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In vitro evaluation of biodegradable ε-caprolactone-co-D,L-lactide/silica xerogel composites containing toremifene citrate

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Abstract

Poly(ε-caprolactone-co-D,L-lactide) polymers were blended with toremifene citrate or with toremifene citrate impregnated silica xerogel in order to develop a controlled release formulation. The copolymers were synthesized by bulk polymerization and characterized by nuclear magnetic resonance, size exclusion chromatography and differential scanning calorimetry analyses. The in vitro release of toremifene citrate, an antiestrogenic compound, and silica was carried out in simulated body fluid (pH 7.4) containing 0.5 wt% sodium dodecylsulphate at 34°C. The in vitro release studies indicate that the release flux of toremifene citrate increases with increasing weight fraction of caprolactone in the copolymer. Silica xerogel had a minor enhancing effect on the release rate of toremifene citrate. Copolymers containing larger amounts of D,L-lactide (PLA–CL20 and PLA–CL40 copolymers) were not suitable matrices for the delivery of toremifene citrate in a controlled manner because of the burst effect. The fraction of toremifene citrate released from PLA–CL80 matrix increased with the increasing loading of toremifene citrate. The results of the study indicate that the in vitro release of toremifene citrate can be adjusted by varying the polymer composition and also the initial drug loading.

Keywords: Biodegradable polymers; Drug release; Silica xerogel; Toremifene citrate; ε-Caprolactone/D,L-lactide copolymer

1. Introduction

The growing interest in controlled drug release in human medicinals can be attributed to the promise of increased patient compliance due to a

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reduced frequency of administration, improvements in the safety and efficacy of drug substances (particularly those with a narrow therapeutic index), and a reduction in undesirable side effects (Thombre and Cardinal, 1988).

A major class of synthetic biodegradable polymers is aliphatic poly(esters). Polycaprolactone provides a very good permeation for steroids, but its degradation time (3–5 years) is usually a disadvantage for medical applications such as drug delivery systems (Ye and Chien, 1996a). Since polylactide behaves in the opposite way, a possible solution to this problem is to adjust the properties by copolymerization (Hiljanen-Vainio et al., 1996). The permeation and degradation rates can be controlled by adjusting the composition of the block copolymer. Copolymers of ε-caprolactone and D,L-lactide are biocompatible and may be used in diffusion-controlled delivery systems that biodegrade after drug exhaustion (Pitt et al., 1979b; Vert et al., 1992). They have been studied for various delivery systems and the effects of the subcutaneous implantation have also been reported (Pitt et al., 1979a; Den Dunnen et al., 1992; Buntner et al., 1996; Bero et al., 1997; Lemmouchi and Schacht, 1997). It was concluded that the foreign-body reaction is mild. Silica xerogels used in this study belong to the group of porous glasses produced by a sol–gel process.

Porous glasses have been used in analytical applications and as bone substitutes (Lev, 1992; Hench and Andersson, 1993). Parenterally implanted sintered sol–gel produced glasses (Na_2O–CaO–SiO_2) containing 85% silica and pure sintered silica gels are biocompatible and bioactive (Wilson et al., 1981; Li et al., 1992; Klein et al., 1995; Kortesuo et al., 1999). Resorption behaviour can be controlled with the sintering temperature and the composition of the glass (Li et al., 1992; Klein et al., 1995). Adsorption and desorption of drug molecules on the sol–gel processed sintered silica xerogels has been studied previously (Sieminska et al., 1997; Ahola et al., 1998). The main factor limiting the diffusion rate was the pore diameter (Sieminska et al., 1997).

Bioceramic/copolymer composites have not previously been used in controlled drug delivery devices, whereas bioceramics and copolymers have separately been used in that field. Instead, these composites have been used to improve the strength characteristics of medical devices (Lowry et al., 1997). Bioceramic/copolymer composites may have practical applications in clinical orthopaedics for delivering antibiotics or growth factors and giving sufficient mechanical support in osseous defects caused by tumor resection/curettage or in osteomyelitic cavity during bone healing process. In these composites, the biodegradable polymer provides the matrix for the bioceramic and may also control the release rate of the active agent depending on the application.

