Influence of the Operative Conditions on the Characteristics of Poly(D,L-lactide-*co*-glycolide) Synthesized in Supercritical Carbon Dioxide

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Summary: The co-polymerizations of D,L-lactide and glycolide in supercritical carbon dioxide ($scCO_2$) using zinc (II) ethylhexanoate ($ZnOct_2$) as catalyst and methanol as initiator have been investigated. The influence of stirring rate (N), temperature (T), and mass carbon dioxide (m_{CO2}) on molecular weight distribution (MWD); co-polymer composition; and conversion has been studied by means an experimental factorial design. The stirring rate has the greatest influence on conversion. Due to the heterogeneous nature of the process the mass transfer enhancement, that the grater turbulence produces, favors greatly the incorporation of monomers into the polymer phase. An important decrease of molecular weight is observed independently of reaction conditions for high conversion values because some thermal degradation or rearrangement reactions are taking place. The influence of the initiator, methanol, on the molecular weight has been also studied. Methanol acts as an effective chain transfer agent initiating more growing chains than expected, what also contributes to get low molecular weights.

Keywords: poly(D,L-lactide-co-glycolide); ring-opening polymerization; supercritical carbon dioxide; zinc octoate

Introduction

Aliphatic polyesters such as polylactides (PLA), polyglycolides (PGA) and their co-polymers (PLGA) 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.[1,2] The best method to synthesize this kind of polymers is the coordination-insertion ring-opening polymerization, due to the easy control of the molecular weight and low risk of side reactions.[3] Among a wide variety of substances, zinc (II) ethylhexanoate (also known as zinc octoate, $ZnOct_2$) has been tested as a very promising catalyst for this polymerization mechanism, since it is commercially available and it is less citotoxic than tin octoate, which has been the most usually used up to now.[3–5] On the other hand, supercritical carbon dioxide ($scCO_2$) has been used to polymerize different plastics because of its extraordinary green solvent characteristics. Several monomers and polymers have high solubility in CO_2, then homogeneous polymerization takes place.[6] However, PLGA is hardly soluble in it.[7] But even so working with carbon dioxide and heterogeneous reaction have a large number of advantages such as the elimination of the residual monomers, the possibility of obtaining particles directly as in a conventional heterogeneous polymerization or the feasibility of the manipulation of the

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polymer to introduce medicines and other active principles or produce a certain foaming of the polymer.

In this work, the influence of the operating conditions on the characteristics of the co-polymers of D,L-lactide and glycolide prepared in supercritical carbon dioxide using zinc (II) ethylhexanoate as catalyst and methanol as initiator has been studied.

Experimental Part

Experiments were carried out in a high pressure lab-scale equipment described in a previous paper.[4] Its main components are: a pump for liquid CO_2 (miniPump® model 396/74 and positive displacement type); a Coriolis flow meter (Rheonik, RHM 03 GNT); a stirring tank reactor (Autoclave Engineers) with a nominal internal volume of 300 mL and maximum operating pressure of 372 bar at 343 °C; and a depressurization line with different components such as pressure regulators. The monomers, catalyst, and initiator were charged into the reactor. After that it was closed and CO_2 was also loaded. Heating and stirring were connected and zero time was considered when temperature reached the value of 80 °C. When the reaction time was over, heating and stirring were switched off and the reactor was cooled as quickly as possible by a serpentine refrigerator. Afterwards, the reactor was opened and the sample was taken. For the experiment with polymer, the procedure followed was exactly the same but PLA was charged instead of monomer and catalyst.

Molecular weight distribution was measured by Gel Permeation Chromatography (GPC) using THF as a mobile phase. Total mass conversion was calculated by Thermal Gravimetric Analysis (TGA). And Fourier transform infrared (FTIR) spectroscopy was also used to characterize the composition polymers.

The materials were used as received. They were: D,L-lactide (3,6-dimethyl-1,4-dioxane-2,5-dione; Purac Biochem bv, The Netherlands), with purity higher than 99.5%; glycolide (1,4-dioxane-2,5-dione; Purac Biochem bv, The Netherlands), with purity higher than 99.5%; zinc octoate (zinc(II) 2-ethylhexanoate; Nusa, Spain) with a metal content of 12%; methanol anhydrous (SDS S.A., Spain) with purity higher than 99.85%; poly(D,L-lactide) (Purasorb PDL 02, Purac Biochem bv, The Netherlands); and carbon dioxide (Carburos Metálicos, S.A., Spain) with a purity of 99.8%. Potassium bromide (KBr) (Sigma-Aldrich, Spain) with purity higher than 99%, for FTIR measures; and tetrahydrofuran (THF) for GPC analysis (HPLC grade; SDS S.A., Spain) were used.

