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Development of biodegradable polymeric paste formulations for taxol: an in vitro and in vivo study

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Abstract

Biodegradable polymeric paste formulations ('surgical pastes') for local delivery of taxol were developed and characterized. Taxol was mixed into melted poly(D,L-lactide)-*block*-poly(ethylene glycol)-*block*-poly(D,L-lactide) (PDLLA-PEG-PDLLA) copolymers and blends of low molecular weight poly(D,L-lactic acid) and poly-ϵ-caprolactone (PDLLA:PCL) to obtain the paste formulations. The release of taxol into PBS albumin buffer was measured by HPLC. The polymers and pastes were characterized by gel permeation chromatography (GPC), differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR) and scanning electron microscopy (SEM). Taxol was released in a sustained manner from the PDLLA-PEG-PDLLA paste over a period of 2 months by diffusion and polymer erosion. The release from the blend was mainly erosion controlled and consisted of a burst followed by a period of slow release. Efficacy of the pastes in inhibiting tumor growth in mice was evaluated. Molten, taxol loaded paste formulations were placed at subcutaneous tumor sites in mice (pastes harden at 37°C). After 16 days, the reduction in tumor weight was measured. Both the taxol loaded copolymer and 90:10 PDLLA:PCL blend formulations significantly inhibited tumor growth in mice. The pastes with faster in vitro release rates resulted in greater efficacy in inhibiting tumor growth. The results showed that biodegradable polymeric surgical pastes are promising formulations for the local delivery of taxol to inhibit tumor growth.

Keywords: Biodegradable polymers; Taxol; Paste; In vitro release; Tumor inhibition

1. Introduction

Taxol has shown efficacy in clinical trials against advanced breast, ovarian and non-small cell lung cancer (Spencer and Faulds, 1994). It has also been shown to be a potent inhibitor of angiogenesis (Onetto et al., 1993).

Tumor growth and metastasis are dependent upon tumor neovascularization which is an angiogenic process involving basal lamina disintegration, migration of endothelial cells in the direction

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of the angiogenic signal and endothelial cell proliferation (Rooney et al., 1995). Taxol inhibits many of the cellular events in angiogenesis, including cell proliferation, migration and collagenase secretion (Stearns and Wang, 1992). The combination of cytotoxic and anti-angiogenic properties should result in a more effective agent to treat cancer.

We are developing drug delivery systems for taxol, termed 'surgical pastes', for application to a tumor resection site, where a controlled release of drug may potentially eliminate remaining tumor cells and prevent local recurrence of disease. These surgical pastes are based on polymer blends which have a low melting point and/or a 'pasty' consistency and which may be delivered via a syringe following gentle warming (Winternitz et al., 1996).

An injectable polymeric paste formulation containing lidocaine has been investigated for its ability to prolong anaesthesia in rabbits following epidural injection of the lidocaine loaded glycolic acid/caprolactone copolymer paste (Sato et al., 1995). Brem, Langer and co-workers have developed biodegradable polyanhydride polymeric discs loaded with carmustine or taxol for implantation into the cavity of resected brain tumors (Wu et al., 1994; Walter et al., 1994). Local interstitial delivery of taxol in a rat model of malignant glioma resulted in high taxol concentrations in the brain and increased median survival time (Walter et al., 1994). Kubo et al. (1994) treated patients with malignant gliomas with drug-polymer implants inserted into the remaining tumor wall at the resection site or implanted into the tumor using a CT guided stereotactic method and showed marked reduction in tumor mass. Kanekal et al. (1995a,b) formulated the anti-cancer drugs 5-FU and cisplatin into a pasty collagen gel and showed marked increases in retention of the drugs at tumor sites after intratumoral delivery of the paste in mice.

The objectives of this work were to develop biodegradable, taxol-loaded surgical paste formulations of poly(D,L-lactide)-*block*-polyethylene glycol-*block*-poly(D,L-lactide) (PDLLA-PEG-PDLLA) and blends of low molecular weight poly(D,L-lactic acid) (PDLLA) with poly-ϵ-caprolactone (PCL). The formulations were characterized and the anti-tumor efficacy of the formulations in mice was evaluated.

