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Spatiotemporal Programing for the On-Demand Release of Bupivacaine Based on an Injectable Composite Hydrogel

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ABSTRACT

We report a programed drug delivery system that can tailor the release of anesthetic bupivacaine in a spatiotemporally controlled manner. The drug delivery system was developed through the combination of a collagen-based injectable hydrogel and 2 types of poly(lactic-co-glycolic acid) (PLGA) particles. As a rapid-release platform (90% release after 24 h), bupivacaine hydrochloride was incorporated into collagen/poly(γ-glutamic acid) hydrogel, which exhibited gel formation at body temperature. PLGA microparticles (diameter 1-3 μm) containing bupivacaine base showed a very slow release of bupivacaine (95% after 240 h), whereas PLGA nanoparticles (124 ± 30 nm) containing bupivacaine base demonstrated an intermediate release rate (95% after 160 h). By changing the relative composition ratio between the 3 components in these injectable composite hydrogels, the release of bupivacaine could be easily controlled from very rapid (within 1 day) to very delayed (up to 9 days). The experimental results on the release data (cumulative release, time point release, average release rate) were coincident with the release profile generated by computer simulation. These injectable composite hydrogels with systematically tunable mixing ratios are expected to serve as a promising technology for the on-demand release of bupivacaine in pain management.

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Introduction

Pain represents a protective mechanism that acts as a warning system and has adaptive value. Abnormalities in sensing pain lead to serious consequences that can be life threatening.[1,2] However, unrelieved and severe acute pain, especially during postoperative course or trauma, has many undesirable effects on respiratory, cardiovascular, gastrointestinal, and urinary systems. Furthermore, acute pain causes anxiety and mental illness and prolongs the recovery period after surgery.[3,4] Bupivacaine is a local anesthetic drug that is widely used in clinical practice, such as for intraoperative local anesthesia, postoperative analgesia, and in chronic pain treatment.[5] Owing to the relatively short half-life (about 3.5 h) of bupivacaine, many formulations have been investigated to achieve extended postoperative pain relief. For example, liposomal bupivacaine has been shown to prolong the duration of action in animals and humans.[6,7] However, the disadvantages of liposomes include their rapid elimination from the blood and the capture of the liposomal preparations by the reticuloendothelial system, primarily in the liver.[8] Another approach to prolong the blockade period of bupivacaine involves the use of biodegradable polymer particles. This system allows for treatment with smaller total drug doses and minimizes side effects.[9]

In this study, we have developed a programed drug delivery system that has the ability to tailor the release profile of bupivacaine over wide range of time periods. To effect spatiotemporal programing of the on-demand release of bupivacaine, we suggested a novel type of injectable composite hydrogel fabricated through the combination of a collagen-based injectable hydrogel and 2 types of poly(lactic-co-glycolic acid) (PLGA) particles (Scheme 1). Hydrogels comprise hydrophilic polymer networks that become swollen in aqueous environments owing to water absorption.[10] This material has a variety range of applications in biomedical and pharmaceutical practice including tissue engineering, drug delivery, contact lenses, and wound dressings.[11,12] In particular, injectable hydrogels that are able to form a gel following injection have attracted much attention because the low viscous sol state under ambient conditions may be transformed into a nonflowing gel state under physiological conditions in the body. Such *in situ* gel-forming hydrogels can be used for the local delivery of

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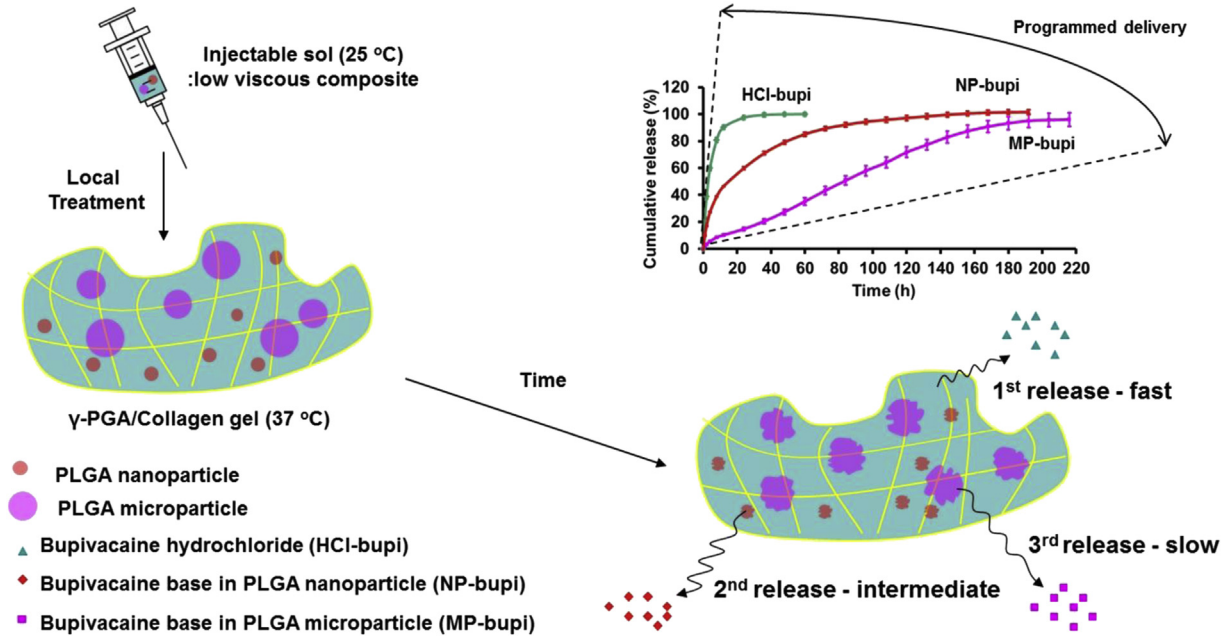