In this work, toremifene citrate was used as a model drug in bioceramic/copolymer composites. Toremifene citrate is an antiestrogenic compound that exerts its antitumor action through inhibition of the estrogen-mediated growth stimulus (Valavaara, 1990). Antiestrogens have been used in the systemic treatment of hormone-dependent breast cancer (Kallio et al., 1986). Local hormone therapy after breast cancer surgery could provide targeted and long-lasting disease control.

The goal of this study was to develop a controlled release formulation of toremifene citrate using biodegradable delivery systems based upon matrix of copolymers of ε-caprolactone and D,L-lactide and silica xerogel. The effect of drug loading and copolymer composition on the release rate of toremifene citrate was investigated. In addition, the role of hydrophilic silica xerogel, impregnated with toremifene citrate, in the release of the drug from different copolymers was examined. It was assumed that silica xerogel could improve the release properties of copolymer matrix, for example, by adding hydrophilicity.

2. Methods

2.1. Preparation of silica xerogel

Silica xerogel was prepared using the sol–gel method published by Nakanishi (1991). The solution contained tetraethoxysilane (TEOS) (Aldrich), polyethylene glycol (PEG) (M_w 10 000 g/mol; J.T. Baker), deionized water and nitric acid

(HNO_3) (Merck) in a molar ratio 1.0:0.0024:14.2:0.41. The PEG was dissolved in distilled water and a small amount of nitric acid was added to accelerate the reaction. Hydrolysis occurred when TEOS was added into the stirred PEG solution.

The solution was kept at 40°C for 18 h in an oven for hydrolysis, polycondensation and ageing. The aged silica gels were soaked in an ethanol–water solution to leach out residual organic compounds within the gel and dried at 40°C for 6 days to obtain a raw silica xerogel. The dried xerogels were heated at the rate of 10°C/h and held isothermally for 2 h at 700°C. Silica xerogel rods were ground and sieved to a grain size between 56 and 200 μm. Before use, they were washed with ethanol and dried in an oven at 60°C for a few hours.

2.2. Adsorption of toremifene citrate on the surface of silica xerogel

Toremifene citrate (Orion Corporation, Finland) was dissolved in 5% lactic acid (J.T. Baker) (adjusted to pH 2.5 with 1 M NaOH) at a concentration of 1 mg/ml. The grains were impregnated with the drug solution for 4 h at room temperature. The samples were washed with distilled water and dried at 37°C for a few hours.

2.3. Synthesis of ε-caprolactone/D,L-lactide copolymers

2.3.1. Materials

ε-Caprolactone (ε-CL) (Fluka) was dried over molecular sieves. D,L-Lactide (DLLA) (Purac) was recrystallized twice from dried toluene and dried at 40°C for 24 h under reduced pressure before polymerizations. Stannous octoate (Sigma) and glycerol (Rhône-Poulenc) were used as received.

2.3.2. Polymerization procedure

The polymerizations were carried out in bulk under an argon atmosphere with Sn(II) octoate as the catalyst (0.1 mmol/mol monomer) and glycerol as an initiator (0.5 mmol/mol monomer). The polymerization glass flask with stirrer was immersed in an oil bath at 120°C for 54 h The copolymers were stored in dry conditions.

2.3.3. Blending

ε-CL/DLLA copolymers were blended with toremifene citrate impregnated silica xerogel or toremifene citrate in a batch mixer at 100°C. The speed was 50 rpm for 5 min (Brabender W50EH).

2.3.4. Moulding

The samples for dissolution tests were prepared by compression moulding. Test specimens were punched out from moulded plates with an Elastocon EP 02 puncher. The average size of the square shaped test specimen was 3 mm × 10 mm × 10 mm.

2.4. Determination of physical and chemical characteristics

2.4.1. 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 xerogel columns: 10^4, 10^5, 10^3 and 100 Å connected in series). Chloroform was used as solvent and eluent. The samples were filtered through a 0.5 μm Millex SR filter. The injected volume was 200 μl and the flow rate 1 ml/min. Monodisperse polystyrene standards were used for primary calibration.

2.4.2. Thermal analysis

Glass transition and melting temperatures were measured by differential scanning calorimetry (DSC) (PL). Nitrogen was used as a sweeping gas. The samples (5–10 mg) were heated twice (at a rate of 10°C/min, from −80 to 180°C) to ensure that their thermal histories were similar.

