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Effect of the molecular weight of poly(ε-caprolactone-co-DL-lactide) on toremifene citrate release from copolymer/silica xerogel composites

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Abstract

The purpose of this study was to develop a biodegradable polymeric carrier system for toremifene citrate based on ε-caprolactone/DL-lactide copolymers and silica xerogel. The effect of the molecular weight of poly(ε-caprolactone-co-DL-lactide) affecting the release rate of toremifene citrate from copolymer/silica xerogel composites was evaluated by in vitro dissolution study. Lower and higher molecular weight copolymers (LMW 60 000 g/mol and HMW 300 000 g/mol) were used in the devices. Drug release was compared from the (copolymer/drug) matrix device and the (copolymer/drug impregnated silica xerogel) composite device. Hydrolysis of the copolymer devices was evaluated by water absorption, weight loss and change of molecular weight by size exclusion measurements (SEC). Controlled release of toremifene citrate was obtained from both matrix and composite devices and the release rate was most affected by the initial molecular weight of the copolymer. Throughout the study better results were obtained with LMW devices, since drug release was steady for nearly 1 year and no changes in the release rate were observed. The drug release was diffusion controlled from both LMW matrix and composite devices. Incorporation of toremifene citrate into the silica xerogel was found to enhance the drug release rate. The copolymer matrices degraded by random hydrolytic chain scission and, unexpectedly, HMW P(CL/LA) degraded faster than LMW P(CL/LA). The release of toremifene citrate from HMW devices was not complete before the second stage of polymer degradation began.

Keywords: Biodegradable polymers; Drug release; Silica xerogel; Toremifene citrate; Poly(ε-caprolactone-co-DL lactide)

1. Introduction

The performance of medical devices constructed of polymers is crucially dependent upon the stability of the material (Williams and Zhong,

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1994). Generally, polymers are chosen for devices based on their apparent stability, while in some cases intentional degradation is an advantage. Most biodegradable polymers break down by hydrolysis and thus the advantages in using hydrolysable polymers are their relatively shorter degradation period and ease of control. On the other hand, the mechanism of drug release at a molecular level is controlled by the interactions between drug molecules and polymer chains as well as the dynamic motions of these two components. Desired drug release profiles can be obtained through the use of different types of polymers, comonomer ratios in copolymers, biocompatible excipients, geometries, and sizes, which in turn greatly influence the degradation rates of the polymers (Schwendemann et al., 1997). The drug release profile can also be influenced by varying the initial molecular weight of the polymer device, which in turn will affect the degradation rate (Wada et al., 1991).

The high permeability of polycaprolactone and its copolymers coupled with a controllable induction period prior to polymer weight loss enables the development of delivery devices that are based on diffusion-controlled delivery of the drug (Pitt et al., 1979). Poly(DL-lactide), polycaprolactone and their copolymers degrade with random chain scission by ester hydrolysis in a process autocatalyzed by the generation of carboxylic acid end groups. The mechanical properties of copolymers persist for a relatively long time during hydrolysis, making it possible to design long term controlled release devices (Karjalainen et al., 1996). The subsequent biodegradation of the polymer after drug exhaustion serves the purpose of eliminating the need to recover the spent device (Pitt et al., 1979).

The possibility of using sol-gel processed silica xerogels for controlled drug delivery was introduced in 1983 (Unger et al., 1983). The sol-gel method enables the incorporation of heat-sensitive bioactive agents during room temperature processing. Sol-gel processed silica xerogels are biocompatible and non-toxic materials (Radin et al., 1998 Kortesuo et al., 1999). The degradation of silica xerogel occurs through hydrolysis of the siloxane bonds. Silica diffuses from the implant into the local tissue around the implant, enters the bloodstream or lymph system and is excreted in the urine through the kidneys or is actively phagocytised by the macrophages (Lai et al., 1998). The release period of drug from silica xerogel implants is, however, usually quite short compared to the release from biodegradable polymers, such as aliphatic polyesters. The release period of toremifene citrate was a few days in vitro and 6 weeks in vivo from silica xerogel devices (Kortesuo et al., 1999). Combining silica xerogel with P(CL/DL-LA) copolymer enables longer release periods (Ahola et al., 1999).

