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Expert Review

Application of Micro- and Nano-Electromechanical Devices to Drug Delivery

Mark Staples,[1,4] Karen Daniel,[2] Michael J. Cima,[3] and Robert Langer[2]

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Abstract. Micro- and nano-electromechanical systems (MEMS and NEMS)-based drug delivery devices have become commercially-feasible due to converging technologies and regulatory accommodation. The FDA Office of Combination Products coordinates review of innovative medical therapies that join elements from multiple established categories: drugs, devices, and biologics. Combination products constructed using MEMS or NEMS technology offer revolutionary opportunities to address unmet medical needs related to dosing. These products have the potential to completely control drug release, meeting requirements for on-demand pulsatile or adjustable continuous administration for extended periods. MEMS or NEMS technologies, materials science, data management, and biological science have all significantly developed in recent years, providing a multidisciplinary foundation for developing integrated therapeutic systems. If small-scale biosensor and drug reservoir units are combined and implanted, a wireless integrated system can regulate drug release, receive sensor feedback, and transmit updates. For example, an "artificial pancreas" implementation of an integrated therapeutic system would improve diabetes management. The tools of microfabrication technology, information science, and systems biology are being combined to design increasingly sophisticated drug delivery systems that promise to significantly improve medical care.

KEY WORDS: combination products; drug delivery; integrated medical systems; microelectromechanical systems (MEMS); nano-electromechanical systems (NEMS).

INTRODUCTION

Micro- and nano-electromechanical systems (MEMS or NEMS)-based drug delivery devices offer opportunities to address unmet medical needs related to dosing. Such devices should be considered when conventional dosing methods perform suboptimally in terms of safety, efficacy, pain, or convenience. In addition, applications of these technologies may create totally new drug delivery paradigms. MEMS technologies may create new therapies with existing molecular entities. This review addresses progress and prospects for combination product implementations of MEMS- and NEMS-based polymeric and electromechanical delivery devices.

Factors limiting the capabilities and convenience of conventional drug administration may include long-term treatment, a narrow therapeutic window, a complex dosing schedule, combination therapy, an individualized or emergency-based dosing regimen, and labile active ingredient (1). These limitations are being countered as new approaches emerge for developing drug and medical device combinations that can protect labile active ingredients, precisely control drug release kinetics (timing and amount), deliver multiple doses, eliminate frequent injection, and/or modulate release using integrated sensor feedback. Innovative delivery devices have the capability to completely control drug release: doses may be administered in pulses or continuously for periods of months to years, or doses may be stored in a device pending immediate need for emergency administration.

Technologies contributing to advanced drug delivery system design include MEMS or NEMS, materials science, data management (gathering, using, and communicating data), and biological science. Nanotechnology encompasses an additional group of emerging technologies that are primarily defined by the nanometer scale to which they are applicable. Proteins, nucleic acids, and other biomolecules are also in this size range. Micro- and nanotechnologies overlap

[1] MicroCHIPS, Inc., 6-B Preston Court, Bedford, Massachusetts 01730, USA.
[2] Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.
[3] Department of Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.
[4] To whom correspondence should be addressed. (e-mail: mstaples@mchips.com)

ABBREVIATIONS: ANN, artificial neural network; AUC, area under the plasma drug concentration *vs.* time curve; a measure of drug exposure; BCNU, carmustine, an antineoplastic agent; Bio-IT, convergence of bioscience with information technology; BLA, biologics license application; DNA, deoxyribonucleic acid; DRIE, deep-reactive ion etching; FDA, Food and Drug Administration of the United States Dept. of Health and Human Services; HGH, human growth hormone; NDA, New Drug Application; MEMS, micro-electromechanical systems; NEMS, nano-electromechanical systems; OCP, Office of Combination Products; PDMS, polydimethylsiloxane; PLA, poly(L-lactic acid); PLGA, poly(lactide-co-glycolide); PMA, Premarket Approval (Device Application); PMMA, polymethylmethacrylate; PZT, piezoelectric transducer; SD, standard deviation.

with regard to some methods and applications. However, the ability to control materials, surfaces, and structures at the nanometer scale can provide distinctive solutions as a consequence of properties unique to the nanometer scale (2,3).

New technologies are only useful if they can be commercialized, and drug delivery applications cannot be commercialized without a regulatory environment sufficiently adaptable to support marketing approval of innovative products. In 2002, the Food and Drug Administration (FDA) created the Office of Combination Products (OCP) to provide an appropriate regulatory framework for products that do not fit the established categories of drugs, devices, and biologics. A combination product may include a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device, and a biological product (4). The combination products surveyed in this review are composed of two or more elements. At least one element will be a drug or biologic, and at least one element will be a drug delivery device constructed using MEMS- or NEMS-based technologies.

CONVERGING TECHNOLOGIES

MEMS and NEMS

MEMS enables the manufacture of small devices using microfabrication techniques similar to the ones that are used to create silicon computer chips. MEMS technology has been used to construct microreservoirs, micropumps, nanoporous membranes, nanoparticles, valves, sensors, and other structures using biocompatible materials appropriate for drug administration (5–7). Using NEMS, complex mechanical nanostructures can be built with lateral dimensions as small as tens of nanometers. By incorporating transducers, control and measurement functions can be built into these systems (8). Innovative nanometer-scale materials and structures include quantum dots (9), nanowires (10,11), and nanotubes (12).

MEMS- or NEMS-based devices are fabricated by adapting techniques developed for the electronics industry to integrate complex programmable and structural elements on a substrate. Originally the substrate was silicon (13), but (especially for biologically and medically oriented applications) the category is no longer limited to silicon-based devices. Also, initially the object was to integrate electrical and mechanical features that could be controlled by programmable circuitry. In addition to programming-based control, however, specific properties of composition and geometry may be enlisted to determine amount of drug release, timing, and rates.

Structures have been constructed using MEMS technologies with arrays of uniform channels as narrow as 7 nm. Protein diffusion kinetics under sink (dilute) conditions across nanoporous membranes are non-Fickian as the nanopore width approaches the hydrodynamic diameter of the solute, and Fickian at greater pore widths. A 13-nm nanopore membrane was loaded with radiolabeled bovine serum albumin and implanted in rats to test its suitability for drug delivery. Slow release of protein was demonstrated, indicating that devices constructed in this fashion could be designed with high loading capacity and could deliver proteins with zero-order release kinetics (14).

Performance and reliability impairment of MEMS- and NEMS-based devices due to tribological (friction and wear)-

Table I. Marketed Combination Product Examples: Drug and Device

Company	Product and description	Use and indication(s)
American Medical Systems	AMS InteMesh™ silicone-coated sling and surgical mesh with InhibiZone™ (antibiotic).	For treatment of urinary incontinence resulting from urethral hypermobility and for implantation to reinforce soft tissues where weakness exists in the urological, gynecological, or gastroenterological anatomy.
EMPI, Inc.	Lidocaine HCl 2% and epinephrine 1:100,000 solution for topical iontophoretic system. For use with Empi Dupel® Iontophoretic Bi-Layer Ultra Electrodes and Dupel® Iontophoretic Controller.	Iontophoretic production of local analgesia for superficial dermatological procedures such as venipuncture, shave removals, and punch biopsies.
Vyteris, Inc.	LidoSite™ Topical System composed of the LidoSite™ Patch (lidocaine HCl/epinephrine topical iontophoretic patch) 10%/0.1% and the LidoSite™ Controller.	Topical local anesthetic delivery system indicated for use on normal intact skin to provide local analgesia for superficial dermatological procedures such as venipuncture, intravenous cannulation, and laser ablation of superficial skin lesions.
PhotoCure ASA	CureLight BroadBand (Model CureLight 01). Use in combination with methyl aminolevulinate cream.	For treatment of nonhyperkeratotic actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation.
Boston Scientific Corporation	TAXUS™ Express 2™ paclitaxel-eluting coronary stent system (monorail and over-the-wire).	For improving luminal diameter for the treatment of *de novo* lesions in native coronary arteries.
Axcan Scandipharm, Inc.	PHOTOFRIN® (porfimer sodium) for injection in conjunction with Wizard X-Cell™ photodynamic therapy balloon with fiber optic diffuser, OPTIGUIDE™ fiber optic diffuser (DCYL Cylindrical Diffuser Series), or Diomed 630 PDT laser, model T2USA.	For ablation of high-grade dysplasia in Barrett's esophagus patients who do not undergo esophagectomy.

related problems need to be better understood, because wear properties may limit practical implementation of micro- and nanoscale devices for many applications (15). Improvements in atomic force microscopy methods may improve characterization of tribological properties of materials in micro- and nanoscale systems where relatively high sliding velocities (up to 10 mm/s) occur (16).

Alternative materials for constructing MEMS- and NEMS-based devices are being actively investigated to improve reliability and design flexibility, and to decrease cost. Polymers have superior properties to silicon for BioMEMS applications with regard to cost and versatility of physical properties. To provide more design flexibility, biocompatible polymers like polymethylmethacrylate (PMMA) and polydimethylsiloxane (PDMS) are being investigated as alternative materials to silicon (17).

