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Study of Different Catalysts and Initiators in Bulk Copolymerization of d,l-Lactide and Glycolide

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Poly(d,l-lactide-co-glycolide), PLGA, is a biodegradable polyester with many medical applications. In this article, several catalysts are studied as potential substitutes of the conventional catalyst, tin (II) 2-ethylhexanoate (known as tin octoate, SnOct₂). Namely, different metal carboxylates have been examined, in order to study the influence of the metal counterion. Among them, most promising results have been obtained when using zinc (II) 2-ethylhexanoate (ZnOct₂) followed by potassium (I) 2-ethylhexanoate. Furthermore, in the case of ZnOct₂, the use of alcohols as initiators was examined in order to improve reaction rate and to study their effect on molecular weight distribution, polymer microstructure, and side reactions, such as transesterification reaction.

Keywords: ring-opening polymerization, polylactide, polyglycolide, biopolymers, catalysts

1 Introduction

Lately, the industrial interest in biodegradable polyesters is increasingly growing. On the one hand, such polymers are suitable substitutes for conventional plastics in large scale applications such as packaging while exhibiting reduced environmental impact (1–4). On the other hand, some of them such as glycolic and lactic homo-polymers and copolymers, have been widely used in many medical applications for many years, for instance, as absorbable sutures or for tissue engineering and controlled drug delivery applications (5). In particular, the co-polymer poly(d,l-lactide-co-glycolide), PLGA, has many advantages because of its tuneable properties (degradation, processability, mechanical strength) which change with monomer composition (6, 7). There are two main methods for the synthesis of PLGA: direct polycondensation reaction from glycolic and lactic acid, and ring-opening polymerization (ROP) of the cyclic dimers of these acids, glycolide and lactide, respectively. The last route is preferred because higher molecular weights are obtained in short reaction times, with improved control of chain lengths and reduced impact of side reactions (5, 6, 8). Ring-opening polymerization can

occur by different mechanisms: cationic, anionic, enzymatic and coordination-insertion polymerization. About the polymerization process, bulk polymerization is preferred for medical applications because of the elimination of potential residual presence of organic solvents (5).

Tin alkoxides and carboxylates have been the most used catalysts for the polymerization of cyclic esters up to now, especially stannous (II) 2-ethylhexanoate (SnOct₂). Such compound is attractive because of its high reactivity. However, it seems to be cytotoxic, a decisive drawback when the copolymer has to be implanted to tissues especially sensitive to intoxication, such as brain or nervous tissues (9, 10). Although there is not agreement among the scientific community, several groups are studying alternative, more biocompatible catalysts (9–16). Zinc 2-ethylhexanoate (also called zinc octoate, ZnOct₂) has been previously pointed out as a very promising candidate (17, 18). The main aim of this work is to study the influence of different catalytic systems on the bulk co-polymerization of glycolide and d,l-lactide. In order to better understand the influence of the metal counterion both non-toxic and toxic cations have been included. The following compounds have been considered: potassium (I) 2-ethylhexanoate (KOct); barium (II) 2-ethylhexanoate (BaOct₂); sodium (I) 2-ethylhexanoate (NaOct); strontium (II) 2-ethylhexanoate (SrOct₂); lithium (I) 2-ethylhexanoate (LiOct); calcium (II) 2-ethylhexanoate (CaOct₂); yttrium (III) 3-ethylhexanoate (YOct₃); zinc (II) 2-ethylhexanoate (ZnOct₂); zinc

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acetate; cobalt (II) 2-ethylhexanoate (CoOct_2); copper (II) 2-ethylhexanoate (CuOct_2); and nickel (II) 2-ethylhexanoate (NiOct_2).

About the scale at which experiments were performed, it is worthy to stress that most previous studies were carried out at a very small, laboratory scale, i.e., with no more than one gram of substance and ampoule devices. Besides strict purifications of monomers, catalysts and initiators were done in order to avoid impurities (19). In this study, on the contrary, a stirred tank reactor was used, 100 g of monomers were charged into it and all of the reagents were used as received, what made the system closer to industrial conditions. In this sense, this reaction system could be considered a semi-pilot plant.

2 Experimental

2.1 Materials

Glycolide (G) (1,4-dioxane-2,5-dione; Purac Biochem by, The Netherlands) and d,l-lactide (L) (3,6-dimethyl-1,4-dioxane-2,5-dione; Purac Biochem by, The Netherlands) both with a purity higher than 99.5%. Zinc octoate (ZnOct_2) (zinc (II) 2-ethylhexanoate; Nusa, Spain) with a metal content of 12%. Strontium octoate (SrOct_2) (strontium (II) 2-ethylhexanoate; Nusa, Spain) with a metal content of 10%. Nickel octoate (NiOct_2) (nickel (II) 2-ethylhexanoate; Nusa, Spain) with a metal content of 10%. Cobalt octoate (CoOct_2) (cobalt (II) 2-ethylhexanoate; Nusa, Spain) with a metal content of 6%. Lithium octoate (LiOct) (lithium (I) 2-ethylhexanoate; Nusa, Spain) with a metal content of 2%. Potassium octoate (KOct) (potassium (I) 2-ethylhexanoate; Nusa, Spain) with a metal content of 10%. Calcium octoate (CaOct_2) (calcium (II) 2-ethylhexanoate; Nusa, Spain) with a metal content of 10%. Sodium octoate (NaOct) (sodium (I) 2-ethylhexanoate; Aldrich Química, Spain) with purity of 97%. Copper octoate (CuOct_2) (copper (II) 2-ethylhexanoate; Aldrich Química, Spain) with high purity. Barium octoate (BaOct_2) (barium (II) 2-ethylhexanoate; Aldrich Química, Spain) with purity of 98%. Yttrium octoate (YOct_3) (yttrium (III) 3-ethylhexanoate; Aldrich Química, Spain) with purity of 99.9%. Zinc acetate (ZnAc_2) (Aldrich Química, Spain) with purity of 99.99%. 4-phenyl-2-butanol (Aldrich Química, Spain) with purity of 97%. 2-methyl-2-propanol (Sigma-Aldrich, Spain) with purity of 99.7%. 1-dodecanol (Aldrich Química, Spain) with purity of 98%. Methanol anhydrous (MeOH) (SDS S.A., Spain) with purity higher than 99.85%. Potassium bromide (KBr) (Sigma-Aldrich, Spain) with purity higher than 99%, for FTIR measures. Tetrahydrofuran (THF) (HPLC grade; SDS S.A., Spain). 1,1,1,3,3,3-hexafluor-2-propanol (Sigma-Aldrich, Spain) with purity higher than 99.8%. And hexane (analytical grade; Brenntag Químicas S.A., Spain). All products were used as received.