2. Materials and methods

2.1. Materials

D,L-lactide was purchased from Aldrich. Polyethylene glycol (PEG) with molecular weight 8000, stannous octoate and D,L-lactic acid were obtained from Sigma. Poly-ϵ-caprolactone (PCL) with molecular weight 20 000 was obtained from Birmingham Polymers (Birmingham, AL). Taxol was purchased from Hauser Chemicals (Boulder, CO). Polystyrene standards with narrow molecular weight distributions were purchased from Polysciences (Warrington, PA). Acetonitrile and methylene chloride were HPLC grade (Fisher Scientific).

2.2. Synthesis of PDLLA-PEG-PDLLA and low molecular weight PDLLA

The triblock copolymer of PDLLA-PEG-PDLLA was synthesized by a ring opening polymerization (Cohn and Younes, 1988; Deng et al., 1990; Zhu et al., 1990). Monomers of D,L-lactide and PEG in different ratios were mixed and 0.5 wt% stannous octoate was added. The polymerization was carried out at 150°C for 3.5 h. Low molecular weight PDLLA was synthesized through polycondensation of D,L-lactic acid (Fukuzaki et al., 1991). The reaction was performed in a glass flask under the conditions of gentle nitrogen purge, mechanical stirring, and heating at 180°C for 1.5 h. The PDLLA molecular weight was about 800 measured by titrating the carboxylic acid end groups.

2.3. Manufacture of paste formulations

Taxol at loadings of 20 or 30% was thoroughly mixed into either the PDLLA-PEG-PDLLA copolymers or blends of PDLLA:PCL 90:10, 80:20 and 70:30 melted at about 60°C. The taxol loaded pastes were weighed into 1 ml syringes and stored at 4°C.

2.4. Characterization of PDLLA-PEG-PDLLA and the paste blends

The molecular weights and distributions of the PDLLA-PEG-PDLLA copolymers were determined at ambient temperature by GPC using a Shimadzu LC-10AD HPLC pump and a Shimadzu RID-6A refractive index detector (Kyoto, Japan) coupled to a 10^4 Å Hewlett Packard Plgel column. The mobile phase was chloroform with a flow rate of 1 ml/min. The injection volume of the sample was 20 μl at a polymer concentration of 0.2% (w/v). The molecular weights of the polymers were determined relative to polystyrene standards. The intrinsic viscosity of PDLLA-PEG-PDLLA in $CHCl_3$ at 25°C was measured with a Cannon-Fenske viscometer.

Thermal analysis of the copolymers was carried out by DSC using a TA Instruments 2000 controller and DuPont 910S DSC (Newcastle, Delaware). The heating rate was 10°C/min and the copolymer and taxol/copolymer matrix samples were weighed (3–5 mg) into crimped open aluminum sample pans.

^{1}H NMR was used to determine the chemical composition of the polymer. ^{1}H NMR spectra of taxol loaded PDLLA-PEG-PDLLA were obtained in $CDCl_3$ using an NMR instrument (Bruker, AC-200E) at 200 MHz. The concentration of the polymer was 1–2%.

The morphology of the taxol/PDLLA-PEG-PDLLA paste was investigated using SEM (Hitachi F-2300). The sample was coated with 60% Au and 40% Pd (thickness 10–15 nm) using a Hummer instrument (Technics, USA).

2.5. In vitro release of taxol

A small pellet of 20% taxol loaded PDLLA:PCL paste (about 2 mg) or a cylinder (made by extrusion of molten paste through a syringe without needle) of 20% taxol loaded PDLLA-PEG-PDLLA paste were put into capped 14 ml glass tubes containing 10 ml phosphate buffered saline (PBS, pH 7.4) with 0.4 g/l albumin. The tube was incubated at 37°C with gentle rotational mixing. The supernatant was withdrawn periodically for taxol analysis and replaced with fresh PBS/albumin buffer. The supernatant (10 ml) was extracted with 1 ml methylene chloride. The water phase was decanted and the methylene chloride phase was dried under a stream of nitrogen at 60°C. The dried residue was reconstituted in a 40:60 water:acetonitrile mixture and centrifuged at 10 000 g for about 1 min. The amount of the taxol in the supernatant was then analyzed by HPLC. HPLC analysis was performed using a 110A pump and C-8 ultrasphere column (Beckman), and a SPD-6A uv detector set at 232 nm, a SIL-9A autoinjector and a C-R3A integrator (Shimadzu). The injection volume was 20 μl and the flow rate was 1 ml/min. The mobile phase was 58% acetonitrile, 5% methanol and 37% distilled water.

