AAPS PharmSciTech, Vol. 13, No. 1, March 2012 (© 2011)
DOI: 10.1208/s12249-011-9743-6

Research Article

Microchip for Sustained Drug Delivery by Diffusion Through Microchannels

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Received 12 July 2011; accepted 21 November 2011; published online 4 January 2012

Abstract. To enable sustained drug delivery, we prepared microchips of simple structure for drug release based on diffusion through microchannels. The microchips were fabricated with poly(methyl methacrylate), embedded with one or more microwells and microchannels of controlled length. The channels were filled with biocompatible polymer, poly(ethylene glycol), to serve as a drug diffusion barrier. The wells served as drug reservoirs and were filled with a fine powder of a model compound, fluorescein. Three different drug delivery microchip designs were prepared, each equipped with a channel of 1, 4, or 8 mm length. Drug release from these devices all exhibited a delay followed by sustained release over time. As the channel length increased from 1 to 8 mm, the onset time and duration of drug release also increased from 0.5 to 7 day and from 11 days to 28, respectively. We also prepared microchips equipped with multiple microwells, each connected to a channel of different length. In this way, a chip with channels of 1, 4, and 8 mm length exhibited a continuous drug release from 0.5 to 35 days. A future study is in progress to develop the microchips made of biodegradable materials. Therefore, we conclude that a microchip embedded with multiple sets of microwells and microchannels of different length can be designed to enable sustained drug release for controlled and prolonged periods of time.

KEY WORDS: drug delivery microchip; microchannel; poly(methyl methacrylate) (PMMA); programmed drug delivery; sustained drug release.

INTRODUCTION

There has been a great deal of interest in sustained drug delivery systems to achieve a temporal drug profile for maximum therapeutic benefits (1,2). The advantages of sustained drug delivery include predictable and extended duration of drug action with less frequent administration, as well as a reduced risk of side effects. For this reason, many systems enabled with sustained drug release have been actively developed in a number of different forms, such as rod, wafer, pellet, and particle, mostly employing biocompatible polymers as a wall material (3,4). Thus, the drug encased in a polymeric matrix can be slowly released by drug diffusion or polymer degradation. However, such systems are often limited in a short period of effective drug delivery due to a large initial burst release, which can be more problematic for the delivery of hydrophilic and small molecule drugs (5–7). In addition, precise control of drug release is often difficult since drug release via diffusion is determined strongly by the dimensions or shape of the drug-loaded systems, which can be hard to accurately tailor with conventional polymeric drug delivery systems (8,9).

To address these limitations, drug delivery systems have been prepared using more sophisticated methods, such as microfabrication technology (10–12). These microfabricated drug delivery devices have been equipped with precisely controlled geometry to deliver drug in a highly controlled manner, which is advantageous especially for optimal drug regimens (13). For example, a device embedded with a micropump and microchambers was capable of precisely delivering liquid drug (14). Multiple drug reservoirs, each covered with a thin gold membrane, were prepared on a single chip, which allowed pulsatile drug release at the exact times of activation by an integrated electronic circuit (15).

In spite of those benefits, microfabricated devices are often limited by a complicated fabrication procedure. A substrate may require multiple processing steps involving photolithography, deposition, and etching to produce a three-dimensional structure to serve as a drug delivery device (16). Also, the devices are often not self-contained and require additional units, such as a power supply, which is usually bigger than the drug delivery device itself, leading to a bulky system for administration (10,14,15,17,18). This complicated structure and fabrication process may be needed for drug delivery devices enabled with highly programmed drug delivery. However, this may not be necessary to achieve a sustained and continuous drug release,

Electronic supplementary material The online version of this article (doi:10.1208/s12249-011-9743-6) contains supplementary material, which is available to authorized users.

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which may enable cost-effective manufacturing of microfabricated drug delivery systems.

