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Biodegradable copolymers with succinimide and lactic acid units

Part II. KINETICS OF THERMODEGRADATION, THERMAL CHARACTERISTICS AND ZETA POTENTIAL OF THE PRODUCT**)

Summary — Biodegradable copolymers based on succinimide and lactic acid units prepared by two synthesis routes (variants A and B described in Part I, see [11]) were characterized. Variant A consists in the *in situ* copolymer synthesis using maleic anhydride, ammonium hydroxide and L(+)-lactic acid and accordingly variant B previously prepared poly(succinimide) is modificated be means of L(+)-lactic acid by mass polycondensation procedure. A comparison of thermodegradation kinetics (TG, DTG), thermal properties (DSC, DTG) and zeta potential was compared for the products obtained through both procedures. Differences in the thermal properties of the copolymers — especially in the glass transition temperatures — were observed.

Keywords: poly(succinimide-*co*-lactic acid), thermodegradation, thermal properties, zeta potential, electrical conductivity.

BIODEGRADOWALNE KOPOLIMERY ZAWIERAJĄCE JEDNOSTKI SUKCYNOIMIDU I KWASU MLEKOWEGO. Cz. II. KINETYKA DEGRADACJI TERMICZNEJ, WŁAŚCIWOŚCI CIEPLNE I POTENCJAŁ ZETA PRODUKTÓW

Streszczenie — Przedmiotem badań były powyższe kopolimery otrzymywane w wyniku dwóch różnych wariantów ich syntezy szczegółowo opisanych w części I [11]. Wariant A polegał na syntezie *in situ* z zastosowaniem bezwodnika maleinowego, wodorotlenku amonu i kwasu L(+)-mlekowego, a wariant B obejmował modyfikację uprzednio uzyskanego poli(sukcynoimidu) kwasem L(+)-mlekowym na drodze polikondensacji obydwu tych substancji. W niniejszej publikacji scharakteryzowano wpływ metody syntezy na kinetykę termodegradacji (metody TG i DTG, tabele 1—3, rys. 1—7), właściwości cieplne (metody DSC i DTG, rys. 8) oraz potencjał zeta i związane z nim przewodnictwo elektryczne (zależności od pH i temperatury, rys. 9—12). W szczególności zinterpretowano przy tym zaobserwowane różnice w wartościach temperatury zeszklenia.

Słowa kluczowe: kopolimery sukcynoimid/kwas L(+)-mlekowy, degradacja termiczna, właściwości cieplne, potencjał zeta, przewodnictwo elektryczne.

Poly(lactic) acid (PLA) is an innovative, thermoplastic and biodegradable polymer developed for a wide range of applications, especially in biology and medicine. PLA's medical applications are due to its biocompatibility because it's degradation product — lactic acid — is metabolically innocuous [1—3].

PLA has been copolymerized with a wide range of polyesters and other monomers either by the polycondensation of lactic acid (LA) with these compounds to obtain low molecular weight copolymers, or through ring opening copolymerization of a lactide with cyclic monomers, such as glycolide, ε-caprolactone, δ-valerolactone or trimethylene carbonate, as well as with linear monomers like ethylene glycol [4] to produce high molecular weight copolymers.

The presence of acid and hydroxyl groups in LA makes copolymerization possible through polycondensation. Thus, L-lactic acid and ε-caprolactone have been copolymerized without catalyst to produce low molecular weight [M_w ~ (6.8—8.8) · 10^3] copolymers with excellent *in vitro* (enzymatic) and *in vivo* degradation properties for biomedical applications [5].

An alternate route for PLA copolymer synthesis is, as mentioned above, the ring opening copolymerization of L-lactide initiated by hydroxyl groups present in compounds such as alcohols or polyols [6]. This method has been used extensively due to its precise chemistry control

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**) Part I — see [11].

and the resulting favorable copolymer properties [4]. The polymerization mechanism can be ionic, co-ordination, or free radical depending on the type of catalyst system used [4, 7].