2.6. Animal studies

Ten week old DBA/2j female mice were acclimatized for 3–4 days after arrival. Each mouse was injected subcutaneously in the posterior lateral flank with 10×10^5 MDAY-D2 tumor cells in 100 μl of PBS on day 1. On day 6, the mice were randomly divided into two groups. Group 1 were implanted with paste alone (control), and group 2 were implanted with paste loaded with taxol. A subcutaneous pocket near the tumor was surgically formed under anaesthesia and approximately 100 mg of molten paste (warmed to 50–60°C) was placed in the pocket and the wound closed. On day 16, the mice were sacrificed, and the tumors were removed and weighed. Day 16 was selected to allow the tumor growing into a easily measurable size within the ethical limit.

3. Results and discussion

3.1. Molecular weight and thermal properties of PDLLA-PEG-PDLLA

The molecular weight and molecular weight distribution of PDLLA-PEG-PDLLA, relative to polystyrene standards, were measured by GPC (Table 1). The intrinsic viscosity of the copolymer in $CHCl_3$ at 25°C was determined using a Canon-Fenske viscometer (Table 1). The molecular

Table 1
Melting temperature, enthalpy, molecular weight (M_n), polydispersity (M_w/M_n), and intrinsic viscosity ([η]) of PDLLA-PEG-PDLLA

PDLLA-PEG-PDLLA PEG content	Melting temp.[a], °C	ΔH[a], J/g	M_n[b], $\times 10^{-4}$	M_w/M_n[b]	[η][c], dl/g
100%	61.8	184.8	0.8[d]	—	—
70%	50.2	72.2	2.1	1.2	0.27
40%	46.3	42.8	4.5	3.5	0.29
30%	None	None	5.9	3.0	1.0
20%	None	None	5.1	3.0	1.45
10%	None	None	11	2.4	1.5
Taxol	212	59.3	—	—	—
20% Taxol loaded copolymer (30% PEG)	212.1	5.6	—	—	—

[a]Measured by DSC.
[b]Measured by GPC, relative to polystyrene standard.
[c]In $CHCl_3$ at 25°C.
[d]Data supplied by manufacturer.

weight and intrinsic viscosity decreased with increasing PEG content. Since hydroxyl end groups of PEG acted as initiation sites in the polymerization of D,L-lactide, a high PEG content provided a high initiator concentration and therefore resulted in low polymer molecular weight (Li and Kissel, 1993). The polydispersities of PDLLA-PEG-PDLLA with PEG contents of 10–40% were from 2.4 to 3.5. However, the copolymer with 70% PEG had a narrow molecular weight distribution with a polydispersity of 1.21. This might be because a high PEG content reduced the chance of side reactions such as transesterfication which results in a wide distribution of polymer molecular weight. Alternatively, a coiled structure of the hydrophobic-hydrophilic block copolymers may result in an artificial low polydispersity value.

DSC scans of pure PEG and PDLLA-PEG-PDLLA copolymers are given in Fig. 1 and Table 1. The PEG and PDLLA-PEG-PDLLA with PEG contents of 70 and 40% showed endothermic peaks with decreasing enthalpy and temperature as the PEG content of the copolymer decreased. The endothermic peaks in the copolymers of 40 and 70% PEG were probably due to the melting of the PEG region, indicating the occurrence of phase separation. While pure PEG had a sharp melting peak, the copolymers of both 70 and 40% PEG showed broad peaks with a distinct shoulder in the case of 70% PEG. The broad melting peaks may have resulted from the interference of PDLLA with the crystallization of PEG. The shoulder in the case of 70% PEG might represent the glass transition of the PDLLA region. No thermal changes occurred in the copolymers with PEG contents of 10, 20 and 30% in a temperature