The aim is to develop a biodegradable polymeric carrier system for toremifene citrate based on ε-caprolactone/DL-lactide copolymers and silica xerogel. Toremifene (Fareston®) is an antiestrogenic compound, which is used after surgery in the treatment of hormone-dependent breast cancer. At present the treatment is taken lifelong as daily peroral medication. In the previous study, the toremifene citrate release rate was found to be directly proportional to the toremifene citrate load in the poly(?-caprolactone-co-DL-lactide) matrix device and copolymer composition with 80 wt.% caprolactone showed the most uniform release of toremifene citrate in vitro. The purpose of this study was to investigate how the release rate of toremifene citrate from poly(?-caprolactone-co-DL-lactide) composites with the same comonomer ratio can be further modified by varying the molecular weight of the copolymer. Drug release was compared from the (copolymer/drug) matrix device and the (copolymer/drug impregnated silica xerogel) composite device. The devices were of an appropriate size for subcutaneous or intramuscular implantation i.e. discs. The effect of the silica xerogel and the effect of molecular weight on the hydrolysis behaviour of copolymer composites were evaluated by determination of weight loss, water absorption, molecular weight, polydispersity and thermal properties.

2. Materials and methods

2.1. Preparation of silica xerogel

Silica xerogel was prepared by the hydrolysis and

polycondensation of tetraethoxysilane (TEOS) with polyethylene glycol and water. The solution with a mole ratio of TEOS:PEG4600:H_2O:CH_3COOH = 1.0:0.0012:14.2:0.5 was kept at 40°C in an oven for hydrolysis, polycondensation and ageing for 18 h. The model drug, toremifene citrate was dissolved after 1 hour's hydrolysis at a concentration of 40 mg/ml. Silica gel was crushed into particles before drying at 40°C to constant weight. The concentration of toremifene citrate in dried silica xerogel granules was 21.9 wt.%.

2.2. Synthesis of poly(ε-caprolactone-co-DL-lactide) and production of composites

Materials: ε-caprolactone (Fluka) was dried over molecular sieves. DL-lactide (Purac) was recrystallized twice from dried toluene. Purified lactide was dried at 40°C for 24 h under reduced pressure before polymerisation. Sn(II) octoate (Sigma) and glycerol (Rhône-Poulenc) were used as received.

Polymerisation procedure: The ring-opening polymerisation of ε-caprolactone and DL-lactide was carried out in bulk under an argon atmosphere with Sn(II) octoate as catalyst (0.1 mmol/mol monomer). Glycerol was used as an initiator; 0.5 mmol/mol monomer in high molecular weight (HMW) and 5.0 mmol/mol monomer in lower molecular weight (LMW) copolymer. Monomer ratio (w/w) in the feed was 80/20 (CL/ DL-LA). Typically a batch of 300 g of monomers, initiator and catalyst in a glass polymerisation flask with magnetic stirrer was immersed in an oil bath. The polymerisation time was 54 h at 120°C (HMW) and 24 h at 140°C (LMW). The copolymers were stored in dry conditions and used without further purification.

Blending: P(?-CL/DL-LA) copolymers were blended with silica xerogel containing toremifene citrate or pure toremifene citrate in a Brabender W50EH Batch mixer (100°C, 50 r/min, 5 min). Unloaded polymer samples also underwent the batch mixing.

Moulding: Two different specimen shapes for dissolution tests were prepared by compression moulding (Fontijne TP 400). Different compositions and specimen geometry used are listed in Table 1.

