Dedicated to Prof. P.T. Frangopol on the occasion of his 75th anniversary

Influence of Different Initiators Against the Mechanical Properties of Poly(ε-caprolactone) used for Biodegradable Bone Implants

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The ability of a strict control for the advanced macromolecular structures synthesis has been an important objective in our research. The development of polymers with defined structures and properties, aimed at biomedical applications, leads to complex and advanced architecture and diversity of the biodegradable polymers. Ring-opening polymerization is one of the most common methods for the synthesis of polymers with improved characteristics. Poly ε-(caprolactone) (PCL) is prepared by ring-opening polymerization of the monomer ε-caprolactone. The main factors which influence the ring-opening polymerization are the reaction conditions, such as the nature of the initiator, type and concentration of catalyst, reaction temperature and time. Stannous (II) 2-ethylhexanoate is used to catalyze the polymerization and alcohols are used as initiators. The initiators are also used to control the polymers molecular weight. Despite the long use of this catalyst in both industrial use and polymer research, several questions about the properties of the final product still remain. Our study describes the polymerization of ε-caprolactone performed in the presence of catalyst (stannous (II) 2-ethylhexanoate) and initiator (1, 6 hexandiol or trimethylol propane) at moderate temperature (110°C). The polymerization of ε-caprolactone was also performed in the presence of catalyst alone in order to evaluate the effect of the initiator against the polymers molecular weight. The obtained polymers were characterized by FTIR, GPC and TGA with respect to their mechanical properties. It is crucial to control the molecular weight of PCL for biomedical and pharmaceutical applications, because its molecular weight determines the hydrolysis rate. Several ratios among monomer, catalyst and initiator were studied, and we chose an optimum composition, in order to control the mechanical properties, degradation profiles respectively, and to avoid the cytotoxicity given by the reagents used.

Keywords: ring-opening polymerization, biodegradable bone implants, bending and compression tests

In the past decade, bioabsorbable polymeric materials became of notorious use in bone tissue engineering. The advantages of bioabsorbable implants in bone surgery are significant: there is no need for removal operation, and osteoporosis associated with rigid metallic implants can be avoided or at least reduced and the bone itself heals faster [1-3]. The avoidance of removal procedures leads to financial benefits, psychological advantages, and it increases operative capacity [4]. The main disadvantage of current biodegradable materials is the premature loss of mechanical properties before the healing process is complete. The screws, plates and other implants made of such materials are applied in medicine during surgical operations when treating a bone fracture [5-7].

Poly ε(caprolactone) (PCL) is considered a non-cytotoxic, tissue compatible and biodegradable polymer, currently used as biomaterial. PCL degrades at a much lower rate than other polymers (polylactic acid, polyglicolic acid) so is a useful base polymer for developing long-term implantable systems [8, 9]. The homopolymer has a degradation time of the order of two to three years. PCL with an initial average molecular weight of 50,000 takes about three years for complete degradation *in vitro.*

The ring-opening polymerization of ε-caprolactone has been widely studied [10, 11]. Several factors are known to affect the ring-opening polymerization of cyclic esters. The main factors which influence the ring-opening polymerization are the reaction conditions, such as the nature of the initiator, type and concentration of catalyst, reaction temperature and time. Metal carboxylates such as stannous (II) 2-ethylhexanoate are used to catalyze the polymerization and alcohols are used as initiators. The former ones serve also to control the molecular weight of the obtained polymers.

This study describes the polymerization of ε-caprolactone performed in the presence of catalyst (stannous (II) 2-ethylhexanoate) and initiator (1, 6 hexandiol or trimethylol propane) at moderate temperature (110°C). The polymerization of ε-caprolactone was also performed in the presence of catalyst alone in order to evaluate the effect of the initiators against the polymer's molecular weight. It is crucial to control the molecular weight of PCL for biomedical and pharmaceutical applications, because its molecular weight determines the hydrolysis rate. Several ratios among monomer, catalyst and initiator were studied, and we chose an optimum composition, in order to control the mechanical properties, and degradation profiles respectively, and to avoid the cytotoxicity given by the reagents used.