The ring-opening polymerization of (3*S*,6*R*,*S*)-3-[(benzyloxycarbonyl)methyl]-6-methylmorpholine-2,5-dione{Cyclo[Lac-Asp(OBzl)]} and its copolymerization with D,L-lactide in the presence of $Sn(Oct)_2$ as catalyst at 140 °C has been described in [8]. With the removal of protective groups, biodegradable alternating and random copolymers were obtained. The products containing carboxylic groups in the side chain exhibit enhanced hydrophilicity compared to the polylactide and possess sites suitable for chemical modifications.

Some methods in the literature on the synthesis of poly(aspartic) acid (PAS) and poly(succinimide) (PSI) as PAS precursor have been presented in Part I of this publication (see references [21] and [22] in Part I).

Poly(aspartic acid) possesses a carboxylic acid pendant group in its structural unit making it suitable for further modification. So, for example, the synthesis of PAS carried out in a microwave reactor has also been reported [9]. The cyclic product, *i.e.* polysuccinimide, was further subjected to alkaline hydrolysis in the presence of NaOH to obtain a linear derivative — poly(aspartic acid) sodium salt (PAspNa). The influence of monomer:solvent weight ratio and the type of non-solvent used for precipitation of the polymer on the product yield, molecular weight and polydispersity were investigated by changing the above-mentioned parameters.

Investigations on the application of microwave irradiation for the preparation of aspartic/lactic acid biodegradable copolymers have presented also authors of [10]. The reactions were carried out made various parameters of reagent molar ratio, temperature and radiation dose, in solution or in bulk, with or without H_3PO_4 as catalyst. Materials varying in molecular weights, crystallinity, solubility and thermal stability were obtained depending on the copolymerization method applied and reaction parameters.

In Part I of this publication the synthesis of biodegradable copolymers with succinimide and lactic acid units *via* two different reaction routes was presented [11]. In the present study, the characterization of these previously synthesized copolymers is reported and the differences in their properties depending on the chosen synthesis procedures evaluated.

EXPERIMENTAL

Synthesis

The biodegradable copolymer comprising of succinimide and lactic acid units was synthesized using two different procedures described precisely in [11] as variants A and B. In the first, the copolymer was synthesized using maleic anhydride, ammonium hydroxide and L(+)-lactic acid while in second the poly(succinimide) was initially synthesized then further modified with L(+)-lactic acid by mass polycondensation.

Methods of investigations

— Thermal degradation of polymers was performed using a Jupiter STA 449F1 thermogravimetric balance (Netzsch, Germany). Samples (mass ranging from 7 to 10 mg) were heated from 30 to 600 °C, at rates of 5, 10 or 20 °C/min. Nitrogen (99.99 % purity) was used as a carrier (flow rate 50 ml/min) and protective purge for the thermobalance (flow rate 20 ml/min). The samples were heated in an open Al_2O_3 crucible using Al_2O_3 as reference material. Data was processed with Proteus® software.

— DSC thermal analyses were carried out in a Perkin Elmer Pyris Diamond in a differential scanning calorimeter at a heating rate of 10 °C/min in nitrogen.

— Zeta potential measurements were performed with a Zetasizer Nano ZS instrument (Malvern Instruments, UK) by laser light diffusion method, using aqueous solutions (1 g/dL) of the samples. The instrument works with a laser Doppler electrophoresis (4 mW He-Ne, 633 nm) technique. Electrophoretic mobilities (μ) of particles were measured and converted to zeta potential (ζ) according to the Smoluchowski equation:

$$\zeta = \eta\mu/\varepsilon \quad (1) \qquad \text{and} \qquad k\alpha >> 1 \quad (2)$$

where: η — *viscosity,* ε — *dielectric constant of the medium, k and* α — *Debye-Hückel parameter and the particle radius, respectively.*

The average (results from 5 measurements) is taken as zeta potential value. The difference between measurements and their average is less than 2.5 %. Zetasizer Nano ZS instrument also enables the determinations of the electrical conductivity.

