Expert Opinion

Microfabricated nanochannel implantable drug delivery devices: trends, limitations and possibilities

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This is a review of the application of microfabrication technologies, borrowed from the semiconductor industry, to drug delivery implants incorporating structures in the nanometer dimension. In the futuristic ideal, these systems would involve the implantation of precisely microfabricated drug delivery systems with nanopores, nanochannels and/or nanoreservoirs fabricated from silicon, coupled with electronic sensing and actuator systems, for the precise, timed and/or targeted delivery of drugs. After more than a decade in conceptualisation and experimentation, four systems that have commercial potential are discussed: i) implantable microchips with on-demand microdosage for one or more therapeutic agents under internal control or external control using a wireless link; ii) nanopore pumps, implantable titanium pumps, consisting of a drug reservoir with a nanopore-release membrane, capable of delivering potent small or macromolecules at constant serum levels for sustained periods of time; iii) nanocages, microfabricated nanopore immunoisolation chambers for cellular implants, capable of natural feedback-controlled delivery of proteins and peptides; and iv) nanobuckets, micromachined silicon porous particles with drug-loading capacity and targeting ligands for localised delivery. Each of the systems, along with future trends in microfabrication manufacturing, limitations and possibilities, are discussed.

Keywords: bioMEMS, drug delivery, implantable, microchips, microfabrication, microparticles, nanochannels, nanopores

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1. Introduction

Convergence of the fields of silicon microfabrication and drug delivery has long been predicted but only recently have strides towards true clinical drug delivery systems been made. The hope that microfabrication technologies borrowed from the semiconductor industry can precisely develop nanopore membranes and/or reservoirs that can aid in the controlled and targeted release of drugs has been explored in the literature for over a decade. The issue has become particularly important with the advent of injectable, large-molecule biopharmaceuticals, many of which are nearing patent-life expiration and are thus entering the market arena for product differentiation: the latter including improved pharmacokinetics for enhanced efficacy and lower side effects, as well as alternative means of administration other than syringes and needles.

It is important from the outset to define what will not be included in this review of microfabricated nanochannel implantable drug delivery devices. The designation microfabrication is interpreted to define systems that are made from the 'top-down' process (i.e., 'the material is fabricated into its final shape from a larger piece through the removal of unwanted regions by machining or etching' [1]). Therefore, this review does not focus on such 'bottom up' technologies developed from the molecule-by-molecule

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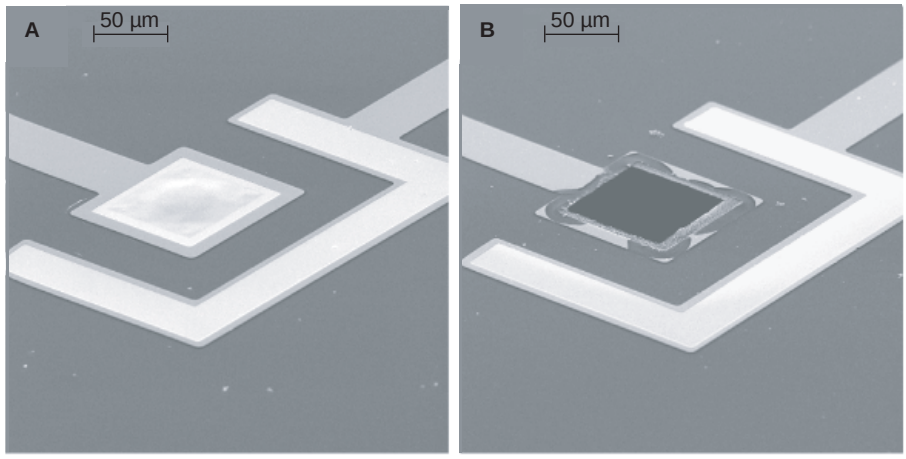

