공학석사학위논문

Polymeric Tube-Shaped Devices with Controlled Geometry for Programmed Drug Delivery

프로그램형 약물전달을 위한 기하학적으로 제어된 고분자 튜브형태의 디바이스

2012년 8월

서울대학교 대학원

바이오엔지니어링 협동과정

박 민

Polymeric Tube-Shaped Devices with Controlled Geometry for Programmed Drug Delivery

지도교수 최 영 빈

이 논문을 공학석사 학위논문으로 제출함

2012년 6월

서울대학교 대학원

바이오엔지니어링 협동과정

박 민

박 민의 석사학위논문을 인준함

2012년 8월

위 원 장 _____ (인)

부 위 원 장 _____ (인)

위 원 _____ (인)

Abstract

Polymeric Tube-Shaped Devices with Controlled Geometry for Programmed Drug Delivery

Min Park

Interdisciplinary Program of Bioengineering

College of Engineering

Seoul National University

We developed a modular tube-shaped device as a proof of principle to enable programmed release of encapsulated molecules for controlled drug delivery. Each drug-delivery

tube module was prepared by assembling two separate silicone tubes in series, one filled with a model compound (sodium fluorescein) and the other with a diffusional barrier material, polyethylene oxide (PEO). We varied the length of the PEO-filled tubes to control release from the drug-delivery tube devices. The onset times and periods of drug release increased with the length of the PEO tube in the drug-delivery tube device. To program drug release, therefore, we prepared devices with combinations of drug-delivery tube modules with PEO-filled tubes of different lengths. The combination of drug-delivery tubes with PEO-filled tubes each with very different lengths achieved pulsatile drug release, while a continuous drug release was realized by using a collection of PEO-filled tubes with small differences in length. We conclude that the modular combination of drug-delivery tubes, each composed of a diffusion-barrier tube of different length, demonstrates potential applications in programmed drug delivery.

Keywords : Continuous drug release, Drug-delivery tube, Polyethylene oxide (PEO), Programmed drug delivery, Pulsatile drug delivery, Silicone

Student Number : 2010 - 23351

List of Tables

List of Figures

tubes, each equipped with a PEO tube of different length (a) during the whole release period and (b) just for the period after the onset of drug release (i.e., the profiles with omitting the period of delayed drug release)

Figure 8. Optical images of the combinations of (a) 0.5DDT, 1.5DDT and (b) 1DDT and 3DDT

Figure 9. Optical images of the combinations of (a) 0.5DDT, 1.5DDT and (b) 1DDT and 3DDT

Figure 10. Optical images of the combinations of (a) 1DDT, 1.5DDT and (b) 1DDT, 1.5DDT and 2DDT

Figure 11. In vitro drug release profiles from the combinations of (a) 1DDT and 1.5DDT and (b) 1DDT, 1.5DDT and 2DDT in the PBS at pH 7.4 at 37 ℃. The dashed lines show the linear least linear square fits to the in vitro release data (a) from 2 d to 9 d and (b) from 2 d to 14 d, suggesting a fairly good correlation with zero-order release (R^2>0.98)

Figure 12. In vitro drug release profiles from the combinations of (a) 1DDT and 1.5DDT and (b)1DDT, 1.5DDT and 2DDT in the PBS at pH 7.4 and 37 ℃. A dashed line shows a drug release profile predicted with the experimental data from the individual drug-delivery tubes shown in Figure 8

Contents

1. Introduction

Controlled drug release systems have attracted attention for several decades to enhance drug bioavailability and reduce side effects, thereby improving therapeutic efficacy and patients' compliance[1, 2]. To achieve this goal, many drug delivery systems focus on sustained drug release to maintain drug concentration in a therapeutic window for a prolonged period of time[3]. Although such a sustained release property was indeed advantageous for drugs such as an anti-inflammatory drug [4], this regimen is not always applicable to all different types of drugs. For example, a lag phase of drug release would be needed for treatment of diseases like asthma and angina pectoris, where pulsatile drug release may be advantageous especially to satisfy the circadian rhythm requirements of diseases [5]. A pulsatile drug release profile may also be beneficial for delivery of some bioactive agents, such as hormones or vaccines [6, 7]. In this sense, a drug delivery system, which can be easily manufactured to

customize for a specific drug delivery profile, either continuous or pulsatile, is needed for its wide applicability to many different types of the drugs.

Various types of implantable drug delivery devices have been suggested to achieve pulsatile or continuous drug release. For example, polymeric microparticles have been widely studied for continuous drug delivery due to their ease of fabrication and simplicity of administration [7]. However, achieving precise control of drug release is difficult since drug release is mostly determined by drug diffusion or polymer degradation through microparticles, typically with wide size distribution. In addition, many polymeric microparticles often exhibit an initial burst of drug release and thus, may not be suitable especially for hydrophilic or small-molecule drugs [8-10].

One of the strategies to achieve more active control of drug delivery would be the use of microfabricated devices [11]. A sophisticated structure can be fabricated in a micron scale to tailor the drug loading and releasing amounts precisely, providing exceptional chances for programmed drug release

[12]. Thus, numerous devices have been microfabricated to give porous membranes, needles and fluidic channels embedded on microchips, which were often equipped with micro-pumps or -valves to actively control drug release [13, 14]. However, these devices often require additional units, such as a power supply, which is usually bigger than the drug-delivery system itself, to work in programmed manners, hence a bulky device for administration [11, 15]. Besides, the microfabrication method is not simple, requiring a multi-step process [16].

2. Strategy

In this work, we propose a drug delivery system for programmed drug release with a simple assembly of drug-delivery tube modules as a proof-of-principle device. For many years, drug-delivery tubes have been studied and commercialized [17-19]. These systems, however, were designed mainly for a sustained drug release for a long-term period. On the other hand, the drug-delivery tubes prepared

in this work were purposed to customize drug release, either pulsatile or continuous release, just by controlling the geometry of the tubes and the combination of multiple drug-delivery tube modules. As discussed below, we believe that the concept of using a polymer-filled tube as a kind of "fuse" that determines the onset of drug delivery has not been reported before.

To prepare a single drug-delivery tube, we first filled two distinct silicone tubes with a model compound (sodium fluorescein) and a polymer, polyethylene oxide (PEO), respectively, which were then aligned and assembled in series. The tube material, silicone is already widely accepted as an implantable biomaterial [20]. PEO was selected as the barrier material because it is biocompatible [21] and also easy to process due to its relatively low melting temperature (~ 65 ℃). The silicone tube filled with fluorescein acted as a drug reservoir (i.e., the drug tube) and the one filled with PEO worked as a diffusion barrier (i.e., the PEO tube) (Fig. 1). In this way, there is a delay time as the water diffuses into

the PEO tube. After the diffusion, the water reaches the drug tube and dissolves the drug powder, giving freed drug molecules in solution. Then, the drug diffuses out via the PEO tube. To control drug release from each of the drug-delivery tubes, therefore, we varied the length of the PEO tube: the longer the PEO tube, the later the onset of drug release and the longer the period of drug release.

