Release of Model Compounds from Modified Lactone Copolymers

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ABSTRACT: The applicability of three different P(ϵ-caprolactone-*co*-DL-lactide) copolymers for injection-molded controlled release devices was evaluated. The copolymers of ϵ-caprolactone and DL-lactide were polymerized in bulk using Sn(II) octoate as the catalyst. Glycerol, polyethylene glycol 1000, and polyethylene glycol 4000 were used as initiators. Copolymers were characterized by size exclusion chromatography, differential scanning calorimetry, and nuclear magnetic resonance spectroscopy measurements. The release of two model compounds, theophylline and propranolol hydrochloride, at different loadings (2–30 wt %) was studied. The solubility of the model compounds into the matrices was confirmed to be low by DSC measurements. Increasing the hydrophilicity of the copolymer matrix increased the release rates of both model compounds. The results clearly demonstrate that the desired release rates of these model compounds can be tailored by varying the compound loading or modifying the hydrophilicity of the matrix copolymer. The copolymers were found to be relatively stable during the 4-month hydrolysis. Addition of hydrophilic polyethylene glycol blocks into the backbone of the copolymer chain increased water absorption and thus the degradation was faster. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 81: 2118–2126, 2001

Key words: biodegradable copolymers; P(ϵ-caprolactone-*co*-DL-lactide); *in vitro* release; hydrolytic degradation

INTRODUCTION

Aliphatic polyesters are an important family of biodegradable materials. In particular, hydrolytically unstable lactone polymers have been widely explored for their usefulness in biomedical applications. Poly(ϵ-caprolactone) (PCL) is a very attractive biodegradable polymer, which is nontoxic, biocompatible, and permeable, and can be blended with various other polymers. Biodegradable poly(lactic acid) (PLA) has a long history of use in sutures and bone plates. PLA, PCL, and copolymers of lactide (LA) and ϵ-caprolactone (CL) have also been studied as controllable dosage forms that biodegrade after drug exhaustion.[1–3] The copolymers exhibit a broad range of properties depending on the type and proportions of their constituent monomers. Copolymerization of ϵ-caprolactone with LA produces faster degradation than PCL homopolymer.[4–6] Introducing nontoxic and biocompatible polyethylene glycol (PEG) into lactone polymers increases the degradation rate and the hydrophilicity of the polymer.[7–9]

The growing interest in controlled drug release in medicinals is due to the promise of an increase in patient compliance. The range of formulation variables available to control the rate of drug release from controlled-release devices is broad.

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Of foremost importance are the properties of the polymers to be combined with the drug.[10] The availability of biodegradable polymers provides a good opportunity to develop a slow release system by means of an implantable device consisting of a drug dispersed in a polymer matrix.[3]

Designing a suitable formulation for a drug delivery device using biodegradable polymers is a challenge. A suitable combination of drug and polymer is to be especially tailored for each application. The desired drug release profile can be obtained by adjusting the molecular weight of the polymer, comonomer composition, polymer crystallinity, shape and preparation method of the device, interaction between polymer and drug, and drug loading.[11–13] Hydrogen bonds are the strongest specific interactions that can exist in heterogeneous systems and they can be formed, for example, between carbonyl, hydroxyl, and amine groups present in polymer and drug molecules. Specific interactions have an effect on model compound solubility into the polymer, which in turn plays a rate-controlling role in the diffusion and permeation of drug molecules through a polymeric device. Physicochemical properties of the drug candidate strongly influence the diffusion behavior.[14–16] The design of materials for specific applications demands a good understanding of properties and the ability to modify them in a controlled way.

In this work, we report the results of an *in vitro* release study of model compounds from matrices composed of biodegradable ϵ-caprolactone and DL-lactide copolymers with minor DL-lactide content. The hydrophilicity of the copolymers was modified using different initiators (i.e., glycerol and polyethylene glycols). DL-lactide, instead of L-lactide, was used as a comonomer, because in a related study copolymers with minor ϵ-caprolactone content were studied and amorphous polymers were preferred. Two different model compounds, theophylline [3,7-dihydro-1,3-(1*H*)-purine-2,6-dione, mol wt 180.17 g/mol], a basic drug, and propranolol hydrochloride {1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-2-propanol hydrochloride, mol wt 295.81 g/mol}, a hydrophilic drug, were mixed with copolymers in melt by using a laboratory scale extruder to produce homogenous mixtures. The aim of the study was to investigate how the release rate of theophylline and propranolol hydrochloride from the copolymers can be modified by changing the copolymer composition and the amount of model compound in the device. These factors affect the solubility of the model compound into the matrix and thus the release rate. The copolymer composition was varied by initiating ring-opening polymerization by using initiators with different hydrophilicity. The effect of the model compound on copolymer degradation is also discussed.