Experimental part

Material and method

ε-caprolactone (εCL) was purchased from Aldrich, 99%, dried over CaH_2 and distilled under argon before use. The catalyst, stannous 2-ethyl-hexannoate ($SnOct_2$), and the initiators 1,6-hexanediol (HxD) and trimethylol propane (TmP) (Sigma), and other reagents (Chimopar) were analytical grade and used as received.

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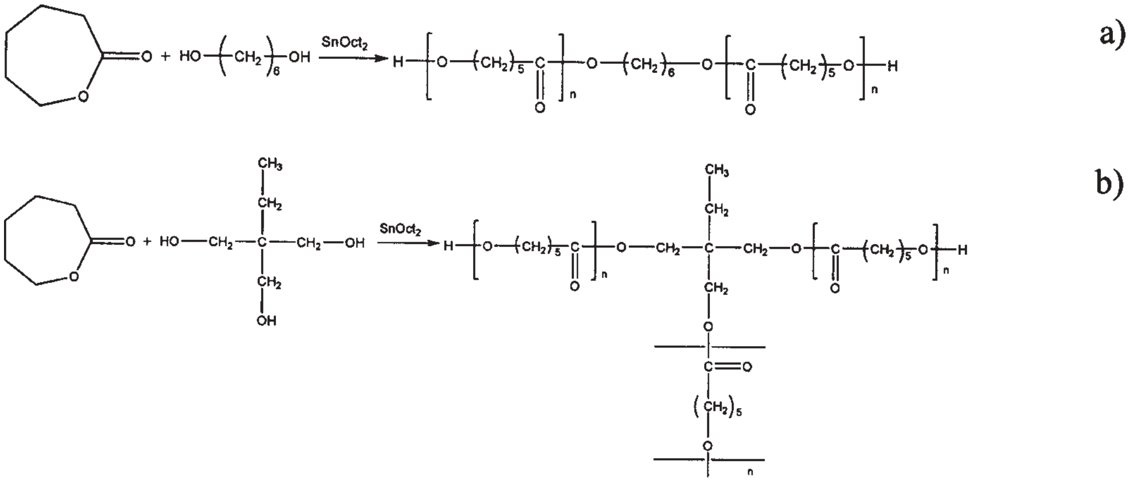

Fig. 1. Ring-opening polymerization of εCL in the presence of: a) HxD; b) TmP

Synthesis of the polymer

The bulk polymerization was performed under nitrogen, in a three-neck glass reactor (50 mL) equipped with glass mechanical stirrer and refrigerant. The reactor and the stirrer were first silanized and dried in vacuum, at 100°C. SnOct$_2$ (0.5 mM) was added to εCL (100 mM) and the mixture was homogenized at room temperature (1). For the other two systems studied, the initiators HxD (0.5 mM) (2), or TmP (0.5 mM) (3) were added under magnetical stirring. The polymers obtained were coded as **PCL1** (1), **PCL2** (2), **PCL3** (3).

The reactor vessel was kept under vacuum for 2.5 h, in order to remove any traces of moisture and then was closed with a glass stopper and immersed in a thermostatically controlled oil bath at 110°C. Nitrogen was bubbled through the solution, in order to remove the oxygen. A rich nitrogen atmosphere was enabled for polymerization to accomplish. Reaction occurred after 24 h.

Afterwards, the flask was removed from the heating oil bath and allowed cooling to 50°C. Chloroform was added under stirring to the solid polymer mass in the reactor, in order to allow dissolution. The polymer solution in chloroform was transferred into a 500 mL beaker and was magnetically stirred 24 h at room temperature for complete dissolution.

The reaction mixture was then poured into cold methanol, to precipitate the polymer. The residual monomer, catalyst and initiator were repeatedly washed with cold methanol and separated from the polymer under centrifugation, for 15 min, at 4000 rpm. The solvent was evaporated in a vacuum oven, at 40°C, for 48 h.

