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Surgical suture braided with a diclofenac-loaded strand of poly(lactic-*co*-glycolic acid) for local, sustained pain mitigation

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ABSTRACT

In this work, we propose a surgical suture that can sustainably release diclofenac (DF) for the local pain relief of surgical wounds. We separately fabricated a DF-loaded strand composed of a biodegradable polymer, poly(lactic-*co*-glycolic acid) (PLGA), which was then braided with a surgical suture already in clinical use, i.e., VICRYL™. In this way, the drug-delivery suture presented herein could release DF in a sustained manner for 10 days while maintaining the mechanical strength needed for wound closure. According to the in vivo results of an induced-pain animal model, the drug-delivery suture mitigated pain throughout the period of persistent pain. The histological analysis of tissue around the sutures showed that the drug-delivery suture exhibited biocompatibility comparable to that of the VICRYL™ suture in clinical use.

1. Introduction

To treat local, surgical pain in clinical settings, patients are often prescribed drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), to be administered systemically via the oral route or injection [1,2]. As pain generally persists after surgery, long-term, repeated drug administrations are required until the surgical wounds have completed healing. Such long-term systemic drug exposure can cause adverse side effects, including Reye's syndrome, platelet dysfunction and renal impairment [3,4]. Moreover, for oral administration, drug bioavailability, especially at the local level in the wounded site of interest, could be low due to the first-pass metabolism of the liver [5,6]. Therefore, to be effective, frequent oral administrations or high drug doses are often needed, which may cause gastric hemorrhage, ulcer perforation or gastrointestinal tract obstruction [7,8].

As such, local drug delivery is considered advantageous for treating pain at surgical wound sites. Therefore, in this study, we pursued to alleviate the pain via local drug delivery only in a way of promoting the pain relief efficacy, as well as minimizing the side effects possibly caused by conventional systemic drug exposure. In this sense, surgical sutures can be considered good candidate devices for incorporation with local drug-delivery functionality. Sutures could close wounds while concurrently relieving pain via local drug release. Many surgical sutures already available for clinical use are made of various biocompatible polymers, such as polycaprolactone, polydioxanone, poly(lactic acid), poly(glycolic acid) and poly(lactic-*co*-glycolic acid) (PLGA) [9–11]. Sutures eluting the anti-infective drug, triclosan, have already been commercialized [12]. For drug elution, sutures have mostly been dip-coated in a drug solution [13–17]. However, this strategy may degenerate the inherent mechanical properties of the suture, which are required for proper wound closure [16].

The sustained release of a pain-reliever is advantageous for treating pain persisting during wound healing. However, this type of release is not easily achievable via conventional dip-coating processes [18]. Therefore, we propose a biodegradable surgical suture that is physically braided with a drug-delivery carrier to allow local, sustained drug release while maintaining its own mechanical properties. To accomplish this, we separately fabricated a polymer strand containing a pain-relief drug and physically braided it with a commercially available surgical suture (VICRYL™, Ethicon, USA). According to this approach, we

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could modulate drug-release scenarios by varying the drug-delivery strand without affecting the suture itself. In this study, we employed diclofenac (DF) as an NSAID pain-reliever [19]. DF is a COX-2-specific targeted inhibitor that reduces the secretion of prostaglandin, which is a known factor involved in the generation of pain [20,21]. For pain-relief indications, DF is already approved for clinical use via both oral administration and injection [22,23].

In this work, to achieve sustained drug release, we first prepared a sheet by electrospraying a solution containing a blend of the biodegradable polymer, PLGA and DF. The drug-loaded sheet was then cut into strands to be braided with a surgical suture (VICRYL™ W9114, Ethicon, USA). We characterized the drug-delivery strand via X-ray diffraction and Fourier transform infrared (FTIR) spectroscopic analyses. To examine the mechanical properties of the suture braided with the drug-delivery strand (i.e., the drug-delivery suture), a tensile strength test was performed. The drug-delivery suture was also applied in an induced-pain rat model to examine in vivo pain-relief efficacy.

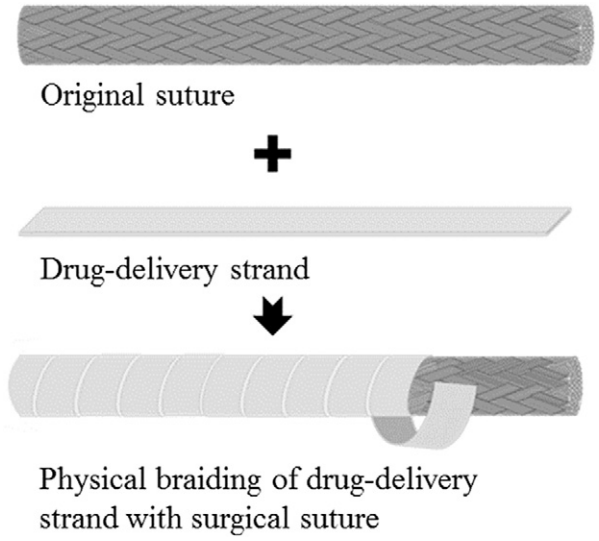

Fig. 1. Schematic showing the process of preparing the drug-delivery suture.