Data Management, Device Control, and Communication

Information science and wireless communication technology play multifaceted roles in expanding the potential utility of MEMS-based drug delivery systems. Commercial software and hardware is readily available for gathering, transmitting, manipulating, storing, retrieving, and classifying recorded information. Data can be transmitted using wireless communication from a biomonitor to a central system or to a drug delivery device as part of a feedback loop. The data itself may serve as a passive log, an alert system for patients and health care providers, or a basis for controlling drug release from a delivery device. Autonomous self-monitoring delivery systems require algorithms for translating monitor data into the control commands for timing and amount of drug to release. The continuous glucose monitoring field, in particular, has developed a number of algorithms to translate raw data from glucose sensors into alerts for impending hypoglycemia, although the ultimate goal of an implantable closed-loop system with automatic control of insulin delivery has not been realized (18). The convergence of information technology and biological (and medically related) applications has become known as "bio-IT" (19).

Data interpretation may be complex, involving interrelated environmental variables, noise and drift, possibly requiring an artificial neural network (ANN) to generate control algorithms. ANNs are mathematical constructs that contain interconnected processing elements ("neurons"), schematically similar to biological neural connections. The

Table II. Marketed Combination Product Examples: Biologic and Device

Company	Product and description	Use and indication(s)
Biomimetic Therapeutics, Inc.	GEM 21S™ (Growth-Factor Enhanced Matrix). The product, a fully synthetic regeneration system, combines recombinant human platelet-derived growth factor BB (rhPDGF-BB) with a resorbable synthetic bone matrix (β-tricalcium phosphate, β-TCP). The rhPDGF-BB provides the biological stimulus for healing by stimulating the proliferation and in-growth of osteoblasts, cells responsible for the formation of bone, whereas the β-TCP provides the framework of scaffold for the new bone growth.	For treating the following periodontally related defects: 1) intrabony periodontal defects, 2) furcation periodontal defects, 3) gingival recession associated with periodontal defects.
MedImmune Vaccines, Inc.	Influenza virus vaccine, live, intranasal (FluMist): 0.5-mL single dose, prefilled nasal spray system consisting of a glass syringe barrel and a Teflon sprayer nozzle.	For active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, 5–17 years of age, and healthy adults, 18–49 years of age.
Medtronic Sofamor Danek	INFUSE® Bone Graft/LT-CAGE lumbar tapered fusion device; consists of three components split among two parts: a metallic tapered spinal fusion cage (known as the LT-CAGE lumbar tapered fusion device) and a bone graft substitute (known as the InFUSE Bone Graft). The InFUSE Bone Graft consists of a genetically engineered human protein (rhBMP-2) and a carrier/scaffold for the protein (manufactured from bovine [cow] type 1 collagen) that are placed inside the fusion cage.	To be used in the lower region of the spine as a treatment for degenerative disc disease. Alternatively, the INFUSE® Bone Graft can be used with a metal rod, called an intermedullary nail or IM nail, which is surgically implanted inside the tibia bone to stabilize the fracture. The INFUSE® device is implanted at the fracture site to help the bone heal. Used along with internal stabilization (an IM nail) to help heal a fresh, open fracture of the tibia.
OMRIX Biopharmaceuticals, Ltd.	Fibrin Sealant (Human). A single-use kit consisting of two packages. The first contains one vial each of frozen sterile solutions of 40–60 mg/ml fibrinogen and 800–1200 IU/ml thrombin and the second contains a sterile administration device. When the thawed fibrinogen and thrombin solutions are combined by simultaneous application using the administration device supplied, a fibrin clot is formed through the cleavage of fibrinogen by thrombin.	Adjunct to hemostasis in patients undergoing liver surgery, when control of bleeding by conventional surgical techniques is ineffective or impractical

neurons accept multiple inputs, apply a weighting system to the summed inputs, and produce an output signal to another neuron. The interunit connections are optimized during the training process until the error in predictions is minimized and a targeted accuracy level is achieved. The ANN can be fed with new input information posttraining to make decisions or perform actions. ANNs have a number of properties and capabilities that are important for critical, computation-intensive applications: parallel processing, fault tolerance, self-organization, generalization ability, and continuous adaptivity (20,21). ANNs are being applied to a wide range of data-intensive medical applications, including evaluation of physiological data, epidemiological phenomena, medical image analysis, and monitoring the effectiveness of treatment regimens. Pharmaceutical research has used ANNs for tasks such as evaluation of analytical data, drug design, dosage form design (formulation and delivery), and pharmacokinetic/pharmacodynamic modeling (22–28).

Biological Sciences

Advances in biological sciences have produced many new drugs and biological molecules that are candidates for administration via drug delivery devices due to factors such as stability requirements and high potency. Manufacturing operations to produce biological molecules (recombinant DNA, cell fusion, and new bioprocessing techniques) have not changed greatly in the last 5 years, but systems biology approaches to understanding links between the genome (via the Human Genome Project), proteins ("proteomics") and metabolites ("metabolomics" (29)) have blossomed into a set

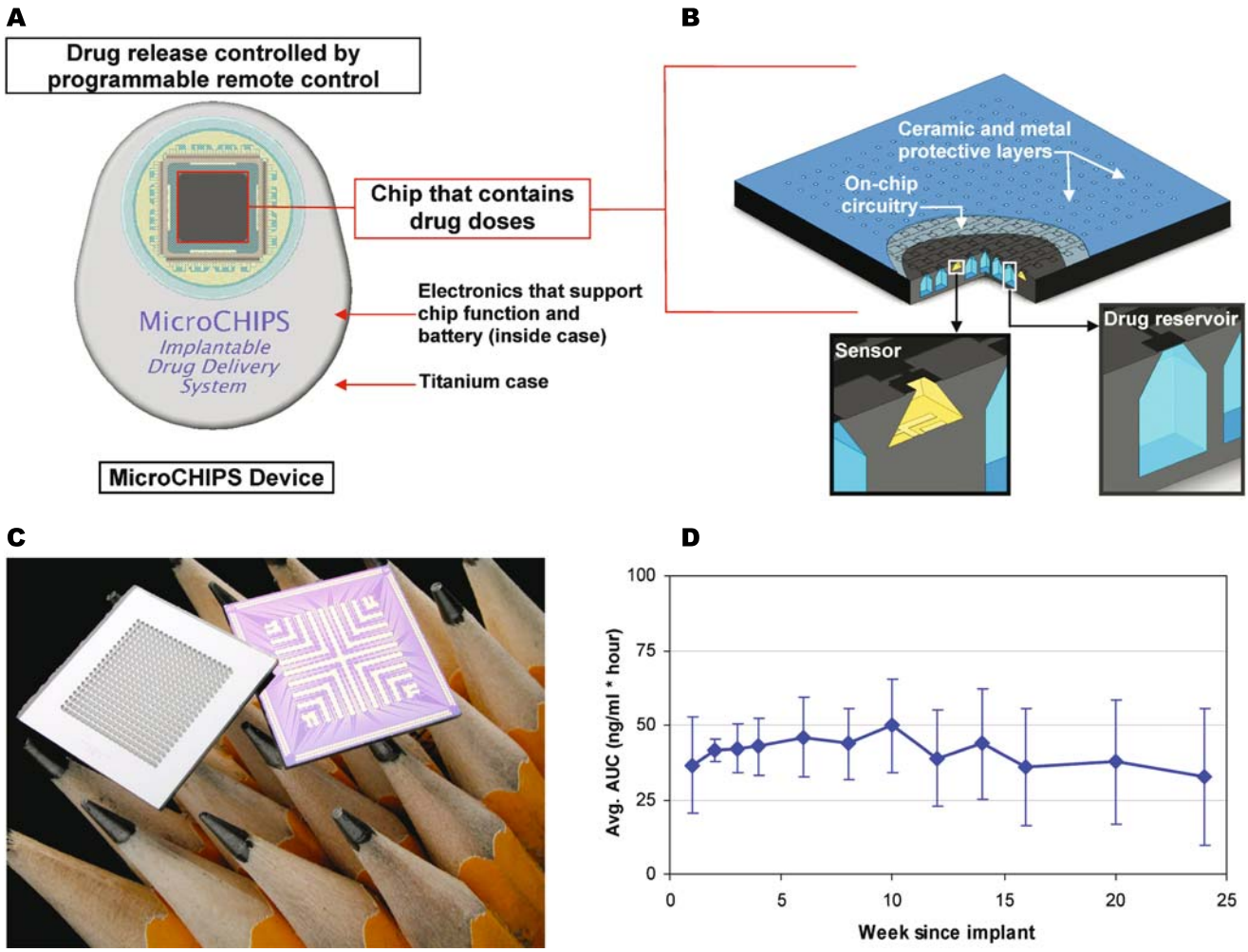

Fig. 1. A microchip-based electronically controlled drug release device (45). Panel A. A prototype implantable microchip-based device for controlled release: the microchip is mounted in a biocompatible case containing electronics, power source, and antenna for wireless communication (45). Panel B. Drug Delivery/Biosensor Array: A microchip for controlled release showing the reservoir array and the shape of single reservoirs for delivery or sensor applications (45). Panel C. A microchip for controlled release: one side is filled with drug (left); the other side (right) exhibits circuitry and membranes (source: MicroCHIPS, Inc.; photo credit: Dana Lipp Imaging). Panel D. *In vivo* Release – Leuprolide (Model Peptide); n = 6 dogs, error bars are ± 1 SD (45). Each reservoir on the 15 mm × 15 mm × 1.0 mm microchip was filled with 25 μg leuprolide in 125 nL solution, followed by lyophilization and a secondary fill of 125 nL of molten polyethylene glycol. The backs of the filled reservoirs were individually sealed with solder. One device (approximate dimensions for the device 4.5 cm × 5.5 cm × 1 cm, volume approximately 30 mL) was implanted into the subcutaneous tissue of each dog. Dosing was conducted at weekly to monthly intervals over six months. The devices were programmed by RF telemetry to open selected reservoirs, thereby initiating drug release.

of fields that has the potential to greatly enrich discovery of therapeutic drugs and biomolecules (30,31).

