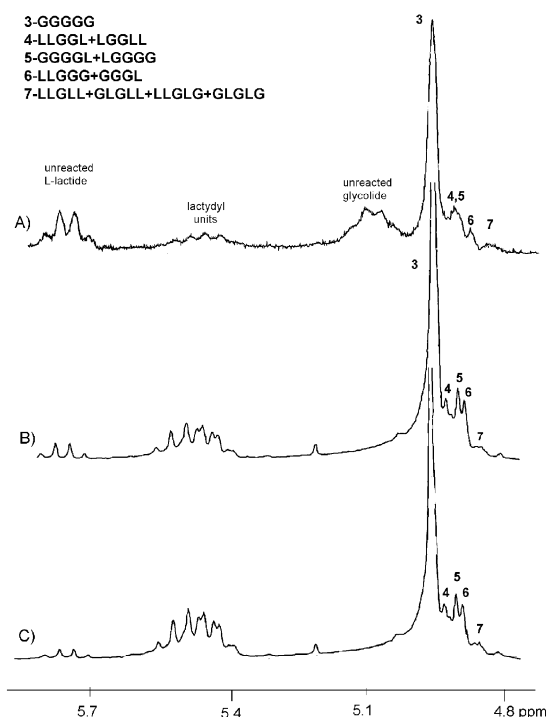


Fig. 4. ^1H NMR spectra of poly(glycolide-*co*-L-lactide) (region of glycolide methylene protons and lactide methine protons) obtained at different conversion with using $\text{Fe}(\text{acac})_3$ as initiator: (A) conversion 35% (Table 2, pos. 1A), (B) conversion 70% (Table 2, pos. 1C), and (C) conversion 89% (Table 2, pos. 1E).

