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# Controlled-release microchips

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Efficient drug delivery remains an important challenge in medicine: continuous release of therapeutic agents over extended time periods in accordance with a predetermined temporal profile; local delivery at a constant rate to the tumour microenvironment to overcome much of the systemic toxicity and to improve antitumour efficacy; improved ease of administration, and increasing patient compliance required are some of the unmet needs of the present drug delivery technology. Microfabrication technology has enabled the development of novel controlled-release microchips with capabilities not present in the current treatment modalities. In this review, the current status and future prospects of different types of controlled-release microchips are summarised and analysed with reference to microneedle-based microchips, as well as providing an in-depth focus on microreservoir-based and nanoporous microchips.

Keywords: controlled release, MicroCHIPS, microelectromechanical systems, microneedles, microreservoirs, nanoporous silicon microchips

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## 1. Introduction

Drug delivery, in simplistic terms, can be defined as any mechanism to introduce therapeutic agents into the body. Chewing the leaves and roots of medical plants and the inhalation of soot from the burning of medical substances from the earliest times are examples of drug delivery. However, these primitive approaches of delivering drugs lacked a very basic need in drug delivery: consistency and uniformity of the drug dose. This led to the development of different drug delivery methods in the late 1700s and the early 1800s. These methods included pills, syrups, capsules, tablets, elixirs, solutions, extracts, emulsions, suspension, cachets, troches, lozenges, nebulisers and many other traditional delivery mechanisms. Many of these delivery mechanisms use drugs that are derived from plant extracts. The modern era of medicine development started with the discovery of vaccines in 1885 along with techniques for the purification of drugs from plant sources. This was followed by the introduction of penicillin, after its discovery in 1929, and a subsequent era of prolific drug discovery.

The development and production of many pharmaceuticals involves the genetic modification of microorganisms to transform them into drug-producing factories. Such examples include recombinant DNA, human insulin, IFN, hairy cell leukaemia, IL-2, erythropoietin, chemotherapy-associated anaemia and tissue fibrinolysin (human)ogen activators [1]. It is now possible to produce oligonucleotide, peptide and protein drugs in large quantities, whereas gene therapies seem to be clinically feasible. Each of these therapeutic agents, by virtue of size, stability, or the need for targeting, requires a specialised drug delivery system [2].

Whereas the conventional drug delivery systems such as oral, topical, inhaled or injections are simple, more sophisticated delivery systems need to take into account pharmacokinetic principles, specific drug characteristics and variability of response depending on the patient as well as other conditions.

The efficacy of many therapeutic agents depends on their action on target macromolecules located either within or on the surface of particular cells types. Many drugs interact with enzymes or other macromolecules that are shared by a large

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number of cell types, although most often a drug will exert its action on just one cell type.

An ideal gene delivery system should allow the gene to find its target cell, penetrate the cell membrane, and enter into the nucleus. Furthermore, genes should not be released until they find their target and one has to consider whether to release the genes only once or repeatedly via a predetermined pathway [2]. Thus, the therapeutic efficacy of a drug can be improved whereas the toxic effects can be reduced by augmenting the amount and persistence of the drug in the vicinity of the target cells, whilst at the same time reducing the drug exposure to the nontarget cells. This is the basic rationale behind controlled drug delivery.

A controlled drug delivery system requires simultaneous consideration of several factors, such as the drug property, route of administration, nature of delivery vehicle, mechanism of drug release, ability of targeting and biocompatibility. The extensive independency of these factors make it complicated to achieve them all in one system. Furthermore, reliability and reproducibility of drug delivery systems are the most important factors when designing such a system. The emphasis here is on the need for precise control of the amount of released drug and to minimise any contribution to intra- and intersubject variability associated with the drug delivery system.

The rest of this review is constructed as follows. Section 2 will discuss the approaches for controlled drug delivery. Subsequently, some controlled-release devices will be described. Controlled-release microchips fabricated out of silicon will be discussed, briefly detailing microneedle-based chips and looking in-depth at microreservoir-based chips and nanoporous microchips. Conclusions will be drawn and the authors' expert opinion given, including a short market overview.

## 2. Approaches for controlled drug delivery

There are many different approaches for controlled drug delivery [3]. In many cases, it is desired to deliver a drug to a particular diseased tissue or organ. Localised drug delivery reduces systemic toxicity and achieves a peak drug level directly at the target site. Targeted drug delivery releases the drug exclusively to targeted cells or cellular components. Although localised drug delivery simply implies localisation of therapeutic agent at an organ or tissue site, targeted drug delivery implies a more subtle delivery to specific cell types.

Generally, injected or ingested drugs follow first-order kinetics, with initial high blood levels of the drug after the first administration, followed by an exponential fall in blood concentration. Toxicity often occurs when blood levels peak, whereas efficacy of the drug diminishes as the drug levels fall below the therapeutic range (Figure 1A). Such drug kinetics are undesirable, especially in the case where the therapeutic concentration range is narrow. Sustained drug delivery helps to achieve a zero-order release profile, in which the release rate of the drug is constant and not bound by Fick's diffusion laws (see Section 4.3.2) [4]. Zero-order kinetics reduce toxicity and improve drug efficacy (Figure 1B).

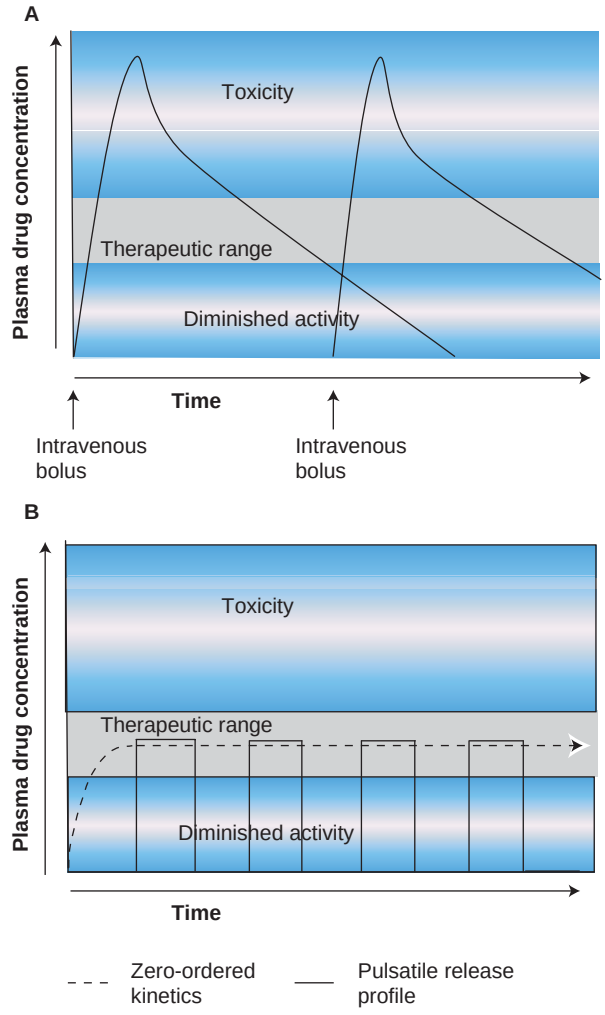


**Figure 1. First-order versus zero-order kinetics in drug delivery. A.** Plasma concentration versus time curve for intravenous drug administration showing first-order kinetics. **B.** Plasma concentration versus time curve for sustained release profile of zero-order kinetics and pulsatile release profile.

The therapeutic advantages of sustained-release drug delivery systems are thus significant and encompass:

- *in vivo* predictability of release rates on the basis of *in vitro* data,
- minimised peak plasma levels and, hence, a reduced risk of toxic effects,
- predictable and extended duration of action, and
- reduced inconvenience of frequent dosing and, thereby, improved patient compliance [5,6].