REGULATORY DIMENSIONS

It is critical to understand the fundamentals of current regulatory procedures because of the complexity of obtaining combination product approval. Additionally, relevant procedures and guidances have been evolving extensively in the last several years (32). Although no MEMS- or NEMS-based combination products have been approved yet, Tables I and II provide examples of combination products that have a device component plus a drug (Table I) or biologic (Table II) component (33). MEMS- and NEMS-based systems will primarily be differentiated on the basis of whether micro- or nanoscale features are the most critical contributors of functionality.

Although the FDA recognizes the need to specifically address requirements for product manufactured using nanotechnology-based processes (3), there are currently no testing or safety evaluation requirements specific to nanotechnology products, and the FDA does not anticipate any new guidance documents regarding nanomaterials in the near future. Many aspects of these products that concern quality and efficacy are already encompassed by existing guidances for more conventional products (34). The FDA OCP will coordinate the regulatory framework for nanotechnology products and will designate the FDA center responsible for evaluating the application, with consultation from other centers (35).

As an increasing number of innovative drug delivery products were presented to the FDA for approval, it became

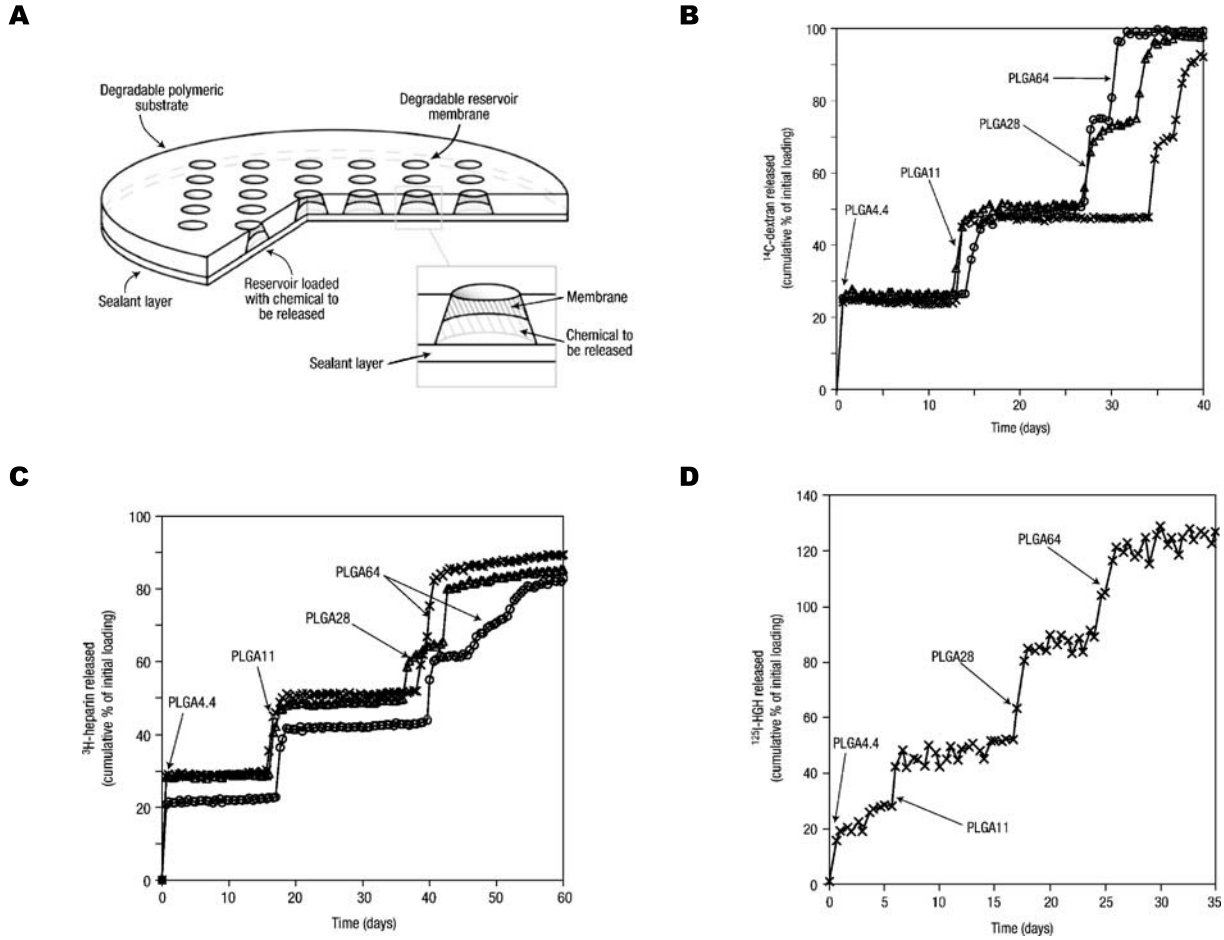

Fig. 2. A polymeric controlled drug release device without electronics. (A) Diagram of polymeric microchip device. The main body of the device is composed of a reservoir-containing substrate that is fabricated from a degradable polymer. Truncated conical reservoirs in the substrate are loaded with the chemical to be released and 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 (46). (B–D) Cumulative percentage of initial loading released from microchip devices *in vitro*. Each symbol (triangle, cross or circle) in a panel represents data collected for a different device. Each device had a total of four reservoirs that were loaded with radiolabeled molecules and sealed with a membrane, and each reservoir had a different membrane that was fabricated from one of the PLGA4.4, PLGA11, PLGA28, or PLGA64 copolymers. 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*. Devices represented by triangles are included for comparison. (B) Cumulative release results for devices loaded with [^{14}C]dextran. (C) Cumulative release results for devices loaded with [^{3}H]heparin. (D) Cumulative release results for a device loaded with ^{125}I-HGH (46).

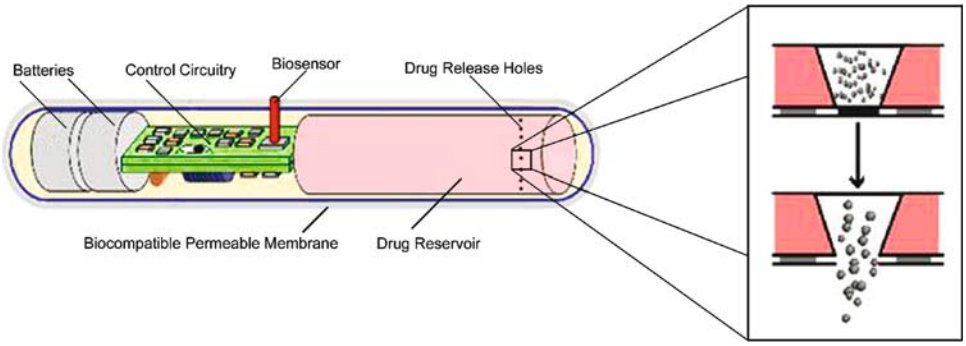

Fig. 3. Smart pill implant from ChipRx (50). Left: schematic of self-regulating responsive therapeutic system; Right: close-up of drug release holes.

clear that the division of products into drugs, biologics, and devices was not an adequate system for evaluation. Consequently, the OCP was established, as outlined in the Medical Device User Fee and Modernization Act of 2002. The OCP assigns a lead center for premarket review and regulation of combination products based on the primary mode of action and coordinates a wide range of administrative functions related to combination product review and approval (4).

The FDA provides a device definition that distinguishes between devices and drugs or biologics. A device provides diagnostic or therapeutic benefit and "does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes (36)." If the primary product use involves chemical action or metabolism of the product, this is the key consideration for identifying a product as a drug. A drug is intended for use "in diagnosis, cure, mitigation, treatment, or prevention of disease, or an article (other than food) intended to affect the structure or function of the body (36)."

