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Mini review

Microfabricated drug delivery devices

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Abstract

We review newest developments in the design and fabrication of drug delivery devices based on micropatterned structures. Electronic devices have now reached a stage of dimensions comparable to those of biological macromolecules. This raises exciting possibilities for combining microelectronics and biotechnology to develop new technologies with unprecedented power and versatility. While molecular electronics use the unique self-assembly, switching and dynamic capabilities of molecules to miniaturize electronic devices, nanoscale biosystems use the power of microelectronics to design ultrafast/ultrasmall biocompatible devices, including implants, that can revolutionize the field of bioengineering. Thus, in recent years we have seen an explosion in the field of novel microfabricated and nanofabricated devices for drug delivery. Such devices seek to develop a platform of well controlled functions in the micro- or nano-level. They include nanoparticulate systems, recognitive molecular systems, biosensing devices, and microfabricated and microelectronic devices.

Keywords: Microfabrication; Drug delivery; Microdevice; Microneedle

1. Introduction

With the sales of advanced drug delivery systems in the United States approaching US$ 20 billion annually, extensive research has focused on improving and creating advanced drug delivery systems (Langer, 1998; Langer and Peppas, 2003). In recent years, microfabrication technologies have been applied in drug delivery and have led to the development of novel advanced drug delivery microsystems. These microfabricated drug delivery devices enable tailored drug delivery that is essential for the successful therapeutic activity of a drug. Although still in its infancy, the field of microfabricated drug delivery devices has demonstrated immense potential for surmounting barriers that are common to traditional drug delivery technologies.

1.1. Drug delivery

The process for delivering a drug is as important as the actual activity of the drug in determining the therapeutic effect. For optimum therapeutic effect, the

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right amount of a drug needs to get to the right place at the right time. Consequently, advanced drug delivery formulations have been developed over the past 20 years that do not simply release a drug at a specific rate, but release the drug in a way that the pharmaceutical scientists and engineers have designed (Langer and Peppas, 2003; Peppas et al., 2000). Additionally, because drug delivery can improve safety, efficacy, convenience and patient compliance, improving delivery methods has become a major focus of pharmaceutical companies (Peppas, 2004a; Peppas et al., 2004b; Byrne et al., 2002).

In traditional drug delivery, common delivery routes include oral, pulmonary, transdermal and injection, and they each have certain advantages and disadvantages associated with them. For instance, all of these routes, except for direct injection into a vein or muscle tissue, have cellular layers that are encountered, which function as a barrier to transport into the systemic circulation.

Controlled release in drug delivery can significantly enhance the therapeutic effect of a drug. Typically, controlled release is used to achieve sustained or pulsatile drug release. Sustained release is used to achieve a constant release of a drug over an extended period of time. For example, many drugs have an optimum range of concentrations that if the concentration of the drug is above or below this range, the drug is toxic or has no therapeutic effect, respectively. In this case, controlled release would be used to maintain the concentration of drug delivered within the optimum range for maximum therapeutic effect. In contrast, there are many situations where it is not optimal to have sustained release because it fails to mimic the body's natural response. For instance, a healthy individual produces insulin in a pulsatile manner, and therefore, a pulsatile delivery is typically utilized in the treatment of diabetes to mimic the insulin production of the body (Peppas, 2004a).

1.2. Microfabrication

Integrated circuits and microelectronics have revolutionized our world over the past three decades (Schulz, 1999). This rapid pace of growth has fueled the subsequent development of additional microtechnology devices. Microfabrication techniques that are utilized at present have developed as a result of integrated circuit manufacturing technologies, such as photolithography, thin film growth/deposition, etching and bonding.

In recent years, the methods used in microfabrication have been applied to either significantly enhancing a device relative to its conventional counterpart or enabling entirely new devices in a wide range of fields. For example, these fabrication techniques have led to the development of microelectromechanical systems (MEMS), bioMEMS, micro-total analysis systems (μ-TAS), lab-on-a-chip and other microdevices.