Figure 1. Removal of an anode membrane to initiate release from a reservoir in a microchip device. Scanning electron micrographs of a gold membrane anode covering a reservoir are shown before (**A**) and after (**B**) the application of +1.04 V. Reprinted from SANTINI JT Jr, CIMA MJ, LANGER R: A controlled-release microchip. *Nature* (1999) **397**:335-338 [4], copyright (1999), with permission from Elsevier.

assembly of parts. Examples of the latter include self-assembly carbon nanotubes and liposomes. Nanochannel implies pores or channels in the nanometer scale (i.e., < 1 µm in diameter). Therefore, this review will not include such technologies as the implantable osmotic pump (DUROS® by ALZA Corp.) [101]. The term implantable excludes such promising microfabricated technologies that have been incorporated into the so-called smart transdermal patches with microfabricated needles, coupled with sensors and electronic actuator mechanisms. Finally, drug delivery devices excludes all of the life science applications of microfabricated nanochannel systems that are not for the therapeutic delivery of drugs, but rather for the purposes of imaging, diagnostics, sensors or surgical applications [2].

With that narrow definition in mind, coupled with the proviso that the reported systems must have been tested at least in a mammalian model, this review will focus on four systems that meet the designated criteria. These systems include:

- controlled-release microchips;
- nanopore membrane implantable pumps, hereby designated as nanopore pumps;
- microfabricated silicon membranes for immunoisolation of cellular implants, hereby designated as nanocages;
- microfabricated porous silicon reservoirs for targeted drug delivery, hereby designated as nanobuckets.

2. Microfabricated nanochannel implantable drug delivery systems

2.1. Microchips

A goal in drug delivery is to incorporate the photolithographic capabilities borrowed from the semiconductor industry to create miniaturised, integrated microsystems that are capable of fast sensory and actuation capabilities [3]. Such a system has been invented in the Massachusetts Institute of Technology laboratories of R Langer and M Cima [4] and is now being commercially developed by the company MicroCHIPS Technology [102]. This invention offers the potential of on-demand microdosage of one or more therapeutic agents from an implanted device under internal or external control using a wireless link [5]. The net result is a uniform and reproducible device that is capable of greater temporal control, including *in vivo* pulsatile delivery [6]. The device is microfabricated by means of a sequential process using silicon wafer and microelectronic processing techniques (including ultraviolet photolithography, chemical vapour deposition, electron beam evaporation and reactive ion etching) from a solid-state silicon microchip [4]. The resultant microchip contains tens to hundreds of individual drug reservoirs that are etched into the silicon surface (volumes of ~ 25 nl). Each reservoir is sealed on the small square end (50 × 50 µm) with a 0.3-µm thick gold membrane anode, or alternatively multiple layers of titanium and platinum [7]. Under command by preprogrammed microprocessors, wireless telemetry, or sensor feedback, the drug is actively released by electrochemical dissolution of the gold membrane covering the individual reservoirs (Figure 1). By this means, controlled, pulsatile, systemic or targeted single- or multi-dose drug delivery can be achieved [4,7]. Representative drug-release profiles can be seen in Figure 2.

Silicon-based microchips require retrieval from the body. If a bioerodible substance other than silicon could be employed, one could design a bioerodible microchip that did not require retrieval. *In vitro* experiments support the theoretical possibility of biodegradable polymeric microchips. Microfabrication methods created bioerodible polymeric microchips, into which microholes were made and then sealed with polymers of different biodegradation rates. *In vitro* release of multiple pulses of tested materials proceeded at variable controlled