2.4.3. Nuclear magnetic resonance measurements

The structures of the copolymers were determined with a Varian Unity 400 nuclear magnetic resonance (NMR) spectrometer working at 100.577 MHz for ^{13}C and at 399.96 MHz for ^{1}H. Sample concentrations, in 5 mm tubes, were 10% by weight in chloroform-d_1 for ^{13}C NMR and 1%

by weight for ^{1}H NMR. The measurement temperatures were 45°C for ^{13}C NMR and 18°C for ^{1}H NMR. Tetramethylsilane was used as an internal standard.

2.5. Appearance and homogeneity of the copolymer samples

The surface morphology of the fractured surfaces was evaluated on the basis of micrographs taken with a scanning electron microscope (JSM-840A; Jeol, Tokyo, Japan). The samples were prepared for electron microscopy according to U.S.P. 23.

2.6. In vitro release experiments

The dissolution profiles (each data point is the mean of three values) of toremifene citrate and silica from silica xerogel/copolymer composites were studied using a planar shaker at a constant temperature. Simulated body fluid (SBF) (pH 7.4) containing 0.5 wt% sodium dodecylsulphate (SDS) was used as a dissolution medium. SBF was prepared by dissolving reagent grade NaCl (136.8 mM), $NaHCO_3$ (4.2 mM), KCl (3.0 mM), $K_2HPO_4{\cdot}3H_2O$ (1.0 mM), $MgCl_2{\cdot}6H_2O$ (1.5 mM), $CaCl_2{\cdot}2H_2O$ (2.5 mM) and Na_2SO_4 (0.5 mM) in distilled water. The solution was buffered at pH 7.4 with tris(hydroxymethyl)aminomethane (50 mM) and hydrochloric acid.

The volume of the dissolution medium was 25 ml. At each sampling interval, the medium was changed. The rotation speed was 50 rpm and the temperature 34°C. The absorbance values of the dissolution samples were measured on an UV–visible spectrophotometer (Hewlett Packard 845/A, USA) at the maximum absorbance of toremifene citrate, 278 nm. Degradation of the silica xerogel was determined by measuring dissolved $Si(OH)_4$ spectrophotometrically as a molybdenum blue complex at 820 nm (Koch and Koch-Dedic, 1974).

2.7. Determination of drug content in the composite samples

The drug content in the copolymer composites was determined by dissolving the copolymer in a 1:1 solution of acetonitrile:methanol and by precipitating the copolymer with 10 mM NaH_2PO_4 buffer at pH 2.0. After centrifugation, the amount of toremifene citrate in the supernatant was analyzed by spectrophotometer at 278 nm.

3. Results

3.1. Polymer synthesis

Monomer compositions and average molecular weights ($\overline{M}_w$ and $\overline{M}_n$) of the copolymers used are shown in Table 1. The copolymer samples were named according to the monomer ratio in the feed; for instance, the copolymer obtained by polymerization with 20 wt% caprolactone in the feed is named PLA–CL20. Differences between the ratio of ε-caprolactone in the feed and copolymer for PLA–CL20 and PLA–CL40 are mainly due to different monomer reactivities, i.e. lactide is more reactive than ε-caprolactone (Hiljanen-Vainio et al., 1996). The weight average molecular weight of copolymers was around 300 000 g/mol. The copolymers were amorphous, except for

Table 1
Characteristics of D,L-lactide (DLLA)/ε-caprolactone (CL) copolymers

Polymer code	CL in monomer feed (wt%)	CL in copolymer (wt%)	$\overline{M}_w$ (g/mol)	$\overline{M}_n$ (g/mol)	T_g (°C)	T_m (°C)	Length of CL sequence
PLA–CL20	20	9	346 000	225 500	30	–	2.2
PLA–CL40	40	30	289 500	172 900	11	–	4.0
PLA–CL60	60	62	283 500	164 000	−33	–	6.4
PLA–CL80	80	81	299 900	171 000	−51	45	7.2