Results

The influence of stirring rate, temperature, and the total amount of CO_2 charged into the reactor, i.e. pressure, on the co-polymerizations of D,L-lactide and glycolide in supercritical carbon dioxide ($scCO_2$) using zinc octoate ($ZnOct_2$) as catalyst and methanol (MeOH) as initiator has been studied by experimental design methodology with two levels. The highest and lowest factor levels are shown in Table 1. In each experiment, 10 g of monomers were charged in the stirred tank reactor. To ensure that a high conversion level is attained reaction time was fixed in 24 h.[4] The molar ratio of monomers to catalyst was fixed in 100 and the ratio of initiator to catalyst in 1. The molar ratio between monomers lactide:glycolide was set in 80:20.

Conversion (X), co-polymer composition expressed as glycolide molar percentage in polymer (G), number average

Table 1.
Factor levels for the factorial design.

Factor	Highest level	Lowest level
Stirring rate (rpm)	1500	500
Temperature (°C)	160	120
CO_2 quantity (g)	100	50

Table 2.
Experimental results of the factorial design. Estimated total mass conversion (X); co-polymer composition in glycolide molar percentage (G); number average molecular weight (Mn); and polydispersity index (PD). Catalyst: $ZnOct_2$; initiator: MeOH; Ratio lactide:glycolide: 80:20.

		100 g of CO_2		50 g of CO_2	
		500 rpm	1500 rpm	500 rpm	1500 rpm
120°C	**X (%)**	83.7	95.7	81.0	75.7
	G (%)	23.7	21.8	24.1	25.1
	Mn (-)	900	650	900	800
	PD (-)	1.38	1.23	1.47*	1.36
160 °C	**X (%)**	79.3	97.7	85.8	100
	G (%)	24.4	21.5	23.3	20.9
	Mn (-)	2700	700	900	1050
	PD (-)	2.18	1.27	1.42*	1.49

*Partially soluble in THF.

molecular weight (Mn) and polydispersity index (PD) for the different experiments carried out are shown in Table 2.

All the samples were characterized by Fourier transform infrared spectroscopy in order to demonstrate the formation of poly(D,L-lactide-co-glycolide) in the experiments. All of them showed similar spectra. As an example, in Figure 1 the spectrum of one of the samples is compared with the one of a commercial sample of PLGA supplied by Sigma-Aldrich with a molar ratio lactide to gylcolide equal to 75:25. The spectra of the commercial PLGA 75:25 and the product obtained are quite similar. 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 1000–1300 cm^{-1}) can be observed in both of them. The absorption bands attributed to bending of CH bonds are around 1200–1460 cm^{-1}. For PLGA, the absorption band of methylene group is near to 1424 cm^{-1} and the one of methyl group is at 1455 cm^{-1} to be precise. The absorbance ratio of them can be used to obtain the molar composition of the co-polymer.

Finally, it is worthy to stress that for whatever achieved conversion, the obtained polymer from the polymerization in supercritical carbon dioxide did not show any monomer peak in the IR spectra contrary to the polymer from a conventional bulk polymerization. This suggests an extra purification process in $scCO_2$. Therefore, the monomers must exhibit some solubility in carbon dioxide.