2.2 Solubility Study

To analyze the solubility of different catalysts into the monomer mixture, test tubes were filled with the monomer mixture (5 g, molar ratio d,l-lactide:glycolide 80:20) and a constant amount of catalyst (molar ratio monomer to catalyst: 500). In order to molten the monomer mixture, the test tubes were heated until 130°C. After that, the selected catalyst was added and the mixture was stirred for one hour to facilitate the dissolution when possible.

2.3 Bulk Polymerizations

Bulk polymerizations were carried out in a stirred-tank reactor with nitrogen atmosphere, constant stirring rate of 100 rpm and controlled temperature. Firstly, the monomer mixture (100 g, molar ratio d,l-lactide:glycolide 80:20) was added and heated until 130°C. After complete thermal equilibration, given quantities of catalyst and initiator (molar ratio monomer to catalyst 100 or 500 and initiator to catalyst 1) were injected into the reactor. The moment of this addition was considered time zero of the reaction. The duration of all reaction experiments was 3 h. Several samples were taken at different times and they were cooled just after sampling in order to quench the reaction. Mass conversion was determined by a gravimetric method. A known amount of sample was dissolved in THF and an excess of hexane was added to precipitate the polymer. Finally, the suspension was filtered and the polymer was oven dried to remove solvent traces and weighted. In order to ensure the reliability of this method, the conversion of several samples was also measured by thermogravimetry (TGA). In all cases, the results obtained by the two techniques were fully equivalent.

2.4 Polymer Characterizations

2.4.1. FTIR (Fourier Transform Infrared Spectroscopy)

A spectrophotometer FTIR 16 PC (Perkin Elmer) was used. Polymer samples were dissolved in THF or 1,1,1,3,3,3-hexafluor-2-propanol (THF-insoluble samples) with a concentration of 35 mg • mL⁻¹, and were applied on KBr pellets prepared by a manual hydraulic press (Perkin Elmer, Spain) and heated in oven at 70°C to fully remove the solvent. All samples were scanned from 370 to 4400 cm⁻¹. FTIR was used to determine the copolymer composition of PLGA in order to use a simple and cheap technique. The accuracy of the results using FTIR was checked using ¹H-NMR, the difference being less than 0.5%.

2.4.2. ¹H-NMR (Proton Nuclear Magnetic Resonance)

A spectrophotometer Varian Unity FT-300 was used for ¹H-NMR measurements. Deuterated chloroform (CDCl_3) and deuterated dimethyl sulfoxide (DMSO) (for CDCl_3 -insoluble samples) were used as solvents.

2.4.3. GPC (Gel Permeation Chromatography)

A liquid chromatograph (Waters) equipped with two columns Waters Styragel (HR1 and HR4) was used to determine the molecular weight distribution of polymer samples soluble in THF. The effective molecular weight range is 100 to 500,000 Da. Analysis conditions were 35°C of temperature, 1 mL \bullet min⁻¹ of solvent flow rate and injection volume of 100 μ L. All samples were dissolved in THF at a concentration of 1.5 mg \bullet mL⁻¹ and filtered before injection with a pore size of 0.45 μ m. Since no specific calibration was available, all measured molecular weights are polystyrene-equivalent values and can be used only as relative quantities. However, it is possible to assume that the polystyrene-equivalent values overestimated 25–30% the absolute molecular weight of the copolymer using these analysis conditions. Since the final product is highly enriched in d,l-lactide, the absolute molecular weight for the copolymer should be similar to the absolute one for the homopolymer applying the universal calibration and considering the Mark-Houwink constants for the poly(d,l-lactide) and polystyrene from the literature (1).

2.4.4. DSC (Differential Scanning Calorimetry)

These measurements were performed on a DSC (TA Instruments Q1000) equipped with a refrigerated cooling system (RCS) and autosampler. The typical sample weights for DSC measurements were 4–10 mg. The DSC cell was purged with nitrogen gas flow of 50 mL min⁻¹. The experiments were run in aluminum hermetic pans. The sample was heated until 280°C, followed by a cooling until -50°C and, finally, it was heated until 280°C, always with a ramp of 10°C \bullet min⁻¹. For analyses in DSC, TA Universal Analysis 2000 software was used.

2.4.5. TGA (Thermogravimetric Analysis)

A TGA (TA Instruments, Q600) with a refrigerated cooling system was used. Sample weights were between 3–10 mg and the measures were run in aluminum pans. The TGA

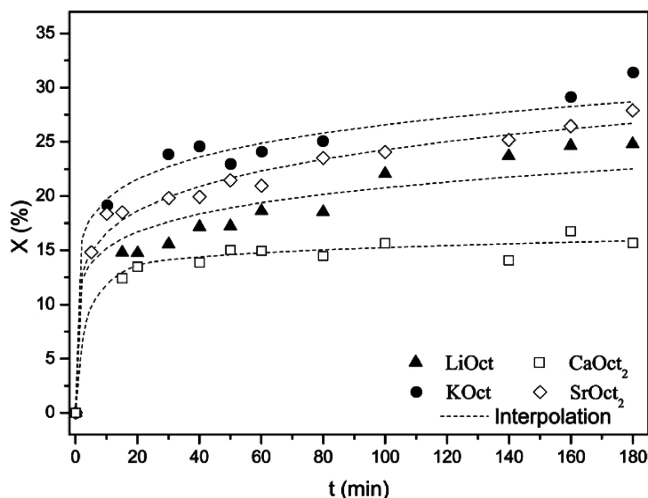


Fig. 1. Total mass conversion as a function of reaction time for the bulk copolymerization of d,l-lactide and glycolide using different catalysts. Molar ratio (L:G) in the initial monomer mixture: 80:20; molar ratio monomer to catalyst: 500; temperature: 130°C; stirring rate: 100 rpm.

cell was purged with nitrogen gas flow of 100 mL min⁻¹. To estimate the polymer amount, i.e., the conversion, TA Universal Analysis 2000 software was used.

