Model Compound Release from DL-Lactide/ε-Caprolactone Copolymers and Evaluation of Specific Interactions by Molecular Modeling

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ABSTRACT: The applicability of poly(DL-lactide-co-ε-caprolactone) copolymers P(DL-LA/CL) for controlled-release devices was evaluated. The copolymers of DL-lactide and ε-caprolactone were polymerized in bulk using Sn(II)octoate as the initiator. The release of three model compounds, theophylline, propranolol hydrochloride, and lidocaine (10 wt%), from high–lactide content copolymer was studied. The results showed that the copolymer with only minor caprolactone content was not suitable for controlled release of these small–molecular weight model compounds in matrix-type devices. A burst in the release rate was observed when the degradation of the matrix replaced diffusion-controlled release. Increasing the permeation properties of the copolymer matrix through blending and using a different comonomer ratio with an increased caprolactone content were both studied. A release that was more controlled but relatively slow was obtained by using copolyester blends as release matrices. Hydrolytic degradation of the copolymers was also recorded, and the copolymers were found to be very susceptible to hydrolytic chain scission at 37°C. Molecular modeling studies were performed to study the interactions between the theophylline model compound and the homo- and copolymers of lactide and ε-caprolactone units. In agreement with experimental results, the calculations showed increasing interaction between theophylline and the polymer matrix as a function of increasing amount of lactide units. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 86: 1–9, 2002

Key words: drug delivery systems; degradation; molecular modeling

INTRODUCTION

Biodegradable and biocompatible linear polyesters are widely studied for biomedical applications. The properties of copolymers of lactide and ε-caprolactone have been well documented, and the obtainability of a variety of thermal and mechanical properties has been demonstrated.[1–2] The effects of different types of model compounds on the degradation and release kinetics as well as the effects of the molecular weight of the polymer and the size of the release device on release profiles have been studied extensively.[3–7] In many cases, the release from polylactides is governed by the degradation of the matrix or percolation phenomena and not by diffusion.[8,9] When the degradation of the polymer governs release, in the case of bulk-degrading as opposed to surface-eroding polymers, the release is not uniform and a clear burst can usually be observed. The release of the active agent from the bulk-degrading biodegradable polymers is usually designed to be complete before the degradation takes place. With careful design of the device, the release can be adjusted to the desired level, where it is governed by both diffusion and degradation. Modification of the matrix by changing the constituent monomers of a copolymer also affects the secondary bonding between the active agent and the polymer matrix. This can have a great influence on the release rate.

Blending has also been used as a method of modifying the release rates from biodegradable devices.[10] The phase morphology of the blend affects the release rates: Immiscible blends present faster drug release rates than miscible blends. This is because the phase separation contributes extra drug release through microchannels formed among the phase-separated domains.[10] Low–molecular weight polylactide (PLA) has been blended with high–molecular weight PLA to alleviate the burst observed in the drug release caused by the degradation of the matrix.[11]

In this article, we report the results of an *in vitro* release study of model compounds from matrices composed of biodegradable DL-lactide and ε-caprolactone copolymers. Three different model compounds, theophylline (basic drug), propranolol hydrochloride (hydrophilic drug), and lidocaine base (hydrophobic drug), were mixed with copolymer in melt

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using a laboratory-scale extruder to produce homogenous devices. The aim of the study was to investigate whether copolyester high in lactide content could be used for the controlled release of small–molecular weight compounds. The release of theophylline was further studied from two blended matrices consisting of copolyesters and an amorphous elastomer matrix.

In addition, molecular modeling was applied to provide insight into the interactions between the polymer matrix and the active component. The estimation of whether secondary bonding could affect the release rates of the model compounds from polymer matrices was of interest. For the evaluation, modeling the interactions between the theophylline model compound and the homo- and copolymers of lactide and ϵ-caprolactone units was chosen. The Flexiblend method, which is used for the estimation of miscibility and phase separation, was used.[12–14] The detailed interactions of the polymer or copolymer constituents with the model compound were calculated using chain segments containing various amounts of lactide and ϵ-caprolactone units.

