Industrial Utilization of Tin-Initiated Resorbable Polymers: Synthesis on a Large Scale with a Low Amount of Initiator Residue

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This article presents the successful large-batch synthesis of a resorbable polymer with a minimal amount of residual tin. Ring-opening polymerization of ϵ-caprolactone was performed in toluene, with a tin (IV) alkoxide as the initiator. A number of parameters were varied in order to study the polymerization with respect to the purity of solvent, batch size, and the residual amount of tin in the polymers. The synthesis of ϵ-caprolactone in undistilled toluene with 1-di-*n*-butyl-1-stanna-2,5-dioxacyclopentane as the initiator was successfully performed in batches of 5, 20, and 50 g with no differences in the final conversion, molecular weight, or molecular-weight distribution. The residual amount of tin was significantly reduced from over 1000 to 23 ppm. This study examines the industrial utility of the materials regarding the size and purity of the synthesis.

Introduction

The tin-initiated ring-opening polymerization of lactones and lactides has been studied thoroughly for many years. The resulting polymers, degradable aliphatic polyesters, are used in a number of biomedical applications such as tissue engineering. Tin (II) 2-ethylhexanoate ($Sn(Oct)_2$) is the most frequently used initiator for these systems, and it has, therefore, been evaluated and compared with respect to its mechanism, effectiveness, and reaction control. Our group has for many years worked with the controlled ring-opening polymerization of L-lactide (L-LA),[1−3] ϵ-caprolactone (ϵ-CL),[4] and dioxanone (DXO).[5,6] The systems are based on tin initiators, $Sn(Oct)_2$ as well as different tin alkoxides, and the materials are today tested in both *in vivo* and *in vitro* studies. The use of tin alkoxide initiators provides opportunities to synthesize very specific architectures, that is, regular block copolymers as well as star-shaped polymers.[1,3,4,7−10] The materials have been shown to have a wide range of mechanical properties that are interesting for tissue engineering applications.

Despite the knowledge of the individual reactions, little has been reported regarding the use of these initiators in larger batch sizes. If the materials are to advance toward industrial production, it is of key interest to identify a large-scale batch polymerization method. A regular laboratory batch size is about 1 g because only a few samples are needed for kinetic and mechanistic investigations. In these small batches, however, distilled solvents are used in an inert atmosphere, and this is a problem in larger scale synthesis. It is, therefore, important to establish whether there really is a purity demand for the synthesis and whether the reaction can be controlled without the distillation of the solvent. It is crucial that the polymerization does not lose its reactivity and that it is still possible to achieve a well-defined polymer.

Another important issue is the residual amount of tin in the material after the polymerization and its possible toxicity. The FDA (Food and Drug Administration) has set a limit of 20 ppm of residual tin in commercially used medical polymers, and it is essential not to exceed that limit. The toxicity of the compounds depends on the nature and number of alkyl groups. Di and triorganotin compounds are the most dangerous because the Sn−O bond in these compounds has covalent character.[11] We have noticed a difference in toxicity between $Sn(Oct)_2$ and tin alkoxide initiators, that is, between Sn^{II+} and Sn^{IV+}, respectively, because cell growth seems to be impossible on materials containing traces of Sn^{IV+}-based initiators. $Sn(Oct)_2$ is used commercially, and there are a number of reports of different purification procedures for these materials.[12,13] There are, however, no reports of any attempts to reduce the amount of Sn^{IV+} from tin alkoxides. Because tin alkoxides are important for the next step in these biomedical materials, it is necessary to significantly reduce the residual amount of tin in these materials. Kricheldorf et al. reacted the tin alkoxide-initiated crude polymer with 1,2-ethanedithiol before precipitation in order to terminate the chain.[14−17] This procedure made it possible to selectively remove the dialkyl tin compound in the subsequent precipitation because of its higher solubility in organic solvents. We have studied this method further to investigate the extent to which the tin residue content can be reduced. Another way to avoid tin residues in the materials is, of course, to use an initiator containing atoms other than tin,- for example, zirconium,[18,19] germanium,[20] and bismuth.[21] Interesting initiators are also those containing metals already present in the human body, such as magnesium[22] or calcium. The problem with these polymerizations has been that the molecular weight of the resulting polymer has been too low for the polymer to be useful in industrial applications.[18]

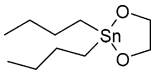

Figure 1. Initiator **1** (1-di-*n*-butyl-1-stanna-2,5-dioxacyclopentane).

