

Responsive Drug Delivery Systems

Applying micromachining, biosensors, telemetry, and other techniques at the interface of analytical chemistry and bioengineering to revolutionize drug delivery.

Each person responds to a certain drug or combination of drugs in a unique manner. Drug absorption, distribution, and metabolism can vary widely among individuals, even within the same family (1), and especially for drugs that act upon a receptor or are involved in some other binding event within the body. The ability to monitor a disease's progression and respond to the unique changes in the body chemistry of each patient offers an unprecedented opportunity to deliver individualized medical care. An effective approach to individualized therapy involves ascertaining a marker molecule indicative of a disease state and subsequently delivering the type and dose of drug most appropriate for treatment (2). Using chemical biosensors to determine the levels of important marker molecules may serve to guide therapeutic regimens, thereby improving drug safety and efficacy. The need for this sort of responsive, individualized therapy has been a long-held, but largely unattainable, goal. The aim of this article is to describe the progress that has been made in the field of responsive drug delivery and to discuss the challenges that still need to be addressed.

Controlled release

Many of the most advanced drug delivery systems available operate on the principle of controlled release—a certain amount of drug is delivered over a specified time period in a predictable manner. The problem is that individuals and their health problems are often not predictable. Therefore, controlled-release systems are, in general, limited because they cannot respond directly to the needs of a given individual for a particular drug therapy. Nevertheless, controlled-release delivery systems provide a low therapeutic index (a measure of a drug's safety margin) and improved patient compliance (3). The fluctuations in the plasma concentrations of drugs are smaller with controlled-release drug delivery, thereby decreasing the risks of over- or under-dosing the patient.

Addressing the problems of individual variability becomes formidable when the therapeutic regimen involves multiple drugs, and this difficulty is compounded by certain medical conditions manifesting themselves uniquely in different patients. For example, each patient develops his or her own form of breast cancer on the basis of the particular mutations that occur in his or her tissue (4). There can

Sapna K. Deo
Elissavet A. Moschou
Serban F. Petcu
Leonidas G. Bachas
Sylvia Daunert
University of Kentucky
Patricia E. Eisenhardt
ChipRx
Marc J. Madou
University of California—Irvine

Table 1. Types of drug delivery systems.

	Main features	Reference
Commercially available		
Implantable fusion pumps	Preprogrammed to deliver at any release rate through a catheter to a specific body location	6
Noninvasive reverse iontophoresis devices	Electric current applied across skin to extract analyte from within/beneath the skin	12
Controlled release		
Duros implant technology	Continuous release for pain medication, individually tailored using an osmotic gradient	22
Responsive		
Closed loop	Delivers as a function of sensor signal; includes sensing and release systems	50
Responsive polymers	Release from a smart polymer in response to a stimulus	27–33
Micro and miniature systems		
Microfabricated “sacrificial” valves	Contains nano- to low-microliter volumes of therapeutic agents in individually sealed reservoirs; drug is released by electrochemically removing each microvalve’s lid	37, 38
“Artificial muscle” miniature valves	Based on a soft hydrogel and polymer blend that mimics natural muscle functions	39, 40

even be multiple forms of cancer, stemming from multiple mutation events, within a single patient. Because individual responses to chemotherapy and radiation can vary dramatically, accurate and sensitive methods that help fine-tune drug therapy are critical.

In some cases, a medical condition can create unpredictable episodes, and noticeable symptoms are not sufficient to support timely and accurate dosing. Examples include metabolic disorders such as diabetes, cardiovascular disease, and acute pain. Physicians and patients may choose a prophylactic approach, using controlled-release medication to maintain a constant presence of the therapeutic substance in the body, whether the patient needs it or not. Although this approach may prevent a medical crisis, the patient can quickly develop a tolerance to the drug and suffer significant side effects associated with constant exposure, as seen in the use of the nitroglycerin patch for treating angina (5).

Responsive drug delivery

The other alternative to managing this sort of unpredictable condition is for the patient to be on constant alert for the warning signs of an impending medical crisis. This is the technique most commonly used by diabetics to detect the onset of hypoglycemia (low blood sugar), a potentially serious complication of insulin therapy. Aside from being psychologically stressful, frequent finger pricks for blood glucose testing can be inconvenient and painful (6). A responsive drug delivery system located inside the patient’s body could sense continuously, detect the early onset of a crisis, and immediately respond with the appropriate countermeasure with minimal disruption to the patient’s daily life.

