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Synthesis and characterization of biodegradable non-toxic poly(ester-urethane-urea)s based on poly(ε-caprolactone) and amino acid derivatives

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Abstract

Non-toxic biodegradable linear poly(ester-urethane-urea)s with different hydrophilic character were synthesized from poly(ε-caprolactone) as macrodiol, L-lysine diisocyanate (LDI) and ethyl ester L-lysine or L-ornithine as chain extenders. Linear segmented polymers were synthesized by the prepolymer method with a tertiary amine playing a critical role in the chain extension in heterogeneous conditions. The prepared segmented polymers were fully chemically and physically characterized, including water uptake and hydrolytic stability measurements. Depending on the poly(ε-caprolactone) length, the segmented polymers were amorphous or semicrystalline. The crystallinity degree strongly affected the mechanical properties and water uptake behaviour.

Keywords: Biodegradable polyurethanes; Lysine diisocyanate; Amino acid chain extenders

1. Introduction

In the biomedical area, the use of polyurethanes and poly(urethane-urea)s (PUs) exceeds that of other polymeric materials including natural rubber, polyethylene, PVC, fluoropolymers and silicones, because of the various options they offer to mimic the behaviour of different tissues and relatively good biocompatibility. Of the developed PUs, the overwhelming majority are biostable materials, designed to stand in service for long periods of time [1].

Currently there is a great interest on the development of biodegradable polymers suitable for a variety of biomedical applications, such as temporary scaffolds that facilitate tissue regeneration or matrices for controlled drug release. Most of the developed materials have been rigid materials, useful for applications such as drug delivery systems or fracture fixation devices. In contrast, few biodegradable elastomeric polymers have been synthesized. Biodegradable elastomers are expected to be suited for any application requiring the use of a flexible, elastic material such as in soft tissue engineering (e.g. skin, vasculature).

Among the possible materials to mimic soft tissues are PUs. The highly variable synthetic chemistry of segmented PUs may be exploited to generate polymers having properties ranging from very soft elastomers to very rigid plastics. Linear segmented PUs are built from a moderate molecular weight diol, usually polyether or polyester, a diisocyanate, and a low molecular weight difunctional compound (usually diol or diamine) referred as chain extender. The long chain diol segments in the polymer are called 'soft' segments (SS) whereas the segments resulting from the reaction of the diisocyanate and the chain extender are called 'hard' segments (HS), and in favourable conditions they can segregate in a phase separated morphology that completely influences the properties of the polymer.

In addition to the physical properties, because the intended use of these biodegradable polymers is to be inserted in a living organism, a great care has to be taken in the choice of the building blocks. Their degradation products have to be biocompatible, non-toxic and metabolized or eliminated by the living organism. Convenient long chain diols are polyethers such as polyethylene oxide diols or polyester such as polycaprolactone (PCL) diols. Polycaprolactone is known to be biocompatible and slowly hydrolytically and enzymatically

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degradable [2], and its degradation product, 6-hydroxyhexanoic acid, is transformed by microsomal ω-oxidation to adipic acid, a natural ocurring metabolite. The diisocyanate and chain extenders typically used in the hard segment of conventional PUs are not biocompatible. For example, conventional PUs are often based on 4,4′-diphenylmethane diisocyanate (MDI) or toluene diisocyanate (TDI). The degradation products of these diisocyanates include toxic and carcinogenic compounds such as aromatic diamines, thereby making them undesirable for use in vivo. Therefore, aliphatic diisocyanates are preferred over conventional aromatic diisocyanates. Amino acid based diisocyanates were patented by Merck in 1968 [3] and PUs based on this (or other amino acids) diisocyanate have been described at the end of the 1980s [4], but the number of them has grown rapidly since the availability of the L-lysine diisocyanate (LDI, as methyl ester) at research quantities from the company Kyowa Hakko of Japan.

Bruin et al. reported that biodegradable poly(ester-urethane)s using LDI did not produce adverse tissue reactions [5]. Other researchers used LDI and not significant toxic or tumorigenic responses to the materials upon implantation were found [6]. It is surmised that the hydrolysis of the urethane or urea bonds of the polymer during degradation regenerates L-lysine, an essentially non-toxic biomolecule. The possibilities for non-toxic chain extenders to constitute the biodegradable hard segment are far wider than for diisocyanate, and several combinations with LDI have been described [4–17], some of them based on amino acids [11,12,18].

When synthesizing the PUs, aliphatic diisocyanates have lower reactivity than aromatic ones and a catalyst is necessary to speed up the reaction with polyols or water. However, catalysts such as amines or organometallic compounds may be highly toxic. Among them, stannous 2-ethylhexanoate (commonly referred as stannous octoate) is a good choice based on the acceptance by FDA as catalyst in the formulation of polymeric coatings in contact with food [19].

In this work, we have synthesized and characterized a series of biodegradable non-toxic poly(urethane-urea)s based on polycaprolactone diols of different molecular weight, LDI and two different amino acid chain extenders, ethyl ester of L-lysine or L-ornithine. The interesting features of these systems, not previously reported, are presented in this article. In view of the future application of the synthesized PUs in the biomedical field, their biocompatibility is currently being investigated by means of cell adhesion and proliferation tests by using fibroblasts cells.

2. Materials and methods

2.1. Materials

Polycaprolactone diols with nominal molecular weights of 530 (PCL530), 1250 (PCL1250) and 2000 (PCL2000), L-lysine monohydrochloride, L-ornithine hydrochloride and stannous 2-ethylhexanoate were purchased from Aldrich. L-lysine diisocyanate (LDI, diisocyanate of the L-lysine methyl ester or methyl-2,6-diisocyanatohexanoate) was kindly donated by Kyowa Hakko Kogyo Co., Ltd, Japan.

Absolute ethanol, thionyl chloride, triethylamine, and *N*,*N*-dimethylacetamide (DMAc) were supplied by Scharlau.

PCL diols were dried at 70 °C and vacuum for at least 5 h, and were stored at ambient temperature in a dessecator at vacuum until used.

N,*N*-Dimethylacetamide was vacuum distilled from isocyanates (commercial polymeric MDI) in order to eliminate residual water and amines that would unbalance the stoichiometry on the synthesis of the polymers. Distillation temperature was kept below 60 °C to avoid solvent decomposition, and the distilled solvent was stored in an amber flask blanketed with nitrogen for not more than a week before use.

The rest of the products were used as received.

2.2. Characterization

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were obtained on Varian spectrometers (Gemini 200, Inova 300 and Inova 400) using D_2O, $CDCl_3$ or DMSO-d_6 as solvent. The residual signal of the deuterated solvent was used as the internal reference (4.60 ppm for D_2O, 2.49 and 39.5 ppm for the DMSO-d_6, and 7.24 and 77.0 ppm for the $CDCl_3$).

Elemental analysis was determined using a Heraus analyzer model CHN-Rapid.

Number- and weight-average molecular weights (M_n and M_w) and molecular weight distributions were determined by size exclusion chromatography (SEC) using a Waters 244 gel permeation chromatograph equipped with a refractive index detector. A set of 10^4, 10^3 and 100 Å Waters columns conditioned at 25 °C was used to elute samples at 1 mL min^{-1} HPLC-grade chloroform flow rate. Polystyrene standards (Polymer Laboratories) were used for calibration.

Differential scanning calorimetry (DSC) was performed in a Perkin–Elmer DSC-7 instrument. Samples were heated using a scanning rate of 10 °C min^{-1} under nitrogen purge. Melting points (M_p) were taken as the maximum of the endothermic transition, whereas glass transition temperatures (T_g) were taken as the mid point of the transition.

Thermogravimetric analysis (TGA) was carried out in a Mettler Toledo TGA/SDTA851^e instrument. Disc samples cut from films were preheated at 100 °C for 10 min and heated at 10 °C min^{-1} under nitrogen atmosphere.

Fourier transform infrared (FTIR) spectra were obtained at room temperature using a Perkin–Elmer spectrometer model spectrum one equipped with an ATR accessory.

Wide angle X-ray diffraction (WAXD) patterns were obtained at room temperature by using a Philips Geiger X-ray diffractometer, operating at a rate of 1° min^{-1} using Ni-filtered Cu Kα radiation.

Polymer in vitro degradation was evaluated as weight change of the hydrated polymer film in a phosphate buffer solution at 37 °C without solution renovation. A certain amount of film was put into a vial of 15 mL capacity, filled with buffer solution, closed and immersed in a water bath at 37 °C.

At selected time intervals the films were extracted, blotted with tissue paper, immediately weighted and returned to the vial. The water uptake percentage was taken from the maximum of the relation: weight change (%) = $[(W_m - W_0)/W_0] \times 100$ where W_m is the weight of hydrated specimen and W_0 is the initial weight of the specimen. Polymers were tested by duplicate.

Scanning electron microscopy (SEM) photographs were taken in a Philips XL30 environmental scanning electron microscope at vacuum (4 Torr) operated at 15 kV. Optical microscopy was performed in a Nikon Eclipse E400 instrument at room temperature.

