Hydrolytic degradation of poly(ϵ -caprolactone) with different end groups and poly(ϵ -caprolactone-co- γ -butyrolactone). Characterization and kinetics of hydrocortisone delivery.

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Abstract

Asymmetric telechelic α -hydroxyl- ω -(carboxylic acid)-poly(ϵ -caprolactone) (HA-PCL), α -hydroxyl- ω -(benzylic ester)-poly(ϵ -caprolactone) (HBz-PCL) and an asymmetric telechelic copolymer α -hydroxyl- ω -(carboxylic acid)-poly(ϵ -caprolactone-co- γ -butyrolactone) (HA-PCB) were synthesized by ring-opening polymerization of ϵ -caprolactone (CL). CL and CL/ γ -butyrolactone mixture were used to obtain homopolymers and copolymer respectively at 150°C and 2 h using ammonium decamolybdate (NH₄) [Mo₁₀O₃₄] (Dec) as catalyst. Water (HA-PCL and HA-PCB) or benzyl alcohol (HBz-PCL) were used as initiators. The three polylactones reached initial molecular weights between 2000-3000 Da measured by proton nuclear magnetic resonance (¹H-NMR). Compression-molded polylactone caplets were allowed to degrade in 0.5 M aqueous *p*-toluenesulfonic acid at 37°C and monitored up to 60 days for weight loss behavior. Data showed that the copolymer degraded faster than the PCL homopolymers, and that there was not difference in the weight loss behavior between HA-PCL and HBz-PCL. Caplets of the three polylactones containing 1% (w/w) hydrocortisone were placed in two different buffer systems, pH 5.0 with citrate buffer and pH 7.4 with phosphate buffer at 37°C, and monitored up to 50 days for their release behavior. The release profiles of hydrocortisone presented two stages. The introduction of a second monomer in the polymer chain significantly increased the release rate, being the degradation rate for HA-PCB faster than those for HBz-PCL and HA-PCL. At the pH studied, only slight differences on the liberation profiles were observed. SEM micrographs indicate that hydrolytic degradation occurred mainly by a surface erosion mechanism.

Key words: ϵ -caprolactone, γ -butyrolactone, hydrolytic degradation, hydrocortisone, drug-delivery systems

1. Introduction

Biodegradable polyesters and co-polyesters have been the focus of extensive research for several decades, as a result of their ease of manufacturing and desirable characteristics. Their ranges of physical properties and hydrolytic degradation profiles have made them attractive candidates for use in a variety of biomedical products such as degradable sutures, temporary orthopedic fixtures and controlled pharmaceutical delivery matrices. Biodegradable materials degrade in vivo under a controlled manner, yielding nontoxic small molecules that can be excreted from the body ^[1].

Poly (ϵ -caprolactone) (PCL) is a hydrophobic and biodegradable polymer that has found widespread uses in biomedical applications ^[2]. PCL is a synthetic polymer used for fibrous meshes and porous scaffolds in the field of tissue engineering. ^[3] However, the high degree of crystallinity decreases its biocompatibility with soft tissues and lowers its rate of biodegradability. PCL shows a high degree of permeability toward low molecular weight drugs (<400 Da), and this property made it attractive for the manufacture of long-term and diffusion-controlled delivery drug delivery systems. In the scope of the local drug delivery applications, PCL has been successfully tested as a vehicle for slow release of drugs at tumor reactions sites ^[4, 5].

Ring opening polymerization of lactones provides a convenient route to obtain biodegradable aliphatic polyesters, being PCL the most important member of this family. Different catalysts have been used to catalyze the polymerization and low-molecular weight alcohols can be used as initiators and to control the final polymer molecular weight. We have reported the use of ammonium decamolybdate $((\text{NH}_4)_8[\text{Mo}_{10}\text{O}_{34}])$ as an efficient catalyst to obtain aliphatic polyesters and their

copolymers with different architectures ^[5, 6]. In this work, we have used this catalyst to obtain the polymers tested for degradation and as drug delivery carriers.