However, from this single drug-delivery tube, the only possible profile of drug release would be a lag phase followed by a sustained pattern of drug release. Therefore, we combined multiple drug-delivery tube modules in parallel, each equipped with a PEO tube of different length, to obtain a variety of drug release profiles. For example, to realize pulsatile drug release, we combined a collection of drug-delivery tubes that possess a wide gap between the onset times of drug release (i.e., a large difference in length of the PEO tubes). To realize continuous or sustained drug release for a prolonged period of time, we combined the drug-delivery tubes that possess a small gap between the onset

times of drug release (i.e., a small difference in length of the PEO tubes). This modular approach allows the combination of drug-delivery tubes, each simple in design, to achieve complex drug delivery profiles.

The diameter of the tubes used in this work was 2 mm at most to envision minimally invasive implantation of the device. The size is as small as typical implantable electrodes or catheters in clinical use [22, 23], although we are working on still smaller drug-delivery tube systems for future study. Considering biocompatibility, we minimized the number of materials utilized to prepare the drug-delivery tubes in this work. Only silicone and PEO were chosen to be the tube and diffusion-barrier materials, respectively, both of which are known to be biocompatible after implantation [21, 24]. Although the PEO (MW = 600,000 Da) employed in this work may cause toxicity when delivered in a large dose (> 100 g) in human [25], this is not expected to be a significant concern in our system, since the total amount of PEO in a combination of drug-delivery tube modules in this work (< 300 mg) was more

than two orders of magnitude less than the dose of toxicity. In addition, the daily release of PEO should be much smaller due to its slow dissolution via the tube.

3. Experimental

I. Materials

Polyethylene oxide (PEO; average MW = 600,000) and sodium fluorescein were purchased from Sigma (MO, USA). Medical epoxy (EPO-TEK®301-2) was obtained from Epoxy Technology (Billerica, USA). Silicone tubes of two different sizes (1 mm in inner diameter and 1.5 mm in outer diameter; 1.5 mm in inner diameter and 2 mm in outer diameter) were purchased from Han Mi (Korea). Phosphate-buffered saline (PBS; pH 7.4) was obtained from the Clinical Research Institute in Seoul National University Hospital.

II. Preparation of drug-delivery tubes

A drug-delivery tube was prepared by assembling a drug tube and a PEO tube in series, as described in Figure 1. To prepare

the drug tube, i.e., the tube as a drug reservoir, an empty silicone tube of about 7 cm (1 mm in inner diameter and 1.5 mm in outer diameter) was densely filled with a fine powder of a model compound (sodium fluorescein). The resulting tube was then cut to 0.3 cm, 0.4 cm or 0.5 cm to vary the drug loading amount. To prepare the PEO tube, i.e., the tube as a diffusion barrier, an empty silicone tube, 5 cm in length, (1 mm in inner diameter and 1.5 mm in outer diameter) was filled with PEO melted at 90 – 100 ℃ and then cured at room temperature for 3 h to solidify the PEO in the tube. The resulting tube was cut to 0.5 cm, 1 cm, 1.5 cm, 2 cm or 3 cm to give PEO tubes of five different lengths.

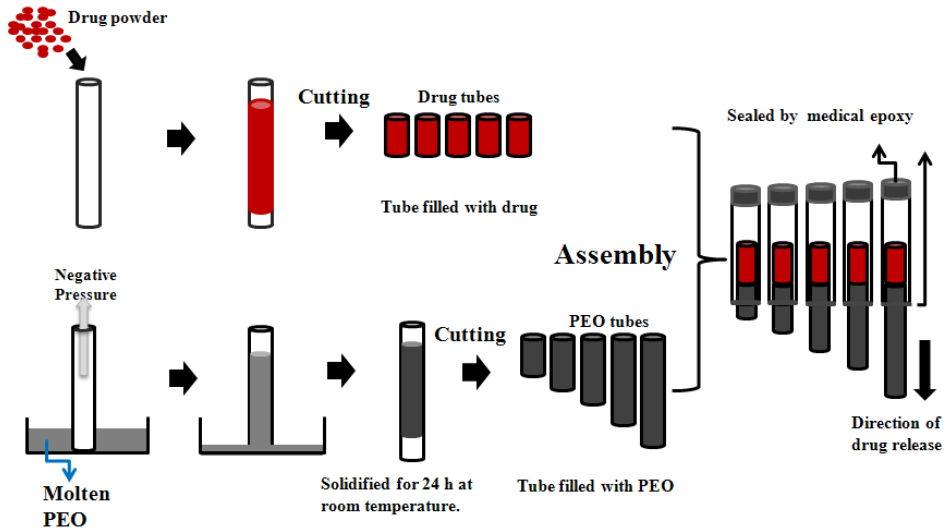


Figure 1. Schematic procedure for fabrication of drug-delivery tubes

To cut the tubes, we designed a cutting apparatus like a ‘hay cutter’ as described in Figure 2, where a caliper was installed to accurately determine the purposed length of the tube.

(a) (b)

Figure 2. Optical images of (a) the overall cutting apparatus like a hay cutter and (b) the caliper equipped to cut accurately the purposed length of the tube

To form a complete drug-delivery tube, we bonded a drug tube and a PEO tube in series with medical epoxy and cured them at room temperature for 24 h, during which the PEO could be

further solidified. The silicone layer on the tubes was not removed during this process. The resulting tubes were the then inserted into a larger silicone tube (1.5 mm in inner diameter and 2 mm in outer diameter) to prepare a drug-delivery tube. This large tube used for assembly was shorter than the combined piece of the bonded drug and PEO tubes. In this way, one end of the PEO tube could still be positioned outside of the large tube, which served as the only opening for water infiltration and drug diffusion. To prevent leakage, both ends of the large tube were sealed with medical epoxy, as described in Figure 2. Thus, in this work, we prepared five different drug-delivery tubes, consisting of PEO tubes of 0.5 cm, 1 cm, 1.5 cm, 2 cm and 3 cm length (i.e., 0.5DDT, 1DDT, 1.5DDT, 2DDT and 3DDT, respectively). All drug-delivery tubes in this work contained a drug tube of 0.5 cm and were used right after fabrication for in vitro drug release study.

III. Scanning electron microscopy(SEM)

To examine the cross-section, PEO tubes and empty tubes,

each cut to 5 mm, were placed on a SEM sample mount and sputter coated with platinum for 10 min (208HR, Cressington Scientific, England). The samples were then imaged with a scanning electron microscope (7401F, Jeol, Japan).