In this work, therefore, we developed a drug delivery microchip (*i.e.*, DDM) with a simple structure for sustained drug release. The proof-of-principle chip was made of biocompatible poly(methyl methacrylate) (PMMA) (19), where a microwell and microchannel were embedded to serve as a drug reservoir and drug diffusion barrier, respectively. To prepare this DDM, we made two separate plates of PMMA, each containing a well or channel, to give a well plate (WP) or channel plate (CP), respectively. On each CP, the microchannel was filled with biocompatible polymer, poly(ethylene glycol) (PEG) (20), while the well of each WP was filled with a fine powder of a model compound, fluorescein. These two plates were then aligned and bonded using methyl methacrylate (MMA) to provide a water-tight seal. In this way, water could diffuse only via the microchannels to reach the drug-filled well and, then, the drug could diffuse out via the same microchannel. We also varied the length of the channels to 1, 4, and 8 mm to further control drug release, since the onset time and period of drug release were determined by the length of the microchannel.

Guided by the results from single microchannel chips, we also prepared microchips of still smaller size equipped with multiple sets of drug wells and microchannels, each of different length. In this way, a short channel allowed drug release initially, while later drug release could be determined by the longer channels. By tailoring the length of the channels properly, therefore, a continuous drug release was possible with a single microchip.

MATERIALS AND METHODS

Materials

Polyethylene glycol (average MW=6,000 Da) was purchased from Acros Organics (Geel, Belgium) and sodium fluorescein and methyl methacrylate (99.0% purity) were purchased from Sigma (St. Louis, MO, USA). PMMA sheets (thickness=1.3 mm) were purchased from EunSung Polytechnology (Seoul, South Korea). Phosphate-buffered saline (PBS; pH 7.4) was obtained from the Seoul National University Hospital Biomedical Research Institute.

Preparation of Drug Delivery Microchips

To prepare a drug delivery microchip, we first fabricated two separate PMMA plates, one containing a microchannel (*i.e.*, CP) and one containing a microwell (*i.e.*, WP), as shown in Fig. 1. To prepare a CP, a PMMA sheet was first cut to give a circular plate, 20 mm in diameter, on top of which a microchannel, 280 μm in width and 270 μm in depth, was fabricated with a CO_2 laser (FC-200RA LASER Machinery, Bucheon, South Korea). We varied the lengths of the channels to 1, 4, and 8 mm to give CP1, CP4, and CP8, respectively. Each of the channels was then filled with molten PEG at 80°C, which was then solidified at room temperature for 5 h.

To prepare a WP, a PMMA sheet was again cut to give a circular plate, 20 mm in diameter, which was then microdrilled to prepare a well, 2 mm in diameter and 800 μm in depth (FA-NA2500 CNC Machinery, Bucheon, South Korea). The locations of the well on each of the WPs were determined by the length of the channel on a CP to be paired: the end of each of the channels of different length was aligned to meet the wells. Thus, the centers of the wells were located at 2, 5, and 9 mm from the outer boundary of a WP to give WP1, WP4, and WP8, which were paired with CP1, CP4, and CP8, respectively.

The resulting pairs of CPs and WPs were aligned and bonded with MMA (Chen *et al.* 2008) to give the drug delivery microchips of DDM1, DDM4, and DDM8. The chips were dried under vacuum (≤0.1 MPa) at 20°C overnight to remove any residual MMA.

Morphology Analysis of Microchannels

To examine the cross-section and the surface of a channel filled with PEG, a CP8 was placed on a sample mount and sputter coated with platinum for 10 min (208HR, Cressington Scientific, Watford, England). The sample was then imaged with a scanning electron microscope (7401F, Jeol, Tokyo, Japan).