To date, attempts at individualized therapy have included ex vivo detection of a marker molecule and in vivo delivery of a drug or in vivo detection of a marker molecule coupled to an external delivery system. Although both approaches have merit and are

important advances in the field of individualized therapy, no proven systems are available that are capable of the in vivo detection and delivery functions that would make a truly responsive drug delivery system a reality.

The implantable cardio defibrillator (ICD) is an example of a device that responds to a patient’s needs. An ICD continuously monitors the heart-beat and, upon detecting a certain type of irregularity, sends a pulse of electricity to the heart (7). This device is used to treat ventricular fibrillation, a condition in which the heart cannot pump blood and death can occur within 5–10 min if not treated with electrotherapy. Although an ICD is not a drug delivery device, it is an example of an individualized responsive system.

In an ideal responsive drug delivery system, the detection method should be able to determine, in some cases, minute amounts of the marker molecule in a precise location of the body. The system must also be able to sense the biomolecule acting as the marker/indicator of the dose of adminis-

tered drug. If detection and delivery are to be performed in vivo, analytical methods that can perform both tasks in the patient’s body have to be developed. Furthermore, the sensing and delivery systems must be small, biocompatible, and capable of performing in an accurate and reproducible manner. Responsive therapeutic devices driven by unique biochemical sensor systems should revolutionize human and veterinary medicine by enabling individualized therapy in clinical areas where it is desperately needed.

Sensing

Highly sensitive, selective, and robust sensors capable of monitoring small volumes of body fluids are one of the key components for developing responsive drug delivery systems. Protein engineering and molecular biology have facilitated the molecular design of bioreagents, which are used as the sensing elements in various biosensing systems that offer high selectivities, good response times, and low detection limits. In addition, biosensors have been developed for physiologically relevant biomolecules, such as neurotransmitters and hormones (8–11).

Numerous biosensors with desirable characteristics that potentially could be integrated into responsive delivery systems have been reported. Most work in an ex vivo situation; however, a few have demonstrated in vivo capabilities. This situation is exemplified by the large number of glucose biosensors. Only a small number have been shown to work in vivo, and even fewer have reached the marketplace. The challenge of in vivo detection has limited the number of commercially available devices. That is because the levels of a target analyte in a physiological fluid are continuously affected by the dynamics of the body—namely, metabolic, hormonal, and chemical processes. In addition, human physiology may affect a biosensor’s working lifetime. It is not surprising that only a few biosensors for glucose are effective in an in vivo situation.

One example is the Glucowatch, a wristwatch-like glucose monitoring device that uses reverse iontophoresis—a weak electric current passed through the skin—to sample the interstitial fluid (12). The Glucowatch is not technically an in vivo sensor, but it integrates an ex vivo device that samples physiological fluid. An electrochemical sensor is used to detect glucose levels, which are displayed on the watch. The Medtronic MiniMed sensor acts like an artificial pancreas and continuously monitors glucose in vivo electrochemically (6). The needle-shaped sensor is surgically implanted under the skin of the patient's abdomen and determines glucose levels for 72 h, after which the sensor needs to be removed and replaced with another implant. This sensor may one day be coupled to MiniMed's 2007 implantable insulin pump, which delivers insulin on the basis of glucose levels detected by the biosensor. This would be an example of a closed-loop sensing and delivery system, in which a sensor determines the dose that needs to be administered at a given time. Although the MiniMed sensor is the first truly implantable biosensor that has reached the market, the 72-h lifetime is still a serious drawback.

In addition to sensors for glucose monitoring, biosensors for markers of other life-threatening diseases are needed. There are various systems for ex vivo detection of biochemical markers of myocardial injuries and other emergency health risk factors. Examples include the Alpha Dx, the OPTI critical care analyzer, the SenDx 100, and I-Stat point-of-care blood analysis products (13–16). These systems, which measure electrolytes, blood gases, myoglobin, and creatine kinase, are used in ambulances, emergency rooms, and surgery units to aid in rapid diagnosis. Although these advances have improved the speed of diagnosis and treatment, there is still a need for closed-looped sensing and delivery systems that can respond to an emergency situation almost instantaneously. For example, sometimes patients suffering from myocardial infarction cannot reach the emergency room in time; they would receive valuable, life-sustaining benefit from implanted sensors for cardiac markers with closed-loop drug delivery systems.