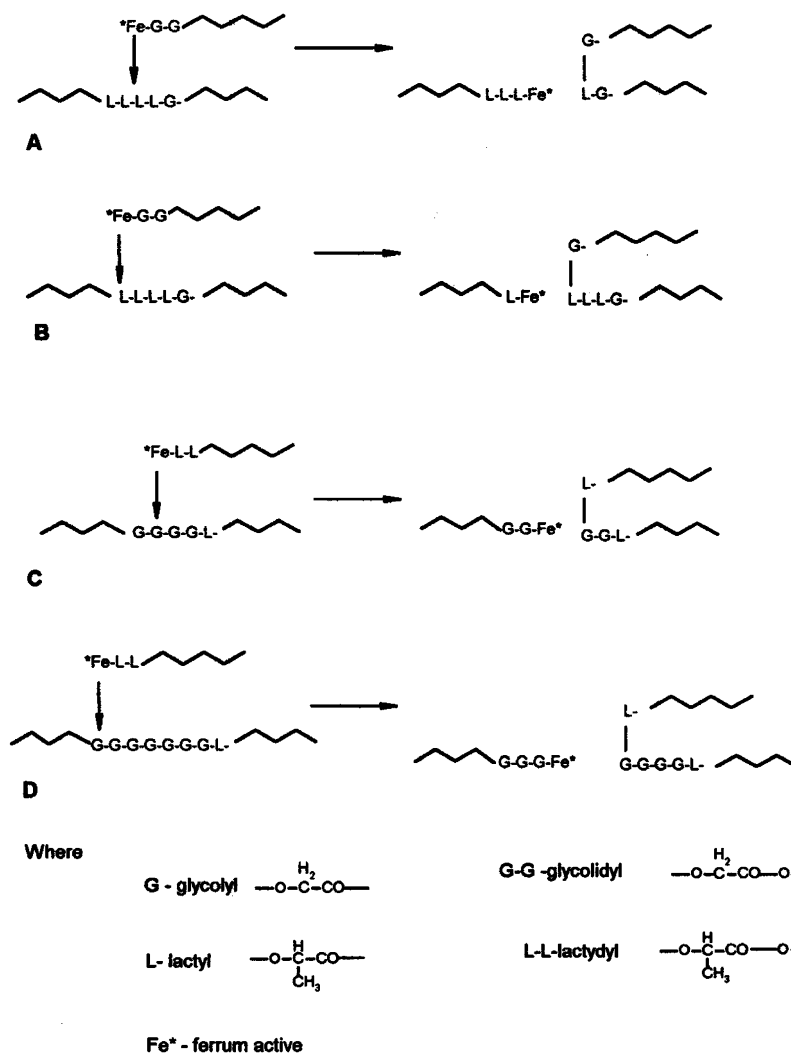


Fig. 5. Scheme of the transesterification of first and second mode proceeded during of the copolymerization.

copolymer is observed at the initial stage of the reaction. A significant peak corresponding to the -GLG- sequences is observed in the ^{13}C NMR spectrum (Fig. 3), which testifies the attack of active glycolidyl ends on forming lactidyl

sequences (transesterification of the second mode— Fig. 5a). The formation of -LGGL- sequences (Fig. 4) can also be observed already at the initial stage of the reaction. These sequences are formed undoubtedly as a result of the

Table 2

Date describing the chain propagation process (Time—time of reaction, Conv.—total conversion of reaction, C_G —conversion of glycolide, C_L —conversion of L-lactide, F_G —contents of glycolide in copolymer, l_{GG} , l_{ll} —average length of glycolidyl or lactidyl blocks in copolymer chains, T_{II} [GLG]—yield of the second mode of transesterification (sequences GLG), T_{II} [LGL]—yield of the second mode of transesterification (sequences LGL))

No.	Initiator	Time (h)	Conv. (%)	C_G (%)	C_L (%)	F_G (%)	l_{GG}	l_{ll}	T_{II} [GLG]	T_{II} [LGL]
1A	Fe(acac) ₃ temperature 100 °C	1	35	60	10	80	7	1.2	3.2	
1B		3	57	90	24	74	6.3	1.7	2.8	0
1C		18	70	97	50	66	5.6	2.9	2.5	0
1D		36	85	99	71	60	5	3.5	2.1	0
1E		144	89	≈ 100	79	58	4.5	3.6	2	0.1
1F		240	95	≈ 100	91	54	3.9	3.6	2.1	0.1
2A	Fe(OEt) ₃ temperature 150 °C	3	49	76	24	82	5.5	1.1	3.4	0.1
2B		18	60	90	32	75	5.5	1.2	2.9	0.2
2C		36	84	97	72	67	4.5	2.5	2.7	0.2
2D		144	96	≈ 100	82	55	3.7	3	2.7	0.2

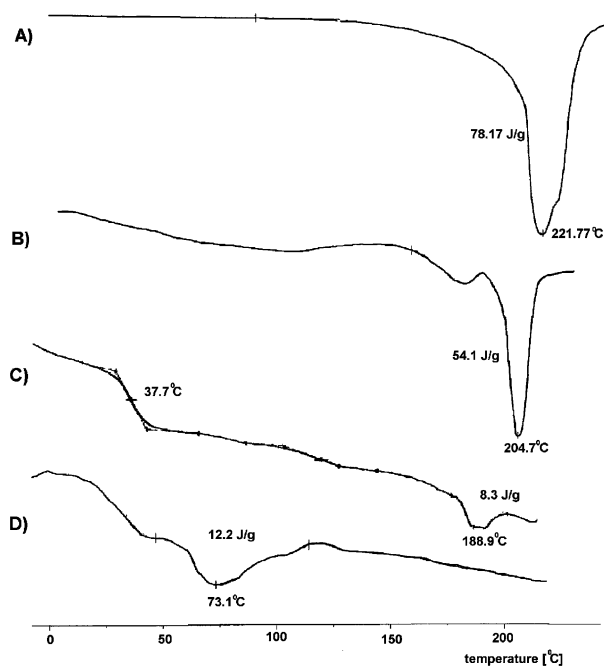


Fig. 6. DSC thermograms (run I) of glycolide/lactide copolymers, obtained with using $\text{Fe}(\text{OEt})_3$ initiator: (A) at 150 °C polyglycolide, (B) at 100 °C 80 mol% glycolide: 20 mol% L-lactide, (C) at 100 °C 50 mol% glycolide: 50 mol% L-lactide, and (D) at 100 °C 15 mol% glycolide: 85 mol% L-lactide.