The rate of PCL hydrolysis can be accelerated by copolymerization with other lactones. In that regard, copolymers of CL with δ -valerolactone and DL-lactide (e.g. a commercial suture MONOCRYL, Ethicon) show higher degradation rates ^[7]. In the case of poly (ϵ -caprolactone-co- γ -butyrolactone) (PCB), the appearance of new physical properties and the observance of higher rate of degradation make them amenable for tailored applications as biodegradable materials ^[6, 8]. Therefore biodegradable polymer with desired degradation rates should be synthesized and the degradation rate should be determined by an effective method. Generally, *in vitro* degradation of biodegradable polymer is studied in buffer solutions. However, the degradation rates of some polymers are very slow, and for PCL, it will take more than 1 year to get a complete degradation of the polymeric matrices ^[9].

Hydrocortisone ((11 β) 11,17,21-trihydroxy-(11 β)-pregn-4-ene-3,20-dione) is a hydrophobic corticosteroid drug used in the treatments of allergies and inflammations. It relieves symptoms related to certain hormone shortage and has an immunosuppressive action. Hydrocortisone is applied as topical and oral administration or intravenous injection. It can also be combined with antibiotics and antifungal agents to treat infections. Hydrocortisone has been used to treat certain types of cancer such as leukemia, lymphoma and multiple myeloma ^[10]. In this study, hydrocortisone was used as a drug model.

A common procedure to test different systems for controlled release applications is the incorporation of the active agent into a biodegradable polymer matrix, followed by the study of its degradation behavior under hydrolytic conditions. Degradation rates for polymers mainly reside on polymer characteristics, such as chemical structure, water

permeability (hydrophilicity/hydrophobicity), morphology and molecular weight. It is known that aliphatic polyesters provide a good permeable system for steroid release. However, degradation times observed for these polymers are relatively long ^[11,12]. For poly(ϵ -caprolactone), degradation can be accelerated by using (a) low-molecular weight samples and (b) by copolymerization with other monomers such as γ -butyrolactone, BL. In this article, degradation and hydrocortisone release behavior from caplets made from (a) poly(ϵ -caprolactone) with different end groups, and (b) (ϵ -caprolactone-co- γ -butyrolactone) (HA-PCB) were studied. Effects of end-groups and copolymerization (by insertion of butyrolactone onto the polymeric chains) on degradation and of drug release from these polymers were evaluated. Results show that significant higher rates of degradation and hydrocortisone release are obtained for the copolymer system.

2. Experimental

2.1 Materials

CL (Aldrich Chemicals Co.), BL (Aldrich) were dried over calcium hydride and distilled under reduced pressure before used. Distilled water was purchased from Baker. Benzyl alcohol (BzOH), *p*-toluenesulfonic acid and hydrocortisone were purchased from Aldrich and used without further purification. Ammonium heptamolybdate tetrahydrate (NH₄)₆ [Mo₇O₂₄] (Hep)(Fluka) was grounded in a mortar and passed through a 100 mesh sieve before used ^[2, 5].

2.2 Synthesis of poly(ϵ -caprolactone)s and poly(ϵ -caprolactone-co- γ -butyrolactone)

α -Hydroxyl- ω -(carboxylic acid)-poly(ϵ -caprolactone) (HA-PCL), α -hydroxyl- ω -(benzyl ester)-poly(ϵ -caprolactone) (HBz-PCL) and α -hydroxyl- ω -(carboxylic acid)-poly(ϵ -caprolactone-co- γ -butyrolactone) (HA-PCB) were synthesized by ring-opening polymerization with ammonium decamolybdate (NH₄)₈[Mo₁₀O₃₄] (Dec) as catalyst, using an initial monomer/catalyst ratio of 20,000, as described elsewhere ^[5, 6]. Water was

used as initiator for HA-PCL and HA-PCB, and benzyl alcohol for HBz-PCL. A monomer/initiator ratio of 20 was used, in order to obtain polymers in the range between 2000 and 3000 Da. Polymerizations were carried out in 100 mL vials previously dried and purged with dry nitrogen. Vials were stoppered with a rubber septum and placed in a thermostated bath at 150°C for 2 h. Final polymers were carefully crystallized from chloroform/methanol and dried under vacuum. No monomer was detected by ^1H -NMR in the final polymer used for the tests.