This study reports the industrial utility of the materials with regard to their the size and purity of synthesis. Our first aim was to examine whether the polymerization of ϵ-caprolactone with 1-di-*n*-butyl-1-stanna-2,5-dioxacyclopentane as initiator can

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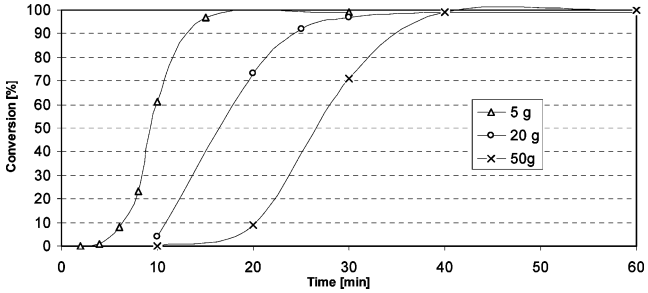

Figure 2. Conversion vs time for the different batch sizes (△, 5 g; ○, 20 g; ×, 50 g).

be successfully achieved in considerably larger batches without the distillation of the solvent. The impact on the final conversion, average molecular weight (M_n), and molecular weight distribution (MWD) was studied. The second aim was to reduce the residual amount of tin in the polymers as much as possible.

Experimental Procedures

Materials. L-Lactide (L-LA) (Serva Feinbiochemica, Germany, 98%) was purified by recrystallization in dry toluene and subsequently dried under reduced pressure (10^{-2} mbar) at room temperature for at least 48 h prior to polymerization. ϵ-Caprolactone (ϵ-CL) was dried over calcium hydride for 24 h and distilled under reduced pressure in an inert atmosphere. Dibutyl tin oxide (Aldrich, Germany) and ethylene glycol (Merck, Germany) were used as received. The cyclic tin initiator **1** (1-di-*n*-butyl-1-stanna-2,5-dioxacyclopentane) was synthesized from dibutyl tin oxide and ethylene glycol as previously described in the literature.[5] Chloroform (Merck, 99.8%), stabilized with 2-methyl-2-butene, was dried over calcium hydride for at least 24 h and distilled under reduced pressure in an inert atmosphere just before use. The undistilled chloroform (Merck, 99.8%) was used as received. Toluene (Lab-Scan, 99.8%) was dried over a Na wire before use.

Polymerization of L-Lactide with Initiator 1 (1 g Batch). For [M]/[I] = 400, 1 g (6.94 mmol) of L-LA and 5.09 mg (0.0174 mmol) of initiator **1** were weighed into a 25 mL silanized round-bottomed flask, equipped with a magnetic stirring bar and fitted with a three-way valve, inside a dry box (Mbraun MB 150B-G-I). The flask was closed and then removed from the dry box. Chloroform (distilled or undistilled) was added to the flask using a flamed syringe under anhydrous conditions. The reaction vessel was immersed in a thermostated heating bath preheated to 60 °C. The temperature was held constant (±1 °C) using an Ikatron ETS D3 temperature regulator. Nuclear magnetic resonance (^{1}H NMR) and size exclusion chromatography (SEC) samples for the kinetic and mechanistic investigations were withdrawn from the polymerization mixture at given times, using a flamed syringe while flushing with inert gas (Ar). After full conversion, the reaction mixture was precipitated in a mixture of cold hexane and methanol (90:10).

Polymerization of ϵ-Caprolactone with Initiator 1 (50 g Batch). For [M]/[I] = 400, 50 g (438 mmol) of ϵ-CL and 0.321 g (1.096 mmol) of initiator **1** were weighed into a 100 mL silanized round-bottomed flask inside a dry box (Mbraun MB 150B-G-I). The flask was closed by a three-way valve and then removed from the dry box. A small portion of dry toluene (40 mL) was added to the flask. The mixture was then transferred to the reaction vessel, which was a silanized round-bottomed flask (2 L) equipped with a magnetic stirring bar and fitted with a three-way valve. The rest of the solvent (836.6 mL) was added, and the reaction vessel was immersed in a thermostated heating bath preheated to 110 °C. The temperature was held constant (±1 °C) using an Ikatron ETS D3 temperature regulator. ^{1}H NMR and SEC samples were withdrawn from the polymerization mixture at given times, using a flamed syringe while flushing with inert gas (Ar). After full conversion, the reaction mixture was precipitated in a mixture of cold hexane and methanol (90:10).