An additional advantage of an implantable responsive delivery device is that it continuously monitors a set of parameters and disease markers in patients with known risk factors. Physicians could closely follow the changes in the patient's health by examining the data obtained by the sensing device. The sensors could also serve as an alarm for the onset of a disease state, such as angina, a stroke, or a recurrence of cancer. Biocompatibility and foreign body response are still issues of major concern in implantable devices. Several different approaches are being evaluated to overcome this problem, including the use of biomimetic surfaces (17), polyethylene oxide coatings (18), and NO-releasing material (19).

Delivery

The global drug delivery market was estimated to be more than \$25 billion in 2002 (20). The drug delivery industry reported U.S. sales of ~\$14 billion for 2001, with sales of implantable devices ac-

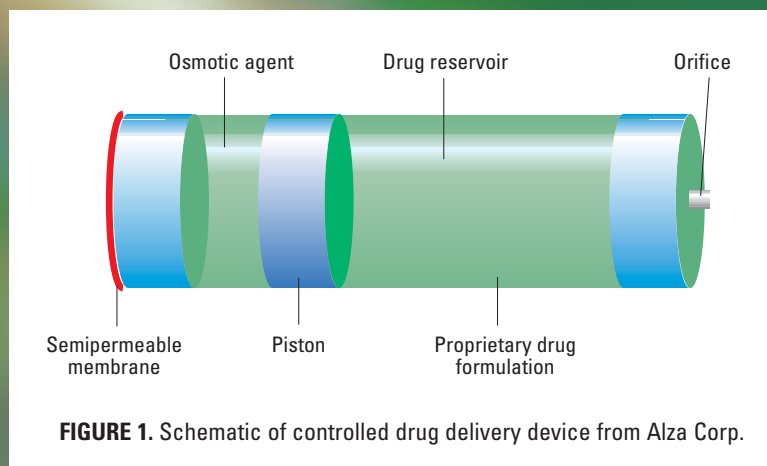


FIGURE 1. Schematic of controlled drug delivery device from Alza Corp.

counting for \$1.6 billion. Over the next several years, the annual growth rate of the drug delivery industry is projected to remain above 10%, with a significant portion of this growth due to the sale of implantable drug delivery devices (20). This growth will be based on new drug discoveries, new delivery platforms that will extend a company's hold on brands whose patents are expiring, and more accessible and safer products. The keys to success will likely rest on whether a company addresses needs in the marketplace and overcomes technological limitations, especially those associated with the delivery of biopharmaceuticals, such as proteins and peptides.

Only two different types of devices for drug delivery systems are currently commercially available (Table 1): implantable infusion pumps (MiniMed) and noninvasive reverse iontophoretic devices (6, 12). The infusion pumps can be programmed to deliver drugs of any molecular size through a catheter to a specific location in the body at any desired release rate. The drug reservoir can be refilled, extending the lifetime of the delivery system. Although these systems are currently used in diabetic patients to deliver insulin, the pumps are quite large, and implanting them requires major surgery. The Swiss-based company Debiotech is developing a piezo-actuated implantable silicon micropump using microelectromechanical systems (MEMS) technology for drug delivery applications (21). The size of the chip containing this pump will be $16 \times 12 \times 1.86$ mm, with a flow rate of 100 $\mu\text{L}/\text{h}$.

Durect Corp. has a controlled-release device called Duros under development, which is intended for pain medication (Figure 1; 22). The system can release medication from a reservoir through a semipermeable membrane for at least 1 month and up to 1 year. It measures 4 mm in diam and 44 mm in length and holds 150 μL of drug formulation, which is delivered at rates as low as 0.4 $\mu\text{L}/\text{day}$. When the device is implanted, water from surrounding tissues enters one end of the cylinder through the semipermeable membrane, causing the osmotic agent inside the device to swell and push a piston to release the drug through a port at the other end. By varying the composition of the osmotic agent, surface area, and thickness of the semipermeable membrane, the drug release rate can be tailored. Other types of controlled-release systems use an environmental stimulus, such as temperature, pH, and electric potential, to trigger the on/off release of a drug (23–26). Responsive drug delivery couples the release of the drug to the physiological signal from the patient's body, and thus, can overcome one of the limitations of controlled-release delivery. One