EXPERIMENTAL

Materials

ϵ-caprolactone (Fluka) was dried over molecular sieves. DL-lactide (Purac) was recrystallized from toluene and dried for 24 h at 40°C under reduced pressure before polymerizations. Polyethylene glycol 1000 and 4000 (Fluka, mol wt 950-1050 and 3500–4500 g/mol, respectively) were dried under reduced pressure for 24 h before polymerizations. Sn(II) octoate (Sigma), glycerol (Rhône-Poulenc), theophylline (Fluka), propranolol hydrochloride (Fluka), and buffer solution pH 7.0 ± 0.01 (Reagecon) were used as received.

Polymerization

The bulk polymerizations were carried out in a batch reactor under a nitrogen atmosphere by using 0.01 mol % of Sn(II) octoate as catalyst. Polymerizations were initiated by using 0.1–0.5 mol % of either glycerol or polyethylene glycol. The polymerization temperature was 160°C and polymerization time was between 4.5 and 5.5 h. Polymers were stored in dry conditions and dried further under reduced pressure for 24 h before sample preparation. Polymers were used without further purification after polymerization.

Preparation of Samples

Model compounds were mixed into copolymers in a corotating twin screw midiextruder (DMS; capacity = 16 cm^3, screw length L = 150 mm). The midiextruder has a back-flow channel and was operated as a batch mixer. The screw speed was 75 rpm and the mixing time was 3 min at 100°C. Rectangular-shaped devices of 10 × 4 mm, thickness 1.8 mm, were prepared by using a miniinjection molding machine attached to the midiextruder. The devices weighed, on average, 70 mg.

In Vitro Release Experiments

For each *in vitro* time point, three weighed parallel test specimens were immersed in 10 mL

phosphate buffer solution (pH 7.0) in test tubes at a temperature of 37°C. The buffer solution was changed to maintain sink condition during *in vitro* experiments. The gently mixed airbath (Infors Ag) was set to maintain the temperature with an accuracy of ±0.2°C. The test specimens were recovered from individual test tubes at different intervals and weighed, excess buffer solution having been wiped off. The amount of released model compound was determined from the buffer solution. Specimens were then vacuum-dried for 6 days at room temperature and stored in a desiccator for further analysis.

Molecular Weight Determination

Molecular weights were determined by room temperature SEC (Waters System Interface module, Waters 510 HPLC Pump, Waters 410 Differential Refractometer, Waters 700 Satellite Wisp, and four linear PL gel columns: 10^4, 10^5, 10^3, and 100 Å connected in series). Chloroform was used as solvent and eluent for copolymers. The samples were filtered through a 0.5-μm Millex SR filter. The injected volume was 200 μl and the flow rate was 1 mL/min. Monodisperse polystyrene standards were used for primary calibration.

Thermal Analysis

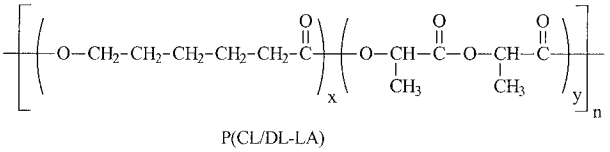
Glass transition and melting temperatures were measured by DSC (Mettler). Nitrogen was used as a sweeping gas. The devices were characterized by heating them twice to ensure that their thermal histories were similar. First heating and cooling rates were 10°C/min and the second heating rate was 40°C/min. Changes in crystallinity of the devices as a function of hydrolysis time were evaluated from the first heating scan at the rate of 10°C/min. The temperature range was between −100 and +200°C.