A significant challenge in drug delivery is to create a delivery system that can achieve a manipulable non-zero-order release profile, known as modulated drug delivery. A pulsatile release profile within the therapeutic range is shown in Figure 1B. The ideal drug delivery system has a monitored or triggered feedback that releases the drug in response to a therapeutic

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marker. A modulated device involves the ability to monitor the chemical environment and to change the drug delivery rate continuously in response to the external marker, whereas in a triggered device no drug release takes place until it is stimulated by a marker.

These approaches to drug delivery can have different routes of administration. Some of the most preferred routes are oral, pulmonary inhalation, transdermal, transmucosal and implantable systems. Although most controlled drug delivery systems are designed for transdermal, subcutaneous or intramuscular uses, implantable devices are very attractive for a number of drugs, particularly those that cannot be delivered via the oral route or are irregularly absorbed via the gastrointestinal tract [7].

Implantable systems can either be designed to deliver therapeutic agents into the bloodstream or to a particular site. This replaces repeated insertion of intravenous catheters. These systems are particularly suited for drug delivery requirements of insulin, steroids, chemotherapeutics, antibiotics, analgesics, contraceptives and heparin. Implantable systems are generally placed completely under the skin; usually in a convenient but inconspicuous location. Benefits includes reduction of side effect (drug delivery rate within the therapeutic range) caused by traditional administration techniques as well as a better control over the drug concentration and location of delivery.

## 3. Controlled-release devices

A variety of devices have been developed to achieve controlled drug delivery over the years. These devices use different routes of administration, and different methods and materials for device fabrication. Typically, each of these devices is targeted towards delivering one or a few therapeutics. These include osmotic pumps, micropumps, polymeric devices and microelectromechanical systems (MEMS)-based devices.

The first such device that saw extensive clinical use was reported in the 1970s [8-11]. This system used a bellows-type pump activated by partially liquefied Freon® (DuPont). The Freon was reliquefied with each transcutaneous refill of the implantable device and the administration was constant. In subsequent years, extensive research enabled the development of more sophisticated devices that could offer better control and more clinical options.

Another device that has a peristaltic pump to deliver the drugs was developed by Medtronic Company [12], which was controlled by electronics. Another system, developed by MimiMed Technologies, employs a solenoid pump, a reservoir and advanced electronic control [13]. The Infusaid Company developed an advanced, programmable, implantable pump that employed a bellows-type pump with a solenoid valve set to control the drug flow [14].

### 3.1 Polymeric devices

Polymers have been used extensively in controlled drug delivery systems. A detailed description of all of the types of polymeric devices is beyond the scope of this review. Briefly, these can be generally classified into two categories:

- nondegradable polymeric reservoirs and matrices
- biodegradable polymeric devices

Nondegradable polymeric reservoirs and matrices are prepared by homogeneous dispersement of the drug particles throughout a polymeric matrix [15]. Drug release occurs by diffusion through the polymer matrix or by leaching or a combination of both [16]. Nevertheless, achieving constant rates of the drug release remains an elusive goal with nondegradable matrix systems. For instance, the rate of release of carmustine from an ethylene–vinyl acetate copolymer-matrix device dropped continuously during incubation in buffered water [17]. Water-soluble, crosslinked polymers are used as matrices and release is then activated by swelling of the matrix after exposure to water [18]. A magnetically controlled-release system where magnetic beads are dispersed within the matrix has also been used for achieving sustained release [15].

Biodegradable polymeric devices are formed by physically entrapping drugs into matrices or microspheres. The polymers dissolve when implanted, and release the drug [19]. Examples of the commercially available polymeric devices are Decapeptyl® (Debiopharm), Lupron Depot® (microspheres; TAP Pharmaceutical Products Inc.) and Zoladex® (cylindrical implants; AstraZeneca). Methods have been developed to achieve controlled drug delivery profiles with implantable polymeric systems [20,21]. These technologies include preprogrammed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical simulation. Nevertheless, the current methodology used for polymers is not efficient enough to achieve the high-precision control that is required for controlled drug delivery.

### 3.2 Silicon-based devices

Silicon microfabrication technology has provided an attractive method to achieve high precision and control for drug delivery application. From a modest beginning ~ 40 years ago that allowed few transistors on a chip, it has reached an integration level of tens of millions of components in a square centimetre of silicon. The minimum feature size on silicon is reducing and, thus, the number of devices per $cm^2$ is increasing.

Silicon fabrication technology has now extended to machining mechanical microdevices known as MEMS. In recent years, MEMS technology has been extensively used for biological and biochemical applications, called bio-MEMS [22,23]. Furthermore, the integration of microfluidic devices and integrated circuits over the last decade has revolutionised the chemical and biological analysis systems, and has opened the possibility of fabricating devices with an increased functionality and complexity for these applications [24-26].

These tiny devices hold promise for precision surgery with nanometre control, rapid screening of common diseases and genetic predispositions, and autonomous therapeutic



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management of allergies, pain and neurodegenerative diseases [5]. The development of retinal implants to treat blindness [27], neural implants for stimulation and recording from the CNS [28], and microneedles for painless vaccination [29] are all examples in which MEMS technology has been used.

With microfabrication technology it is also possible to produce the novel drug delivery modalities with capabilities that are not present in the current systems. A variety of microfabricated devices, such as microparticles, microneedles, microchips, nanoporous membranes and micropumps, have been developed in the recent years for drug delivery applications [29-33]. The detailed description of all types of MEMS drug delivery devices is beyond the extent of this review.

In this article, the main focus will be on controlled-release silicon microchips that employ photolithographically defined silicon templates for their fabrication, including microreservoir-based chips and nanoporous microchips in detail, but first briefly touching on the subject of drug delivery through microneedles.

## 4. Controlled-release microchips

### 4.1 Microneedle-based chips

MEMS technology has provided an attractive alternative approach to transdermal drug delivery. The transdermal route has some advantages over oral and intravenous routes as it avoids the degradation of molecules in the gastrointestinal tract and the first-pass effects of the liver, both of which are associated with oral drug delivery, as well as eliminating the pain associated with intravenous injection [33-39]. Nevertheless, the major barrier for transdermal delivery is the stratum corneum, the outermost dead layer of the skin. It is an excellent barrier in that it efficiently separates that which needs to be kept in from that which needs to be excluded, whereas at the same time allowing transpiration, for example, to cross. The human stratum corneum is 10 – 20 µm thick. The microneedle-based chips that have been developed for transdermal drug delivery enhance the poor permeability of the skin by creating microscale conduits for transport across the stratum corneum [31,38]. Needles of micrometre dimensions can pierce the skin surface to create holes that are deep enough for molecules to enter, but short enough to avoid pain or other significant damage.

In this paper, the reader is not given a complete overview of all of the microneedle drug delivery systems. Two excellent reviews on microneedles have recently been published [40,41]; therefore, a couple of important silicon contributions to this field will be mentioned. The main focus will be on devices with which researchers have actually tried to puncture the stratum corneum itself, or at least an imitation of the stratum corneum.

Although the microneedle concept was proposed in the 1970s [201], it was not demonstrated experimentally until the 1990s [41]. Microneedles can be fabricated in-plane, where the needle lumen (flow channel) is parallel to the substrate surface, or out-of-plane, where the lumen is normal to the substrate.

There are two manners of releasing drugs from (micro) needles. The first way is common in the medical macroworld, where the needles are hollow and the drugs are delivered through a hollow channel in the needle from a reservoir on the rear side. However, in microfabrication it is complicated to create a well-defined channel in a microneedle. Therefore, many microfabricated needles do not have a hollow channel through which the drug is delivered, yet they contain a coating on the microneedle that dissolves after puncturing the stratum corneum. Venomous spines on animals often deliver their own drug, or rather poison, in this way. Most coated microneedles are, however, not used for drug delivery but instead for gene or DNA delivery, and thus fall past the confines of this paper [29,43-51].

