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Biodegradable and thermoreversible PCLA–PEG–PCLA hydrogel as a barrier for prevention of post-operative adhesion

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ABSTRACT

Biodegradable polymers can serve as barriers to prevent the post-operative intestinal adhesion. Herein, we synthesized a biodegradable triblock copolymer poly(ε-caprolactone-*co*-lactide)-*b*-poly(ethylene glycol)-*b*-poly(ε-caprolactone-*co*-lactide) (PCLA–PEG–PCLA). The concentrated polymeric aqueous solution was injectable, and a hydrogel could be rapidly formed due to percolation of a self-assembled micelle network at the body temperature without requirement of any chemical reactions. This physical hydrogel retained its integrity *in vivo* for a bit more than 6 weeks and was eventually degraded due to hydrolysis. The synthesized polymer exhibited little cytotoxicity and hemolysis; the acute inflammatory response after implanting the hydrogel was acceptable, and the degradation products were less acidic than those of other polyester-containing materials. A rabbit model of sidewall defect-bowel abrasion was employed, and a significant reduction of post-operative peritoneal adhesion has been found in the group of *in situ* formed PCLA–PEG–PCLA hydrogels.

1. Introduction

Post-operative intestinal adhesion is one of the common and serious complications in surgery. It can cause pain, infertility, and intestinal obstruction etc [1,2]. The incidence of adhesions following surgery was estimated as high as 80% [2]. Especially, the intestinal adhesion occurred in most of patients after abdominal and pelvic surgery [3]. The anti-adhesion approach could primarily be divided into two categories: pharmacological treatment [4–6] and barrier-based devices [7–11]. Among those methods, solid or liquid barriers are currently the most useful for reducing adhesion [12–18]. Biodegradable solid barrier devices, such as films of hyaluronic acid-carboxymethyl cellulose (Seprafilm® Genzyme) [19,20] and polylactide (PLA) [21,22] have been commercialized. The films are hard to cover over the tissues of complex geometry, and aggressively adhere to any moisture even on the surgeon's gloves during placement. Polymer solutions such as sodium hyaluronic acid and carboxymethyl cellulose have also been reported as anti-adhesion materials [23], but the short persistent time of solutions reduces their efficacies.

Recently, much attention has been paid on injectable hydrogels in the fields of biomaterials and polymer science [24–29]. These materials are flowable aqueous solutions before administration, and once injected, they rapidly form gels under the physiological condition. Implantation of those materials could thus bring with minimal invasiveness. A series of *in situ* formed chemically crosslinked injectable hydrogels have been successfully tried to prevent peritoneal adhesion, and they are usually made of dextran [13], gelatin [14], hyaluronic acid [30–32], cellulose derivatives [33] or macromonomers of poly(ethylene glycol) (PEG) [34,35]. For a chemical hydrogel, the addition of chemical initiators or any other treatments for triggering chemical reactions in the body may bring with biocompatibility problems to a certain extent. Physically crosslinked hydrogels have got to be an alternative choice. For instance, Ishihara et al. prepared physical hydrogels of phospholipid polymers crosslinked by Fe^{3+} and successfully prevented peritendinous adhesion in a chicken model [7]. Among physical hydrogels, thermoreversible hydrogels are very attractive due to their spontaneous gelling behaviors at the body temperature and avoidance of any *in vivo* reaction or extra additives [3,36,37]. Thermosensitive Pluronic® (Poloxamer) has been used to prevent postsurgical adhesion [38]; however Pluronics are nondegradable and the disappearance of the hydrogel is just by dissolution in

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water, which suffers from short persistence time *in vivo*, usually less than 2 days, and thus further weak chemical crosslinking is still required [39].

Thermoreversible hydrogels composed of polyester and polyether are particularly interesting because they are biodegradable and exhibit relatively long persistence. Our group has also investigated some thermoreversible physical hydrogels of amphiphilic block copolymers composed of hydrophilic PEG and hydrophobic biodegradable polyesters such as polylactide (PLA), polyglycolide (PGA), polycaprolactone (PCL) or their copolymers [40,41]. The concentrated polymeric aqueous solution is able to be gelled due to the formation of percolated micelle network [42,43]. The resulting hydrogels have shown potentials as drug delivery carriers [44–46] and tissue engineering materials [47]. However, there is little work on examination of its prevention of post-operative intestinal adhesion in the literature.