NMR Measurements

The structures of copolymers were determined with a Varian Gemini 2000, 300 MHz BB NMR spectrometer working at 75 MHz for ^{13}C and at 300 MHz for ^{1}H. The sample concentration was 10 wt % in chloroform-d_1 for ^{13}C-NMR and 1 wt % for ^{1}H-NMR. The measurement temperature was 25°C.

UV Measurements

The released amount of model compound was determined by using a Unicam UV–Vis spectrometer with a calibration curve at an absorption wavelength of 275 and 214 nm, respectively, for maximum absorption for theophylline and propranolol hydrochloride. Buffer solutions were diluted appropriately.



P(CL/DL-LA)

Scheme 1

RESULTS AND DISCUSSION

Characterization of the Copolymers and Devices

The copolymers of ϵ-caprolactone and 4 mol % DL-lactide were polymerized in bulk using Sn(II) octoate as the catalyst. The chemical structure of P(CL/DL–LA) copolymers is presented in Scheme 1. Glycerol, polyethylene glycol 1000 (PEG1), and polyethylene glycol 4000 (PEG4) were used as initiators in ring-opening polymerization of lactones. P(CL/DL–LA), P(CL/PEG1/DL–LA), and P(CL/PEG4/DL–LA) are block copolymers with initiator as a part of the polymer backbone. Monomer conversion in bulk polymerization was complete, because no monomer peaks were observed in ^{1}H-NMR spectrographs. The monomer composition of the copolymers determined by ^{13}C-NMR analysis was 97/3 (mol/mol) P(CL/DL–LA), which is nearly the same as the theoretical composition. Using polyethylene glycol as an initiator adds a hydrophilic block into the copolymer and, as a result, lower contact angles were observed. Contact angle measurements by means of advancing water contact angle measurements in air were carried out to establish differences in the hydrophilicity of the copolymers. Characteristic properties of the copolymers, the amount of ϵ-caprolactone in the feed, initiators, the average sequence lengths, molecular weights, molecular weight distribution, and contact angles are presented in Table I. The average sequence lengths were determined as before.[17]

The Thermal Characterization and Solubility of Model Compounds

Model compounds, theophylline (T) and propranolol hydrochloride (P) (**Scheme 2**), were mixed in

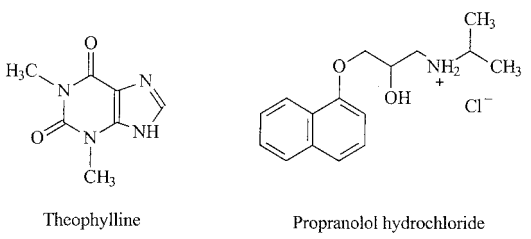
Table I Characteristics of the (ε-caprolactone/DL-lactide) Copolymers

Polymer Code	Theoretical Composition CL/DL–LA (mol/mol)	Initiator (mol %)	^{13}C-NMR		SEC			Contact Angle (°)
			Average Caproyl Sequence Length	Average Lactidyl Sequence Length	$\bar{M}_n$ (g/mol)	$\bar{M}_w$ (g/mol)	MWD	
P(CL/DL–LA)	96/4	Glycerol 0.3	19.7	1.6	81,400	146,000	1.8	71 ± 1
P(CL/PEG1/DL–LA)	96/4	PEG1000 0.5	17.5	1.7	45,300	79,500	1.8	59 ± 1
P(CL/PEG4/DL–LA)	96/4	PEG4000 0.1	17.3	1.9	67,800	155,000	2.3	63 ± 1

melt with the copolymers in a midiextruder and devices were prepared by using a miniinjection molding machine. The mixed amounts of theophylline were 2, 5, 10, 15, and 30 wt % (codes are T2, T5, T10, T15, and T30, respectively) and of propranolol hydrochloride were 2, 5, and 10 wt % (codes are P2, P5, and P10, respectively). In the sample code, the number after the model compound, T or P, indicates the amount of model compound in the device as percentage weight (Table II).