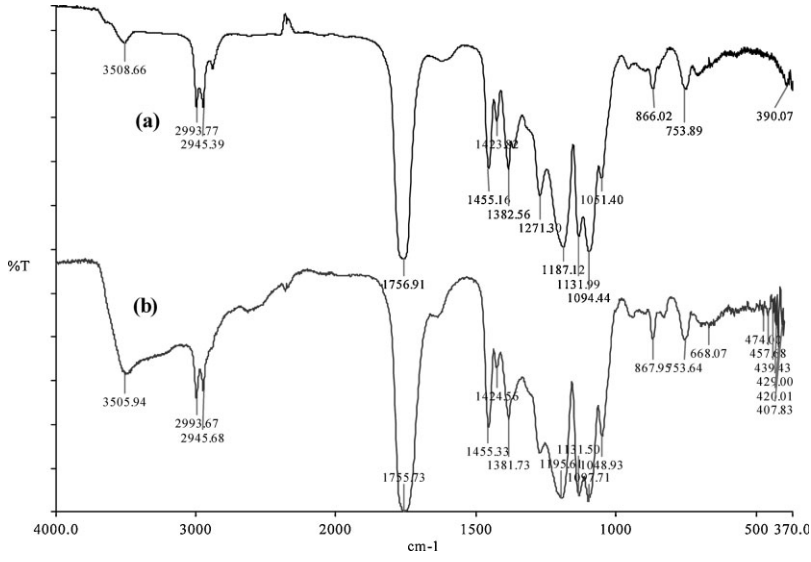

Figure 1.
IR spectra of (a) commercial PLGA (molar composition of D,L-lactide to glycolide: 75:25) and (b) sample from experiment at 160 °C, 1500 rpm and 100 g of CO_2.

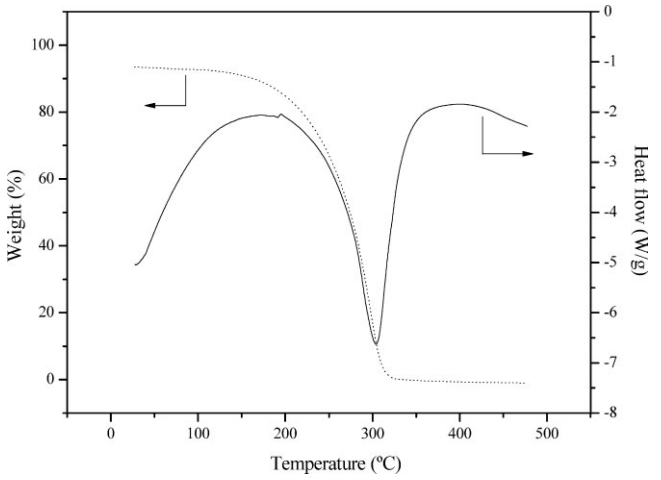

Figure 2.
Thermogram of a sample from experiment at 160 °C, 1500 rpm and 100 g of CO_2. Heating rate: 40 °C · min^{-1}.

Moreover, the samples were also analyzed by TGA. The TGA analysis of the previous sample characterized by IR is shown in Figure 2. In the curve of heat flow vs. temperature it is possible to observe that there is one big endothermic peak around 300 °C, which corresponds to degradation of polymer, and another one much lower is observed at 200 °C, which is from the monomer evaporation. However, there is not any other peak before them so the sample is totally amorphous. Similar results have been observed in all of the experiments. On the other hand, as the achieved conversion in this experiment was very high (cf. Table 2), most of the observed weight loss is due to the polymer degradation instead of evaporation of monomers (curve of weight vs. temperature in Figure 2).

To analyze the influence of the three studied factors (stirring rate (N), temperature (T), and amount of carbon dioxide charged (m_{CO2})) on polymer composition, conversion, and molecular weight distribution, an experiment at intermediate levels of the three factors was replicated and Student's t-distribution with a confidence level of 90% was used as probability distribution to calculate the experimental error. Experimental errors (e) are given in Table 3 along with simple and combined factor effects (I). All factor effects underlined had influence on studied parameters.

As it has been commented in the introduction the monomers and polymer are basically insoluble in $scCO_2$. In this way, the polymerization process is clearly heterogeneous and even the monomers and the polymer are poorly soluble between them.

As can be seen in Table 3, the individual contribution of any factor has a positive effect on conversion and negative one on the content of glycolide in the polymer. The highest influence is made by the stirring rate. Its positive influence on conversion is

Table 3.
Experimental errors (in square brackets) for total mass conversion (X); co-polymer composition in glycolide molar percentage (G); number average molecular weight (Mn); and polydispersity index (PD); and factor effects (I) of stirring rate (N); temperature (T); and the amount of carbon dioxide charged into the reactor (m_{CO2}).