Herein, we report that the poly(ε-caprolactone-*co*-lactide)-*b*-poly(ethylene glycol) -*b*-poly(ε-caprolactone-*co*-lactide) (PCLA–PEG–PCLA) triblock copolymer hydrogel could serve as a barrier material to prevent post-operative intestinal adhesion, as schematically presented in Fig. 1. The hydrophobic blocks will be copolymerized by ε-caprolactone (CL) and D,L-lactide (LA) to avoid the crystallinity of PCL blocks in the desired *sol* state [48–50]. Besides, the presence of CL reduces the acidic effect of degradation products compared with using LA alone. The concentrated polymeric aqueous solution could form a physical hydrogel with a *sol–gel*

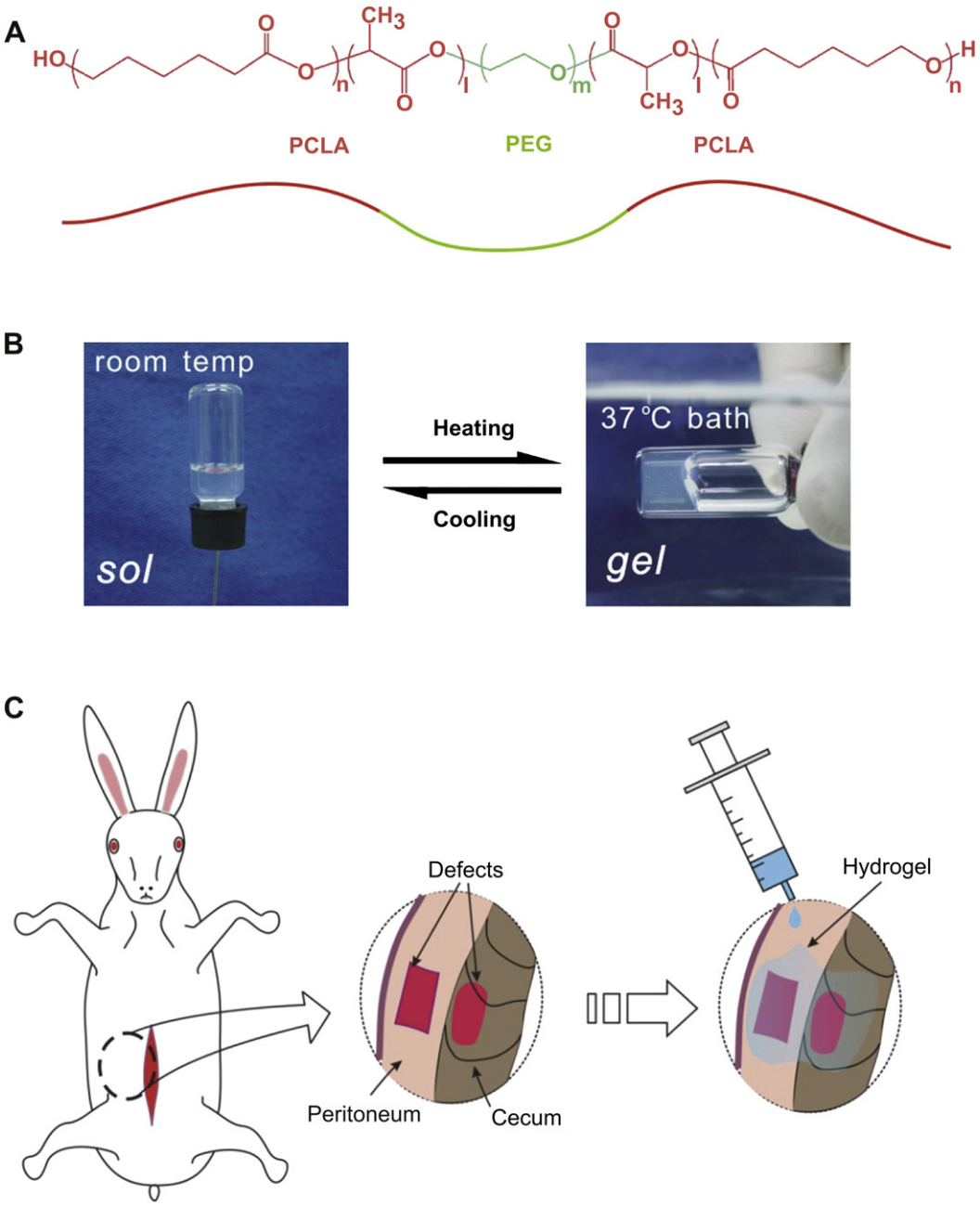

Fig. 1. (A) Chemical structure of PCLA–PEG–PCLA and a presentation of this amphiphilic block copolymer; (B) Photographs of the polymer solution (20 wt% in the normal saline solution) exhibiting a *sol* at room temperature and a *gel* after heated to the body temperature; (C) Schematic diagram showing the application of the PCLA–PEG–PCLA hydrogel onto a peritoneal wall defect of a rabbit. The defect (4×3 cm^2) comprising the parietal peritoneum and a layer of muscle (~1 mm thick) was excised starting 1 cm from the midline of peritoneal wall, and the corresponding site on cecum was abraded until bleeding by a surgical brush.