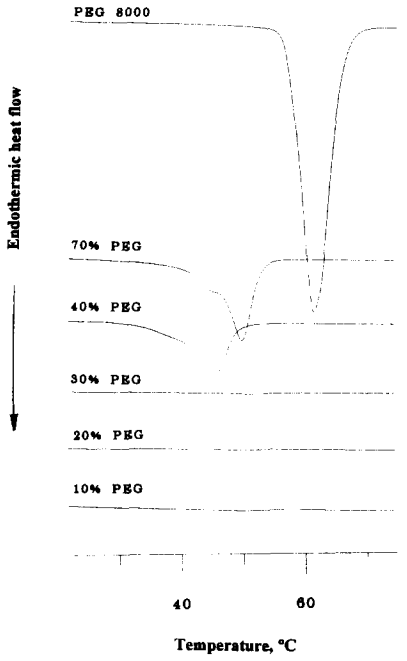

Fig. 1. DSC thermograms of PDLLA-PEG-PDLLA and PEG. The heating rate was 10°C/min. See Table 1 for melting temperatures and enthalpies.

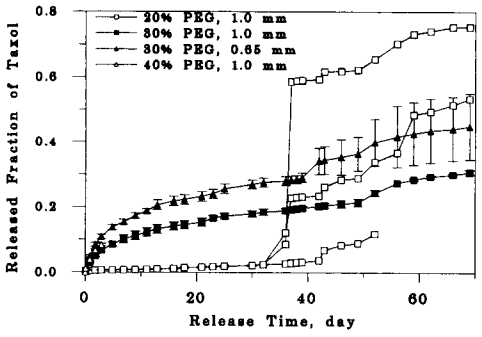

Fig. 2. Cumulative release of taxol from 20% taxol loaded PDLLA-PEG-PDLLA cylinders into PBS albumin buffer at 37°C. The error bars represent the S.D. of 4 samples from the same batch. Cylinders of 40% PEG were discontinued at 4 days due to disintegration.

range of 10–250°C, indicating that no significant crystallization (therefore may be the phase separation) had occurred.

DSC thermograms of PDLLA:PCL (70:30, 80:20, 90:10) blends without taxol or with 20% taxol showed an endothermic peak at about 60°C, resulting from the melting of PCL. Due to the amorphous nature of the PDLLA and its low molecular weight (800), melting and glass transitions of PDLLA were not observed. No thermal changes due to the recrystallization or melting of taxol was observed since taxol may have dissolved in the blends during the heating process (Winternitz et al., 1996).

PDLLA-PEG-PDLLA copolymers of 20 and 30% PEG content were selected as optimum formulation materials for the paste for the following reasons. PDLLA-PEG-PDLLA of 10% PEG could not be melted at a temperature of about 60°C. The copolymers of 40 and 70% PEG were readily melted at 60°C and the 20 and 30% PEG copolymer became a viscous liquid between 50 and 60°C. The swelling of 40 and 70% PEG copolymers in water was very high resulting in rapid dispersion of the pastes in water.

3.2. In vitro release of taxol from PDLLA-PEG-PDLLA paste

The in vitro release profiles of taxol from PDLLA-PEG-PDLLA cylinders are shown in Fig. 2. The experiment measuring release from the 40% PEG cylinders was terminated since the cylinders had a very high degree of swelling (about 200% water uptake within 1 day) and disintegrated in a few days. The released fraction of taxol from the 30% PEG cylinders gradually increased over 70 days. The released fraction from the 20% PEG cylinders slowly increased up to 30 days and then abruptly increased, followed by another period of gradual increase. A significant difference existed in the extent to which each individual cylinder (20% PEG content) showed the abrupt change in taxol release. Before the abrupt increase, the release fraction of taxol was lower for copolymers of lower PEG content at the same cylinder diameter (1 mm). The 40 and 30% PEG cylinders showed much higher taxol release rates than the 20% PEG cylinders. For example, the cylinder of 30% PEG released 17% taxol in 30 days compared to a 2% release from the 20% PEG cylinder. The cylinders with smaller diameters resulted in faster release rates, e.g., in 30 days, the 30% PEG cylinders with 0.65 mm and 1 mm diameters released 26% and 17% taxol, respectively (Fig. 2).