2.3. Determination of physical and chemical characteristics

2.3.1. 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 4 linear PL gel columns: 10^4, 10^5, 10^3 and 100 Å connected in series). Chloroform was used as solvent and eluent. The flow rate was 1 ml/min. Monodisperse polystyrene standards were used for primary calibration.

2.3.2. Thermal analysis

Glass transition and melting temperatures were measured by DSC (PL). Nitrogen was used as a sweeping gas. Samples were heated twice (at a rate of 10°C/min) to ensure that their thermal histories were similar. The measured temperature range was −80–85°C.

2.3.3. NMR measurements

The structures of copolymers were determined with a Varian Unity 400 NMR spectrometer working at 100.577 MHz for ^{13}C. Sample concentration, in 5 mm tubes, was 10 wt.% in chloroform-d. Tetramethylsilane was used as an internal standard.

Table 1
Composition and geometry of the devices

Composition	Device geometry
HMW P(CL/LA)	Tablet (ϕ10.0mm, $h = 2.0$ mm)
HMW P(CL/LA)+2 wt.% toremifene citrate	Tablet and thin plate ($10.0 \times 10.0 \times 0.6$ mm^3)
HMW P(CL/LA)+8.7 wt.% Si-gel, including toremifene citrate	Tablet
LMW P(CL/LA)	Tablet
LMW P(CL/LA)+2 wt.% toremifene citrate	Tablet
LMW P(CL/LA)+8.7 wt.% Si-gel, including toremifene citrate	Tablet

Table 2
Characteristics of P(CL/ DL-LA) copolymers

Polymer code	CL in feed (wt.%)	SEC			DSC		^{13}C-NMR	
		$\overline{M}w$ (g/mol)	$\overline{M}n$ (g/mol)	MWD	Tg (°C)	Tm (°C)	ε-CL/ DL-LA (wt.%)	Length of CL sequence
HMW P(CL/LA)	80	338 000	196 000	1.7	−53	46	78.3/21.7	9.2
LMW P(CL/LA)	80	63 000	44 000	1.4	−54	43	82.5/17.5	7.0

2.4. Water absorption and weight loss

Water absorption was calculated as the difference between the weight of the wet copolymer after hydrolysis and the weight of the dried polymer, divided by the weight of the dried copolymer. Similarly, weight losses were calculated as the difference between the initial weight of the copolymer and the weight of the dried copolymer, divided by the initial weight of the copolymer.

2.5. Dissolution test

Two series of in vitro dissolution tests were performed. Simulated body fluid (SBF, pH 7.4) containing 0.5% (m/v) sodiumdodecylsulphate (SDS) was used as dissolution medium (Ahola et al., 1999). For the hydrolysis test to study polymer degradation, two parallel samples for each hydrolysis time point were immersed in 25 ml of dissolution medium in test tubes at 34°C. At predetermined time points, test specimens were removed from test tubes, weighed, vacuum dried in a vacuum chamber and weighed again for further analysis. For dissolution profiles of silica and toremifene citrate, three parallel test specimens were placed in test tubes in 25 ml of dissolution medium at 34°C in a planar shaker (50 rpm). The buffer solution was changed every other week in both dissolution series. The amount of drug and silica in the dissolution samples was determined as before (Ahola et al., 1999).

3. Results and discussion

3.1. Physical and chemical characteristics

Copolymers were prepared by ring-opening polymerisation initiated by polyfunctional hydroxy initiator. The data in Table 2 show molecular weights, compositions, glass transition temperatures and melting temperatures of the copolymers used as matrices for drug delivery devices. The weight average molecular weights of copolymers were 338 000 g/mol for HMW P(CL/LA) and 63 000 g/mol for LMW P(CL/LA). The level of the molecular weight was adjusted by the amount of glycerol initiator used. Average sequence lengths and copolymer compositions were determined from ^{13}C NMR spectrographs as before, according to Kasperczyk and Bero, (1993).