Reaction of the Polymer with 1,2-Ethanedithiole. ϵ-CL was polymerized in toluene at 110 °C (0.5 M, [M]/[I] = 400). After full conversion, the polymer solution was treated as follows.

Treatment A: 35 mL of the polymer solution was withdrawn, and toluene was removed through rotor evaporation. The polymer was then dissolved in chloroform and precipitated in hexane/methanol (90:10).

Treatment B: 35 mL of the polymer solution was withdrawn, and toluene was removed through rotor evaporation. The polymer was then dissolved in 25 mL of dichloromethane. Then, 8.25 mg (200 mol %) of 1,2-ethanedithiole was added, and the polymer solution was left for 24 h at room temperature under stirring. Finally, the polymer was precipitated in hexane.

Nuclear Magnetic Resonance (NMR). The conversion of the monomers and the degree of polymerization were determined using ^{1}H NMR spectroscopy. The measurements were performed using a Bruker AC-400 Fourier-Transform Nuclear Magnetic Resonance spectrometer (FT-NMR) operating at 400 MHz, at room temperature, with chloroform-d_1 ($CDCl_3$) as the solvent. The samples (10 mg) were prepared in sample tubes with a diameter of 5 mm and dissolved in $CDCl_3$. Non-deuterated chloroform was used as an internal standard (δ = 7.26 ppm).

Size Exclusion Chromatography (SEC). The changes in number average molecular weight (M_n) and in the molecular weight distribution (MWD) during polymerization were determined by size exclusion chromatography. Both chloroform and dimethyl formamide (DMF) were used as eluents. When chloroform was used, the analysis was performed at room temperature using a Waters 717 plus autosampler and a Waters model 510 apparatus equipped with three PLgel 10 μm mixed B columns, 300 × 7.5 mm, from Polymer Labs., U.K. Spectra were recorded with a PL-ELS 1000 evaporative light-scattering detector from Polymer Labs., U.K., connected to an IBM-compatible PC. The Millenium 32, version 3.05.01, software was used to process the data. The flow rate of the eluent was 1.0 mL/min. Narrow polystyrene standards in the range of 580−498.000 g/mol were used for calibration. The same system was used with DMF as the eluent, with some exceptions. The solvent pump was a Waters model M-6000A, and the detector was a PL-EMD 960 evaporative light-scattering detector from Polymer Labs., U.K. The columns were two PLgel 10 μm mixed B columns, 300 × 7.5 mm, from Polymer Labs., and one Ultrahydrogel linear column, 300 × 7.8 mm, from Waters.

Tin Analysis. The tin content analysis was performed by Analytica AB in Luleå, Sweden, using ICP-AES (inductively coupled plasma with atomic emission spectroscopy) and ICP-SFMS (inductively coupled plasma with sector field mass spectroscopy).

Results and Discussion

Influence of Solvent Purity. The first step in the scale-up process was to examine how solvent purity affects synthesis. In a first experiment, we chose a monomer/initiator ratio of 400 and synthesized PLLA using distilled and undistilled chloroform. The temperature was set to 60 °C, and the reaction time was determined to be 4 days and 16 h, calculated from earlier conversion tests. The conversion was 100% according to the ^{1}H NMR spectrum, and the M_n values of the polymers were comparable: 54 000 g/mol in the undistilled solvent and 50 000 g/mol in the distilled solvent. These were not the absolute values because we were using polystyrene standards, but they provided a sufficiently good comparison between the reactions. The MWD did not vary very much either: 1.17 in the undistilled and 1.25 in the distilled solvent. It was thus concluded that the reactions could be performed without the purification of the solvent and still reach 100% conversion and a low MWD. On the basis of this conclusion, the polymers throughout this study have been synthesized in undistilled solvents.