In a seminal paper (Petersen, 1982), the great potential of using silicon in microdevices as a mechanical material and no longer solely based on its well-established electrical properties was described. This paper outlined the excellent mechanical properties of silicon, and then, the goal of developing a broad range of inexpensive, batch-fabricated, high-performance sensors and transducers that could be easily interfaced with advanced microelectronics was discussed. Although silicon was initially the material of choice in these microfabricated devices because of its favorable electrical and mechanical properties, other materials, such as ceramics and polymers, have been applied recently in the fabrication of microdevices because of their desirable properties (e.g. biocompatibility and price) (Peppas, 2004a; Peppas and Byrne, 2003).

Microfabrication techniques can be categorized into surface or bulk micromachining, which are based on IC manufacturing technologies. Surface micromachining is an additive process, which consists of fabricating micromechanical structures from deposited thin films, such as silicon nitride, polycrystalline silicon and other materials (Bustillo et al., 1998). Bulk micromachining is a subtractive process that uses the selective removal of significant amounts of silicon, or other material, from a substrate to form microstructures (Kovacs et al., 1998). These fabrication techniques have been utilized to manufacture a wide range of sensors, actuators and microdevices, including pressure sensors, accelerometers, flow sensors, ink-jet printer heads and micromirrors for projection.

Microscale devices inherently have many advantages over their conventional counterparts. For instance, miniaturization of a device can lead to the manufacture of portable, hand-held, or implantable devices, which is highly desirable for drug delivery applications. In addition, as a result of their minute size, microdevices typically need less than a microliter

of sample or drug for analysis or operation, which saves money and time. Moreover, where materials and/or processes are inhibited by lengthy diffusion times, miniaturization provides a mechanism for abbreviating these times. A further advantage, which is a consequence of microfabrication originating from the IC industry, is the resulting simplicity of integrating a microfabricated device with electronic elements, which allows for straightforward control and manipulation of the operation of the device. All of the aforementioned advantages of miniaturization assist in facilitating the development of multifaceted devices that can accomplish new or improve on existing functions or processes.

2. Microfabricated drug delivery devices

Advances in micro- and nanotechnologies have accelerated the development of new drug delivery