EXPERIMENTAL

Materials

DL-lactide (Purac, Gorinchem, Netherlands) was recrystallized from toluene and dried for 24 h at 40°C under reduced pressure before the polymerizations. ϵ-caprolactone (Solvay Interox Ltd., Warrington, U.K.) was dried over molecular sieves. Sn(II) octoate (Aldrich Chemical Co., Milwaukee, WI), glycerol (Prolabo, France), theophylline (Fluka Chemie AG, Buchs, Switzerland), propranolol hydrochloride (Fluka Chemie AG, Buchs, Switzerland), lidocaine (Sigma-Aldrich Chemie Gmbh, Steinheim, Germany), and buffer solution pH 7.0 (Reagecon, Clare, Ireland) were used as received.

Polymerization

The ring-opening polymerization of ε-caprolactone and DL-lactide was carried out in bulk with 0.01 mol% of Sn(II)octoate as an initiator. Glycerol was used as a co-initiator. Typically, 1000 grams of monomers, glycerol, and Sn(II)octoate were charged into a 2.5-L batch reactor designed for the agitation of viscous materials. The polymerizations were carried out at 160°C for 4.5–8 h under a nitrogen atmosphere. The viscous polymer was removed from the reactor, cooled at room temperature, and stored in dry conditions. Copolymers were used without further purification.

Preparation of samples

Model compounds (10 wt%) were mixed into copolymers in a corotating twin-screw midi extruder (DMS, capacity = 16 cm^3, screw length [L] = 150 mm). In the case of blend devices, the model compound was mixed together with the blend components in one batch. The midi extruder had a back-flow channel and was operated batchwise. The screw speed was 75 rpm, and the mixing time was 3 min at 100°C. Rectangular shaped devices (10 × 4 mm, thickness 1.8 mm, average weight 70 mg) were prepared using a miniature injection-molding machine attached to the midi extruder.

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 air bath (Infors Ag., Bottmingen, Switzerland) 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 after excess buffer solution had been dried off. Specimens were then vacuum dried for 6 days at room temperature. The amount of released model compound was determined from the buffer solution.

Molecular weight determination

Molecular weights were determined by room temperature size-exclusion chromatography (SEC; Waters System Interface module, Waters 510 HPLC Pump, Waters 410 Differential Refractometer, Waters 700 Satellite Wisp, and four linear PL gel columns: 10^4Å, 10^5 Å, 10^3 Å, and 100 Å connected in series) (Waters Corp., Milford, MA). 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

Dynamic mechanical thermal analysis (DMTA) was performed on a Perkin Elmer 7 Series instrument (Perkin Elmer Inc., Shelton, CT). The measurements were carried out using the three-point bending method over a temperature range of −90° to 100°C at the rate of 4°C/min. All measurements were performed at 1 Hz. The glass transition temperature, T_g, was determined as the peak of tanδ. A differential scanning calorimeter (DSC, Mettler-Toledo Ag., Greifensee, Switzerland) was also used for carrying out thermal measurements. The T_g of the samples were determined from the second heating scan to ensure that their thermal histories were similar. The temperature range was between −100°C and +200°C, and the heating rate was 10°C/min.

TABLE I
Characteristics of the DL-lactide/ε-caprolactone Copolymers

Polymer Code (wt%/wt%)	Glycerol Content (mol%)	Monomer Composition in Feed DL-LA/CL (mol/mol)	^{13}C-NMR			Size-exclusion chromatography			Differential Scanning Calorimetry	
			Composition DL-LA/CL (mol/mol)	Average Sequence Length		$\bar{M}_n$ (g/mol)	$\bar{M}_w$ (g/mol)	MWD	T_g (°C)	T_m (°C)
				lactidyl	caproyl					
P(DL-LA90/CL10)	0.5	88/12	92/8	21.6	—[a]	43300	60300	1.4	30	—
P(DL-LA5/CL95)	0.3	4/96	3/97	1.6	19.7	81400	146000	1.8	−59	52
P(DL-LA40/CL60)	0.05	35/65	37/63	3.0	3.4	150000	280000	1.9	−31	—

[a]P(DL-LA/CL) = poly(DL-lactide/ε-caprolactone); MWD = molecular weight distribution; T_g = glass-transition; T_m = melting temperature. Not determined.

NMR measurements

The structures of copolymers were determined with a Varian Gemini 2000, 300 MHz NMR spectrometer (Varian, Inc., Fort Collins, CO) 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 measurements were carried out at room temperature.

Ultraviolet measurements

The released amount of model compound was determined using a Unicam UV/VIS spectrometer (Unicam Ltd., Cambridge, UK) with calibration curves at absorption wavelengths of 275, 214, and 262 nm for maximum absorption for theophylline, propranolol hydrochloride, and lidocaine, respectively. Buffer solutions were diluted appropriately.