Tensile properties were measured in a MTS Synergie 200 testing machine equipped with a 100 N load cell. Type 3 dumb-bell test pieces (according to ISO 37) were cut from film. A crosshead speed of 200 mm min^{-1} was used. Strain was measured from crosshead separation and referred to 12 mm initial length. At least six samples were tested for each polymer composition.

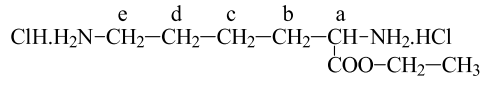
2.3. Synthesis

2.3.1. L-Lysine dihydrochloride and L-ornithine dihydrochloride ethyl esters (Lys and Orn)

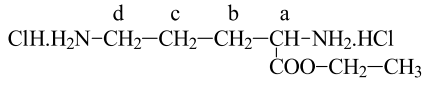
Amino acids were converted to their correspondent ethyl esters following the procedure found in literature by refluxing a mixture of amino acid, absolute ethanol and thionyl chloride [20,21]. When the mixture turned clear, after 7 h reflux, the excess ethanol was distilled off on a rotary evaporator at 70 °C. The solid product was recrystallized by dissolving in ethanol and pouring over cooled diethyl ether. Finally, the precipitate was filtered off, washed with diethyl ether and dried under vacuum. The final products were characterized by ^{1}H NMR, DSC and elemental analysis. Elemental analysis proved that the ethyl ester derivatives crystallized with a hydrochloride molecule for each amine group present on the molecule. The chemical structure and assignments for NMR analysis are shown in Scheme 1.

2.3.2. L-Lysine dihydrochloride ethyl ester

Mp 135 °C (lit. 143.5–144.5 °C [22]). Elemental analysis ($C_8H_{18}N_2O_2 \cdot 2HCl$). Calcd: C 38.87%, H 8.16%, N 11.33%, Cl 28.69%. Found: C 38.62%, H 8.31%, N 11.48%, Cl 28.71%. ^{1}H NMR (D_2O, ppm): 1.07 (3H, trip, CH_3 ethyl); 1.29 (2H, quad, c); 1.49 (2H, quint, d); 1.76 (2H, quint, b); 2.78 (2H, trip, e); 3.91 (1H, trip, a), 4.08 (2H, quad, CH_2 ethyl).



L-Lysine ethyl ester



L-Ornithine ethyl ester

Scheme 1. Structure of the amino acids ethyl esters (Lys and Orn).

2.3.3. L-Ornithine dihydrochloride ethyl ester

Mp 179 °C. Elemental analysis ($C_7H_{16}N_2O_2 \cdot 2HCl$). Calcd: C 36.06%, H 7.78%, N 12.01%, Cl 30.41%. Found: C 35.73%, H 7.46%, N 12.14%, Cl 30.27%. ^{1}H NMR (D_2O, ppm): 1.11 (3H, trip, CH_3 ethyl); 1.65 (2H, mult, c); 1.85 (2H, mult, b); 2.87 (2H, trip, d); 3.99 (1H, trip, a), 4.13 (2H, quad, CH_2 ethyl).

2.4. Hard segment models

Polymers from LDI and amino acid ethyl esters were synthesized in DMAc. Briefly, LDI and DMAc were charged in a flask at 0.34 M concentration and heated at 85 °C with stirring; then, an equimolecular amount of amino acid dihydrochloride ethyl ester was added and stirred until it dissolved; solution was cooled to room temperature and triethylamine (2× moles of amino acid dihidrochloride ethyl ester) was slowly added. Immediately a white precipitate ($Et_3N \cdot HCl$) developed, and after some minutes, FTIR spectra showed the reaction was completed. The reaction mixture was poured over distilled water, and the resulting precipitate was decanted, washed with water and dried at vacuum.

Another two model products, resulting from the reaction of LDI and *n*-butylamine and LDI and ethylamine hydrochloride, useful to qualitatively study the reaction and to assign the signals on the ^{1}H NMR spectra, were synthesized following the same procedure as above except that, for LDI and *n*-butylamine no heating was necessary and no triethylamine was added, and for LDI and ethylamine hydrochloride the triethylamine was added in equimolecular amount.

The resulting products were characterized by NMR, DSC and TGA. The chemical structure and assignments for NMR analysis are shown in Scheme 2.

2.4.1. L-Lysine methyl ester diethylurea

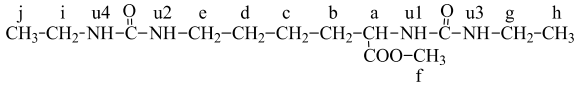
^{1}H NMR (DMSO-d_6, ppm): 0.95 (3H, trip, j); 0.96 (3H, trip, h); 1.27 (4H, mult, c,d); 1.54 (2H, quint, b); 2.95 (6H, mult, e,g,i); 3.59 (3H, sing, f); 4.08 (1H, quad, a); 5.76 (1H, trip, u4); 5.82 (1H, trip, u3); 5.95 (1H, trip, u2); 6.24 (1H, dobl, u1). ^{13}C NMR (DMSO-d_6, ppm): 15.5, 15.7 (Ch,j); 22.6 (Cc); 29.7 (Cd); 31.5 (Cb); 33.98, 34.02 (Cg,i); 38.9 (Ce); 51.5 (Cf); 52.4 (Ca); 157.6 (COu1); 158.1 (COu2); 173.9 (COO).

2.4.2. L-Lysine methyl ester dibutylurea

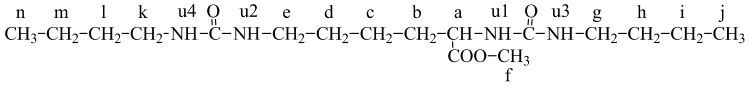
^{1}H NMR (DMSO-d_6, ppm): 0.95 (6H, trip, j,n); 1.28 (12H, mult, c,d,h,i,l,m); 1.55 (2H, quint, b); 2.94 (6H, mult, e,g,k); 3.60 (3H, sing, f); 4.08 (1H, quad, a); 5.71 (1H, trip, u4); 5.73 (1H, trip, u3); 5.92 (1H, trip, u2); 6.16 (1H, dobl, u1). ^{13}C NMR (DMSO-d_6, ppm): 13.62, 13.64 (Cj,n); 19.47, 19.52 (Ci,m); 22.6 (Cc); 29.7 (Cd); 31.7 (Cb); 32.06, 32.17 (Ch,l); 38.8 (Cg); 38.9 (Ce); 39.0 (Ck); 51.5 (Cf); 52.4 (Ca); 157.6 (COu1); 158.1 (COu2); 173.8 (COO).

2.4.3. Poly(L-lysine ethyl ester—L-lysine methyl ester)urea (LDI:LYS)

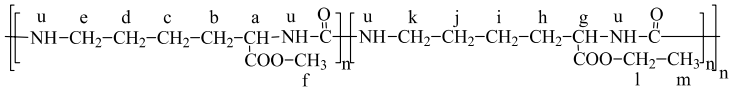
^{1}H NMR (DMSO-d_6, ppm): 1.16 (3H, trip, m); 1.29 (8H, mult, c,d,i,j); 1.56 (4H, mult, b,h); 2.93 (4H, mult, e,k); 3.60



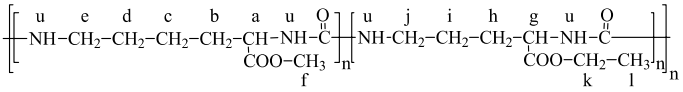
L-Lysine methyl ester diethylurea



L-Lysine methyl ester dibutylurea



Poly(L-lysine ethyl ester - L-lysine methyl ester)urea



Poly(L-ornithine ethyl ester - L-lysine methyl ester)urea

Scheme 2. Chemical structure of the models.

(3H, sing, f); 4.07 (2H, mult, a,g); 5.78 (1.4H, trip, u); 5.98 (0.6H, trip, u); 6.18 (0.6H, trip, u); 6.40 (1.4H, trip, u).

2.4.4. Poly(L-ornithine ethyl ester—L-lysine methyl ester)urea (LDI:ORN)

^{1}H NMR (DMSO-d_6, ppm): 1.17 (3H, trip, l); 1.30 (6H, mult, c,d,i); 1.56 (4H, mult, b,h); 2.94 (4H, mult, e,j); 3.60 (3H, sing, f); 4.08 (2H, mult, a,g); 5.76 (1.3H, quad, u); 5.98 (0.7H, quad, u); 6.16 (0.7H, trip, u); 6.38 (1.3H, trip, u).