NMR data for HA-PCB copolymer: ^[6] ^1H NMR (300 MHz, CDCl_3 , ppm): δ 4.12 (t, 2H, $[-\text{CH}_2\text{O}-]$, BL), 4.06 (t, 2H, $[-\text{CH}_2\text{O}-]$, CL), 3.68 (t, 2H, $[-\text{CH}_2\text{OH}]$, BL), 3.64 (t, 2H, $[-\text{CH}_2\text{OH}]$, CL), 2.39 (t, 2H, $[-\text{CH}_2\text{CO}_2-]$, BL), 2.31 (t, 2H, $[-\text{CH}_2\text{CO}_2-]$, CL), 1.96 (q, 2H, $[-\text{CH}_2-]$, BL), 1.65 (m, 4H, $[-(\text{CH}_2)_2-]$, CL), 1.38 (q, 2H, $[-\text{CH}_2-]$, CL). ^{13}C NMR (50 MHz, CDCl_3 , ppm): δ 176.80 [end-group $-\text{COOH}$], 173.60 [ester end-group $-\text{C}=\text{O}$], 173.41 [ester $-\text{C}=\text{O}$], 173.25 and 172.70 [ester $-\text{C}=\text{O}$, BL], 64.19 $[-\text{CH}_2\text{O}-]$, CL], 63.96 $[-\text{CH}_2\text{O}-]$, CL], 63.14 $[-\text{CH}_2\text{O}-]$, BL], 62.29 $[-\text{CH}_2\text{OH}]$, CL] and 61.68 $[-\text{CH}_2\text{OH}]$, BL], 34.04 $[-\text{CH}_2\text{CO}_2-]$, CL], 33.92 $[-\text{CH}_2\text{CO}_2-]$, CL], 33.83 and 33.46 $[-\text{CH}_2\text{CO}_2-]$, CL], 32.08 $[-\text{CH}_2\text{CH}_2\text{OH}]$, 30.58 $[-\text{CH}_2\text{COO}-]$, BL], 28.14 $[-\text{CH}_2\text{CH}_2\text{OCO}-]$, CL], 25.33 $[-\text{CH}_2(\text{CH}_2)_2\text{OCO}-]$, CL], 25.12 $[-\text{CH}_2(\text{CH}_2)_2\text{OCO}-]$, CL], 24.50 $[-\text{CH}_2(\text{CH}_2)_2\text{OCO}-]$, CL], 24.38 $[-\text{CH}_2\text{CH}_2\text{CO}_2-]$, CL], 24.18 $[-\text{CH}_2\text{CH}_2\text{COO}-]$, CL], 23.87 $[-\text{CH}_2(\text{CH}_2)_2\text{OCO}-]$, BL].

2.3 Caplets preparation

HA-PCL, HBz-PCL homopolymers and HA-PCB copolymer were compression molded at 4 tons and room temperature to yield caplets of 7 mm diameter and 1.5 mm thickness. Weights were in the range between 45 and 55 mg.

2.3.1 Preparation of Caplets containing 1% hydrocortisone (w/w)

HA-PCL, HBz-PCL homopolymers and HA-PCB copolymer were mixed in solution (THF as solvent) with 1% (w/w) of hydrocortisone; the solution previously frozen was dried at vacuum and room temperature. The powder was compression molded at 4 tons and room temperature to yield caplets of 7 mm diameter and 1.5 mm thickness and weights in the range between 45 and 55 mg.

2.4 In vitro hydrocortisone release studies of polylactones caplets

Hydrocortisone release was evaluated by UV-vis spectroscopy. The polylactones caplets (50mg and 7.0 X 1.5 mm) were placed in 15 ml of 0.1M aqueous citrate buffer at pH 5.0 or 0.1M aqueous phosphate buffer at pH 7.4 (both containing 0.05% w/v sodium azide as preserving agent) in a oven incubator at 37°C. The hydrocortisone concentration (248 nm) was determined by UV-Vis spectrophotometer 8453 (Agilent Germany), taking upper layer aliquot (3.0 ml) for UV-Vis measurement. Samples were then returned to the original solution. Three runs were made for each sample tested at pH = 5.0.

2.5 In vitro degradation

The polylactones caplets previously weighed were placed in 50 mL falcon tubes containing 10 mL of 0.5 M aqueous p-toluenesulfonic acid (pH = 0.7) and maintained at 37°C in an incubator. Samples were removed at select times within 58 days, filtered through a 0.45-µm membrane (Gelman Laboratory Nylaflo ®), and washed with distilled water. The solid samples were collected and dried in vacuum at room temperature over 3 days. The remaining polymer solid was then weighed to determine the dry weight. The percentage of the weight remaining was calculated from the ratio of the dry weight divided by the initial weight of the polymers. Three runs were made for each sample.