2. Materials and methods

2.1. Materials

PLGA (50:50; end-capped; average MW = 58 kDa; inherent viscosity = 0.41 dl/g) was obtained from Lakeshore Biomaterials (Birmingham, USA). Diclofenac sodium and phosphoric acid were purchased from Sigma-Aldrich (MO, USA). The biodegradable surgical sutures (3-0 VICRYL™ W9114) were purchased from Ethicon (NJ, USA). Dimethylformamide (DMF), dichloromethane (DCM), potassium phosphate and sodium hydroxide (NaOH) were acquired from Daejung (Siheung, Korea). Acetonitrile (ACN) was purchased from JT Baker (NJ, USA). Zoletil 50 was purchased from Virbac (TX, USA), and xylazine was purchased from Bayer (Lerverkusen, Germany). Paraformaldehyde (4%) was supplied from Korea CFC (Ansan, Korea). For the hematoxylin and eosin (H&E) staining, xylene, ethanol and hydrochloric acid (35–37%) were purchased from Duksan Pure Chemicals (Ansan, Korea). Ammonia solution (28–30%) was obtained from Junsie Chemical (Tokyo, Japan). Modified Mayer's Hematoxylin and Eosin Y solutions were supplied by Richard-Allan Scientific (MI, USA). Paraffin was supplied from Merck (NJ, USA).

2.2. Fabrication of drug-delivery strands and sutures

In this work, we first prepared a PLGA sheet loaded with DF. For this, both PLGA (4% w/v) and DF (5% w/w) were dissolved in a solvent mixed with DMF and DCM (1:100, v/v), and the solution was then electrosprayed for 3 h under the following conditions (Nano NC, Siheung, Korea): voltage, 25 kV; infusion rate, 10 ml/h; distance between tip and collector, 10 cm; and needle, 24 G. We also prepared a sheet of PLGA only as a control by electrospraying a PLGA solution in DCM (4% w/v) under the same conditions stated above. The resulting sheet was cut into strands, 1.5 mm in width, which were then braided with a VICRYL™ surgical suture, as shown in Fig. 1. Thus, we prepared two distinct strands: the strand cut from a PLGA sheet loaded with DF (i.e., the PLGA_DF strand) and the strand cut from a sheet of PLGA only (i.e., the PLGA strand). The assembled sutures were treated at 47 °C for 1 h to improve strand attachment and were then sterilized using an ethylene oxide gas [24]. Thus, we employed three distinct sutures in this work: the intact VICRYL™ suture (i.e., the original suture); the suture assembled with a PLGA_DF strand (i.e., the PLGA_DF suture); and the suture with a PLGA strand (i.e., the PLGA suture).

2.3. Characterization methods

To measure the thickness of a strand, 5 different locations from a single strand were randomly selected and measured using a micrometer (Mitutoyo America, IL, USA). To examine the presence of DF and PLGA, the strand was examined by FTIR (JASCO, Japan) in a range of 400–4000 cm^{-1} with a resolution of 4 cm^{-1} using the KBr disk method. The strands were also assessed with an X-ray diffractometer (D/MAX RINT 220-Ultima, Rigaku, Japan), where Ni-filtered CuK_{α} radiation at a wavelength of 1.5418 Å was used to scan the samples at a constant rate of 2°/min and a tube voltage of 40 kV with a current of 30 mA. To measure the residual solvent, 8 mg of the PLGA_DF strand was fully dissolved in chloroform, and 2 μl of the resulting solution was assessed with gas chromatography–mass spectrometry (GC–MS; Agilent technologies 7890B/5977A GC/MSD, USA) under selected ion monitoring mode using an Agilent DB-624 column (30 m × 0.25 mm × 1.4 μm). During measurement, the flow rate was set at 1 ml/min, and the temperature was increased from 50 °C to 100 °C at a rate of 5 °C/min and from 100 °C to 240 °C at a rate of 20 °C/min.

We imaged all the sutures with scanning electron microscopy (SEM; 7501F, JEOL, Japan). To investigate the mechanical properties of the sutures, the straight- and knot-pull tests were performed using a universal testing machine (UTM; Instron 5543, MA, USA) with a 1-kN load cell [25]; the sutures were pulled at a cross-head speed of 200 mm/min. To measure the amount of loaded DF, 4 cm of the PLGA_DF suture was fully dissolved in 10 ml of DMF, an aliquot of which was measured at 276 nm with a spectrophotometer (UV-1800, Shimadzu, Japan) [26].

2.4. In vitro drug-release study

To examine the in vitro drug release profiles, the PLGA_DF suture was cut into 1-cm pieces, and 4 randomly selected pieces were placed into 1 ml of pH 7.4 phosphate-buffered saline (PBS), which was shaken at 125 rpm at 37 °C. At the scheduled times of 1, 2, 3, 5, 7 and 10 days, 1-ml aliquots were collected and replaced by an equal volume of fresh PBS. The aliquot was measured via high-performance liquid chromatography (HPLC; 1260 Infinity Quaternary LC system, Agilent, CA, USA) with a C_{18} analytical column (150 mm × 4.6 mm; 5 μm) [27]. The UV detection was set at 270 nm, and the mobile phase consisted of ACN and 20 mM PBS at pH 2.5 (40:60, v/v).

2.5. In vivo pain-relief evaluation

To evaluate pain relief in vivo, we prepared an induced-pain animal model based on the protocol we used in a previous study [28]. For this evaluation, 9-week-old Sprague-Dawley rats were used, and the animals were maintained under a 12-h light/dark cycle with free access to food and water. All in vivo procedures were approved by the Institutional Animal Care and Use Committee at Seoul National University