

# **SUPERCRITICAL CARBON DIOXIDE COPOLYMERIZATION OF D,L-LACTIDE AND GLYCOLIDE USING ZINC OCTOATE AS CATALYST.**

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The objective of the study is the development of a new technique based on supercritical technology for the production of bioabsorbable polymeric microparticles containing pharmaceutical principles, for their use in the controlled release of medicines. For this purpose, the ring-opening copolymerization of D,L-lactide and glycolide in supercritical carbon dioxide, using zinc(II) 2-ethylhexanoate ( $\text{ZnOct}_2$ ) as catalyst, was studied in a discontinuous mode in a batch reactor.

## **1. INTRODUCTION**

Aliphatic polyesters such as polylactide (PLA), polyglycolide (PGA) and their co-polymers (PGLA) have recently become an important class of polymers as specialty biomedical materials and large-scale production commodity thermoplastics. These applications are mainly related to their biocompatibility and biodegradability combined with useful mechanical and thermal properties [1].

This kind of polymers can be synthesized by direct melt polymerization of the hydroxyacids lactic and glycolic acid, as well as by ring-opening of lactide and glycolide. Ring-opening polymerization can take place by cationic, anionic, coordination-insertion and enzymatic mechanisms. The coordination-insertion method has drawn the major attention and has been widely employed due to advantages such as the easy control of the molecular weights, the lower risk of side reactions and the higher molecular weights obtained [2]. Despite the high knowledge and applications of these materials there is a certain lack of information in literature about thermodynamics and kinetics of these co-polymerizations.

Tin alkoxides and tin carboxylates are the most widely used as catalysts for this mechanism [3]. However, tin compounds have the disadvantage of a significant cytotoxicity, and thus it would be desirable to find a suitable substitute for pharmaceutical or biomedical applications. As a result, several research groups are exploring the usefulness of catalysts/initiators based on less or non toxic metals, such as magnesium, calcium, iron, zinc or bismuth but up to now these have not been applied for PLGA synthesis in supercritical fluid [3].

In order to be employed as controlled release drug delivery carriers the formation of particles of suitable size is the other main objective. To get a controlled particle size distribution using a polymer previously obtained different techniques such as “Rapid Expansion of Supercritical Solution” (RESS) or “Gas (or Supercritical fluid) Anti-solvent” (GAS or SAS) can be used. On the other hand, suspension or emulsion polymerizations in supercritical fluid would allow to obtain microparticles of these polymers in an only one step [4].

The present work was focused on the previous studies to the production of PLGA co-polymer in  $\text{scCO}_2$  using zinc (II) 2-ethylhexanoate as catalyst. With the objective of a better understanding of the process, the polymer obtained with the selected catalyst was compared to the one achieved using tin octoate ( $\text{SnOct}_2$ ) and to the one gotten from a bulk polymerization.

## 2. MATERIALS AND PROCEDURE

The materials used were glycolide (1,4-dioxane-2,5-dione; Purac Biochem bv, The Netherlands) and D,L-lactide (3,6-dimethyl-1,4-dioxane-2,5-dione; Purac Biochem bv, The Netherlands) both with purity higher than 99.5%. Zinc octoate (zinc (II) 2-ethylhexanoate; Nusa, Spain) with a metal content of 12%. Stannous octoate (Tin (II) 2-ethylhexanoate; Sigma-Aldrich Química, S.A., Spain) with 95% of purity. And carbon dioxide (Carbueros Metálicos, S.A., Spain) with a purity of 99.5%. All products were used as received.

The procedure in the supercritical polymerization and the lab-scale unit used were described in our previous paper [5].

The molecular weight distribution of polymers was determined by gel permeation chromatography on a GPC Waters chromatograph. It is equipped with two columns (Styragel HR1 and Styragel HR4) and a refractive index detector. Tetrahydrofuran (THF, HPLC grade; SDS, Spain) was used as eluent at 35 °C (flow: 1 mL min<sup>-1</sup>). Polystyrene standards (Waters, USA) were used for MWD calibration. Samples were dissolved in THF at a concentration of 1.5 mg mL<sup>-1</sup> and then filtered (pore size 0.45 µm).