Controlled Polymerization in Large-Scale Synthesis. In these experiments, we chose ϵ-CL as the monomer mainly

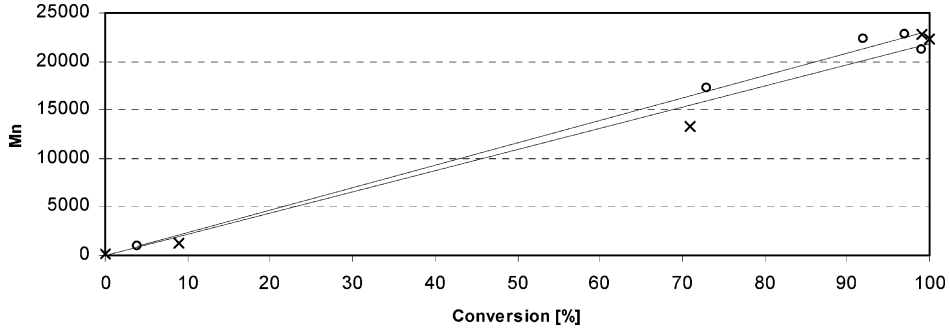

Figure 3. Average molecular weight vs the degree of conversion (○, 20 g; ×, 50 g).

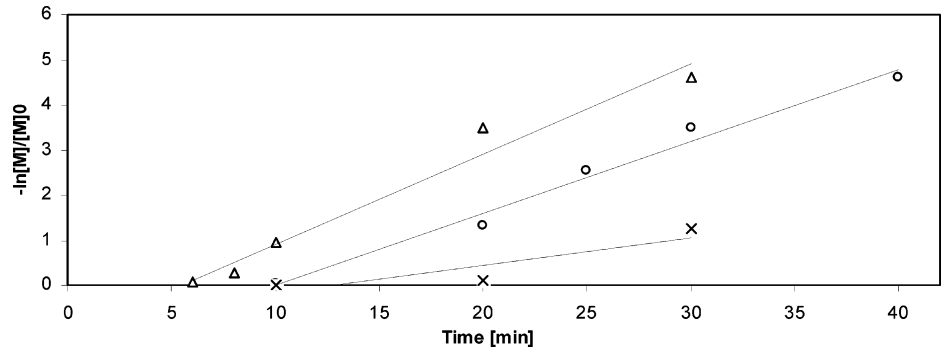

Figure 4. Semilogarithmic plot of the reactions (△, 5 g; ○, 20 g; ×, 50 g).

because of the cost of large quantities of L-LA but also because ϵ-CL has a much shorter reaction time than L-LA. ϵ-CL was polymerized in toluene at 110 °C with a concentration of 0.5 M. Three different batch sizes were synthesized: 5, 20, and 50 g. The polymerization results are presented in Figures 2−4. The curve in Figure 2 shows that all of the reactions reached 100% conversion. The reaction time was, as expected, dependent on the batch size. The 5 g batch reached 100% conversion in 15 min, whereas the 50 g batch needed 40 min. It is also obvious that the induction time of the reactions increased with increasing batch size, probably because of the longer time needed to heat the larger volume of solvent to the reaction temperature, 110 °C. In the 50 g batch, as much as 880 mL of toluene at 25 °C was used in the reaction, and because the clock measuring the reaction time was started when the reaction flask was immersed in the heating bath, the induction time is not surprisingly long.

In Figure 3, M_n is plotted against the percentage conversion for the larger batch sizes in order to evaluate the control of the reactions. The linearity of the curves shows that there was only a low amount of transesterification during the polymerizations. Hence, the batch size had no influence on the reaction control.

Using the conversion results from the reaction, a semilogarithmic plot, $-\ln([M]/[M]_0)$ versus the reaction time, is presented in Figure 4, where $[M]_0$ is the initial ϵ-CL monomer concentration, and [M] is the ϵ-CL concentration at a given reaction time. The trend line for the 5 and 20 g batches is linear up to 99% conversion, and the 50 g reaction is linear up to 70% conversion. The linearity of the curves confirms that the polymerization kinetics of ϵ-CL, with $[M]_0/[I] = 400$, $[M]_0 = 0.5$ M, and $T =$ 110 °C, were first order with respect to the monomer and also that the amount of termination reactions was low, which suggests that the number of growing chains was constant.