There are some regulatory hurdles specific to combination products that can add uncertainty, lengthen the preparation for submitting an application to the FDA, or delay the approval process. In the United States, the OCP assigns the FDA center that has "primary jurisdiction" and the type of application [premarket approval (PMA), new drug application (NDA), or biologics license application (BLA)] that must be prepared, based on the primary mode of action. From an organizational skills standpoint, drug and device companies have very different sets of expertise. Typically, a device company will have difficulty preparing a successful NDA or BLA. Consequently, assignment of a combination product to a regulatory center unfamiliar to the applicant can cause additional applicant uncertainty and delay in approval. Another important consideration involves judging when the formulation, dosing amount, dosing frequency, or delivery mechanism sufficiently differ from an approved NDA that a new NDA is required. Cross-labeling (correspondence between device labeling and drug labeling) must also be resolved. The most challenging part of the submission will often be the data interpretation of *in vivo* and clinical studies: if a case cannot be made that the pharmacokinetic/pharmacodynamic data, toxicology, safety, dosing, and efficacy are sufficiently similar for the active ingredient in an approved product and the combination product, additional clinical studies may be required. In the European Union, the categorization is determined by the Principal Mode of Action, followed by assignment to "medical product" or "medical device" categories. (L. R. Horton, "Gaining Regulatory Approval for Combination Products in the U.S. and Europe," June 9, 2005, "Developing Combination Products" Barnett International Conference).

A combination product application also requires technical details for the interaction of each component as well as data on the components themselves, and the amount and type of data must be considered on a case-by-case basis. Quality control groups need to provide additional testing specific to the drug/device combination. As an example, for drug-coated stents, testing should measure the impact of the

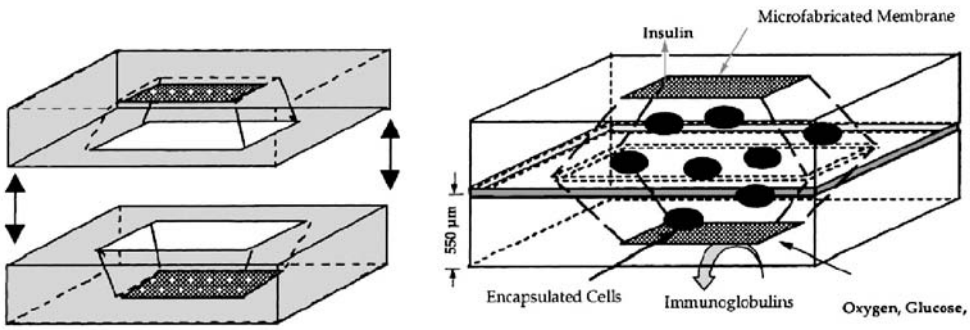

Fig. 4. Schematic of assembled biocapsule of two micromachined membranes bonded together to form a cell-containing cavity bounded by membranes (54).

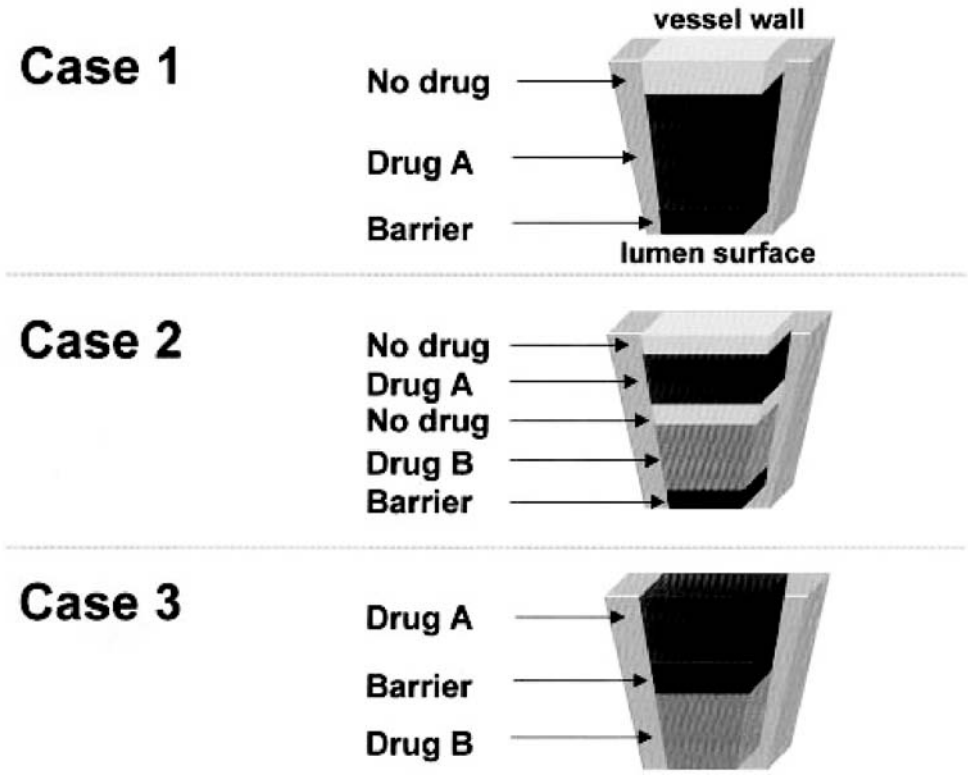

Fig. 5. Options for filling drug in stent reservoirs (60).

polymer coating on drug efficacy. The drug-release rate and factors that affect the release from the stent should be determined as well as the optimal *in vivo* release profile. Localized effects should be identified, and *in vitro* test methods specific to the combination product should be designed (A. Hussein in 37). Stability testing must include the impact of the product components on each other. The manufacturing description should describe assembly of the system, and preparations need to be made for additional site and record inspection for these operations. A device must be proven safe and effective for each drug used with it even if the device design and operation remain the same because the system performance may depend on how the device (for instance, a pump) and drug interact. Similarly, drug chemistry and packaging compatibility must be verified for each new combination of products. The importance of testing the whole system can be illustrated by an example where crystalline insulin formed in a pump seal, causing failure of the titanium seal due to increased brittleness and cracking (W. Van Antwerp in 37).

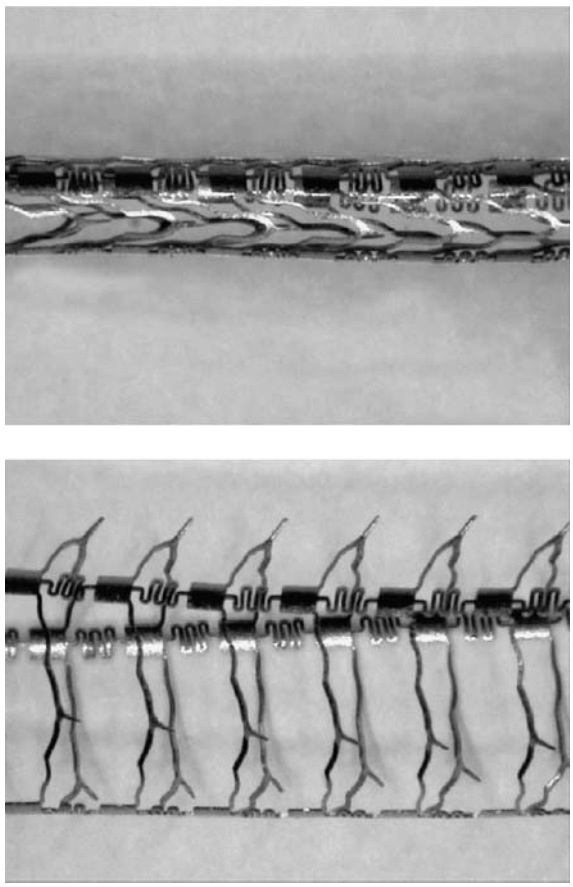

Fig. 6. Translamina stent in its undeployed (top) and deployed (bottom) state (63).

EXAMPLES

Implantable Devices: Reservoirs for Controlled Parenteral Release

Implantable devices require minor surgery to implant and remove, need to be as unobtrusive as possible, and may be relatively expensive. Suitable candidate drugs will be potent and will be formulated as high-concentration preparations stable for extended periods at body temperature. Suitable dosing regimens either require long-term adminis-

tration (months to years) or availability on demand. There is a fundamental limitation of device size imposed by the need to have sufficient storage capacity for a chronic dosing regimen, and the most potent drugs require microgram quantities per day. If a device needs to last a year, even high-concentration formulations occupy sufficient volume to place a lower limit in the milliliter range for total device volume, once space is assigned for power, electronics, the drug reservoir, communication, and packaging.

An ideal implant would protect the drug or biosensor from the body until needed, allow continuous or pulsatile delivery of both liquid and solid drug formulations, and be controllable by the physician or patient. A device meeting these criteria would include an array of individually sealed reservoirs that could be opened on command to expose their contents to the body. One or more drug formulations could be sealed in the reservoirs, protecting them from the environment until the reservoir was opened and the drug was released. Alternatively, biosensors could be sealed in the reservoirs to protect them from the biofouling that normally occurs in the body. Sensing would be initiated by opening a reservoir to expose the biosensor to the body. The process of sequentially exposing new sensors as old ones foul would enable long-term implanted sensing using currently available, short-term sensors. One of the important advantages of implantable delivery systems with individually addressable drug-containing reservoirs is the ability to totally control drug delivery amount and timing: continuous or pulsatile delivery could be accommodated. There is great flexibility in tailoring these systems for specific applications because the release characteristics can be governed independently by release mechanism, reservoir geometry, or drug formulation.