Monomers ratio in the polymers was measured by infrared analysis using Fourier transform infrared spectrometer (FTIR 16 PC, Perkin Elmer, Spain). Samples were dissolved in THF, poured over potassium bromide (KBr, standard infrared grade; Sigma-Aldrich Química, S.A., Spain) pellets prepared in a manual hydraulic press (Perkin Elmer, Spain) and heated at 60 °C in a drying oven during 15 minutes to allow the solvent evaporated leaving a solid film. Poly(D,L-lactide) and co-polymers of poly(D,L-lactide-co-glycolide) standards with different molar compositions of two co-monomers (Sigma-Aldrich Química, S.A., Spain) were used as reference for the estimation of the co-monomer ratio in the polymer.

Differential scanning calorimetry experiments were performed on a TA Instruments Q1000 DSC 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<sup>-1</sup>. The experiments were run in aluminium hermetic pans. To analyses TA Universal Analysis 2000 software was used. Two scans were registered for each sample. During the first one, the sample was heated from 40 to 280 °C. Then, the sample was cooled to -50 °C and heated again. The heating rates were kept at 10 °C min<sup>-1</sup> for all the measurements.

## 3. RESULTS AND DISCUSSION

In order to compare the catalytic activity in scCO<sub>2</sub> of Zn and Sn octoate (the most used catalyst up to now), two experiments in identical conditions were carried out. Molecular weight distribution (MWD), polydispersity, molar composition of the co-polymers and conversion are shown in Table 1. As it can be seen the MWD obtained with SnOct<sub>2</sub> and ZnOct<sub>2</sub> were analogous. However, the conversion was higher when the tin octoate was used due to the higher activity of this catalyst [3].

Table 1. Polymerization of PLGA in scCO<sub>2</sub>. Effect of catalyst on molecular weight average (Mw); molecular number average (Mn); polydispersity (PD = Mw/Mn), molar composition of glycolide in the polymer obtained and conversion.  
P: 200 bar, T: 130 °C and stirring rate = 500 rpm.

Catalyst	Mw	Mn	PD	Glycolide (%)	Conversion (%)
ZnOct <sub>2</sub>	9000	4000	2.22	27	61
SnOct <sub>2</sub>	8800	3700	2.35	24	80

Figure 1 shows IR spectra of commercial PLGA with lactide to glycolide molar ratio 75:25 and the polymers previously characterized by GPC. The absorption band of stretching vibration of carbonyl group at 1760 cm<sup>-1</sup> and the corresponding one due to stretching vibration of ester group (around 1000 – 1300 cm<sup>-1</sup>) appear in them. The absorption bands attributed to bending of CH bonds are around 1200 – 1460 cm<sup>-1</sup>: the absorption band of methylene group is at 1422 cm<sup>-1</sup> and the one of methyl group is near to 1452 cm<sup>-1</sup>. As it can be seen, the spectra of commercial PLGA 75:25 and the products obtained with the two catalysts in supercritical carbon dioxide are quite similar.