3 Results and Discussion

3.1 Comparative Evaluation of Different Catalysts

As anticipated, several different catalysts were examined as possible substitutes for tin octoate in the bulk copolymerization of d,l-lactide and glycolide. In order to study the metal counterion influence, all of them were metal carboxylates, namely octoates. Although metal alkoxides are the most usual catalysts for this kind of polymerization, at high temperatures the metal carboxylates can be also active (20). All examined catalysts are summarized in Table 1. According to several authors, an anionic

Table 1. Solubilities of different catalysts in the monomer mixture at molar composition D,L-lactide:glycolide: 80:20. Temperature: 130°C

Catalyst	Purity (%)	Physical state	Catalyst solvent	Catalyst colour	Solubility
YOct ₃	99.9	Solid	—	White	No
NiOct ₂	10	Liquid	Hydrocarbons	Blue-green	No
CoOct ₂	6	Liquid	Hydrocarbons	Navy blue	No
BaOct ₂	98	Solid	—	White	No
CuOct	100	Solid	—	Turquoise	No
ZnAc ₂	99.99	Solid	—	White	No
NaOct	97	Solid	—	White	Partial
LiOct	2	Liquid	Hydrocarbons	Dark orange	Total
CaOct ₂	10	Liquid	Hydrocarbons	Brown	Total
SrOct ₂	10	Liquid	Hydrocarbons	Orange	Total
KOct	10	Liquid	Isodecyl alcohol	Transparent	Total
ZnOct ₂	12	Liquid	Hydrocarbons	Light yellow	Total

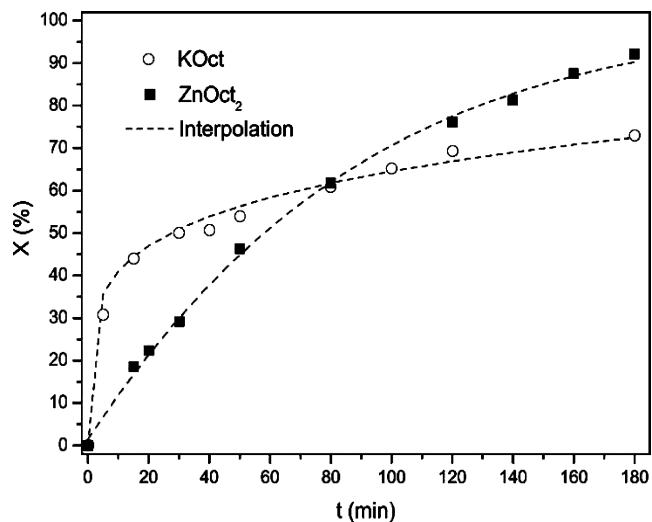
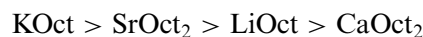


Fig. 2. Total mass conversion as a function of reaction time for the bulk copolymerization of d,l-lactide and glycolide using different catalysts. Molar ratio (L:G) in the initial monomer mixture: 80:20; molar ratio monomer to catalyst: 100; temperature: 130°C; stirring rate: 100 rpm.

mechanism could be expected for the alkaline and alkaline earth metal carboxylates (KOct, BaOct₂, NaOct, SrOct₂, LiOct, and CaOct₂) and a coordination-insertion mechanism for the others (compounds of Y, Zn, Co, Cu and Ni) (20–22). In order to exhibit some catalytic activity, the catalyst should be at least partly soluble into the molten monomer mixture. For this reason, the estimated solubility in the monomer mixture is also reported in the table along with some additional characteristics such as purity and physical state.

Polymerization experiments were carried out only with totally soluble catalysts (lithium, calcium, strontium, potassium, and zinc octoates). The time evolutions of the total mass conversion using Li, Ca, Sr, and K octoates are presented in Figure 1. In all cases, the molar ratio of monomer to catalyst was quite large and equal to 500. Such value was selected to produce high molecular weight polymer but, most probably because of the very low catalyst amount, the conversions after 3 h of reaction were quite small in all cases, never larger than 35%. Therefore, in order to get higher conversion and shorter reaction times, larger catalyst amounts were used for the following experiments, thus reducing the monomer to catalyst molar ratio from 500 to 100.

The conversion profiles were almost equivalent for all of the catalysts studied in Figure 1, with a very steep initial increase of the conversion curve followed by a much slower increase during the rest of the reaction. So the alkaline and alkaline earth metal catalysts could be ranked by catalytic activity as follows:



Looking at the resulting catalyst ranking, it appears that the atomic metal electronegativity is the most influential parameter with respect to the catalytic activity for anionic mechanism. In fact, such property is related to the metal dissociation from the carboxylate group, which is the expected reaction initiator: the lower electronegativity is, the more effective the dissociation (21, 22). For the specific metals under examination, the electronegativity values are: 0.82 for K, 0.95 for Sr, 0.98 for Li, and 1 for Ca. The resulting catalyst ranking fits exactly to the electronegativity one.