An electrochemical mechanism has been employed to selectively open reservoirs in a microfabricated drug delivery device containing an array of reservoirs (38–41). Individual reservoirs in the device were opened *in vitro* and *in vivo*, exposing the contents, by applying a potential to a gold membrane covering each reservoir. An electrochemical reaction created soluble gold complexes and caused the membrane to dissolve. This device has demonstrated *in vitro* and *in vivo* pulsatile release of both model and therapeutic compounds (38,42,43). In subsequent versions of this device, Pyrex layers were bonded to the silicon chip to increase reservoir capacity. When this increased capacity device was used to deliver a chemotherapeutic agent (BCNU) locally to rat tumors, dose-dependent inhibition of tumor growth

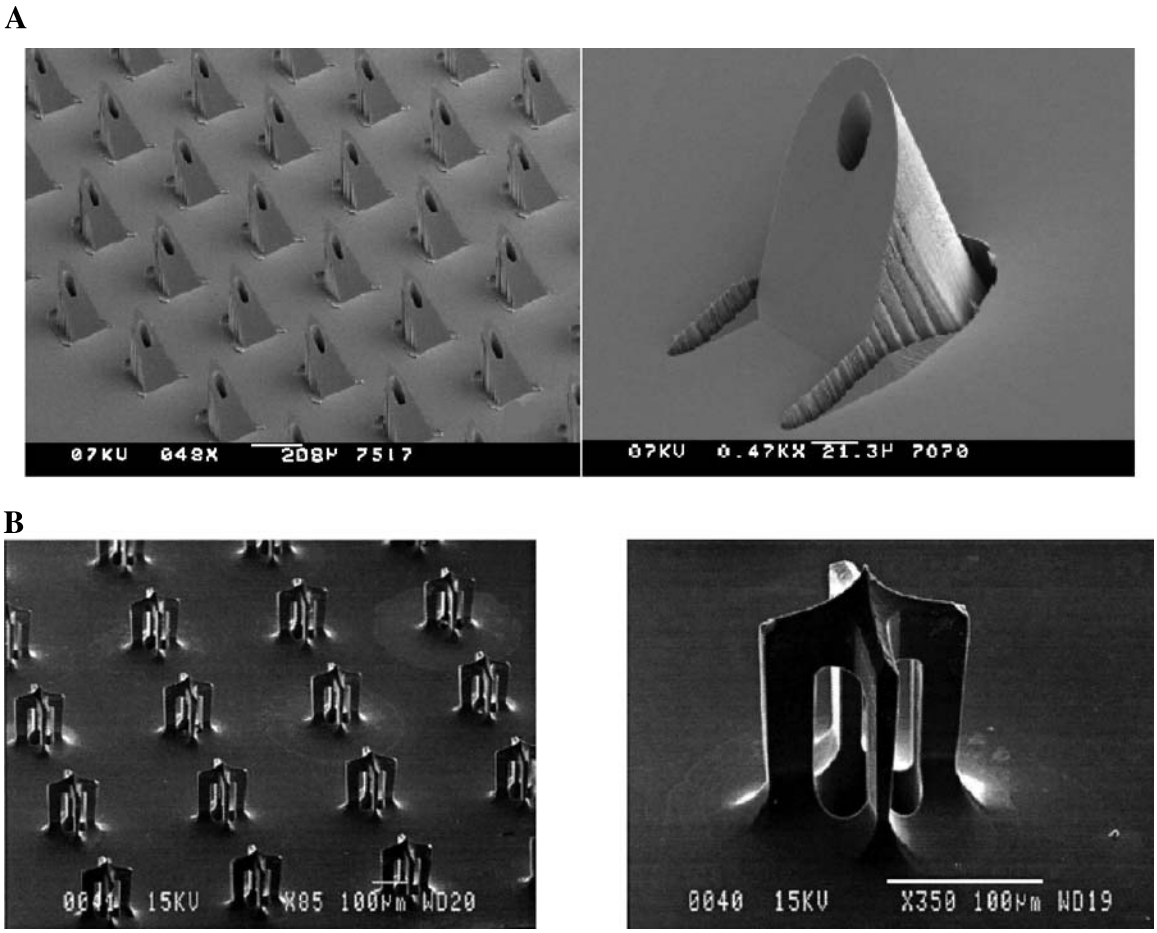

Fig. 7. MEMS-based microneedles for drug delivery. (A) Scanning electron micrographs of silicon microneedles fabricated using MEMS-based technology. The distance between needles in the array (left) is 555 μm. The array (left) illustrates needles with sharp tips and (right) a needle with a large radius of curvature (73). (B) Scanning electron micrographs of silicon microneedles fabricated using MEMS-based technology. Left, a Debiotech MicroJect needle array; right, a needle with sharp tips and side holes (74).

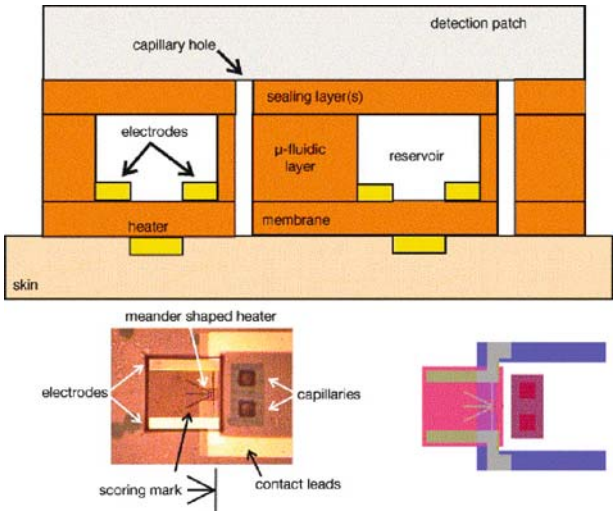

Fig. 8. Overview of transdermal glucose sensor structure. Top, cross section of two units; bottom, top view (photograph and mask layout) (75).

occurred that was comparable to results from subcutaneous injections (43).

MicroCHIPS has developed a device similar in size and appearance to an implantable cardiac defibrillator, although the volume of future devices can be significantly reduced through the incorporation of custom electronic components. The microchip, wireless communication hardware, power supply, and electrical components are embedded and hermetically sealed inside the device (Fig. 1 Panel A). Each 15 mm × 15 mm × 1.0 mm microchip (Fig. 1 Panels B and C illustrate a similar design) consists of a silicon/glass bonded substrate containing 100 individually addressable, 300 nl (capacity) reservoirs. The membranes over each reservoir, composed of platinum and titanium layers, are removed by local resistive heating from an applied current (44). This electrothermal method is independent of the chemistry of the surrounding medium and is many times faster than an electrochemical method. The MicroCHIPS device has been shown to deliver a controlled pulsatile release of the polypeptide leuprolide from discrete, individually addressable reservoirs implanted in a canine model for nearly six months. The Area Under the Curve (AUC) values for five of the six devices were constant for six months (Fig. 1 Panel D). This is the first demonstration of a fully self-contained microchip implant that provides chronic programmed delivery of therapeutic drugs (45).

A biodegradable polymer chip version of an implantable multireservoir drug delivery device (illustrated in Fig. 2) incorporates an array of reservoirs capped with resorbable membranes that may differ from other membranes in the array by thickness or chemical composition (46). The interior of each reservoir contains drug formulation(s). An advantage of biodegradable polymer-based systems compared to microchip-based systems is the elimination of a requirement for a second surgery to remove the device. In addition, the lack of electronics reduces any size restrictions in terms of device manufacture. Such systems are simpler but will not deliver reservoir contents with as much precision as the analogous microelectronic devices.

These polymeric devices and the reservoirs are formed by compression-molding polylactic acid (PLA). Individual membrane recipes are prepared using various ratios of lactic acid/glycolic acid and different molecular weight polymers to control release of reservoir contents from the devices. Prototype devices were approximately 11.9 mm in diameter, 480–560 μm thick, and contained 36 individual 120- to 130-nL reservoirs. Poly(lactide-*co*-glycolide) (PLGA) polymer membranes representing a molecular weight range of 4400 to 64,000 Da were used to control the release rates of the polymers human growth hormone (HGH), dextran, and heparin (46,47). The activation of reservoirs in sequence was illustrated by *in vitro* release of HGH, dextran, and heparin (Fig. 2). Similar results are obtained *in vivo* (48). The device has been shown to be biocompatible (49).

ChipRx (Lexington, KY, USA) has proposed an implantable, single-reservoir device (Fig. 3) that, in theory, could be adjusted to deliver drugs with targeted pharmacokinetics and bioavailability. The release mechanism employs polymeric "artificial muscles" that ring micrometer-sized diameter holes and that open to release drug. The polymer ring expands or contracts in response to an electrical signal transmitted through a conducting polymer that contacts a swellable hydrogel. Development work on this "smart pill" has been suspended by ChipRx, however (50).