The above observations may be explained by the release mechanisms of taxol from the cylinders. Taxol was dispersed in the polymer as crystals as observed by optical microscopy. The crystals began dissolving in the copolymer matrix at 170°C and completely dissolved at 180°C as observed by hot stage microscope. DSC thermograms of 20% taxol loaded PDLLA-PEG-PDLLA (30% PEG) paste revealed a small recrystallization exotherm (16 J/g, 190°C) and a melting endotherm (6 J/g, 212°C) for taxol (Table 1) indicating the recrystallization of taxol from the copolymer melt after 180°C. In this type of drug/polymer matrix, taxol could be released via diffusion and/or polymer erosion.

In the diffusional controlled case, drug may be released by molecular diffusion in the polymer and/or through open channels formed by connected drug particles (Siegal, 1990). Extensive channel formation occurs normally above a threshold volumetric drug loading of about 30% (Siegal, 1990). Therefore at 20% loading, some particles of taxol were isolated and taxol may be

released by dissolution in the copolymer followed by diffusion. Other particles of taxol could form clusters connecting to the surface and be released through channel diffusion. In both cases, the cylinders with smaller dimension gave a faster drug release due to the shorter diffusion path (Fig. 2).

The dimension changes and water uptake of the cylinders were recorded during the release (Fig. 3). The changes in length, diameter and wet weight of the 30% PEG cylinders increased rapidly to a maximum within 2 days, then remained unchanged for about 15 days, and finally decreased gradually. The initial diameter of the cylinder did not affect the swelling behavior. For the cylinder of 20% PEG, the length decreased by

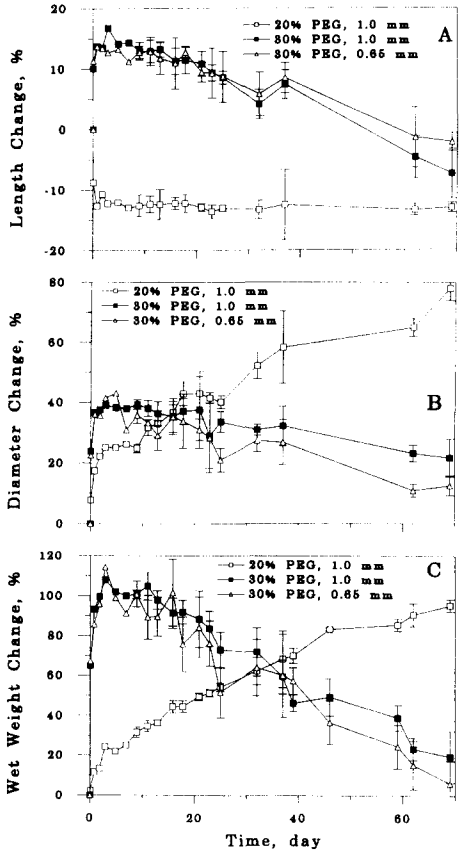

Fig. 3. Change in dimensions, length (A), diameter (B) and wet weight (C) of 20% taxol loaded PDLLA-PEG-PDLLA cylinders during the in vitro release of taxol at 37°C.

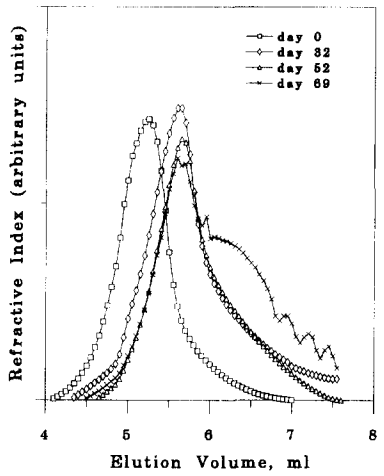

Fig. 4. Gel permeation chromatograms of PDLLA-PEG-PDLLA cylinders (20% PEG, 1 mm diameter) loaded with 20% taxol during the release in PBS albumin buffer at 37°C.

10% in 1 day and leveled off, while the diameter and water uptake gradually increased over time. Since more PEG in the copolymer uptaken more water to facilitate the diffusion of taxol, a faster release was observed (Fig. 2).