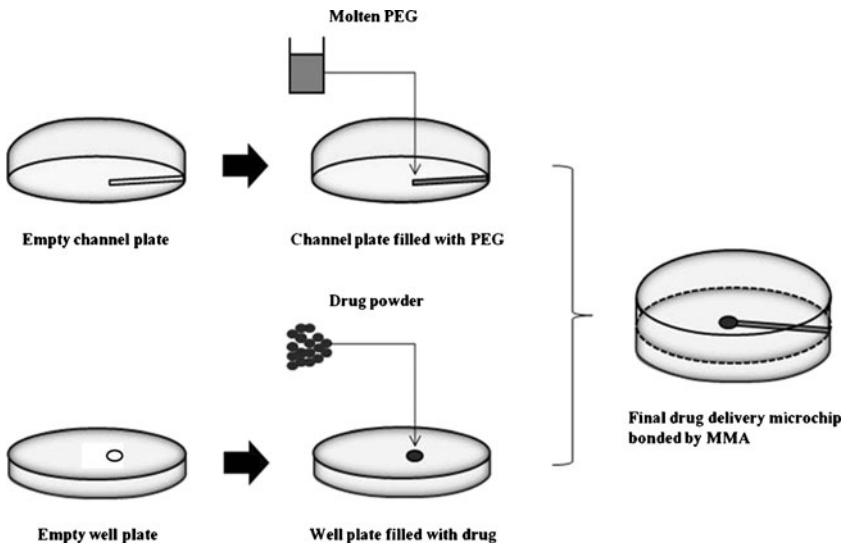

Fig. 1. Schematic procedure for fabrication of drug delivery microchips

Quantitative Analysis of Drug Loading Amount

To analyze the drug loading amount, a WP filled with the model drug (fluorescein) was fully immersed in 40 ml of PBS to completely dissolve the drug, which was then measured using a UV–Vis spectrophotometer (UV-1,800, Shimadzu, Columbia, MD, USA) at an absorption wavelength of 321 nm. The experiments were done in triplicate to assess the reproducibility of drug loading.

Measurement of Water Infiltration Rate into the Microchip

To examine the rate of water infiltration into microchannels, a CP8 and a non-patterned, circular PMMA plate, 20 mm in diameter, (*i.e.*, a plate without a drug well), were bonded with MMA and dried under vacuum at 20°C overnight, which was then immersed in 40 ml PBS with continuous stirring at 125 rpm at 37°C. At scheduled intervals, the interface between the solid PEG and water in the channel was found with an optical microscope (GL99TIS, DMOPT, Seoul, South Korea) and the distance from the opening of the channel to this solid–water interface was measured. The experiments were performed in triplicate.

In Vitro Drug Release Study

To examine the *in vitro* drug release profiles, the DDMs were each immersed in 40 ml PBS while continuously stirred at 125 rpm in a shaking incubator at 37°C. At scheduled intervals, an aliquot of release medium (5 ml) was collected and an equal amount of fresh PBS was added back to maintain sink conditions. The sampled aliquots were measured using a UV–Vis spectrophotometer (UV-1,800, Shimadzu). The experiments were performed in triplicate for each type of DDM.

RESULTS

Characterization of Drug Delivery Microchips

We developed DDMs simply by aligning and bonding two separate plates of a WP and CP, as shown in Fig. 1 (also see Fig. S1 in the Supplementary Information). On a CP, a microchannel was formed with a CO_2 laser, which was then filled with PEG to work as a drug diffusion barrier. The length of the channel was varied to 1, 4, and 8 mm to give CP1, CP4, and CP8, respectively. Figure 2 shows the morphology of the channels before and after filling with PEG. After etching with a CO_2 laser, the channel, 280 μm in width and 270 μm in depth, could be successfully formed (Fig. 2a), showing a rough inner surface of the channel possibly due to melting of PMMA by the CO_2 laser (Fig. 2b) (21). Figure 2c, d reveals that the channel could be densely and seamlessly filled with PEG with the method employed in this work.

