A biodegradable, injectable, gel system based on MPEG-b-(PCL-ran-PLLA) diblock copolymers with an adjustable therapeutic window

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\textbf{A B S T R A C T}

In situ-forming gel systems have drawn increasing attention for their potential use in a variety of biomedical applications. Here, we examined an in situ-forming gel system comprised of MPEG-b-PCL and MPEG-b-(PCL-ran-PLLA) diblock copolymers with different PLLA contents (0–10 mol%) in the PCL segment. The crystalline region of the PCL-ran-PLLA segment decreased with increasing PLLA content. The MPEG-b-(PCL-ran-PLLA) diblock copolymer solutions were liquid at room temperature and only MPEG-b-(PCL-ran-PLLA) diblock copolymer solutions with a PLLA content \textless{} 5 mol\% in the PCL segment showed a sol-to-gel transition as the temperature was increased. The viscosity change associated with sol-to-gel phase transition depended on the PLLA content in the PCL segment. A MPEG-b-PCL diblock copolymer solution incubated \textit{in vitro} showed increasing viscosity without degradation, whereas the viscosity of MPEG-b-(PCL-ran-PLLA) diblock copolymer solutions continuously and sharply decreased with increasing PLLA content in the PCL segment. As the amount of PLLA increased, the size of in vivo-formed MPEG-b-(PCL-ran-PLLA) gels after initial injection tended to gradually decrease because of hydrolytic degradation of the PLLA in the PCL-ran-PLLA segment. An immunohistochemical examination showed that in vivo MPEG-b-(PCL-ran-PLLA) diblock copolymer gels provoked only a modest inflammatory response. Collectively, our results show that the MPEG-b-(PCL-ran-PLLA) diblock copolymer gel described here could serve as a minimally invasive, therapeutic, in situ-forming gel system that offers an experimental window adjustable from a few weeks to a few months.

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1. Introduction

Injectable in situ-forming gel systems are fluids that can be introduced into the body in a minimally invasive manner prior to solidifying or gelling within the desired tissue, organ, or body cavity [1]. In the past few decades, an increasing number of in situ-forming gel systems have been developed and reported for various biomedical applications, including drug delivery, cell encapsulation, and tissue engineering [2]. Injectable in situ-forming gels can fill complicated defect geometries; are able to incorporate various therapeutic agents, such as growth factors, gene products, and cells by simple mixing; and, if biodegradable, do not require surgical procedures for replacement, thus facilitating patient compliance and comfort.

Various natural biomaterials, including collagen, heparin, hyaluronate, fibrin and ECM, have been employed for the preparation of injectable in situ-forming gels [3–5]. Several block copolymers consisting of polyethylene glycol (PEG) and biodegradable polyesters, such as poly-L-lactic acid (PLLA), polyglycolic acid (PGA) (or their PLGA copolymers), and the pluronic series, have been prepared as synthetic biomaterials and examined as candidate in situ-forming gel systems [6–8].

Recently, we reported on a diblock copolymer formed from PEG and polycaprolactone (PCL), referred to in abbreviated form as MPEG-b-PCL [9,10]. Aqueous solutions of such copolymers exhibit sol-to-gel transitions at body temperature. Although PCL undergoes hydrolytic degradation, the rate of degradation in vivo is rather slow (2–3 years) compared to that of PLA, PGA, or PLGA under physiological conditions [11]. Thus, PCL has been investigated mainly as
a long-term biomaterial for use in biomedical applications. We also found that MPEG-b-PCL gels maintained their structure for at least 10 months (unpublished observations). Thus, after serving the function in delivering therapeutic agents in vivo, an in-situ forming MPEG-b-PCL gel should remain in the body under physiological conditions for an uncertain period.

This is not a relevant concern for long-term biomedical applications. However, for this candidate to be a suitable in situ-forming gel for short-term implantation, the material must show satisfactory biodegradation properties. Over the course of a series of investigations, our laboratory has sought to develop an injectable, in situ-forming gel with biodegradation properties, both in vivo and in vitro, that are suitable for short-term implantation. Generally, the degradation of PLA, PGA, or PLGA involves scission of ester bond linkages in the polymer backbone by hydrolytic attack of water molecules [12]. Thus, compared to the PCL segment only, incorporation of PLLA into the PCL segment can lead to faster chain scission because of better accessibility of water to the ester bonds of PLLA.