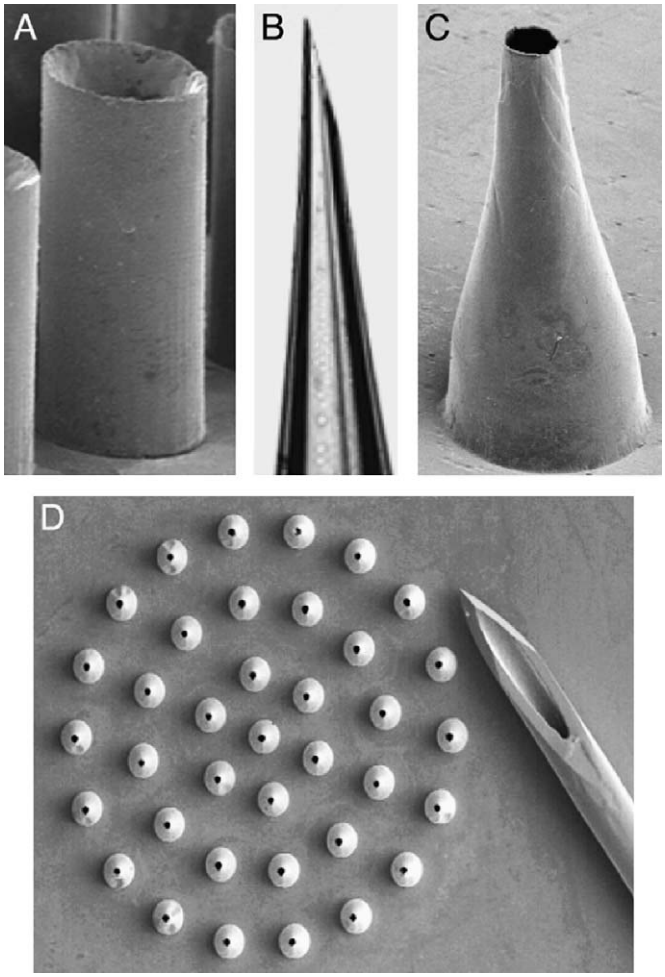

Fig. 1. Hollow microneedles fabricated out of silicon, metal and glass imaged by optical and scanning electron microscopy. (A) Straight-walled metal microneedle from a 100-needle array fabricated by electrodeposition onto a polymer mold (200 μm tall), (B) tip of a tapered, beveled, glass microneedle made by conventional micropipette puller (900 μm length shown), (C) tapered, metal microneedle (500 μm tall) from a 37-needle array made by electrodeposition onto a polymeric mold and (D) array of tapered metal microneedles (500 μm height) shown next to the tip of a 26 gauge hypodermic needle. Copyright (2003) National Academy of Sciences, USA (McAllister et al., 2003).

technologies that are required to transform biological potential into medical reality (Langer and Peppas, 2003; LaVan et al., 2002). Only in the last decade, the aforementioned advances in microfabrication methods have been applied in creating drug delivery microdevices. For instance, microfabrication techniques have enabled the development of novel drug delivery microdevices or components of therapeutic microdevices that can improve therapeutic benefits of drugs, such as microneedles, micropumps, microvalves and implantable drug delivery microdevices. In contrast to the numerous biological applications of microfabrication technologies, the application of these technologies to drug delivery has been limited. The field of microfabricated drug delivery devices, which is undoubtedly still in its infancy has tremendous potential.

2.1. Microneedles

For over 150 years, syringes and hypodermic needles have been utilized to deliver drugs into patients (McAllister et al., 2000). Because of the transport barriers that exist in other delivery routes, injection is still a prominent method for drug delivery today. Currently, the smallest needles that are commercially available for injections are 30 gauge for conventional syringes and 31 gauge for pen injectors, which are utilized mainly for insulin delivery. The 30 and 31 gauge needles have outer diameters of 305 and 254 um, respectively (Trimmer et al., 1995). Microfabrication has been utilized to create microneedles, which are orders of magnitude smaller in diameter, capable of localized and painless delivery of drugs into cells or tissues. Research into the application of microneedles for gene and drug delivery has been divided into three broad areas: cellular delivery, local delivery and systemic delivery.

Microneedles have been applied for the delivery of membrane impermeable molecules into cells. For application in molecular and cell biology, methods for the delivery of peptides, proteins, oligonucleotides, DNA and other probes that alter or assay cell function is desired. Arrays of microneedles were fabricated and utilized to deliver DNA into plant and mammalian cells, as a method for transforming cells (Trimmer et al., 1995; Reed et al., 1998).

Additionally, microneedles have been utilized to target drug delivery to a specific region or tissue in the body, thus avoiding detrimental effects that can result from administering certain drugs systemically. This targeting can reduce side effects, minimize the dose of an expensive drug, and/or provide a means of delivery to a location that is difficult to treat (Langer and Peppas, 2003). For instance, a multichannel silicon microneedle has been microfabricated to deliver bioactive compounds into neural tissue while simultaneously monitoring and stimulating the neurons in vivo (Chen and Wise, 1997). In addition, microneedles have been used to penetrate vessel walls of normal and atherosclerotic rabbit arteries in vitro demonstrating potential use for targeted delivery of antirestenosis drugs (Reed et al., 1998).

Furthermore, microneedles have been microfabricated for application in transdermal drug delivery (McAllister et al., 1999a,b, 2003). In conventional transdermal drug delivery, the outer 10–20 μm of skin,