Microscopy

The morphology of the cross sections of the cryogenically fractured samples was examined by scanning electron microscopy (SEM; Zeiss Digital Scanning Microscope 962) (Carl Zeiss, Jena, Germany). Surfaces were coated with a thin layer (10–20 nm) of platinum (Agar Sputter Coater) (Agar Scientific Ltd., Stanstead, UK) before examination.

Modeling

For molecular modeling, the Polymer software package by MSI (Molecular Simulations Inc., San Diego, CA) was used.[12] The calculations were carried out on a Silicon Graphics workstation Indigo^2 Impact 10000. The structure of theophylline was optimized using the semiempirical AM1 method. The partial charge distribution (electrostatic potential (ESP) charges) and the dipole moment were also calculated.[15] ESP charges are the partial charges of the atoms in the molecule, optimized to reproduce the quantum chemically calculated electrostatic potential around the molecule. The molecular mechanics and dynamics simulations were performed using the Discover 97.0/4.0.0.P software by MSI[16]. The polymer consistent force field (pcff) force field was used in these calculations.

RESULTS AND DISCUSSION

Characterization of the copolymers and devices

The copolymers of DL-lactide and ε-caprolactone were polymerized in bulk in weight proportions (90/10, 40/60, and 5/95, respectively), using Sn(II)octoate as the initiator. Glycerol was used as the co-initiator in ring-opening polymerization to adjust the average molecular weight to the desired level. Total monomer conversion was nearly complete, as no monomer peaks could be observed in ^{1}H nuclear magnetic resonance (NMR) spectra. The molar compositions of the copolymer and average sequence lengths were determined by ^{13}C-NMR spectroscopy according to Kricheldorf and coworkers.[17] Characteristic properties of the copolymers (composition, average sequence lengths, molecular weights, molecular weight distributions, and glass transition and melting temperatures) are presented in Table I.

Caprolactone (10 wt%) was introduced as a comonomer to lower the T_g of amorphous P(DL-LA), which is in the range of 50°–60°C. As the temperature is lowered and approaches T_g, the rate of diffusion decreases, reflecting a diminishing molecular motion.[18] Copolymerization lowered T_g below body temperature to 30°C, which was expected to enhance the diffusion of the model compounds in the matrix. P(DL-LA90/CL10) containing 90 wt% of DL-lactide in the feed was amorphous and very hydrophilic because of the high lactide content. The molecular weight was moderate, which should also have enhanced diffusion compared with the high molecular–weight polymer. Elastomeric copolymer matrix, P(DL-LA40/CL60), was polymerized using 40 wt% of DL-lactide in the feed. P(DL-LA5/CL95) copolymer,

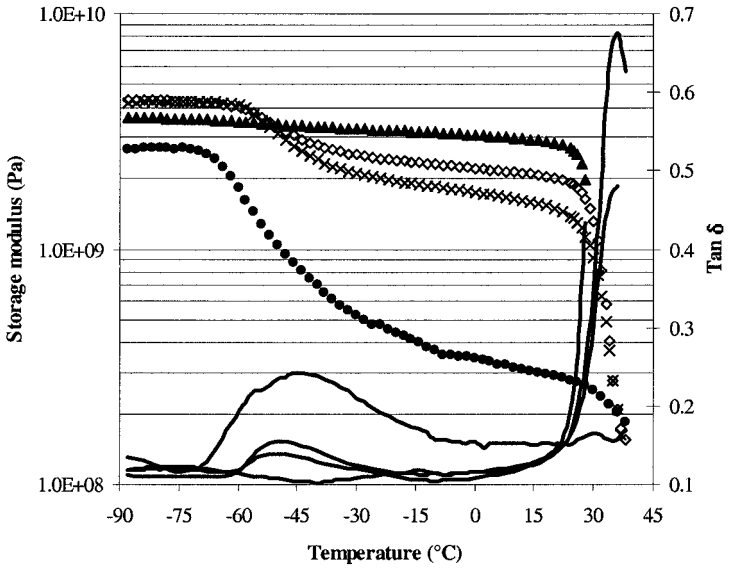


Figure 1 Dynamic mechanical properties of copolyesters and their blends; (▲) P(DL-LA90/CL10), (●) P(DL-LA5/CL95), (◇) Blend (50/50), and (×) Blend (30/70).

which has been found to be a very good matrix for the controlled release of small molecules,[19] was used in blends to alter the permeability of the high–lactide content copolymer.