Introduction of the hydrophilic polyethylene glycol block did not alter the glass transition temperature (T_g) of the modified copolymers (Table II). The values of T_g and melting temperature did not change significantly when different amounts of theophylline or propranolol were mixed into the copolymer. Because the presence of model compounds did not alter the T_g of copolymers, they are assumed to have low solubility in copolymers.[18–20]

The changes in crystallinity of the samples were evaluated by comparing enthalpy of fusion values, because no estimation for crystallinity of these copolymers is available in the literature. Enthalpy of fusion values for copolymers and model compounds were calculated in theoretical proportions from DSC curves of the compound-loaded devices. The presence of small molecular weight compounds did not affect the crystallinity of the copolymers, except in P(CL/DL–LA) T5, where enthalpy increased 9%. Flexible polyethylene glycol blocks in the copolymer backbone hinder the alignment of long macromolecular chains (i.e., slightly lower crystallinity was observed in PEG modified copolymers).



Scheme 2

In dispersed devices, the drug concentration exceeds the saturation solubility of drug in the polymer and discrete drug particles exist within the matrix.[10] In such cases, the melting peak of the model compound can be determined by DSC. To study the solubility of theophylline (mp 274.6°C) in the copolymer, the DSC was heated once up to 320°C at a rate of 10°C/min. No theophylline peaks were seen in P(CL/DL–LA) T2 and P(CL/DL–LA) T5 samples. Melting of the theophylline crystals around 220°C was observed in all of the samples with higher loadings [i.e., P(CL/DL–LA) T10, P(CL/DL–LA) T15, and P(CL/DL–LA) T30, P(CL/PEG1/DL–LA) T10, and P(CL/PEG4/DL-LA) T10]. The tendency of theophylline to exist in crystal form in a variety of samples suggests that it has a limited solubility in copolymers. The measured enthalpy values indicate that theophylline was soluble in copolymers when less than 10 wt % was added and was partly dispersed at higher loadings (Table II).

Apart from P(CL/DL–LA) P2 the DSC thermograms of all the samples containing propranolol hydrochloride showed a peak around 160°C. No melting peak in that area was seen in P(CL/DL–LA) P2, which indicates that propranolol hydrochloride was dissolved in the matrix. The peak around 160°C is attributed to the melting of propranolol hydrochloride, which melts at 164.9°C. Propranolol hydrochloride is partially dispersed in the copolymers and has very low solubility in the copolymers. Propranolol hydrochloride had a lower solubility in copolymers compared to theophylline, because a larger portion of loaded pro-

Table II Glass Transition Temperatures, Melting Temperatures, Heat of Fusion of Copolymers and Model Compounds Determined by DSC

Sample	Polymer			Model Compound	
	T_g (°C)	T_m (°C)	ΔH (J/g)	(wt %)	ΔH (J/g)
P(CL/DL–LA)	−56	52	66	0	—
P(CL/PEG1/DL–LA)	−55	52	62	0	—
P(CL/PEG4/DL–LA)	−55	55	59	0	—
Theophylline	—	—	—	100	117
P(CL/DL–LA) T2	−55	52	64	2	[a]
P(CL/DL–LA) T5	−55	53	72	5	[a]
P(CL/DL–LA) T10	−55	54	63	10	70
P(CL/DL–LA) T15	−56	53	64	15	120
P(CL/DL–LA) T30	−55	54	62	30	117
P(CL/PEG1/DL–LA) T10	−55	53	53	10	50
P(CL/PEG4/DL–LA) T10	−54	56	60	10	60
Propranolol hydrochloride	—	—	—	100	80
P(CL/DL–LA) P2	−54	53	59	2	[a]
P(CL/DL–LA) P5	−55	53	61	5	50
P(CL/DL–LA) P10	−55	53	61	10	60
P(CL/PEG1/DL–LA) P2	−55	53	62	2	8
P(CL/PEG1/DL–LA) P5	−56	52	62	5	60
P(CL/PEG1/DL–LA) P10	−55	53	61	10	90

[a] No peak.
T, theophylline; P, propranolol hydrochloride.

pranolol chloride was measured to exist in the crystal form.

Model Compound Release from Copolymer Samples

Cumulative release profiles of theophylline (10 wt %) (T10) from P(CL/DL–LA), P(CL/PEG1/DL–LA), and P(CL/PEG4/DL–LA) copolymers are shown in Figure 1. The release profiles of different copolymer samples containing 10 wt % theophylline were very similar. In the beginning, the release is fast from all copolymers. After approximately 30% is released, the release rate decreases and the differences between the copolymer matrices become evident. Theophylline is released by diffusion from all devices. The model compound dissolves and diffuses by random molecular motion through the free volume between the polymer chains.