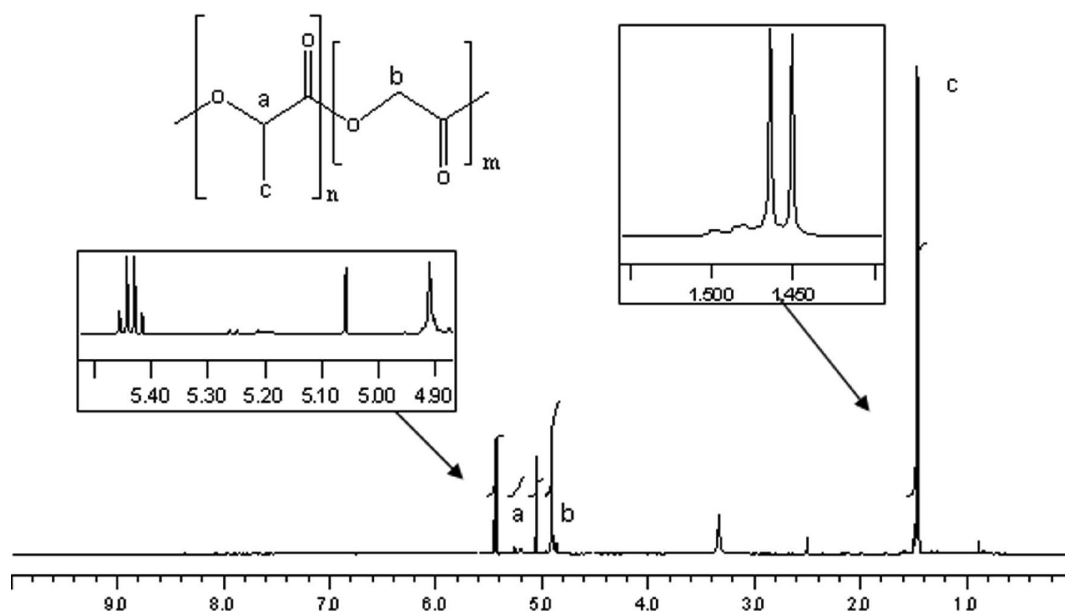


Fig. 3. ¹H-NMR spectrum of the co-polymer PLGA prepared with ZnOct₂ using DMSO as solvent.

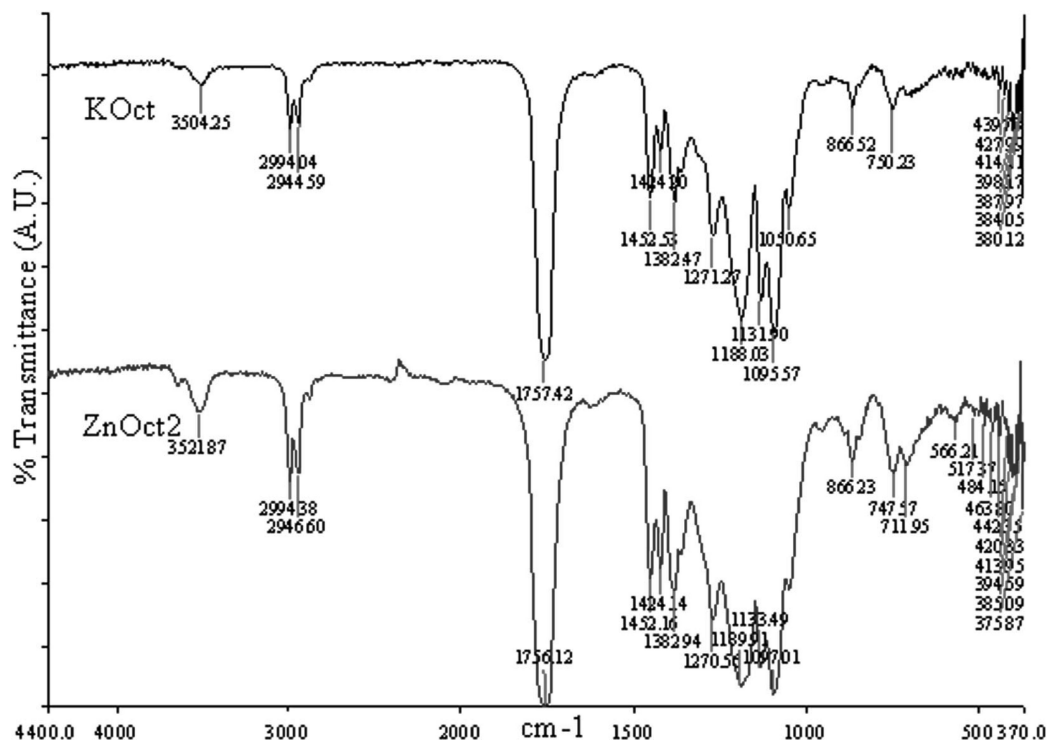


Fig. 4. IR spectra of two polymer samples of PLGA obtained using KOct and ZnOct₂ as catalysts, with a co-polymer composition of 75:25 d,l-lactide:glycolide and 63:37, respectively.

The conversion vs. time curves shown in Figure 2 have been obtained when using zinc and potassium octoates; note that the last one was reconsidered with the new amount of catalyst since it was the most effective out of the first series of reactions (Fig. 1). Comparing the results, the largest

conversion after 3 h of reaction time (along with a less pronounced decrease of the reaction rate) was observed in the case of zinc octoate, most probably due to the different catalytic mechanisms mentioned above (20–22). Summarizing, the best results were obtained with Zn and K octoates

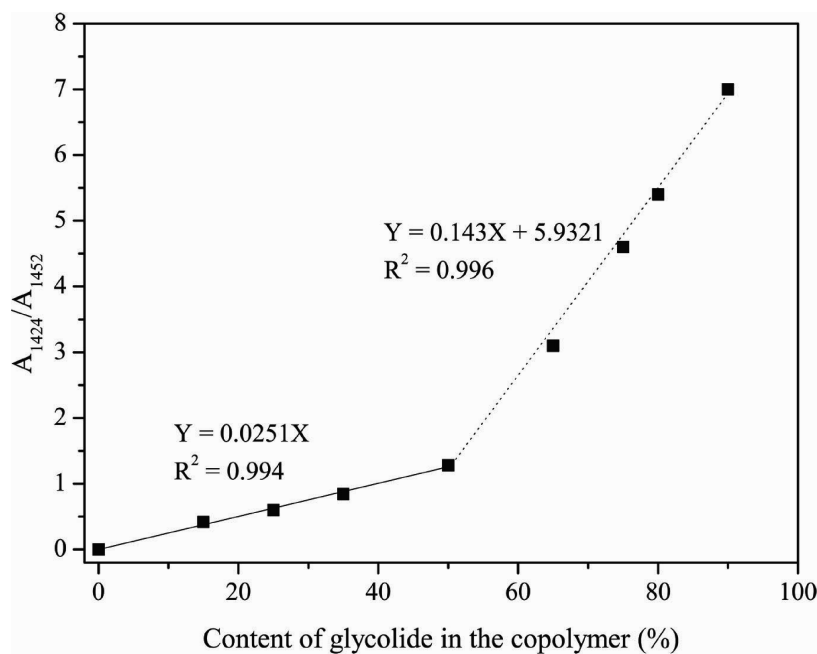


Fig. 5. FTIR calibration curve to obtain the molar composition of co-polymer. Absorbance ratio of absorption bands of CH₂ and CH₃ groups vs. Glycolide content in the co-polymer.

following a coordination-insertion and an anionic mechanism, respectively.