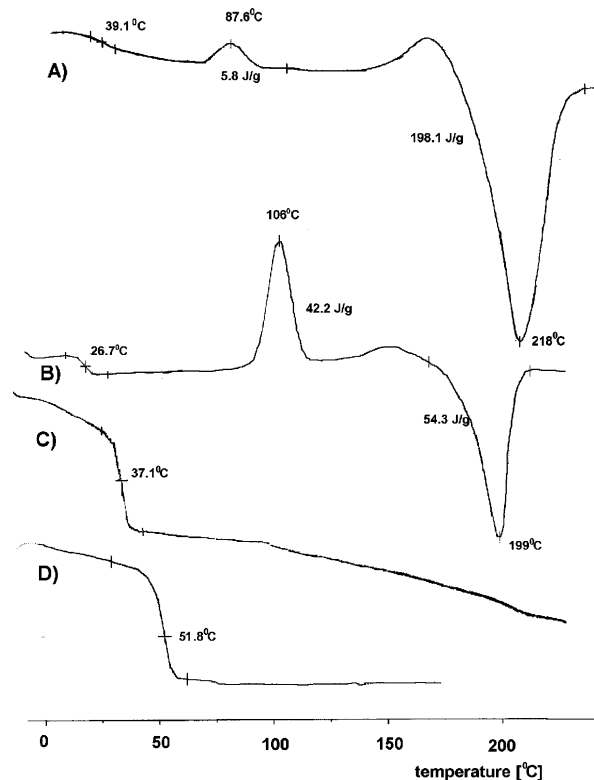


Fig. 7. DSC thermograms (run II) of glycolide/lactide copolymers, obtained with using $\text{Fe}(\text{OEt})_3$ as initiator: (A) at 150 °C polyglycolide, (B) At 100 °C 80 mol% glycolide: 20 mol% L-lactide, (C) at 100 °C 50 mol% glycolide: 50 mol% L-lactide, and (D) at 100 °C 15 mol% glycolide: 85 mol% L-lactide.

first mode transesterification, where active lactidyl chain ends attack glycolidyl sequences (Fig. 5c); however, the presence of -LGL- sequences in the chain is insignificant. With the progression of the reaction and the decrease in glycolide in the reaction mixture, the length of glycolidyl microblocks diminishes and the length of lactidyl ones grows. The average length of glycolidyl microblocks diminishes also after all free glycolide has reacted, which testifies the transesterification of glycolidyl sequences caused by active ends of the growing chains. Due to lack of T_{II} coefficient's rise, it is necessary to assume that in the last step of reaction mainly the first mode transesterification runs.

The process of copolymerization carried out in the presence of $\text{Fe}(\text{OEt})_3$ is very similar with a bit higher rate of the second mode transesterification, which is shown in calculations of its coefficients (Table 2).

3.3. Properties of the obtained copolymers

The results of DSC studies are presented in Figs. 6 and 7. The thermogram of polyglycolide corresponds to the DSC traces of high molecular polyglycolide described by Cohn [27]. The lack of exotherm and big melting endotherm are characteristic features of polyglycolide with high molecular mass. Similar melting endotherm is also characteristic for copolymers containing 80% of glycolide (Fig. 6). The ones that contain less than 80% of glycolide have low resolution melting regions of non-defined ordered structures.

Fig. 7 shows thermograms of copolymers after melting and quick cooling of the samples at liquid nitrogen temperature (reheating-run II). In this case the melting endotherm has not been observed for the copolymers containing less than 80% of glycolide. It agrees with the previous examinations of morphology of copolymers of glycolide with lactide which showed that the degree of crystallization decreased with the growing content of lactide fraction in such copolymers [15,29].