The release rates of theophylline can be modified by introducing hydrophilic PEG blocks into the backbone of the copolymer. Faster theophylline release rates were obtained when the hydrophilicity of the copolymer was increased {i.e., release fluxes from P(CL/PEG1/DL–LA) T10 and P(CL/PEG4/DL–LA) T10 [114 (mg/cm^2)/h$^{1/2}$ and 149 (mg/cm^2)/h$^{1/2}$, respectively] are higher than the release flux from P(CL/DL–LA) T10 (88 (mg/cm^2)/h$^{1/2}$)}. A linear relationship between cumulative release and square root of time was determined for all dispersed devices and the consequent calculated release fluxes are presented in Table III.

The effect of theophylline loading on the *in vitro* release was studied more carefully with

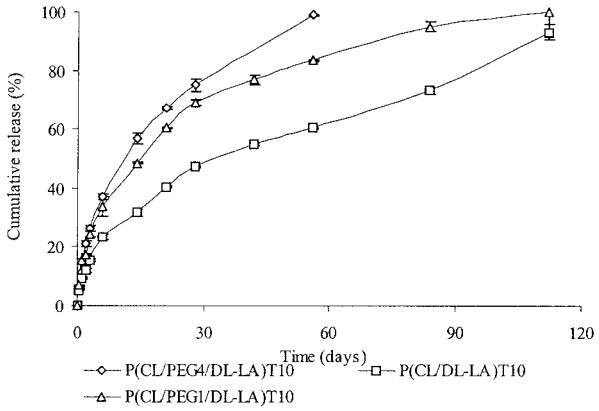


Figure 1 The cumulative release profile of theophylline from P(CL/DL–LA) T10, P(CL/PEG1/DL–LA) T10, and P(CL/PEG4/DL–LA) T10 copolymer samples.

Table III Amount of Model Compounds Released by Square Root of Time Kinetics (propranolol hydrochloride release is over 112 days of study)

Copolymer Device	Release Flux [(μg/cm^2)/h$^{1/2}$]	Correlation Factor
P(CL/DL–LA) T2	44[a]	0.96
P(CL/DL–LA) T5	66[a]	0.97
P(CL/DL–LA) T10	88	0.99
P(CL/DL–LA) T15	137	1.0
P(CL/DL–LA) T30	291	1.0
P(CL/PEG1/DL–LA) T10	114	0.96
P(CL/PEG4/DL–LA) T10	149	0.99
P(CL/DL–LA) P2	17[a]	1.0
P(CL/DL–LA) P5	23	1.0
P(CL/DL–LA) P10	45	1.0
P(CL/PEG1/DL–LA) P2	17	0.96
P(CL/PEG1/DL–LA) P5	51	0.97
P(CL/PEG1/DL–LA) P10	105	0.98

[a] Up to 60% release.

P(CL/dL–LA) copolymer containing different amounts of model compound, namely 2, 5, 10, 15, and 30 wt %. The cumulative release profiles of theophylline in samples containing 10 to 30 wt % were nearly the same [Fig. 2(a)]. This is expected, because theophylline was apparently above its saturation solubility and existed as dispersed particles in the matrix. However, the 2 and 5 wt % samples showed a faster theophylline release with decreasing drug content. In these samples, theophylline was dissolved in the copolymer according to DSC measurements, because no melting peak for theophylline was observed. When active agent is dissolved in the matrix, release rate can be estimated by early and late time approximations. The approximations state that the release rate decreases as $t^{-1/2}$ over the first 60% of the release and the remainder of the release rate decays exponentially.[21] This was seen in the release profiles of the dissolved devices. On the other hand, the presence of the model compound did not affect the T_g, so theophylline might still not be completely dissolved. The results are in good agreement with Higuchi[22] (i.e., the higher the solubility, the greater the release rate of the model compound).