3.2 Characterization

In order to compare obtained copolymers using the two different catalytic mechanisms, different samples for the corresponding most representative catalysts, Zn and K octoates, respectively, were analyzed by $^1\text{H-NMR}$, FTIR, DSC, TGA, and GPC. So, different properties of the copolymers, such as crystallinity or molecular weight distribution, are evaluated below.

The polymers were characterized by the standard procedures of $^1\text{H-NMR}$ and FTIR. The $^1\text{H-NMR}$ spectrum of one of the obtained samples when using ZnOct_2 as catalyst is shown in Figure 3. In the spectrum, the characteristic methine group peak of the lactide unit at 5.1 ppm approximately (peak a) and the methylene group of the glycolide unit at 4.9 ppm approximately (peak b) can be observed. Along with the peak of methyl group of lactide which also appears in the spectrum at 1.5 ppm approximately (peak c). Note that the co-monomer ratio in the copolymer can be determined using the integrals of these peaks.

As is possible to observe in Figure 4, where IR spectra of two polymer samples obtained using KOct and ZnOct_2 as catalysts are shown, the same product is produced independently on the catalyst. The absorption band of stretching vibration of carbonyl group at 1760 cm^{-1} and the corresponding ones due to stretching vibration of ester group (around $1000\text{--}1300\text{ cm}^{-1}$) appear in both spectra. The absorption bands attributed to bending of CH bonds are around $1200\text{--}1460\text{ cm}^{-1}$. For these copolymers, there is an absorption band at 1424 cm^{-1} due to CH_2 group and the absorption band of methyl group is at 1452 cm^{-1} . It is possible to observe in Figure 4 that the relative intensity of the two last mentioned absorption bands depends on the composition. In order to find an alternative technique to NMR for further studies, the accuracy of FTIR for determining copolymer composition has been checked. In Figure 5, a calibration curve is shown where the absorbance ratio of absorption bands of CH_2 and CH_3 groups is used to obtain the molar composition of co-polymer (known composition commercial copolymers and blends of both commercial homopolymers were used for the calibration). In all the cases, the value obtained by FTIR was very close to the one by $^1\text{H-NMR}$, what confirms the utility of this technique to obtain the composition of PLGA.

3.2.1. Characterization-molecular weight distribution

In order to study the molecular weight distribution of the obtained polymers using both catalysts, number average molecular weight (M_n) and polydispersity (PD) vs. conversion were plotted for each catalyst in Figure 6. The

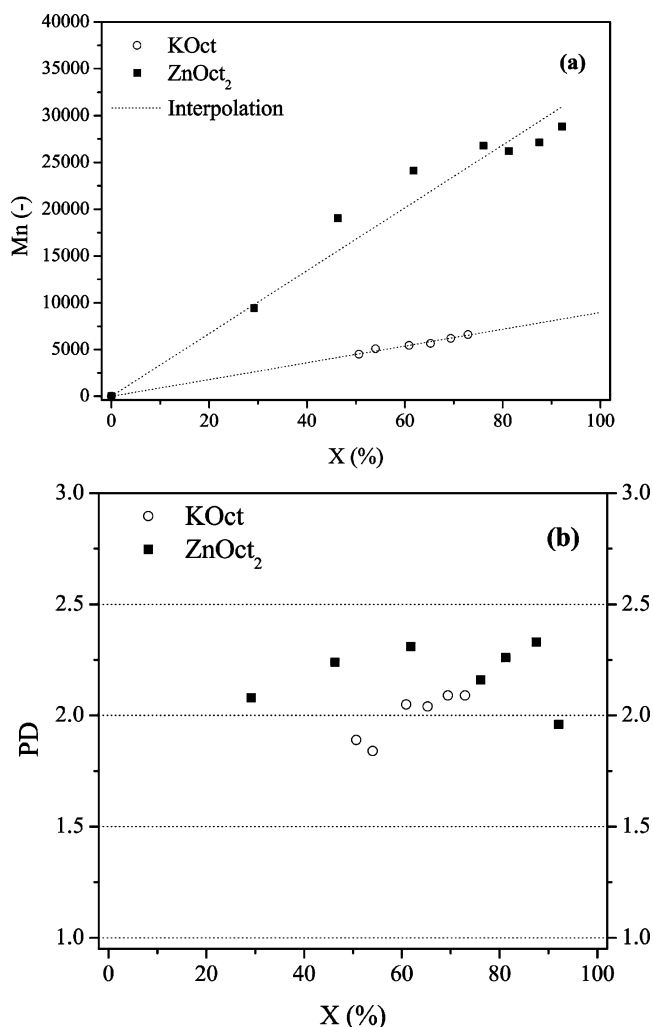
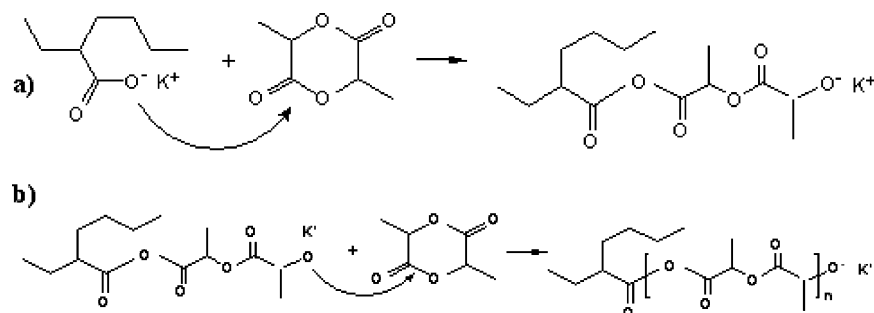


Fig. 6. Number average molecular weight (M_n) and polydispersity (PD) measured by GPC vs. total mass conversion (X). Bulk copolymerizations of d,l-lactide and glycolide. Molar ratio monomer to catalyst: 100; temperature: 130°C ; stirring rate: 100 rpm.

molecular weight distributions were measured only for samples fully soluble in THF.