#### 4.1.1 *In-plane microneedles*

Wise *et al.* introduced in-plane microneedles in 1986 [52], and in subsequent work microfluidic channels were added [53]. Pisano and Lin also fabricated hollow microneedles in silicon [54]. These microneedles were 1 – 6 mm in length with lumens 9 µm high and 30 – 50 µm wide. The needles can be repeatedly inserted into and retracted from animal muscle tissue, such as a porterhouse steak, without damage to the microneedles (Figure 2A) [55].

Brazzle *et al.* [56-59] used a similar design to that of fabricated hollow metal microneedles and microneedle arrays using a micromoulding process and electroplated metals. The arrays were typically 9 mm wide and 3 mm high, with 3 – 17 needles per array. Oka *et al.* have imitated the jagged shape of a (hollow) mosquito needle [60]. This group confirmed that the needle can penetrate into hard silicon rubber and that it can aspirate red ink without leakage. Paik *et al.* fabricated 2-mm long hollow microneedles that were 100-µm thick and wide [61]. They showed that their microneedles can inject ink into methanol, and Rhodamine B dye into an agarose gel, chicken breast and the ear of a rabbit (Figure 2B). The channel into the lumen is a so-called buried channel [62].

#### 4.1.2 *Out-of-plane microneedles*

Out-of-plane arrays of rigid hollow microneedles were fabricated by Stoeber and Liepmann [63-65]. These microneedles were 200-µm tall, with a base diameter of 425 µm tapering to a 40-µm lumen, which is also the channel diameter. Fluid injection was demonstrated by delivering the drug under the skin of a chicken breast at a depth of ~ 100 µm. In human volunteers, it was shown that methyl nicotinate was successfully injected through the stratum corneum [66]. Griss and Stemme presented side-opened microneedles; these avoid problems of clogging of the channel exit at the apex of the microneedle with debris from the skin puncture [67]. Davis *et al.* presented hollow microneedles in patch-like arrays and delivered insulin to diabetic rats, reducing the blood glucose level by ~ 50% over the delivery period [69].

Solid microneedles with no lumen were demonstrated by Henry *et al.* [38,70]. The tapered microneedles were 150-µm tall and were fabricated in dense arrays. Gardeniers *et al.* fabricated

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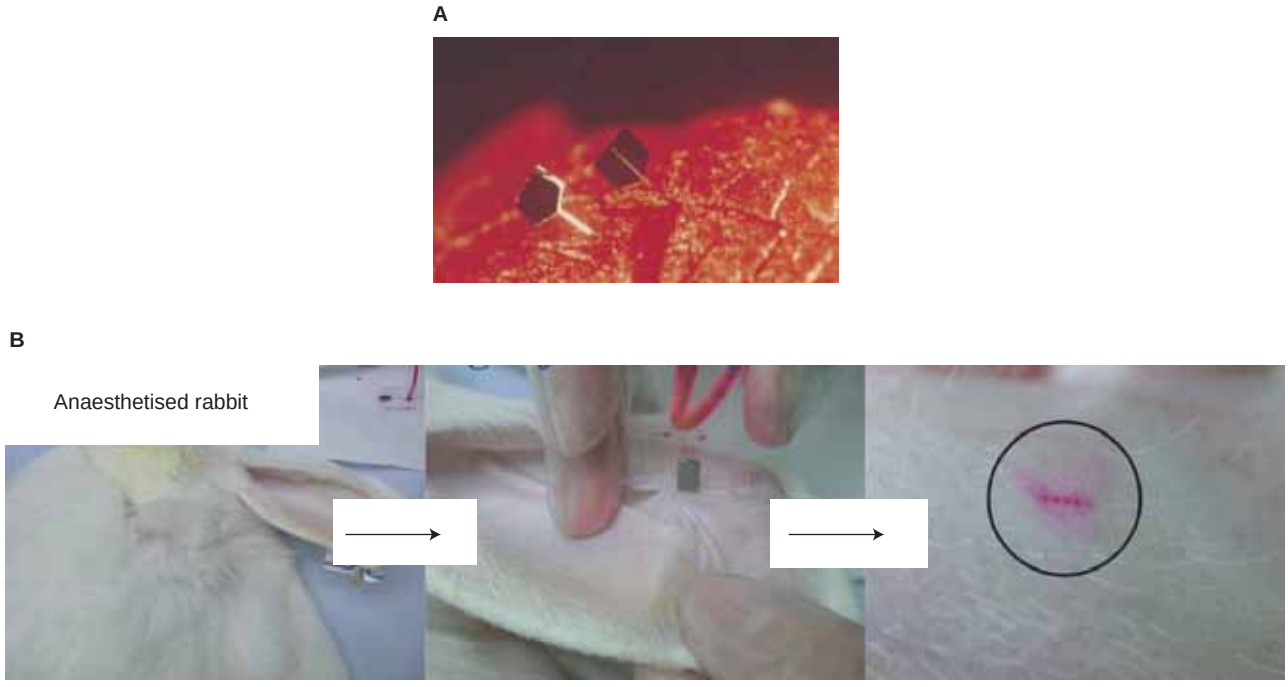


**Figure 2. Microneedles in action. A.** Two microneedles penetrating a porterhouse steak. Reprinted with permission from LIN L, PISANO AP: Silicon processed microneedles. *J. Microelectromech. Syst*. (1999) 8(1):78-84 [54]. **B.** Injection procedure of the Rhodamine B dye into the ear of the anesthetised rabbit and the several injection marks on the surface. Reprinted from PAIK S-J, BYUN S, LIM J-M *et al.*: In-plane single-crystal-silicon microneedles for minimally invasive microfluid systems. *Sens. Actuators A Phys.* (2004) **114**:276-284 [61]. Copyright (2004), with permission from Elsevier.

very sharp out-of-plane microneedles [71]. These authors measured transdermal water loss on human skin, and drug infusion into a test animal showed that diclofenac plasma levels increased hundreds of times depending on the number of microneedles applied.

Generally, existing microneedle-based microchips offer several advantages, such as the ability to inject drugs directly through the stratum corneum at reproducible and accurate depth of penetration, minimal pain, and the on-board ability to probe or sample the same device. Local irritation and low mechanical stability are some of the potential drawbacks.

### 4.2 Microreservoir-based chips

For the therapies that require many injections daily or weekly, implantable devices can improve patient compliance and efficacy of treatment. These devices can either be implanted into the human body or placed under the skin, consequently reducing the risk of infection by eliminating the need for frequent injections. Most of the implantable microsystems are virtually invisible and are not expected to cause pain or tissue trauma owing to their small size.

Silicon microfabrication technology has been used to develop a drug delivery microchip consisting of an array of microreservoirs [30,72,73] (Figure 3A – C). This device is currently being developed by MicroCHIPS, Inc., for use as external and implantable systems for the delivery of proteins, hormones, pain medications and other pharmaceutical compounds [301]. In this design, each dosage is contained in a separate reservoir that is covered with a gold membrane. The membrane dissolves in the presence of chloride ions when anodic voltage is applied to the membrane of interest. This causes the membrane to weaken and rupture, allowing the drug within the reservoir to dissolve and diffuse into the surrounding tissues.

This device allows for the release of a potent substance in a pulsatile manner. Each microreservoir can be individually filled, so multiple substances can be delivered from a single MEMS device. The release of fluorescent dye and radiolabelled compounds has been demonstrated from these microreservoir-based microchips *in vitro* in saline solution and serum [30].

The release studies from this device demonstrated that the activation of each reservoir could be controlled individually, creating a possibility for achieving many complex release patterns. Varying amounts of chemical substances in solid, liquid or gel form could be released into a solution in a pulsatile or a continuous manner, or a combination of both, either sequentially or simultaneously from a single device.