On a WP, a drug well, 2 mm in diameter and 800 μm in depth, was formed by micro-drilling and filled with a fine powder form of a model drug, fluorescein. The drug could be loaded in a well in a reproducible manner by a doctor blade method (22), giving the loading amount of 1.74±0.04 mg. Since the location of each well should be aligned to the end of a channel of different length (*i.e.*, 1, 4, and 8 mm), each well

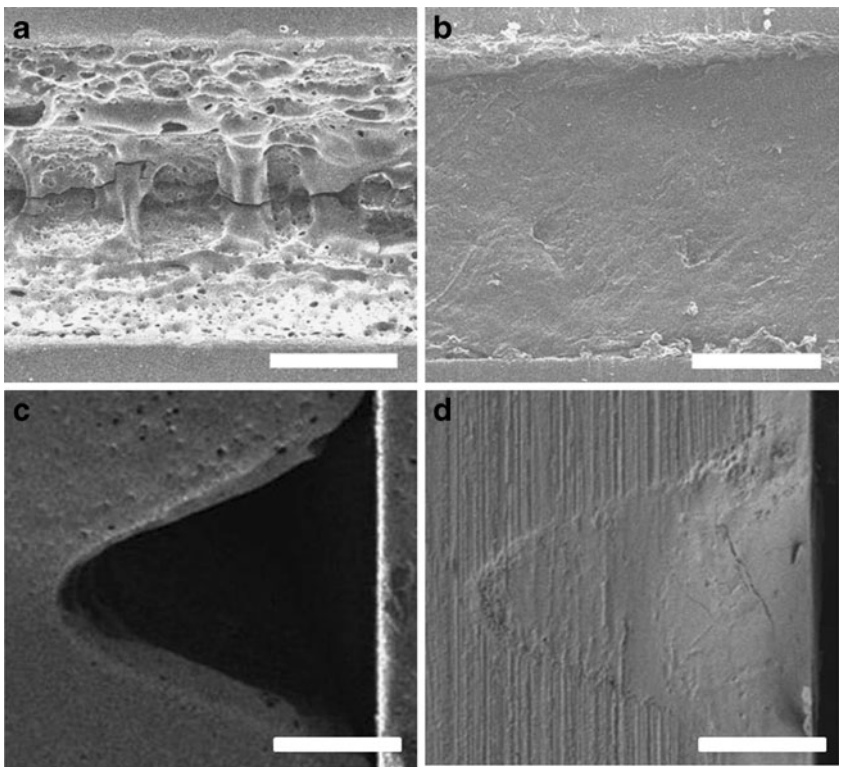

Fig. 2. Scanning electron micrographs of the microchannels. The images were (**a**) top view and (**c**) side view of an empty microchannel and (**b**) top view and (**d**) side view of a microchannel filled with PEG. The *scale bars*=100 μm

was placed at 2, 5, or 9 mm from the outer boundary of a WP to give WP1, WP4, and WP8, respectively.

The pairs of CP1 and WP1, CP4 and WP4, and CP8 and WP8 were then bonded with MMA to give DDM1, DDM4, and DDM8, respectively, as shown in Fig. 3. The resulting DDMs were 20 mm in diameter and 2.6 mm in thickness (*i.e.*, a total volume of 260 μl). In this way, the water can infiltrate through a microchannel to reach a drug well where it dissolves the drug powder. After that, the dissolved drug molecules can diffuse out via the same channel to the outer release medium.

Infiltration Rate of Water Via the Microchannel

We examined the infiltration rate of water via microchannels since the time it takes for water to infiltrate through the different lengths of different channels is a critical determinant of the onset time of drug release from the DDM. The longer the channel is, the later the water should reach the drug well. As the freed drug molecules in solution are released via the microchannel, the period of drug release also depends on the channel length. Figure 4 shows the water infiltration rate via the 8-mm-long channel filled with PEG when the chip was immersed in PBS at 37°C. As expected, the water infiltrated into the channel steadily over time, showing that the times for water to reach a drug well at the end of the channel to be 1, 20, and 80 h (*i.e.*, 0.04, 0.83, and 3.33 days, respectively) for DDM1, DDM4, and DDM8, respectively (see Table S1 in the Supplementary Information). However, it should be noted that the onset time of drug release is expected to be later than the time for the water to reach a drug well, considering an additional delay caused by dissolution of drug powder followed by the out-diffusion of drug via the same microchannel.