The same data as in Figure 2(a), plotted as cumulative release (mg/cm^2) as a function of square root of time, show that the release of theophylline increased as loading increased [Fig. 2(b)]. The release fluxes (Table III) are calculated from data presented in Figure 2(b). The release fluxes of theophylline from P(CL/DL–LA) matrices increase from 44 (μg/cm^2)/h$^{1/2}$ to 291 (μg/cm^2)/h$^{1/2}$ with increasing theophylline loading. The release rate of theophylline from the device containing 2 wt % of active agent was fastest. In dispersed devices, increase in loading increased the matrix permeability directly. The release of theophylline followed the square root of time kinetics in all dispersed devices and up to 60% release in devices where theophylline was dissolved. These results show that the desired release rate of theophylline is obtainable by varying the compound loading under and above solubility limit.

Cumulative release profiles of propranolol hydrochloride with different loadings (2, 5, 10 wt %) from P(CL/DL–LA) and P(CL/PEG1/DL–LA) copolymers are shown in Figure 3(a). Propranolol hydrochloride releases by diffusion and the release followed square root of time kinetics over

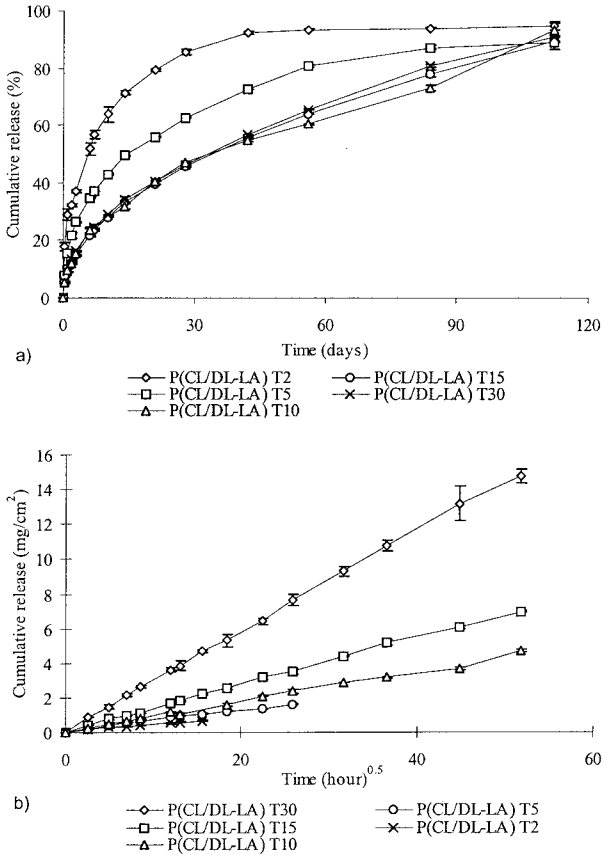


Figure 2 The effect of loading (2, 5, 10, 15, and 30 wt %). (a) Cumulative release profiles of theophylline as a function of time; (b) cumulative release of theophylline as a function of square root of time from the P(CL/DL–LA) samples.