A microbattery, multiplexing circuitry and memory could be integrated directly onto the device, allowing the entire device to be mounted onto the tip of a small probe, implanted, swallowed and integrated with microfluidic components to develop a 'laboratory-on-a-chip', depending on the particular application. Proper selection of biocompatible device materials may result in the development of an autonomous, controlled-release implant or a highly controllable tablet for drug delivery applications [30].



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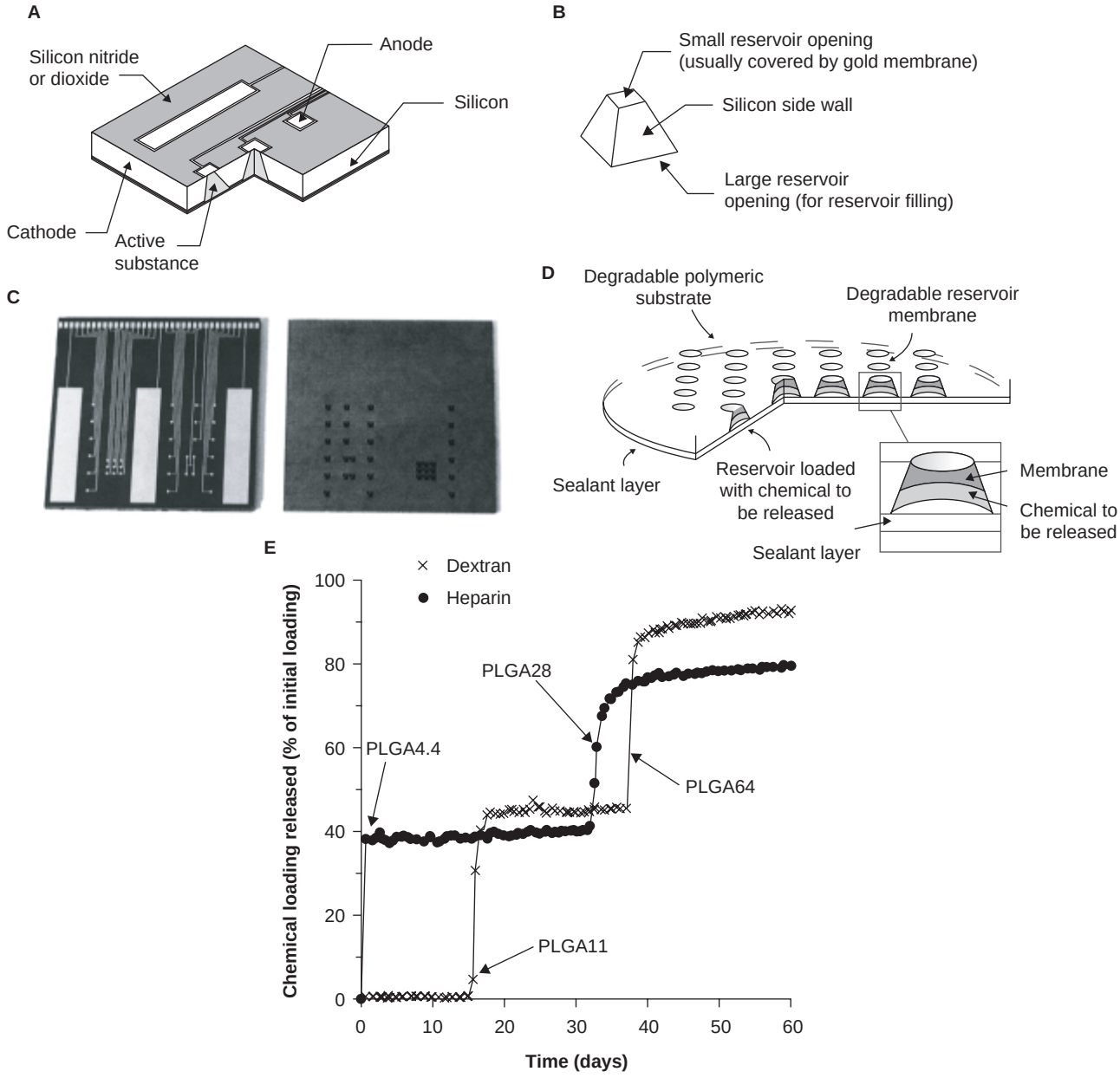


**Figure 3. A schematic of a silicon microchip for controlled release. A.** Cut-away section showing anodes, cathodes and reservoirs. **B.** Shape of an individual reservoir. **A** and **B** reprinted with permission from SANTINI JT Jr, CIMA MJ, LANGER R: A controlled-release microchip. *Nature* (1999) **397**:335-338 [72]. **C.** Photograph of a prototype microchip: the electrode-containing front side and the back side with openings for filling the reservoirs. Reprinted with permission from SANTINI JT Jr, RICHARDS AC, SCHEIDT RA, CIMA MJ LANGER R: Microchips as controlled drug delivery devices. *Angew. Chem. Int. Ed. Engl.* (2000) **39**:2396-2407 [30]. **D.** The main body of the device is composed of a reservoir-containing substrate that is fabricated from a degradable polymer. Truncated conical reservoirs in the substrate are loaded with the chemical to be released and are sealed with polymeric, degradable, reservoir membranes on one end and a sealant layer (polyester tape) on the opposite end. Inset: close-up of a reservoir, reservoir membrane, sealant layer and chemical to be released. **E.** Cumulative percentage of the initial loading released from the microchip device *in vitro*. Release results are shown for a representative device that was loaded with both $^{14}$C-dextran and $^{3}$H-heparin. Similarly to the results obtained for devices that were loaded with only one chemical, the release times of the chemicals from the reservoirs increased as the molecular mass of the reservoir membrane polymers was increased, as shown by the arrows indicating the opening of each type of membrane on the devices. Experiments were conducted in saline solution at 28 – 33°C *in vitro*. **D** and **E** reprinted with permission from RICHARDS GREYSON AM, CHOI IS, TYLER BM *et al.*: Multi-pulse drug delivery from a resorbable polymeric microchip device. *Nat. Mater.* (2003) **2**:767-772 [74].
PLGA: Poly(lactic-co-glycolic acid).

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Langer and colleagues have recently developed polymer microreservoir chips in which the sealed membrane of reservoirs is made from the biodegradable polymer (Figure 3D). This device could provide multi-dose drug delivery for the long-term treatment of conditions requiring pulsatile drug release. The devices were fabricated from poly(L-lactic acid) and had poly(D, L-lactic-co-glycolic acid) membranes of different molecular masses covering the reservoirs to control the time at which various chemicals (dextran, heparin and human growth hormone) were released from the devices.

These biodegradable polymeric microchips released four pulses of radiolabelled dextran, heparin or human growth hormone *in vitro* (Figure 3E). The heparin that was released over 142 days retained on average 96 ± 12% of its bioactivity. The microchips were 1.2 cm in diameter, 480 – 560-µm thick and had 36 reservoirs that could each be filled with a different chemical. Preliminary results obtained *in vivo* showed that pulsatile release is analogous to that demonstrated *in vitro*.

This device offers some advantages such as biodegradability and the ability to achieve pulsatile release, whilst increasing the number of chemicals and/or doses that could be achieved from a single polymeric device without the application of a stimulus to trigger drug release. In addition, it is possible to tailor the release characteristics for specific applications by simply varying the attributes of the device (e.g., size, polymer), reservoirs (e.g., number, volume) and membranes (e.g., thickness, molecular mass, material and copolymer ratio).

The separation of the reservoir membranes from the chemicals within the reservoirs potentially allows a greater independence of the formulations that control drug release and drug stability. This independence of the two formulations may in turn provide a greater flexibility in the device design than is currently available with other controlled-release drug delivery systems. This device could be implanted for clinical applications and could enable the patterned delivery of multiple potent drugs [74].