IV. Quantitative analysis of drug-loading amount

To analyze the amount of fluorescein filled in a tube, the drug tubes of 0.3 cm, 0.4 cm and 0.5 cm were each immersed in 100 ml of phosphate-buffered saline (PBS, pH = 7.4) to completely dissolve the drug, which was then measured at 321 nm using a UV-Vis spectrophotometer (UV-1800, SHIMADZU, USA). At least three samples were prepared and measured for each length of the drug tube.

V. Measurement of water infiltration rate into the PEO tube

To examine the rate of water infiltration into the PEO tube, a 3.5 cm PEO tube with one end sealed with medical epoxy was immersed in 5 ml PBS (pH = 7.4) at 37 ℃. At scheduled

intervals, the boundary between the solid PEO and water in the tube was found and a distance between this boundary and the opening of the PEO tube (i.e., the end not sealed with epoxy) was measured. The experiments were done in triplicate.

VI. In vitro drug release study

To examine the in vitro drug release profiles, the drug-delivery tubes were each immersed in 40 ml PBS (pH = 7.4) while continuously stirring at 125 rpm in a shaking incubator at 37 ℃. In this way, a sink condition could be maintained since even with the complete release of fluorescein from the device, the concentration (~ 0.2 mg/ml) would be well below its aqueous solubility (> 100 mg/ml). At scheduled intervals, an aliquot of release medium (5 ml) was collected and medium was added back. The sampled aliquots were measured at 321 nm using a UV-Vis spectrophotometer (UV-1800, Shimadzu, USA). The experiments were performed with three different batches for each type of drug-delivery tube.

4. Results

I. Characterization of drug-delivery tubes

We prepared drug-delivery tubes by assembling a drug tube and a PEO tube in series, as depicted in Figure 2. The drug tubes were filled with a fine powder of fluorescein particles with a size of 16 ± 9 μm (Figure 3). As shown in Table 1, a loading amount of the fluorescein could be varied in a reproducible manner, depending on the length of the drug tube.

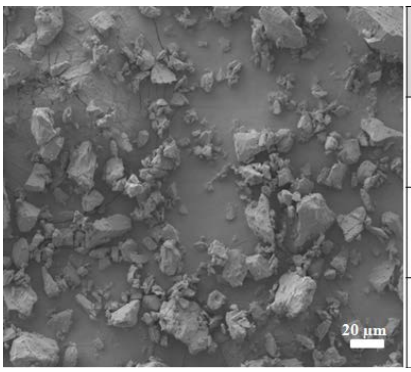


Figure 3.

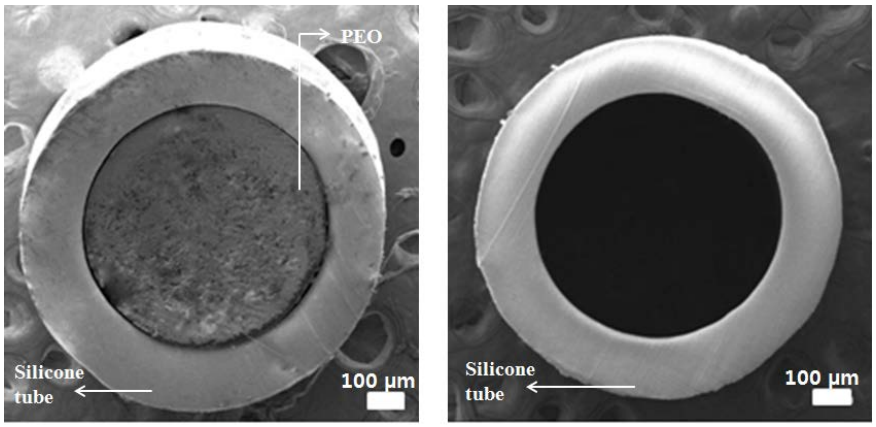
Tube length (cm)	Drug amount (mg)
0.3	1.85 ± 0.03
0.4	2.14 ± 0.05
0.5	2.62 ± 0.04

Table 1.

Figure 3. Scanning electron micrograph of the fluorescein particles

Table 1. Drug loading amounts in the drug tubes of different length

We utilized a 0.5 cm drug tube (i.e., 2.62 ± 0.04 mg of fluorescein loading) for all drug-delivery tubes prepared in this work. Figure 4 shows the cross-sections of the PEO tube, indicating that the PEO was densely and seamlessly packed in the tube with the preparation method employed in this work. The resulting tube was cut into five different lengths (i.e., 0.5 cm, 1 cm, 1.5 cm, 2 cm and 3 cm) before assembly.



(a) (b)

Figure 4. Scanning electron microphotographs of the cross-sections of (a) a tube filled with PEO and (b) an empty tube

A drug tube was aligned and bonded to a PEO tube with medical epoxy. The combined tube structure was inserted into

a larger tube for better leak prevention. Both ends of the larger tube were then sealed with medical epoxy. Therefore, the water and drug diffusion occurred only through the PEO tube. By using PEO tubes of five different lengths, 0.5 cm, 1 cm, 1.5 cm, 2 cm and 3 cm, the drug-delivery tubes prepared in this work were equipped with five distinct types of diffusion barriers, giving 0.5DDT (i.e., 0.5 cm-long PEO tube in a drug delivery tube, DDT), 1DDT, 1.5DDT, 2DDT and 3DDT, respectively. Figure 5 shows the optical images of the drug-delivery tubes prepared in this work. For all drug-delivery tube devices, we utilized a 0.5 cm drug tube and the part of the larger, outer tube sealed by epoxy extended an additional 0.3 cm. Thus, the total lengths of the drug-delivery tubes were 1.3 cm, 1.8 cm, 2.3 cm, 2.8 cm and 3.8 cm for 0.5DDT, 1DDT, 1.5DDT, 2DDT and 3DDT, respectively. The diameters of the drug-delivery tubes were 2 mm at most. Therefore, we envision that the tubes prepared in this work can be implanted via small surgical incision as suggested with the other tube-type devices previously introduced [17].