2.5. Segmented poly(urethane-urea)s

Segmented polymers from PCL diols, LDI and amino acid ethyl esters were synthesized by the prepolymer method following a similar procedure to that on Ref. [23]: dry PCL diol and LDI in the appropriate amounts and DMAc were charged in a reaction flask to produce a 50:50 (w/v = weight of reactants in gram/volume of DMAc in mL) mixture. The catalyst, stannous 2-ethylhexanoate, was added (1% mol by PCL diol moles), and the stirred mixture, blanketed with nitrogen, heated at 80 °C for 3 h. After this time, the appropriate amount of amino acid ethyl ester chain extender was added to the viscous transparent liquid. After 15 min, triethylamine (3 mol for each mole of extender—50% excess) was added. The concentration was adjusted by adding DMAc until a 0.25–0.30 M solution with respect to PCL diol (36–92% weight of polymer/v; 11–20% weight of formed $Et_3N{\cdot}HCl$/v), was produced. After stirring for three further hours at 80 °C and overnight at room temperature, the resulting slurry was poured over water/ice, and the precipitated polymer washed with water and dried at vacuum.

The molar ratio between the monomers was kept at approximately 1:2.5:1.5 (PCL:LDI:aminoacid ethyl ester) for all polymers except for one, for which the hard segment content was increased. In Table 1, the synthesized polymers are listed.

Polymer films were obtained from an approximately 10% w/v solution in chloroform by casting in a leveled glass within a fume cupboard. The cast solution was covered by a conical funnel to protect it from dust and to avoid an excessively fast solvent evaporation, and allowed to stand at ambient temperature for 48 h. The film was then released and dried for further 24 h in vacuum. Samples for physical characterization were cut from films unless otherwise stated. Film thickness ranged from 50 to 250 μm.

3. Results and discussion

3.1. Synthesis and characterization

In order to obtain polymers with high molecular weight in linear polymerization, the concentrations of monomers must be adjusted. In polyurethane synthesis, the stoichiometric imbalance r of the bifunctional monomers is given by r = number of diisocyanate functional groups/number of diol and diamine functional groups, and it should be as close as possible to unity. For this reason, great care was taken to determine as accurate as

Table 1
Segmented poly(urethane-urea)s synthesized in this work

Polymer name	Nominal PCL M_n (Da)	Amino acid ethyl ester	Reactants molar ratio[a]	%HS[b]
2000LY-S132	2000	L-Lysine	1:3.7:2.7	37.6
2000LYS	2000	L-Lysine	1:2.6:1.6	28.2
1250LYS	1250	L-Lysine	1:2.7:1.7	39.2
530LYS	530	L-Lysine	1:2.7:1.7	61.2
2000ORN	2000	L-Ornithine	1:2.5:1.5	26.7
1250ORN	1250	L-Ornithine	1:2.5:1.5	35.8
530ORN	530	L-Ornithine	1:2.5:1.5	58.6

[a] PCL:LDI:aminoacid ethyl ester.
[b] %Hard segment = [weight of LDI + weight of aminoacid ethyl ester]/total weight of monomers; because HCl molecules do not enter the polymer, they were not included on the calculation.

possible the M_n of PCL diols before starting the synthesis of the polyurethanes.

Mass analysis techniques (ESI, MALDI-ToF) failed to give accurate results for M_n, despite that they resulted accurate when we analyzed several poly(ethylene glycols) with M_n up to 2000. For MALDI-ToF it has already been observed that whereas for polyaddition polymers with a near to gaussian narrow distribution MALDI-ToF reports fairly accurate values of M_n, for polycondensation polymers, with a distribution closer to the Schultz–Flory model, MALDI-ToF does not give accurate results for M_n [24]. Nevertheless, the technique gave useful structural information on the PCL diol oligomers. From the spectra it could be determined that diethylene glycol (DEG) was the polymerization initiator (M_n of the detected peaks were consistent with DEG + xCL), and that the maximum length of the chains was equal to DEG + 42 CL (4900 Da), DEG + 59 CL (6840 Da) and DEG + 71 CL (8210 Da) units for PCL 530, 1250 and 2000, respectively.

H NMR was the most convenient technique to determine rapidly and accurately the M_n of the PCL diols, and to afford some structural information. In situ derivatization of the PCL diols in the NMR tube with trifluoroacetic anhydride shifted downfield the signals of the terminal groups, leaving isolated signals easy to quantify. In Fig. 1 the spectrum of derivatized PCL530 is shown. The analysis confirmed that the oligomers were constituted by DEG + CL units, and the ratio of CL signals to DEG signals afforded the value of M_n. A simple set of experiments showed that a relaxation relay time of 5 s between pulses was safe enough to get a constant value for M_n (the difference in the value from no pulse delay to 10 s was 3% maximum).

A detailed analysis to the signals on the region 4.60–3.60 ppm allowed us to deduce some structural information. In Fig. 2, this expanded region is shown along with the assignments. The signals at around 4.30 and 4.05 correspond to the CH_2 end-group of the CL block (a') and the CH_2 unit next to the oxygen of the ester group (a), respectively. For the rest of the signals in this region, coming from the DEG, the analysis revealed the presence of three different types of DEG units: free DEG (HO–DEG–OH), monosubstituted DEG (HO–DEG–CL_n–OH) and disubstituted DEG (HO–CL_n–DEG–CL_n–OH). A complete signal assignment could be carried out without uncertainty by comparing the spectra of PCL diols with the spectra of synthesized triblocks of (polyethylene glycol/ε-CL) [25]. Thus, the signal around 4.48 was assigned to CH_2 end-group in the monosubstituted DEG (α'), the signal around 4.26 corresponded to CH_2 attached to the ester group formed by reaction with CL (two superposed signals, mono- and disubstituted DEG, ω' and α, respectively), the signal around 3.81 was assigned to CH_2 attached to the ether group in the monosubstituted DEG (β'), and the signals around 3.75 to be related to CH_2 attached to DEG ether group (3.76 approx. for disubstituted and 3.74 approx. for monosubstituted DEG, β and γ', respectively). The difference in the spectra of our synthesized triblocks and the commercial PCL samples is on the 4.48 and 3.81 signals. In our triblocks these signals appeared as clean triplet with approximately equal intensity peaks, related to CH_2 end-group of monosubstituted

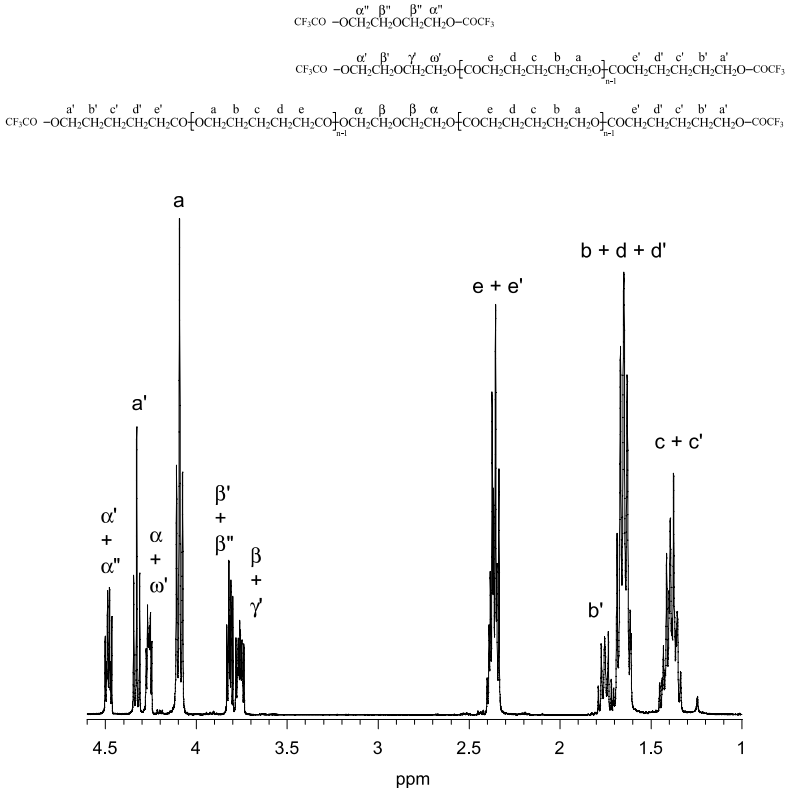


Fig. 1. ^{1}H NMR spectrum of derivatized PCL530 ($CDCl_3$, 400 MHz), and structure of the corresponding species.