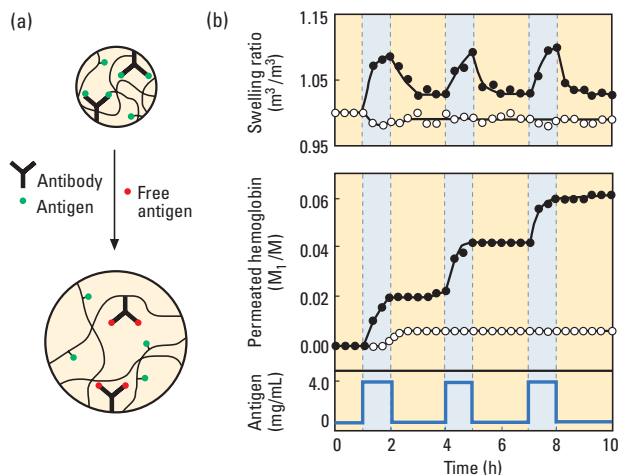


FIGURE 2. (a) Schematic of a “smart polymer” based on antigen–antibody interaction. (b) Profile of drug release through the smart polymer. The white circles represent changes in the polyacrylamide hydrogel in the presence of drug; the black circles indicate swelling of the antigen–antibody hydrogel in the presence of drug.

strategy is to use a closed-loop approach that involves a sensing and delivery system integrated within a single device, in which delivery depends on the signal measured by the sensor.

Alternatively, “smart” polymers or devices can be prepared that are responsive to the individual patient’s therapeutic requirements and deliver a certain amount of a drug in response to a biological stimulus. One promising, model smart polymer is based on antigen–antibody interactions. A semi-interpenetrating polymer network was prepared consisting of a polymer containing rabbit antibody (IgG) and goat anti-rabbit IgG as the antigen (27). This hydrogel swelled in the presence of the free antigen, rabbit IgG, because of competition between free and polymer-immobilized antigen. Upon removal of the free antigen, the hydrogel shrank, thus exhibiting reversible behavior that is dependent on free antigen concentration (Figure 2). To demonstrate the application of this system to drug delivery, a model drug was entrapped behind the hydrogel membrane. With stepwise changes in antigen concentration, the drug permeated the membrane as a function of the changing antigen levels.

Tanihara et al. also demonstrated a responsive delivery system that detects *Staphylococcus aureus* through increased thrombin activity and releases an appropriate amount of antibiotic (28). Specifically, the antibiotic gentamicin was bound on a poly(vinyl alcohol) hydrogel through a peptide linker, Gly-(D)-Phe-Pro-Arg-Gly-Phe-Pro-Ala-Gly-Gly, which contains the Arg-Gly thrombin recognition site. Thrombin’s presence released the biologically inactive antibiotic–linker conjugate that was converted to the biologically

active free gentamicin by leucine aminopeptidase, which is present at high levels in wound fluid. No biologically active gentamicin was detected, alone or in noninfected wound fluid, in the presence of thrombin or leucine aminopeptidase. The rate of gentamicin release depends on the concentration of thrombin. Implanting gentamicin hydrogel in rats verified the effective release of biologically active gentamicin in vivo. Although this is an interesting approach, it is difficult to imagine that this system could be implanted over long time periods because of the passive release of the biologically inactive antibiotic and the possible cleavage of the peptidic linker by nonspecific serum proteases. The latter could cause uncontrolled release of gentamicin and compromise the lifetime of the responsive delivery system.

Several self-regulating insulin delivery devices have been coupled with insulin release to construct artificial pancreas systems. Although several of these systems have been reported over the past 20 years (29–31), none can trigger release of insulin at physiological concentrations of glucose in vivo. One of the approaches is based on immobilizing glucose oxidase (GOx) in a pH-sensitive hydrogel, which is used as the insulin-release controller. GOx catalyzes the oxidation of glucose to gluconic acid. This reaction generates a localized pH change, which causes, because of a volume change in the pH-sensitive hydrogel, the release of the entrapped insulin. GOx has been immobilized on a wide variety of polymers and hydrogels (32). Because the sensing is based on an oxidase, the pH change of the GOx-based hydrogel is limited by the oxygen level. Therefore, to improve the hydrogel’s performance, catalase has been incorporated into the polymer matrix along with GOx. This enzyme regenerates oxygen from hydrogen peroxide while at the same time reducing the levels of toxic hydrogen peroxide.