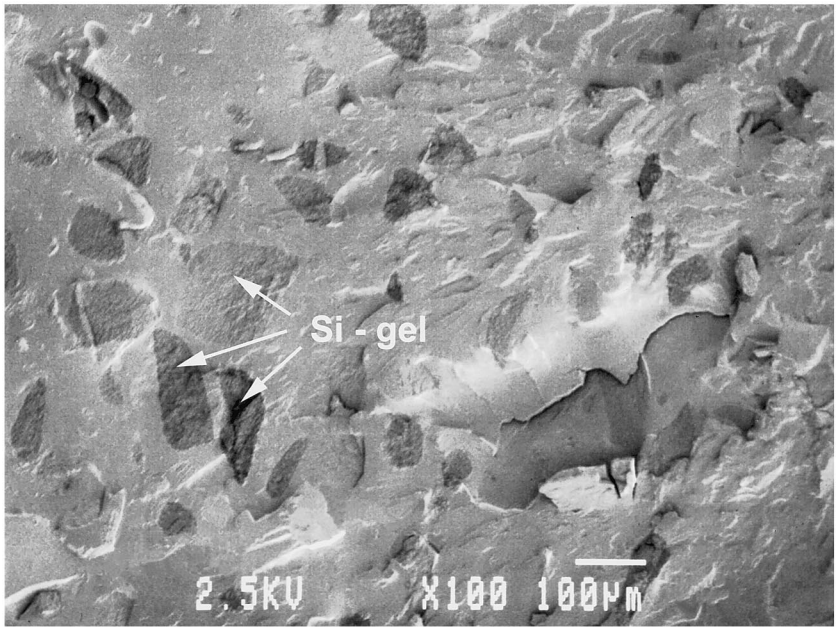

Fig. 1. Scanning electron micrograph of fractured copolymer/silica gel composite.

PLA–CL80, which showed a clear melting endotherm. Average caproyl sequences were determined as previously (Kasperczyk and Bero, 1993; Hiljanen-Vainio et al., 1996, 1997).

3.2. Fracture morphology and homogeneity

Silica xerogel particles were well dispersed in the copolymer matrix in all samples. The fractured surfaces showed that silica xerogel particles were fractured with the polymer matrix (Fig. 1).

3.3. In vitro release studies

Copolymer matrices varied in weight fraction of caprolactone from 20 to 80 wt% but contained the same drug (2 wt%) or silica xerogel loading (20 wt% containing 1.6 wt% toremifene citrate). The actual amount of silica xerogel content varied between 15.3 and 17.1 wt% in the copolymer composites. In vitro dissolution tests were carried out until 100% toremifene citrate was released.

3.3.1. Silica xerogel/copolymer composites

The toremifene citrate release results for drug impregnated silica xerogel/copolymer matrices are shown in Fig. 2. The results indicate that the release profiles of toremifene citrate follow matrix-diffusion kinetics at the beginning, before the burst phase. The release flux of toremifene citrate increases from 0.7 to 1.1%/$h^{1/2}$ within 42 days, with increasing weight fraction of CL in the copolymer. The total release time of toremifene citrate increases from 74 to 203 days with increasing weight fraction of CL in the composite.

The release flux of silica increases from 1.7 to 21.5 µg/$h^{1/2}$ within 42 days, with increasing weight fraction of CL in the copolymer (Fig. 3). Measured silica releases differed greatly between copolymers because the experiment measuring silica release was terminated after 100% toremifene citrate was released. Only PLA–CL20 degraded completely during dissolution and 18.3 mg of silica was released. Silica xerogel delayed the beginning of the burst effect in PLA–CL20 copoly-

mer compared with the copolymer without silica xerogel.

The mass loss of the PLA–CL20 copolymer was 100%, that of PLA–CL40 72% and that of PLA–CL60 64% during dissolution. The mass loss of the PLA–CL80 copolymer was only 29% (Table 2). In the end, the $\overline{M}_w$ of the copolymers varied between 12 000 g/mol for PLA–CL40 and 16 900 g/mol for PLA–CL80. Changes in the molecular weights of the samples are shown in Fig. 4.

3.3.2. Drug–copolymer composites

The results from drug dispersed copolymer matrices are compared in Fig. 5. The results indicate that the release profiles of toremifene citrate were quite similar compared with the release profiles from composites containing silica xerogel. However, at the beginning, toremifene citrate eluted more slowly from copolymers PLA–CL20, PLA–CL40 and PLA–CL60 without silica xerogel than from copolymers containing silica xerogel. The release profiles of toremifene citrate from PLA–CL80 matrices with or without silica xerogel are similar. The release fluxes of toremifene citrate from copolymer matrices increases from 0.4 to 1.4%/$h^{1/2}$ within 42 days, with increasing weight fraction of CL in the copolymer. The total release time of toremifene citrate increased from 70 to 197 days with increasing weight fraction of CL in the copolymer.