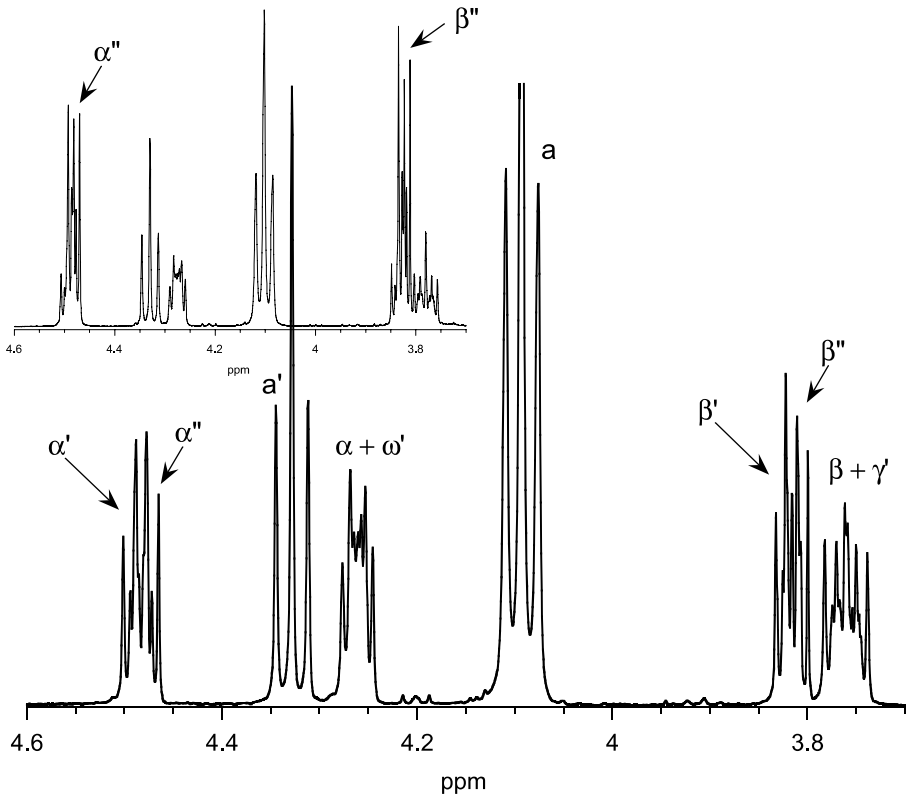


Fig. 2. Expanded region of derivatized PCL530 with insert of the signals for the admixture PCL530+DEG. For the assignments of CL peaks see Fig. 1.

polyethylene glycol, and the cleanness of the signal was independent of the number of CL units attached to the other end of the species. However, for commercial PCL diols, both signals are composed of two superimposed signals, and because all the monosubstituted DEG species give a single signal, the only possible species to give a different signal is the free DEG. The confirmation of this fact was done by registering the spectrum of an admixture of PCL530 and DEG, in which, as expected, the signals at 4.47 (α'') and at 3.80 (β'') ppm grow, as shown on the insert in Fig. 2. The results from ^{1}H NMR analysis are summarized in Table 2.

The mean length of the CL segments should be, if all chains were disubstituted, 1.89, 4.98 and 7.96 CL units for PCL530, 1250 and 2000, respectively. For the mixture of three different substituted species, this length could be calculated from the ratio of CL signals at 4.30 (a') ppm and at 4.05 (a'') ppm, giving the following results: 3.70, 7.20 and 10.22 CL units for PCL 530, 1250 and 2000, respectively, that is, longer values than theoretical.

3.1.1. Model synthesis

In order to establish the appropriate conditions for the chain extension reaction and hard segment model synthesis, the reaction of LDI with some monofunctional monomers was studied. Reaction of LDI with a free aliphatic amine, *n*-butylamine, showed to be a very fast and clean reaction. The isocyanate band, initially observed at 2260 cm^{-1}, disappeared in seconds, and the expected product was obtained. When ethylamine hydrochloride was reacted with LDI without triethylamine, long reaction times were needed for isocyanate band disappearance, and after reaction completion, the isolated product was not the expected one, displaying signals attributed to urea groups of very low intensity in the ^{1}H NMR spectrum. Triethylamine addition at the reactants mixture changed completely the situation, a complete reaction of isocyanate groups took place within some minutes and the resulting product was identified as the expected diurea molecule.

From these studies became clear the critical role of triethylamine. This tertiary amine acts as an acid binding

Table 2
Composition of PCL diols from ^{1}H NMR analysis (relaxation time 5 s)

Nominal PCL M_n (Da)	Calculated M_n (^{1}H NMR) (Da)	Total number of CL units per DEG molecule[a]	Species molar ratio[b] (%)		
			Free DEG	Monosubstituted DEG	Disubstituted DEG
530	539	3.79	24	50	26
1250	1243	9.96	7	41	52
2000	1923	15.92	5	32	62

[a] Calculated from the ratio (total CL signals/total DEG signals).
[b] Due to partial merging of DEG, monosubstituted DEG and disubstituted DEG signals, their corresponding molar percentages are approximated values.

agent, and not only to help to dissolve the amino acid salt [23]. It is well known the retardant effect of acids in urethane and urea formation reactions from isocyanate [26], and thus, organic acids are included in polyurethanes for coating applications to control reaction rate. In our case, it was demonstrated that the hydrochloride molecules present in equimolecular amount respect to isocyanate groups slowed down the reaction so much to take hours to complete isocyanate consumption. In addition side reactions took place producing different products.

Reaction of LDI with Lys or Orn in the presence of triethylamine gave the expected model hard segment polymers, confirmed by the urea corresponding signals on the ^{1}H NMR spectra.

3.1.2. Segmented polymers synthesis

Previous experiments carried out by us at the chosen temperature and catalyst concentration indicated that a complete prepolymerization was produced in 3 h. Then PCL diols and LDI were reacted during that reaction time. When the aminoacid salt derivative chain extender was added to prepolymer solution, a slurry was formed under stirring. No extensive salt dissolution was apparent before triethylamine addition. Stirring the solution with the added tertiary amine did not make any visible change. However, solution viscosity increased steadily with time due to simultaneous amino acid reaction and insoluble triethylamine hydrochloride formation. After salt dissolution in water and polymer precipitation, the obtained polymer resulted to be soluble in chloroform. Films were cast from these solutions.

Although LDI has been widely used in degradable PUs in recent years, the use of amino acid chain extenders has not been exploited except for a few cases [7,12,18,23,27]. In some published works, LDI was combined with an amino acid based chain extender [7,12], and in one of them, it was used the same L-lysine based chain extender we used [23], but in no work L-ornithine based chain extender has been used to our knowledge. All polymers presented here were synthesized for the first time.

SEC data for the resulting polymers are listed in Table 3. Molecular weight of the polymer increases with the increase in length of the starting PCL diol as already found in other polymers based on LDI and PCL [28]. There are no big differences in the polymer molecular weights when the chain extender is changed from Lys to Orn, specially for the M_w value. Both series exhibited high polydispersity, with PI values above 2. For the L-lysine series (LYS), polymer 2000LYS132 with higher hard segment content reaches lower molecular weight than 2000LYS.

Table 3
SEC results for the synthesized poly(urethane-urea)s

Polymer name	M_n (Da)	M_w (Da)	PI
2000LYS132	11,300	36,300	3.2
2000LYS	25,600	49,900	2.0
1250LYS	14,700	36,700	2.5
530LYS	7200	19,000	2.6
2000ORN	16,800	50,900	3.0
1250ORN	10,900	38,800	3.5
530ORN	9600	24,400	2.5

Molecular weight data reported in literature for PUs based on PCL [12,23,28–31] are in general higher than the values reported here. From literature values is clear that asymmetric diisocyanates or chain extenders reach lower molecular weights than symmetric (isophorone diisocyanate (IPDI) vs. hexamethylenediisocyanate (HDI) [31], Lys vs. butanediamine (BDA) [23], LDI vs. HDI [12,18]). Bearing in mind that in our polymers both diisocyanate and chain extender are asymmetrical, it is to be expected a further reduction in molecular weight. Besides, whereas for hard segment model synthesis the aminoacid chain extender dissolved before triethylamine addition, in our segmented PUs synthesis the chain extender did not dissolve and reaction took place in heterogeneous conditions. Possibly, the increase in viscosity of the reaction medium after the pre-polymerization step plus the hydrophobibity of the dissolved PCL diol chains, limit the solubility of the aminoacid chain extender salt. During chain extension a further increase in viscosity is evident (proving that chain extension is taking place); this increase could bring the solubility limit of the aminoacid chain extender further down leading to an incomplete solution of the chain extender, and therefore to an unbalanced stoichiometry and low polymer molecular weights.

The polydispersity values are broad, above 2.0, which seems logical taking into account that reaction takes place in heterogeneous conditions.

Although the numerical values (referred to polystyrene standards) obtained for the molecular weight of our polymers are not very high, molecular weights achieved were enough to get tough polymers with good mechanical properties, as it will be shown later.

3.2. Infrared analysis

In Fig. 3 the regions for the carbonyl and amine groups for the Lys extended series are displayed. For better discussion, the spectrum of the un-extended polymer PCL2000:LDI (1:1 mol ratio) is included. The Orn extended series, not shown, had spectra that almost overlapped with the corresponding Lys extended polymers.