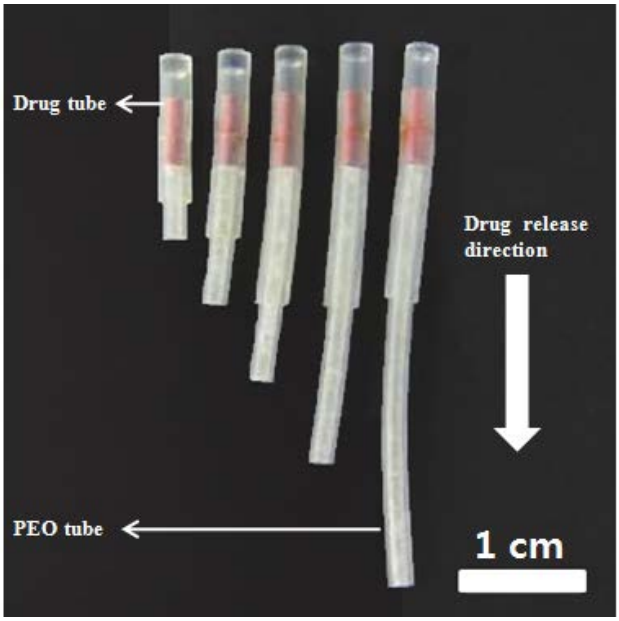


Figure 5. Optical image of drug-delivery tubes

II. Infiltration rate of water into the PEO tubes

We examined the infiltration rate of water into PEO tubes since the length of a PEO tube, i.e., the time for the water to reach a drug tube, would determine the drug release profile, i.e., the longer the PEO tube is, the later the water reaches the drug tube. As shown, for example, in Figure 6, the water infiltrated via the 3.5 cm-long PEO tubes in a diffusional

manner when immersed in the PBS media (pH = 7.4) (Table 2) [26].

We analyzed the concentration profiles of water molecules using Fick's law:

$$D\frac{\partial^2 c}{\partial x^2} = \frac{\partial c}{\partial t}$$

where D is the diffusion coefficient, c is the concentration of water molecules, x is the position, and t is the time. Assuming an infinite length of the PEO tube, the boundary conditions become

$c\ (x,t) = 0;\quad for\ 0 < x < \infty\ t = 0$

$c\ (x,t) = c_o;\quad for\ x = 0;\quad t > 0$

$c\ (x,t) = 0;\quad for\ x \rightarrow \infty;\quad t > 0$

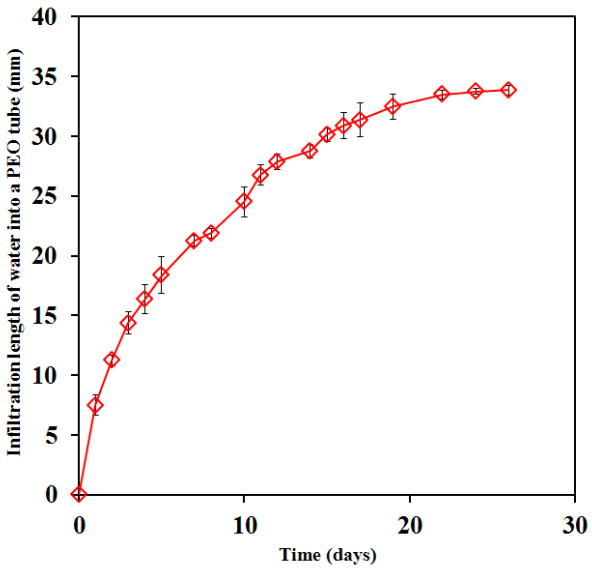
Then, the solution of this equation yields

$$\frac{c}{c_0} = erfc(\frac{x}{2\sqrt{Dt}})$$

The condition at the water front should be $\frac{c_w}{c_0}$ = constant and thus, $\frac{x}{2\sqrt{Dt}} = k'$, wihch is a constant as determined by the error function complement.

Therefore, the relation becomes $x = 2k'\sqrt{Dt}$, which fitted well with our experimental data in Figure 6.

According to this result, therefore, the times for the water to reach a drug tube would be 0.5 d, 1 d, 4 d, 6 d and 15 d for 0.5DDT, 1DDT, 1.5DDT, 2DDT and 3DDT, respectively. However, the onset times of drug release are expected to be later than the times for the water to reach a drug tube, considering an additional delay caused by dissolution of drug powder followed by diffusion of drug out of the device via a PEO tube.



PEO tube length (cm)	Time for the water to reach the drug tube (day)	Onset time of drug release (day)
0.5	0.5	0.5
1	1	1
1.5	3	4
2	6	8
3	15	17

Figure 6. Infiltration rate of water into a PEO tube in the PBS media (pH = 7.4)

Table 2. Comparative analysis of the times for water to reach the drug tube and the onset times of drug release for each different length of the PEO tubes

III. In vitro drug release profiles

We investigated the in vitro drug release profiles of the drug-delivery tubes prepared in this work in PBS media (pH 7.4) at 37 ℃. Since we employed PEO tubes of different lengths as a diffusion barrier, the difference in onset time of drug release was evident for each type of drug-delivery tube. As shown in Figure 7(a), the onset time of drug release increased as the length of the PEO tube increased. The drug release started on 0.5 d, 1 d, 5 d, 8 d and 17 d for 0.5DDT, 1DDT, 1.5DDT, 2DDT and 3DDT, respectively. As expected, the onset times of drug release were later than the times for the water to reach a drug tube predicted in Figure 6 (Figure 7 (a)). However, for 0.5DDT, a 0.5 cm-long PEO tube appeared to be short enough to release the drug almost instantaneously after the water reached the drug tube. The period of sustained drug release increased with the length of the PEO tube. Thus, after the onset day, more than 90% of drug was released for 2 days, 4 days, 5 days, 6 days and 9 days for 0.5DDT, 1DDT, 1,5DDT, 2DDT and 3DDT, respectively (Figure 7 (b)).

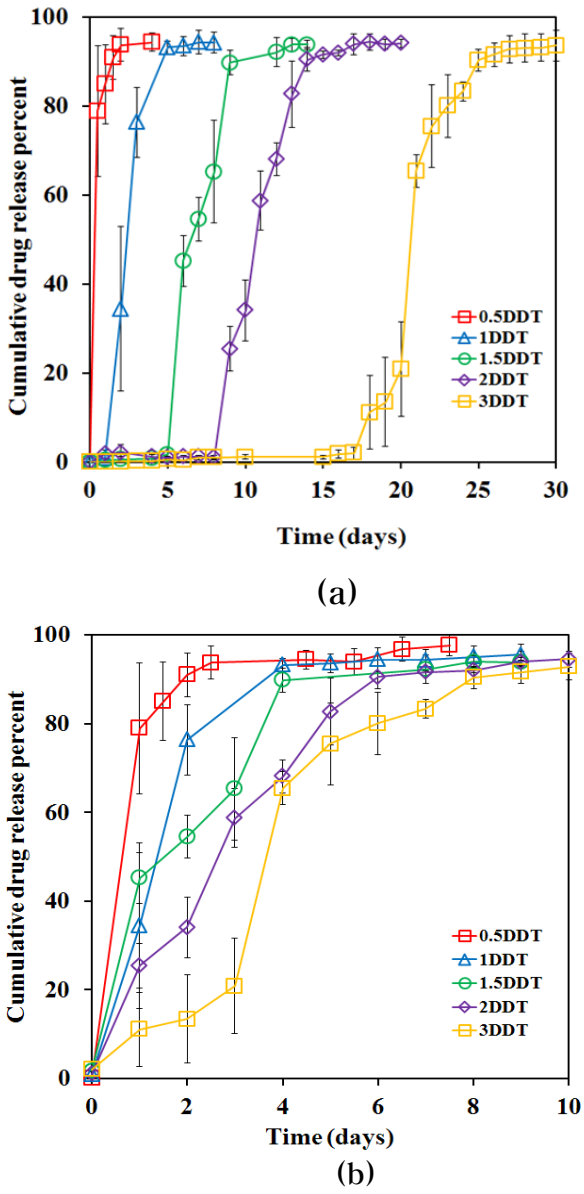


Figure 7. In vitro drug release profiles of the drug-delivery tubes, each equipped with a PEO tube of different length (a)

during the whole release period and (b) just for the period after the onset of drug release (i.e., the profiles with omitting the period of delayed drug release)