3.3.3. Effect of drug loading

The in vitro study with drug–PLA–CL composites revealed that the copolymer PLA–CL80 provided the most uniform rate of toremifene citrate release. This copolymer was therefore selected for drug loading studies. Fig. 6 shows the effect of initial drug loading on the toremifene citrate release from PLA–CL80 matrix. The toremifene citrate release was linear to the square root of time from copolymer mixtures containing 2, 3, 4 and 10 wt% drug, but the release rate from copolymer with 10 wt% was accelerated after 40%

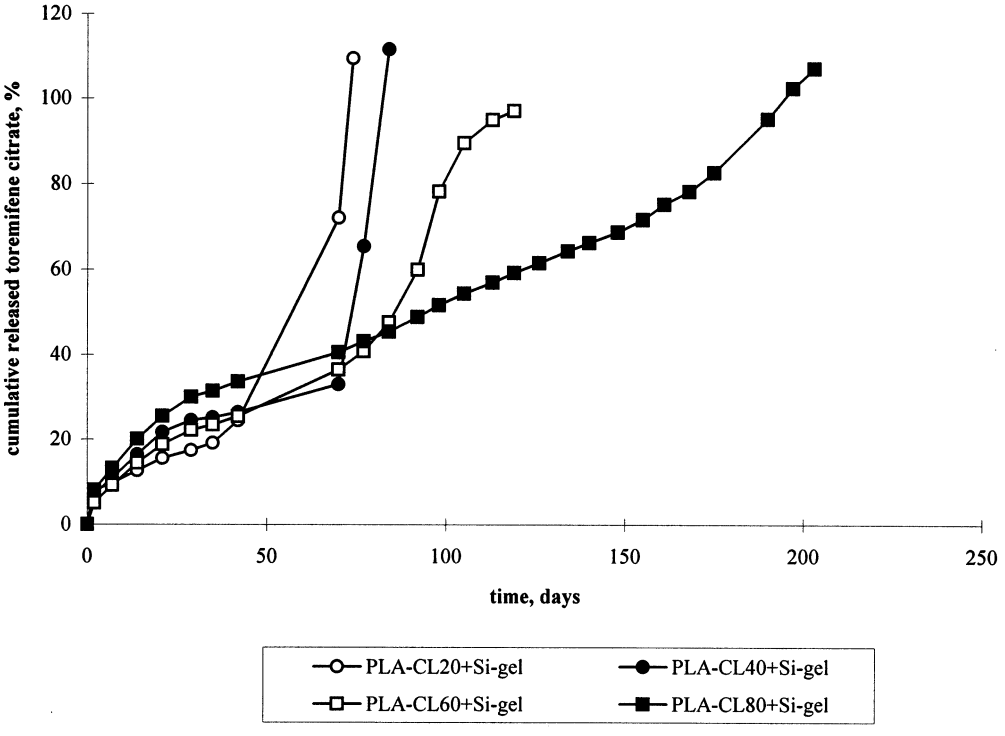

Fig. 2. Release of toremifene citrate from PLA–CL matrices containing drug impregnated silica xerogel.