RESULT AND DISCUSSION

Thermodegradation

TG and DTG curves illustrating the weight loss by thermal decomposition in inert medium (N_2 gas) of

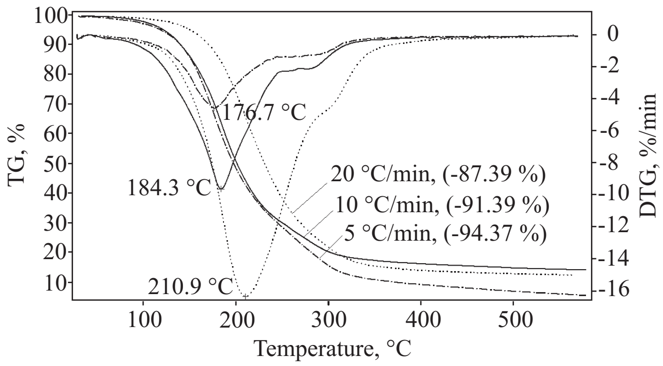

Fig. 1. TG and DTG curves for PSI-co-LA, variant A

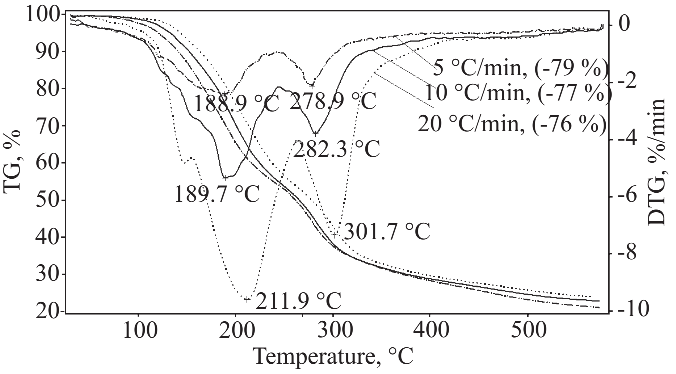

Fig. 2. TG and DTG curves for PSI-co-LA, variant B

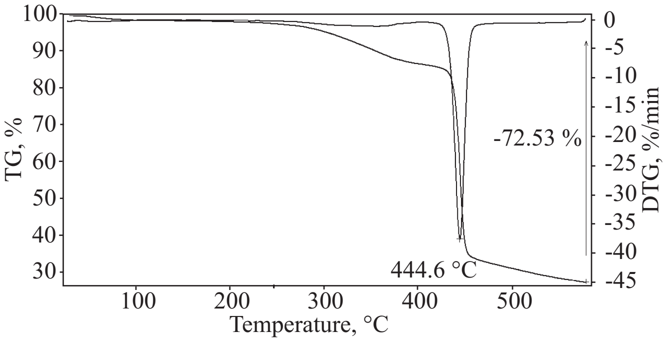

Fig. 3. TG and DTG curves for PSI

PSI-*co*-LA copolymers synthesized by the two variants and of intermediary product (PSI) are presented in Figs. 1—3. Generally, two main thermal decomposition stages are characteristic for the studied copolymers and as part of these stages some superposed processes exist that are not very well separated. The thermal stability of copolymers is much lower than that of the intermediate (PSI). The two copolymers exhibit a weight loss of 50 % in the 197—278 °C temperature range at the applied heating rate (10 °C/min) while for PSI an equivalent weight loss is recorded at 446 °C (Table 1). The copolymer synthesized by polycondensation procedure, using PSI as intermediate (variant B), exhibited a higher thermal stability as compared to the product obtained in the *in situ* procedure (variant A).