The copolymers showed a clear melting endotherm due to the crystallization of caproyl sequences. The melting temperature of pure semicrystalline PCL is in the range 59–61°C, which can be modified by copolymerisation with DL-lactide. Copolymerisation with 20 wt.% DL-lactide lowers the melting temperature without affecting the good permeability properties of pure PCL. Also, the more hydrophilic lactide block promotes the degradation of copolymer compared with PCL homopolymer. Melting enthalpies of the copolymers were 34 J/g (HMW P(CL/LA)) and 36 J/g (LMW P(CL/LA)). The higher the polymerisation temperature the more ester interchange processes occur, resulting in a more ran-

dom structure, i.e. shorter sequence lengths (Pitt, 1990). The average sequence length of the caproyl unit in HMW copolymer was longer than in LMW copolymer due to the lower polymerisation temperature (Hiljanen-Vainio et al., 1997).

3.2. Hydrolysis of the composites

3.2.1. Molecular weights as a function of hydrolysis time

The weight average molecular weight of HMW P(CL/LA) samples containing drug or drug impregnated silica dropped 35% in just 14 days of hydrolysis. On the other hand, the weight average molecular weight of LMW P(CL/LA) hardly changed at all over the same time. The changes in the weight average molecular weights of the samples as a function of hydrolysis time are presented in Fig. 1. In general, the drug or silica impregnated samples degraded slightly faster than the polymer samples. This difference in degradation rate was more noticeable in HMW P(CL/LA) samples. Polydispersity of the samples changed hardly at all during hydrolysis (Table 3). No small fragments were observed in the SEC curves, even at advanced stages in the hydrolysis.

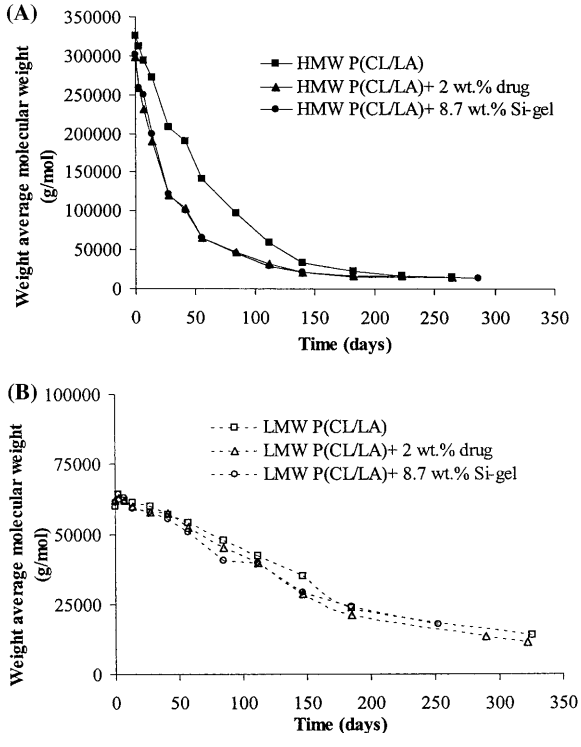

Fig. 1. Molecular weights of the devices as a function of hydrolysis time. (a) HMW P(CL/LA); (b) LMW P(CL/LA).

3.2.2. Degradation kinetics of copolyesters

The first stage of the degradation involves a decrease in molecular weight produced by non-enzymatic, random hydrolytic scission of ester cleavage, and its duration is determined by the initial molecular weight of the polymer and its chemical structure (Pitt et al., 1981; Malin et al., 1996). The semilog plot of the in vitro rate of hydrolytic chain scission for the polymer samples is shown in Fig. 2. The rate of chain scission for the HMW P(CL/LA) is higher than the rate of chain scission that can be observed in LMW P(CL/LA). The LMW copolymer structure may be better protected against the hydrolysis since the shorter chains can better organise and form crystallites than the longer chains of HMW. Some hydrogen bonds may also be formed, since initiation by polyfunctional glycerol results in a hydroxyl end-blocked branched polymer (Pitt, 1990). The lactide content in HMW P(CL/LA) is slightly higher than in LMW P(CL/LA) which partly accounts for the faster hydrolysis rate. LMW P(CL/LA) composites containing drug or drug incorporated in silica xerogel exhibited similar degradation rates compared with the copolymer sample.