In Vitro Drug Release Profiles

We examined the *in vitro* drug release profiles of each type of DDM prepared in this work. As shown in Fig. 5, the onset time of drug release increased as the length of the channel increased. The drug release started on 0.5, 3, and 7 days for DDM1, DDM4, and DDM8, respectively, which was later than the times for the water to reach the drug well shown in Fig. 4 for reasons discussed immediately above (also see Table S1 in the Supplementary Information).

After the onset times, drug was released in a sustained manner for all DDMs. An initial burst of drug release was not observed due to the presence of the channel as a strong diffusion barrier between the drug reservoir (*i.e.*, drug well) and release medium. The period of drug release also increased as the channel length increased. Thus, after the onset time, the drug was released continuously for 11, 22, and 28 days from DDM1, DDM4, and DDM8, respectively.

Drug Delivery Microchips Embedded with Multiple Wells and Channels

Although the DDM described above realized sustained drug release for up to 35 days (including a delayed period of drug release), a single pair of microwell and microchannel could not achieve both rapid onset and prolonged drug release. A long channel enables prolonged drug release, but also has a delayed onset of drug release. It would often be desirable to start drug release without delay and to sustain drug release for a prolonged period with a single device administration.

Therefore, we prepared a single drug delivery microchip with multiple pairs of drug wells and channels of different lengths. Two different prototype microchips were fabricated: a microchip embedded with two pairs of wells and channels, one of 1 mm and the other of 4 mm length (*i.e.*, DDM14) and a microchip with three pairs of wells and channels, measuring 1, 4, or 8 mm in length (*i.e.*, DDM148). Considering the ease of administration, the size of the microchips was reduced to 11 mm in diameter and 2.6 mm in thickness to give 79 μl of volume, as shown in Fig. 6.

Using this design, both DDM14 and DDM148 exhibited a fairly prompt onset of drug release at 0.5 day (Fig. 7), which could be accounted for the shortest channel, 1 mm in length, which was embedded in both microchips. The drug was released for 25 days from DDM14 and for 35 days from DDM148, which was ascribed to the longest channel in the microchip, 4 and 8 mm in length, respectively. The release profiles with both DDM14 and DDM148 matched well with those predicted with the experimental data from the individual DDMs shown in Fig. 5 (see Fig. S2 in the Supplementary Information).

Notably, both DDM14 and DDM148 exhibited approximately linear drug release initially. In the prior examples with a microchip embedded with a single pair of well and channel, the drug was released more rapidly right after the onset time and slowed down as time elapsed due to a diffusion-mediated release pattern. However, with the DDM14 and DDM148, a decrease in drug release rate from the short channel could be

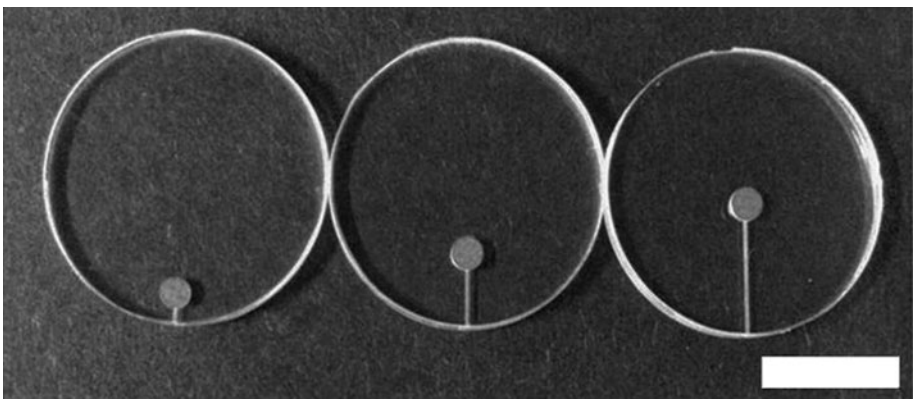

Fig. 3. Optical image of drug delivery microchips. The lengths of microchannels were 1, 4, and 8 mm from left to right. The *scale bar*=1 cm