The potential advantages of microreservoir chips include the small size, quick response times, low power consumption and the therapeutics with multiple drugs. In addition, all chemical substances that are to be released are stored in the reservoirs of the device itself, creating a possibility for the future development of autonomous devices. Nevertheless, the *in vivo* stability and functionality over long periods remains an issue because the membrane needs to remain stable to prevent excessive degradation under *in vivo* stress. The burst release of the drug from the microreservoir may exceed the therapeutic ranges. Furthermore, in the current configuration, drug delivery on demand is not possible. Packaging the microreservoir chip is probably the most challenging part in the manufacturing.

### 4.3 Nanoporous and nanochannel microchips

Silicon nanoporous/nanochannel microchips (known as nanopore/nanochannel membranes) were developed by Ferrari and colleagues. These authors introduced the surface and bulk silicon nanomachining protocols that are required for the fabrication of nanopores/channels with exquisite control over pore/channel dimensions and surface composition. A variety of progressively improved designs of silicon-based nanochannel systems has been developed, patented and investigated for a range of applications, including bioseparation, immunoisolation and controlled drug delivery [42,75-80,202-215].

These nanoporous/nanochannel microchips have uniform pore/channel size and very low thickness and, therefore, are ideally suited for drug delivery applications, including controlled diffusion and sustained release. It is possible to design nanoporous/nanochannel microchips, which achieve an almost constant rate of drug delivery, avoiding the burst effect. By precisely controlling pore/channel size, pore/channel length and pore/channel density, the nanoporous/nanochannel microchip fitted with a drug reservoir that is suitable for subcutaneous implantation can serve as a diffusion barrier for a variety of biological drugs [4,33,68,81]. Commercial development of this technology for therapeutic use is currently being carried out by iMEDD, Inc.

The nanoporous silicon microchips, with highly uniform pores in the nanometre range, were first fabricated using standard microfabrication techniques of photolithography, thin-film deposition and selective etching [78]. Nanopores were generated by a key process step, based on the use of thermally grown, sacrificial, silicon oxide layer, sandwiched between two structural layers; a process termed sacrificial-oxide nanopore formation [76,78,202,207,215].

Over the years, nanopore technology has undergone continued improvements. Nevertheless, the basic structure and fabrication protocol for the nanopores has remained the same. The membrane area is made of thin layers of polysilicon, silicon dioxide and/or single crystalline silicon depending on the design employed. The other main part of the membrane is the anisotropically reverse side-etched wafer.

As photolithography in general has a lower limit of resolution of ~ 1 µm (current state of the art production is 0.09 µm, and may go to 0.045 µm), strategies using sacrificial layers were used to achieve desired pore size down to the tens of nanometres [4,82]. The strategies were initially based on the use of a sacrificial oxide layer, sandwiched between two structural layers, for the definition of the pore pathways. However, all of the designs of the microfabricated membrane consisted of a micromachined membrane on top of an anisotropically etched silicon wafer, which provides mechanical support. Changes in pore size, density and geometry, as well as path length, were the main features that changed whilst optimising the membrane design.

#### 4.3.1 *Early designs of silicon nanoporous microchips*

The first design of nanoporous microchips (or membranes) consisted of a bilayer of polysilicon with L-shaped pore paths. The flow path of fluids and particles through the membrane is depicted in Figure 4A [80]. As shown, fluid enters the pores through openings in the top polysilicon layer, travel



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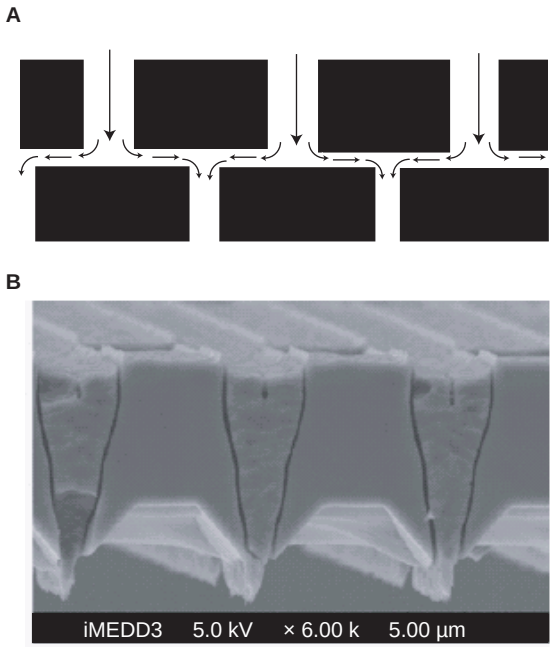


**Figure 4. Nanoporous microchips. A.** Flow path through a nanoporous membrane, with lateral diffusion through the nanopores defined by sacrificial oxide. **B.** Side view in detail. **A** and **B** reprinted from LEONI L, BOIARSKI A, DESAI TA: Characterization of nanoporous 601 membranes for immunoisolation: diffusion properties and tissue 602 effects. *Biomed. Microdev*. (2002) **4**(2):131-139 [82], with kind permission of Springer Science and Business Media.

laterally through the pores, make a 90° turn and exit the pores through the bottom of the pore where both the top and bottom polysilicon layers reside on the etch stop layer.

Although this design performed well for preventing the diffusion of the larger, unwanted immune system molecules, its L-shaped path slowed down and, in some cases, prevented the diffusion of the smaller molecules of interest. The pores in this design were fairly long, which led to the slow diffusion of the desired molecules. In addition, because of the large area per pore, it was difficult to increase the pore density and thus the diffusion rate.

The next design had an improvement in the production of short, straight, vertical pores through a single crystal base layer. This design had the advantage of direct flow paths. This direct path allows the smaller molecules of interest to diffuse much quicker through the membrane, whilst size still separates the larger molecules.

To further improve the reliability of the nanoporous membranes, several basic changes were made in the fabrication protocol from the previous membrane design to eliminate problems with the diffused etch stop layer [82]. This design also incorporated a shorter diffusion path length, based on the thicknesses of the two structural layers. The design of a new membrane fabrication protocol incorporated several desired improvements: a well-defined etch stop layer, precise control of pore dimensions and a lower stress state in the membrane (Figure 4B). The new protocol also increased the exposed pore area of the membranes. These nanoporous microchips have been studied extensively for use in immunoisolation and drug delivery applications [80,82,83].

#### 4.3.2 *Silicon NanoGATE microchips*

Improvements in the microfabrication protocols have enabled the development of robust and reproducible methods for the mass production of silicon nanoporous microchips of various pore sizes and areas of precise dimensions (Figure 5A). These nanoporous microchips have been especially designed by iMEDD, Inc. for their NanoGATE drug delivery implant. NanoGATE is a subcutaneously implantable device that uses silicon nanoporous microchips to deliver therapeutic doses of a biologically active molecule at a constant output rate (Figure 5B). Coupled with the development of a high-throughput testing platform, a detailed analysis of the diffusion characteristics of various biological molecules shows that these NanoGATE microchips possess the capability of generating sustained release of drugs for long durations. *In vivo* NanoGATE microchip biocompatibility data demonstrated that even after 6-month implantation, the glucose release rates through these microchips remain unchanged, illustrating that these microchips did not affect the implantion duration (Figure 5C) [4]. A photograph of the implant site after 30 days of implantation in a rodent model is shown in Figure 5D. As can be seen, only a thin vascular capsule forms around the implant as opposed to the avascular fibrous capsule [88], a major problem for any subcuatenously implanted device [89]. Thus, the lack of any diffusion retardation along with the ability to minimise fibrous encapsulation at the site of implantation suggests that the NanoGATE device is highly impervious to diffusion fouling events *in vivo*, permitting long-term biocompatibility for drug delivery.

