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Biodegradable micro-osmotic pump for long-term and controlled release of basic fibroblast growth factor

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Abstract

Microelectromechanical system (MEMS) technology not only provides the possibility of integration of multiple functions but also enables more precise control of dosing of therapeutic agents when the therapeutic window is very limited. Local delivery of basic fibroblast growth factor (bFGF) over a specific dose and time course is critical for mesenchymal tissue regeneration. However, bFGF is degraded quickly in vivo and difficulty of controlling the dose level impedes its effective use in angiogenesis and tissue regeneration. We constructed biodegradable micro-osmotic pumps based on MEMS technology for long-term controlled release of bFGF. The devices were constructed by micro-molding and thermal assembly of 85/15 poly(L-lactide-co-glycolide) sheets. The release of bFGF was regulated at 40 ng/day for four weeks; bioactivity was assessed by monitoring the growth of 3T3 fibroblasts. The proposed devices can be further miniaturized and used for the delivery of multiple therapeutic agents at the individual releasing schedules.

Keyword: Controlled drug delivery; MEMS; Micro-fabrication; Osmotic pump; Biodegradable polymers; PLGA; Basic fibroblast growth factor

1. Introduction

Micro- and nanosystems for drug delivery offer the possibility of integration with diagnostic functions or implants and allow precise dosage control for highly potent drugs [1–3]. Recent examples include micro-particles for oral delivery [4,5], micro-needles for transdermal delivery [6], micro-fluidic probes for convection enhanced drug delivery [7], micro-pumps based on osmosis [8] or piezoelectricity [9], electro-chemically controlled micro-chips [10,11], and micro-fabricated nanochannel systems [12]. Even though micro-fabricated materials for these microelectromechanical system (MEMS) drug delivery devices showed biocompatibility and reduced biofouling [13], the non-degradability of these devices is still disadvantageous in comparison to devices made of biodegradable materials.

There have been great advances in delivery devices made of biodegradable polymers. However, most of these relied on polymer erosion for controlled delivery [14–20]. As this erosion-based control depends on the property of polymers, it limits effective treatment of a disease when more delicate control of drug release is necessary. MEMS technology has shown great promise for more versatile and precise control of many chemicals. Nonetheless, less work of MEMS has been done on biodegradable materials, mainly due to the absence of appropriate technologies. A few examples include sandwich devices made of a biodegradable polymer by 3D printing [21] and micro-reservoir devices with the biodegradable membranes for pulsatile delivery [22]. However, there still remains great need for further improvement of MEMS-based drug delivery devices. In particular, more attention needs to be paid to the delivery of relatively unstable therapeutic molecules such as peptides and growth factors.

In the United States, approximately 800,000 surgical procedures are performed annually in which some form of bone graft is used [23]. Autograft bone has been used in diverse clinical situations such as in spinal fusion, fractures, non-unions, revision total joint replacements, and tumors. However, autograft bone is limited in supply and the morbidity associated with harvesting of bone from a remote site may be substantial [24–

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29]. Bone graft substitutes and extenders attempt to limit the use of autologous bone grafts. The use of allograft bone, ceramics, demineralized bone matrix, and composite grafts may become more effective when it is combined with bone derived growth factors [30–32].

Basic fibroblast growth factor (bFGF) is a protein with autocrine and paracrine effects, and affects numerous cell types in different systems in the body. In bone, bFGF is produced by cells of the osteoblastic lineage. Its major effects on bone include the induction of neovascularization, and modulation of osteoblastic proliferation and differentiation. It has been shown that addition of bFGF enhances the incorporation of allograft bone in rats in a dose- and time-dependent manner and accelerates the healing of fractures in rabbits [33,34]. For these reasons, local delivery of bFGF could potentially be advantageous in clinical scenarios of bone loss and repair, such as fracture healing, periprosthetic osteolysis, etc. Ideally, delivery devices of bFGF can be placed proximate to fracture sites by wrapping the devices around the fractured bones during the surgery, or incorporating the devices into implants during primary or revision total hip replacement for enhancing oseeointegration and reducing osteolysis. Due to the relatively short half-life time of bFGF in vivo [35], effort has been focused on the delivery of bFGF over a more prolonged time period [36–42]. However, most of the methods have delivered bFGF over only a few days or required complex processes to synthesize delivery vehicles.