In order to compare the thermostability of discussed products we can consider the thermal stability (T_C) parameter that was calculated in all cases at a heating rate of 10 °C/min. This parameter is expressed in equation (3), on the basis of two temperatures that can be considered the criterions of thermal stability — T_{onset} and T_{peak} of the first stage of degradation:

$$T_C = \frac{C_1 \cdot T_{onset} + C_2 \cdot T_{peak}}{C_1 + C_2} \tag{3}$$

where: C_1 *and* C_2 — *the coefficients that quantify the influence of these two parameters, respectively.*

T a b l e 1. Thermal properties of PSI-*co*-LA copolymers and PSI

Sample	Heating rate °C/min	Degradation step	T_{onset}, °C	T_{peak}, °C	T_{endset}, °C	W, %	T_{50}*), °C	T_C**), °C
PSI-*co*-LA (variant A)	5	I	129	177	212	70.47	198	148
		II	247	270	320	23.90		
		residue				5.63		
	10	I	134	184	229	68.50	197	
		II	252	277	320	22.89		
		residue				8.61		
	20	I	152	211	269	69.25	231	
		II	277	306	339	18.14		
		residue				12.61		
PSI-*co*-LA (variant B)	5	I	113	189	210	37.80	262	151
		II	251	280	294	41.20		
		residue				21.00		
	10	I	136	190	222	45.38	266	
		II	264	282	318	31.62		
		residue				23.00		
	20	I	119	212	253	46.55	278	
		II	268	302	336	29.45		
		residue				24.00		
PSI	10	I	183	357	388	14.10	446	233
		II	444	445	454	58.43		
		residue				27.47		

*) T_{50} — the temperature corresponding to 50 % weight loss.

**) T_C — thermal stability parameter (see text).

The values of these coefficients have been estimated at 5 and 2, respectively, after the evaluation of data, since the initial temperature at which the thermal degradation begins (T_{onset}) was considered the parameter with the most important role in determining the thermostability of a compound [12]. The value of T_C was higher in the case of PSI, confirming the higher thermostability of this intermediary product as compared to the two synthesized copolymers.

For a kinetic analysis it was considered that the two copolymers degraded according to equation (4) where the solid polymer A(*s*) decomposed to a solid residue B(*s*) and gaseous products C(*g*):

$$A(s) \rightarrow B(s) + C(g) \tag{4}$$

The kinetic model is expressed in equation (5):

$$\frac{d\alpha}{dt} = Ae^{-\frac{E}{RT}} f(\alpha) \tag{5}$$

where: *t — time (min), T — temperature (K), A — pre-exponential factor* (s^{-1}), *E — activation energy* ($kJ \cdot mol^{-1}$), *R — gas constant, f(α) — conversion function, α — conversion degree of sample degradation*.

The degree of sample degradation was calculated from equation (6):

$$\alpha = \frac{W_o - W_t}{W_o - W_f} \tag{6}$$

where: W_o, W_t *and* W_f *— the weight of sample before degradation, at a given time t, and after complete degradation, respectively [13]*.

In order to obtain additional information about the degradation behavior, the influence of the conversion degree on the activation energy was evaluated, using the Friedman and Ozawa—Flynn—Wall methods [14—16].

Based on equation (5), Friedman proposed the application of the logarithm of the conversion rate dα/d*t* as a function of the reciprocal of temperature [equation (7)]:

$$\ln\frac{d\alpha}{dt} = \ln A - \frac{E}{RT} + \ln f(\alpha) \tag{7}$$

The Ozawa—Flynn—Wall method is derived from the shift of thermograms to higher temperatures with an increasing heating rate. For the same α value, the plot of the logarithm of heating rate (lnβ), as a function of reciprocal temperature (1/*T*) is linear and its slope is proportional to the activation energy according to Eq. (8):

$$\ln\beta = \ln\left(\frac{AE}{R}\right) - \ln G(\alpha) - 5.3305 + 1.052\frac{E}{RT} \tag{8}$$

where:

$$G(\alpha) = \frac{A}{\beta}\int_0^T e\frac{E}{RT}dt \tag{9}$$

The activation energy shows a clear dependence on the conversion degree, which is an indication of the presence of a complex reaction path. Thermogravimetry under non-isothermal conditions reveals a multi-step character of the decomposition processes for both copolymers. Thermogravimetry data obtained at different linear heating rates were processed with "Netzsch Thermokinetics" computer program in the 30—600 °C temperature range. The kinetic data obtained by a non-linear regression method are presented in Table 2. It can be noted that thermal degradation of copolymers is characterized by different values of activation energy and pre-exponential factor. Namely, both these quantities increase during the transition from one decomposition stage to another.