Erosion controlled release is mainly governed by polymer degradation. The degradation of the polyester-polyether block copolymers depends on their composition (Sawhney and Hubbell, 1990; Li et al., 1994). The copolymer molecular weight degradation of PDLLA-PEG-PDLLA paste was monitored by GPC. For the 20% PEG cylinder, the elution volume at the peak position increased with time indicating a reduced polymer molecular weight during the course of the release experiment (Fig. 4). A biphasic molecular weight distribution was observed at day 69. Polymer molecular weight was also decreased for 30% PEG cylinders (1 mm and 0.65 mm). However, no biphasic distribution was observed (data not shown).

NMR spectra revealed a PEG peak at 3.6 ppm and PDLLA peaks at 1.65 ppm and 5.1 ppm. The peak area of PEG relative to PDLLA in the copolymer decreased significantly after 69 days (Table 2), indicating the dissolution of PEG after its dissociation from PDLLA. The dry mass loss of the cylinders was also recorded (Table 2) and shows a degradation rate decreasing in the order

Table 2
Mass loss and polymer composition change of PDLLA-PEG-PDLLA cylinders (loaded with 20% taxol) during the release into PBS albumin buffer at 37°C

Sample[a]	Time, day	Dry wt loss, %	1.65/5.1[b]	3.6/5.1[b]
20% PEG-1 mm	0	0	3.51	1.65
20% PEG-1 mm	32	7.9	—	—
20% PEG-1 mm	69	19.2	3.63	0.68
30% PEG-1 mm	0	0	3.39	3.91
30% PEG-1 mm	32	28.9	—	—
30% PEG-1 mm	69	45.5	4.3	0.56
30% PEG-0.65 mm	0	0	3.39	3.91
30% PEG-0.65 mm	32	26.7	—	—
30% PEG-0.65 mm	69	57.5	5.8	0.21

[a]PDLLA-PEG-PDLLA copolymer cylinders showing PEG content and diameter of cylinder.
[b]Measured by ^{1}H NMR in $CDCl_3$; 1.65/5.1 represents the ratio of peak areas at 1.65 ppm (due to -CHCH$^*_3$- in PDLLA) and 5.1 ppm (due to -CH*CH$_3$- in PDLLA); 3.6/5.1 represents the ratio of peak areas at 3.6 ppm (due to -CH$^*_2$CH$^*_2$- in PEG) and 5.1 ppm.

30% PEG-0.65 mm > 30% PEG-1 mm > 20% PEG-1 mm.

The morphological changes of the dried cylinders before and during taxol release were observed using SEM (Fig. 5). Solid taxol crystals and non-porous polymer matrices were seen before the release (Fig. 5A and Fig. 5B). After 69 days of release, no taxol crystals were observed and the matrices contained many pores due to polymer degradation and water uptake (Fig. 5C and Fig. 5D).

The 30% PEG cylinders showed extensive swelling after only 2 days in water (Fig. 3) and therefore the hindrance to diffusion of the detached water soluble PEG block and degraded PDLLA (i.e., D,L-lactic acid oligomers) was reduced. Since the mass loss and degradation of the 30% PEG cylinders was continuous, the contribution of erosion release gradually increased resulting in a sustained release of taxol without any abrupt change (Fig. 2). For the 20% PEG cylinders, the swelling was low initially (Fig. 3) resulting in a slow diffusion of the degradation products. Therefore, the degradation products in the interior region are primarily retained while there are much less degradation products in the outer region due to the short diffusion path. The degradation products accelerated the degradation rate since the carboxylic acid end groups of the oligomers catalyzed the hydrolytic degradation. This results in a high molecular weight shell and a low molecular weight interior as indicated by the biphasic copolymer molecular weight distribution (Fig. 4, day 69). The same degradation phenomena has been observed for poly(D,L-lactide), poly(L-lactide) and poly(D,L-lactide-co-glycolide) samples (Li et al., 1990). At some time point, a weak part of the shell may disintegrate and release the interior water soluble degradation products along with the taxol leading to a burst release as observed for cylinders of PDLLA-PEG-PDLLA with 20% PEG (Fig. 2). A similar type of burst or pulsatile release has been observed for antibiotics (Zhang et al., 1994) and peptides (Maulding, 1987). Since the shell rupture was dependent on factors such as the strength, thickness and defects of the shell and interior degradation products, the onset and the extent of the loss of interior degradation products are very variable. Because the shell rupture is not consistent and the drug in the polymer is not microscopically homogenous, the time point for the release burst and the extent of the burst were different for the 4 samples tested (Fig. 2).