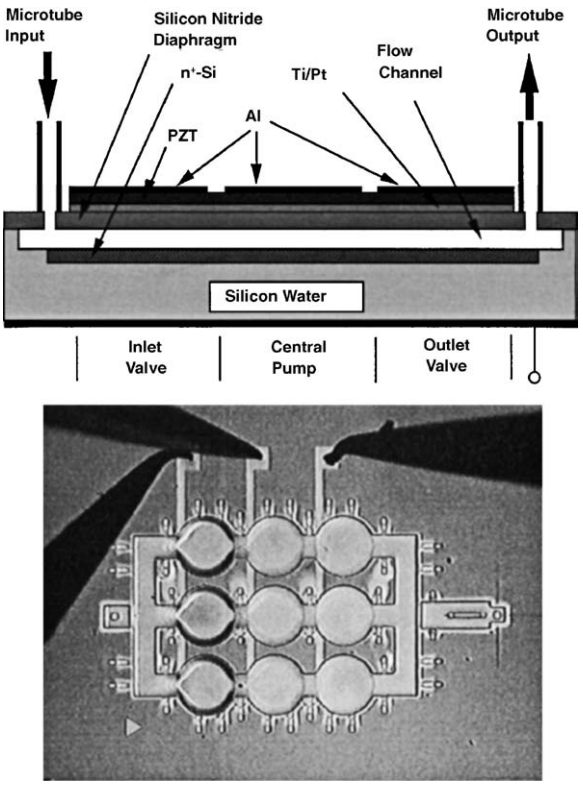

Fig. 2. Cross section (top) and photograph (bottom) of a microelectromechanical systems-based microfluidic pump. The three-stage design operates as a peristaltic pump. Each diaphragm measures 300 μm in diameter (Polla et al., 2000).

the stratum corneum, acts as a barrier to the diffusion of the drug molecules and limits the applicability to small drug molecules. Because the stratum corneum does not have any nerves, microneedles that are long enough and robust enough to penetrate across this layer, but short enough to not stimulate the nerves in the deeper tissue, have the potential to make transdermal delivery a painless and much more viable option (Trimmer et al., 1995). Examples of the microfabricated microneedles for transdermal drug delivery are included in Fig. 1.

In other research, SU-8 has been utilized to fabricate microneedles for transdermal drug delivery (Polla et al., 2000). The SU-8 is advantageous relative to silicon because it is non-brittle, which reduces the risk of breaking off in skin, and is relatively inexpensive. Recently, novel methods have been developed to fabricate nanoneedles, which have been proposed to enhance performance even further (Mani et al., 2003; Prinz et al., 2003). Microneedles have been demonstrated as effective devices for the delivery of genes and drugs to cells, local region of tissues and transdermally. By combining microneedles with a device containing a pump and logic circuitry, novel drug delivery microdevice will be created.

2.2. Micropumps and microvalves

Micropumps and microvalves are key components to any microfluidic device. For the creation of an implantable drug delivery system, micropumps and microvalves are critical for the control of the dispensing system.

By surface micromachining techniques, micropumps have been microfabricated utilizing piezoelectric thin films based on the lead zirconate titanate (PZT) material system (Polla, 1999; Cao, 2001). A schematic of this device is included in Fig. 2. This MEMS device has been proposed for application in implantable drug delivery systems. In addition, another research group (Teymoori and Abbaspour-Sani, 2005) has developed an electrostatic peristaltic pump for application in drug delivery systems.

The microfabrication of miniature valves is one of the most difficult aspects in the development of microfluidic systems (Madou, 2002). Because valves with moving parts are prone to malfunction through mechanisms, such as clogging, it is desirable to create valves with no moving parts. Single-use valves were created based on micromachined chambers capped