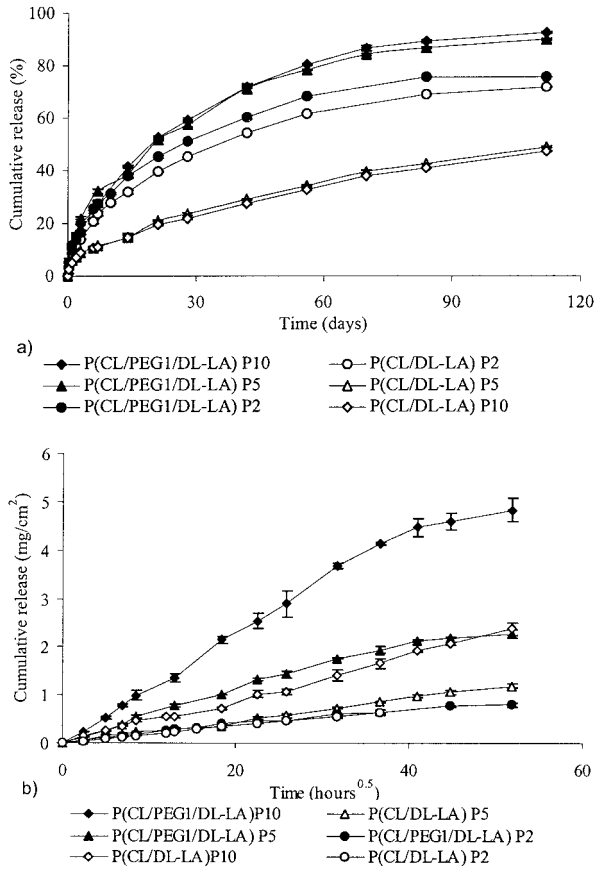


Figure 3 The effect of loading (2, 5, and 10 wt %). (a) Cumulative release profiles of propranolol hydrochloride as a function of time; (b) release rate of propranolol hydrochloride as a function of square root of time from the P(CL/DL–LA) and P(CL/PEG1/DL–LA) samples.

the 4 months measured. Modification of the copolymer matrix with PEG1 increased the release rate of propranolol hydrochloride significantly. Propranolol hydrochloride has a low solubility in the copolymers. According to DSC, 2 wt % was dissolved in P(CL/DL–LA) and, as a result, faster cumulative release compared to higher loadings was obtained. The release rate can be tailored by changing the loaded amount of propranolol hydrochloride.

The higher release fluxes of theophylline compared to propranolol hydrochloride obtained for the same loadings (Table III) indicates faster release of theophylline from P(CL/DL–LA) copolymer. This is probably due to the higher solubility of theophylline in the P(CL/DL–LA) copolymer. In the case of P(CL/PEG1/DL–LA) samples, both model compounds released at the same rate.

The Degradation of Copolymer Matrices

The *in vitro* degradation of copolymers was determined at the same time as the release of model compounds was measured. Degradation was monitored by weight loss, water absorption, and molecular weight changes. Water absorption was calculated according to eq. 1:

$$\mathrm{WA}\% = 100(w_w - w_r)/w_r \quad (1)$$

where w_w is the weight of the sample after hydrolysis and w_r is the residual weight after drying of the sample at each data point. Weight loss was calculated according to eq. 2:

$$\mathrm{WL}\% = 100(w_0 - w_r)/w_0 \quad (2)$$

where w_0 is the initial weight of the sample.

The copolymer matrices were rather stable over 4 months of hydrolysis and the measured weight losses and water absorptions were relatively moderate for all samples. Model compound loading had two effects on the water absorption: both model compounds showed increased absorption compared to absorption into the neat copolymer sample, and the more model compound added, the higher the water absorption. Increasing theophylline loading increased the water absorption from 0.6 wt % of neat copolymer to nearly 17 wt % for samples containing 30 wt % model compound (Fig. 4).

Differences in the hydrophilicity of the matrices were evident for the samples loaded with 10 wt % theophylline, because water absorption in-

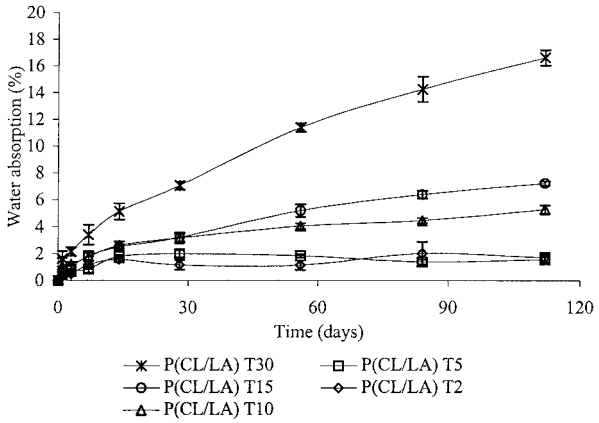


Figure 4 The effect of theophylline loading (2, 5, 10, 15, and 30 wt %) on water absorption of the P(CL/DL–LA) copolymer *in vitro*.