2.6 Analysis and characterization

Differential scanning calorimetry (DSC) analysis was carried in a Mettler Toledo (DSC 822e) calorimeter. Samples weighting 5 to 15 mg, were sealed in aluminum pans. Samples were heated at $10\text{ }^{\circ}\text{C min}^{-1}$ under nitrogen purge from 25 to 80°C , then cooled at -90°C , hold at this temperature for 12 minutes, and reheated at $10\text{ }^{\circ}\text{C min}^{-1}$ from -90 to 80°C . Data were recorded from the first run.

Surface morphologies of polymers films were recorded with a scanning electron microscope (SEM) LEICA S420 σ , after coating samples with gold.

Wide-angle X-ray diffraction (WAXD) patterns were obtained by means of a Phillips PW 1130 diffractometer (Cu K α radiation), at a scan rate of $2^{\circ}\text{ min}^{-1}$ over the 5 - $35\text{ }2\theta$.

Solution ^1H spectra were recorded at room temperature on a Varian Unity Inova 500 ($500\text{ MHz }^1\text{H}$) spectrometer. Chloroform-*d* (CDCl_3) was used as solvent. Spectra were referenced to the residual solvent signal at 7.26 ppm .

GPC-MALLS spectra were determined using a multidetector system: a multi-angle light scattering (MALS) Dawn EOS photometer, that measures the intensity of the scattered light at 16 angular locations ranging from 12.5° to 164.9° ; a ViscoStar viscometer for measuring the differential pressure in a four-capillary bridge; an interferometer refractometer detector (Optilab rEX) as a concentration detector. The MALS photometer uses a GaAs laser operating at a nominal wavelength of 690 nm . The chromatographic set-up used consists of an Alliance HPLC Waters 2695 Separation Module having a vacuum degassing facility online, an autosampler, a quaternary pump, a columns thermostat, and a Waters 2414 Differential Refractometer for determining the distribution of molecular weight. A bank of four columns with the following characteristics was used: HSPgel: HR 1.0, HR 2.5, HR 4.0, and HR MB-M (dimensions $150\text{ mm} \times 6.0\text{ mm}$) with pore sizes of $50\text{ \AA}$, $500\text{ \AA}$, $1.0\text{E}+4$ and a mixed bed pore size

(100 Å to 1.0E+6 Å) respectively, and particle size 3 and 5 µm. HPLC Tetrahydrofuran (THF), previously filtered (in a 0.45 µm pore size filter) and degassed, was used as the eluent. Typical conditions were: flow rate of 0.5 ml/min; 100 µL injection volume; analysis time per sample 35 min. The temperature of the columns was controlled at 33 °C by the thermostat. The relative values of molecular weight distribution were obtained by using Alliance Empower software. However, to obtain the absolute values, the ASTRA software version 5.3.2.10 (Wyatt Technology Corp., Santa Barbara, CA) was used.

3. Results and discussion

3.1 Characterization of polymer samples

The number-average molecular weights for the three studied polylactones, and thermal and degradation properties for their 1% hydrocortisone composites, are summarised in Table I.

Number-average molecular weights (M_n) and copolymer composition were calculated by $^1\text{H-NMR}$ ^[5,6]. The number-average molecular weights of the three polylactones were in the range of 2000-3000 Da. It was found that a 7% of BL insertion was achieved. M_n and M_w values are overestimated by GPC-MALLS, but give an idea of the samples polydispersities.

Because of the importance of the crystallinity on the degradation, we carried out a detailed study on the crystallinity of our materials.

Degree of crystallinity is closely related with the molecular weight M_n , and this value increases as the molecular weight decreases. The three precipitated polylactones possess high degrees of crystallinity, in the range 78 to 84 (HA-PCL > HA-PCB > HBz-PCL), due to CL segments crystallization^[13, 14]. For our copolymer HA-PCB we did not find a significant lowering in CL segments crystallinity found by other authors^[8]. It is

reported that PCL melting points occur in the range of 59-64 °C, and the values of T_m depend upon the crystallite size ^[14]. Observed melting points obtained from the endotherm maxima for the polymers studied here are different (see Fig. 1 and Table 1), with copolymer HA-PCB showing a significant lower value than those recorded for the homopolymers. Both homopolyesters show higher melting points than copolymer, being lower than that for HBz-PCL ($T_m = 60.3$ °C). If we relate this value to the size of the PCL crystallites, it is obvious that the bulky benzyl end-group interferes the ordering for crystallization more than carboxylic acid groups, and that the inclusion of a comonomer in the main chain has even a stronger effect. In the second scan, after melting at approximately 10°C lower than in the first scan, the same trend is observed for the melting point, indicating again the difference in crystallites sizes, but the amount of crystallinity for co-polymer HA-PCB is higher than for homopolymers HA-PCL and HBz-PCL (63, 60, 59% respectively). This difference is explained by the faster crystallization of the shorter segments of caprolactone in the copolymer.

