

IMPLANTABLE MEMS DRUG DELIVERY SYSTEMS FOR ADMINISTRATION OF UNALTERED THERAPEUTIC AGENTS

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We have developed the first implantable intraocular microelectromechanical systems (MEMS) drug delivery device capable of being refilled for targeted intraocular delivery of therapeutic compounds in their unaltered format. In particular, this approach enables a practical drug delivery vehicle for treating difficult-to-reach diseases affecting the posterior segment of the eye.

Drug therapy intervention plays a major role in the management of many ocular diseases. However, precise delivery of pharmaceutical solutions to a specified target within the body is an ongoing challenge in many areas of drug delivery. Current routes of ocular treatment (topical, systemic or intraocular injections) have limited efficacy due to physiological barriers, potential side effects, and occasional patient compliance. Thus, a new paradigm for treatment ocular diseases using micromachined drug delivery devices is explored as an optimal means of pharmacologic management. Our intraocular MEMS drug delivery devices are refillable for chronic use and capable of controlled delivery of unaltered therapeutic agents. Only a single surgical intervention is required to implant the device following which long term operation with potentially fewer side effects is possible.

Manually and electrically-controlled device prototypes have been designed, fabricated, and tested (benchtop, *ex vivo*, and *in vivo*). Both systems share a common layout, containing a refillable drug reservoir and a transscleral cannula. The reservoir is implanted subconjunctivally, while the cannula is inserted through an incision into either the anterior or posterior segment. Placement of the tip of the cannula is determined by the desired site of therapy. A specific dose of medication is electronically dispensed from the device reservoir, directed into the eye via the cannula, and is released from the cannula tip. Once the drug is depleted, the reservoir can be refilled by injection using a 30 G non-coring needle with the same or alternate medication. Needles no larger than 25 G eliminate the need for sutures as the tissue is able to reseal following puncture. Repeated refillability is a key feature and enables prolonged use of the device up to several years.

The manually-controlled device also includes a check valve that prevents backflow of fluids into the drug reservoir. Drugs are dispensed through the pressure-sensitive valve into the eye when the reservoir is gently depressed by the patient. The simple manual format offers convenient rapid prototyping of functional drug delivery systems as surgical models for developing the surgical technique and assessment of biocompatibility. The electrically-controlled device includes an electrolysis pump that utilizes gas generation associated with electrolysis for intraocular drug delivery.

Reliability of the drug reservoir following multiple refills was confirmed in benchtop experiments and repeated refills were performed *ex vivo* (porcine eyes) and *in vivo* (rabbits). Bolus delivery was demonstrated in benchtop experiments and enucleated porcine eyes with the manually-controlled surgical models. Bolus and continuous dispensation (pL/min- μ L/min), with a fixed or variable rate, were also demonstrated with the electronically-controlled device. Flow rate was conveniently adjusted by varying the applied current (μ A-mA). In both systems, delivery of 25 μ L of phenylephrine solution (1.5%) was performed in rabbit eyes and resulted in a real-time physiological response (pupil dilation). Electrically-controlled devices were used only in acute experiments, however, the surgical models are being followed for a total of 6 months with periodic examination, color photography and fluorescein angiography. This is the first demonstration of physiological response to MEMS-based drug delivery. A new generation of drug delivery implants are currently being developed for treatment of glaucoma and retinitis pigmentosa.