As shown in Figure 6(a), the molecular weight exhibits a linear trend with conversion for both catalysts, so the pseudo-living behavior agrees for this particular copolymerization (21,23). Moreover, M_n values for ZnOct_2 are much larger than when using KOct . According to different authors, when an anionic mechanism is followed (cf. Scheme 1, note that in order to simplify the scheme just the homopolymerization of lactide has been considered), only moderate molecular weights are achieved due to the fact that the monomer anion is also capable of initiating a new chain, and thus, the deprotonation of the monomer may involve a chain transfer process (8, 20). On the other hand, comparably high molecular weights have been previously reported in the literature when using tin octoate as catalyst

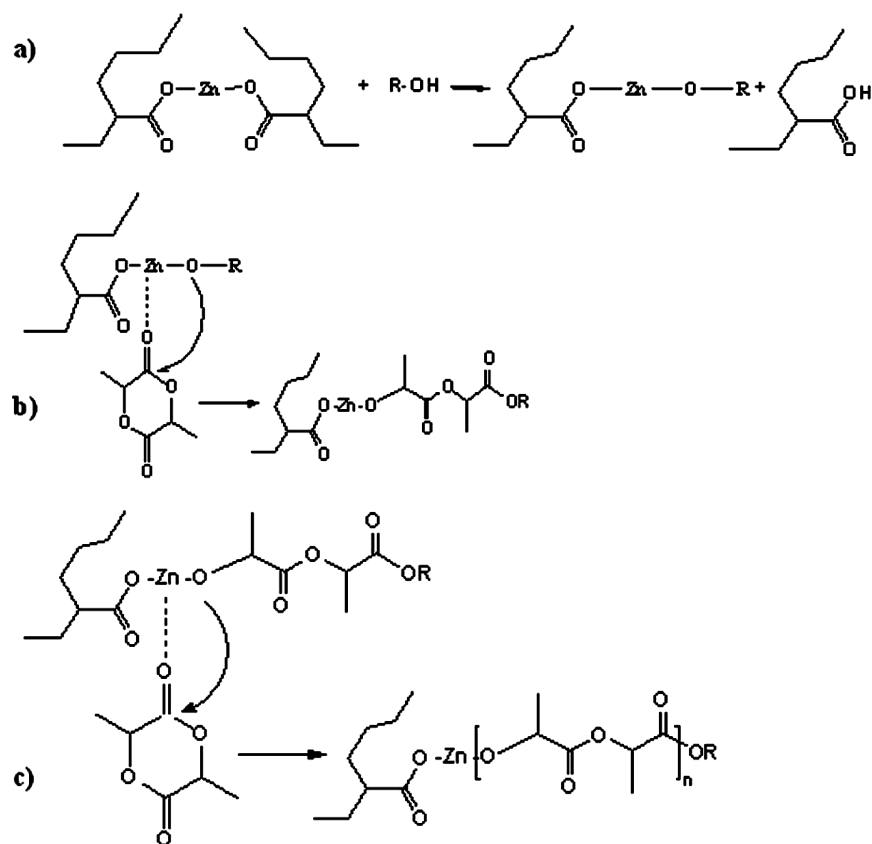


Sch. 1. Reaction scheme of polymerization carried out with KOct as catalyst. Anionic mechanism. a) Initiation stage. b) Propagation stage.

and without the addition of any initiator or co-catalyst (17). According to this literature, when a coordination-insertion mechanism is active, the polymerization starts in a metal-oxygen bond from a metal alkoxide ($-\text{Me}-\text{OR}$) (17, 20, 24). This bond can be produced by interchange between the carboxylate group from the catalyst and the hydroxilic group from the selected initiator (cf. stage of activation of the catalyst from Scheme 2). When an alcohol is used as initiator in a coordination-insertion mechanism, Scheme 2 is followed, where ROH is the alcohol. However, when no initiator is added purposely, any OH-bearing species (e.g.

water) can act as an initiator, thus activating an amount of catalyst which is usually smaller than that initially charged (17). In this case, impurities from the monomers, i.e. hydroxiacids, lactic or glycolic acids, can substitute part of the carboxylate groups from the catalyst (25).

In Figure 6 (b), the polydispersity values are shown. In an ideal living system, such values should be close to one; however, when chain transfer to macromolecules (transesterification) takes place, larger values are achieved and a limiting value of 2 is expected (26–29). The experimental values are close to 2 or even a little bit larger for both



Sch. 2. Reaction scheme of the polymerization carried out with ZnOct_2 as catalyst. Insertion-coordination mechanism. a) Activation of the catalyst with the initiator; b) Coordination of the catalyst with the ring and initiation of the reaction; c) Propagation stage.

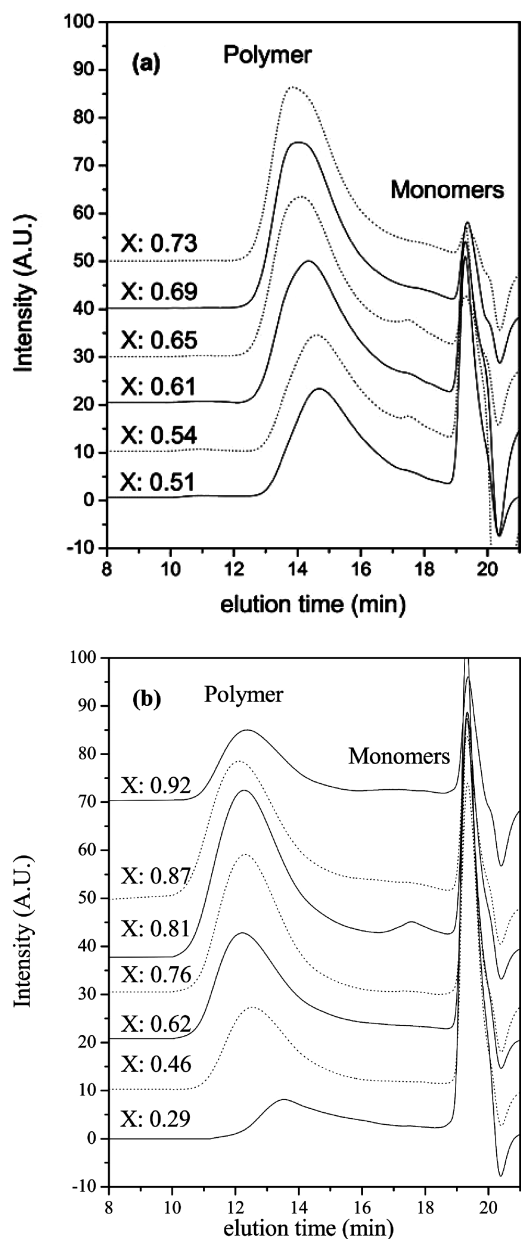


Fig. 7. GPC chromatograms. Bulk copolymerizations of d,l-lactide and glycolide. Molar ratio monomer to catalyst: 100; temperature: 130°C; stirring rate: 100 rpm. (a) KOct; (b) ZnOct₂.