Here, we prepared MPEG-b-(PCL-ran-PLLA) diblock copolymers by incorporating PLLA into the PCL segment. We next evaluated the resulting MPEG-b-(PCL-ran-PLLA) diblock copolymers in the context of the following specific questions: 1) Do these MPEG-b-(PCL-ran-PLLA) diblock copolymers act as in situ-forming gels in vitro and in vivo? 2) Does degradation of these MPEG-b-(PCL-ran-PLLA) diblock copolymers occur over a defined experimental period? 3) Does the MPEG-b-(PCL-ran-PLLA) gel provoke an in vivo inflammatory response?

2. Experimental section

2.1. Materials

MPEG, with a number-average molecular weight (Mn) = 750 g/mol (Aldrich), and Sn(Oct)2 (Aldrich) were used as received. ε-Caprolactone (CL) was distilled over CaH2 under reduced pressure. ε-Lactide (LA; Boehringer Ingelheim, Germany) was recrystallized twice in ethyl acetate.

2.2. Characterization

1H NMR spectra were measured using a Bruker 300 MHz instrument with CDCl3 in the presence of TMS as an internal standard. Molecular weights and molecular weight distributions of MPEG–PCL diblock copolymers were measured on a Waters 4000 GPC System (Shodex RI-101 detector) using three columns (ShodexKF 804, 803 and 802). CHCl3 was used as the eluent at a flow rate of 0.8 ml/min. The crystallinity of the diblock copolymers was measured by X-ray diffraction (D/MAX-II B, Rigaku, Japan). Radiation was generated with a Ni filter at 35 kV and 15 mA. The samples were placed in a quartz sample holder and scanned from 0° to 60° at a scanning rate of 5°/min. The degree of crystallinity was calculated as the ratio of the crystalline peak areas to the total area under the scattering curve. The glass transition temperature (Tg), heat of fusion (∆Hm) and melting temperature (Tm) were determined with a differential scanning calorimeter (Q1000, TA Instruments, New Castle, DE, USA) from −100 to 150 °C at a heating rate of 10 °C/min for diblock copolymers in the bulk state, and from 20 to 80 °C at a heating or cooling rate of 10 °C/min for aqueous solutions of diblock copolymers under a nitrogen atmosphere. The heat of fusion per gram of sample was calculated from the area under the peak.

2.3. Synthesis of the MPEG-b-(PCL-ran-PLLA) diblock copolymer, CSS5L

All glasses were dried by heating in a vacuum and were handled under a dry nitrogen stream. The typical polymerization process to yield MPEG-b-(PCL-ran-PLLA) with a CL:LA ratio of 95:5 (CSS5L) is as follows: MPEG (1.5 g, 2 mmol) and toluene (80 ml) were introduced into a flask. Water was removed from the MPEG solution by azeotropic distillation, and toluene was then distilled off to give a final volume of 40 ml. C. All solutions were liquid at room temperature. After 48 h, the viscosity of each polymer solution was measured using a Brookfield Viscometer DV-III ultra with a programmable Rheometer and a TC-502P temperature-controlled, programmable circulating water bath. The viscosity of diblock copolymer solutions was investigated using a T-F spindle at 0.2 rpm from 10 to 60 °C in increments of 1 °C. For viscosity change in in vitro incubation of diblock copolymer solutions at body temperature, the viscosities of the formed gel were constantly shaken at 300 rpm and 37 °C, and viscosity of gel samples were measured at intervals over the course of 6 weeks.

2.4. Viscosity measurements

MPEG-b-PCL and MPEG-b-(PCL-ran-PLLA) diblock copolymers in 4-mL vials were dissolved with deionized water to yield a 20 wt% concentration and were stored at 4 °C. All solutions were liquid at room temperature. After 48 h, the viscosity of each polymer solution was measured using a Brookfield Viscometer DV-III ultra with a programmable Rheometer and a TC-502P temperature-controlled, programmable circulating water bath. The viscosity of diblock copolymer solutions was investigated using a T-F spindle at 0.2 rpm from 10 to 60 °C in increments of 1 °C. For viscosity change in in vitro incubation of diblock copolymer solutions at body temperature, the viscosities of the formed gel were constantly shaken at 300 rpm and 37 °C, and viscosity of gel samples were measured at intervals over the course of 6 weeks.