The same trends observed for precipitated polylactones are found for caplets made from the polylactones: the evaporated 1% hydrocortisone composites and the 1% hydrocortisone composite caplets. Respect to the absolute values, in the second scan, the difference in the results for these series of materials is within 1°C for the melting point, and within 3% in the enthalpy value, showing that crystallization is not significantly modified by the addition of the hydrocortisone neither by the method of preparation (precipitated powder or caplets). However, the difference in absolute values is bigger for the first scan, as a consequence of the previous thermal history of the material. For this reason, we have determined as precisely as possible (Table I) the crystallization value of the 1% hydrocortisone caplets, which are the samples tested for hydrocortisone release.

The WAXS diffractograms show a typical crystalline pattern of PCL crystals (peaks at 21.5 and 23.8, corresponding to PCL) ^[13]. The observed pattern for HA-PCB pattern is alike to those observed for HA-PCL and HBz-PCL, showing that the presence of BL does not have an important effect in the crystalline pattern observed by WAXS.

Degradation rates are significantly different for copolymer with respect to homopolymers, but only a small difference could be detected between HA-PCL and HBz-PCL.

3.2 Hydrolytic acid degradation of polymer caplets

In order to test the degradation properties of caplets, an accelerated stability test was performed. Degradation test performed at pH = 7.4 phosphate buffer (physiological conditions) involves degradation times ranging from one to two years. Accelerated degradation methods allow obtaining degradation results in a shorter period of time. The *in vitro* hydrolytic degradation of polylactone caplets were carried out at 37°C in 0.5 M aqueous p-toluenesulfonic acid as degradation catalyst ^[4].

The possible factors contributing to accelerated degradation are the degree of crystallinity and the nature and number of the end groups ^[9, 15].

Figure 2 illustrates the weight loss occurred after immersion in 0.5 M aqueous p-toluenesulfonic acid at 37 °C. As it can be seen, and taking into account the values of CL crystallinity and of the remaining amorphous material for these polylactones, at the experimental conditions tested the degradation depends also on 1) the chemical structure of the chain and 2) the nature of end groups. For the homopolymers, the lower crystallinity of the HBz-PCL polymer respect to HA-PCL polymer is compensated by the hydrophobicity of the benzyl group respect to the carboxylic group, and both homopolymers follow the same degradation profile. For the copolymer HA-PCB, with carboxylic acid end groups and molecular weight practically the same as for

homopolymer HA-PCL, the effect of the introduction of the BL units, less stable to hydrolysis than CL units, combined with a higher amount of amorphous material, leads to a faster degradation rate.

Surface morphology changes were followed by SEM. Figures 3, 4 and 5 show the SEM micrographs of HA-PCL caplets before degradation and after 8 and 22 days respectively under hydrolytic acid degradation. These images are consistent with a degradation mechanism by erosion. Initially, the surface appears fairly flat, and surface morphology is induced by the mold used for compression molding. After 8 days of degradation by p-toluensulfonic acid, a homogeneous and porous structure indicating hydrolytic attack at the amorphous phase at the surface is observed. After 15 and 22 days, the severity and frequency of surface cracks increased with the time. Similar behavior is observed for HBz-PCL (not shown) and HA-PCB polylactones, although for HA-PCB, the appearance of cracks began earlier, at 8 days of hydrolytic degradation (see Fig. 6).

3.3 In vitro drug release studies of polylactones caplets

Polymer samples with no residual monomers (less than 0.1% as determined by $^1\text{H-NMR}$) were used for the tests. The model low molecular weight drug was hydrocortisone, which is a hydrophobic molecule. A hydrophobic drug is supposedly more compatible with the polyester carrier, hydrophobic in nature, and the resulting composite should be stable with time, avoiding a possible leaching of the drug, that would be more likely if the drug were hydrophilic in nature. In addition, if drug was not soluble on the polymer, would form microdomains of pure drug embedded in the polymeric matrix, and the release profile would not be probably steady, but irregular. A 1% weight concentration of hydrocortisone was chosen as this is the usual concentration found on commercial formulations.