IV. Mathematical modeling

The drug release profiles with the drug-delivery tubes were analyzed by mathematical modeling in this work. This could be explained by drug dissolution at the interface between the drug powder in the drug tube and water that infiltrated via the PEO tube, as well as drug out-diffusion via the same PEO tube. Thus, the Noyes Whitney's equation, implying Fick's Law, can be employed:

$$\frac{dM}{dt} = \frac{D}{L} X (Cs - C) X A \quad \text{---------- (a)}$$

where, M, D, L, C_s, C, A and t are an amount of dissolved drug, diffusion coefficient of the drug, thickness of diffusion layer, solubility of the drug, concentration of the drug in the medium, surface area and time respectively. Assuming the sink condition, therefore, the drug concentration at the interface is much greater than that in the medium, thereby C

<< $C_{s.}$ Given this, the equation (a) can be reasonably approximated to:

$$\frac{dM}{dt} = \frac{D}{L} X Cs X A \quad \text{---------- (b)}$$

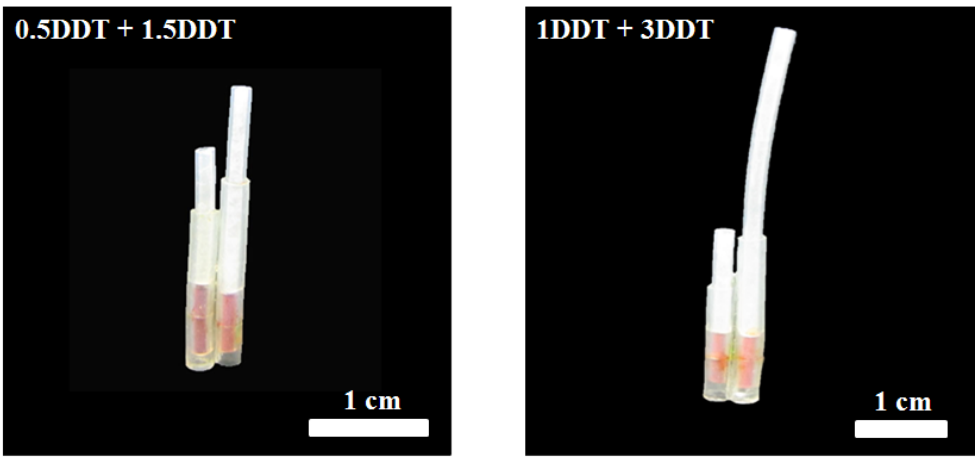
As the L represents the length of the PEO tube, the amount of dissolved drug per time can be mainly determined by the geometric parameter of the PEO tube: the diffusion coefficient and solubility of the drug, and surface area are considered to be constant. This diffusion model, therefore, can explain the extension of the onset time and period of drug release, depending on the length of PEO tube, as shown in Figure 7.

V. Pulsatile drug release from a combination of drug-delivery tube modules

These devices were designed to achieve pulsatile drug release by combining multiple drug-delivery tubes, each equipped with a PEO tube of different length. For this reason, we combined two drug-delivery tubes showing a large gap between the onset times of drug release. In this way, the

drug-delivery tube with a short PEO tube starts and finishes drug release much before the onset time of drug release from a long PEO tube.

In this work, the combination of 0.5DDT and 1.5DDT and that of 1DDT and 3DDT were prepared by bonding the drug-delivery tubes together in parallel with medical epoxy to realize pulsatile drug release (Figure 8).



(a) (b)

Figure 8. Optical images of the combinations of (a) 0.5DDT, 1.5DDT and (b) 1DDT and 3DDT

As shown in Figure 9, two distinct pulses of drug release were observed for both combinations of the drug-delivery tubes. A

combination of 0.5DDT and 1.5DDT exhibited the first onset of drug release at 0.5 d and the second one at 5 d. As we employed the longer PEO tubes for a combination of 1DDT and 3DDT, the times of pulses increased, where drug release started on 1 d and exhibited a plateau from 5 d for 12 days, followed by the second onset of drug release on 17 d. Those profiles were consistent with the predicted data from the in vitro drug release profiles of each of the individual drug-delivery tubes shown in Figure 7 (Figure 9).

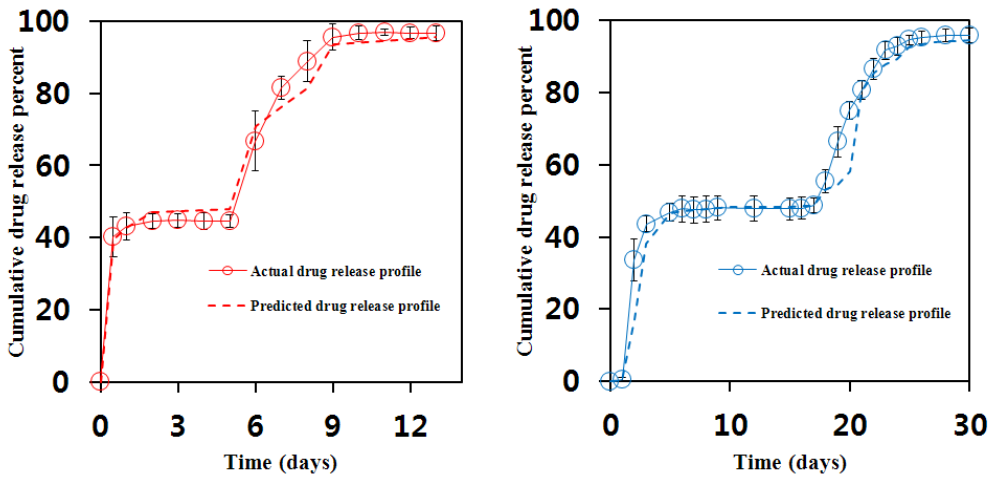
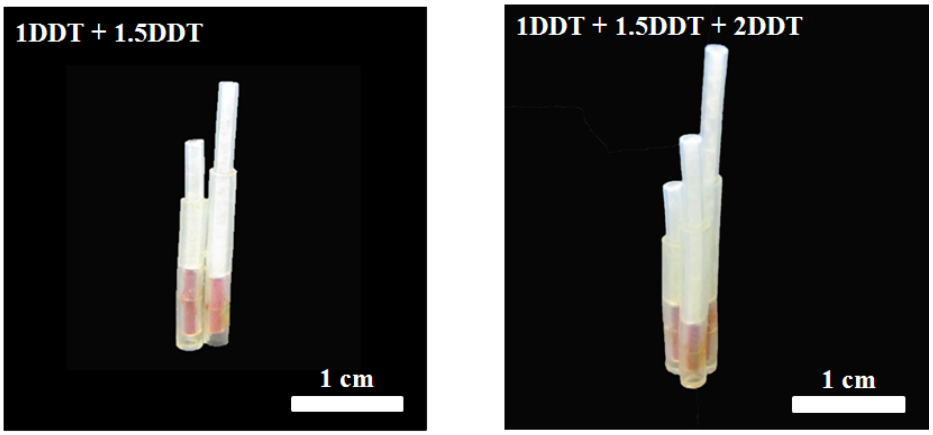