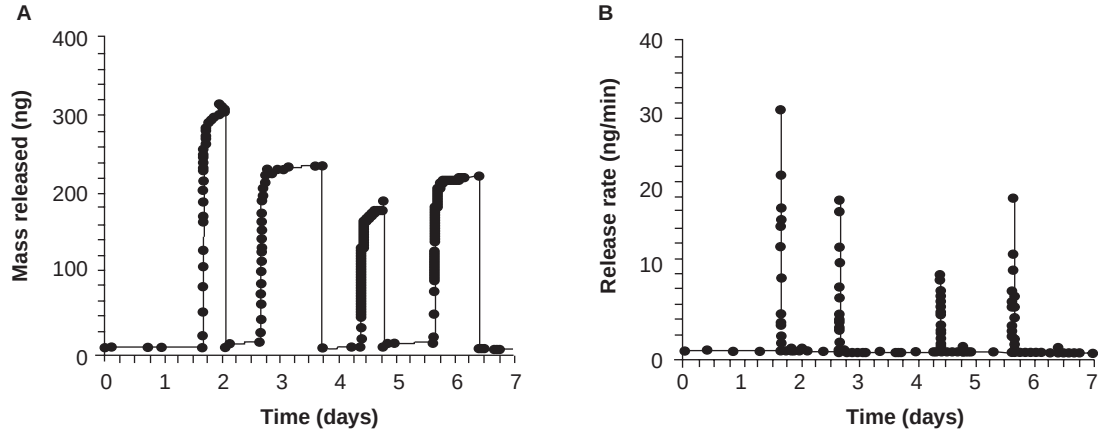

Figure 2. Pulsatile release of a single substance from a microchip device. A. The total mass of sodium fluorescein released into phosphate-buffered saline over a period of several days is shown for each of the four reservoirs. **B.** The release rate for the same experiment. Reprinted from SANTINI JT Jr, CIMA MJ, LANGER R: A controlled-release microchip. *Nature* (1999) **397**:335-338 [4], copyright (1999), with permission from Elsevier.

rates. This supports the concept of a bioerodible, micromachined implant that is designed to release pulses of different drugs at various intervals based on reservoir seals with different molecular masses or materials [8,9].

In vivo experiments with microchips demonstrate future potential applications. A drug delivery microelectromechanical system (MEMS) microchip device (microreservoirs etched into a silicon substrate that contain individual doses of drug, with each dose released by the electrochemical dissolution of the gold membrane covering the reservoir), was tested in a rat tumour model [10,11]. Carmustine (BCNU) delivered from the actuating devices was as effective as equipotent subcutaneous injections of BCNU in inhibiting tumour growth. The possibility of local tumour targeting of BCNU and other cytotoxic drugs directly to tumours, thereby minimising systemic toxicity, is raised by these experiments. In addition, preliminary *in vivo* experiments with similar microchips demonstrate biocompatibility and functionality without the formation of an inhibiting fibrous capsule [12].

Other embodiments of similar microchip concepts have also been reported. For example, IQ Micro [103] has acquired exclusive sales and marketing licensing rights to a microfluidic technology originating in a Norwegian company. This company produced microfabricated low-voltage actuators (pumps) that can be integrated in large numbers on a single chip. An application that is apparently under development is a combined glucose sensor and insulin delivery device [104]. A nanochannel delivery system, a microfabricated silicon-based implant, was recently tested for the zero-order release of antineoplastics in a rat tumour model [13].

2.2 Nanopore pumps

This technology, an implantable titanium pump reservoir with a nanopore drug release membrane, is currently under commercial development by iMEDD, Inc. (pers. commun.). It is being developed for sustained (3 – 6 months), zero-order release of potent molecules and is near clinical testing in human subjects. It consists of a small medical grade titanium cylinder $\leq 4 \times 30$ mm, filled with the drug, and sealed at the end with titanium end caps (Figure 3A and 3B). On one end, a press ring holds a nanopore silicon membrane that is the key to the technology that was originally conceived for immunoisolation and biosensor applications [14]. By means of differential pore size, length and density, this membrane controls the rate of diffusion of the drug out of the implant. The implant is inserted subcutaneously for 3- to 6-month drug administration.