Blending of P(DL-LA90/CL10) and P(DL-LA5/CL95) was carried out in a weight proportion of 50/50—Blend (50/50)—and 30/70—Blend (30/70). Dynamic mechanical characterization of the blend devices showed that the copolymers form an immiscible system (Fig. 1). Two different T_g were observed in the blends, indicating that the blends were not miscible. It should be noted that the melting temperature of the PCL crystallites is around the same temperature range as the glass transition temperature of the polylactide. The unchanged T_g of the polycaprolactone component is the strongest indication of the two-phase structure of the blends. The storage modulus values of the blends were higher than the value for either copolymer, showing good compatibility between the two phases. If the blends were miscible, the modulus values would lie somewhere between the modulus values of the respective components.

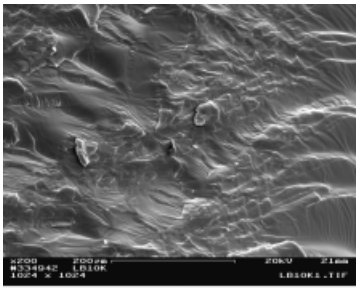
The release of three model compounds, theophylline, propranolol hydrochloride, and lidocaine, was studied from P(DL-LA90/CL10) copolymer. Only the rate of theophylline release was measured from blend and elastomer devices.

Solubility of model compounds

The level of solubility the model compound has when it enters the polymer matrix affects the rate of release, and thus estimating whether the model compounds were dissolved or dispersed into the polymer matrices was of interest. Release from dissolved monolithic systems is faster than the release rate from dispersed monolithic devices; that is, according to Higuchi,[20] the higher the solubility the greater the release rate of the model compound. According to DSC measurements presented in Table II, only lidocaine affected the T_g of the copolymer by shifting it down significantly and thus acting as a plasticizer in the matrix. This, together with the fact that the polymer device remained transparent after the introduction of lidocaine, indicates that 10 wt% was dissolved in the matrix. Scanning electron micrographs of the fracture surfaces of all different P(DL-LA90/CL10) copolymer and model compound devices are shown in Figure 2. SEM micrographs revealed clear differences in the morphologies of the P(DL-LA90/10) copolymer samples containing 10 wt% of different model compounds. The morphology of the copolymer containing lidocaine appears very smooth, and no particles can be observed. However, the morphology of the samples containing theophylline or propranolol hydrochloride was coarser. A transparent device was also obtained when 10 wt% theophylline was mixed in the P(DL-LA40/CL60) ma-

TABLE II
Glass-transition Temperatures (T_g) Measured by Differential Scanning Calorimetry and Physical Appearance

Polymer Code	T_g (°C)	Appearance
P(DL-LA90/CL10)	32	Transparent
P(DL-LA90/CL10) L10	24	Transparent
P(DL-LA90/CL10) T10	32	Opaque
P(DL-LA90/CL10) P10	32	Opaque
P(DL-LA40/CL60)	−31	Transparent
P(DL-LA40/CL60) T10	−32	Transparent



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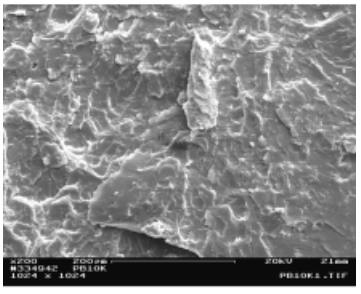

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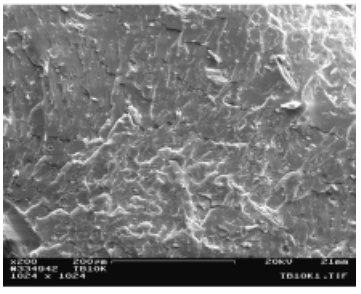

(c)

Figure 2 Scanning electron microscopy micrographs of the P(DL-LA90/CL10) copolymer containing 10wt% of (a) lidocaine, (b) propranolol hydrochloride, and (c) theophylline.

trix, although no significant change in T_g was observed. The solubility of theophylline in the blend devices cannot be estimated by visual characterization, as immiscible blends are opaque and P(DL-LA5/CL95) is opaque because of its inherent crystallinity. In a previous study, small quantities (2%–5%) of theophylline were found to be soluble in P(DL-LA5/CL95) according to DSC measurements.[19] As theophylline is less soluble in P(DL-LA90/CL10), it is probable that some theophylline exists in crystal form in the blend devices.