Figure 9. Optical images of the combinations of (a) 0.5DDT,

1.5DDT and (b) 1DDT and 3DDT

VI. Continuous drug release from a combination of drug-delivery tube modules

We were also interested to achieve continuous drug release from a combination of multiple drug-delivery tube modules of different types, where the drug-delivery tubes with a small gap between the onset times of drug release were combined. In this specific case, the end time of drug release (i.e., the time when drug release is complete) from a short tube should overlap the onset time of drug release from a long tube, providing continuous drug release without a plateau. We first prepared a combination of 1DDT and 1.5DDT by bonding those two tubes together in parallel with medical epoxy (Figure 10 (a)).

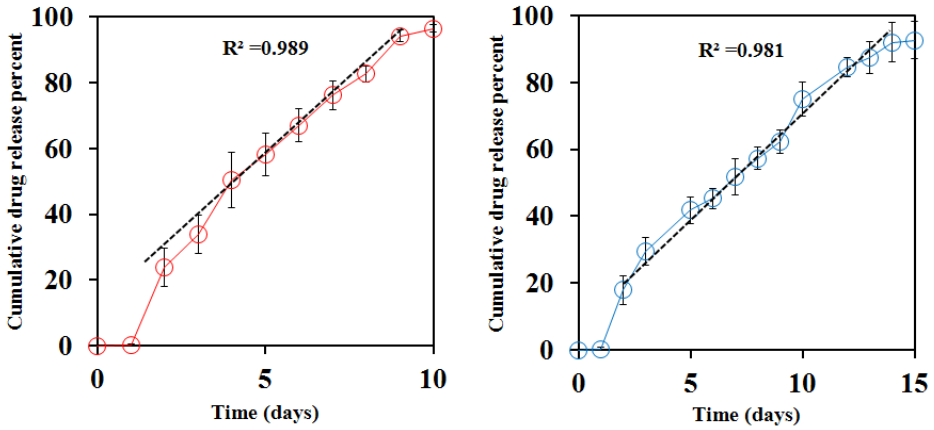


(a) (b)

Figure 10. Optical images of the combinations of (a) 1DDT, 1.5DDT and (b) 1DDT, 1.5DDT and 2DDT

As shown in Figure 7, the end time of drug release from 1DDT was 5 d, which was the onset time of drug release from 1.5DDT. Thus, this combination exhibited continuous drug release for 9 days after the onset of drug release on 1 d, showing almost linear release from 2 d to 9 d (R^2=0.989) (Figure 11(a)). For a more prolonged drug release, we also combined three different drug-delivery tubes, 1DDT, 1.5DDT and 2DDT (Figure 10 (b)), which resulted in continuous drug

release for 14 days after the onset of drug release on 1 d (Figure 11(b)). The onset time of drug release from 2DDT was 7 d, which was again the same with the end time of drug release from 1.5DDT (Figure 7). For this combination, an almost linear release pattern was observed for a longer period of time from 2 d to 14 d (R^2=0.981). The drug release profiles from those combined tubes again matched well with the data predicted from the in vitro drug release profiles of the individual drug-delivery tubes, as shown in Figure 12.



(a) (b)

Figure 11. In vitro drug release profiles from the combinations of (a) 1DDT and 1.5DDT and (b) 1DDT, 1.5DDT

and 2DDT in the PBS at pH 7.4 at 37 ℃. The dashed lines show the linear least linear square fits to the in vitro release data (a) from 2 d to 9 d and (b) from 2 d to 14 d, suggesting a fairly good correlation with zero-order release (R^2>0.98)

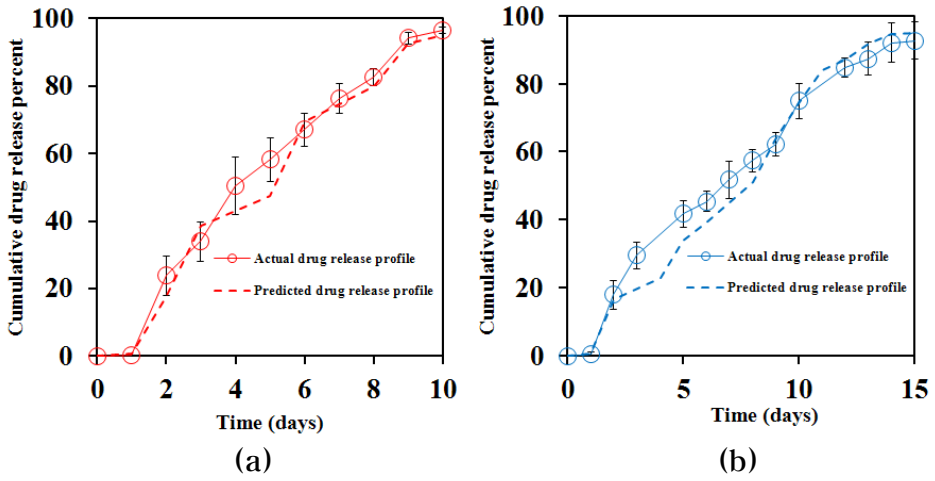


Figure 12. In vitro drug release profiles from the combinations of (a) 1DDT and 1.5DDT and (b)1DDT, 1.5DDT and 2DDT in the PBS at pH 7.4 and 37 ℃. A dashed line shows a drug release profile predicted with the experimental data from the individual drug-delivery tubes shown in Figure 8

5. Discussion

To provide effective therapy, each different type of drug should come with its own optimal regimen. For the drugs that benefit from a prolonged systemic exposure, sustained drug release would be an appropriate delivery profile [27, 28]. On the other hand, for drugs, such as hormones or vaccines, the time schedule of administration is also important [29, 30]. However, many drug delivery systems are designed only to offer sustained drug release [3] and thus, are unfortunately limited in versatility of their delivery scenarios. Therefore, a drug delivery system that can easily customize a release profile would be needed for its wide applicability to many different types of drug regimens.