The second stage of degradation is characterised by weight loss, loss of mechanical strength and a change in the rate of chain scission. The change in the rate of chain scission was observable for HMW P(CL/LA) after 182 days of hydrolysis (Fig. 2). At that time the weight loss was 10.0 wt.%. No change in the rate of chain scission was observed in the studied hydrolysis time for the LMW P(CL/LA), although the weight loss at 326 days of hydrolysis was 25.0 wt.%

The kinetics of the degradation were investigated by applying the approach of Pitt and Gu (1987). The rate of chain scission of an aliphatic polyester autocatalyzed by the generated carboxylic acid end groups is given by Eq. (1).

$$d[COOH]/dt = k_1[COOH][ester][H_2O] \quad (1)$$

Table 3
Changes in the polydispersity of HMW and LMW P(CL/LA) samples as a function of hydrolysis time at 34°C

Time (days)	Polydispersity HMW P(CL/LA)			Polydispersity LMW P(CL/LA)		
HMW/ LMW	Polymer	2 wt.% drug	8.7 wt.% Si-gel+drug	Polymer	2 wt.% drug	8.7 wt.% Si-gel+drug
0	1.8	1.9	1.8	1.5	1.4	1.4
3	1.7	2.0	1.9	1.4	1.5	1.5
7	1.9	1.9	1.8	1.5	1.6	1.4
14	2.1	2.0	1.9	1.4	1.4	1.5
28	1.9	1.9	2.1	1.4	1.4	1.5
42	1.9	2.1	2.1	1.5	1.5	1.5
56/57	2.0	1.9	2.1	1.7	1.5	1.5
84/85	2.0	2.1	2.4	1.6	1.6	1.6
112	1.8	2.3	2.3	1.7	1.8	1.8
140/147	2.1	2.2	2.2	1.9	1.8	1.7
182/185	2.2	2.7	1.8	1.7	1.9	1.8
223	2.1	1.8	–	–	–	–
265/253	1.8	1.8	1.8	–	–	1.8
290	–	–	–	–	1.7	–
326	–	–	–	1.7	1.7	1.7

The process generates carboxylic acid end groups that further catalyse the hydrolysis (Pitt and Gu, 1987; Löfgren and Albertson, 1994). The equation assumes that the carboxylic acid group is not ionised in the hydrophobic polymer bulk. For a small number of chain scissions, the ester concentration as well as the water concentration can be assumed constant and thus Eq. (1) simplifies after integration into Eq. (2).

$$[\mathrm{COOH}]/[\mathrm{COOH}]_0 = \exp(k_2 t) \quad (2)$$

This expression is valid until the loss of oligomers sufficiently reduces the carboxylic end group concentration of the polymer bulk. Provided $[\mathrm{COOH}] = \overline{M}_n^{-1}$, Eq. (2) can be rewritten and the rate constant k_2 for the autocatalyzed hydrolysis system calculated according to Eq. (3).

$$\mathrm{In}(\bar{M}_n) = (\bar{M}_n^0) - k_2 t \quad (3)$$

The autocatalyzed mechanism showed a good fit with the data obtained in the experiments. By plotting the experimental number average molecular weight ($\overline{M}_n$, initial molecular weight is designated by superscript 0) data before the onset of the major weight loss, the degradation rate constants can be determined. For drug and silica containing samples, the onset of increased weight loss occurred earlier than for the polymer samples and the rate constants were also slightly higher for those samples. The kinetic data is presented in Table 4. Pitt et al. (1981) determined an in vivo degradation rate constant of 1.54×10^{-2} per day for P(CL/DLLA) containing 13.5 wt.% DL-lactide which compares well with the constants obtained for HMW P(CL/LA) in vitro.