e (0.1)	X (%)	G (%)	Mn (-)	PD (-)
	[1.1]	[0.2]	[477]	[0.03]
I_N	10.4	−1.5	−533	−0.27
I_T	7.3	−1.1	533	0.23
I_{mCO2}	2.9	−0.5	319	0.08
I_{N-T}	7.0	−1.1	−362	−0.15
I_{N-mCO2}	4.8	−0.9	−556	−0.25
I_{T-mCO2}	−8.4	1.4	402	0.19
$I_{N-T-mCO2}$	−3.8	0.6	−495	−0.24

related to the enhancement of mass transfer induced by the increase of the turbulence. The positive effect of temperature on conversion has to be related to the increase of reaction rate. And the favourable effect of the total amount of CO_2 may be also related to a better mass transfer because the polymer swells in $scCO_2$. It is also known that a pressure increase improves the swelling making both factors, pressure and swelling, easier the diffusion of monomers into the polymer.[8] Obviously, the combined effects of stirring rate and temperature, and stirring rate and amount of carbon dioxide also enhances the conversion. Surprisingly the combination of temperature and CO_2 and the combination of the three factors has a negative effect on conversion. The mathematical treatment in two levels can offer such paradoxical results for the combination of experimental factors.

In order to get the optimum conditions' regarding conversion, its evolution is graphically analyzed in Figure 3. It seems that almost complete conversion in the studied interval is achieved with high stirring rate almost independently of the other factors affecting the polymerization process. As abovementioned, there must be a mass transfer related problem avoiding that part of the monomers will be incorporated to the polymer chains in those experiments carried out with low stirring rate. Probably the insufficient turbulence in the experiments with the lower stirring speed and the greater viscosity of the monomers and the polymer in the experiment at 120 °C and 1500 rpm make that the major part of them remain decanted in the bottom of the reactor being not favoured the polymerization.

The influence of the operation conditions (stirring rate, temperature and CO_2 quantity) on molecular weight distribution at long reaction times (24 h) is presented in Figure 4. Only stirring rate and temperature have a significant effect, although their influence was opposite (cf. Table 3). Only in the case of using 160 °C and 100 g of CO_2 an important variation of Mn is observed with the stirring rate and also it is important to point out that only in the experiment at 500 rpm the PD takes a value greater than 2.

After reaching a certain conversion value, it seems that degradation (also called depolymerization)[9] or rearrangement reactions of the polymer chains happen to give finally very low molecular weights and short chains with a narrower molecular weight distribution consequence of a strong intramolecular process of chain transfer to polymer.[10] Only at 160 °C and the smaller stirring rate it is obtained a greater Mn with greater PD.

To interpret properly the effect on molecular weight distribution of the operative

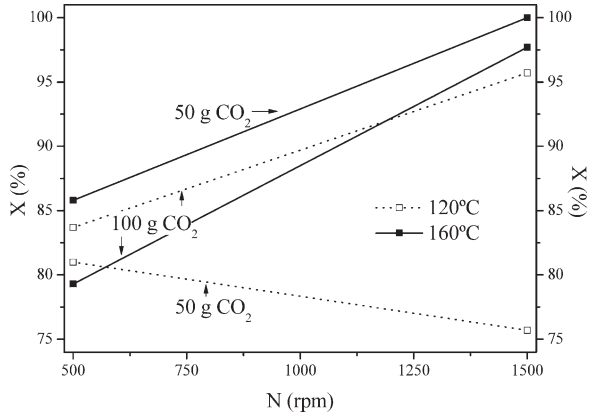

Figure 3.
Conversion evolution as a function of the different factors studied. Catalyst: $ZnOct_2$; initiator: MeOH; initial monomers composition lactide:glycolide: 80:20.

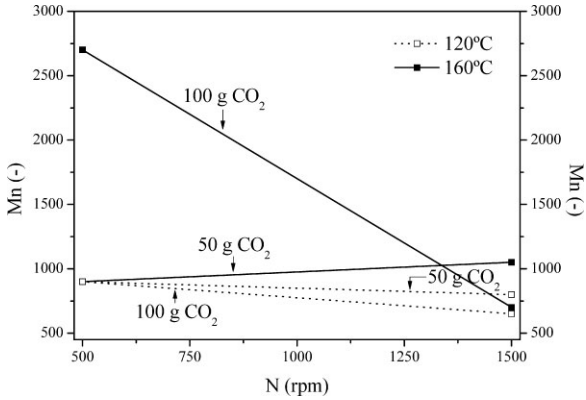

Figure 4.
Number average molecular weight evolution as a function of the different factors studied. Catalyst: $ZnOct_2$; initiator: MeOH; initial monomers composition lactide:glycolide: 80:20.

conditions, first of all it has to be pointed out that all the molecular weights obtained are much lower than the expected ones assuming that there are two active centers for each zinc catalyst molecule.[11] The theoretical molecular weight that have to be obtained should be given by the following equation:

$$Mn = \frac{M}{2 \cdot C} \cdot \frac{X(\%)}{100} \cdot M_{weighted} \quad (1)$$

where *M/C* is the molar ratio monomer to catalyst, *X* is the total monomer conversion and $M_{weighted}$ is a weighted molecular weight for a pseudo-monomer formed by a mixture of both co-monomers assuming that monomer mixture composition does not change along the reaction (80:20 for D,L-lactide and glycolide, respectively). So, for a conversion of 100% Mn should be 6900 approximately. Note that since no specific calibration was available, all measured molecular weights are values polystyrene-equivalent values and can be used only as relative quantities.