In figure 1 the ring-opening chemical reactions regarding the initiator used are shown.

Characterization methods

Gel permeation chromatography (GPC) was performed in order to determinate the molecular weights, molecular weight distributions (M$_w$/M$_n$) and polydispersity of polymers relative to polystyrene standards. Tetrahydrofurane (THF) was used as eluent. Samples were dissolved in THF, the injected volume was 0.2µL and the flow rate was 1.5 mL/min. The instrument was also very helpful in monitoring the depletion of the monomer in the polymerization system.

Fourier Transform Infrared Spectroscopy (FTIR) was used in order to confirm the ring-opening polymerization of εCL. A JASCO FT-IR 6200 equipment with the resolution of 4 cm^{-1} and the number of scans 50, in the region between 4000 and 350 cm^{-1} was used.

Thermal stability characterization was performed through Thermogravimetrical Analysis (TGA). The TGA graphs were recorded on a TA Q500 instrument by sample heating (10 mg) in N$_2$ atmosphere up to 500°C at 10°C/min heating rate.

Mechanical properties of the obtained materials were evaluated by bending and compression tests using an universal testing machine Hounsfield H10KT, by means of two dedicated software: QMAT XT and QMAT Professional. The tests were performed using a 1 mm/min crosshead speed and a load cell of 250 N. For research purposes, 0.4g powder of polymer were tabletted in standard pressing moulds using a load cell of 10kN, and round (3 mm thickness) and plate tablets (8.2 mm width, 2.5 mm thickness) were obtained. The plate tablets were used for bending tests (fig. 2a) and the round ones for compressive stress tests (fig. 2b), in triplicate for each polymer series.

Resultd and discussions

From the GPC profiles we found a molecular weight distribution relatively broad in PLC1, in comparison with PCL2 and PCL3 which exhibit a narrower distribution (data not shown). This allow us to conclude that the use of TmP as initiator leads to a higher mechanical resistance for biodegradable bone implants.

The conclusion drawn from the FT-IR spectra is that the ring-opening polymerization took place, taking into account that for PCL the specific peaks of C=O bond at 1721 cm^{-1} and that of C-O, at 1177 cm^{-1}, of ketone and ether functional groups respectively (fig. 3) appear.

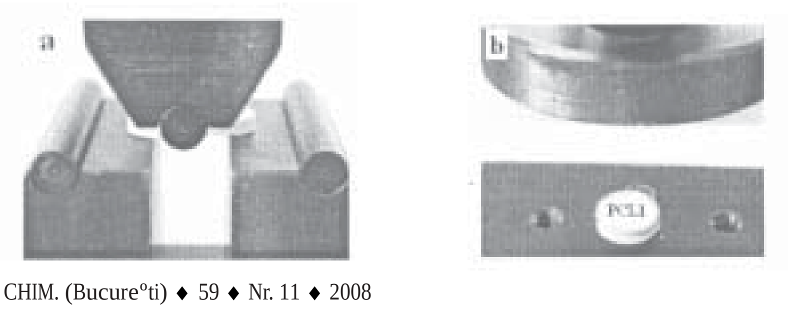

Fig. 2. a) Bending tests on plate tablets; b) Compression system for round tablets