Model compound release from P(DL-LA90/CL10)

The release of three different model compounds from P(DL-LA90/CL10) copolymer matrix as well as the change in the molecular weights of the copolymers are presented in Figure 3. In each case, release is ultimately governed by the matrix degradation. Diffusion-controlled release is slow, and the model compounds are only released rapidly following a significant loss of molecular weight, after about 40 days of hydrolysis. There is a slight delay in the burst of propranolol hydrochloride but, in all cases, less than 20% of the release of the model compounds was diffusion controlled. The solubility of the model compound in the matrix did not affect the release rate observed. Lidocaine was dissolved in the copolymer, but the release was nonetheless governed by the degradation of the matrix.

The *in vitro* degradation of copolymer 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 as the difference between the weight of the wet and dried samples divided by the weight of the dried sample. Weight loss was calculated as the difference between

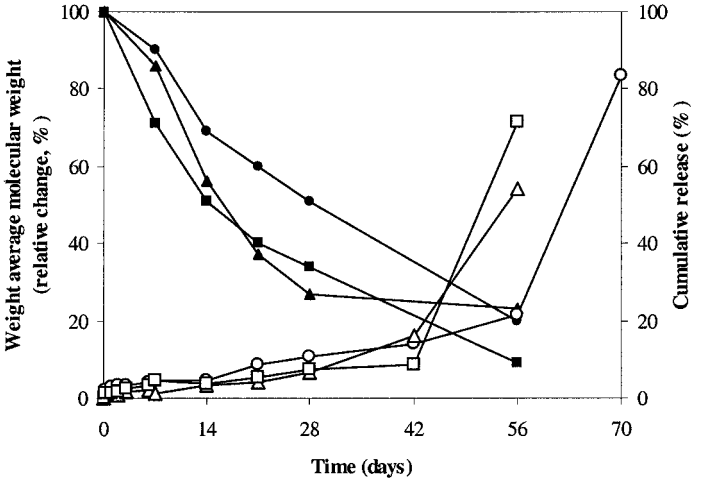

Figure 3 Cumulative release profiles of model compounds (10 wt%) from P(DL-LA90/CL10) copolymer devices and their relative loss of molecular weight: (●) propranolol hydrochloride device, (■) lidocaine device, and (▲) theophylline device.

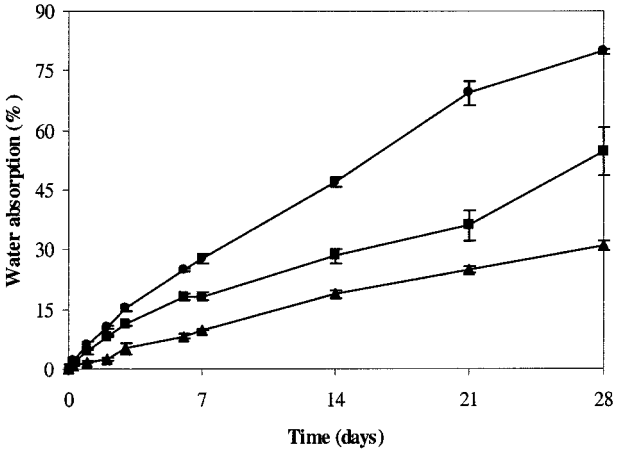

Figure 4 Water absorption into P(DL-LA90/CL10) devices containing 10wt% (●) propranolol hydrochloride, (■) lidocaine, and (▲) theophylline.

the initial weight of the sample and the weight of the dried sample divided by the initial weight of the sample. The degree of water absorption into P(DL-LA90/CL10) was dependent on the model compound used; hydrophilic propranolol hydrochloride increased the uptake most. Figure 4 shows that water absorption over 1 month reaches 31% for theophylline, 55% for lidocaine, and 80% for propranolol hydrochloride–containing devices. The copolymer itself absorbs 30% water in 28 days. No vital change in the weight of the copolymers (besides theophylline loss from devices) was observed in 28 days, although all devices lost their form by that time, and therefore, water absorption and weight loss were not determined further. The rate of degradation was not significantly affected by the presence of model compounds, which was rather surprising, as there was a difference in the amounts of water absorbed.