Zhang et al. reported an example of such a polymer in which GOx and catalase were entrapped in an ethylcellulose membrane with dispersed poly(*N*-isopropylacrylamide-*co*-methacrylic

acid) nanoparticles (33). In this system, the local pH decrease caused by the oxidation of glucose by GOx results in the collapse of the nanoparticles, permitting the diffusion of insulin through voids in the membrane. The rate of in vitro insulin delivery by this membrane at physiological pH presented a 6-fold increase when the glucose concentration changed from 50 to 400 mg/dL (2.8–22.2 mM). Further optimization of this system is required for reproducible insulin release, quicker response times, and elimination of passive insulin release at physiological glucose levels, the latter being the major limitation of this approach due to the potential risk of hypoglycemic episodes. Problems encountered with smart polymer drug release systems include passive drug release, nonphysiological working pH, nonreproducible drug release, slow response time, biocompatibility, and limited lifetimes.

Responsive therapeutic devices should revolutionize medicine by enabling individualized therapy.

Microfabrication

Microfabrication provides new opportunities for manufacturing responsive drug delivery systems. Given the desired small size of implantable devices, micromachining techniques will be essential. Although conventional silicon-based materials have been often used to microfabricate devices for *in vivo* applications, their general lack of biocompatibility is still an issue (34). To circumvent this problem, alternative nonconventional MEMS polymeric materials and coatings have been proposed to control surface hydrophilicity and minimize nonspecific protein adsorption (35).

As discussed earlier, one of the major drawbacks of biosensors is their limited *in vivo* lifetimes, caused by the labile nature of biosensing reagents, mostly enzymes or other proteins, at body temperature; thus, they are not active for long periods of time. The limited lifetime of the bioreagents compromises a biosensor's service life. Likewise, the stability of an implanted drug can also be affected by *in vivo* conditions. Microfabrication may provide a solution to these problems in the form of microreservoirs capable of storing the active drug or the sensing reagent(s) in either solid or liquid form. Conventional MEMS materials and techniques allow the size, shape, volume, and surface characteristics of these drug delivery components to be tailored (36). Incorporating microactuators as valves along with microreservoirs permits drug release at desired times.

One example of this type of drug delivery system is a microchip-based device that delivers nanoliters of chemical substances from sealed, individual reservoirs (Figure 3). Madou first introduced this microreservoir concept in 1994 (37), and Langer used it in the form of a microchip (38). The release mechanism is based on electrochemical dissolution of a metal cover film that seals the microreservoir containing the chemical substance. These types of valves are commonly known as sacrificial valves. An array of individually addressable microvalves in the device allows for the delivery of multiple doses of drug in a controlled manner. Interestingly, sacrificial valves can also be used to protect sensing elements within microvials and to store solutions for calibrating the device *in vivo*. This approach would allow for the *in vivo* "unpacking" of sensors from individual reservoirs on an as-needed basis, such that, if an individual sensor fails, a subsequent one is activated by electrochemically removing the lid of the microvial that contains it.

A recent trend in microactuator chemistry is the development of soft hydrogel- and polymer-based miniature valves, which mimic natural muscle functions and are synthesized from monomers, such as 2-hydroxyethyl methacrylate, acrylic acid, or pyrrole, and are available on a microscale level (39, 40). However, most do not function at physiological pH, which is a significant obstacle. Our laboratory recently circumvented this problem by synthesizing a novel artificial muscle blend integrated with microreservoirs that can be electroactuated rapidly and reversibly at physiological pH (41).

As the size of drug delivery systems shrinks, the need for

smaller implantable batteries becomes paramount. Recently, two approaches for microbatteries that are $<100\ \mu\text{m}$ thick and have a cell area of $0.001\ \text{cm}^2$ have been developed. In one, a thin-film process is used to create a rechargeable planar battery containing zinc and nickel electrodes plus an electrolytic KOH reservoir on a chip. Ryan et al. reported a microbattery that delivered current densities of $>12\ \text{mA}/\text{cm}^2$ at $\sim 1.5\ \text{V}$ (42). In the other approach, Nathan et al. constructed a thin microelectrochemical energy storage cell in the form of a microbattery with a carbon anode, composite polymer electrolyte, and composite LiCoO_2 as a cathode (43). Kawata et al. demonstrated wireless recharging of implanted lithium batteries using near-IR light (44). The biotechnology company Quallion is dedicated to developing batteries

