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# Tissue anti-adhesion potential of ibuprofen-loaded PLLA–PEG diblock copolymer films

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**Abstract**

This study was designed to evaluate the effect of polyethylene glycol (PEG) and nonsteroidal anti-inflammatory drug (ibuprofen) on the prevention of postsurgical tissue adhesion. For this, poly(L-lactic acid) (PLLA)–PEG diblock copolymers were synthesized by ring opening polymerization of L-lactide and methoxy polyethylene glycol (Mw 5000) of different compositions. The synthesized copolymers were characterized by gel permeation chromatography and $^1$H-nuclear magnetic resonance spectroscopy. PLLA–PEG copolymer films were prepared by solvent casting. The prepared copolymer films were more flexible and hydrophilic than the control PLLA film, as investigated by the measurements of glass transition temperature, water absorption content, and water contact angle. The drug release behavior from the ibuprofen (10 wt%)-loaded copolymer films was examined by high performance liquid chromatography. It was observed that the drug was released gradually up to about 40% of total loading amount after 20 days, depending on PEG composition; more drug release from the films with higher PEG compositions. In vitro cell adhesions on the copolymer films with/without drug were compared by the culture of NIH/3T3 mouse embryo fibroblasts on the surfaces. For in vivo evaluation of tissue anti-adhesion potential, the copolymer films with/without drug were implanted between the cecum and peritoneal wall defects of rats and their tissue adhesion extents were compared. It was observed that the ibuprofen-containing PLLA–PEG films with high PEG composition (particularly $PLLA_{113}$–$PEG_{113}$ film with PEG composition, 50 mol%) were very effective in preventing cell or tissue adhesion on the film surfaces, probably owing to the synergistic effects of highly mobile, hydrophilic PEG and anti-inflammatory drug, ibuprofen.


*Keywords:* Poly(L-lactic acid); Poly(ethylene glycol); Block copolymer; Anti-inflammatory drug; Tissue anti-adhesion

## 1. Introduction

Tissue adhesions occur after inflammation or surgical treatment, most frequently of peritoneum and pelvis. Adhesion is a physiologically important part of wound healing, but undesirable adhesions after surgical treatment often induce serious complications, including patient's pain, functional obstruction, and difficult reoperative surgery. It is recognized that adhesion formation is associated with various factors such as tissue trauma, ischemia, foreign body reaction, infection, and hemorrhage [1].

In order to reduce postsurgical adhesion formation, several agents such as fibrinolytic agents, anticoagulants, anti-inflammatory agents, and antibiotics, have been employed [2]. However, these agents alone did not prevent adhesion formation effectively because of their short-term residence. Other attempts to reduce adhesion formation have focused on the use of physical barriers. Various natural and synthetic polymer films, membranes, and nonwoven fabrics have been developed as nonabsorbable or absorbable physical barrier materials. Several natural materials including peritoneum, omentum, amnion, fibrin, gelatin, collagen, and hyaluronic acid have been tried [3–6], however synthetic polymers are sometimes preferred for use as physical barriers rather than natural ones because synthetic polymers are easier to handle, have better mechanical properties, contain fewer biological contaminants, and show lower level of immunogenicity. Synthetic polymers include nonabsorbable ones such as silicone and polytetrafluoro ethylene (PTFE), and absorbable ones such as cellulose derivatives, polyvinyl alcohol, and poly(hydroxyl acid)s [1,7–10]. Although the nonabsorbable membranes can

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effectively isolate an injured site from adjacent tissues, they remain at the applied site without degradation and needs laparoscopical removal after injury healing. The absorbable membranes are often rapidly degraded and sometimes induce a severe acute inflammatory reaction to cause tissue adhesion.

In this study, nonsteroidal anti-inflammatory drug (NSAID; ibuprofen)-loaded poly(L-lactic acid) (PLLA)-polyethylene glycol (PEG) diblock copolymer films were prepared to estimate their potential to use as tissue adhesion barrier membranes. Many research groups have synthesized PLLA–PEG di-, tri-, or multi-block copolymers for drug delivery and tissue engineering applications [11–16]. PLLA is one of the most widely used biomedical polymers owing to its biodegradability and biocompatibility. However, its application has been limited because of its stiffness and hydrophobicity. Introducing PEG can enhance the flexibility and hydrophilicity of PLLA [10,16,17]. It can also allow the PLLA films to prevent tissue adhesion [10,18]. Ibuprofen can reduce inflammatory response in adhesion formation step and thus allow to reduce tissue adhesion [19]. Ibuprofen-loaded PLLA–PEG films were investigated in this study to figure out whether both PEG chains and anti-inflammatory drug (ibuprofen) in the films have a synergistic effect for the prevention of tissue adhesion.