Modification of Theophylline Release: Blend and P(DL-LA40/CL60) Devices

The modification of theophylline release was studied by blending P(DL-LA90/CL10) with different amounts of P(DL-LA5/CL95) copolymer. Theophylline release from blend devices is shown in Figure 5, along with the release from P(DL-LA40/CL60) copolymer and the relative change in the weight-average molecular weights. SEC did not display bimodal molecular weight curves for the blends. The peaks for respective copolyesters in the blends were overlapping, and thus, only one value was recorded for the molecular weight. After 56 days of hydrolysis, the weight-average molecular weights of the blends containing 10 wt% of theophylline had been reduced to 37% (Blend 50/50) and 63% (Blend 30/70) of the original. This, once again, indicated a slower rate of ester hydrolysis of the caprolactone blocks in the system. Water absorption was 11% for Blend (50/50) and 2.1% for Blend (30/70) in 56 days of hydrolysis. The higher water absorption for Blend (50/50) was caused by the higher lactide content and the thus more hydrophilic nature of the blend. The weight losses were 2.3% and 3.3 %, respectively. By using blend devices for the release, the burst observed in P(DL-LA90/CL10) could be delayed, but the rate of release was relatively slow. Blend (30/70), containing higher amounts of caprolactone units, released theophylline slightly faster; the high caprolactone content, usually providing good permeability, must have been overridden by the heterogeneous phase structure in the device or the tendency for theophylline to remain in the PLA phase. As only 2 months release from these devices was studied, it is not certain that the burst would be completely avoided. In Blend (50/50), it is possible that the entire load of active agent would not be released be-

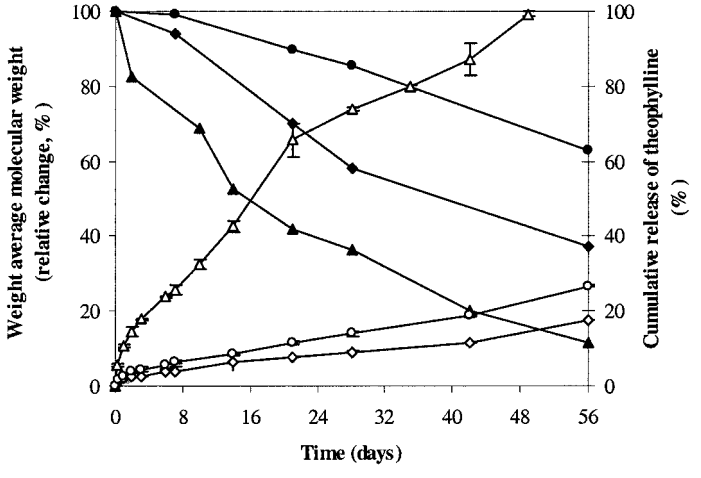

Figure 5 Cumulative release of theophylline (10 wt%) from copolyester and blend matrices and the relative loss of molecular weight: (Δ) P(DL-LA40/CL60), (△) Blend (50/50), and (◇) Blend (30/70).

fore the disintegration of the device and that, thus, a burst of the remaining drug would occur.

Constant, nearly zero, order release of theophylline was obtained with P(DL-LA40/CL60) copolymer. Apparently the amorphous nature of the copolymer together with caprolactone blocks enhanced the rate of the release compared with the copolymer of higher lactide content. Also, the higher solubility of theophylline promoted the release. Because of its low T_g and lack of crystalline structure, the copolymer did not retain its form well at 37°C. Nevertheless, the copolymer provided a very steady rate of release, and concurrent degradation of the device would enable repeated administration with a new device if required. Water absorption increased to 19.8%, and weight loss on top of the theophylline loss was 12.4% for the copolymer in 56 days. It can be concluded, based on these and previous results,[18] that changing the comonomer ratio is the more efficient method for modifying the release rate compared with blending two aliphatic copolyesters to prepare a controlled release device.

Modeling Results

In the Flexiblend method, the energy of mixing is estimated by calculating the interaction energies between short polymer chain segments (A) and a model molecule (B), as well as between like pairs A–A and B–B. The energy of mixing ΔE is then calculated as

$$\Delta E(\mathrm{AB}) = E_{\mathrm{AB}} - \frac{1}{2}(E_{\mathrm{AA}} + E_{\mathrm{BB}}).$$

A negative result indicates that the compounds are miscible; that is, the overall interactions between A and B are strong enough to provide miscibility. The more negative the result, the more likely it is that miscibility occurs.