3.2.3. Water absorption and weight loss as a function of hydrolysis time

The profile in water absorption of HMW P(CL/

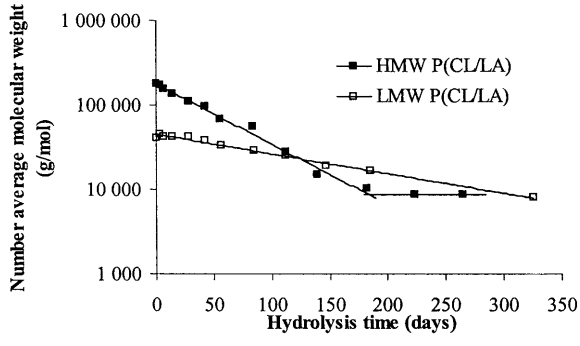

Fig. 2. Semilog plot of the in vitro rate of hydrolytic chain scission of the copolymers.

Table 4
Kinetic data for the hydrolysis of P(CL/LA) copolymers at 34°C

Polymer code	Slope $k_2^*10^2$ (days^{-1})	Correlation factor r
LMW P(CL/LA)	0.55	0.98
LMW P(CL/LA)+2 wt.% toremifene	0.60	0.97
LMW P(CL/LA)+8.7 wt.% Si-gel inc. toremifene	0.57	0.98
HMW P(CL/LA)	1.61	0.99
HMW P(CL/LA)+2 wt.% toremifene	1.99	0.98
HMW P(CL/LA)+8.7 wt.% Si-gel inc. toremifene	2.09	0.97

LA) devices showed a lag time during which the water content reached 7 wt.% (Fig. 3). This was followed by an increase in the water uptake process after 112 days for copolymers containing silica xerogel, 140 days for copolymers containing toremifene citrate, and 182 days for copolymers. Water content increased from 7 wt.% to about 40 wt.% for HMW copolymers containing drug impregnated silica or toremifene citrate and to about 34 wt.% for copolymer in 265 days of hydrolysis. Addition of silica xerogel or drug made the period of slow water uptake shorter compared to the copolymer. Water absorption in LMW P(CL/LA) devices was moderate and slower than in HMW P(CL/LA) devices (At Fig. 3). At the end of the study, water content was 20 wt.% for LMW co-

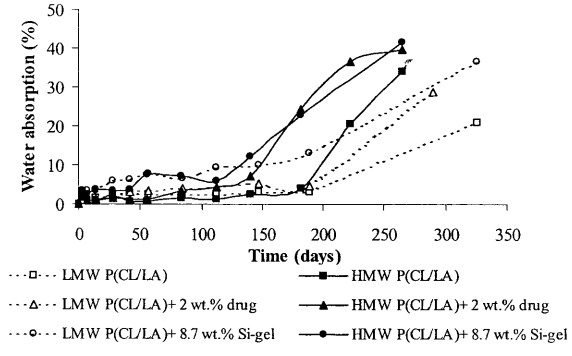

Fig. 3. Water absorption during hydrolysis.

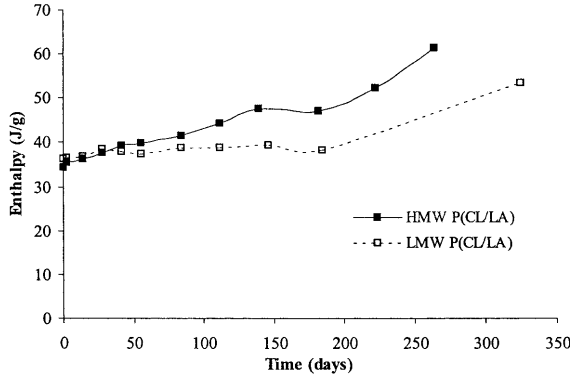

Fig. 4. Melting enthalpies of the HMW and LMW copolymers as a function of hydrolysis time.