We have developed biodegradable MEMS devices for delivery of growth factors for a prolonged time period. The MEMS devices are comprised of a drug reservoir and micro-channels which connect between the reservoir and the open end of the micro-channels. The MEMS device operates by either osmotic or diffusion pumping depending on the choice of geometric parameters and water permeability of polymers used. In this study, stronger osmosis was induced by enlarging the area of the water-permeable membrane and incorporating highly potent osmotic agents (polyethylene glycols). The diffusional delivery was suppressed by elongating the micro-channels. The release of the bFGF from the MEMS devices was maintained at a constant level of 40 ng/day on average over four weeks. The corresponding bioactivity of the released bFGF was maintained 80% except during the first week (30% bioactivity). In addition, the effect of micro-channel length on the release profiles of the devices was investigated. It was shown that elongation of micro-channels down-regulated the release of fluorescent red dye for two weeks.

2. Materials and methods

2.1. Device design and principle

A thin biodegradable device as an osmotic pump was designed for sustained and constant release of growth factors. The pumping device was micro-fabricated on a layer of a synthetic biodegradable polymer by micro-molding. A diagram of the device is shown in Fig. 1. The bottom layer (75 μm thick) contains a reservoir ($A=2$ cm^2, depth$=50$ μm)

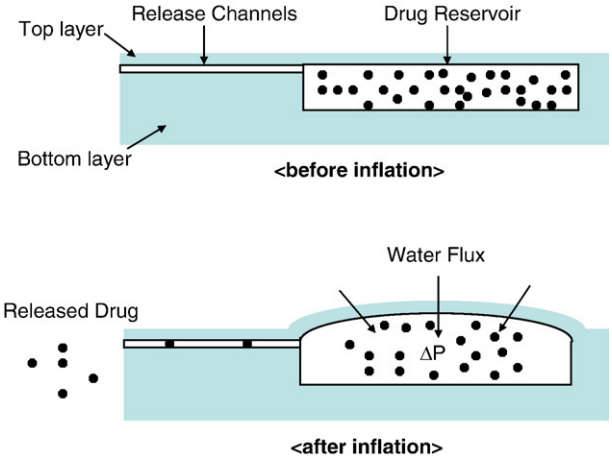

Fig. 1. Device configuration and principles of operation. The device has a micro-fabricated reservoir and four micro-channels in a biodegradable polymer layer. This layer is sealed by another biodegradable polymer layer. Drugs and osmotic agents are loaded in the reservoir. Water flows into the reservoir by osmosis and a hydrostatic pressure builds up in the reservoir leading to the inflation of the device. This pressure drives drug molecules through release channels to the outside of the device.

for drugs and micro-channels (50×50 μm^2) for release of the drugs. Another layer (25 μm thick) of the 85/15PLGA acts as a semi-permeable layer (water permeability, $k=1\times10^{-21}$ m^2/Pa s). Once the device is immersed in an aqueous environment, osmotic pressure drives water into the reservoir area, as shown in Fig. 1. This inflates the reservoir and the internally-built pressure begins to propel drugs through the micro-channels.

The release rate from the proposed devices can be estimated from an osmotic pumping principle [43]. When the device operates in the steady state condition, the osmotic delivery rate of any substance contained in the devices is given by:

$$\left(\frac{dm}{dt}\right)_{\text{osmotic}} = \left(\frac{dV}{dt}\right)_{\text{osmotic}} \cdot C = \frac{A}{h} k \cdot \Delta\pi \cdot C \tag{1}$$

where dm/dt is the osmotic release rate; dV/dt is the volume flux of a solvent; $\Delta\pi$ is the osmotic pressure; C is the concentration of a substance to be delivered; k is the water permeability; A is the membrane area; h is the membrane thickness. Once the device is fully inflated by the in-flux of water through the reservoir membrane, the solution in the reservoir starts flowing through the micro-channels. This solution flow through the micro-channels is governed by Poiseuille's law [44]:

$$\frac{dV}{dt} = -\frac{wh^3}{12\mu}\frac{\Delta P}{L} \tag{2}$$

where dV/dt is the volume flow rate; w, h, and L are the width, depth, and length of a channel, respectively; μ is the viscosity of a solution; ΔP is the pressure difference between the inside and outside of the device. As long as the ΔP remains constant, the release profile can be modulated by the change of the geometric parameters.