Table IV Weight Loss and Water Absorption of the Copolymer Samples and Propranolol Hydrochloride Containing Devices after 4 Months in Hydrolysis

Sample	Weight Loss (%)	Cumulative Release (%)	Water Absorption (%)
P(CL/DL–LA)	0.6	—	0.8
P(CL/DL–LA) P2	2.1	72	2.2
P(CL/DL–LA) P5	2.9	49	3.2
P(CL/DL–LA) P10	5.1	47	5.7
P(CL/PEG1/DL–LA)	1.4	—	2.3
P(CL/PEG1/DL–LA) P2	1.0	76	2.7
P(CL/PEG1/DL–LA) P5	6.0	90	6.7
P(CL/PEG1/DL–LA) P10	10.2	93	11.3

creased as the hydrophilic nature of the matrix increased [i.e., P(CL/DL–LA) 5.3% < P(CL/PEG1/DL–LA) 6.2% < P(CL/PEG4/DL–LA) 8.3%]. Water absorptions in propranolol hydrochloride-loaded samples were similar and increased as the loading increased or the hydrophilic nature of the matrix increased. P(CL/PEG1/DL–LA) loaded with 10 wt % of propranolol hydrochloride absorbed the most, 11% in 4 months (Table IV). Measured weight losses for devices containing propranolol hydrochloride were between 1.0 and 10.2%, but the differences between samples were due to released model compounds (Table IV). Similarly, no significant weight loss was observed in any of the theophylline-containing devices. Samples did not disintegrate during the study period.

Decrease in molecular weights was not affected by the model compound used or the load of the compound compared to the native copolymer. Figure 5 shows the relative decrease in the weight-average molecular weight of the copolymers containing 10 wt % theophylline. PEG4-modified copolymer degraded faster, and at the end of the 4 months of hydrolysis, only 31% of the initial molecular weight remained. Although the modification of P(CL/DL–LA) with PEG1 increased the hydrophilicity of the matrix, and thus increased the release rate of theophylline and propranolol hydrochloride, the degradation rate was not faster.

Crystallinity increased slightly in all the devices during the hydrolysis (data not shown). This may affect the release of the model compound (i.e., the rate of the model compound release decreases as a function of time because of the increasing crystallinity of the samples).

CONCLUSION

The applicability of three different P(ϵ-caprolactone-*co*-DL-lactide) copolymers for controlled release devices was evaluated by studying the release of two model compounds, theophylline, a basic drug, and propranolol hydrochloride, a hydrophilic drug, at different loadings. The addition of model compounds did not have an effect on the T_g or melting temperatures of the copolymers, which indicates low interaction between the macromolecular chain and model compounds. The solubility of the model compounds in the matrices was confirmed to be low by DSC measurements, where melting of the dispersed particles could be observed in most samples. Theophylline was soluble in copolymers when < 10 wt % was added and was partly dispersed at higher loadings. The difference in the release rate profiles was also

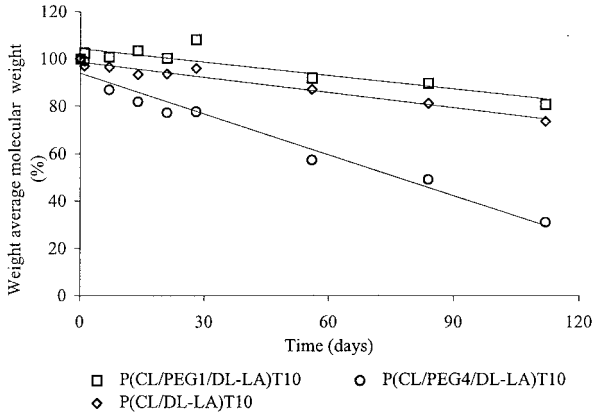


Figure 5 The relative decrease of the weight average molecular weight *in vitro* of copolymers P(CL/DL–LA), P(CL/PEG1/DL–LA), and P(CL/PEG1/DL–LA) containing 10 wt % theophylline.

evident when samples containing different amounts of theophylline, under and above the solubility limit, were compared. Release was initially faster from the samples where the model compound was molecularly dissolved. The release of both model compounds followed square root of time kinetics in dispersed devices.

Hydrolytic degradation of the matrices was also recorded and they were found to be relatively stable over 4 months of hydrolysis. The addition of hydrophilic polyethylene glycol blocks into the backbone of the chain increased water absorption and also the degradation was faster when PEG 4 was used as an initiator. Increasing the hydrophilicity of the matrix also increased the release rates of both model compounds. The results clearly demonstrate that the desired release rates of these model compounds can be tailored by varying the compound loading or by modifying the hydrophilicity of the matrix copolymer.

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