One explanation could be that the initiator, in this case, methanol, acts as a reversible chain transfer agent, as follows:[12]

$$Oct\text{-}ZnO\text{-}M_n\text{-}OR + ROH \leftrightarrow Oct\text{-}Zn\text{-}OR + HO\text{-}M_n\text{-}OR \quad (2)$$

where *Oct-ZnO-M_n -OR* is the growing polymer chain with *n* monomer units (*M*), *ROH* is the methanol, *Oct-Zn-OR* is a metal alkoxide (the real active specie), and *HO-M_n -OR* is a polymeric alcohol. Thus the active specie would be regenerated and higher number of growing chains would be produced decreasing molecular weight. That possibility has been observed in the living polymerization of alkilene oxide where a reduced amount of alkaline catalyst is initiating a large number of polymer chains.[13]

In order to confirm that the methanol can be acting as initiator of a greater number of polymer chains an experiment without methanol was carried out at 90 °C, 1000 rpm, 100 g of CO_2 and keeping constant the others variables. The molecular weight without methanol was 1700 with a PD of 1.60, whereas with methanol their values were 600 and 1.16, respectively. Consequently, it is clear than methanol favors the abovementioned chain transfer reactions; however, Mn was still too low compared with the theoretical model of chain growth proposed.

Another possible explanation for this low molecular weight could be in the impurities that accompanies CO_2 or even the proper CO_2. The composition of the commercial CO_2 employed in the experiments is given in Table 4. It can be confirmed that several substances are present in the reaction media and that

Table 4.
CO_2 composition. Minimal purity of 99.8%.

Substance	Maximum value (ppm mol. mol^{-1})	Substance:monomers* (mol %)
Water	50	0.17
Oxygen	60	0.20
Total hydrocarbons	100	0.33
Carbon monoxide	10	0.04
Nitrogen	250	0.82

*Percentage of substance considering 10 g of monomers and 100 g of CO_2.

their proportion although small in the CO_2 can be considered as noticeable in relation to the proportion of the catalyst at the experimental conditions. Among them only water could act as initiator, although can be discarded because CO_2 is passed through a molecular sieve before going into the reactor. On the other hand, apparently none of them seems to be effective chain transfer agents.

A series of homopolymerizations of D,L-lactide was carried out keeping constant the CO_2 amount but increasing the amount of monomer charged with the aim of testing the influence of the relation between phases, the continuous phase, $scCO_2$, and the polymer. The complete results are shown in Table 5 and Mn versus the amount of monomer is presented in Figure 5. As it can be seen, the conversion gotten for all the experiments is almost the same, but however, Mn increases as the initial mass monomer so does, until it reaches almost the theoretical value with the largest amount of monomer.

Once again in the experiment with the greatest amount of monomer, that must to have the greatest amount of solid decanted, the largest Mn and PD are shown. As the catalyst is mainly soluble in the monomers the behavior, in this case, is quite similar to those in bulk. However, as greater is the proportion of suspended phase lower is the molecular weight obtained. It is possible that the degradation of the polymer chains once reaches a certain conversion is favoured by a better contact with CO_2 that

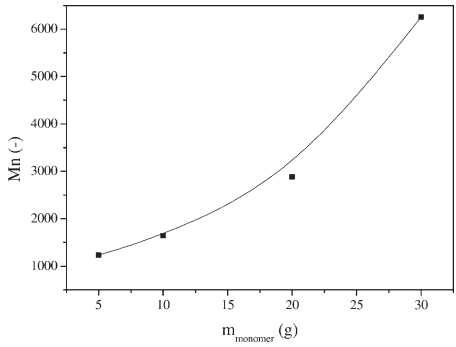

Figure 5.
Number average molecular weight vs. monomer mass charged. D,L-lactide homo-polymerizations in supercritical CO_2. Catalyst: $ZnOct_2$, molar ration monomer to catalyst: 100, N: 500 rpm, T: 160 °C, CO_2 mass charged: 100 g, reaction time: 2 h.