## 2. Materials and methods

### 2.1. Materials

L-lactic acid and PLLA were purchased from Boehringer Ingelheim (Germany) and used as received. Number-average molecular weight ($M_n$) of PLLA determined by gel permeation chromatography (GPC; Waters 2690, USA) using polystyrene (PS) standards (Polysciences, USA) was 95,000. Methoxy polyethylene glycol (MPEG; Mw 5000) was purchased from Polysciences and purified by dissolving in tetrahydrofuran, reprecipitating in hexane, and vacuum drying overnight. Stannous octoate as a catalyst for the synthesis of PLLA–PEG diblock copolymers and ibuprofen as a hydrophobic NSAID were purchased from Sigma (USA). They were used without further purification. All other chemicals were analytical grade and were used as received.

### 2.2. Synthesis of PLLA–PEG diblock copolymers

PLLA–PEG diblock copolymers were synthesized by ring-opening polymerization of L-lactide and MPEG with monomer feed ratios, listed in Table 1. The monomers, L-lactide and MPEG, were mixed and the solution was vacuum dried for more than 2 h. Then the catalyst, stannous octate (0.05 wt%, monomer base) was added into the monomer solution, and the mixture solution was purged with dry nitrogen. The polymerization was carried out at 150°C for 2 h with continuous dry nitrogen purging. The resulting polymer was dissolved in methylene chloride (MC), filtered, and precipitated in cold hexane. The prepared polymers were then dried under vacuum for 2–3 days. The $M_n$ and molecular weight distribution ($M_w/M_n$) of the synthesized copolymers were estimated by GPC using dimethyl formamide as an eluent. The monomer composition in the copolymers was characterized by $^1$H-nuclear magnetic resonance spectroscopy (NMR; Varian 300, USA) using $CDCl_3$ as a solvent.

Table 1
Composition and molecular weights of PLLA–PEG diblock copolymers synthesized.

| Copolymer | PLLA/PEG mole ratio in monomer feed | PLLA/PEG mole ratio in copolymer[a] | $M_n$ of copolymer[b] |
|---|---|---|---|
| $PLLA_{1017}$–$PEG_{113}$ | 9/1 | 8.6/1.4 | 97,000 |
| $PLLA_{452}$–$PEG_{113}$ | 8/2 | 7.7/2.3 | 65,000 |
| $PLLA_{264}$–$PEG_{113}$ | 7/3 | 6.8/3.2 | 37,000 |
| $PLLA_{170}$–$PEG_{113}$ | 6/4 | 5.5/4.5 | 23,000 |
| $PLLA_{113}$–$PEG_{113}$ | 5/5 | 4.8/5.2 | 18,000 |

[a] Determined by $^1$H-NMR measurement.
[b] Determined by GPC measurement ($M_w/M_n$, 1.4–2.0).

### 2.3. Preparation of copolymer films

Films from PLLA as a control and the PLLA–PEG diblock copolymers with different PEG compositions were prepared by solvent casting using 20 wt% polymer solutions. The prepared films (thickness, ~50 μm) were transparent. To prepare drug-loaded polymer films, ibuprofen was added in polymer solutions (10 wt%, polymer base) and the solutions were casted in a same way above. The glass transition temperatures ($T_g$) of the PLLA–PEG films were measured by a differential scanning calorimeter (DSC; TA Instruments 2190, USA) at a 10°C/min heating rate. The swelling property of the copolymer films was examined by measuring the water absorption content. The polymer films (about 5 × 5 cm) were weighed after thorough drying ($W_{dry}$) and immersed in purified water. After predetermined times up to 14 days, the films were taken out from the water, wiped dry with tissue paper, and weighed again immediately ($W_{wet}$). Water absorption was determined as follows: Water absorption (%) = $[(W_{wet}–W_{dry})/W_{dry}] \times 100$. The PLLA–PEG film surfaces were characterized by the measurement of water contact angles to investigate the effect of PEG on the surface hydrophilicity of the films. The water contact angles were measured by a Sessile drop method [17]. Immediately and after 30 min equilibrium, the microscopic measure-