polymer (326 days), 29 wt.% for copolymer containing toremifene citrate (290 days) and 37 wt.% for copolymer containing drug impregnated silica (326 days). The presence of silica xerogel granules or drug increased the quantity of water taken up by the copolymers. Also, the molecular weight of the copolymer affected the water uptake profile. HMW P(CL/LA) samples absorbed more water, the increase in rate coinciding with the increasing chain scission rate.

Weight losses for polymer samples HMW P(CL/LA) and LMW P(CL/LA) were 30 wt.% (265 days) and 25 wt.% (326 days) respectively at the end of the hydrolysis time. Measured weight losses for drug devices were comparable to those for copolymers when corrected for released toremifene citrate and silica.

3.2.4. Thermal properties as a function of hydrolysis time

Glass transition temperatures of all HMW P(CL/LA) samples lowered somewhat from the initial level and finally no transition temperatures could be determined after 224 days of hydrolysis. Melting temperatures of HMW P(CL/LA) samples did not change during hydrolysis, apart from a double melting peak appearing and persisting after 84 days. A double melting peak indicates some realignment of the macromolecular chains. For LMW P(CL/LA) samples, a double melting peak appeared at 147 days but the glass transition temperatures did not change from the initial level.

The crystallinity of the HMW P(CL/LA) samples increased steadily during the hydrolysis, as shown in Fig. 4. This can be partly explained by a weight loss from the amorphous phase, and partly by the ability of the chain fragments in the hydrolysed amorphous region to realign into crystallites (Malin et al., 1996). The crystallinity of the LMW P(CL/LA) samples did not change noticeably until the weight average molecular weight of the samples had dropped under 20 000 g/mol in about 200 days of hydrolysis.

3.3. Drug release studies

Toremifene citrate release was compared from the (copolymer/drug) matrix device and the (copolymer/drug impregnated silica xerogel) composite device. Matrix devices contained 2 wt.% toremifene citrate and composite devices contained 8.7 wt.% silica xerogel, corresponding to 2 wt.% drug content (Table 1).

Toremifene citrate release was clearly faster in the beginning from both matrix and composite devices made with LMW P(CL/LA) than from devices with HMW P(CL/LA), as shown in Fig. 5a and Fig. 5b. Similar findings regarding the role of the molecular weight of P(CL/LA) copolymer controlling the release rate have been reported by (Wada et al., 1991). The toremifene citrate released at a constant rate from the LMW P(CL/LA)/drug matrix device according to square root of time kinetics ($r = 0.995$, $b = 4.54\%$ per day$^{1/2}$). The release rate was clearly enhanced by incorporation of drug into silica xerogel ($r = 0.967$, $b = 8.95\%$ per day$^{1/2}$) (Fig. 5a). The release rates were determined from the slopes of the curves, using only data points obtained with less than 70% of the loaded toremifene citrate released.

Toremifene citrate released from the HMW P(CL/LA)/drug tablet device according to square root of time kinetics before the abrupt change in the rate of release ($r = 0.948$, $b = 3.5\%$ per day$^{1/2}$) (Fig. 5b). The incorporation of drug into silica xerogel moderated the change of release rate, but did not affect the release before the abrupt change in the rate of release ($r = 0.968$, $b = 3.92\%$ per day$^{1/2}$). No effect on drug release was observed in the previous study when the drug was adsorbed