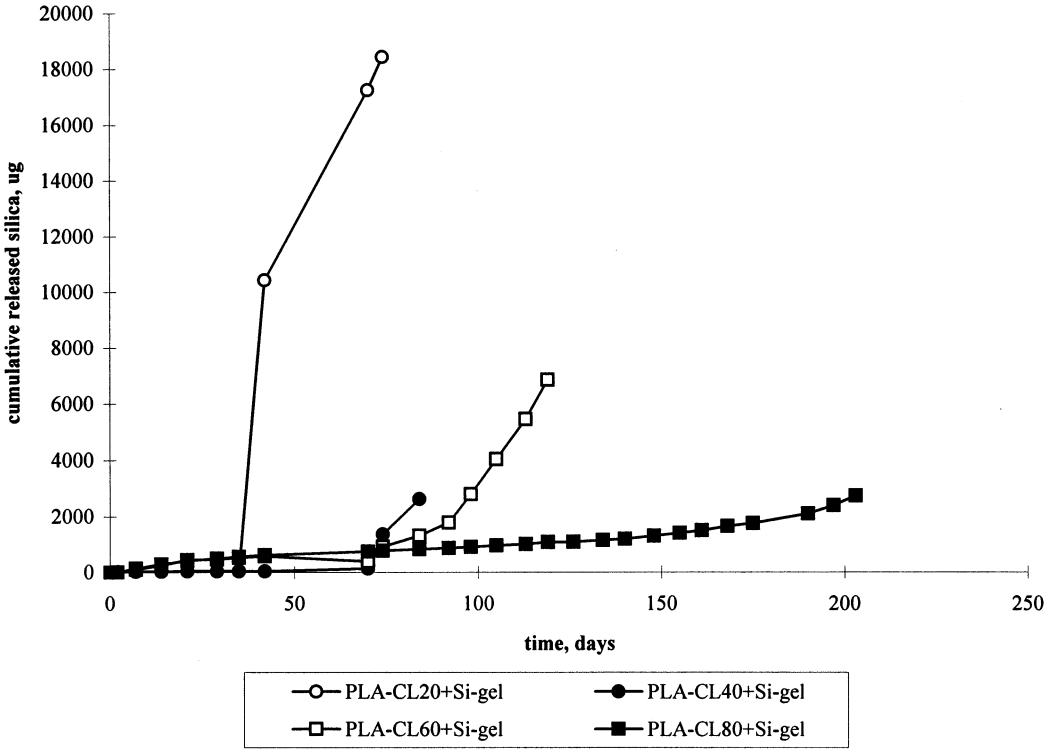

Fig. 3. Release of silica from PLA–CL matrices containing drug impregnated silica xerogel.

of the drug had been released (sigmoidal release profile). The release rates determined from the slopes of the curves, using only the data points obtained with less than 70% of the loaded toremifene citrate released, were plotted versus the corresponding drug load. The correlation between the slope of the release curve ($\mu g/h^{1/2}$) and the drug load was linear ($r = 0.99$).

4. Discussion

The in vitro study with drug–PLA–CL composites revealed that the copolymer PLA–CL80 provided the most uniform rate of toremifene citrate release. The copolymers PLA–CL20, PLA–CL40 and PLA–CL60 had a steady-state phase which was followed by a very rapid release of toremifene citrate within a few days, especially from PLA–CL20 and PLA–CL40. The PLA–CL20 copolymer, containing the largest amount of hydrophilic lactidyl units, swelled and burst out toremifene citrate and silica. The other copolymers did not swell as much as PLA–CL20. A significant difference existed in the extent to which each individual copolymer showed the abrupt change in toremifene citrate release. Before the abrupt increase, the released fraction of toremifene citrate was lower for copolymers with

Table 2
Mass loss after the dissolution test

Polymer code	Mass loss % (SD)
PLA–CL20 +20 wt% Si gel	100
PLA–CL40 +20 wt% Si gel	72 (2)
PLA–CL60 +20 wt% Si gel	64 (3)
PLA–CL80 +20 wt% Si gel	29 (0)
PLA–CL20+2 wt% toremifene	100
PLA–CL40+2 wt% toremifene	89 (4)
PLA–CL60+2 wt% toremifene	73 (1)
PLA–CL80+2 wt% toremifene	31 (0)