The miscibility between theophylline and different chain segments composed of lactide (dimer of lactic acid) and ε-caprolactone units was estimated using this method. For each chain, and for theophylline as well, 100 conformations were generated using high-temperature molecular dynamics. The pairs between like compounds (A–A and B–B), as well as the various combinations (A–B), were constructed by docking two randomly chosen conformations and refining the structures by molecular dynamics followed by energy minimization, using molecular mechanics. For each combination of pairs, 200 structures were calculated. Because of the local nature of interactions, only short-chain segments need to be treated in the Flexiblend approach. For the calculations, three chain segments of approximately the same length were constructed: a chain of lactic acid units with five ester groups (L5), a

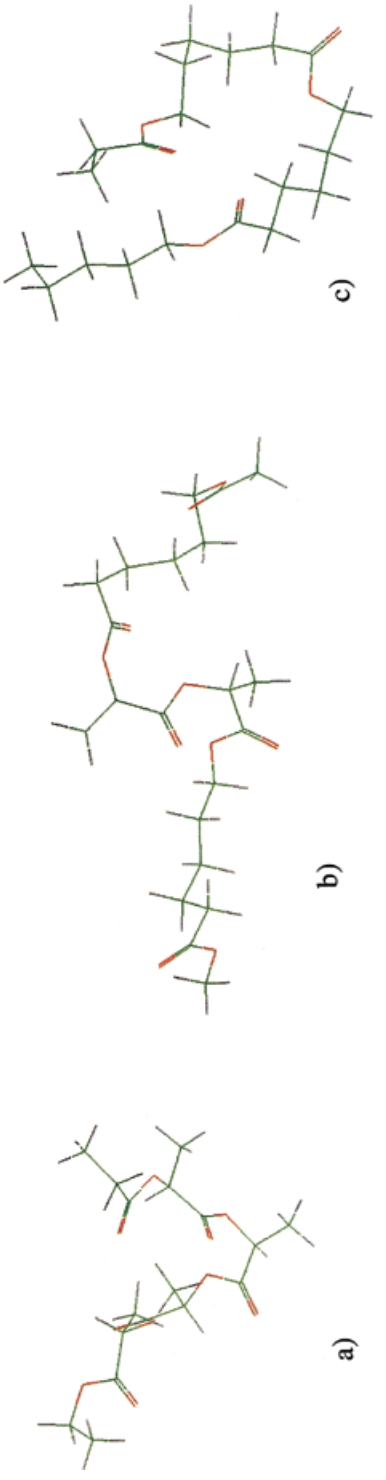

Figure 6 The chain segments used in the miscibility calculations: (a) L5, (b) EC-L2-EC, and (c) EC3.

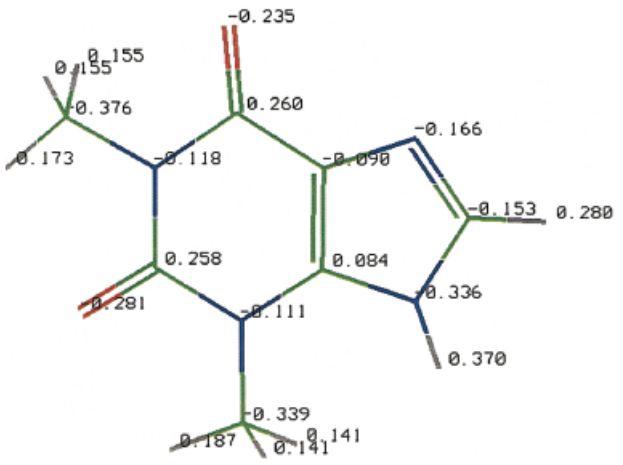

Figure 7 The AM1 optimized structure of theophylline together with the ESP charges.

segment having a lactide unit (two ester groups) between caprolactone units (EC–L2–EC), and a chain consisting of three ε-caprolactone units (EC3). In all cases, the segments end with alkyl groups to avoid artificial effects caused by the chain ends. A conformation of each chain is given in Figure 6.