2.5. In vivo injection

The diblock copolymers were sterilized using ethylene oxide gas, and then prepared as 20 wt% solutions in PBS at room temperature. All animals were treated in accordance with the Institutional Animal Experiment Committee at Ajou University School of Medicine. Twelve, 8-wk-old Sprague–Dawley (SD) rats (320–350 g), divided into four groups (1, 2, 4, and 6 wk) of three rats each, were used for GPC and NMR measurements, and histological analyses. A 1 cc syringe with a 26-gauge needle was used to inject the copolymer solution in the subcutaneous dorsum of rats that had been anesthetized with ethyl ether. Each rat was injected with a single aliquot of copolymer solution. The resulting gel implants were then allowed to develop in vivo, and were biopsied over the experimental period. At each of the post-injection sampling points, the rats were sacrificed and the gel implants were dissected individually and removed from the subcutaneous dorsum. Each gel implant was placed in a test tube to which CH2Cl2 (1 mL) was added to dissolve the copolymer portion of the implant. Then, 1 ml of distilled water was added to solubilize the tissue. The resulting mixture was sonicated for 90 min at 25 °C and centrifuged at 10,000 rpm for 5 min. The CH2Cl2 solution was collected, the CH2Cl2 was removed, and the remaining copolymer containing degraded compounds was freeze-dried until it reached a constant weight and then measured by GPC. The degraded compounds was separated into soluble and insoluble parts in n-hexane and ethyl ether (v/v = 4/1) and measured by NMR.

2.6. Histological analysis

At each time point after implantation, removed gel implants were immediately fixed with 10% formalin and embedded in paraffin. The embedded specimens were sectioned (4 μm) along the longitudinal axis of the implant and slide-mounted. Slides were washed with PBS-T (0.05% Tween 20 in PBS), blocked with 3% bovine serum albumin (BSA; BOVOCEN, Australia) and 3% horse serum (HS; CIBCO, Invitrogen) in PBS for 1 h at 37 °C. The sections were then incubated overnight at 4 °C with mouse anti-rat CD68 (ED1; Serotec, Oxford, UK) or CD4 (Chemicon, EU) antibodies, washed with PBS-T, and then incubated with the secondary antibody (goat anti-mouse Alexa Fluor 594; Invitrogen, San Diego, Calif. USA) for 3 h at room temperature in the dark. The slides were washed again with PBS-T, counterstained with 6-diamino-2-phenylindole hydrochloride (DAPI; Sigma–Aldrich, St Louis, MO, USA) and then mounted with fluorescent mounting solution (DAKO, Carpinteria, CA, USA). Immunofluorescent images were visualized under an Axio Imager A1 (Carl Zeiss Microimaging GmbH, Göttingen, Germany) equipped with Axiovision Rel. 4.8 software (Carl Zeiss Microimaging GmbH, Göttingen, Germany). Before acquisition of immunofluorescent images, the delimitation between gel and host tissue was determined from a differential interference contrast (DIC) optical microscopic image. The sections were also stained with hematoxylin and eosin (H&E) using standard procedures.

2.7. Statistical analysis

Assessments of ED-1 or CD4 immunoreactivity were carried out in independent experiments (n = 16 for each data point), and data are expressed as the mean ± standard deviation (SD). The results of one representative experiment are displayed for each analysis. Data were analyzed by a Student’s t-test. P-values less than 0.05 or 0.005 were considered statistically significant. All values are reported as mean ± SD.

3. Results

3.1. Synthesis and characterization of MPEG-b-(PCL-ran-PLLA) diblock copolymers

Our previous reports suggested that aqueous solutions of MPEG–PCL diblock copolymers could serve as thermo-responsive signal of MPEG at δ = 3.38 ppm, the methylene proton signal of PCL at δ = 2.31 ppm, and the methylene proton signals of PLLA at δ = 5.15 ppm.
polymers, remaining in solution at room temperature and exhibiting sol-to-gel phase transition as the temperature was increased [9,10]. The current study tested diblock copolymers with an MPEG chain (MW = 750), varying compositions of PCL and PLLA (total MW = 2400). Table 1 summarizes the results obtained for MPEG-b-PCL and MPEG-b-(PCL-ran-PLLA) diblock copolymers. The colorless diblock copolymers were obtained in almost quantitative yield after isolation by precipitation in n-hexane and ether. The diblock copolymers exhibited peaks characteristic of PCL and PLLA as well as MPEG in 1H NMR spectra. CL and LA monomers were randomly incorporated into the PCL-ran-PLLA copolymers in proportion to changes in the feed ratio; representative NMR data for C95L5 are shown in Fig. 1a (the spectra of other copolymer solutions not shown). The molecular weights of PCL and PLLA, measured by 1H NMR, were in good agreement with those calculated from the feed ratio of each monomer to MPEG.