It is crucial for the scale-up process that all reactions reach high M_n and low MWD values, regardless of batch size. Table 1 shows the results of the SEC measurements of the synthesis of ϵ-CL.

The results show that the M_n values for all of the reactions were high, regardless of batch size. The MWD in the reactions was approximately 1.2 for all samples, and hence, this was also independent of the batch size of the reaction.

Table 1. Polymerizations of ϵ-CL in 0.5 M Toluene at 110 °C with 1-Di-*n*-butyl-1-stanna-2,5-dioxacyclopentane as the Initiator, DP 400

batch size (g)	eluent for SEC measurement	reaction time (min)	conversion[a] (%)	M_n[b] (g/mol)	MWD[b]
5	chloroform	30	100	50000	1.21
20	chloroform	40	99	39000	1.20
50	chloroform	60	100	56000	1.21

[a] The conversion was measured by ^{1}H NMR. [b] The M_n and MWD values were determined with chloroform as the eluent.

Residual Amount of Sn^{IV+}. The next challenge with this polymerization system was to reduce the residual amount of tin in the polymer, to enable the material to be used in medical applications. The limit for these materials in commercial products is 20 ppm according to the FDA; therefore, it is extremely important to focus on considerably reducing the amount of tin in order to reach that limit. When the materials are precipitated into hexane/methanol, the Sn−O bonds are broken through methanolysis, but unfortunately, this does not lead to a quantitative removal of the dibutyl tin groups. Furthermore, cyclic diorganotin alkoxides are known to self-associate in many organic solvents, preventing cleaning by precipitation.[23] Earlier unpublished results from our group showed that a material precipitated once in hexane/methanol had a residual value of 1000−1200 ppm tin. It is concluded that purification by precipitation does not sufficiently remove the catalyst from the polymer. The dilemma is that it is impossible to add less tin to the reactions because it is an initiator; the only solution is to find another cleaning procedure. We reacted the crude polymer with 1,2-ethanedithiol before precipitation, as described in the Experimental Procedures section. The mechanism is shown in Figure 5. This reaction takes place because of the fact that the Sn−S bond is more stable than the Sn−O bond. The S-containing dibutyl tin

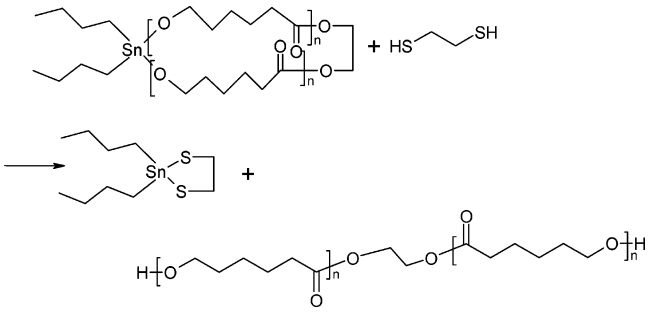

Figure 5. Reaction of the crude polymer with 1,2-ethanedithiol.

compound will be more soluble in organic solvents, and will thus be eliminated through precipitation.[16]

The results of the tin analysis clearly showed that the residual amount of tin decreased considerably. After treatment A (without 1,2-ethanedithiol), the tin content in the polymer was 1460 ppm, and after treatment B (with 1,2-ethanedithiol) the tin content had decreased to 23 ppm. This was a remarkably good result because the procedure was performed only once.

Conclusions

In this article, we present a successful large-batch synthesis of PCL with a low amount of residual tin. It is shown that the polymerization of ϵ-caprolactone initiated by 1-di-*n*-butyl-1-stanna-2,5-dioxacyclopentane can be scaled up to a batch of 50 g of the monomer, without any change in final conversion, average molecular weight, or molecular weight distribution. We also present a way to considerably reduce the residual amount of tin by reacting the polymer with 1,2-ethanedithiol. This resulted in a tin content of 23 ppm, which is close to the limit of 20 ppm set by the FDA.

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