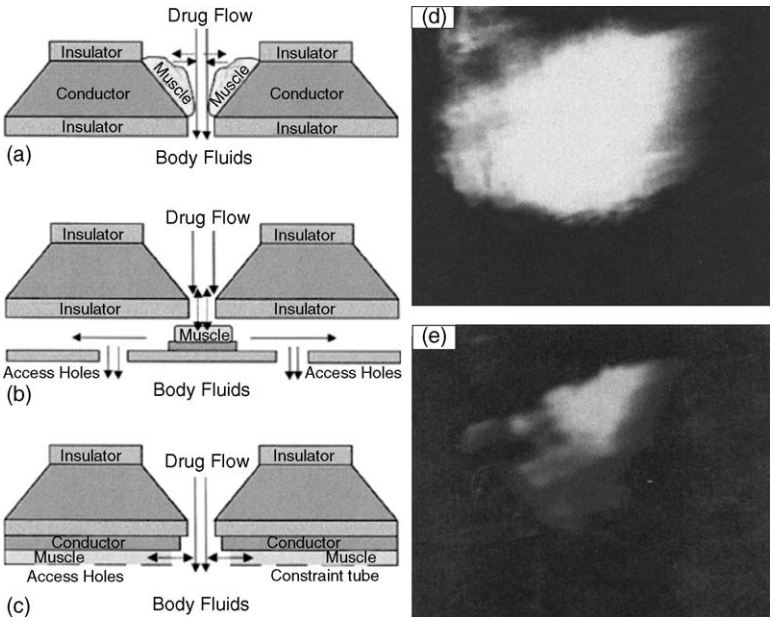

Fig. 3. Schematic of alternative designs for opening and closing holes in a drug reservoir using the artificial muscle concept. Sphincter configuration (a), plunger configuration (b), tube configuration (c), artificial muscle blend at (d) shrunken (open) state at −0.2 V (SCE) and (e) swollen (closed) state at +0.3 V (SCE). Dramatic change in the size of the hole is observed. Reprinted with permission from Elsevier (Low et al., 2000).

with a metal valve that could be electrochemically opened, and then the drugs that were stored in the microchambers would be released. Using this system, different drugs could be released at different times, and by systematically opening more valves, the rate of drug delivery could be controlled. The mechanism of operation is that a small current applied between the valve and counter electrode leads to local electrolysis of water and bursts the thin metal cap. In additional work, a reversible valve was designed based on an "artificial muscle" (Low et al., 2000). "Artificial muscle" refers to a chemomechanical actuator composed of a blend of a hydrogel and an electronically conducting redox polymer like polyaniline and polypyrrole, or their derivatives (Madou and Florkey, 2000). This polymer blend exhibits a swelling that is controllable with an electrical bias, and therefore, the polymer blend can be swollen and shrunk to close and open a valve using electrical control, as shown in Fig. 3.

In other work, Beebe and co-workers have developed microvalves and micropumps utilizing responsive hydrogel systems for actuation (Eddington and Beebe, 2004; Beebe et al., 2000). The micropumps and microvalves discussed above can be applied to create drug delivery systems that enable enhanced control over the delivery of therapeutic agents.

2.3. Implantable microchips

Microchips have been created for the storage and then delivery of multiple drugs in a controlled manner. For instance, a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand was fabricated and