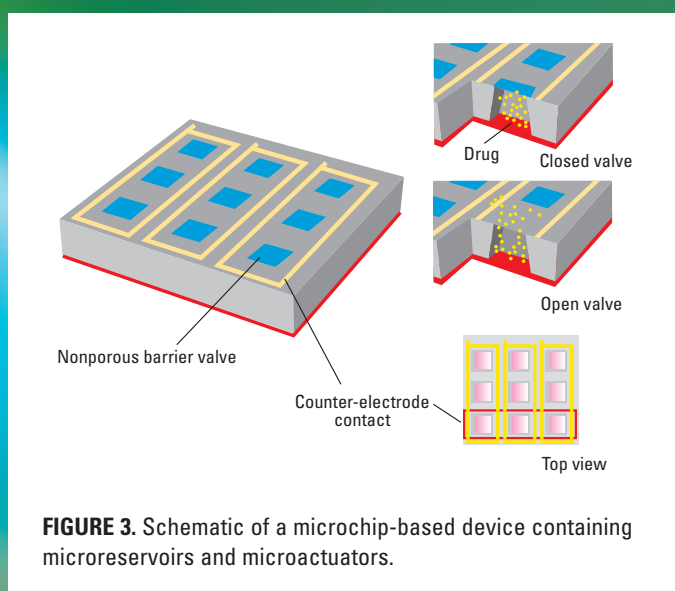


FIGURE 3. Schematic of a microchip-based device containing microreservoirs and microactuators.

that have long lives and are smaller and more lightweight. For example, an implantable, rechargeable, 2.9×13.0 -mm lithium battery constructed by Quallion has a lifetime of 10 years.

Telemetry

Telemetry is the wireless transmission of data, which has long been exploited in the military and aerospace industries and is now finding use in health-related applications. Telemetric systems have been integrated with implantable defibrillators, pumps, or retinal prosthetics. Collaboration between NASA Ames and the University of California–San Francisco led to the development of an implantable biotelemetry device (22 mm in length with an 8 mm diam) for monitoring intrauterine pressure changes, body tem-

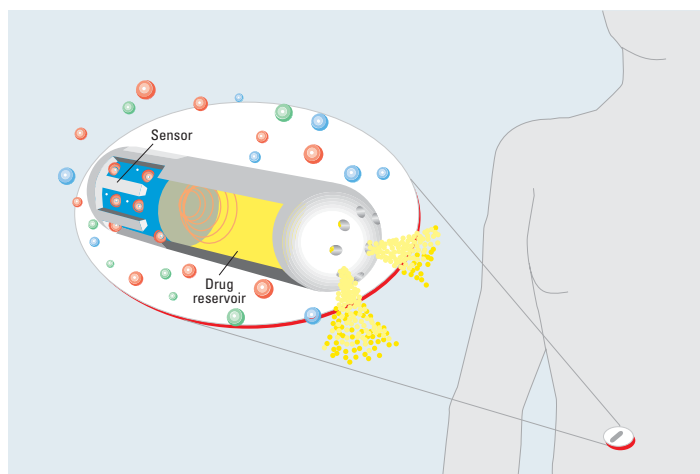


FIGURE 4. Schematic of an implantable responsive drug delivery system containing a sensor and delivery component.

perature, and the heart rate of a fetus (45).

Pill-sized wireless cameras and image sensors from Given Imaging are being used as endoscopic capsules. The patient swallows the camera capsule (30 mm long, 11 mm diam), which provides color images of the gastrointestinal tract as it travels from the stomach to the intestine. The image sensors combine the high-quality image of CCD chips with the advantages of complementary metal oxide semiconductor (CMOS) technology, such as low power consumption. CMOS image sensors also allow integration of several electronic functions, making it possible to develop smart pixel arrays. This device could incorporate sensing and imaging within a single unit and perhaps deliver a bolus of drug to locations identified by the sensors and imaging camera. A 100-fold smaller version of this technology may one day be designed as a “submarine” that can navigate to diseased cells and image and repair them, very much like in the science fiction movie *Fantastic Voyage* (46).

The Internet combined with wireless data transmission permits instantaneous transfer of data from the patient or laboratory to any other point in the healthcare system and has been an enabling factor in the field of telemedicine (47). This should prove useful in developing drug delivery devices with wireless data transmission to personal data assistants for either physician intervention or monitoring the device’s performance.