The release-control silicon membrane consists of arrays of uniform channels having dimensions as small as 7 nm [15]. The membranes are constructed with top microfabrication techniques (e.g., photolithography, selective etching and thin film deposition) that can achieve pores sizes up to 100-times smaller than conventional photolithography. A key differentiating mechanistic feature is that the drug diffusion kinetics reveal linear non-Fickian behaviour as the nanopore width approaches the hydrodynamic diameter of the enclosed solute [15]. Thus, the pore size must be tailored to the drug molecule size. Nearly perfect, zero-order release of IFN is observed at the nanopore channel width of 20 nm, whereas the same phenomenon occurs with albumin and 13-nm channels, as well as with glucose and 7-nm channels (Figure 4A). In contrast, at larger channel sizes, the drug release rate follows a classical, first-order exponential kinetic profile that is typical of Fickian diffusion. Similar deviation from the kinetics predicted by Fick's law are seen for the diffusion of zeolites through microporous media, and this is interpreted as molecular traffic control and single file diffusion [16-18]. Importantly, the burst effect [19,20], the quick peak and decline of drug levels after injection of erodible polymeric depot drug preparations, is avoided with the nanopore pump. The surface erosion and diffusion mechanism for drug release from bioerodible polymers is almost invariably

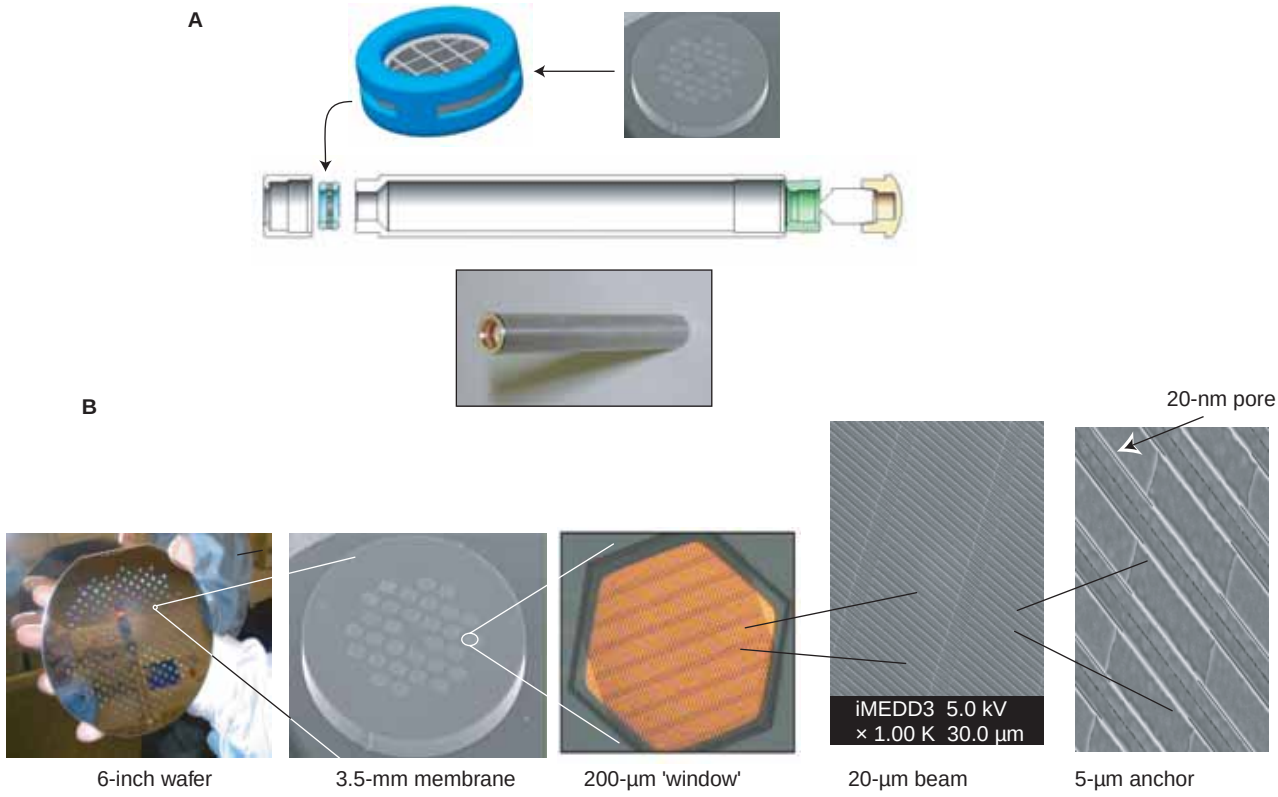

Figure 3. Nanopore pump configuration. A. A composite diagram depicting the components of the nanopore pump, including the titanium drug reservoir, the titanium end caps and the nanopore-release membrane. **B.** A scaled version of the nanopore membrane, consisting of parallel rectangular channels, which, in their smallest aspect, range from 7 to 50 nm.