By tailoring the nanopore dimension to the physical characteristics of the biological molecule of interest, silicon NanoGATE microchips constrict the ability of the molecule to freely diffuse in all dimensions. *In vitro* release curves for bovine serum albumin and IFN-α through these microchips are shown in Figure 5E and F. Strikingly, these data show that diffusion does not follow Fick's law of diffusion for semipermeable membranes. Rather, as the size of the nanopore approaches the molecular dimensions of the diffusant, zero-order kinetics predominate.

Such non-Fickian behaviour of diffusant molecules has also been observed in other microporous media such as zeolites, and is considered to be a result of phenomena such as traffic control, called single-file diffusion [84,85] and/or pore wall drag effects via molecular interaction [86]. Whether a consequence of single-file diffusion-like phenomena or potential drag effects (or a combination of both), the NanoGATE microchip is diffusion rate limiting and, if properly tuned, restricts solute mobility. Thus, by strictly controlling the oxide deposition during the fabrication process of the nanoporous microchip, it is possible

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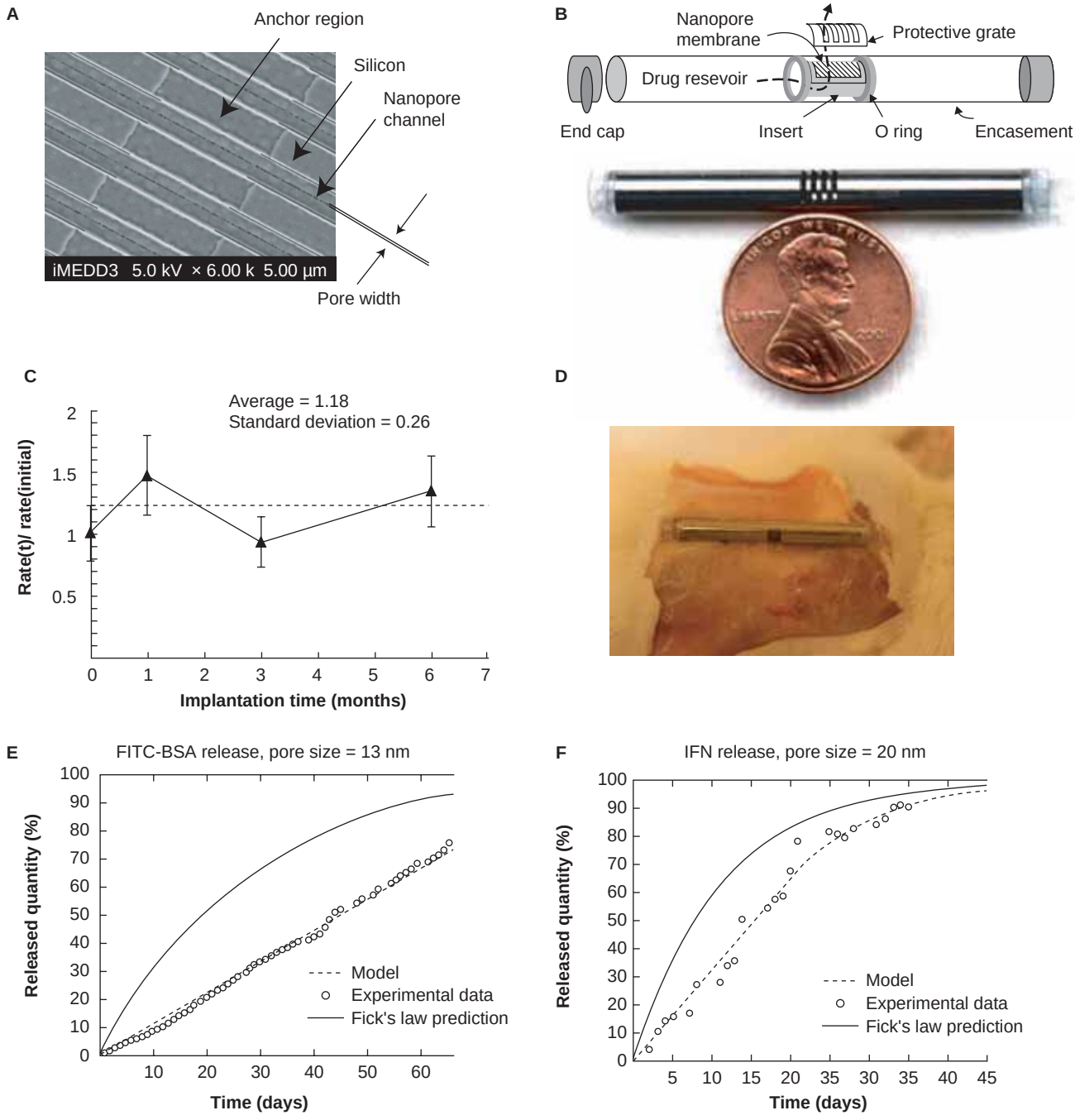


**Figure 5. NanoGATE microchips. A.** Top scanning electron microscopic view of a membrane (× 6000), showing details of pore and anchor structures. **B.** Implant device fitted with nanoporous microchip. Top: drawing illustrating key features of the device. The dashed arrow represents a possible diffusion path of a drug molecule held within the device reservoir. Bottom: photograph of prototype implant to scale. **C.** Ratio of pre- and postimplantion glucose diffusion rates from the NanoGATE device. **D.** *Ex vivo* analysis of implanted devices after the sacrifice of a rat. Note the lack of tissue attachement to both the Ti shell, Si device and polymethyl methacrylate plugs in device. **E.** *In vitro* diffusion kinetics of FITC-labelled BSA through 13-nm pore size. **F.** *In vitro* diffusion kinetics of IFN-$\alpha$ through 20-nm pore size [4]. **A**, **B**, **E** and **F** reprinted from MARTIN F, WALCZAK R, BOIARSKI A *et al.*: Tailoring width of microfabricated nano-channels to solute size can be used to control diffusion kinetics. *J. Control. Release* (2005) **102**:123-133 [4]. Copyright (2005), with permission from Elsevier. **C** and **D** repinted with permission from WALCZAK R, BOIARSKI A, WEST T, SHAPIRO J, SHARMA S, FERRARI M: Long-term biocompatibility of NanoGATE drug delivery implant. *Nanobiotechnology* (2005) **1**(1):35 [88].

BSA: Bovine serum albumin; FITC: Fluorescein isothiocyanate; IFN: Interferon.



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to custom generate an exact pore size that will permit a zero-order release for virtually any molecule of interest.

Furthermore, in order to achieve further insights in the mechanisms involved in nanochannel diffusion and to predict drug release without exhaustive experimentation with desired molecules, a dynamical model has been developed to analyse the experimental phenomenon in mathematical terms. This model makes it possible to simulate the release profiles for a particular drug molecule for a particular microchip pore size. A detailed investigation and description of this model is beyond the scope of this review and is presented elsewhere [87].

The NanoGATE microchips are advantageous for a wide variety of drug classes as potential therapeutic candidates where a long-term sustained release is desired. Peptides and protein drugs are excellent choices for use in the current system, due to both the non-fouling nature of the membrane as well as its immunoisolation properties. By increasing pore area, small, potent biologically active molecules can also be used within the NanoGATE system. Finally, by increasing the pore size, nucleic acid derivatives become likely therapeutic candidates. Nevertheless, this design lacks the capabilities for the development of microchips for preprogrammed and remote-activated delivery of drugs for drug on demand.