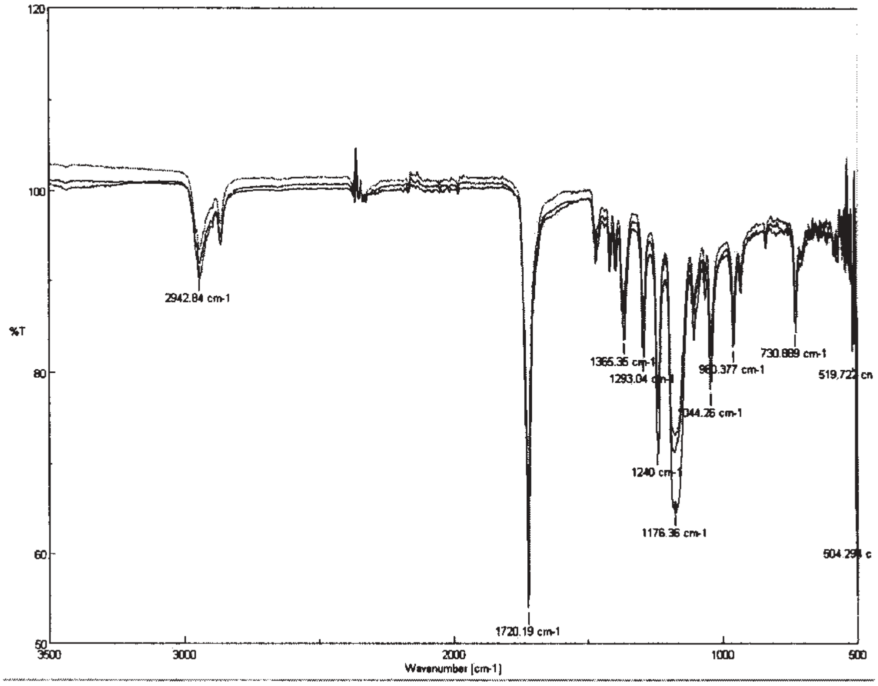

Fig. 3. FTIR spectra for: a) εCL; b) PCL1, PCL2, PCL3

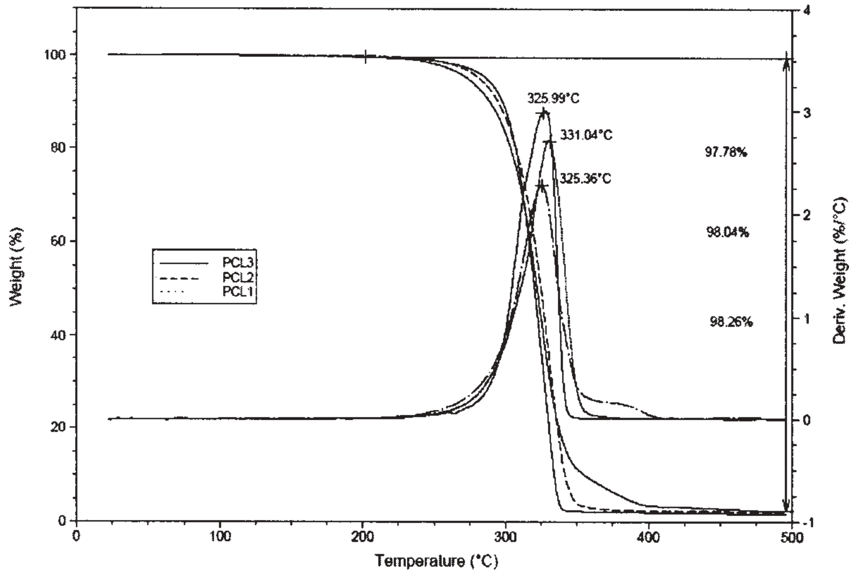

Fig. 4. DTA / TGA curves of the obtained polymers

The thermal stability of polymers is an important feature for their application in hard tissue engineering. The samples exhibit thermal stability up to 325°C, when degradation process starts. From the data shown in figure 4, it can be observed that the structure of the initiator does not significantly influence the thermal stability of the polymers. The weight loss percentage exhibits the same value for PCL1 (98.26%) and PCL2 (98.04%), while PCL3 (97.78%) shows a slight decrease.

Mechanical properties such as compression resistance and bending strength of the polymers are important in preventing implant fracture before their replacement by host bone.

The specimens in both tests (compression and bend) exhibit a plastic behaviour and did not fracture or smash. The variations of the results are due to the heterogeneity of the specimens but the deviations are in the acceptable range (table 1, 2, fig. 5, 6).