In the amine region, a broad peak centered at around 3350 cm^{-1}, corresponding to N–H vibration in hydrogen bonded urea groups [32] grows with the increase in urea group concentration that takes place with the decrease on the PCL length (or increase in %HS, see Table 1), as expected. We do not see evidence of any free (non-hydrogen bonded) N–H groups (vibration to be found at approximately 3450 cm^{-1}) [33]. In the carbonyl region, besides the strong band at approximately 1725 cm^{-1} corresponding to ν(C=O) of ester groups, a new band, absent in the PCL2000:LDI (1:1) polymer, appeared at around 1640 cm^{-1}, corresponding to ν(C=O) of hydrogen bonded carbonyl in urea groups (amide I). As for the 3350 cm^{-1} band, this urea related band increased with the increase in urea group concentration. In between the bands at

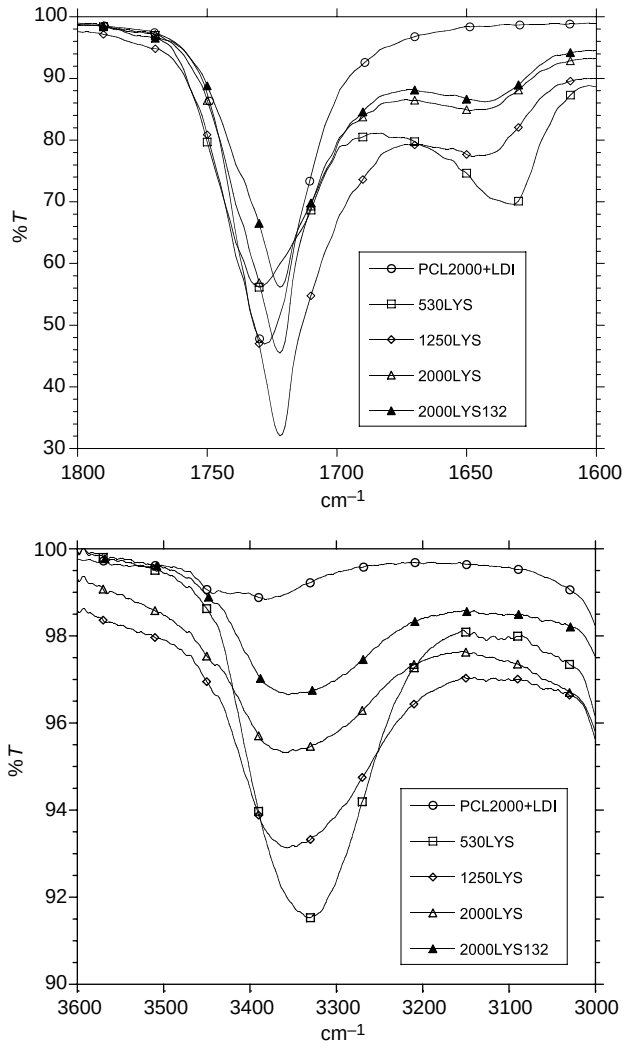


Fig. 3. FTIR spectra of carbonyl (up) and amine (down) regions of the Lys extended and PCL2000:LDI (1:1) polymers.

1725 and at 1640 cm^{-1}, no peaks are observed for urethane groups (absorption in the range 1700–1680 cm^{-1}) due mainly to their low content in the final polymers and also because it is overlapped by the strong absorption of ester groups.

From IR analysis it was demonstrated the urea formation reaction during polymer synthesis.

3.3. Crystallinity and thermal properties

The crystallinity of some polymers was clearly observed by optical microscopy. In polymers based on PCL530, crystallinity was completely absent whereas for polymers based on PCL1250 and PCL2000, spherulites showing the characteristic Maltese Cross pattern and clear boundaries, could be seen when observed under cross-polarized light. Wide angle X-ray diffraction experiments confirmed optical microscopy findings. In addition, the comparative analysis of poly(urethane-urea)s and PCL2000 patterns demonstrated that PCL was the only crystalline species present. PCL crystallinity increased with PCL length, as it can be observed in Fig. 4 for the Orn extended polymers series.

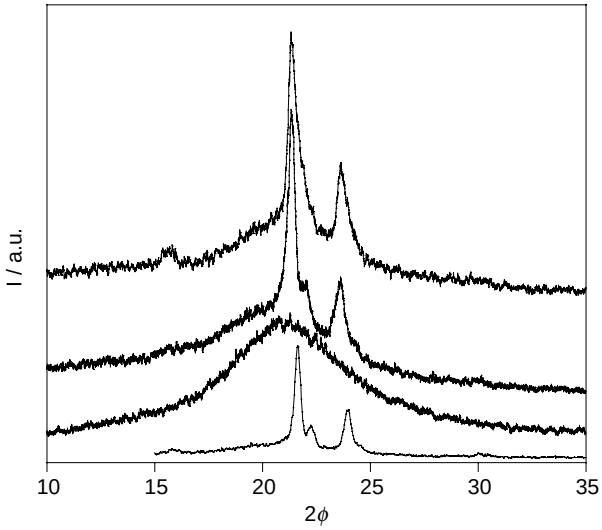


Fig. 4. WAXD spectra of (from the bottom) PCL2000 and 530ORN, 1250ORN, 2000ORN poly(urethane-urea)s.

In segmented PUs, phase separation of soft segments (SS) and hard segments (HS) can take place depending on their relative content, structural regularity and thermodynamic incompatibility. In our polymers, with molar ratio of reactants high enough to achieve phase separation, HS is highly irregular and has an aliphatic structure, meaning that phase mixing is more likely than phase separation. Precedents in literature show that segmented polymers based on PCL and LDI [12] or Lys [23] do not show HS transition except for one case (PCL2000:LDI:BDA) where an endotherm centered at 90.9 °C was assigned to melting of HS.

One of the techniques used for checking phase separated structures is small angle X-ray scattering (SAXS). To prove the existence or not of phase separation, polymer 530LYS was chosen. Because of the PCL crystallinity of the 2000 and 1250 series (meaning the co-existence of a pure PCL phase and other(s) phase(s)), a maximum in SAXS intensity would appear, but the nature of non-pure PCL phase(s) would be uncertain. If a maximum appears on 530LYS polymer, this would be conclusive of the existence of two separated phases, an amorphous PCL rich phase and a hard segment rich phase. The featureless SAXS spectrum of polymer 530LYS with no appreciable scattering on the detector (not shown) indicated the presence of a homogeneous phase or, if some phase separation exists, that the electronic density of the phases were almost equivalent.

Calorimetric measurements were performed first on the hard segment models. The diurea derivative from LDI:*n*-$BuNH_2$ resulted to be a crystalline product melting at 120–150 °C which recrystallized to a certain extent on cooling. For polyureas LDI:LYS and LDI:ORN, an endotherm with peak maximum at around 100 °C registered on the first run, did not appear again on cooling. On the second run, a single T_g was observed, with midpoints at 27 and 83 °C for LDI:LYS and LDI:ORN, respectively. The higher value for Orn derived polyurea is probably due to the higher concentration of polar urea groups.

Table 4
DSC results for the poly(urethane-urea)s segmented polymers

Polymer name	%PCL weight in polymer	First scan (20–90 °C)			Second scan (−90 to 80 °C)			
		Endotherm maximum (°C)	ΔH (J g polymer)	% PCL crystallinity	T_g (°C)	Endotherm maximum (°C)	ΔH (J g polymer)	% PCL crystallinity
2000LYS132	57.2	45.9	45.4	53.6	−59.5	36.8	0.7	0.8
2000LYS	66.0	47.1	43.6	44.7	−59.4	37.6	6.6	6.7
1250LYS	53.8	40.6	39.0	49.0	−53.0	–	–	–
530LYS	30.7	–	–	–	−6.9	–	–	–
2000ORN	66.9	45.0	48.2	48.7	−59.0	40.6	24.9	25.2
1250ORN	55.9	40.2	38.5	46.5	−51.0	–	–	–
530ORN	32.5	–	–	–	−10.0	–	–	–

Thermal properties for poly(urethane-urea)s were registered from 20 to 90 °C followed by fast cooling and reheating from −90 to 80 °C. Above 90 °C, no thermal transitions related to hard segments were found. In Table 4, the results from DSC measurements are listed. In the first run (20–90 °C), PCL530 derived polymers showed a flat baseline, whereas PCL1250 and PCL2000 derived polymers displayed pure PCL phase melting. A good baseline before and after melting allowed for quantitative calculation of crystallinity (Fig. 5). After correction for PCL content on the polymers and ratioing against crystallization heat for pure high molecular weight PCL (16.9 kJ mol^{-1}) [34], the percentage of crystalline PCL could be calculated. These values are quite high for all crystalline polymers, between 45 and 54%. Endotherm maxima are well below the 69 °C value given for pure high molecular weight PCL [34], probably due to the small size of the crystals on the poly(urethane-urea)s due to movements restrictions. Comparison of the crystallinity and melting point values of the polymers with that of PCL starting materials and polymers with no chain extension (LDI:PCL2000 or PCL1250 or PCL530, 1:1 ratio) showed a reduction going from PCL diols to PCL:LDI 1:1 polymers, as a consequence of chain motion restrictions by chain end capping, and a further slight reduction when including amino acid chain extender on the formulation.

In the second run (Fig. 6) crystallinity is lost for PCL1250 derived polymers and almost completely for polymer 2000LYS132. For polymer 2000LIS only a marginal crystallinity was recovered whereas for polymer 200ORN almost half of the initial crystallinity was recovered. This reduction on crystallinity could be due to the mixing of pure PCL phase and mixed PCL-HS phase or to the slow recrystallization of pure PCL phase, or both. For PCL1250 based polymers T_g values were only about 6–8 °C above the value for PCL2000 polymers (Table 4). We do not think that this small difference can be related to phase mixing and we believe that pure PCL phase remains unmixed after heating at 90 °C.