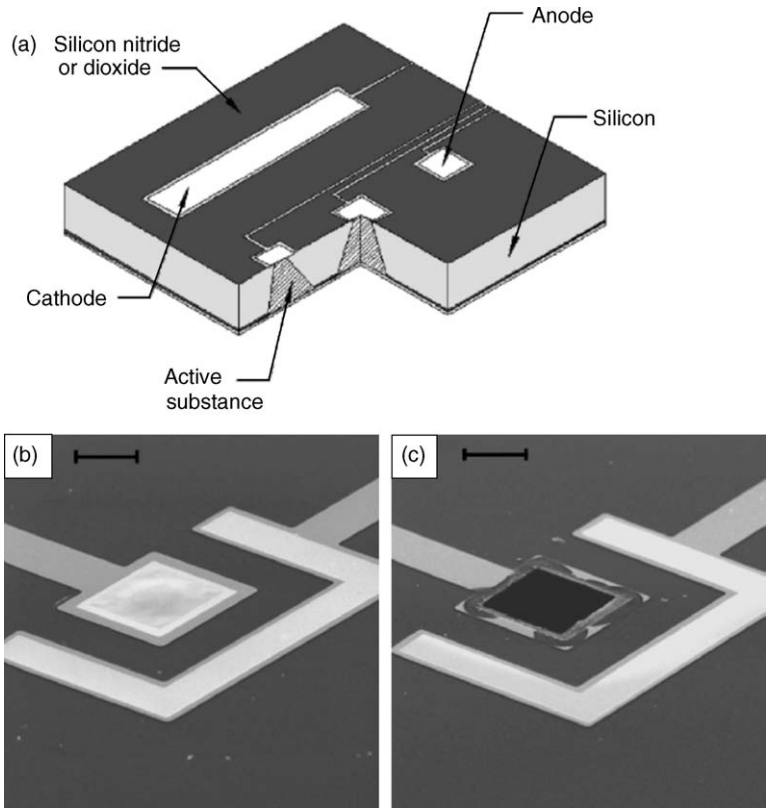

Fig. 4. (a) A prototype microchip for controlled release showing the shape of a single reservoir. Removal of an anode membrane to initiate release from a reservoir. (b and c) Scanning electron micrographs of a gold membrane anode covering a reservoir are shown before (b) and after (c) the application of +1.04 V w.r.t. SCE for several seconds in PBS (scale bar = 50 μm). Figure adapted from Santini et al. (1999) with permission from the Nature Publishing Group (http://www.nature.com/).

demonstrated (Santini et al., 1999, 2000). The release is achieved via electrochemical dissolution of the thin anode membranes covering the microreservoirs filled with chemicals in solid, liquid, or gel form, as shown in Fig. 4. In addition, multipulse drug delivery from a resorbable polymeric microchip device was demonstrated (Grayson et al., 2003).

The advantages of this microdevice include that it has a simple release mechanism, very accurate dosing, the ability to have complex release patterns, potential for local delivery and possible biological drug stability enhancement by storing in a microvolume that can be precisely controlled.

In other work, researchers have microfabricated silicon and poly(methyl methacrylate) particles that contain multiple drug-containing reservoirs (Tao and Desai, 2003). These particles are coated with elements that promote the selective binding to a target release area, such as the intestinal lining, enabling for targeted controlled release of drugs.

2.4. Self-regulated drug delivery microdevices

In the field of controlled drug delivery, self-regulated (closed-loop) in vivo devices that use diagnostic measurements to control drug release are widely considered to be the ultimate goal. Microscale therapeutic and diagnostic systems are fundamental for the development of these self-regulated drug delivery devices because they are capable of being implanted within the body to monitor concentrations of specific target biomolecules and deliver therapeutic agents as necessary (Ward et al., 2000, 2001; Oral and Peppas, 2000; Peppas, 2004b; Peppas et al., 2004a; Bergmann and Peppas, 2004).

Incorporation of both diagnostic and therapeutic components onto a single chip enables for the real-time monitoring of a target biomolecule and the simultaneous delivery of therapeutic agents to counter any undesirable levels. This closed-loop therapy is the ultimate in health care by providing the patient with a self-regulated treatment regiment.

In recent years, a variety of microscale biosensor platforms have been developed. For example, microcantilevers have been applied as ultrasensitive transducers in combination with a wide variety of sensing elements, such as intelligent polymer networks (Hilt et al., 2003; Bashir et al., 2002) and single-stranded DNA (Wu et al., 2001). By integrating a microsensor, such as these microcantilever-based devices with a therapeutic microchip, a self-regulated drug delivery device can be created. The resultant closed-loop drug delivery device will enable superior controlled delivery that is unattainable with conventional drug delivery techniques and result in the enhancement of the therapeutic activity of a drug.

3. Conclusions

Microfabricated microneedles have been demonstrated as powerful tools for the delivery of drugs and other molecules to cells, target regions and systemically. These microneedles have facilitated drug delivery, which was impossible with traditional delivery methods. For example, the capability of utilizing these microneedles for transdermally delivering macromolecules, such as proteins, with no pain was described. This is a key example of the enhancement that microfabrication can bring to the field of advanced drug delivery. In addition, micropumps and microvalves have been demonstrated as viable microfluidic elements that are critical for the development of drug delivery microdevices. These microfabricated components and future improved models will enable the creation of novel microdevices that can be tailored to give any drug delivery profile desired. In addition, the implantable microdevices that were described show promise. These are capable of very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a microvolume that can be precisely controlled.

These microfabricated drug delivery devices can enable efficient drug delivery that was unattainable with conventional drug delivery techniques, resulting in the enhancement of the therapeutic activity of a drug. The future of drug delivery is assured to be significantly influenced by microfabrication technologies.

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