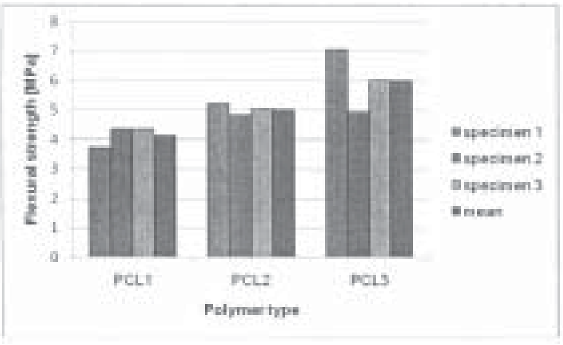

Fig. 5. Flexural strength variation depending on polymer type

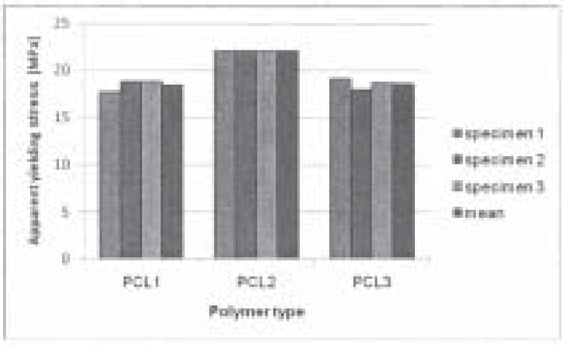

Fig. 6. Apparent yielding stress variation depending on polymer type

Table 1

BENDING TEST RESULTS FOR PLATE TABLETS

Code	Width (mm)	Thickness (mm)	Maximum stress at break [N]	Maximum extension [mm]	Flexural strength [MPa]
PCL1	8.19	3.26	19.58	0.523	3.712
	8.20	2.86	17.67	0.541	4.346
	8.20	2.86	17.68	0.540	4.345
PCL2	8.22	2.44	15.43	0.390	5.200
	8.20	2.52	15.21	0.431	4.819
	8.21	2.51	15.37	0.413	5.025
PCL3	8.16	2.52	22.18	0.524	7.060
	8.20	2.64	17.04	0.829	4.920
	8.18	2.58	19.55	0.678	6.000

Table 2

COMPRESSION TEST RESULTS FOR ROUND TABLETS

Code	Thickness (mm)	Apparent yielding force [N]	Extension at apparent yielding point [mm]	Apparent yielding stress [MPa]
PCL1	3.42	2000	0.884	17.693
	3.24	2120	0.724	18.754
	3.24	2120	0.724	18.754
PCL2	1.86	2500	0.750	22.116
	1.85	2520	0.745	22.120
	1.86	2500	0.750	22.125
PCL3	3.21	2160	0.976	19.108
	3.01	2030	0.360	17.958
	3.11	2100	0.564	18.627

Taking in account the mean value of flexural strength and apparent yielding stress for each kind of polymers, it can be remarked:

-the PCL3 polymer type exhibits the greatest flexural strength and it will be better to be used for implants in fractures where bending stress occurs.

-the PCL2 polymer type exhibits the highest apparent yielding stress and it will be better to use for implants in fractures where compression stress occurs.

Conclusions

By ring opening polymerization we obtained PCL using two differents initiators (demonstrated through FTIR). From the GPC we found the narrowest molecular weight distribution for PCL3. From the TGA it can be observed that the structure of the initiator does not significantly influence the thermal stability of polymers. Also, PCL2 would be appropriate to be used for implants in fractures where compression stress occurs, and PCL3 for implants in fractures where bending stress occurs.

Several ratio of monomer/catalyst/initiator will further be studied in order to optimize the mechanical properties of the final polymer. The future researches can be orientated to increase the compressing tabletting force in order to obtain a better homogeneity of the specimen and repeatability of the results. The microstructure of the homopolymers prepared will be quantitatively and qualitatively studied with ^{1}H- and ^{13}C-NMR. In order to be able to adequately examine the implant, *in vitro* biodegradation studies (enzymatic / non-enzymatic bulk hydrolysis) followed by mechanical testing must be carried on after incubation in various physiological media.

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