Several facts support this view. When the polymer 2000ORN, the one with highest crystallization rate, is isothermally recrystallized at 25 °C following melting at 90 °C, after 135 min time only a 5% of the initial crystallinity is recovered, and after 24 h 86% crystallinity is recovered. For the rest of the initially crystallized polymers, where no or marginal crystallinity is found on the second run, it is expected to take even more time for recrystallization. Samples melted and evaluated after 2 years time of recrystallization at room temperature showed that crystallinity was not only recovered to almost initial values (1250LYS and 1250ORN) but in some cases even surpassed initial values (2000LYS132, 2000LYS, 2000ORN). To further check the possibility of phase mixing, a sample of polymer 1250LYS was heated at 10 °C min^{-1} to

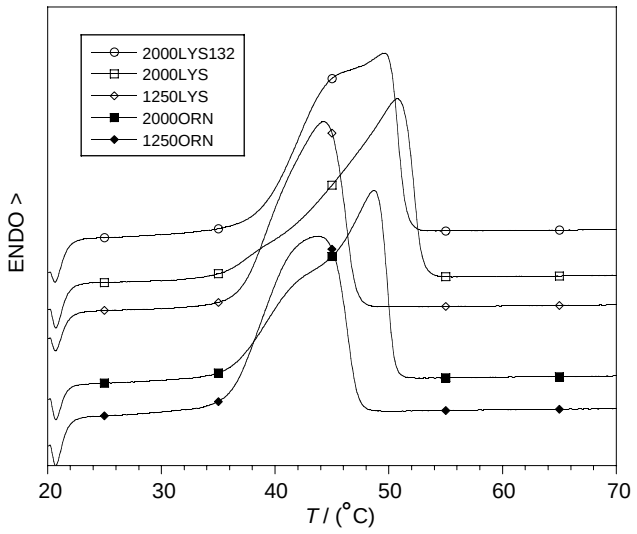


Fig. 5. Normalized first run DSC curves of crystallized polymers.

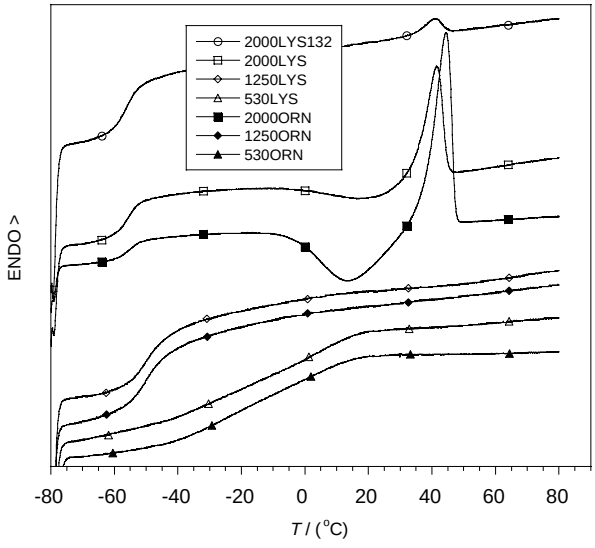


Fig. 6. Normalized second run DSC curves of polymers.

high temperatures in 20 °C steps and after every temperature was reached, polymer was cooled to low temperature and changes in thermal transitions evaluated. No changes in T_g were observed until 210 °C, showing that this polymer is stable up to this temperature and no phase mixing, that should increase T_g, takes place. After heating at 230 °C, a slight crystallinity appears on cooling, and after heating at 250 °C, 42% of initial crystallinity is recovered and T_g is reduced by 2 °C. This crystallinity recovery is due to the increase in mobility produced for the initial decomposition of the polymer above 210 °C, as will be shown later by thermogravimetric analysis. This was confirmed by the molecular weight reduction observed when the sample heated at 250 °C was analyzed by SEC. These facts proved that no phase mixing took place on heating the samples up to the start of decomposition, and that pure PCL phase recrystallizes when enough time is allowed for. Finally, when comparing PCL2000 derived polymers, 2000ORN recrystallizes clearly better than 2000LIS. The reason is unclear for us, given that structures and HS contents are very similar. When comparing 2000LYS and 2000LYS132, the increase in HS content impedes further recrystallization due to an increase of movement restriction given for a higher urea group concentration. The same applies to 1250LYS and 1250ORN, with a higher urea group concentration than 2000LYS and 2000ORN, respectively.

T_g values for PCL530 based polymers were at least 50 °C above values for PCL2000 based polymers, showing again that PCL530 based polymers had a homogeneous mixed phase. However, the extreme breadth of the transition, spanning for 60 °C, could be an indication of some heterogeneities within the sample, that is, areas with a higher concentration of hydrogen-bonded urea groups than others. The electron density difference between these areas would be unnoticeable for its observation in SAXS. We have found in some poly(ether-urea)s [32] that thermal treatment at a certain temperature could induce urea group ordering, and for the PCL530 derived polymers this could lead to some phase separation. Polymer 530LYS was subjected to the same heating program in steps executed above for polymer 1250LYS. No changes were observed in the shape of the T_g transition up to 250 °C, even after some degradation took place above approximately 200 °C as indicated by the change in the baseline of the curve above this temperature and confirmed by the decrease in molecular weight of the sample heated at 250 °C when evaluated by SEC. Therefore, the morphology of the amorphous samples of the polymers derived from PLC530, either homogeneous, more likely, or with undetectable heterogeneities, is stable and remain unchanged up to degradation temperatures.

Thermogravimetric analysis was performed on the polymers and the models mainly to define their processing window. For this reason, in Table 5, the decomposition temperatures listed are for very low percentages of weight loss. In the thermogravimetric curves (Fig. 7 for Orn extended polymers), a small drop below 300 °C is found followed by another high loss above 300 °C. This first weight loss increased with the HS content for the Orn series, but for the Lys series, not order was found. Anyway, hard segment models had higher weight losses

Table 5
Temperatures in °C for different weight losses

Sample	$T_{0.5\%}$	$T_{1\%}$	$T_{2\%}$	$T_{5\%}$	$T_{10\%}$
LDI:*n*BuNH$_2$	169	175	181	194	211
LDI:LYS	157	188	200	214	227
LDI:ORN	162	193	222	241	252
2000LYS132	215	228	243	275	300
2000LYS	172	201	219	247	284
1250LYS	187	212	240	274	296
530LYS	197	210	222	243	261
2000ORN	218	230	244	286	309
1250ORN	213	229	245	270	297
530ORN	195	209	223	245	268

in the first stage than segmented polymers, and took place at lower temperature, indicating that the urea groups were the weakest linkages of the chains, as already proven for other polyureas [35]. The same was concluded from the data presented in Table 5. From data and curves there was not much difference when changing from Orn extended polymers to Lys extended polymers, except for polymer 2000LYS, that had lower stability than 2000ORN. Polymer 2000LYS132 had higher stability than 2000LIS despite having higher hard segment content and lower molecular weight. It is difficult to explain the anomalous behaviour of polymer 2000LYS that cannot be due to differences in polymer molecular weight. For polymer processing by compression, injection or extrusion techniques, it is important to delimit the processing window. The first derivative of the weight loss curves of the poly(urethane-urea)s departed from horizontal above 180 °C. At this temperature weight loss for all the segmented polymers was below 0.5% except for 2000LYS (see Table 5). In the DSC traces there was not evidence of degradation below 180 °C and because of melting or T_g of polymers is below 50 °C, it can be considered that these polymers have a very wide range for processing.

In literature it could be found similar values for thermal degradation. The polymer PCL1160:LDI:BDA was stated to be

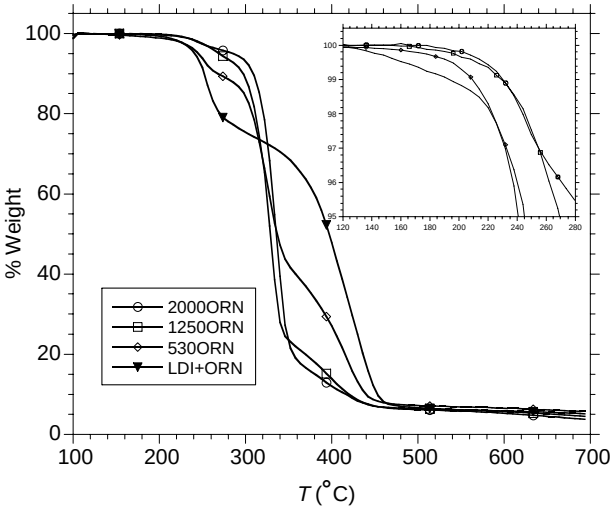


Fig. 7. TGA curves for the polymers extended with Orn. In the insert, a zoom view of the first 5% loss.