Reservoirs can also be used to control therapeutic delivery if the reservoir barrier includes a selective membrane. Bulk and surface micromachining are MEMS technologies that have been used to create diffusion membranes with accurate and precise pore sizes on the nanometer scale. BioSilicon™, a pSividia (Perth, WA, USA) product, is produced from silicon using a MEMS-based process to create nanometer-scale pores that can be loaded with therapeutic agents (51). Similarly, Debiotech's DebioSTAR™ (Lausanne, Switzerland) is manufactured using controlled nanoporous technology, applicable to local or systemic parenteral drug

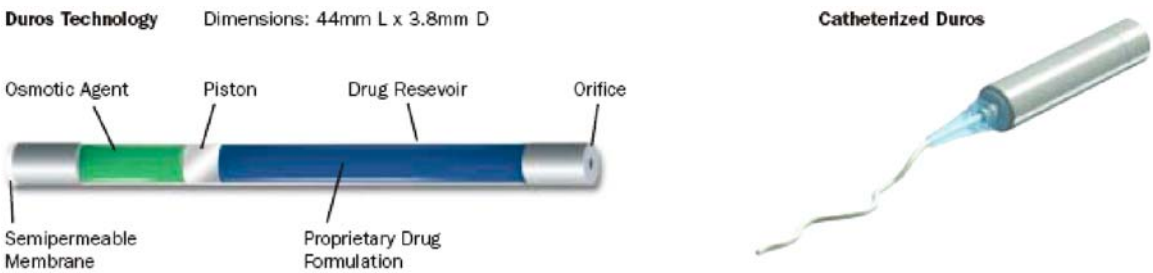

Fig. 9. Viadur System from Durect, illustrating DUROS® technology (80).

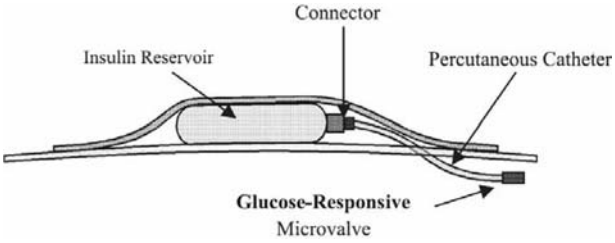

Fig. 10. Schematic of a glucose-responsive external insulin pump (82).

delivery (52). Membrane parameters may be optimized for various biomedical applications, such as cell immunoisolation and viral filtration (see Fig. 4). The pore size successfully regulates permeability, allowing passage of small molecules (oxygen, glucose, and insulin) and restricting passage of large proteins (immunoglobulin G). One target indication, diabetes, requires encapsulation of insulin-secreting pancreatic islets with a membrane that is permeable to insulin and glucose but impermeable to immunologic cells, antibodies, and other immune molecules that might destroy the transplanted cells (53–55). Other indications that could be treated by this approach include Parkinson's disease (56,57), and retinitis pigmentosa (58). Critical performance considerations that must be addressed to achieve commercializable membrane-based systems for long-term implants include designs that will not experience pore obstruction due to biofouling, long-term stability of protein expression in the encapsulated cells, and cell viability.

Stents

Drug-eluting stents [i.e., Taxus™ from Boston Scientific (Natick, MA, USA) (59)] are among the most widely known combination products. Advances in technology for cardiovascular stents have guided products through several generations. Micromachining technology allowed bare metal stents to be manufactured that had the physical capability of propping open occluded vessels. Coating the stent with a drug-containing polymer resulted in combination products featuring localized drug release capability in addition to the mechanical action of the stent. Next generation drug-eluting stents incorporate reservoir-based drug containment on the stent surface, with release properties determined by polymer composition and layer thickness.

The Conor Medsystems (Menlo Park, CA, USA) next-generation stent achieves flexible and controllable pharmacokinetic profiles of paclitaxel release through layered polymer/drug inlay stent technology. Programmable, complex chemotherapy using this approach may be feasible for the treatment of cardiovascular disease. Figure 5 illustrates how several configurations of drug and polymer barrier can be layered in the stent reservoirs to control amount and timing of drug release (60,61).

Bare metal stents may also be embellished with microprobes that allow delivery of antirestenosis drugs or biologicals. This stent design has been tested *in vivo* in rabbit femoral arteries. The microprobes penetrate the atherosclerotic plaque and the internal elastic lamina, reducing the diffusion barrier layer for delivery of genes or drugs. Figure 6 shows a prototype of this modified stent. The device uses controlled balloon expansion to cause the microprobes to pivot upward during inflation, lifting them into position. The design specifies the microprobe penetration depth, so the stent can be tailored to vessel sizes. The outer surface of the device is a nanoporous layer that controls active agent delivery (62,63).

Addition of communication capabilities provides another way to increase stent functionality. A micromachined stent has been developed that serves as an antenna for wireless monitoring of implantable microsensors. The stent expands

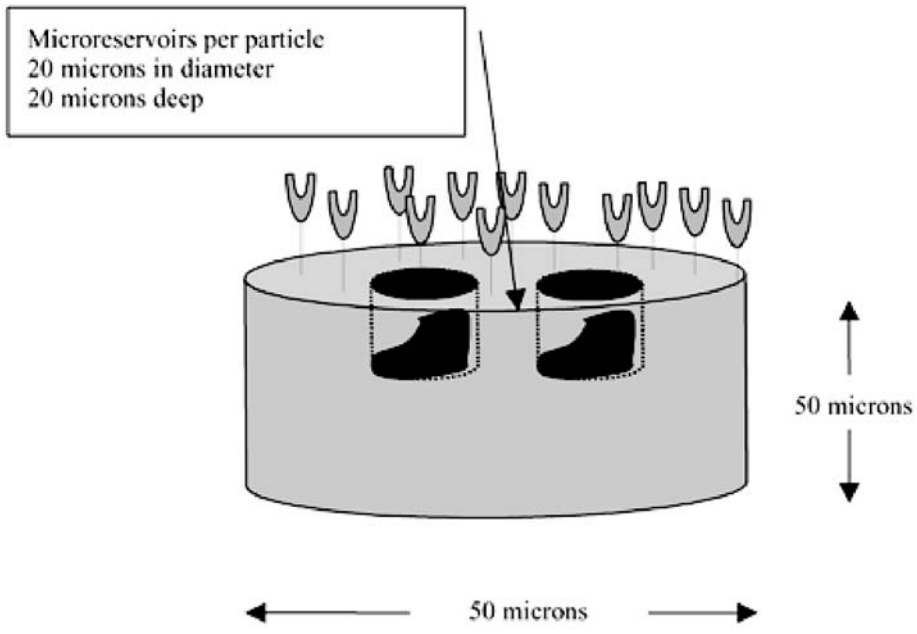

Fig. 11. Schematic of proposed bioadhesive microdevice (95).

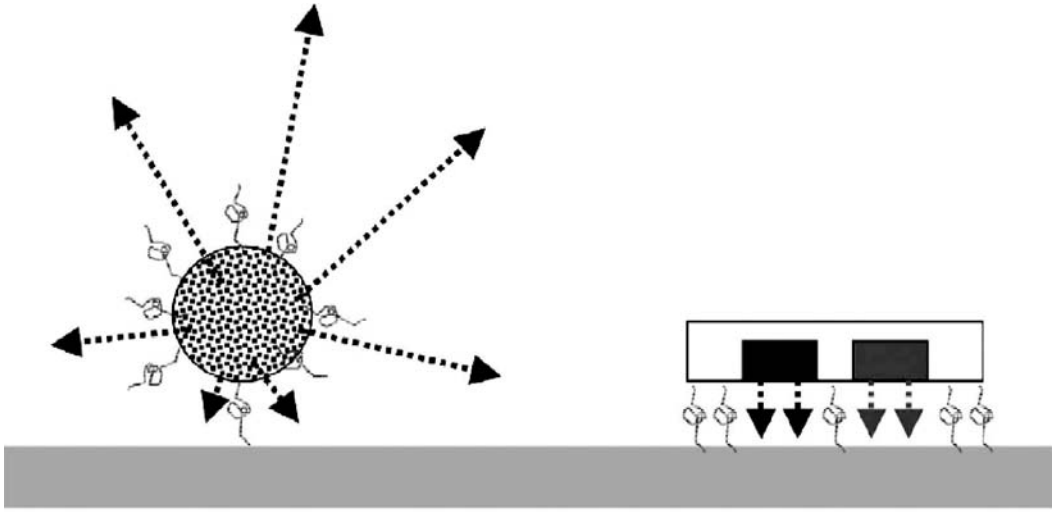

Fig. 12. A comparison between (A) a typical spherical drug delivery particle and (B) a microfabricated drug delivery device (97).

into an inductive coil after implantation, after links in the structure break and alter the electrical characteristics (64).