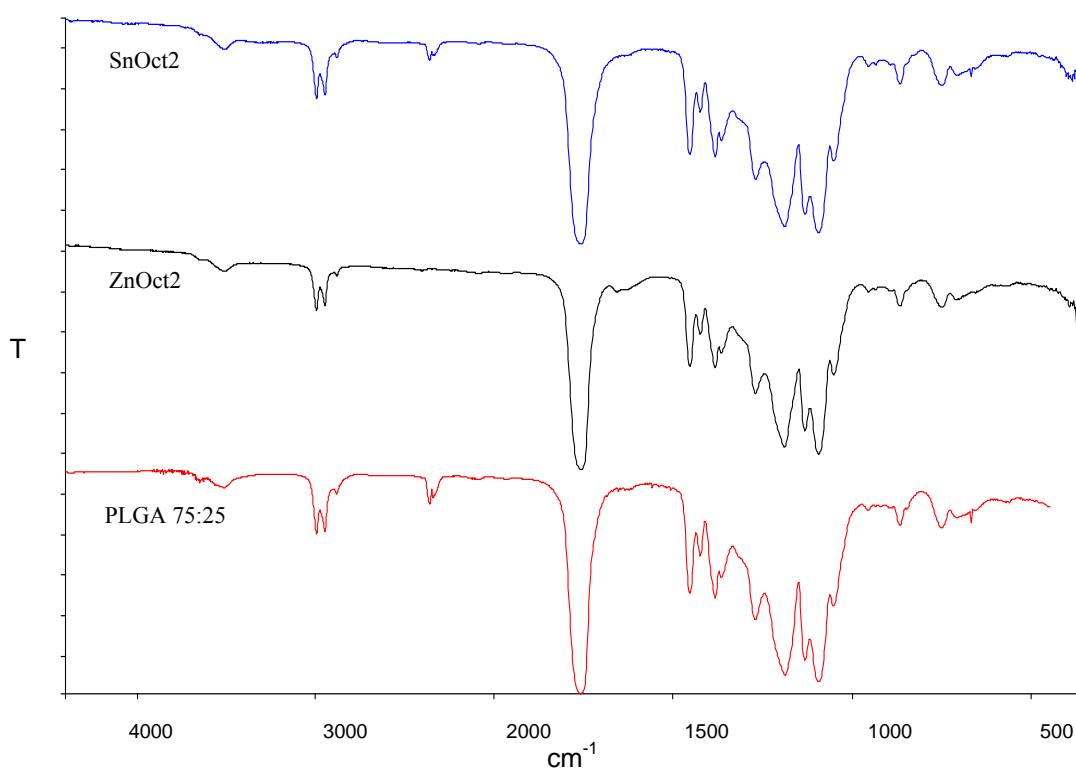


Figure 1. Polymerization of PLGA in scCO<sub>2</sub>. FTIR spectra of co-polymers obtained using SnOct<sub>2</sub> and ZnOct<sub>2</sub>. P: 200 bar, T: 130 °C and stirring rate: 500 rpm. And spectrum of a commercial co-polymer.

Both polymers were characterized by DSC too (Figure 2). First of all, it is outstood to see that in the first DSC heating (from 40 to 280 °C), the polymer synthesized with Sn showed an endothermic peak around 250 °C, therefore there must be some crystalline part in it. The peak is near to the melting point of the PGA homopolymer. So it would be possible that the copolymer

produced with SnOct<sub>2</sub> had kind of PGA blocks and so a bit of heterogeneity. On the contrary, the copolymer synthesized with zinc did not show any peak, what indicates its amorphous and homogeneous state. For drug delivery a maximum homogeneity of the matrix is looked for, consequently, ZnOct<sub>2</sub> can be considered a better catalyst than the tin compound for this application.