Table 2. Kinetic parameters of the two stages of thermal decomposition of the copolymers

Sample	Thermal decomposition stage*)	log *A* s^{-1}	E_a $kJ \cdot mol^{-1}$	*n***)
PSI-*co*-LA (variant A)	A → B	7.9502	89.87	3.36
	A → C	1.804	45.08	1.96
PSI-*co*-LA (variant B)	A → B	7.5477	84.69	3.37
	A → C	1.9305	34.17	2.58

*) See Equation (4).

**) Order of reaction.

The accuracy of kinetic parameters was assessed by comparing the experimental thermograms with those simulated by a computer, using the data presented in Table 2. A comparison of the experimental results (points) and the theoretical (line) is presented in Figures 4 and 5. It can be noticed that in both cases thermal decomposition takes place according to similar kinetic models — in two phases, reactions of the n order. The optimum values of reaction order after processing results are n = 2.43 (variant A copolymer) and n = 2.76 (variant B copolymer). The experimental and theoretical results were found to correlate well: the correlation coefficient is 0.99749 for variant A and 0.99124 for variant B.

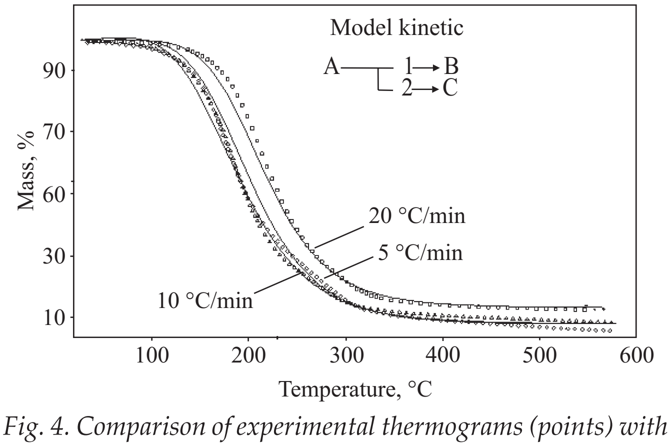

Fig. 4. Comparison of experimental thermograms (points) with ones calculated from kinetic data (line) according Friedman diagrams for PSI-co-LA, variant A

Table 3. Dependence of activation energy (E_a) and lg of pre-exponential factor (lg A) on degree of conversion (α) for the thermal decomposition reaction (Friedman analysis)

α	PSI-*co*-LA (variant A)		PSI-*co*-LA (variant B)	
	E_a, kJ · mol^{-1}	lg A, s^{-1}	E_a, kJ · mol^{-1}	lg A, s^{-1}
0.020	46.14	2.54	68.86	5.75
0.050	49.14	2.88	89.88	8.30
0.100	49.82	3.01	100.65	9.40
0.200	57.61	3.98	99.00	8.71
0.300	63.64	4.65	118.96	10.66
0.400	61.93	4.40	134.59	11.99
0.500	66.04	4.72	196.27	17.84
0.600	73.25	5.29	277.81	24.62
0.700	63.21	3.96	227.04	18.78
0.800	42.06	1.55	272.86	22.96

In Table 3 the values of the activation energy and of the pre-exponential factor as a function of the conversion degree are presented. In the case of PSI-*co*-LA copolymer (variant B) these values of are higher, indicating a better thermal stability than the copolymer synthesized according to variant A. The activation energies present two maximum values at conversions α = 0.3 and α = 0.6 (variant A copolymer) and α = 0.6 and α = 0.8 (variant B copolymer), suggesting a successive reaction mechanism in two steps for the degradation of the studied copolymers, a feature presented also in Table 2.