In this work, therefore, we suggested a combined entity of assembled drug-delivery tube modules to provide a variety of drug delivery profiles. An individual drug-delivery tube could be easily prepared by attaching a drug tube and a PEO tube in series, serving as drug reservoir and diffusion barrier, respectively. In this way, both dose amount and drug release

pattern could be accurately tailored by the geometric parameter (i.e., the length) of the drug tube (Table 1) and the PEO tube (Figs. 6 and 7), respectively. Although the relatively simple design of the drug-delivery tube devices allowed straightforward fabrication in the lab, design improvements will be needed for mass production. In this work, the dose amount of the model compound was about 2 – 3 mg for each of the drug-delivery tubes equipped with a 0.5 cm drug tube, which could be increased proportionally with the number of drug-delivery tubes employed in a combined system.

Due to the PEO tube, the drug-delivery tubes exhibited a distinct biphasic release pattern: no drug release for a delayed time followed by a sustained drug release. Importantly, the onset times and periods of drug release could be determined by the length of the PEO tube alone (for a given tube diameter and filling material, i.e., PEO). Therefore, a release profile, either pulsatile or continuous, could be customized with a proper combination of drug-

delivery tubes, each equipped with a PEO tube of different length. This is expected to be also applicable to many different drugs with high aqueous solubility like the model compound, fluorescein tested in this work. On the other hand, for drugs with low aqueous solubility, the release could be more sustained due to the slow dissolution of the drug, hence a more prolonged drug release even with the same length of PEO tube.

In this work, by combining 0.5DDT and 1.5DDT modules, we could realize two pulses of drug release on 0.5 d and 5 d (Fig. 9(a)), which could be varied to 1 d and 17 d with a combination of the two drug-delivery tubes with the longer PEO tubes, 1DDT and 3DDT (Fig. 9(b)). The period of continuous drug release could be also tailored to 9 days with a combination of 1DDT and 1.5DDT modules (Fig. 11(a)). To prolong this, we simply added the 2DDT (i.e., a combination of the three tubes of 1DDT, 1.5DDT and 2DDT), showing a continuous drug release for 14 days (Fig. 11(b)). However, it should be noted that in this work, we employed PEO as a

diffusion-barrier material, which dissolved relatively rapidly as the water infiltrated. If a material of a stronger diffusion barrier (e.g., PEO of higher molecular weight, poly(lactic-co-glycolic acid), polylactic acid, polyglycolic acid or cross-linked hydrogels, etc.) could be employed [24, 31, 32], the period of sustained drug release would be prolonged, enabling a wider range of drug release periods. On the other hand, the in vitro drug release profiles could be different from those obtained under the in vivo environment. In this work, the in vitro drug release experiments were performed in PBS (pH = 7.4) with continuous stirring at 125 rpm to maintain an almost perfect sink condition. However, this simulated condition may not occur under the in vivo environment, which would probably delay drug release, thereby more prolonged drug release, as well as a lower daily release amount.

For ease of implantation, the drug-delivery tubes may need to be smaller, which could be realized simply by employing smaller silicone tubes to be filled with drug and PEO for assembly. Targeted or localized drug delivery could also be

possible, since the drug would be released only from the tiny tip of the PEO tube (< 1.5 mm in diameter in the current design, but could be smaller in the future). Therefore, we anticipate that the drug-delivery tubes prepared in this work can be applied to the body sites, especially not easy to access, such as the intraocular, intrabladder or intracranial sites. Although the silicone tubes used in this study do not degrade in the body and thereby, probably require removal after use, we envision that the tube material can be replaced with biodegradable material with a longer biodegradation period than that of complete drug release.

6. Conclusion

Temporal control over drug delivery is an essential part of effective drug therapy, where the optimal administration schedule or duration of systemic exposure is different for each drug and, in some cases, each patient. In this sense, a drug delivery system enabled with programmed drug release is advantageous due to its wide applicability to many different

kinds of drugs. In this work, therefore, we developed a drug-delivery tube assembled with two different kinds of tubes, one filled with model compound to simulate a drug and the other filled with a diffusion-barrier material, PEO. The drug-delivery tube was shown to release the model compound in a sustained manner after a delayed period, where the onset times and duration of drug release were pre-programmed and varied, depending on the length of the PEO tube.

To program a drug release profile, we suggest a simple combination of multiple drug-delivery tube modules. A combination of drug-delivery tubes with large differences in length of the PEO tubes can achieve pulsatile drug release, where the times of each pulse can be determined by the length of each PEO tube. A continuous drug release can also be realized with the combination of multiple drug-delivery tubes with small differences in PEO tube length. In this work, the combination of three different drug-delivery tubes possessing a 0.5 cm, 1 cm or 1.5 cm PEO tube, exhibited release of a model compound continuously for 14 days. The

drug-delivery tubes prepared in this work were small (2 mm in diameter at most), mimicking the dimensions of other implantable tube-type devices in clinical use, and were made of a minimal number of materials (i.e., drug, silicone and PEO) to provide the potential for implantation. Overall, we conclude that a device made by the combination of multiple drug-delivery tube modules, each designed with a diffusion-barrier tube of different length, is a novel system for programmed drug delivery.

7. References

1. Reddy, P.D. and D. Swarnalatha, Recent advances in novel drug delivery systems. International Journal of PharmTech Research, 2010. **2**(3): p. 2025-2027.
2. Orive, G., et al., Drug delivery in biotechnology: present and future. Current opinion in biotechnology, 2003. **14**(6): p. 659-664.
3. Kim, S., et al., Engineered polymers for advanced drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 2009. **71**(3): p. 420-430.
4. Hickey, T., et al., Dexamethasone/PLGA microspheres for continuous delivery of an anti-inflammatory drug for implantable medical devices. Biomaterials, 2002. **23**(7): p. 1649-1656.
5. Reddy, J.R.K., et al., Review on: Pulsatile drug delivery systems. J. Pharm. Sci. & Res, 2009. **1**(4): p. 109-115.
6. Stubbe, B.G., S.C. De Smedt, and J. Demeester, "Programmed Polymeric Devices" for Pulsed Drug Delivery. Pharmaceutical research, 2004. **21**(10): p. 1732-1740.
7. Varde, N.K. and D.W. Pack, Microspheres for controlled release drug delivery. Expert opinion on biological therapy, 2004. **4**(1): p. 35-51.
8. Allison, S.D., Analysis of initial burst in PLGA microparticles. 2008.
9. Yeo, Y. and K. Park, Control of encapsulation efficiency and initial burst in polymeric microparticle systems. Archives of pharmacal research, 2004. **27**(1): p. 1-12.
10. Huang, X. and C.S. Brazel, On the importance and mechanisms of burst release in matrix-controlled drug delivery systems. Journal of controlled release, 2001. **73**(2): p. 121-136.
11. Staples, M., Microchips and controlled-release drug reservoirs. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 2010. **2**(4): p. 400-417.