3.3. In vitro release from PDLLA and PCL blends

The release of taxol from PDLLA and PCL blends and pure PCL are shown in Fig. 6. The released fraction increased with PDLLA content in the blend. For example, within 10 days, the

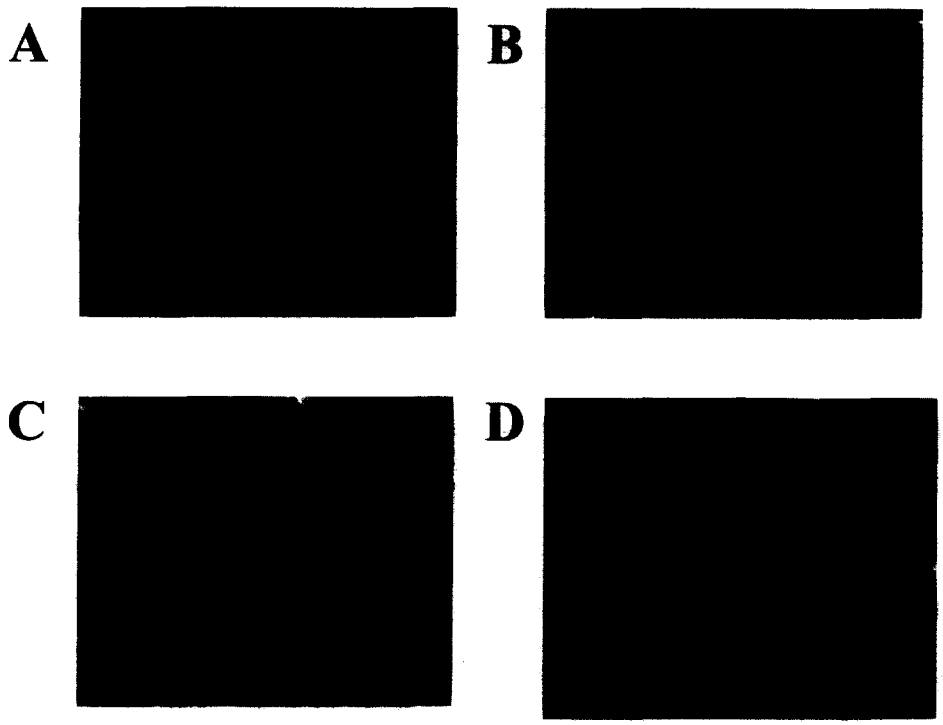

Fig. 5. SEM of dried PDLLA-PEG-PDLLA cylinders (loaded with 20% taxol, 1 mm in diameter) before and during taxol release. A: 20% PEG, day 0; B: 30% PEG, day 0; C: 20% PEG, day 69; D: 30% PEG, day 69.

released taxol from 80:20, 70:30, and 0:100 PDLLA:PCL were 17, 11 and 6%, respectively. After an initial burst in 1 day, approximately constant release was obtained from 80:20 PDLLA:PCL paste. No significant degree of swelling was observed during the release. For the PDLLA:PCL blends, since PDLLA had a very low molecular weight of about 800, it was hydrolyzed rapidly into water soluble products without a long delay in mass loss. PCL served as the 'holding' material to keep the paste from rapidly disintegrating. Therefore the release rate increased with PDLLA content in the blend due to the enhanced degradation. The continuous erosion of the PDLLA controlled the release of taxol and resulted in a constant release. The release of taxol from pure PCL was probably diffusion controlled due to the slow degradation rate (in 1–2 years) of PCL (Pitt et al., 1981).

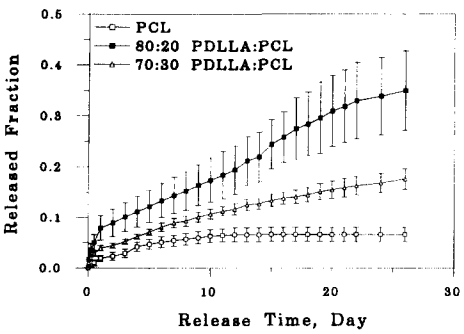

Fig. 6. Cumulative release of taxol from 20% taxol loaded PDLLA:PCL blends and PCL into PBS albumin buffer at 37°C. The error bars represent the S.D. of 4 samples.