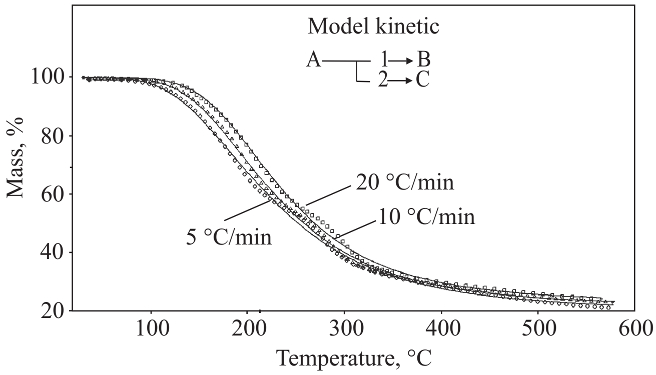

Fig. 5. Comparison of experimental thermograms (points) with ones calculated from kinetic data (line) according Friedman diagrams for PSI-co-LA, variant B of copolymer

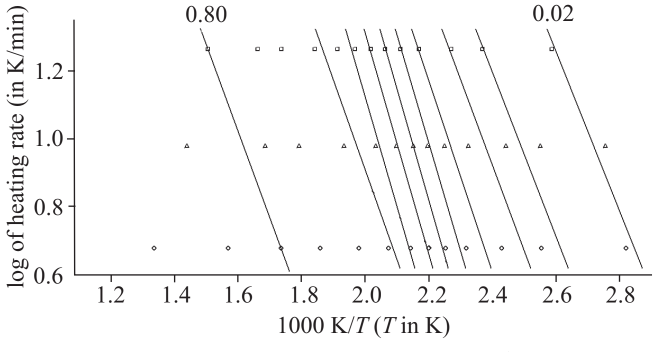

Fig. 6. Dependence of logarithm of heating rate (rate in K/min) on the reciprocal of absolute temperature for variant A of PSI-co-LA degradation — Ozawa—Flyn—Wall diagrams

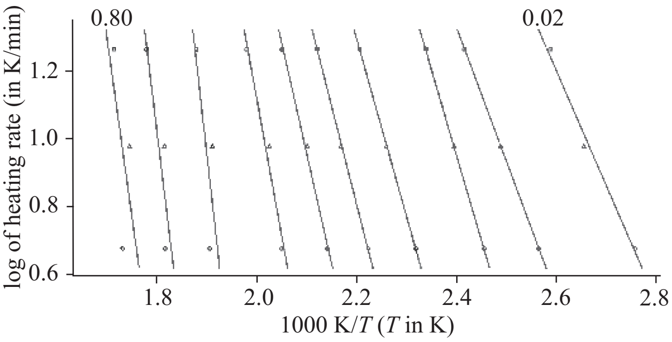

Fig. 7. Dependence of logarithm of heating rate (rate in K/min) reciprocal on the of absolute temperature for variant B of PSI-co-LA degradation — Ozawa—Flyn—Wall diagrams

A similar conclusion is supported by Figures 6 and 7 which reflect a slope modification for certain value of the conversion degree.

Thermal properties

The thermal characteristics of the studied copolymers, determined by DSC method are presented in Fig. 8. The glass transition temperature (T_g) of copolymer obtained according to variant A has a lower value (9.93 °C) as compared to PSI (13.85 °C). The lower glass transition temperature value of variant A of PSI-*co*-LA can be attributed to PLA chains grafted onto PSI. Two T_g values (T_{g1} = -7.26 °C; T_{g2} = 18.69 °C) are observed for the copolymer obtained according to variant B. This can be explained by the presence of two types of chains (PSI and PLA) of different molecular weights in the structure of synthesized