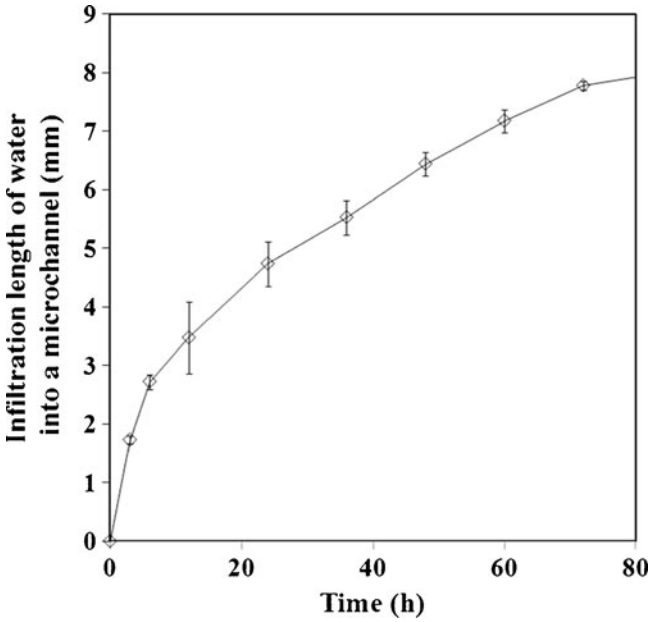

Fig. 4. Infiltration rate of water into a microchannel

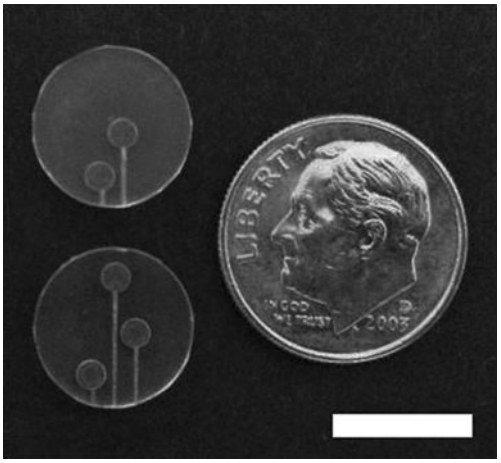

Fig. 6. Optical images of the microchips embedded with multiple pairs of wells and channels. The microchips were DDM14 and DDM148 from top to bottom. A dime was imaged together for comparison. The *scale bar*=1 cm

compensated for by a subsequent release from a long channel. For DDM14, therefore, as drug release via the 1-mm-long channel slowed down, the drug started to be released via the 4-mm-long channel. This continued with the 8-mm-long channel for DDM148. As a result, an almost linear release pattern was observed for 7 days (1–8 days, R^2=0.981) for DDM14, which was extended to 12 days (2–14 days, R^2=0.982) for DDM148 (see Fig. S3 in the Supplementary Information). During this period, more than 77% of the drug was released, after which the drug release rate decreased dramatically (<0.8% per day) because of the depleted concentration gradient driving drug diffusion via the longest channel in the microchip.

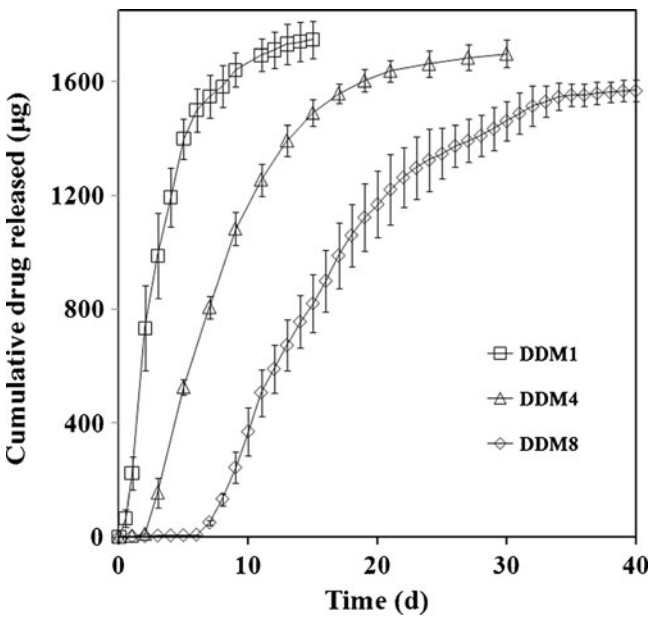

Fig. 5. *In vitro* drug release profiles of the drug delivery microchips embedded with the microchannels of different length. The experiments were performed in the PBS at pH 7.4 at 37°C