Difficulties were encountered in the release study for 20% taxol loaded 90:10 PDLLA:PCL paste due to the disintegration of the paste pellet within 24 h of incubation. During the first 12 h of incubation, samples were taken every hour in order to ensure sink conditions for taxol release. The released taxol from the 90:10 paste was 25–35% within 10 h (data not shown).

Table 3
Efficacy of taxol loaded surgical paste formulations applied locally to subcutaneous tumor in mice

	Non-treated	PCL		80:20 PDLLA:PCL blend		90:10 PDLLA:PCL blend		PDLLA-PEG-PDLLA[a]	
		Control	20% Taxol	Control	20% Taxol	Control	20% Taxol	Control	20% Taxol
n[b]	5	5	4	5	5	12	15	10	13
Death[c]	0	0	1	0	0	0	0	0	0
Weight[d], g	1.71	1.64	1.55	1.63	1.22	1.51	0.87	1.46	0.88
Std[e]	0.61	0.68	0.49	0.75	0.49	0.84	0.57	0.71	0.42
regression[f]	—	—	5.7%	—	25.2%	—	54.0%	—	39.9%
P[g]	—	—	0.818	—	0.331	—	0.0269	—	0.0231

[a]With 0% PEG.
[b]The number of mice.
[c]The number of deaths of mice during the experiment.
[d]The average weight of the tumor.
[e]S.D. of the tumor weights.
[f]Percentage of tumor weight reduction.
[g]The significance level obtained using a two tail t-test.

3.4. In vivo tumor regression

The efficacy of the paste formulations for regressing tumor growth in mice were evaluated (Table 3). The pastes examined were PCL ± 20% taxol, 80:20 PDLLA:PCL ± 20% taxol, 90:10 PDLLA:PCL ± 20% taxol and PDLLA-PEG-PDLLA (30% PEG) ± 20% taxol. The paste formulations, 90:10 PDLLA:PCL and PDLLA-PEG-PDLLA, containing taxol reduced tumor growth in vivo by 54 and 40%, respectively. In contrast, the paste formulations, PCL and 80:20 PDLLA:PCL, containing taxol had little or no effect on tumor growth. All control pastes (drug absent) had no significant effect on tumor growth. The paste formulations with faster release rates of taxol (90:10 PDLLA:PCL and PDLLA-PEG-PDLLA) were also more effective in reducing tumor growth, suggesting that a critical local concentration of taxol is required at the tumor site for tumor growth inhibition. Paste formulations releasing taxol slowly, such as PCL and 80:20 PDLLA:PCL, were not effective. All of the paste formulations examined had no significant effect on the body weights of mice, indicating that the taxol loaded paste was well tolerated in vivo.

These data suggest that local application of taxol at the tumor site is an effective therapeutic strategy to inhibit local tumor growth without increasing systemic toxicity. The inability to the taxol loaded formulations to completely inhibit tumor growth is most likely due to insufficient release of taxol from the polymer and rapid tumor growth of MDAY-D2 tumors. The ability of 90:10 PDLLA:PCL paste containing 30% taxol, which released more taxol than 90:10 PDLLA:PCL paste containing 20% taxol, and which inhibited tumor growth more effectively is consistent with this hypothesis (data not shown). Thus, modulation of the release rate of taxol, which is regulated by the properties of the polymer and chemotherapeutic agents, as well as the site of administration, is a critical step in the development of local therapy for inhibiting tumor growth.

4. Conclusions

Biodegradable paste formulations for local delivery of taxol were developed. The release of taxol from the PDLLA-PEG-PDLLA paste was likely both diffusional and erosion controlled. The blend of 90:10 low molecular weight poly(D,L-lactic acid) and poly-ϵ-caprolactone gave a rapid and erosion controlled release. The pastes

PDLLA-PEG-PDLLA and 90:10 PDLLA:PCL pastes loaded with 20% taxol significantly inhibited tumor growth in mice. Greater tumor inhibition was obtained from the faster taxol releasing pastes.

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