12. Prescott, J.H., et al., Chronic, programmed polypeptide delivery from an implanted, multireservoir microchip device. Nature biotechnology, 2006. **24**(4): p. 437-438.
13. Hilt, J.Z. and N.A. Peppas, Microfabricated drug delivery devices. International Journal of Pharmaceutics, 2005. **306**(1-2): p. 15-23.
14. Staples, M., et al., Application of micro-and nano-electromechanical devices to drug delivery. Pharmaceutical research, 2006. **23**(5): p. 847-863.
15. Santini Jr, J.T., et al., Microchips as controlled drug-delivery devices. Angewandte Chemie International Edition, 2000. **39**(14): p. 2396-2407.
16. Ziaie, B., et al., Hard and soft micromachining for BioMEMS: review of techniques and examples of applications in microfluidics and drug delivery. Advanced Drug Delivery Reviews, 2004. **56**(2): p. 145-172.
17. Croxatto, H.B., Norplant®: levonorgestrel-releasing contraceptive implant. Annals of medicine, 1993. **25**(2): p. 155-160.
18. Rastogi, A., et al., Development and characterization of a scalable microperforated device capable of long-term zero order drug release. Biomedical microdevices, 2010. **12**(5): p. 915-921.
19. Lee, H. and M.J. Cima, An intravesical device for the sustained delivery of lidocaine to the bladder. Journal of controlled release, 2011. **149**(2): p. 133-139.
20. Quinn, K.J. and J.M. Courtney, Silicones as biomaterials. British polymer journal, 1988. **20**(1): p. 25-32.
21. Habal, M.B., The biologic basis for the clinical application of the silicones: a correlate to their biocompatibility. Archives of Surgery, 1984. **119**(7): p. 843.
22. Charvát, J., et al., Implantation of central venous ports with catheter insertion via the right internal jugular vein in oncology patients—single center experience. Supportive care in cancer, 2006. **14**(11): p. 1162-1165.

23. Santos, P.M., Surgical placement of the vagus nerve stimulator. Operative Techniques in Otolaryngology-Head and Neck Surgery, 2004. **15**(3): p. 201-209.
24. Uhrich, K.E., et al., Polymeric systems for controlled drug release. Chemical Reviews-Columbus, 1999. **99**(11): p. 3181-3198.
25. Webster, R., et al., PEG and PEG conjugates toxicity: towards an understanding of the toxicity of PEG and its relevance to PEGylated biologicals. PEGylated Protein Drugs: Basic Science and Clinical Applications, 2009: p. 127-146.
26. Saltzman, W.M., Drug delivery: engineering principles for drug therapy. 2001: Oxford University Press, USA.
27. Shi, Y. and L. Li, Current advances in sustained-release systems for parenteral drug delivery. 2005.
28. Putney, S.D. and P.A. Burke, Improving protein therapeutics with sustained-release formulations. Nature biotechnology, 1998. **16**(2): p. 153-157.
29. Liu, X., et al., Pulsatile release of parathyroid hormone from an implantable delivery system. Biomaterials, 2007. **28**(28): p. 4124-4131.
30. De Geest, B.G., et al., Pulsed drug delivery. 2006.
31. Edlund, U. and A. Albertsson, Degradable polymer microspheres for controlled drug delivery. Degradable aliphatic polyesters, 2002: p. 67-112.
32. Yasukawa, T., et al., Intraocular sustained drug delivery using implantable polymeric devices. Advanced Drug Delivery Reviews, 2005. **57**(14): p. 2033-2046.

국문초록

프로그램형 약물전달을 위한 기하학적으로 제어된 고분자 튜브형태의 디바이스

현 연구에서는 proof of principle로써 정교한 약물의 제어 전달을 위하여 프로그램형 약물 방출이 가능한 튜브형태의 약물 전달 기기를 개발하였다. 모델 약물로써의 sodium fluorescein를 채운 실리콘 튜브와 약물 확산벽(diffusion barrier)의 역할로써 생체 고분자인 폴리에틸렌옥사이드(PEO)를 채운 실리콘 튜브를 각각 직렬로 접합하여 약물 전달 기기를 완성하였다. 이를 바탕으로, 약물 방출을 제어하기 위하여 PEO가 채워진 튜브(PEO 튜브)의 길이를 0.5 cm, 1 cm, 1.5 cm, 2 cm, 3 cm로 다양화 하여 약물의 방출 시점 및 기간을 변화시켰다. 실험 결과, PEO 튜브의 길이가 0.5 cm, 1 cm, 1.5 cm, 2 cm, 3 cm로 증가함에 따라 약물 방출 시점이 0.5 일, 1일, 4일, 8일, 17일로 증가하였으며, 약물 방출 기간 또한 2일, 4일, 5일, 6일, 9일로 증가하였다. 이러한 결과를 토대로, 길이가 다른 PEO 튜브를 가지고 있는 각각의 약물 전달 기기를 조합하여 약물 방출을 프로그램하고자 하였다. 그래서, 0.5 cm, 1.5 cm 의 PEO 튜브를 가진 각각의 약물 전달 기기를 병렬로 접합하여 조합된 약물 전달 기기를 개발하여 펄스 형태의 약물 전달 형상을 구현하였으며, 1 cm, 3 cm 의 PEO 튜브를 가진 각각의 약물 전달 기기

를 병렬로 접합하여 마찬가지로 펄스 형태의 약물 전달 형상을 얻을 수 있었다. 또한, 1 cm, 1.5 cm의 PEO 튜브를 가진 각각의 약물 전달 기기를 병렬로 접합하여 약 9일 동안 지속적이고 서방형태의 약물 전달 형상을 얻을 수 있었으며, 더욱이 1 cm, 1.5 cm, 2 cm의 PEO 튜브를 가진 각각의 약물 전달 기기를 병렬로 접합하여 약 14일 동안 지속적이고 서방형태의 약물 전달 패턴을 구현하였다. 우리는 최종적으로 다른 길이의 PEO 튜브를 가진 개별적인 약물 전달 기기의 적절한 조합을 통하여 펄스 형태 및 지속적인 서방성 형태의 약물 전달 형상이 모두 가능한 튜브 형태의 디바이스를 proof of principle로써 구현하였다.

주요어 : 지속적인 약물 전달, 약물 전달 튜브, 폴리에틸렌 옥사이드, 프로그램형 약물 전달, 펄스형태의 약물 방출, 실리콘
학 번 : 2010 - 23351