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REVIEW

Clinical Applications of Biomedical Microdevices for Controlled Drug Delivery

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Abstract

Miniaturization of devices to micrometer and nanometer scales, combined with the use of biocompatible and functional materials, has created new opportunities for the implementation of drug delivery systems. Advances in biomedical microdevices for controlled drug delivery platforms promise a new generation of capabilities for the treatment of acute conditions and chronic illnesses, which require high adherence to treatment, in which temporal control over the pharmacokinetic profiles is critical. In addition, clinical conditions that require a combination of drugs with specific pharmacodynamic profiles and local delivery will benefit from drug delivery microdevices. This review provides a summary of various clinical applications for state-of-the-art controlled drug delivery microdevices, including cancer, endocrine and ocular disorders, and acute conditions such as hemorrhagic shock. Regulatory considerations for clinical translation of drug delivery microdevices are also discussed. Drug delivery microdevices promise a remarkable gain in clinical outcomes and a substantial social impact. A review of articles covering the field of microdevices for drug delivery was performed between January 1, 1990, and January 1, 2014, using PubMed as a search engine.

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Biomedical microdevices are fabricated devices with critical features on the order of 1 to 100 μm. These microdevices range in complexity from simple microstructures such as microchannels to more sophisticated microfunctional parts such as microtransducers and microelectromechanical systems (MEMS).[1]

These devices integrate mechanisms that activate a variety of physical signals to achieve a specific function. For example, MEMS-based inertial sensors transduce a mechanical signal input to an electrical signal response. Current transducers are able to combine multiple physical inputs with multiple output signals.

Biomedical microdevices present a variety of key advantages for applications in health care owing to their (1) extremely small sizes providing minimally invasive procedures, (2) low power consumption, (3) batch fabrication processes with high reproducibility, and (4) low cost per device, in conjunction with their multiple functionalities and compatibility with very large-scale integration electronics.

These novel technologies have accelerated the development of a variety of micromedical devices, such as catheter pressure sensors, microelectronic components for pacemakers, hand-held point-of-care diagnostic devices, and drug delivery systems, all of which have provided significant improvement over treatment possibilities for numerous chronic and nonchronic illnesses.[1-4] Figure 1 shows a variety of biomedical microdevices for several therapeutic applications.

Controlled drug delivery systems that are based on microdevices contain structural microparts, such as microchannels and microreservoirs, to store drugs. In addition, drug delivery systems based on MEMS incorporate microtransducers such as microactuators and microsensors, which improve the device capabilities.

Drug delivery devices based on MEMS provide an opportunity for improved diagnosis, monitoring, and treatment of numerous illnesses. The MEMS can deliver a variety of drugs, including drugs in combination, using a single device. The MEMS drug delivery devices have the ability to control the rate of drug release to a target area. They can be programmed for pulsatile or continuous delivery and can release the drug locally, which increases treatment efficacy using a smaller amount of drug, reducing systemic concentration levels[1-6] and associated toxicity.

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ARTICLE HIGHLIGHTS

- Drug delivery systems can be classified as passive and active. Passive devices do not incorporate sensors and actuators for drug delivery.
- Active microdevices include microelectromechanical systems (MEMS), which comprise microparts such as microchannels and microvalves and transducers, including microsensors and microactuators, integrated into a singular microdevice.
- Advantages of MEMS drug delivery systems include miniaturization, integration with microelectronics, actively controlled, low cost, multiple pharmacologic therapies in a single device, controlled over release rate, and in vivo long-term storage of drugs.
- The MEMS are being used for a variety of clinical conditions, including diabetes, neurologic disorders, inner ear diseases, and cancer.
- Fluzone is an example of a Food and Drug Administration–approved drug delivery microdevice for vaccine delivery.
- The MEMS drug delivery devices can be considered combination products. Many combination products are considered drugs, requiring a New Drug Application for Food and Drug Administration approval.

Finally, the scope of novel materials for biomedical devices has expanded the potential use of biocompatible platforms with high biological performance, eg, less toxic and nonreactive devices, enabling new therapeutic applications.

This review provides a summary of current state-of-the-art biomedical microdevices for controlled drug delivery and their corresponding clinical applications. The following sections describe passive and active delivery devices based on MEMS technology. Each section provides a technical description of a microdevice followed by its suggested clinical application. The review continues with a summary of the regulatory strategies for obtaining Food and Drug Administration (FDA) approval for such microdevices. Finally, a perspective on the future of these novel devices is presented.

DATA SOURCES AND SEARCHES

A PubMed search between January 1, 1990, and January 1, 2014, was performed. The search terms were *drug delivery* AND *MEMS*, *implantable devices* AND *MEMS*, *control release* AND *microchip, controlled release* AND *BioMEMS*, *neural probes* AND *drug delivery*, *vaccines* AND *microneedles*, *diabetes* AND *microneedles, intraocular* AND *drug delivery devices,* and *inner ear* AND *drug delivery* AND *microfluidics*. Papers were selected following the definition of microdevices and MEMS. Selection also was performed with the aim of having examples of different types of microdevices (passive and active, actuation mechanism, and materials). Examples of different clinical applications for drug delivery microdevices assisted in selecting papers more close to the clinical application than those focused solely on fundamental science. Diagnostic microdevices were specifically excluded from the search.

PASSIVE DEVICES

Passive biomedical microdevices for drug delivery do not rely on an actuation mechanism or on monitoring for feedback. These devices are reservoir based, relying on mass transfer across a permeable membrane to deliver pharmaceutical drugs, the biodegradation of a hermetic membrane, or a unique reservoir structure to achieve controlled release. The rate of release can be controlled by taking into account the following design parameters: (1) the effective permeability of the membranes by fine-tuning structural dimensions and materials (pore size, thickness), (2) the rate of degradation of the polymer contained on the membrane or in the reservoir, (3) the diffusivity properties of the drug, and (4) the osmotic pressure. Passive delivery of drugs cannot be modified after implementation. Other passive-release devices operate based on actuation resulting from in vivo conditions inside the body, such as pH or temperature, to accelerate degradation of the materials that encapsulate the pharmaceutical drugs. Typically, the controlled release is achieved by considering the pharmacokinetics of the selected drug for delivery. Design and material parameters are thereafter adjusted and selected during the design process to provide a constant and superior pharmacokinetic performance, such as an improvement in treatment efficacy duration over the typical half-life of the pharmaceutical drug. Existing passive-release devices, such as the fentanyl transdermal system (DURAGESIC; Janssen Pharmaceuticals Inc) and the fluocinolone acetonide intravitreal implant (Retisert; Bausch & Lomb Inc), are used for either short-term (3 days) or

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