Scheme 1. Programed injectable composite hydrogel for the controlled release of bupivacaine. Two types of PLGA particles (MPs, NPs) containing bupivacaines were dispersed in a collagen/γ-PGA mixture, which is in a sol state at ambient temperature (at 25°C), whereas it is expected to form a gel after injection into the body. Bupivacaine hydrochloride is first released from the hydrogel in a very rapid manner, followed by a slower release from PLGA MPs and NPs.

therapeutic drugs in specific regions with consequent controlled release. Here, a novel type of *in situ* gel-forming hydrogel was generated by combining collagen and poly(γ-glutamic acid) (γ-PGA). The system has been previously reported as a biodegradable cohesive plug cross-linked with water-soluble carbodiimide.[13] The novelty of this study is that we avoided the use of any chemical cross-linker which can cause several toxicities to the surrounding tissue.[14] Furthermore, our hydrogel is quite flexible and easy to handle at room temperature, and it becomes a gel at body temperature. The advantage of our material is the temperature-dependent gelation which cannot be observed in chemically cross-linked systems.

Collagen is considered as one of the most important hydrogel components owing to its biocompatibility and biodegradability. This fibrous protein is characterized as an elegant structure comprising a right-handed cluster of 3 parallel, left-handed polyproline-II-type helices.[15-18] γ-PGA is a water-soluble, nontoxic, and anionic biopolymer produced by *Bacillus subtilis*.[19-22] PLGA is considered as one of the most attractive biodegradable synthetic polymers for biomedical applications and is currently approved for clinical use in humans by the US Food and Drug Administration.[23] Microparticles (MPs) and nanoparticles (NPs) made from PLGA have been extensively used as platforms to tailor the release rate of drug in the body.[24,25] The chemical structures of bupivacaine, PLGA, and γ-PGA are shown in Figure 1.

Here, we presented a novel type of drug delivery system that is capable of delivering bupivacaine into specific regions of the body over a specified time period, by combining the different release profiles of bupivacaine hydrochloride (HCl-bupi) in an injectable hydrogel and bupivacaine base encapsulated in PLGA NPs or MPs (Scheme 1).

Materials and Methods

Materials

PLGA (D,L-lactide-co-glycolide) (Resomer® RG502H, monomer ratio 50:50, M_W = 10-12 kDa) was purchased from Boehringer Ingelheim (Ingelheim, Germany). Polyvinyl alcohol (PVA, 80% hydrolyzed, M_W 9-10 kDa) was purchased from Sigma-Aldrich (St. Louis, MO). γ-PGA (M_W = 500 kDa) was obtained from Bioleaders Corporation (Daejeon, South Korea). Type 1 Atel-collagen from porcine skin (Matrixen™-PSP) was purchased from Bioland

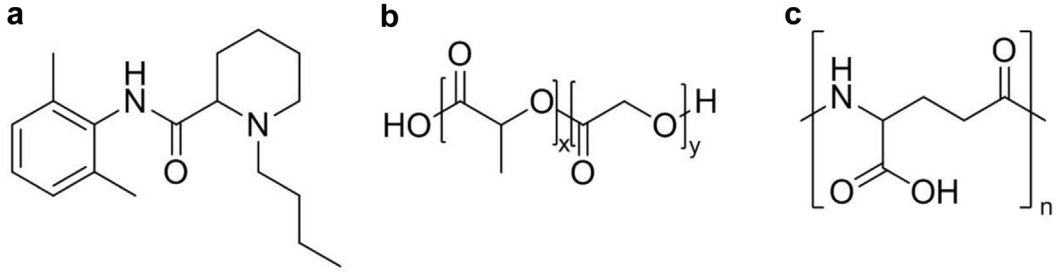

Figure 1. Chemical structure of (a) bupivacaine (M_w = 288.43), (b) poly(lactic-co-glycolic acid) (M_w = 10-12 kDa), and (c) poly(γ-glutamic acid) (M_w = 500 kDa).

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