accompanied by an initial large burst of drug release before settling to more linear release rates. The advantage conferred to the nanopump that does not have a burst effect is the avoidance of toxicities with the peak drug concentrations, as well as drug sparing.

Both *in vitro* and *in vivo* drug-release profiles from these devices demonstrate near perfect zero-order release of drug for periods of up to 3 months (representative example of near linear release over 45 days can be seen in Figure 4B). With proper formulation, the drug can retain requisite biological activity despite maintenance at body temperatures, in part because the silicon membrane not only controls drug release but also prohibits the entrance of proteases and other degradative enzymes.

The product profile for this drug delivery technology consists of highly potent biological or small molecules that have a relatively narrow therapeutic range [21]. Two initial product concepts are IFN-α for hepatitis B and C and risperidone for schizophrenia. For IFN-α, the nanopump could administer therapeutic levels for 3 – 6 months, thereby alleviating the extreme side effects that are seen with peak serum concentrations and maintaining constant antiviral activity. For both IFN-α and risperidone, not only could the side effects be alleviated, but also compliance should be enhanced. For both of these products and other product concepts (e.g., human growth hormone, IFN-β, cytokines and potent analgesics), patent life extension and product differentiation could also be achieved.

Novel technologies beyond solid-state fabrication methods for the fabrication of nanopores are being explored. For example, ion-beam sculpting, a method employing low-energy ion beams implemented in a feedback-controlled sputtering system that provides fine control over ion-beam exposure and sample temperature, is being used to create nanopores in thin insulating solid-state membranes [22].

2.3 Nanocages

A microfabrication/nanotechnology implant application that has received considerable interest is the microfabricated, nanoporous biocapsule for the implantation of cell or tissue transplants. Conceptually, cellular transplantation has engendered considerable interest in such diseases as insulin-dependent diabetes [23,24]. In this procedure, β-cells from pancreatic islets are implanted in the patient, thereby restoring the patient's coupled glucose-sensing and insulin-secretion capacities. Islet cell transplants could potentially substitute for the rigorous glucose monitoring and frequent insulin injection that is