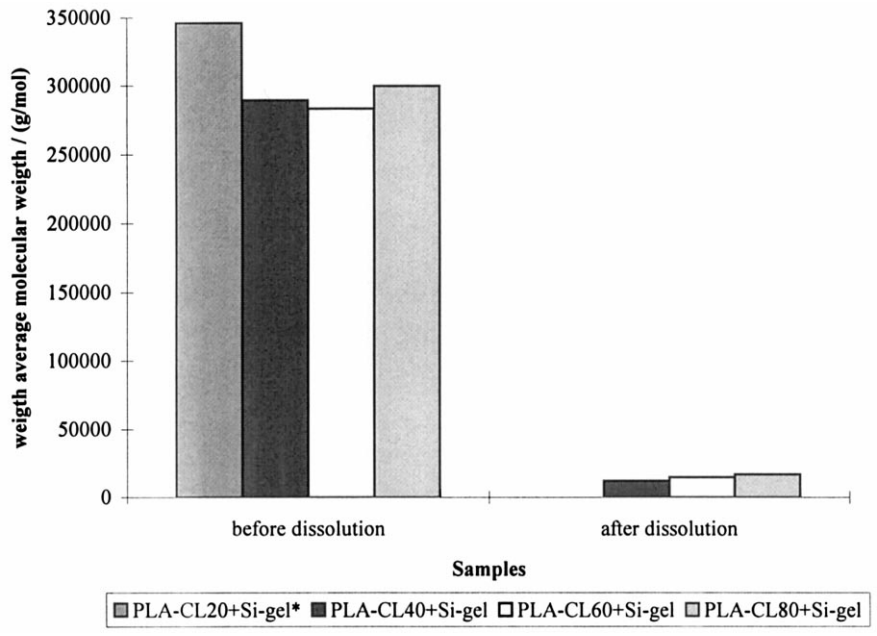

Fig. 4. Changes of the molecular weights of the samples in the beginning and at the end of the dissolution time. *, molecular weight was not determined after dissolution.

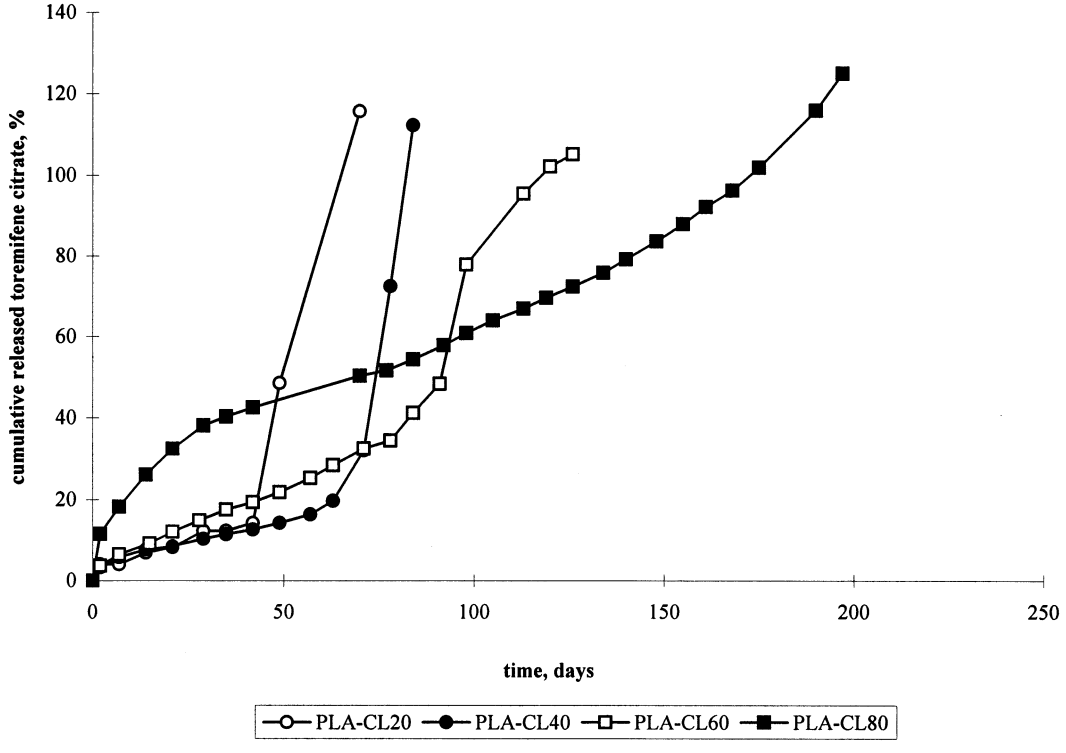

Fig. 5. Release of toremifene citrate from PLA–CL matrices without silica xerogel.