According to the AM1 calculations performed on theophylline, the molecule is almost planar. In addition, theophylline is highly polar, the dipole moment being 6.5 D. The partial charges in theophylline are shown in Figure 7. The results from the Flexiblend calculations are given in Table III, which shows that for all polymer chain segments, the mixing energies, and thus the interactions with theophylline, are small. It is important, however, that the calculations clearly show that the increasing interaction between theophylline and the polymer matrix is obtained as the amount of lactide units increases. This could partly explain the slow diffusion rate observed in the high–lactide content copolymer matrix P(DL-LA90/CL10).

Figure 8 presents an optimized pair of theophylline and chain segment L5 obtained from the Flexiblend calculations. A detailed inspection shows that theophylline resides in a pocket held together by interactions between the carbonyl oxygens in the L5 ester groups and the carbonyl carbon in theophylline. Further, carbonyl carbon in L5 interacts with the oxygen atom in the theophylline carbonyl group. These distances are all in the range of 2.9–3.1 Å. The planarity of theophylline enhances the possibility for simultaneous interactions from several directions, which makes the total effect of the interactions stronger.

TABLE III
Results of the Flexiblend Calculations

Chain Segment	ΔE_{tot} (kcal mol^{-1})
L5	-0.9 ± 0.4
EC-L2-EC	0.5 ± 0.4
EC3	0.7 ± 0.4

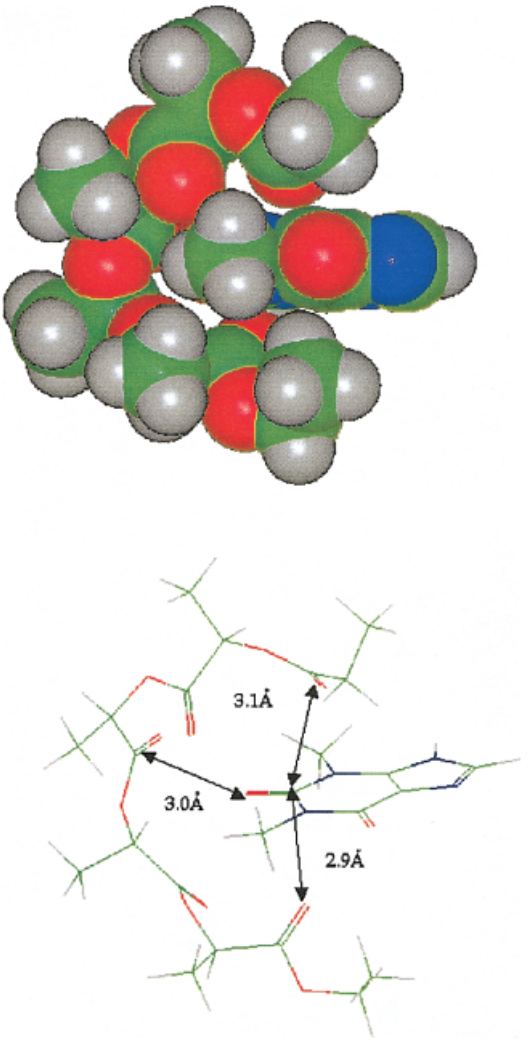

Figure 8 An example of an optimized pair of theophylline and chain segment L5 showing interactions between the functional groups in the molecules. In the structure, the molecules are shown with their van der Waals surfaces.

CONCLUSION

The solubility of the model compound in the matrix material did not affect the rate of diffusion from high–lactide content copolymer. The rate of release of all the studied model compounds, dissolved or dispersed, was most affected by the degradation of the matrix after about 1 month in hydrolysis. At this time, the molecular weight of the copolymer was significantly reduced, the devices lost their form, and a clear burst on the release profile was observed. Using different copolyester blends as the release matrices successfully eliminated the burst effect, but the rate of the release was modest, even with high caprolactone contents. Steady release of theophylline was obtained from an amorphous copolymer matrix containing 40 wt% of

DL-lactide. An advantage of this copolymer was the simultaneous degradation of the matrix, but the low form stability at 37°C was a disadvantage.

According to the molecular modeling calculations, the interactions between theophylline and the polymer matrix increase as a function of increasing the amount of lactide units. Also, the high dipole moment of theophylline and the partial charge distribution enable electrostatic interactions with functional groups in the polymer matrix. The modeling results are consistent with the experimental findings; that is, the diffusion of theophylline from copolymer matrix containing 90 wt% of lactide was slow and possibly hindered by strong interactions formed between theophylline and the copolymer.

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