catalysts, being the molecular weight distributions very broad for all the samples, what means that there is a great influence of transesterification reactions in both cases. Such broadening is quite clear in Figure 7, where the GPC chromatograms are shown: significant tailing is always present towards the region of low molecular weights, especially when KOct is used as catalyst.

3.2.2. Characterization-polymer microstructure

In order to gain at least qualitative information about the copolymer microstructure, a solubility study of the

produced polymers in tetrahydrofuran (THF) was first carried out. If PLGA exhibits more blocklike chain microstructure, it should be insoluble in THF since glycolide blocks are insoluble in almost all organic solvents. On the other hand, if the copolymer microstructure is close to randomness, it becomes more and more soluble independent of composition. The glycolide content of the first soluble sample of copolymer obtained with Zn was 53%, whereas the one with K octoate was only 30%: therefore, the randomness of the monomer units in the copolymer chains was larger in the case of ZnOct₂ rather than KOct. Such heterogeneity in the chain microstructure of the obtained copolymer with KOct is also shown in the DSC analysis. In Figure 8, two DSC thermograms of two THF-insoluble samples of polymer obtained using both catalysts are shown. It is possible to observe that the polymer obtained when using ZnOct₂ is practically amorphous, whereas in the DSC thermogram of the sample obtained with KOct there is a very important endothermic peak around 225°C, which corresponds to the melting point of the PGA homopolymer, indicating a block-like chain microstructure of the sample. However, after the heating treatment, both samples became amorphous, most probably because transesterification reactions take place during the process reorganizing the microstructure of the polymer (26–29).

In general, higher molecular weight can be achieved with a insertion-coordination mechanism to get a more homogeneous product, at least when zinc octoate is used as a catalyst. However, transesterification reactions seem to affect this copolymerization process independently on the followed mechanism.

3.3 Reaction Mechanism—Role of Initiator

With reference to the most effective catalyst, ZnOct₂, the effect of different initiators (also called co-catalysts) was finally studied. The initiators selected were methanol, 1-dodecanol, 4-phenyl-2-butanol and 2-methyl-2-propanol. The data sets of conversion vs. time for the copolymerizations involving the previously mentioned initiators at molar ratio catalyst to initiator constant and equal to 1 are shown in Figure 9. In all cases, the conversion was higher than the one achieved without initiator. The different rates of reaction could be imputed to the different steric hindrance of the alkoxide substituent (30–32), since, as already mentioned, the actual initiating species is the alkoxide formed by substitution for carboxylate group from ZnOct₂ (cf. Scheme 2) (17, 20, 24). Note that a second substitution of the carboxylate group is possible in the stage of activation of the catalyst, so the steric hindrance not only affects the initiation stage (stage b) from Scheme 2), but also the propagation one (stage c) from Scheme 2). As a matter of fact, for tertiary alcohols, the reaction rate was the lowest, whereas the co-polymerizations with primary alcohols were the fastest. Moreover, for the same kind of alcohol,

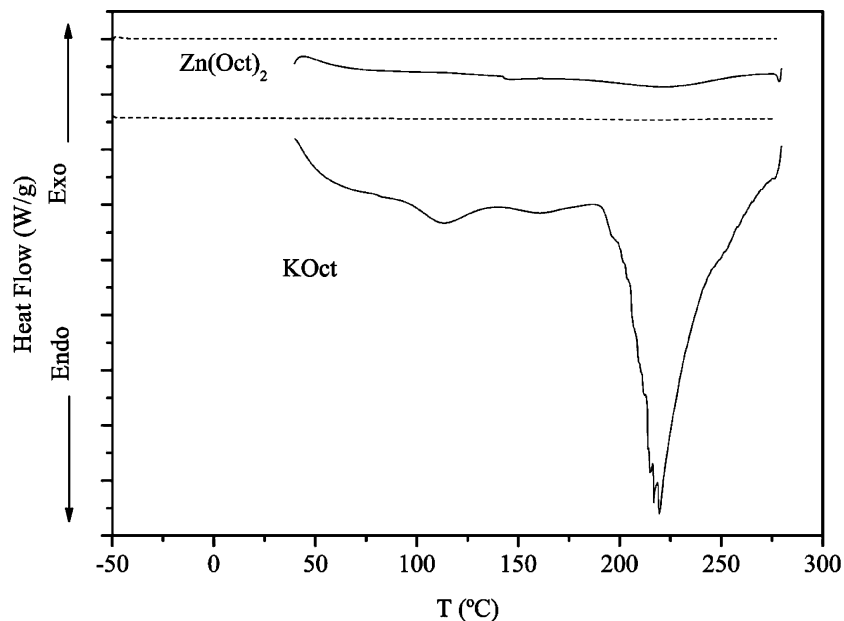


Fig. 8. DSC measurements of PLGA synthesized with $\text{Zn}(\text{Oct})_2$ (up) and KOct (down) in bulk. First run (solid line) from 40 to 280°C and second run (dashed line) from -50 to 280°C.

the reaction rate was faster for the alcohol with smaller molecular size, as it is the case comparing methanol and 1-dodecanol.

Previously, livingness and molecular weight are examined in Figure 10. Similar chain lengths were achieved when using methanol and 1-dodecanol, however, different chain lengths were obtained when using 4-phenyl-2-

butanol and 2-methyl-2-propanol, most probably because experimental disagreements, for instance, when 4-phenyl-2-butanol was used as initiator around 20% more initiator was added, so the number of growing chains increased and lower M_n was achieved. Note that in a living system, shorter chains are obtained when larger numbers of chains are involved (21, 23). However, livingness is somehow achieved with all the catalytic systems, although it seems that there is a certain lack of control when methanol is used (cf. Fig. 10 (a)).