Future perspectives and challenges

An ideal drug delivery device should combine multiplex sensing and delivery in a closed-loop arrangement and be small, easily implanted and removed, long-lived, biocompatible, and inexpensive. It should be inert, mechanically strong, comfortable for the patient, safe from accidental release, easy to fabricate and sterilize, and allow high drug loading. Furthermore, it should permit discrete (i.e., at will) or continuous monitoring, have the capability of telemetric data transfer, and allow for physician intervention, if needed.

Patient compliance is an important factor in the effectiveness of conventional drug delivery. For example, doctors typically have difficulty frequently dosing elderly and mentally ill patients and children because they may not always comply with the drug delivery regimen. Also, current research on human circadian rhythms indicates a potential correlation between the time of day that a drug is administered to a patient and its effectiveness. Human circadian rhythm is the daily cycle that affects heart rate, oxygen consumption, hormone secretions, digestion, and other functions. A growing body of evidence suggests that chronotherapeutics designed around the circadian rhythm are more effective in disease management (48). For example, aspirin takes 2–4 h to reach peak levels in the blood. If a person could take an enteric-coated aspirin tablet at bedtime that would start to release a

few hours later, it may be more effective in preventing heart attacks that normally occur in the early morning.

Such control over drug delivery based on circadian rhythm is possible with responsive drug delivery systems. For example, the drug Covera-HS (Pharmacia), which is approved by the FDA for either hypertension or angina pectoris, is wrapped in a water-soluble “delay” coating (invented by Alza Pharmaceuticals) that disintegrates when exposed to gastrointestinal fluids over a 6- to 8-h period. When administered at bedtime, the coating allows very little absorption of the drug during the night. When the person awakes 8–12 h later, delivery of the drug from the reservoir begins, leading to effective and high concentrations of the drug in the plasma from 6 a.m. to noon (49).

We are collaborating with ChipRx to develop a microfabricated implantable drug delivery device that is loaded with the required drug and equipped with miniature valves and biosensors to regulate delivery (Figure 4; 50). The device will be small (e.g., the size of a match), comfortable, reliable, and easy to use. Subcutaneous implantation of cylinders of the proposed size and geometry is already common as an outpatient procedure for administration of birth control (e.g., the Norplant device) and only requires local anesthesia (51). The sensor is based on genetically engineered proteins that generate a signal in response to the binding of a target analyte. The magnitude of the signal is processed by control electronics and triggers, if needed, the opening of microvalves to release an appropriate dose of drug from microfabricated chambers. Each chamber can be individually addressed and controlled, and thus, the reagents could be stored lyophilized and reconstituted, as needed.

Incorporating telemetry in the device provides access to the sensor and delivery data at all times, ensuring that a physician can intervene during scheduled visits or remotely at any time. Alternatively, in cases of individuals who need to be continuously monitored for performance under high stress, the data can be accessed in a continuous manner from an ex vivo data

logger. We hope that the technology will also have applications in individualized therapy in numerous conditions and diseases in which current drug delivery approaches either do not exist or require substantial improvement.

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Sapna Deo, Elissavet Moschou, and Serban Peteu are postdoctoral fellows at the University of Kentucky. Deo's research interests focus on the development of sensing systems for physiologically important molecules, microfluidics, and design of smart polymers. Moschou's research interests include development of analytical sensors, design of microactuators for use in drug delivery systems, and micro total analysis systems. Peteu's research interests include micro- and nanoscale applications of bioanalytical sensors and smart polymers. Patricia Eisenhardt is a vice-president of ChipRx, and she is interested in the development of responsive drug delivery systems. Leonidas Bachas is a professor at the University of Kentucky. His research interests include electrochemical sensors, microfabrication, and the use of recombinant DNA techniques for new sensing architectures. Marc Madou is a professor of mechanical and aerospace engineering at the University of California—Irvine. His research interests focus on miniaturization science (MEMS and NEMS) with emphasis on chemical and biological applications. Sylvia Daunert is a professor of analytical and biological chemistry and pharmaceutical sciences at the University of Kentucky. Her research interest is at the interface between analytical chemistry, molecular biology, and bioengineering. An additional focus of her research group is the design of sensing arrays for detecting molecules in small volumes and the design and fabrication of miniaturized implantable responsive drug delivery devices. Address correspondence about this article to Daunert at Department of Chemistry, University of Kentucky, Lexington, KY 40506-0055 (daunert@pop.uky.edu).

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