DISCUSSION

Microfabricated drug delivery systems can benefit from a highly programmable drug release at the site of action, thereby considerably improving drug bioavailability (13). For this reason, many devices have been prepared with microfabrication technology, where drug release can be controlled via an accurately tailored three-dimensional structure (23). In addition, because microfabrication technology originated from processes for creating integrated electronic circuits (24), the drug delivery devices could also incorporate an electronic controller to initiate the onset of drug release according to a programmed schedule (25). However, to achieve programmed drug release, the devices often need to be processed with multiple fabrication steps of photolithography, deposition, and etching to give the required three-dimensional structure of the drug delivery devices (16).

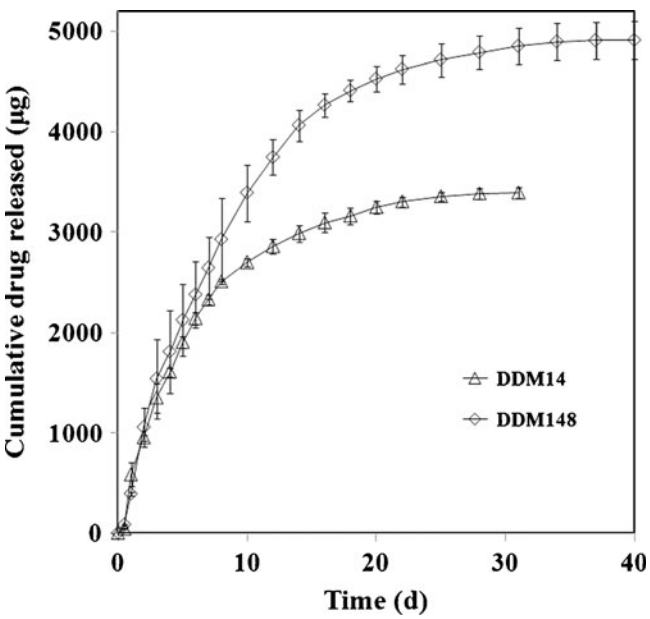

Fig. 7. *In vitro* drug release profiles of DDM14 and DDM148. The experiments were performed in the PBS at pH 7.4 at 37°C

To achieve sustained drug release, however, this complex structure may not always be necessary. For example, many drug delivery systems of a simpler geometry, such as particles, fibers, rods, *etc*., could release drug in a sustained manner to achieve improved drug efficacy with a reduced number of administrations (3,4). These drug delivery systems have mostly been composed of biocompatible polymers as a wall material, where the drug is released by diffusion through the polymer matrix. This diffusional drug release, however, has generally included a relatively large burst of drug release initially and a dramatically decreased drug release rate later. Thus, to achieve adequate delivery rates for an extended period of time, a high drug loading is often needed, which may cause adverse side effects due to an even larger burst of drug release initially.

Therefore, we developed a single drug delivery microchip embedded with microwells and microchannels to enable sustained drug release for an extended period of time. The channels filled with a biocompatible polymer, PEG, served as a diffusional barrier, via which the water infiltrated into a drug well, and then, the drug diffused out towards the release medium. In this way, the onset times and periods of drug release could be controlled, depending on the channel lengths. The channel width should also influence drug release, which, however, was fixed to 280 μm for all microchips prepared in this work. Thus, the onset times and periods of drug release were varied from 0.5 to 7 days and from 11 to 28 days, respectively, by simply varying the channel lengths from 1 to 8 mm (Fig. 5). Due to the presence of the channel between the drug well and release medium, an initial burst release, which has often been found in many polymeric systems, was not observed when using the microchips prepared in this work.