#### 4.3.3 *Nanochannel delivery systems*

Most recently, Ferrari and colleagues have developed a nanochannel delivery systems (called nDS) with improved mechanical stability [90]. These devices are based on bulk micromachining and sandwich encapsulated filter design [77]. The nDS device consists of two bonded wafers: the micromachined filtration structural wafer and the cap wafer (Figure 6A and B). Fluids enter through the hole etched in the cap wafer, then flow horizontally through the filtration channel as defined by the gap between the cap wafer and the machined features on the structural wafer, and then out of the hole etched in the structural wafer. As the flow is between two directly bonded wafers, the filter has more mechanical support and is thus structurally stronger. The features on the structural wafer are shown in Figure 6 A and B and are fabricated using bulk micromachining. To achieve high-throughputs, interdigitated finger geometry was used. With the use of a silicon dioxide sacrificial layer, pore sizes as small as 20 nm were fabricated with size variations of < 4%. It was already established in the case of other types of silicon nanoporous microchips that the diffusion of molecules though nanopores is constant and, therefore, the sandwich design filter could also be used for sustained drug delivery applications.

Further design improvements included replacing the silicon cap wafer with a glass wafer. With a transparent glass top, one can visually check defects, void bonding or blocked channels (i.e., they allow a good quality control). The devices also facilitate nano-fluidic study by means of fluorescent microscopy. This also simplified the fabrication process to make anodic bonding of the silicon–glass cap much easier and efficient compared with silicon–silicon cap direct bonding. Ferrari and colleagues have demonstrated the visual inspection of features and fluid flow inside an nDS-glass top device (Figure 6C), and are investigating the real-time monitoring of drug diffusion through nanochannels.

The first device in this proposed sequence of nanochannel delivery systems is the passive release device called nDS1. Release characteristics of nDS1 were initially investigated using glucose as a model molecule. These studies suggested that these devices (100-nm channel size) permit the release of glucose in a linear fashion, in accordance with zero-order kinetics, for the period investigated (Figure 6D). Release studies using IFN-α also demonstrated sustained release for the period investigated (Figure 6E) [81]. Further studies using phosphorylated STAT1 as a marker of IFN-α activity in viable peripheral blood mononuclear cells and tumour cells confirmed that functionally active IFN-α could diffuse through the nDS1 microchip. In addition, nDS1 microchips used in this study were capable of administering physiologically relevant doses of IFN-α directly to the tumour microenvironment and, therefore, could be used to develop alternative strategies for the treatment of unresectable tumours [81]. It is also important to mention here that IFN-α that was used for these studies was the same as that used for intravenous injections in clinical practice.

Future embodiments of nDS microchips will have the capability of integration of electronics on board, and are being developed for preprogrammed- (electro-osmotically driven, nDS2) and remote-activated (drug on demand, nDS3) delivery of drugs. In these devices, electrodes are integrated in the top glass substrate and the insulating properties of the glass prevents any short circuit between the two electrodes. The bottom substrate is a silicon substrate that has similar features to the nDS1 device. Both of the substrates are bonded together to form nanochannels. An applied electrical current across the electrodes controls the electrokinetic flow of molecules of interest through this device. The connected external circuit can be a preprogrammable circuit, a wireless circuit or a feedback-control circuit for a biological sensor, to achieve preferred control of drug release. This technology offers additional advantages in the scalability of the manufacture and exquisite device replicability. Furthermore, these systems do not require the development of novel formulations for drugs.

## 5. Conclusions

Drug delivery technology has achieved considerable advances, which have introduced many clinical products into the market. However, the major needs for drug delivery devices are still unmet and important classes of drugs have yet to benefit from these technological successes. The central focus of any controlled delivery devices is the control. This can be achieved if:

- the size of the device can be modulated as accurately as possible,
- the device can be produced with a certain reproducibility,

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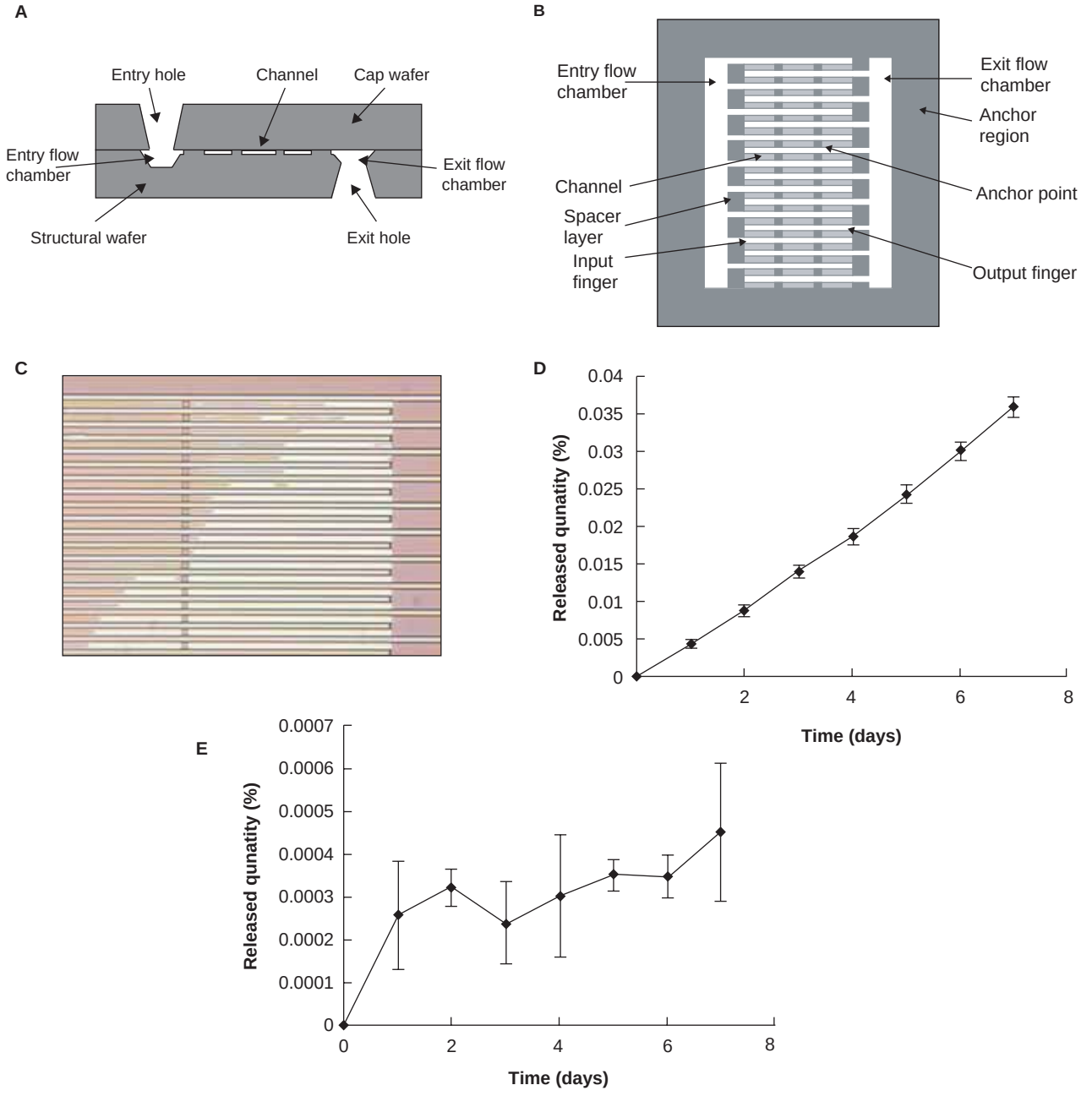


**Figure 6. Nanochannel microchips. A.** Cross-sectional view of the nDS from [4]. **B.** Top and cross-sectional view of nDS structure on the structural wafer. **C.** Snapshot of video: 2-propanol evaporating from the fingers of an nDS device with glass top. **D.** Release profiles from nDS mounted in Costar diffusion chambers mounted on the wells of a transwell plate. Glucose release (depicted as percentage released) was measured on a daily basis using the Glucose-SL assay (Diagnostic Chemicals Limited) for 7 days. Data shown were derived from experiments using three independent devices. **E.** IFN-$\alpha$ release from the nDS. The release profile was measured as explained above and quantitated by a commercially available IFN-$\alpha$ ELISA (R&D Systems). Data shown were derived from experiments using three independent devices. **D** and **E** repinted from LESINSKI GB, SHARMA S, VARKER K, SINHA P, FERRARI M, CARSON WE: Release of biologically functional interferon-alpha from a nanochannel delivery system. *Biomed. Microdev*. (2004) **63**:183-190 [81], with kind permission from Springer Science and Business Media.

nDS: Nanochannel delivery systems.