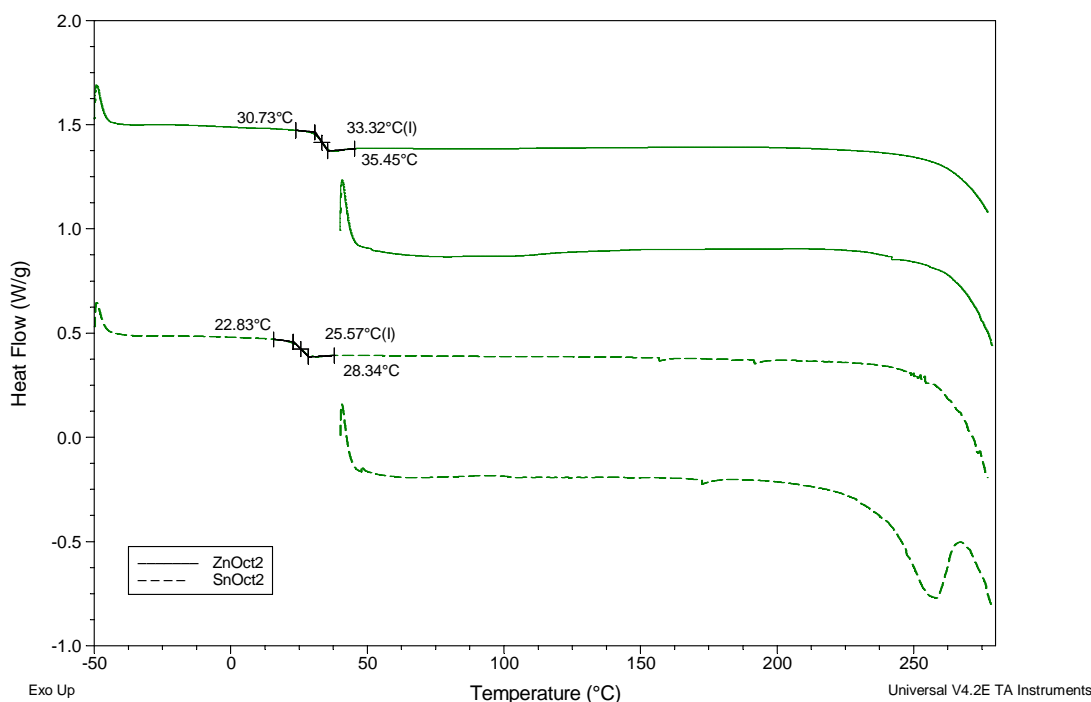


Figure 2. DSC measurements of PLGA synthesized with ZnOct<sub>2</sub> and SnOct<sub>2</sub> in scCO<sub>2</sub>. P: 200 bar, T: 130 °C and stirring rate = 500 rpm. First run from 40 to 280 °C and second run from -50 to 280 °C.

On the other hand, the glass-transition temperatures (T<sub>g</sub>) were obtained from the second heating (from -50 to 280 °C) as it can see in the figure. The T<sub>g</sub> values calculated were 33.35 and 25.57 °C to the polymers synthesized with ZnOct<sub>2</sub> and SnOct<sub>2</sub>, respectively. The two curves for the second heating looked as the one for an amorphous polymer.

PGA has a glass-transition temperature of 35-40 °C and PLA, with the D,L optical configuration, equal to 55-60 °C. In the case of a random copolymer or a homogeneous blend the T<sub>g</sub> should be just one between the respective homopolymers T<sub>g</sub>. Using the Flory-Fox equation:

$$T_g = T_g^\infty - C/M_n \quad (1)$$

Where T<sub>g</sub><sup>∞</sup> is the T<sub>g</sub> at infinite molecular weight and C is a constant representing the excess free volume of the end groups of the polymer chains, the molecular weight effect on the glass-transition temperature can be taken into account [6].

From the literature only the T<sub>g</sub><sup>∞</sup> and C parameters for PLA are available; therefore, we just can calculate the theoretical T<sub>g</sub> for a homopolymer of lactide with the same M<sub>n</sub> than our PLGA

(Table 1). Due to the similar value of two Mn, the Tg estimated for both co-polymers can be around 38 °C. It is expected that the Tg of both polymers would be smaller than 38 °C, because of the glycolide presence but quite similar (due to the very close glycolide composition for both). Even so, the Tg values are rather different. Taking into account the possible glycolide blocks are around into the polymer when the Sn catalyst is used, after the first heating and because of the small sample quantity a very homogeneous blend could be formed whose Tg is only one but different to the one of a random copolymer with similar characteristics such as molecular weight and composition.

The polymerization evolution was studied doing several experiments at the same experimental conditions stopping them at different times. The pressure and temperature profiles were identical for all experiments. In Table 2 are shown the molecular weight distribution, copolymer composition and conversion for these experiments.

Table 2. Polymerization of PLGA in scCO<sub>2</sub>. Polymerization evolution. Molecular weight average (Mw); molecular number average (Mn); polydispersity (PD = Mw/Mn), molar composition of glycolide in the polymer obtained and conversion.  
P: 200 bar, T: 130 °C and stirring rate = 500 rpm.

<b>t (h)</b>	<b>Mw</b>	<b>Mn</b>	<b>PD</b>	<b>Glycolide (%)</b>	<b>Conversion (%)</b>	<b>Mn theoretical<sup>a</sup></b>
1	3000	1700	1.75	37	39	2300
2	6300	2800	2.21	34	45	2700
4	9000	4000	2.21	27	61	3700
18	4600	2300	2.03	23	85	5100

<sup>a</sup>: Mn calculated by  $Mn = (M/C) \times M MW \times Conversion (\%) / 100$ , where M is the monomers molar quantity; C, the catalyst molar quantity times two; M MW, the molecular weight of monomer (an average done considering the molecular weight of each monomer and the composition in the copolymer).

The molecular weight increased with the time in the first hours, but at high reaction times (18 hours) a decrease of Mn and polydispersity can be observed (Table 2). If we compare the experimental and theoretical Mn, it is possible to see like the values are quite close for the low reaction times, indicating a control over the polymerization, however, at high reaction times the disagreement showing the presence of secondary reactions like termination [7].