Table 2 summarizes the properties of the MPEG-b-PCL and MPEG-b-(PCL-ran-PLLA) diblock copolymers in bulk and aqueous solutions. X-ray diffraction and differential scanning calorimetry showed that crystalline regions were present in the PCL and PCL-ran-PLLA segments, even though the copolymers were dissolved in aqueous medium. The intensities of the crystalline regions decreased with increasing PLLA content in the PCL segment. Increasing amounts of the PLLA segment in aqueous solution should lead to a disturbance in the ordering or aggregation of the PCL hydrophobic domains. No crystalline regions were present when the composition of solutions attained C90L10.

3.2. Phase transition of diblock copolymer solutions

Aqueous solutions of the synthesized C100L0, C97L3, C95L5, and C93L7 diblock copolymers were prepared by dissolving diblock copolymers at 80 °C in deionized water at a 20 wt% concentration. The polymer solutions formed a translucent liquid at room temperature that flowed when tilted. Phase transition tests showed
that diblock copolymer solutions dipped at 37 °C did not flow when tilted. The diblock copolymers showing such phase transition behavior are indicated in Table 1. The phase change of each diblock copolymer solution (C100L0, C97L3, and C95L5) indicated a sol-to-gel transition and the formation of a gel at physiological temperature. The MPEG-b-(PCL-ran-PLLA) diblock copolymers, C93L7 and C90L10, with 7 and 10 mol% PLLA content in the PCL segment, respectively, did not exhibit phase transition behavior.

To gain a better understanding of the phase transitions, we examined the change in the viscosity of the diblock copolymer solution as a function of temperature from 10°C to 60°C (Fig. 2). At low temperature, diblock copolymers were completely dissolved in water, yielding a homogeneous solution with a viscosity of 1 cP. As the temperature increased, diblock copolymer solutions exhibited a composition-dependent increase in viscosity, indicating that the solution entered a gel-like zone; for C100L0, C97L3, and C95L5 diblock copolymer solutions, this transition commenced at 29, 31, and 35°C, respectively. The maximum viscosities of C100L0, C97L3, and C95L5 diblock copolymer solutions were $9 \times 10^5$ cP, $2.8 \times 10^5$ cP, and $1.6 \times 10^5$ cP, respectively. C93L7 and C90L10 diblock copolymer solutions showed no temperature-dependent changes in viscosity. These results are in agreement with the results of tilting experiments.

### Table 2

<table>
<thead>
<tr>
<th>No</th>
<th>$T_g$ °C</th>
<th>In bulk state</th>
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<td>Polyester block</td>
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<td>54.7</td>
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</tr>
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<td>C95L5</td>
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<td>C93L7</td>
<td>$-62.1$</td>
<td>44.6</td>
<td>41.8</td>
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</tbody>
</table>

* Measured by DSC.
* $\chi$ was calculated as the ratio of the crystalline peak areas to the total areas under the scattering curve.

3.3. In vitro incubation of diblock copolymer solutions at body temperature

The measured viscosities of C100L0, C97L3, and C95L5 diblock copolymer solutions incubated in vitro at 37 °C for 6 weeks are shown in Fig. 3. The initial ($t_0$) viscosity of a C100L0 solution was close to 1 cP within the temperature range 10°C–30°C, but increased to $\sim 10^5$ cP after 2 days. After 4 weeks, the C100L0 solution showed an infinite viscosity at all incubation temperatures (from low to 53°C), indicating complete gelation. In contrast, the viscosities of C97L3 and C95L5 diblock copolymers were high initially and decreased with increasing incubation times. After 5 weeks, no changes in viscosity were observed for C97L3 and C95L5 diblock copolymers, reflecting complete degradation of the copolymers.