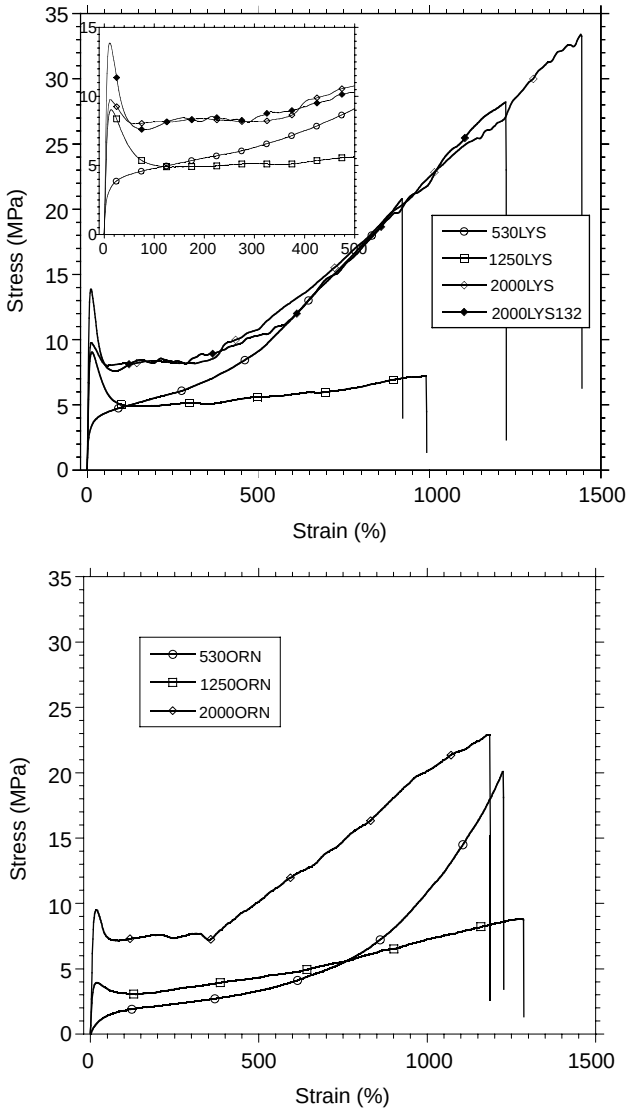


Fig. 8. Stress–strain graphs for Lys extended (top) and Orn extended (bottom) polymers.

stable up to 250 °C, value slightly lower than for the corresponding HDI and BDI based polymers, stable up to 280 °C [15], and it was proved that the difference was intrinsically related to the polymer structure and not due to molecular weight differences. PCL:HDI:BDO polymers had $T_{5\%}$ values between 263 and 313 °C [36], and for polymers with LDI and Lys in their structure here described, their thermal resistance should be reduced, as obtained (243–286 °C for $T_{5\%}$).

3.4. Mechanical properties

Fig. 8 shows the stress–strain curves, and Table 6 summarizes the values for the mechanical properties of the poly(urethane-urea)s. Two completely different behaviours were found due to crystallinity of polymer samples.

On one side, PCL530 based polymers behave as elastomers, with a low modulus and increasing growth of stress with strain until chains aligned and reached their maximum extension before breaking. At very high extension, above 400%, whitening of the neck zone could be due to strain-induced crystallization, as for natural rubber, increasing the slope of the curve in the final part. After rupture, polymer recovered almost completely its initial shape.

On the other side, semicrystalline polymers (PCL1250 and PCL2000 based polymers) behave as tough plastics. After a very stepped stress growth at low strain, they went through a yielding point. At this point, it could visually be observed the formation of a neck on the narrow part of the test specimen. Once yielding was passed, stress dropped to a lower value and remained almost unchanged until a certain strain was reached. At this point (from 350 to 600% depending on the polymer), necking had advanced through all the narrow part of the test specimen and reached the part of the specimen where it widens. As a consequence, the curve changed the slope and the stress increased almost linearly with the strain.

All polymers were tough, with high strain values, above 800%. When comparing polymers, it is clear that an increase in PCL length produced an increase in modulus and, for crystalline polymers, in stress at yield. Lys extended series had higher values than Orn series. It is unclear the origin of these differences. Structural differences between Lys and Orn are minimal, molecular weight of the polymers based on the same PCL diol are of the same order, slightly higher concentration of urea groups in Orn extended polymers would be expected to, if having any influence, increase their mechanical properties, and HS content in Lys extended polymers, although slightly higher than the corresponding Orn extended polymers, we do not feel is enough to explain the differences. Besides, by DSC data, PCL crystallinities were

Table 6
Mechanical properties of the synthesized poly(urethane-urea)s

Polymer	Stress at yield (MPa)	Strain at yield (%)	Stress at break (MPa)	Strain at break (%)	Modulus (MPa)
2000LYS132	14.9±0.8	10.6±0.7	28.3±1.5	1240±30	291±16
2000LYS	9.3±0.6	11.3±1.8	34.0±1.8	1460±50	153±13
1250LYS	8.4±0.6	13.0±0.8	7.6±0.7	970±100	155±9
530LYS	–	–	21.6±4.1	880±80	61±13
2000ORN	8.8±1.4	17.6±1.8	23.5±1.6	1310±110	130±30
1250ORN	4.0±1.0	20.2±0.6	8.9±0.5	1270±70	59±20
530ORN	–	–	20.0±2.4	1280±130	7±2

quite similar between corresponding Lys extended and Orn extended polymers.

The strain at yield, between 10 and 20%, was inversely related to stress at yield, and the stress at break was high for PCL2000 and PCL530 based polymers, with PCL1250 based polymer reaching a moderate value.

When polymers 2000LYS and 2000LYS132 were compared, the increase in HS content led to higher modulus and stress at yield, as expected, whereas strain and stress at break were reduced.

The observed stress–strain values were similar to the reported values for polymers with similar structure. Moreover, these values were lower than values displayed by polymers with the HS with a symmetrical structure. Thus, polymers from PCL:LDI:aminoacid based chain extender, had tensile strength values of 12.5 (PCL530) to 30.8 (PCL2000) MPa [12], polymer PCL2000:LDI:BDA displayed 17 MPa [15], and PCL:BDI:Lys polymers exhibited 9.2 (PCL1250) and 13.0 (PCL2000) MPa [23]. When hard segment had a symmetrical structure, mechanical properties generally increased (PCL:HDI:BDO [29], PCL:BDI:BDO [15]) or in the worst case were of the same order [31]. Mechanical properties of our polymers compared well even with other commercial degradable polymers, as for example DegraPol polymers, composed of polyhydroxybutyrate:PCL:LDI, with tensile values from 7 to 11 MPa [37].

Based on the intended application of these polymers in the human body, at 37 °C, it can be estimated that PCL530 based polymers, for which the end of the T_g transition is around 20 °C, will become softer. PCL2000 and PCL1250 based polymers, if prepared from chloroform solution casting, melting endotherm started above 30 °C. Then, at 37 °C, only a part of the crystallinity would be lost (see Fig. 5) and, therefore, they would retain part of their mechanical properties, given mainly by PCL crystallinity. If these polymers were processed by melting, the properties would vary depending on their thermal history.

Of course, besides temperature, mechanical properties will be strongly affected by swelling within physiological medium, and swelled polymers will have their strength values reduced, the more the higher the swelling, as already seen in other polymers [27].

3.5. Water uptake and degradation

Polymer samples were immersed in a phosphate buffer solution at 37 °C and their changes in weight in the hydrated state followed at time intervals for Lys extended polymers and polymer 1250ORN. Fig. 9 shows the curves for Lys extended polymers, and in Table 7 details the values of maximum weight increase.

Polymer 1250ORN behave almost the same as 1250LYS with respect to swelling and weight change with time, and it is expected the other polymers of the ORN series to behave as their equivalent Lys extended polymers.

From the data in Table 7 it can be concluded that PCL diol molecular weight strongly influenced the swelling of the polymers, increasing at lower length. This differentiated

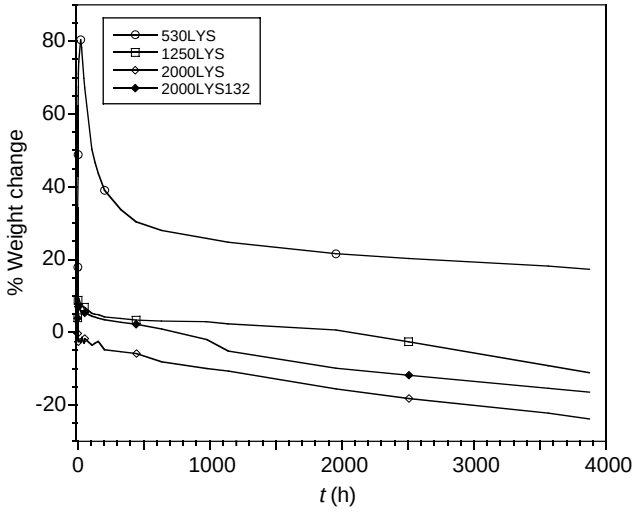


Fig. 9. Dependence of weight with time of immersion in PBS for hydrated Lys extended polymers.

behaviour is due to the differences in polymer morphology. PCL530 based polymer is completely amorphous making it more accessible to water than PCL1250 and PCL2000 based polymer, with a crystalline phase. Also, in Table 7 can be seen that the increase in HS content increases the amount of urea groups and the hydrophilicity of the polymer, swelling being higher (2000LYS132 vs. 2000LYS). This hydrophilicity of the HS was confirmed by a swelling experiment on the model hard segment LDI:LYS polymer, which reached a maximum of approximately 38% weight increase.