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- the device is stable enough for administration purpose,
- the device is biocompatible,
- the rate of drug delivery is independent of the surrounding environment.

From the appearance of the first drug delivery device to the present day, a constant improvement has gained. The microchips discussed here are capable of meeting some of the essential requirements for controlled release over prolonged periods. Nevertheless, a lot of aspects of these drug delivery devices require an improvement to be applied in clinical use. The new challenges in the future are the feasibility of the scaling-up processes to rapidly bring the innovative therapeutic entities to the market and the possibility of obtaining multifunctional microchips that are able to fulfill the different biological and therapeutic requirements in the meantime.

## 6. Expert opinion

The fact that drug delivery technology can bring both therapeutic and commercial value to healthcare products can not be neglected. Big pharmaceutical companies have recently started losing their market share to generic competitors after their patents expired and, therefore, they have started recognising the importance of drug delivery companies. Pharmaceutical companies are looking to extend their patents' lifetimes by making strategic alliances with drug delivery technology companies; by presenting old drugs in new forms.

Therefore, most of the drug delivery products reach the market as a result of strategical alliance between drug delivery and pharmaceutical companies. Pharmaceutical companies provide the drug that may not be delivered efficaciously with a conventional delivery mechanism, whereas the drug delivery companies provide the cutting edge technology to administer the drug more effectively.

The joint venture not only offers considerable advantages over the R&D efforts to bring new drugs into the market as drug delivery systems that provide the means to reformulate existing products, but it also protects the drugs from erosion by generics in the case of patented drugs. As a result, drug delivery technology companies seem to enjoy a good return on their investments in the form of increased revenues and market share [7,91].

The global drug delivery market expanded between 1998 and 2002, with a compound annual growth rate of 13.7%, increasing from US$39.6 billion to slightly over US$66 billion. The market is expected to grow at a slightly lower compound annual growth rate of 11.6% between 2002 and 2007, corresponding to a market value of US$114.3 billion by 2007. One of the contributing factors in this growth is the use of drug delivery systems as a strategy to expand the shelf-life of products (particularly blockbusters), enabling pharmaceutical companies to sustain the revenue streams from their bestsellers.

The US market is the largest for drug delivery systems in the world, having captured 47.9% of the global market's revenue generation in 2002. This figure is forecast to fall to 41.9% by 2007, although the US market will retain its position as the leading market. In 2002, this market for drug delivery systems was worth US$31.7 million in 2002, having experienced a compound annual growth rate of 12.6% between 1998 and 2002. Oral drug delivery systems had the largest market share, taking 47.7% of the total market share. Transmucosal, injectable and implantable systems together had 8.8% of the market share in 2002. The US market value for drug delivery systems is expected grow at a rate of 8.5% annually and to reach a value of US$48 billion by 2007.

Therefore, there is an urgent need to improve our clinical practices. Until now, the most common technique to achieve controlled release in the clinic is the intravenous administration of biologically active agents, which is associated with obvious difficulties in terms of patient inconvenience, discomfort, required hospital stay and adverse affects such as phlebitis and infections. It is noted that the development of drug delivery systems encompasses broad categories, such as implantable devices with percutaneous components, fully implantable devices, polymer-based systems, microchips and osmotic pumps.

Krulevitch and Wang [216] described a microfabricated, fully integrated drug delivery system that was capable of secreting controlled dosages of drugs over long periods of time, whereas Cao, Lai and Lee [92] described a self-regulated drug delivery device that integrates both mechanical and chemical methodologies. Numerous polymer systems have also been employed [92-94] with varying degrees of success. Infection is a major concern with clinically available implantable drug delivery pumps, as are catheter-related complications, such as kinking, dislodgements, disconnections, tears and occlusions [95]. Furthermore, catheter-tip inflammatory masses continue to be a problem with current devices [96]. Poor patient compliance is a significant obstacle that often leads to suboptimal treatment and inferior outcomes [97,98].

In fact, poor compliance is the most common cause of medication failure [99,100]. In particular, for patients with terminal illness discouragement and lack of conviction regarding the effectiveness of treatments result in poor compliance [101]. These problems could potentially be ameliorated though the use of appropriate implantable drug delivery microchips.

Implants with degradable polymers suffer from two major drawbacks. Polymer depots exhibit an initial 'burst effect' prior to sustained drug release and are typically not as efficient in controlling the release rates of small molecules [102]. The use of implantable devices with percutaneous components, such as ambulatory peritoneal dialysis catheters, intravenous catheters and orthopedic implants, is complicated by such occurrences as infection, marsupialisation, permigration and avulsion [103,104].

Therapeutic candidates for the currently designed subcutaneously implantable devices would require potency as well as stability at physiological temperatures for an extended period of time. Several drug classifications that would meet these criteria include anti-inflammatory medicines (fentonyl), antipsychotic

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medicines (risperidone), medicines for the treatment of cancerous tissues (cytokines) and medicines for the treatment of coronary artery disease (simvastatin). Such drugs, once implanted, can be released in treatment durations from 3 to 6 months per device, with implant replacement possibilities for therapy extension if needed.

In spite of all aforementioned developments in the drug delivery technology, there is no clinically available device that has been shown to be able to perform the controlled, long-term diffusion of the pharmaceutical agents. Osmotic pumps have been clinically demonstrated for the constant-rate administration of leuprolide in the management of prostate cancer. These pumps employ an osmotic piston to provide the zero-order release of drugs.

The major concerns are with formulation and mass transport dynamics, leading to expectedly high and potentially unsafe pressures in the ALZET® (DURECT Corporation) chamber, and loss of functionality of the therapeutic moieties. A further disadvantage is the difficulty of developing an effective dosage solution to deliver lipophilic compounds.

Silicon microchips provide a better alternative to achieving controlled release of biologically active molecules. Microreservoir-based microchips developed by Langer and colleagues [72,73] employ the electrochemical dissolution of the membrane on a number of reservoirs to obtain the controlled release of their contents. Ideally, this methodology may yield a desired, and potentially variable, release profile. However, it remains to be proven that the desired release profiles, especially for what concerns the variable rates, could be met with the microchips. Furthermore, in the current configuration, drug delivery on demand is not possible.

The nanoporous microchips fabricated by Ferrari and colleagues [90] are based on constrained diffusion and controllable electrokinetic transport and, therefore, do not lead to any build-up of pressure during its use. Furthermore, they have the capabilities for preprogrammed and remote-activated delivery of drugs for drug on demand.

Other major concerns are with novel formulation development that are specific for the drug delivery microchip and mass transport dynamics. Silicon microchips developed by Langer and colleagues require the development of novel formulations. Nanoporous microchips developed by Ferrari *et al.* could use the already available FDA-approved formulations [81]. Such simplification could help in the transition of this technology to the clinic.

In summary, the authors feel a major effort is necessary, and impending, for the transition from proof-of-principle release and well-characterised release of reletively modest test formulations to preclinical tests on rodent models and clinical tests on human subjects. As aluded to above, major hurdles to be overcome are the exact formulation of the drugs to be released, reproducibility of release rates over large quantities of devices, more solid designs allowing mass fabrication, and long-term physiological and *in vivo* testing.

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