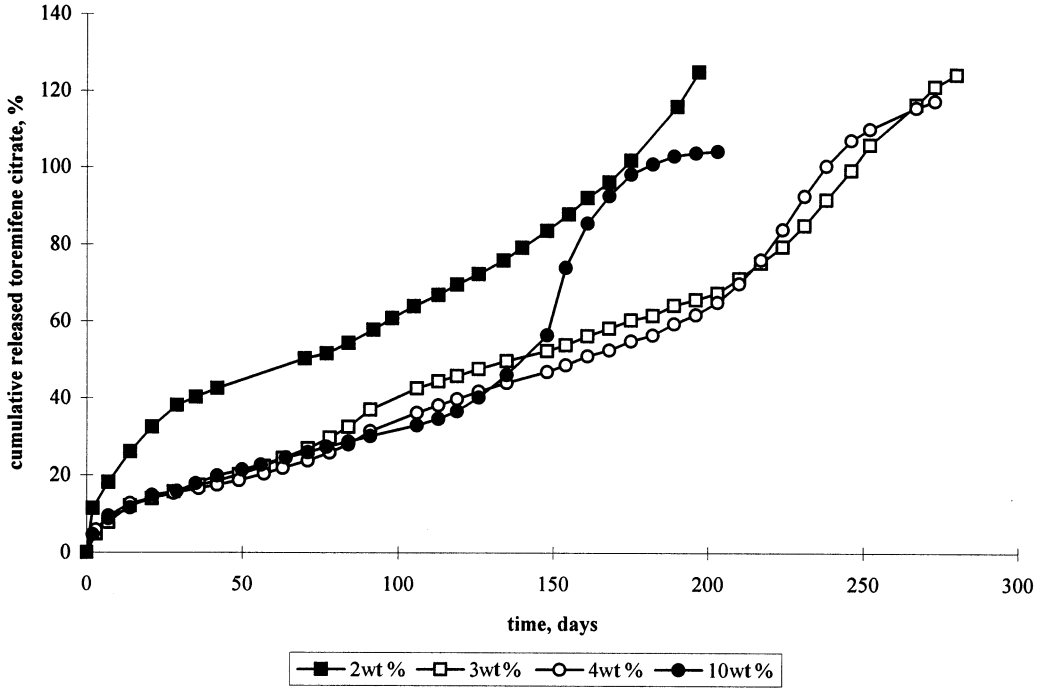

Fig. 6. Effect of drug loading. Release of toremifene citrate from the PLA–CL80 matrix.

a lower caprolactone content. PLA–CL80 showed higher toremifene citrate release rates than PLA–CL20. It has been reported in earlier studies that levonorgestrel and estradiol release fluxes increased as the CL/LA ratio in the copolymer was increased (Ye and Chien, 1996b).

Silica xerogel had a minor effect on the release rate of toremifene citrate. Apparently, toremifene citrate had already been partly released from the surface of silica xerogel during blending with the copolymer, and thus the effect of the silica xerogel on the release rate of the drug is not clear. However, at the beginning, the toremifene citrate release was enhanced by the presence of silica xerogel from copolymers PLA–CL20, PLA–CL40 and PLA–CL60. Hydrophilic silica xerogel may improve the penetration of water into the composites, which in turn increases the matrix degradation and thus the liberation of the drug. Silica xerogel seemed to delay the beginning of the burst phase of toremifene citrate from the PLA–CL20 matrix and the disintegration of all the copolymers. This is probably due to the interaction of the polar groups of the copolymer with silica xerogel particles in the matrix. Good adhesion between silica xerogel particles and the copolymer matrix can also be seen in the scanning electron micrograph.

Increasing the initial drug loading increased the fraction of toremifene citrate released from the matrix. The release rate was found to be directly proportional to the toremifene citrate load. Drug release followed the release kinetics of a freely soluble drug from the matrix and, hence, it is a diffusion controlled process (Lapidus and Lordi, 1968; Lordi, 1986). The deviations from linearity were observed after 70% of the drug had been released. This may be due to the large amount of toremifene citrate used enhancing the degradation of the matrix, and thus leading to an increased release rate.

To conclude, the monomer ratio in the copolymers had a significant effect on drug and silica release. Copolymers containing large amounts of D,L-lactide (PLA–CL20 and PLA–CL40 copolymers) are not suitable for the delivery of

toremifene citrate because of the burst effect. On the other hand, the PLA–CL80 copolymer which releases the active agent steadily, degrades slowly, and the mass of the copolymer was still 70% when all the drug had been depleted. The drug could be incorporated in the silica xerogel during the sol–gel process instead of the adsorption method used in this study, which might have an effect on the release properties of the composites.

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