Focusing now on the molecular weight distribution, broad distributions were also measured by GPC, being the values of polydispersity larger than one for all the samples (Fig. 10 (b)). However, when 4-phenyl-2-butanol was used the PD values were lower than when using the other initiators. So it seems that the transesterification reactions are reduced when this initiator is used (26–29).

About the polymer microstructure, all initiators produce very similar structures, since all the samples were practically amorphous independently on the initiator and the first samples soluble in THF had almost the same content of glycolide in all cases. Namely, for 4-phenyl-2-butanol, methanol, 1-dodecanol and 2-methyl-2-propanol had glycolide contents of 54, 53, 50 and, 49%, respectively.

To conclude, it is possible to point out that the addition of an initiator when using $\text{Zn}(\text{Oct})_2$ can improve the kinetic of the copolymerization. On the other hand, the livingness of the system and the microstructure of the achieved copolymer are practically unaffected, however, it seems that the transesterification reaction effect can be reduced selecting the suitable initiator.

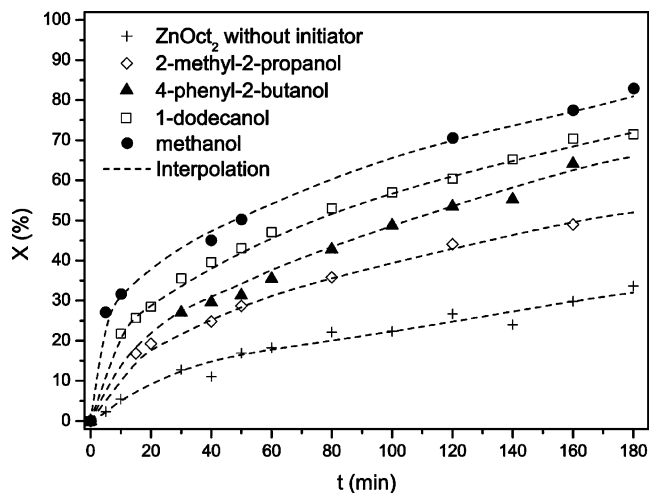


Fig. 9. Total mass conversion as a function of reaction time for the bulk copolymerization of d,l-lactide and glycolide using $\text{Zn}(\text{Oct})_2$ as catalyst with different initiators. Molar ratio (L:G) in the initial monomer mixture: 80:20; molar ratio monomer to catalyst: 500; molar ratio initiator to catalyst: 1; temperature: 130°C; stirring rate: 100 rpm.

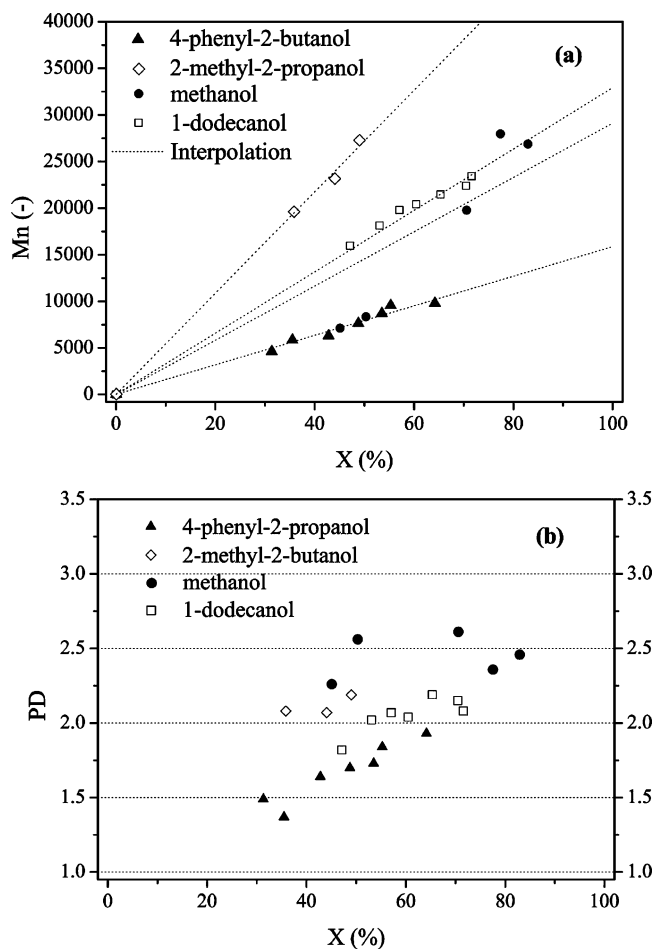


Fig. 10. Number average molecular weight (M_n) and polydispersity (PD) measured by GPC vs. total mass conversion (X). Bulk copolymerizations of d,l-lactide and glycolide using $ZnOct_2$ as catalyst and different alcohols as initiators. Molar ratio monomer to catalyst: 500; molar ratio initiator to catalyst: 1; temperature: $130^\circ C$; stirring rate: 100 rpm.

4 Conclusions

Several different catalysts were tested as substitutes of the very popular tin octoate in the bulk ring opening polymerization of glycolide and d,l-lactide. Some of them were insoluble in the molten monomer mixture and, therefore, were not effective at all. However, they could be suitable catalysts in another kind of polymerization process such as solution, dispersion or emulsion. Among the soluble catalysts in the monomer mixture at the examined operating conditions, the best conversion was given by zinc octoate through an insertion-coordination mechanism. Among alkaline and alkaline earth metal catalysts, maximum conversion values after three hours of reaction were achieved using potassium octoate. About the study of the initiator influence, alkoxides gave more active species than the corresponding octoates, livingness was observed in all the cases

but the effect of transesterification reactions can be reduced using a suitable initiator.

To conclude, $ZnOct_2$ and $KOct$ can be considered attractive substitutes for $SnOct_2$ in the glycolide-lactide copolymerization. By selecting suitable reaction conditions copolymers with the desirable characteristics (composition, molecular weight distribution and microstructure) can be produced.

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