Transdermal

Transdermal drug administration systems have been limited to drugs with the right combination of molecular weight, lipophilicity, and charge. Penetration enhancers or iontophoresis (charge-based transport) may aid delivery. Due to the low permeability of skin, in particular the stratum corneum, sufficient bioavailability of high molecular weight drugs (proteins) has been difficult to achieve (65). Microneedles potentially provide a painless means to penetrate the stratum corneum and create channels to directly administer drugs. Arrays of micrometer-scale needles could enable minimally invasive transdermal delivery of therapeutic agents. Microfabrication techniques have been developed for silicon, metal, and biodegradable polymer microneedle arrays (66). Needles can be produced with solid or hollow bores, tapered or beveled tips, and feature sizes from 1 to 1000 μm. Solid microneedles increase skin permeability orders of magnitude *in vitro* for macromolecules and particles up to 50 nm in radius. Coherent porous silicon etching technology has also been used to fabricate microneedle arrays with different pitch and diameters (67).

One study compared actual and theoretical forces required for microneedles to penetrate living skin and to fracture microneedles. A range of designs was tested to evaluate the safety margin, expressed as the ratio of fracture force to insertion force. This ratio significantly exceeded one for most designs, and increased with increasing wall thickness and decreasing tip radius. These results indicate the feasibility of fabricating microneedles with robust mechanical properties (68). Macroflux® transdermal technology, developed by Alza (Mountain View, CA, USA), involves 200-μm titanium microneedles that disrupt the stratum corneum of the skin. Subsequent application of a conventional transdermal patch allows transdermal delivery of polypeptides (for example, HGH) and other macromolecules. Alternatively, drug can be dry-coated on the needles for direct application (69).

Planar arrays of rigid hollow microneedles have been produced from silicon by combining deep reactive ion etching (DRIE) and isotropic etching techniques. The microneedles are typically 200 μm long with a channel diameter of

Table III. Overview, Development of MEMS- and NEMS-Based Drug Delivery Devices

Present (commercial products; not necessarily MEMS- or NEMS-based but lay the foundation for MEMS- or NEMS-based drug delivery)
Reservoir-based drug-eluting stents (Conor Medsystems) (60,61)
Transdermal patches: iontophoresis devices (33)
Microosmotic pumps—ViaDur (79,80)
Closed loop system for insulin administration: insulin pump controlled by glucose sensor (33)
Near-term (in clinical trials; 1–10 years to market)
Microneedle-based transdermal delivery: Macroflux® from Alza (69)
Mid- to long-term (research or preclinical; 5–25 years to market)
Microchip technology: electrochemical drug release (38–43)
Microchip technology: electrothermal drug release (44,45)
Biodegradable polymer chip technology (46–49)
Microchip technology: "smart polymer" drug release (50)
Selective membrane technologies: BioSilicon™, a pSividia product (51); Debiotech's DebioSTAR™ for drug delivery (52); various others in research (53–58)
Stent technologies: microprobe-based stent technology (62,63); stents as antennas for monitoring implanted sensors (64)
Various microneedle devices in research (66–68,70–72); NanoPass (73); Debiotech (74)
Transdermal drug delivery/biosensor feedback loop (75)
Transcutaneous drug delivery/biosensor feedback loop (81,82)
Debiotech's Chronojet™ micropump for drug delivery (86); many other micropumps in research (83–85,87,88)
Various micro- and nanotechnology implementations of controlled drug release; mucoadhesive particles for oral administration (90–97)

Table IV. Overview, Challenges and Competitive Advantages of Leading MEMS- and NEMS-based Drug Delivery Approaches

Delivery route	Challenges	Potential for impact
Implant/Stent	Limited volume Only for high-potency drugs Mainly for local administration Requires surgery Expense Quality control difficult	If treatment requires local dosing, has potential to require lower total dose than injection Avoids need for injection: better than parenteral administration No impact on oral, probably little impact on products administered via topical or pulmonary routes
Implant/Pump	Limited volume Only for high-potency drugs Only for delivery of solutions (potential to damage polypeptides due to stability limitations in solution) Potential to damage polypeptides due to shear forces Potential fouling or clogging due to polypeptide precipitation or biofilm Requires surgery Expense	Potential to lower total dose due to local administration, better than standard injection Avoids need for injection: better than parenteral administration Local and systemic parenteral administration No impact on oral, probably little impact on products administered via topical or pulmonary routes
Implant/Electronic chip	Limited volume Only for high-potency drugs Potential impact of tissue capsule Requires very stable product formulations for long term use Requires surgery Expense	Potential to lower total dose due to local administration, better than standard injection Capable of precise timing and control: where this is required for chronic administration would have major advantage Avoids need for injection: better than parenteral administration Flexibility of local or systemic parenteral administration depending on formulation Flexibility of pulsatile or continuous administration depending on formulation No impact on oral, probably little impact on products administered via topical or pulmonary routes Potential for incorporation in feedback loop, competitive with therapies that require frequent monitoring to adjust dose
Implant/Polymer chip	Limited volume Only for high potency drugs (but not as high as electronic chips) Not suitable for precisely timed dosing, need a broad therapeutic window Requires very stable product formulations for long term use Requires surgery	Potential to lower total dose due to local administration, better than standard injection Avoids need for injection: better than parenteral administration Flexibility of local or systemic parenteral administration depending on formulation No impact on oral, probably little impact on products administered via topical or pulmonary routes No need for surgical removal, an advantage over electronic chips
Implant/Selective membrane technology	Limited volume Only for high-potency drugs Potential for membrane fouling Only for delivery of solutions (potential to damage polypeptides due to stability limitations in solution) Cell viability for chronic administration, for cell-based therapy Requires surgery	Potential to lower total dose due to local administration, better than standard injection Avoids need for injection: better than parenteral administration Flexibility of local or systemic parenteral administration depending on formulation No impact on oral, probably little impact on products administered via topical or pulmonary routes

Table IV. Continued

Delivery route	Challenges	Potential for impact
Transdermal	Limited volume Only for high potency drugs Safety concern: potential for infection	Potential to lower total dose due to local administration, better than systematic administration by injection Avoid need for injection Flexibility of local or systemic parenteral administration depending on formulation No impact on oral, probably little impact on products administered via pulmonary route
Enteral (mucosal)	Limited volume Short drug residence time, so not suitable for single-dose chronic therapy or slow-acting drugs Limited permeability of epithelial layer Enzymes in mucosal layer can alter drug	Better bioavailability than oral administration: less degradation in gastrointestinal tract and no first-pass metabolism No needles: better than parenteral administration Potential to compete with pulmonary administration in terms of convenience, bioavailability, and dosing accuracy Opportunity to modify surface with specific binding agent to target cell types or particular molecules

40 μm, and can feature blunt or sharp tips. Fluid injection through microneedle arrays has been successfully demonstrated, without needle breakage, into sample tissue 100 μm deep (70). Hollow microneedles have also been used to transdermally transport sufficient (microliter) quantities of insulin to reduce blood glucose levels in diabetic rats (71). In another study of insulin administered with hollow microneedles, blood glucose levels dropped as much as 80% in diabetic rats (an extent similar to 0.05–0.5 U insulin injected subcutaneously) (72).

NanoPass (Haifa, Israel) has fabricated out-of-plane hollow silicon microneedles that penetrate the skin without breakage, using DRIE, anisotropic wet etching, and conformal thin film deposition (Fig. 7A). The needle tip curvature can be controlled. In one sample, the length was 150–350 μm, with a 250-μm base at the widest point (73). Debiotech collaborators have applied a triple DRIE process to construct out-of-plane structures with sharp features several hundreds of micrometers in length and side holes that prevent coring (tissue removal at the insertion site) (Fig. 7B) (74).

Although microneedles can be prepared from different materials and using different technologies, a manufacturing cost analysis would be required to understand which process makes the most sense for a commercial product. Silicon microneedles take advantage of available silicon wafers and processing methods, and allow integration of sensors and devices on the planar back of the silicon needle array. If the main function of the microneedles is simply to create transient paths through the skin to allow drug delivery, the Macroflux® transdermal technology can be applied without adding the cost and complexity of microcircuitry. A comparative study that reported successful microfabrication of microneedles made of silicon, polymer, or metal construction concluded that polymer and metal materials should be less expensive than silicon, the manufacturing environment should require less stringent controls, and the fabrication techniques will involve fewer steps. Additionally, there is a more extensive safety history of metal and polymer materials in medical devices than silicon, and the silicon microneedles were not as strong. Biodegradable polymers would have the added advantage that, should breakage occur, any fragments would eventually degrade (71).