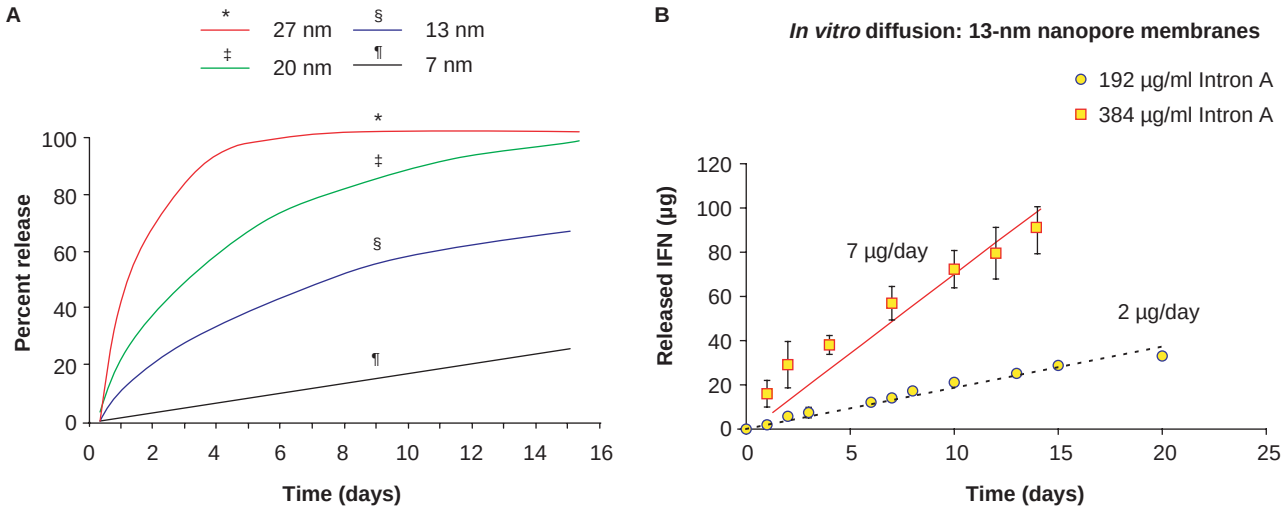

Figure 4. Nanopore pumps release drug with non-Fickian linear kinetics. A. Release rate kinetics are a direct relationship between nanopore size and molecular solute size. *In vitro* diffusion of glucose through nanopore membranes of indicated sizes. **B.** *In vitro* interferon diffusion through nanopore membranes (20-nm pore size) under sink conditions: experimental data, Fick's law prediction and model-based simulation. Near-linear release is seen at this pore dimension for interferon. Reprinted from MARTIN F, WALCZAK R, BOIARSKI A *et al.*: Tailoring width of microfabricated nanochannels to solute size can be used to control diffusion kinetics. *J. Control. Release* (2005) **102**(1):123-133 [15].

recommended by the American Diabetes Association, a regimen required to maintain normoglycaemia and prevent or delay long-term microvascular complications [25,26]. As allografts or xenografts are required in the absence of a patient-derived and differentiated stem cell population (not currently achievable), β-cell transplant rejection remains a constant threat, requiring immunosuppression. With proper immunosuppression following islet cell transplantation, graft viability and insulin independence can be achieved at variable reported levels depending on the immunosuppressive regimen used (e.g., [27]). The immunosuppression that is required to achieve reasonable rates of graft viability and insulin independence is accompanied, however, by generally unacceptable and often life-threatening complications, including infection, lymphoproliferative malignancies and collateral organ damage.

The goal of the microfabricated nanoporous biocapsule, a technology akin to the nanopore silicon membrane described above [14] is to immunoisolate implanted islet cells (allografts, xenografts or engineered β-cells), thereby alleviating the need for immunosuppression [28]. Nanoporous biocapsules are bulk and surface micromachined to present uniform pore sizes in the order of 7 – 20 nm, tailored surface chemistries and precise microarchitectures for cell encapsulation [29-34]. After insertion into an *in vitro* chamber or implantation *in vivo*, microencapsulated β-cells of various origins demonstrate long-term viability and functionality. This occurs because the nanoporous membrane of the biocapsule excludes host lymphocytes, cytokines and antibodies, blocking immunorejection, and prevents egress of graft-borne viruses *in vivo*. Meanwhile, the membranes allow ingress of oxygen, glucose and other nutrients and egress of insulin and waste matter. The physiological function of the β-cell (i.e., to sense glucose and secrete insulin in response) can thereby be maintained.

The key to the microencapsulated cell transplantation is the precise control of the nanopore size of the immunoisolatory membrane, which is achieved by surface and bulk micromachining. Insulin secretion by the encapsulated implants depends greatly on uniform pore sizes of ≤ 18 nm [29]. The nanopore-encapsulated cells are then enclosed in an outer biocapsule with openings of 2 × 2 µm: openings that allow neovascularisation at the membrane–tissue interface without penetrating the nanometer pores, thereby achieving mechanical stability and retrievability of the implant whilst maintaining immunoisolation.