The release profiles for hydrocortisone at two different pH values for three formulations are shown in Fig. 7 and 8. The release of hydrocortisone was a two-stage process: an initial rapid release stage (burst; value calculated by visual observation from the change in the curve slope) followed by a second slower release stage. At 55 days, the amount of hydrocortisone released from HA-PCB caplets was about 75%, while HBz-PCL and HA-PCL tablets released about 31% and 26% of their initial hydrocortisone content, respectively. Only a limited influence of pH was observed, with a slightly faster release at acid pH, being the difference of 10% for the caplets prepared with HA-PCB, and 4% for HA-PCL. A higher burst was observed for HA-PCB ($44 \pm 4\%$), and HA-PCL and HBz-PCL formulations showed a burst significantly lower than HA-PCB ($12 \pm 2\%$ and $18 \pm 1\%$ respectively). Concerning the second stage of hydrocortisone release, the three polylactones displayed a controlled delivery of hydrocortisone for more than 40 days.

When crystallization occurs, the crystallizing phase is a pure phase, and therefore, in the prepared samples, the drug is supposedly dissolved in the amorphous phase of the semicrystalline carrier, which in turn is the more accessible phase for degradation. For the homopolymers, with similar degradation rates, the hydrocortisone release at the burst is related to the amount of amorphous material, and release is faster for HBz-PCL. After the burst, the slope for the release trace is related to the degradation rate, and therefore is the same for both homopolymers. For copolymer HA-PCB, amorphous material measured by DSC starting from 25°C is similar to HBz-PCL homopolymer (see column 9 of Table 1). However, melting endotherm is quite different, and the melting temperature is in the order HA-PCL > HBz-PCL > HA-PCB. At the test temperature, 37°C, part of the crystallinity calculated by DSC is lost, and in more extent for the HA-PCB copolymer, resulting on a higher initial burst. In summary,

the amount of amorphous phase exposed by the polymer at the test temperature seems to govern the initial burst during release.

Once the initial burst is overcome, the release rate is more related to the degradation rate of the carrier. The slope of the linear steady release profile at the second stage is higher for the copolymer than for the homopolyesters, demonstrating again that degradation rate is higher due to the inclusion of labile BL units. For the two polycaprolactone homopolymers, having the same degradation rate as already shown in figure 1, the observed slope is almost the same.

Kinetics and mechanism of drug release.

Results of the drug release study are reported in terms of diffusion efficiency, calculated considering the entire time interval 0-55 days, over which the release curves that are depicted in fig. 7 and 8 were registered.

Kinetics and release mechanisms can be evaluated on the basis of the equation of Ritger and Peppas^[16-18].

$$M_t/M_\infty = k t^n$$

Where M_t/M_∞ is the fraction released at time t , k is a proportionality constant which takes into account the matrix characteristics, and n is an exponent whose value is indicative of the drug release mechanism. The equation was applied to the first 60% of fractional release from caplets like Ritger and Peppas suggested. The parameters k and n can be obtained from initial experimental data through square root of dimensionless time and the fraction release values ≤ 0.60 to the resulting linear curves. This analysis gives k and n as slope and exponent, respectively. The values of k and n obtained from the curves of the different matrices are reported in table 2.

It can be seen that n values varied from 0.85 to 1.13. Taking into account the criteria assumed to be valid in the treatment of drug release from non-swelling devices^[19], these values suggest that release mechanism could be considered, in a general way, as non-Fickian. However, obtained values were very close to the zero order limit of $n = 1$, where the corresponding release mechanism (rate of hydrolysis) is independent of time.

CONCLUSIONS

In this work, we investigated how the polymer architecture (different functional end groups or insertion of a second monomer) can affect the behaviour of polylactone caplets in the release of a hydrophobic drug.

Degradation studies have shown that in these semicrystalline polylactones of similar molecular weight and with degree of crystallinity in the same order, the effect of the end-group for M_n values above 2000 Da is not very significant, and the inclusion of more labile co-monomers is determinant to increase the degradation rate.