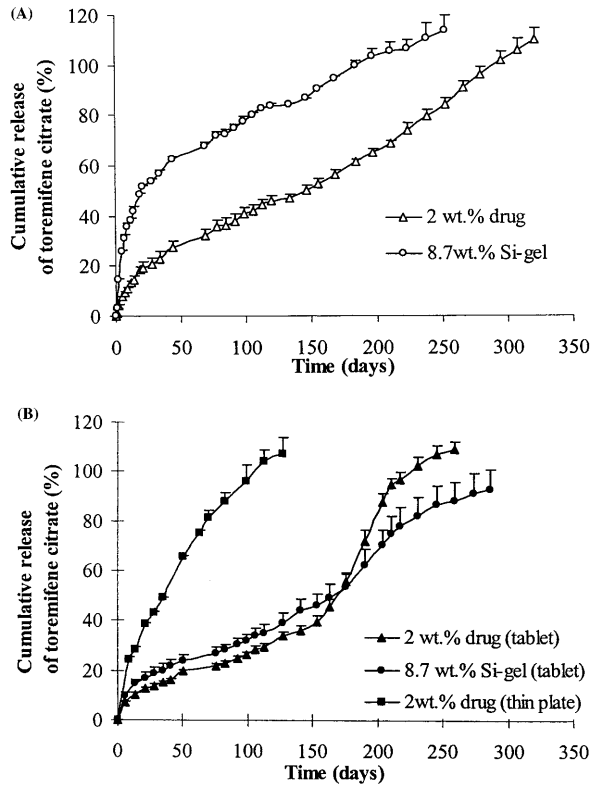

Fig. 5. Release of toremifene citrate from the (copolymer/drug) matrix device and the (copolymer/drug impregnated silica xerogel) composite device. (a) LMW P(CL/LA); (b) HMW P(CL/LA).

on the silica xerogel (Ahola et al., 1999). When adsorbed, toremifene citrate was thought to have been partly released during processing but in this

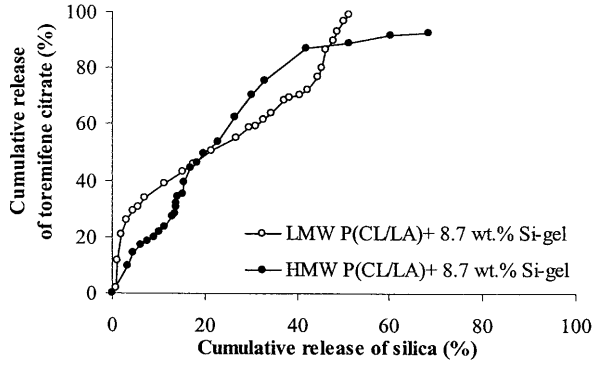

Fig. 6. Release of toremifene citrate and silica xerogel from the (copolymer/drug impregnated silica xerogel) composite device.

study silica xerogel remained as a carrier for the drug. However, the dissolution rate of silica was slower than the drug release rate (Fig. 6). The increase in the release rate of drug was linked to a significant change in the molecular weight, which had decreased below 50 000 g/mol. This is a clear indicator that the drug release is no longer diffusion controlled and the matrix degradation precedes the drug diffusion. The release rate can be modified by changing the device geometry (Wada et al., 1991; den Dunnen et al., 1997; Lemmouchi and Schacht, 1997) and thus a good release profile and release duration of about 3 months was obtained using a thin plate HMW P(CL/LA) device (Fig. 5b).

4. Conclusion

The toremifene citrate release period from poly(ε-caprolactone/ DL-lactide) can be adjusted from 3 months to 1 year by varying the initial molecular weight of the copolymer, by incorporating toremifene citrate in silica xerogel in the composite device or by changing the device geometry. The release rate of toremifene citrate was steady for almost one year and no abrupt changes were observed in the release rate from LMW P(CL/LA) matrix and composite devices.

The presence of silica xerogel moderated the release rate of toremifene citrate as the copolymer matrix degraded and release was no longer diffusion controlled from HMW P(CL/LA) devices. By changing the device thickness of the HMW matrix device, a controlled release rate of toremifene citrate over 3 months was obtained.

Based on these results it is feasible to formulate a device for long term treatment of breast cancer after surgery.

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