Techniques of encapsulating fluid within MEMS devices for analytical applications could, in theory, be applied to drug delivery systems. For example, a microtransdermal glucose sensor that incorporates a 50-nL reservoir has been fabricated from a photopolymer (Fig. 8). The heater ablates the stratum corneum, releasing glucose-containing intracellular fluid and increasing the skin permeability for drug delivery. The reservoir contains two electrodes, is filled with solution, and is bound by two membranes, 5 and 20–40 μm thick. Upon electrolysis of the encapsulated fluid, evolved gas ruptures the 5-μm membrane where it has been thinned to 2–3 μm by DRIE. The fluid exits the reservoir, mixes with the fluid released when the stratum corneum was ablated, and moves up adjacent capillaries through the entire chip (75). A delivery application might transmit drug-containing fluid through the skin, and the need for sensor capability would depend on the indication. This example is provided primarily to indicate the versatility of microfabrication technology applied to medical needs.

External and Implantable Pumps (Mechanical and Osmotic)

Many approaches to delivering drugs with pumps have been developed, using mechanical and osmotic pumping systems; a few representative examples are described here. These pumps could be incorporated in external or implantable drug delivery devices. Although pumping a drug solution is a straightforward method of administering any drug, pumps are limited to solution formulations. This can be a disadvantage for polypeptide drugs, because pumping exposes solutions to shear forces that may decrease polypeptide stability (76–78).

Alza's Viadur® (leuprolide acetate implant, manufactured by Alza, Mountain View, CA, USA and distributed by Bayer), the first approved product to be administered via the

DUROS® System, delivers leuprolide acetate for 1 year from an implantable drug-dispensing osmotic pump (Fig. 9). The pump is 44 × 3.8 mm. In the body, water enters the device through a semipermeable membrane and causes the osmotic agent to swell, displacing a piston that dispenses the drug formulation from the drug reservoir through the exit port. The product can be inserted or removed by a simple outpatient procedure (79,80). The technology has been modified to allow site-specific application, using a microcatheter attached to the DUROS® device for local administration. Site-specific delivery enables a therapeutic concentration of a drug to be administered to the desired target without exposing the entire body to a similar dose (80).

An external pump that administers insulin via a transcutaneous catheter and controls delivery with a glucose-responsive microvalve has been developed (81,82). The valve would be at the tip of a catheter connected to a slightly pressurized insulin reservoir (see Fig. 10). The reservoir size could be small because the contents could be replaced easily. The device delivers insulin through a valve that controls flow as a function of volume change of a glucose-sensitive hydrogel. As for implantable membrane-based systems discussed above, acceptable long-term performance will depend on designs that will not experience pore obstruction due to biofouling. Achieving an appropriate (commercializable) degree of dosing precision long term will also be a significant technical challenge.

Other examples of micropumps designed and fabricated using a range of MEMS technologies (see also (83,84) include:

- A micropump fabricated using sputter-deposited thin-film shape-memory alloy titanium nickel as an actuator, capable of high force and strains. The maximum water flow rate, 50 μL/min, could be useful for drug delivery and other areas (85).
- The DebioTech Chronojet™ product was developed from a silicon piezoelectric (PZT) micropump based on silicon bulk micromachining, silicon Pyrex anodic bonding, and PZT actuation. The flow rate range is 0–100 μL/h (86).
- A planar bidirectional valveless peristaltic micropump that controls water flow bidirectionally at the rate of 0.72 ml/hr (87).
- An implantable drug delivery system that uses three embedded PZT actuators to drive the three micropump chambers in a peristaltic motion (88).
- A 70 × 35 × 1.63-mm peristaltic micropump designed and fabricated using DRIE, anodic bonding, radio frequency sputtering, and oxidation deposition, that can deliver drug solution at 10 μL/min (89).

Enteral (Mucosal Delivery)

The mucosal route offers many advantages for drug delivery, especially for peptides and proteins. Drug bioavailability is improved due to avoidance of degradation in the gastrointestinal tract and hepatic first-pass metabolism. However, a short drug residence time, the presence of enzymes, and a limited permeability of the epithelial barrier are the main drawbacks of mucosal administration. Microfabrication technology, combined with appropriate surface chemistry, may permit the localized dosing and unidirectional release of therapeutic agents (90–92).

Poor oral bioavailability of polypeptide drugs can be alleviated by fabricating 0.1- to 1.0-mm-diameter particles using MEMS technology. Reservoirs in these particles contain controlled-release drug formulations (or drug is sealed in the reservoir with an erodible polymer cap). A mucoadhesive agent on the same face as the opening of the drug reservoir orients drug release toward the mucosal surface. These particles are enteric coated, allowing passage through the stomach before releasing drug. The particle may be fabricated by a "top-down" approach that combines thin film deposition methods, photolithography, photoablation, and etching techniques (90–94).

Microfabrication techniques and surface modification have been combined to create well-controlled, biologically specific drug delivery modules. The delivery module (see Fig. 11) adheres to the gastrointestinal tract while drug is released from the same face (95). Reservoir-containing silicon microdevices have been modified to enhance bioadhesion *in vitro* with a surface chemistry that binds lectin via avidin–biotin interactions. Lectins are a group of proteins that can bind specific cell types in the gastrointestinal tract. This strategy could improve oral bioavailability of therapeutic biopolymers such as peptides, proteins, and oligonucleotides (96). In a related study, a similar approach involved lectin attachment to PMMA microdevices. Aminolysis was used to modify the PMMA to yield accessible amino groups on the PMMA surface, followed by reaction with an active ester to covalently bind avidin molecules to the surface of the particles. Subsequent incubation in a biotinylated lectin solution produced lectin-modified microdevices that were tested *in vitro* for bioadhesion (97). The geometry of the isotropic reservoir maximizes epithelial-specific drug delivery, while minimizing drug dilution and metabolism in the gastrointestinal tract (Fig. 12).

PROSPECTS

Advances in many fields are converging to make commercialization of advanced drug delivery concepts possible. MEMS and NEMS, materials science, information technology, ANNs, wireless communication, and systems biology can all contribute to design of integrated therapeutic systems that have the potential to significantly improve the quality of pharmaceutically based medical care.

Table III summarizes examples of commercially available drug delivery devices, devices that are in clinical trials, and devices that are at the research or preclinical testing stage. Typically, a primary motivator for improved drug delivery systems is the avoidance of repeated parenteral administration. Due to the complexity and cost of device-based methods of administration, if a therapy can be accomplished by oral, pulmonary, or other nonparenteral routes, it is unlikely that sufficient advantage will be gained by introduction of an advanced delivery device. Additional requirements for a commercial device include highly potent active ingredients for implantable devices and stable formulations for long-term administration. Table IV provides an overview of the major technical challenges and competitive advantages of the MEMS- and NEMS-based approaches to drug delivery discussed in this review. For instances where a closed-loop system would be highly desirable, the use of an

implanted sensor with drug administered by an external pump may offer significant advantage (e.g., the insulin pump combined with a glucose monitor described below). NEMS-based devices are still at an early stage of testing. For implantable devices, nanotechnology for drug delivery is more likely to provide incremental rather than major advances because drug potency limits the minimum size of an implant for chronic administration.

Added value may be obtained with regard to increasingly personalized medicine, customized delivery, and implementation of feedback loops between biosensors and control of drug dosing (amount and timing) by applying the evolving tools of information technology to drug delivery. Cardiac pacemakers and defibrillators are examples of commercially available systems that prove the practicality of this concept. Clinicians and other health care providers, and maybe each individual patient, could access real-time medical status and order intervention via controlled dosing. Artificial intelligence and ANN research are being used to develop rules for computer systems and software to mimic biological processes for reasoning, pattern recognition, and processing of sensor data. It may be possible to incorporate ANNs into MEMS-based devices, or such decision-making capabilities could reside external to the device but accessible through wireless communication (98).

Wireless communication allows flexibility in integrated device design, as a device can be physically separated into modules without sacrificing system capabilities. A system providing complete control and feedback, for example, could be implanted as a biosensor unit and a drug reservoir unit. The units could communicate to regulate drug release and could also receive additional instruction from an external agent, as well as send data to an external monitor for use by patient or physician.

A large population of type 1 and type 2 diabetics could greatly benefit from an "artificial pancreas," the most commonly cited example of an integrated medical system (98,99). Better control of insulin administration by taking real-time glucose-monitoring data into consideration would significantly decrease diabetic complications. To construct a commercializable system, four components must be integrated: sampling, glucose sensing, mathematical models and related algorithms to calculate insulin doses, and the insulin delivery system. Currently, the main hurdles to realizing this goal are continuous glucose monitoring and the necessary control algorithms (99). Medtronic MiniMed, Inc. (Northridge, CA, USA) and Becton Dickinson (Franklin Lakes, NJ, USA) market a device/device-combination product for diabetics that "integrates a glucose meter and an insulin pump with a dose calculator into one device as a step toward development of a fully automated glucose monitoring and insulin delivery system." In general, drug/biosensor/delivery device combinations could be designed to respond to specific signals or circumstances, providing more responsiveness to dosing adjustments than is possible with traditionally administered drugs.

We can look forward to continued multidisciplinary advances that will support advanced drug delivery. Recent regulatory initiatives, such as formation of the FDA OCP and the FDA NanoTechnology Interest Group, have helped clarify the pathway for marketing approval of these innovative products. The combination of new technology and flexible regulatory guidance promises to foster further development of innovative drug delivery combination products for the foreseeable future.

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