The microfabricated biocapsule presents many theoretical advantages. First, the microfabrication technology uses relatively robust and biocompatible materials, provides precise determination of pore size in the requisite nanometer range, and is relatively easy to scale-up. Second, by rigorously immunoisolating cell transplants, the biocapsule obviates the issue of scarce β-cell supply, as xenografts or engineered β-cells can be safely used. The ultimate functionality and safety have yet, however, to be demonstrated in large animal models. Once achieved, a variety of applications, such as the implantation of pancreatic islet cells for diabetes or dopamine-containing neurons for Parkinson's disease could be possible.

2.4 Nanobuckets

Porous silicon particles that are coated with a targeted ligand and that are loaded with a cytotoxic drug are envisioned as a

systemic injectable therapy for metastatic tumours [35]. Through targeting and high local concentrations at the tumour site, the goal is to avoid the severe complications and drug resistance that is common with systemic cytotoxic therapy. 'Top-down' microfabrication technologies of the electronics industry (photolithography, thin film deposition, photoablation and etching techniques) can be used to create microscopic particles that are useful for the targeted delivery of drugs [36,37]. Such particles contain pores for drug loading. The pores can be made to open only to the top face, which at the same time can be chemically modified to contain reactive chemical groups such as amino or thiol groups, which can then in turn be used to chemically graft protein or other types of ligands to this face only [21].

A goal is to develop targeted carriers of drugs to systemic sites of action, such as tumours, after intravenous vascular injection. In order to penetrate tumour tissue, particles will need to cross the endothelial barrier into tumour tissue. Particles up to 600 nm can be shown to extravasate from the leaky angiogenic vasculature of metastatic tumours [38,39], but this size limitation excludes the 'top-down' microfabrication technologies that produce particles that are too large to extravasate even the leaky tumour vasculature. Thus, targeting ligands that are specific for tumour neovasculature are conceptualised, thereby killing the angiogenic endothelial cells of the tumour neovasculature and depriving metastatic tumours of nutrients for growth and the spread of disease [40].

The safety of systemic administration of nonbioerodible particles is a major issue. Intravenous administration of nonbioerodible solid silicon particles from 2 to 10 μm and of variable shapes was investigated in a mouse model [41]. Results showed that solid silicon particles > 5 μm in the largest dimension are cleared in the lungs and are not safe for intravenous delivery. Particles from 2 to 5 μm did not lodge in the lung and cause acute toxicity, but they did accumulate in organs such as the liver and spleen. The long-term effects of particle accumulation in organs of the reticuloendothelial system remain to be addressed. In the final analysis, other methods of nanoparticle fabrication, such as polylysine(β-amino ester) bioerodible particles prepared by solvent displacement methods, may be required to create proper sizing for tumour administration, along with bioerodability to avoid long-term toxicity [42,43].

3. Future trends in microfabrication technologies

Although the promises of microfabrication, including precise control of surface architecture and coupling with sensing and actuator systems, are manifold, limitations are recognised. Lithographic etching and mask techniques do not necessarily lend themselves to rapid prototyping, ease of fabrication and biocompatible materials. Thus, alternative microfabrication technologies are being explored. As noted in Section 2.2, investigators are trying ion-beam sculpting for the fabrication of nanopores [22]. Micro electro-discharge machining combined with ultrasonic vibration was evaluated for the fabrication of biocompatible microdevices, achieving feature sizes in the 25-μm range [44]. Combinations of hard and soft micromachining techniques were combined to produce hydrogel-based microfluidic control systems, including one for insulin release in response to changes in glucose concentration [45]. Multilayer soft lithography of nontraditional elastomeric materials was used to create active microfluidic systems with valves and pumps entirely of elastomer [46]. Conventional photolithography has been combined with self assembly to create microreservoirs for controlled drug release [47]. It is clear that the nanosystem technologies are evolving.

4. Expert opinion

Drug delivery technologies have many potential advantages, including the enhancement of drug safety and efficacy, the improvement of patient compliance, and the enablement of product differentiation and patent life extension. Biomolecules, including such blockbusters as IFN-α, growth hormone and erythropoietin, are nearing the end of their patent life, and drug delivery technologies that are suitable for their delivery are eagerly being sought after. However, biomolecules are not amenable to most traditional drug delivery technologies, which focus on oral, passive transdermal and intrabronchial administration. The ability to systemically deliver large macromolecules in new ways thus proposes challenges to the traditional drug delivery field.