Since sustained drug release was necessarily preceded by a delayed onset of drug release when using a single pair of a channel and well, we integrated multiple pairs of wells and channels of different length in one chip (Fig. 6). In this way, the drug release that slowed down from a short channel could be compensated for by release from a longer channel, yielding a continuous drug release for a prolonged period of time (Fig. 7). In this work, a chip embedded with 1, 4, and 8 mm channels (*i.e.*, DDM148) released the model drug for up to 35 days with an onset time of drug release of 0.5 day. Due to this combination of the different channel lengths, almost linear release was also possible for 12 days (2–14 days, R^2=0.982), accounting for more than 77% of drug release (see Fig. S3 in the Supplementary Information).

The drug delivery microchip was prepared using a fairly simple procedure of aligning and bonding of only two plates, as compared with multiple steps of etching and deposition introduced in previous studies (15). Without complex photolithography, the wells and channels could be prepared quickly and reproducibly in this work. Filling the channels could be done in hours (<5 h). The longest procedure was bonding the two plates (~12 h in this work), which is expected to be shortened if a higher vacuum could be employed to facilitate solvent evaporation.

Our drug delivery microchip is a proof-of-principle device, and thus, may need to be improved further. In this work, we employed PEG to fill the channel as a diffusion barrier, which dissolved away as the water infiltrated due to its high aqueous solubility (~550 mg/ml). Therefore, the drug was released via the channel filled with water, where the geometry of the channel was the main factor determining the drug release profile. For a more prolonged drug release, therefore, the channels filled with a biocompatible polymer with low aqueous solubility can be envisioned (26,27). In this way, the drug can be released in a more sustained manner since the polymer should remain in the channel after water infiltration. In this sense, the channel lengths could be further reduced, which would again reduce the size of the devices, much smaller than the ones prepared in this work (Fig. 6). The microchips may need to be retracted after complete drug release since the PMMA used to fabricate the devices is not biodegradable, albeit biocompatible (19). However, the fabrication procedures employed in this work, such as micro-drilling, etching with a CO_2 laser, and bonding with a solvent, could be adapted for the other biodegradable polymers, such as polylactic acids, polyglycolic acids, or poly(lactic-co-glycolic acids) (28). Therefore, biodegradable drug delivery microchips are expected to be easily fabricated with the same geometry of channels or wells using a method similar to the one presented here.

CONCLUSION

A drug delivery system with sustained drug release can be used to enable high drug efficacy for a prolonged period time with less frequent drug administration. For this reason, many systems have been developed with a biocompatible polymer as a wall material controlling the rate of drug release. These systems, however, often have drug release rates that vary over time, mostly due to rapid drug release initially. In this work, therefore, we developed a proof-of-principle drug delivery microchips embedded with microchannels and microwells, which served as a diffusion barrier and drug reservoir, respectively. The drug delivery microchip can release drug in a sustained manner after a lag phase, where the onset times and periods of delivery increase with the channel length. A problematic initial burst release was not observed with the microchips prepared in this work due to the presence of a channel as a resistive diffusion barrier.

Considering the ease of administration and continuous drug release (*i.e.*, a fairly prompt onset of drug release followed by a sustained one), we suggest a more integrated microchip, *i.e.*, a single microchip equipped with multiple pairs of channels and wells. In this work, a drug delivery microchip was prepared with the channels, 1, 4, and 8 mm in length, to give a chip dimension of 11 mm in diameter and 2.6 mm in thickness (79 μl volume), which exhibited continuous drug release from 0.5 for 35 days. Therefore, with a proper combination of channels of different length, a more prolonged drug release can be achieved. We also pursue to develop a fully biodegradable microchip in future, which would not require an inconvenient retraction procedure. Overall, we conclude that a drug delivery microchip embedded with multiple pairs of drug wells and diffusion channels of different length have the potential to enable long-term drug release in a controlled manner.

ACKNOWLEDGMENTS

The study was supported in part by a grant from the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A092052).

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