Finally, we show a comparison between the IR spectra of polymerization samples with a same conversion obtained in bulk and in supercritical carbon dioxide using zinc octoate as catalyst (Figure 3). While the sample directly taken from the scCO<sub>2</sub> synthesis is quite clean, and there are not any monomer peaks. In the spectrum from the bulk polymerization without any purification we can see some peaks belong to monomers, for example around 1000 – 1300 cm<sup>-1</sup>, and the absorption band attributed to bending of CH bonds of methyl group near to 1455 cm<sup>-1</sup> from the lactide unit that overlaps with the one from the copolymer at 1452 cm<sup>-1</sup>. The monomers peaks can be better observed comparing with the spectrum of the same sample after purification. Therefore, in the supercritical polymerization there is an extra purification process due to the slight solubility of the monomers in scCO<sub>2</sub> [8].

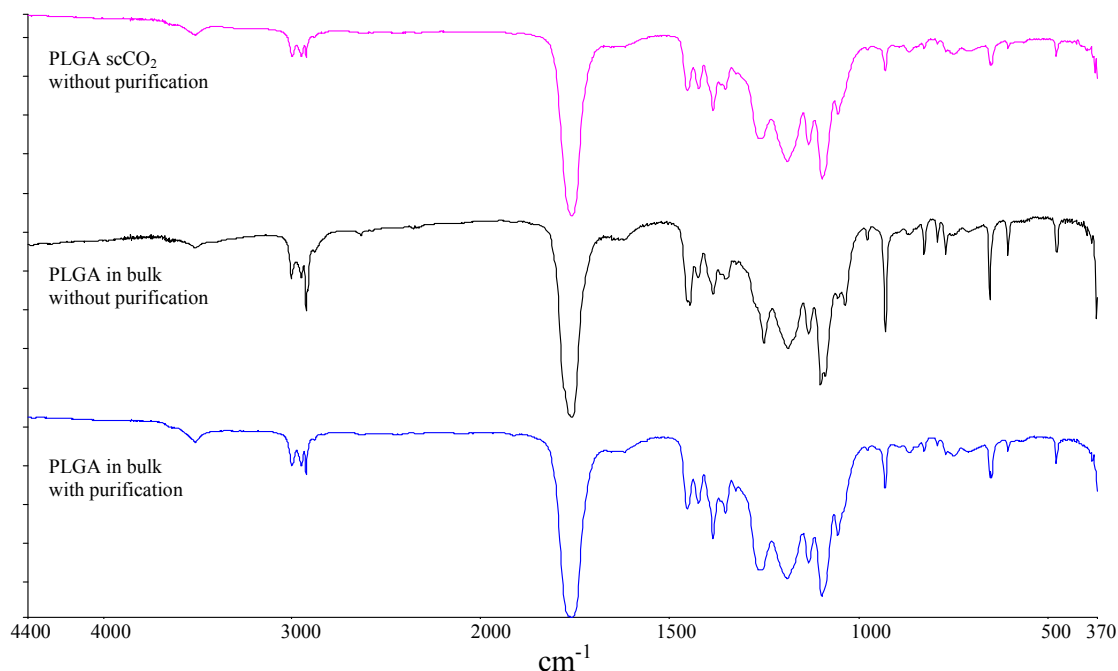


Figure 3. Polymerization of PLGA in scCO<sub>2</sub>. FTIR spectra of polymerization samples with a conversion of 39 % obtained using ZnOct<sub>2</sub> as catalyst in scCO<sub>2</sub> (P: 200 bar, T: 130 °C and stirring rate: 500 rpm) and in bulk (T: 130 °C).

#### 4. CONCLUSION

Zinc (II) 2-ethylhexanoate has been tested as catalyst in the ring-opening polymerization of D,L-lactide and glycolide in supercritical carbon dioxide medium. The results are comparable with those obtained using tin (II) 2-ethylhexanoate, the most used catalyst in this kind of polymerization. The main advantage of ZnOct<sub>2</sub> over tin octoate is its lower cytotoxicity [3]. Other additional advantage related to drug delivery application is the production of a quite homogeneous random co-polymer. These advantages together with the “green” solvent used and the high grade of purity obtained due to the additional extraction process of the monomers in during the depressurization make that the process can be a promising technology to achieve biocompatible polymers for medical applications.

A better understanding of the kinetics and thermodynamics of the system allows to find the optimal conditions to generate particles as well as polymerize.

#### 5. REFERENCES

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