Peptide and protein products have been approved and marketed with newer alternative drug delivery technologies. Systemic delivery of insulin via aerosolisation has been approved; this required the formulation of dry powder insulin particles of < 5 μm in order to achieve alveolar targeting and systemic uptake. Injectable bioerodible depot preparations for peptides and proteins have also been developed and approved. Leuprolide, formulated in bioerodible poly(lactic-co-glycolic acid) (PLGA) microspheres, can be injected at 1 – 6 month intervals for the treatment of prostate cancer. In addition, leuprolide has been delivered for 1-year intervals from an implantable titanium osmotic pump. In contrast to the situation with simple peptides, it is technically formidable to make a bioerodible microsphere preparation of proteins that maintains structural integrity and biological activity over months. However, a bioerodible PLGA preparation of human growth hormone was briefly marketed before being withdrawn for marketing and manufacturing reasons. Each of these systems have major challenges in formulation to achieve biomolecule stability in the body for sustained periods, in drug loading, in toxicological issues and in manufacturing procedures.

There is little surprise then that entrepreneurs have looked to the high-tech world of computer silicon microchip fabrication for potential new innovations in drug delivery, particularly for the delivery of macromolecules, but also for drug targeting and drug release control. Bulk and surface micromachining of

silicon has been employed to make microfluiditic devices with nanochannels (e.g., microdevices), nanopore membranes for controlled drug release at the molecular level (e.g., nanopore pumps), nanopore membranes for immunoisolation of xenographic or allographic cellular implants (nanocages), and nano-sized porous particles that are affixed with ligands for targeted delivery (e.g., nanobuckets). The promise from microfabrication technologies comes from the precision of fabrication of reservoirs, pores and channels in the nano-dimension, including scalability of manufacture; from the ability to work with surface chemistry to add such things as targeting ligands; and from the possibility of adding electronic systems to create MEMS for the precise and variable control of drug release coupled with sensing systems.

The limitations of microfabrication of silicon for the purposes of drug delivery remain to be addressed. The ability to rapidly create prototype drug delivery devices, to modify prototype design, to create drug reservoirs in the nano-dimension that are applicable to any other than the most potent drugs, to develop targeting ligands that confer adequate specificity in systemic delivery, to develop systems that can withstand zero tolerances for failure *in situ*, to avoid membrane fouling *in situ*, and to retrieve nonerodible devices, must be solved before these systems move from 'bench to bedside'.

In the author's opinion, the first application to make it to clinical use will be the nanopore membrane for controlled, zero-order sustained drug delivery (nanopore pump). Implantable titanium pumps are already in clinical use (DUROS). They are highly biocompatible, have a relatively large drug reservoir that protects the drug from degradation by enzymes and antibodies, and are easily implanted and retrieved. The substitution of a nanopore membrane for the osmotic engine and laser-drilled orifice as the release mechanism confers several potential advantages for the nanopore pump over an osmotic pump. It doubles the drug reservoir size by eliminating the 'osmotic engine', and it broadens formulation possibilities by allowing for particulate suspension formulations that are required for many proteins (the exit orifice of the osmotic pump may be plugged by particulate solutions). The critical nanopore release membrane employs standard microfabrication technologies that are easy to scale-up for mass production. Through the use of known drugs that are coupled with a novel form of delivery, product development risk is minimised. The host of therapeutic proteins and peptides, as well as potent small molecules that are optimised by zero-order delivery, will be amenable to nanopore pump delivery for product differentiation and patent life extension; the holy grail of drug delivery.

The rest of the technologies that employ microfabrication technologies face the hurdles that are described in this review before becoming a clinical reality. When true MEMS-type drug delivery devices do become a reality, the ethics of such devices will need to be addressed. Implantation of a full MEMS drug delivery device that is capable of sending and retrieving information raises direct questions about privacy of information.

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