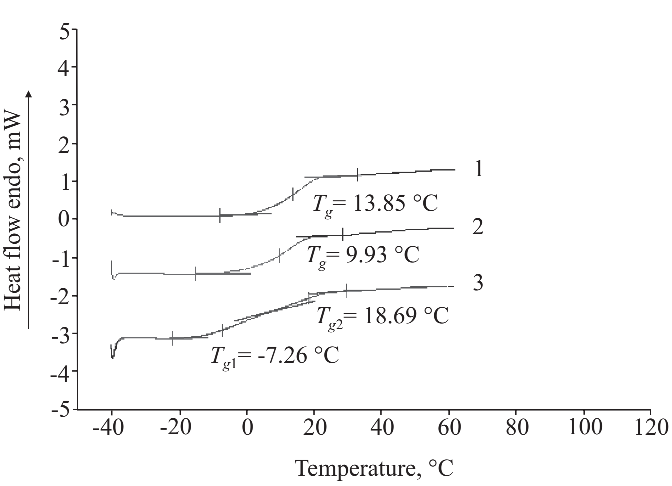

Fig. 8. DSC curves: 1 — PSI; 2 — PSI-co-LA, variant A; 3 — PSI-co-LA, variant B

branched product. This explanation is most likely because in the synthesis of the copolymer according to variant B, PSI ($\overline{M}_n$ = 3500) was used as prepolymer, and the following ring opening of the succinimide ring and NH_3 elimination in the presence of lactic acid (as monomer) and manganese acetate (as catalyst) PLA chains of different molecular weights were obtained. There is also the possibility that separate PSI chains are present with the obtained copolymer. Moreover, the lower T_g values of the synthesized copolymers as compared to PLA ($T_g \approx$ 50—70 °C) are due to the fact that branched copolymers with much lower molecular weights values were also obtained in the synthesis.

Zeta potential and conductivity

Zeta potential (ζ) refers to electrostatic potential generated by the accumulation of ions at the surface of a particle that is organized into an electrical double-layer, consisting of the Stern layer and the diffuse layer. ζ is an important tool in determining the stability of colloidal systems. The surface properties of colloidal systems are critical in determining their drug carrier potential because they control their interactions with plasma proteins. Zeta potential measurements also provide information on the overall surface charge of solid particles, which is affected by changes in the environment such as pH, the presence of counter-ions, or the adsorption of drugs. Zeta potential data are also used to determine the type of interaction between an active substance and its carrier, *i.e.* whether the drug is encapsulated within the body of the particle or simply adsorbed on the surface. This is important because an adsorbed drug may not be protected from enzymatic degradation, or may be released too rapidly after administration.

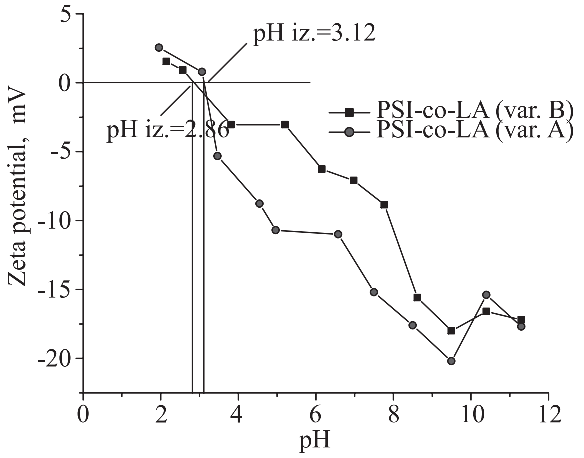

Fig. 9. Zeta potential of PSI-co-LA (variants A and B) as a function of pH

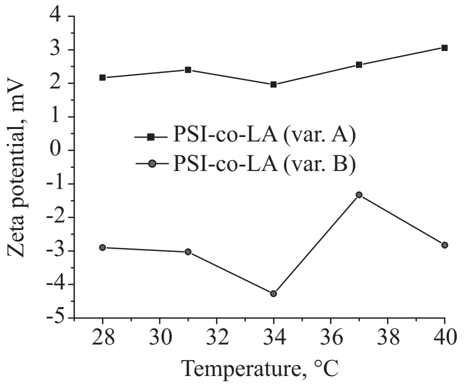

Fig. 10. Zeta potential of PSI-co-LA (variants A and B) as a function of temperature