3.4. In vivo gelation and degradation

To examine the utility of C100L0, C97L3, and C95L5 diblock copolymers as in vivo in situ-forming gels, we injected 20 wt% C100L0, C97L3, and C95L5 diblock copolymer solutions in PBS at room temperature subcutaneously into SD rats. All formulations formed a gel immediately after injection (Fig. 4a). Gels were allowed to develop for up to 6 weeks in vivo, and were excised and examined at various times post-injection. The resulting gels maintained their shapes even after 6 weeks in vivo (Fig. 4b). In addition, thin fibrous capsules containing fibroblasts and vascular vessels formed around the surfaces of the gels over time after injection (Fig. 4c). C100L0 copolymer gels maintained an almost constant size between 1 and 6 weeks. In contrast, the size of excised C97L3 and C95L5 diblock copolymer gels gradually decreased as a function of time after initial injection, reaching final volumes that were approximately 50% and 25%, respectively, of original volumes.

We used GPC, which can detect trace amounts of degraded polymers, to assess degradation of C100L0, C97L3, and C95L5 solutions incubated in vivo for 0–6 weeks. Total GPC profiles, presented in Fig. 5, showed a small, low molecular weight peak.
corresponding to degraded species in the C100L0 sample, indicating that little degradation had occurred even after 6 weeks. In contrast, C97L3 and C95L5 diblock copolymers showed several low molecular weight peaks indicative of more extensive degradation. The intensity of the peaks assignable to degradation species increased as a function of time. The decrease in intensity of the main peaks was larger for C95L5 gel than for C97L3 gel.

Fig. 1 shows 1H NMR changes of the C95L5 diblock copolymer before and after incubation. After 6 weeks of degradation, signals L1 and L2, assignable to lactic acid, appeared in the spectrum at 4.36 and 1.50 ppm, respectively (Fig. 1b). The spectrum also showed that the characteristic peaks of degraded polymer and parent MPEG were obtained after separation in n-hexane and ether (Fig. 1c and d).

3.5. In vivo immunogenicity of gels

To assess the biocompatibility of C100L0, C97L3, and C95L5 gels, we examined fixed tissue sections from implanted gels excised at different times after injection using histological and immunohistochemical staining. H&E staining of C100L0, C97L3, and C95L5 gels revealed the distribution of gel (pink) and penetrating host cells (blue), which exhibited a generally rounded morphology (Fig. 6). A few macrophages, neutrophils, and/or lymphocytes were also evident in the C100L0, C97L3, and C95L5 gels, and new blood vessels were observed. The extent of host cell infiltration and inflammatory cell accumulation within and surrounding the C100L0, C97L3, and C95L5 gels was characterized by staining tissue with ED1 (red) and anti-CD4 antibodies (red) to identify monocytes/macrophages and T cells, respectively; nuclei were stained with DAPI (blue) (Fig. 7, CD4 stained data not shown). DAPI staining revealed the presence of numerous host cells within and surrounding the gel implants. ED1 and CD4 staining showed that macrophages were present in the host tissue as well as at the edges of the C100L0, C97L3, and C95L5 gels. The ED1- and CD4-positive cells were counted and normalized to the total stained tissue area to determine the extent of inflammation (Fig. 8). The number of macrophages (ED1-positive cells) and CD4-positive cells increased slightly with increasing implant duration (*p < 0.05, **p < 0.005), but there were no large differences among C100L0, C97L3, and C95L5 diblock copolymers.

4. Discussion

In situ-forming gels are attractive candidates for injectable therapeutics because these systems remain in solution at low temperatures—allowing incorporation of cells and other biologically active molecules—and then become solid at body temperature in situ. Various biomaterials have been shown to act as in situ-forming gels, and, with further improvements, could prove invaluable in a number of biomedical applications [1,13–15].

In the present work, we systematically evaluated the in situ gel-forming ability of MPEG-b-(PCL-ran-PLLA), in comparison with MPEG-b-PCL, a versatile polymer that can undergo gelation because of hydrophobic interactions. The viscosity of MPEG-b-PCL and MPEG-b-(PCL-ran-PLLA) solutions substantially increased with rises in temperature, and phase transition occurred at approximately body temperature. The abrupt change in viscosity at a particular temperature demonstrates the formation of a structured network that is, a gel. The PCL block affects formation of the crystalline domain of MPEG-b-PCL diblock copolymers. PCL crystalline domains could closely pack or aggregate in the MPEG-b-PCL diblock copolymer solution to induce an aggregated gel through intra- and inter-molecular interactions [9,10]. However, the PLLA in the PCL segments can disturb the pro-aggregation effect of the PCL hydrophobic blocks [16]. Consistent with this idea, we found that increasing the PLLA content in the PCL segment decreased crystallinity, strongly suggesting that aggregation of the PCL blocks was interrupted by PLLA. Thus, as the PLLA content in PCL segments was increased, the maximum viscosity fell.