The release of a hydrophobic drug, hydrocortisone, at a 1% weight concentration, takes place in two differentiate stages: an initial burst mainly influenced by the amount of amorphous material on polymeric carrier at the 37°C of the test temperature, stronger when crystallinity is lower, and a linear stage mainly influenced by the hydrolytic stability of the polymeric carrier, dependent on the inclusion of labile co-monomers. Release rate is increased at acid pH as expected, although this effect is not very strong, with a difference of 10% for the copolymer HA-PCB, and 4% for polycaprolactone HA-PCL.

Acknowledgments

The financial support by Consejo Nacional de Ciencia y Tecnología (CONACYT grant SEP-2004-C01- 47173E) and Universidad de Guanajuato are acknowledged. Authors are indebted to Dr. Guillermo Mendoza-Diaz (Universidad de Guanajuato) for helpful discussions, Dr. Ramón Zarraga (Universidad de Guanajuato) for obtaining SEM micrographs and to Dr. José E. Baez (Universidad del Papaloapan) for his assistance in the preparation of some polymer samples.

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TABLE 1. Thermal characteristics and degradation properties of polylactone caplets containing 1% hydrocortisone.

Poly lactone	Mn ^a	Mn ^b	Mw ^b	P.I. ^b	T _m (°C)	ΔH _m (J/g)	%CL ^c cryst.	% weight ^d amorphous	Degradation Rate (%/day)
HA-PCL	2920	4000	6500	1.63	65.4	121.7	83.5	13.8	1.36
HBz-PCL	2810	5500	6600	1.20	60.3	110.5	78.4	20.7	1.43
HA-PCB	2130	3900	5400	1.38	57.5	110.9	80.7	20.7	1.72

^a Obtained by ¹H-NMR

^b Obtained by GPC-MAALS; P.I. = Polydispersity index: M_w/M_n

^c Calculated from the CL content in the polylactone and ratioing against crystallization heat for pure high molecular weight PCL 16.9 KJ/mol ^[20]

^d Weight of (non- crystallized CL + end groups + 1% hydrocortisone) for homopolymers, and (+ BL content) for the copolymer

TABLE 2. Values k and n ($\pm$ 95% confidence intervals) obtained by plotting hydrocortisone fraction release vs square root of dimensionless time curves from slabs of different compositions at pH 5.0 and 7.4. R^2 values are also reported.

Matrix	k	n	R^2
HA-PCL (pH 7.4)	0.17 $\pm$ 0.09	0.85 $\pm$ 0.03	0.991
HA-PCL (pH 5.0)	0.15 $\pm$ 0.01	0.92 $\pm$ 0.02	0.994
HBz-PCL (pH 7.4)	0.16 $\pm$ 0.01	1.05 $\pm$ 0.09	0.990
HBz-PCL (pH 5.0)	0.16 $\pm$ 0.01	1.03 $\pm$ 0.04	0.997
HA-PCB (pH 7.4)	0.15 $\pm$ 0.02	1.13 $\pm$ 0.13	0.984
HA-PCB (pH 5.0)	0.15 $\pm$ 0.18	1.10 $\pm$ 0.11	0.988

FIGURE CAPTIONS

Fig.1. DSC thermograms of PCL copolymer and PCL homopolymers (HA-PCB, HBz-PCL and HA-PCL).

Fig.2. Hydrolytic degradation of polylactone tablets by immersion in 0.5 M aqueous p-toluene sulfonic acid at 37°C (■) HA-PCL, (●) HBz-PCL and (▲) HA-PCB. Means and S.E.M. are shown.

Fig.3. SEM micrograph of HA-PCL caplets before hydrolytic acid degradation.

Fig.4. SEM micrograph of HA-PCL caplets after 8 days of hydrolytic acid degradation.

Fig.5. SEM micrograph of HA-PCL caplets after 22 days of hydrolytic acid degradation.

Fig.6. SEM micrograph of HA-PCB caplets after 8 days of hydrolytic acid degradation.

Fig.7. Release profiles of hydrocortisone from caplets compressed at 4 ton evaluated in buffer at pH 7.4 and 37°C .

Fig.8. Release profiles of hydrocortisone from caplets compressed at 4 ton evaluated in buffer at pH 5.0 and 37°C.

TABLE CAPTIONS

Table 1. Thermal characteristics and degradation properties of polylactone caplets containing 1% hydrocortisone.

Table 2. Values k and n ($\pm$ 95% confidence intervals) obtained by plotting hydrocortisone fraction release vs square root of dimensionless time curves from slabs of different compositions at pH 5.0 and 7.4. R^2 values are also reported.

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