Table 5.
Experimental results of total mass conversion and molecular weight distribution for D,L-lactide homo-polymerizations in supercritical CO_2. Catalyst: $ZnOct_2$, molar ratio monomer to catalyst: 100, N: 500 rpm, T: 160 °C, CO_2 mass charged: 100 g, reaction time: 2 h.

Initial mass monomer (g)	X_{TGA} (%)	Mn	PD	$Mn^{theoretical}$
5	87.99	1233	1.63	6369
10	91.33	1643	1.83	6610
20	91.99	2879	2.16	6658
30	90.09	6255	3.09	6521

Table 6.
GPC characterization results. Poly(D,L-lactide) commercial sample. Experimental conditions: polymer mass: 5 g, N: 500 rpm, T: 160 °C, CO_2 mass charged: 100 g, t: 2 h.

Sample	Mn	PD
PLA before	5539	2.58
PLA after	4456	2.61

can be also favoring the activating of more growing chains in those experiments with a lower amount of monomer and consequently with a better contact between the CO_2 and the monomers.

In order to check that degradation is happening an experiment was carried out in which commercial poly(D,L-lactide) was subjected to the same conditions (temperature, pressure and stirring rate) at which the polymerizations in CO_2 took place. In Table 6, the molecular weight distribution of the commercial sample before and after the experiment is shown. The number average molecular weight (Mn) decreases after the treatment of the polymer in CO_2 at the described conditions and the polydispersity index increases. So that some thermal degradation reactions or the well-known depolymerization process are taking place along with polymerization or at least when the polymer concentration was high, i.e. at high conversion, what could contribute to reduce molecular weight.[9,14,15]

Conclusion

Among the studied factors stirring rate has the greatest influence on conversion because of the mass transfer enhancement which the grater turbulence produces. So, higher stirring rate improves the suspension and mixing of monomers and polymer. An important decrease of molecular weight was observed independently of reaction conditions for high conversion values because some thermal degradation or reversible polymerization and rearrangement reactions take place. Moreover, methanol acts as a chain transfer initiating more growing chains than expected, what also contributed to get low molecular weights.

[1] A. Duda, A. Kowalski, J. Libiszowski, S. Penczek, *Macromol. Symp.* **2005**, *224*, 71.
[2] R. Auras, B. Harte, S. Selke, *Macromol. Biosci.* **2004**, *4*, 835.
[3] H. R. Kricherdorf, *Chemosphere* **2001**, *43*, 49.
[4] R. Mazarro, A. de Lucas, I. Gracia, J. F. Rodríguez, *J. Biomed. Mater. Res. Part B: Appl. Biomater.* **2008**, *85B*, 196.
[5] A. Kowlaski, J. Libiszowski, K. Majerska, A. Duda, S. Penczek, *Polymer* **2007**, *48*, 3952.
[6] J. L. Kendall, D. A. Canelas, J. L. Young, J. M. DeSimone, *Chem. Rev.* **1992**, *257*, 945.
[7] S. E. Conway, H.-S. Byun, M. A. McHugh, J. D. Wang, F. S. Mandel, *J. Appl. Polym. Sci.* **2001**, *80*, 1155.
[8] D. Liu, D. L. Tomasko, *J. Supercrit. Fluid.* **2007**, *39*, 416.
[9] J.-P. Puaux, I. Banu, I. Nagy, G. Bozga, *Macrom. Symp.* **2007**, *259*, 318.
[10] S. Penczek, A. Duda, R. Szymanski, *Macromol. Symp.* **1998**, *132*, 441.
[11] H. R. Kricheldorf, M. Berl, N. Scharnagl, *Macromolecules* **1988**, *21*, 286.
[12] A. Kowalski, A. Duda, S. Penczek, *Macromolecules* **2000**, *33*, 7359.
[13] A. de Lucas, L. Rodrıguez, M. Perez-Collado, P. Sanchez, *Polym. Int.* **2002**, *51*, 1041.
[14] F. Signori, M. B. Coltelli, S. Bronco, *Polym. Degrad. Stab.* **2008**, doi:10.1016/j.polymdegradstab.2008.10.004.
[15] D. R. Witzke, R. Narayan, J. J. Kolstad, *Macromolecules* **1997**, *30*, 7075.