The dependence of ζ values of PSI-*co*-LA aqueous dispersions on pH and temperature is presented in Figs. 9 and 10, respectively. Values between +0.784 and -20.2 mV were obtained for ζ as a function of pH with the lower values recorded in the alkaline pH domain. Zeta potential had a zero value at izoelectric pH of 3.12 and 2.86 for the PSI-*co*-LA synthesized according to variants A and B, respectively. At this values stability of the system is very low and the particles have tendency to sediment and agglomerate. Generally, ζ value dependence on pH is similar in the case of both variants of copolymers, namely the tendency is for zeta potential to decrease with an increase

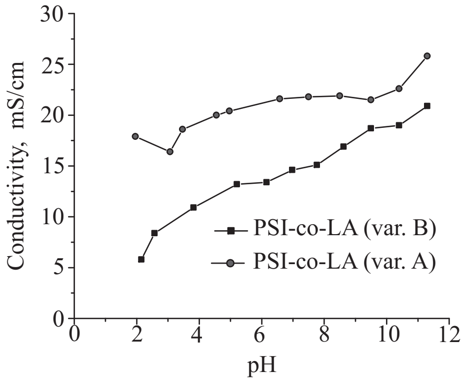

Fig. 11. Conductivity of PSI-co-LA (variants A and B) as a function of pH

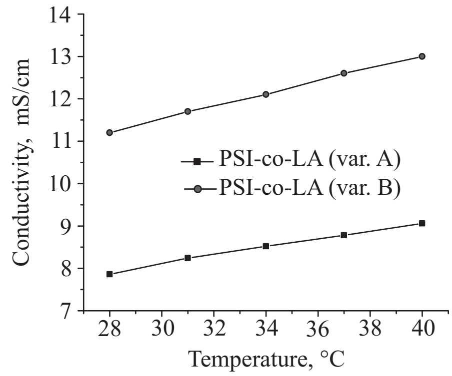

Fig. 12. Conductivity of PSI-co-LA (variants A and B) as a function of temperature

in the pH value. The copolymers solutions are more stable at alkaline pH (lower ζ values), demonstrating that stable matrix/drugs systems in this type of medium can be formulated.

Zeta potential was measured at temperatures between 28 and 40 °C, but variations in its obtained values were minimal. The values were maintained within the ±30 mV threshold where system stability is low.

The electrical conductivity shows a linear growth with temperature and approximately linear with pH in the case of both variants of copolymers — see Fig. 11 and 12.

CONCLUSIONS

The study presents some important properties of the biodegradable copolymers with succinimide and lactic acid units obtained *via* two different methods. In the first case maleic anhydride, ammonia and L(+)-lactic acid (variant A of synthesis) were used as reaction components (*in situ* synthesis, variant A), and in the second case poly(succinimide) previously synthesized was modified by polycondensation with L(+)-lactic acid (variant B of synthesis). Generally, these two types of PSI-*co*-LA present rather similar properties. The copolymers are soluble in water and certain organic solvents (DMF, DMSO, methanol, *etc*). The copolymer PSI-*co*-LA in variant B presents higher thermal stability and higher molecular weight by comparison with copolymer synthesised according to variant A. Additionally, there are some differences between the two variants of copolymers concerning their glass transition: in the case of variant A T_g value is 9.93 °C, whereas in the case variant B the copolymer structure presents two glass transition temperatures (T_{g1} = -7.26 °C and T_{g2} = 18.69 °C). So, it is possible that either independent PSI chains exist in the copolymer structure or the lengths of these segments in the main chain are high, thus modifying the glass transition temperature values.

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