Although PCL has hydrolytically labile aliphatic ester linkages and thus undergoes hydrolytic degradation [11,17], PCL is much less
biodegradable than is PLA, PGA, or PLGA. Both in vitro- and in vivo-formed MPEG-\(b\)-PCL gels maintain their structure for at least 10 months without degradation (unpublished data). Because of this slow degradation property, such formulations may be promising in situ-forming gels for long-term biomedical applications.

Several copolymeric systems containing PCL have been investigated for the potential to improve the slow degradation of native PCL [18–20]. Copolymers of PCL with PLLA have yielded materials with more rapid degradation rates. It is well established that the rapid degradation of the PCL and PLLA diblock copolymer commences with the PLLA segments, because of their amorphous structure and lower hydrophobicity compared with PCL segments.

The viscosities of both in vitro-formed MPEG-\(b\)-(PCL-ran-PLLA) solutions steadily decreased as a function of time, and the size of in

![Fig. 4](image_url) (a) Gel implant formed following subcutaneous injection of copolymer solution. (b) Gel conformation; (c) C100L0, C97L3, and C95L5 gel implants removed from rats after 1–6 weeks.

![Fig. 5](image_url) GPC changes of in vivo gels 0–6 weeks after injection. (a) C100L0, (b) C97L3, and (c) C95L5. Initial (0 wk), plain line; 4 weeks, dashed line; 6 weeks, dashed-dotted line; MPEG, bold line.
vivo-formed MPEG-\(b\)-(PCL-ran-PLLA) gels gradually fell after initial injection. This phenomenon is attributable to the relatively rapid degradation of MPEG-\(b\)-(PCL-ran-PLLA) gels compared with MPEG-\(b\)-PCL gels. The degradation of MPEG-\(b\)-(PCL-ran-PLLA) should depend on chain scissions within the PLLA segment. Degradation was observed to depend on chemical composition, and was accelerated in proportion to the amount of PLLA segment present in the PCL-ran-PLLA structure. Thus, the trend toward decreased viscosity and size was greater in PCL-ran-PLLA structures containing greater levels of PLLA segments, indicating that the degradation period can be controlled from a few weeks to a few months by changing the segments of block copolymers.

With the eventual goal of optimizing our MPEG-\(b\)-(PCL-ran-PLLA) system for injectable therapeutic applications in mind, we...
studied the biocompatibility of our in situ gel-forming MPEG-b-(PCL-ran-PLLA) solutions. Many cells were found scattered within the injected gel site. A number of newly formed blood vessels were also observed, demonstrating that in vivo-formed MPEG-b-(PCL-ran-PLLA) gels might support vascular ingrowth. An examination of the immunological response of host cells toward the MPEG-b-PCL and MPEG-b-(PCL-ran-PLLA) gels using ED1 and CD4 showed that immunoreactivity and inflammation surrounding the injected gel site were modest and similar in MPEG-b-PCL and MPEG-b-(PCL-ran-PLLA) gels.

5. Conclusion

An MPEG-b-(PCL-ran-PLLA) copolymer solution containing less than 5% PLLA in the PCL segment remained liquid at room temperature. As the temperature was increased, these diblock copolymer solutions manifested an increase in viscosity that reflected a sol-to-gel transition. The sol-to-gel phase transition temperature of the copolymer was found to depend on the amount of PLLA in the PCL segment. The diblock copolymer solutions exhibited a decrease in maximum viscosity and level of crystalline domains with increasing PLLA content in the PCL segment because of PLLA-mediated disturbance of the aggregation-inducing effect of PCL hydrophobic blocks in an aqueous medium. The in vitro and in vivo degradation of MPEG-b-(PCL-ran-PLLA) could be controlled by varying the amount of PLLA in the PCL segment. The in vivo-formed MPEG-b-(PCL-ran-PLLA) gels provoked only a modest inflammatory response. These results indicate that MPEG-b-PCL and MPEG-b-(PCL-ran-PLLA) diblock copolymer solutions can act as in situ gel-forming systems with an experimental window that is adjustable from a few weeks to a few months.

Acknowledgments

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Appendix

Figure with essential colour discrimination. Figs. 4, 6 and 7 of this article may be difficult to interpret in black and white. The full colour images can be found in the online version, at doi:10.1016/j.biomaterials.2009.11.115.

References