Table 3 presents T_g and T_m as well as crystalline phase melting heat values of the copolymers obtained with $\text{Fe}(\text{OEt})_3$ and $\text{Fe}(\text{acac})_3$. Glass transition temperatures of

Table 3

Dependence of glass transition, melting temperature and melting heat on the copolymer composition and kind of initiator (T_g —glass transition temperature (°C), T_m —melt temperature (°C), dH —heat of melting of crystalline phase (J/deg))

Initiator	Composition	II Run		
		T_g	T_m	dH
$\text{Fe}(\text{OEt})_3$	Glycolide	39	218	198
$\text{Fe}(\text{acac})_3$	Glycolide	36	226	78
$\text{Fe}(\text{OEt})_3$	0.8 Glycolide, 0.2 L-lactide	27	199	54
$\text{Fe}(\text{acac})_3$	0.8 Glycolide, 0.2 L-lactide	39	—	—
$\text{Fe}(\text{OEt})_3$	0.5 Glycolide, 0.5 L-lactide	37	—	—
$\text{Fe}(\text{acac})_3$	0.5 Glycolide, 0.5 L-lactide	42	—	—
$\text{Fe}(\text{OEt})_3$	0.15 Glycolide, 0.85 L-lactide	52	—	—
$\text{Fe}(\text{acac})_3$	0.15 Glycolide, 0.85 L-lactide	51	—	—

Table 4

Mechanical properties of obtained polymers (N_G/N_L —feed mole ratio of glycolide to L-lactide, $S_{c_{max}}$, $S_{t_{max}}$ —maximum compression strength, tensile strength, E_c , E —shear modulus, Young's modulus, ε —elongation at break, $T_{10\%}$, T_{max} temperature of 10% weight loss, temperature of maximum weight loss)

No.	Initiator	N_G/N_L (%)	M_v ($\times 10^{-3}$)	$S_{c_{max}}$ (MPa)	E_c (MPa)	$S_{t_{max}}$ (MPa)	E (MPa)	ε (%)	$T_{10\%}$ (°C)	T_{max} (°C)
1	Fe(OC ₂ H ₅) ₃	100	> 40	118.1	2840				300	350
2A	Fe(acac) ₃	80/20	145	40.7	1400	30.9	3710	1.5	300	350
2B	Fe(OC ₂ H ₅) ₃	80/20	95	38.5	1190	27.2	3050	2.8	295	350
2C	Sn(oct.) ₂	80/20	119	48.3	1600	36.1	3690	1.1	275	340
3A	Fe(acac) ₃	56/44	64	21.8	340	12.2	1510	10.6	280	340
3B	Fe(OC ₂ H ₅) ₃	57/43	87	33.7	390	25.4	1370	6.0	275	340
3C	Sn(oct.) ₂	54/46	95	28.9	460	18.1	2720	2.8	250	310

amorphous samples obtained by quenching (II run) are generally a bit higher in the case of Fe(acac)₃, which may be caused by the above-mentioned differences in microstructure between the obtained copolymers (Table 1, Figs. 1 and 2).

Tests of mechanical properties have been performed in order to check the utility of the obtained copolymers as materials for biodegradable bone implants. The results have been compared with the properties of analogous copolymers obtained under the same conditions but initiated by Sn(oct.)₂. They are presented in Table 4. The parameters concerning mechanical properties of the synthesized copolymers are similar to the ones of analogous copolymers obtained with Sn(oct.)₂ (Table 4).

The results of our research show that the copolymers obtained with Fe(acac)₃ and Fe(OEt)₃ could replace successfully the ones obtained in the presence of tin compounds as far as their medical application is concerned.

The copolymers received using iron chloride or iron lactate as initiator, for the sake of low molecular weight may be alternatively applied only as drug carriers. But these copolymers must be first separated from coexistent oligomers.

The presence of highly toxic tin in such products can be eliminated in this way so that the troublesome and not always effective stage of extracting tin compounds from material in the production process [30,31] can be avoided.

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