Water absorption data reported in literature showed the same trend with molecular weight of PCL diol, but with important differences in absolute values. In polymers PCL:LDI:aminoacid derived diamine (1:2:1 reactants ratio), values ranged from 9% (PCL530) to 3% (PCL2000) [11]. The chain extender contained aromatic rings, which increase hydrophobicity, and would explain the lower value compared to our polymers, except for polymer with PCL2000 diol, which absorbs 3% compared to the $<1\%$ observed for 2000LYS. The explanation could be that polymer 2000LYS is more crystalline, in a proportion enough not only to counterweight the effect of aromatic rings but to decrease swelling even further. For polymers PCL:BDI:Lys (1:2:1), values were similar for PCL1250 (12%) and higher for PCL2000 (16%) [23] compared to 1250LYS and 2000LYS, respectively. Again, the surprising high value for PCL2000 based polymer compared to our 2000LYS cannot be due to a higher HS content, which we have found increases hydrophilicity, because in fact is lower for the

Table 7
Maximum weight in the hydrated state (%weight increase respect to dry sample)

Polymer name	Sample 1	Sample 2
2000LYS132	7.2	7.2
2000LYS	0.4	0.9
1250LYS	8.9	9.4
1250ORN	11.0	12.7
530LYS	82.6	80.5

literature polymer, nor to a higher hydrophilicity of BDI based polymers, because PCL:BDI:BDO [38] and PCL:HDI:extender [18] polymers with symmetrical hard segment structure showed very low swelling values. Therefore, it should be due to differences in crystallinity (lower crystallinity on the literature polymer).

The swelling value for 530LYS polymer is far superior to other PCL530 based polymers [11,18,30] and is probably due to the combined effect of amorphous morphology plus hydrophilicity afforded by LDI and Lys. Although DEG content could also have some influence, by no means it can explain this high value for 530LYS polymer. DEG content in this polymer is 7.6% by weight (19.7% in the PCL530 diol), and we have found in a previous work that, for block copolymer diols composed of ethylene oxide (EO) and caprolactone (CL) and linked with LDI, water uptake seems to be dependent mainly on the EO/CL ratio and not on the individual block length [25]. For a poly(ester-urethane) with 15.9% by weight of EO, water uptake value was 16.6%, far from the value of approximately 80% for the 530LYS polymer.

The degradation of the films was evaluated as weight change in the hydrated state. Although it has been demonstrated by Storey et al. [14] in similar polymers to ours that this method is less sensitive to mass loss in the polymer than the usual gravimetric method (weight measured in the dry state), it has the advantages of using less material (the same sample specimen is used through the test) and of being simpler. Of course, whereas if not weight change is observed in the hydrated state we cannot be sure that mass loss has not taken place on the polymer, if weight loss is observed in the hydrated state, we can expect that at least the same weight loss is taking place in the polymer. For our polymers in the hydrated state, weight change curves had two differentiated regions. At short times, and after maximum swelling was reached, weight loss was rapid. Afterwards, a very slow, almost linear decay in weight with time took place. This decay was irrespective of the polymer, with roughly parallel lines. For the time of the test, in the second region, the degradation rate was not higher for polymers with higher swelling ratio that in principle would facilitate the contact of hydrolizable groups with water and would diffuse easily the degradation products. PCL intrinsic hydrophobicity and the shape of the weight loss curves led us to conclude that degradation measured as weight loss in the hydrated state was mainly by surface erosion, with very low bulk degradation. In the first region, probably low molecular weight fractions of the polymer were extracted, and in the second region, the weight loss was due to the molecules lost by the hydrolysis reaction. Although the weight loss for our crystalline polymers was slow, still was faster than for similar polymers with HDI as diisocyanate [18,30].

SEM photographs showed the changes in film surface after degradation. For all polymers, surface became rough after degradation with the same pattern except for polymer 2000LYS132 (Fig. 10). In this case, the surface appeared spotted with round pits where material had been removed. For all semicrystalline polymers the amorphous regions are expected to degrade first, producing this rough surface, but it

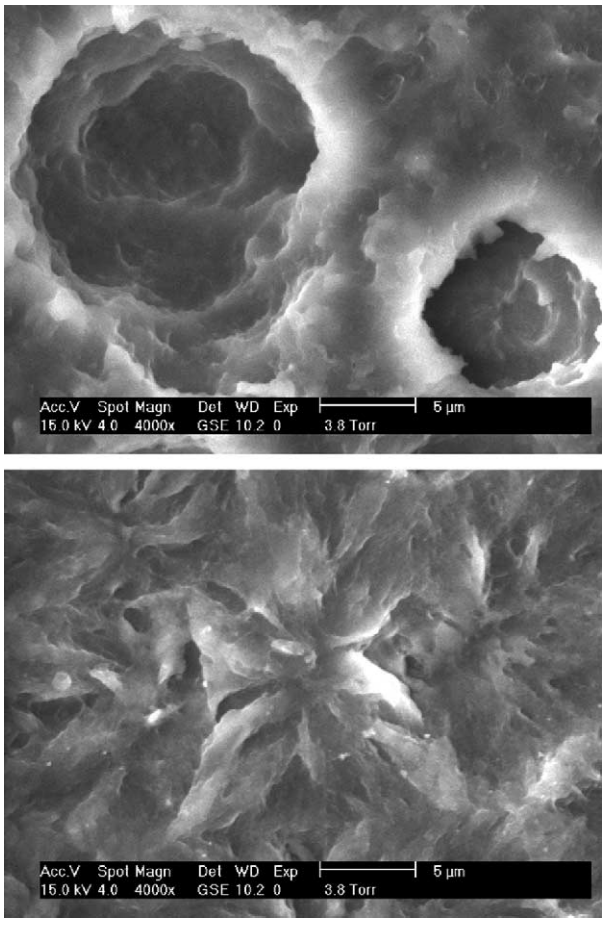


Fig. 10. ESEM images of degraded 2000LYS132 (top) and degraded 1250LYS (bottom) samples.

seems that for this polymer the areas with marked differences in hydrolytic stability were arranged differently. These images contrasted with the surface of the polymer based on PCL 1250 and HDI and the polymers based on PCL 1250 or PCL 2000 and LDI, all with an aminoacid based chain extender, synthesized by Skarja and Woodhouse, after 56 days and 21 days exposure to a buffer solution at 37 °C, respectively [11,18], that showed not surface alteration. Treatment of LDI based polymers with enzymes did produce surface erosion [28], with clearly different pattern depending on the molecular weight of the PCL, more uniform for amorphous PCL530 based polymer, differences not found in our polymers except for 2000LYS132.

4. Conclusions

A series of new biodegradable non-toxic poly(urethane-urea)s were synthesized from well characterized polycaprolactone diols, L-lysine diisocyanate and L-lysine or L-ornithine ethyl esters chain extenders, and the resulting linear segmented polymers were chemically and physically characterized.

During synthesis, chain extension was carried out in heterogeneous phase with the amino acid ethyl ester salts. The critical role of triethylamine was proved through model

reactions, leading to the expected urea groups as confirmed by H NMR and IR.

The molecular weight attained for the synthesized segmented polymers was low, although high enough to achieve tough polymers.

Polymers based on PCL530 resulted to be amorphous, whereas polymers based on PCL1250 and PCL2000 where semicrystalline. Model hard segment polymers showed that their highly irregular structure produced an amorphous phase with low T_g, leading to a mixture of soft and hard segments in the linear segmented polymers. In semicrystalline polymers, chains separated in a pure polycaprolactone phase and an amorphous mixed phase. Pure PCL phase accounted for approximately half of the CL content on the polymers, as obtained from DSC measurements after long crystallization times.

Thermal stability was high enough, with a wide processing window, the urea groups being the weakest link on the chains.

Pure PCL crystallinity strongly affected the mechanical properties and the water absorption behaviour.

Amorphous PCL530 based polymers were elastomeric, with shape recovery after rupture, whereas semicrystalline polymers behave as tough plastics, with a yielding point, and with higher modulus at higher hard segment content. Stress-strain values were close to values of PUs of similar structure and to other non-polyurethane degradable polymers.

Water absorption was very high for the PCL530 based amorphous polymer and low for the semicrystalline polymers. For PCL2000 based polymers, the increase in hard segment content increased the hydrophilicity of the segmented polymer. Weight loss showed that these polymers degraded hydrolitically mainly via erosion after an initial rapid weight loss assigned to low molecular weight fractions extraction.

Results demonstrated that these polymers are good candidates as biodegradable materials for soft tissue engineering and control release applications, with on going investigations into their in vitro biocompatibility.

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