DRUG DELIVERY

Pulsed polymers

Biodegradable polymers can now be used to fabricate microchip implants that release drug doses at predetermined times over many months.

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Recent advances in controlled-release technology — the design of materials or implants to release drugs or other compounds over time — are already affecting our daily lives. Examples in the marketplace include: time-release pills that reduce the number of doses required for medications such as pain relievers, anti-depressants and attention deficit hyperactivity disorder medications for children; contraceptive patches and implants; and even time-release fertilizer formulations that last for several months from a single application. Although these types of continuous-release systems are already quite successful, an area that still requires significant advances is the modulated (pulsatile) delivery of drugs. The work published in this issue by Robert Langer and colleagues is a significant advance in the ability to design polymer-based systems systematically and carefully to release accurate doses of drugs from an implant at predetermined times[1].

Pulsatile drug delivery systems are required for applications in which the continuous release of a drug would be detrimental and repeated dosing would be difficult, painful or otherwise problematic[2]. A key example is insulin delivery for the treatment of diabetes. For effective management, insulin release levels need to be generally very low but significantly elevated after meals. Additional examples of the desirability of pulsatile drug delivery include the delivery of blood-pressure medications and immunization boosters, and many hormone treatments. Pumps have been successfully used for pulsatile drug delivery and are now used for many diabetic patients[3]. However, these suffer from a number of limitations, most notably the need to run tubing across the skin, which produces pathways for infection. Completely implantable systems would reduce this risk.

The system proposed by Langer and co-workers[1] exploits the wide tailorability of biodegradation of the poly(lactic-*co*-glycolic acid) (PLGA) family of biocompatible polyesters (Fig. 1). By varying the relative amounts of lactic acid and glycolic acid in the copolymer and also the molecular weight of the copolymer, one can controllably and widely vary the degradation rate of the material[4]. To release bursts of drug at different times, several PLGA copolymers with different degradation rates were used as 'gatekeepers'. Each copolymer was designed to hold back a burst of drug until that particular membrane had degraded sufficiently to allow the drug to escape. With this system, Langer and colleagues were able to achieve pulsatile release of several types of 'model drugs' with different properties.

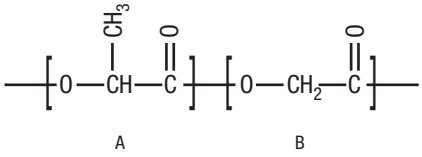

Figure 1 Poly(lactic-*co*-glycolic acid), or PLGA, is a random copolymer of lactic acid (portion A) and glycolic acid (portion B). These materials degrade in the body by the hydrolysis of ester bonds in the polymer backbone. By varying the ratio of lactic acid to glycolic acid and the molecular weight of the copolymer, one can widely vary the degradation rate of the materials.

The drug-delivery system is based on a microchip formed from poly(L-lactic acid), the most slowly degrading of this polyester family. Several reservoirs were indented in the chip surface; drug solutions were microinjected into the appropriate reservoirs, and then PLGA membranes of various compositions were formed to seal each reservoir (Fig. 2). Reservoirs could all contain the same drug, or multiple agents could be loaded into different reservoirs to release a variety of drugs from the device. One could envisage an implantable microchip that would release a battery of childhood immunizations at appropriate times. Such a system would be especially useful in developing countries, where routine access to medical care is difficult and thus booster immunizations are often missed. Furthermore, because the drug molecules are stored in a reservoir rather than suspended in the polymer formulation, this system should be compatible with a wide variety of drugs. For example, heparin — a common anti-coagulant that is hydrophilic — was shown to remain bioactive after incorporation into and release from this drug delivery system, even after 140 days. The superb performance of this new device, along with the long track record for safety and biocompatibility of the polymer materials used to fabricate the device, bode well for success in a variety of clinical applications.

The next advance in pulsatile drug delivery is likely to be systems in which release from an implant can be actively modulated, to increase or decrease dosing in response to demand. Ideally, such systems will eventually be coupled to biosensor devices so that drug delivery can respond to physiological cues in real time. The release of insulin from an implant could be tied to readings from a glucose sensor, thus providing tighter control over blood glucose levels and reducing the effects of diabetes. Drug release from polymeric systems could be controlled through externally generated

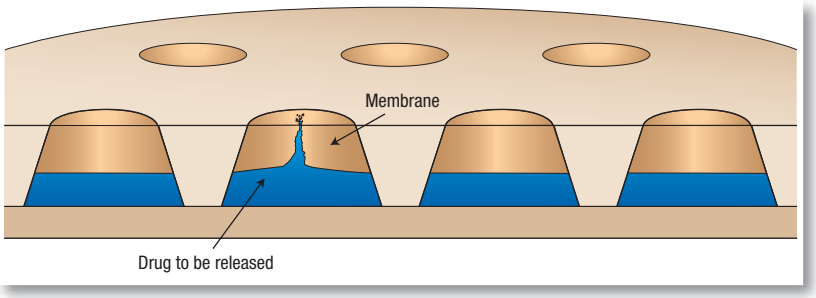

Figure 2 The polymer-based microchip drug-delivery devices designed to release many doses of drug over time[1]. The base of the microchip was made of a slowly degrading polymer, poly(L-lactic acid). Reservoirs were formed in the base, filled with drug solutions, and then sealed with polymer membranes. The composition of each membrane can be varied so that doses of drug are released at the desired times.

environmental changes such as magnetic fields, ultrasound, electric fields, temperature, light and mechanical forces. For example, polyanhydride materials undergo significantly enhanced bioerosion when exposed to therapeutic levels of ultrasound, resulting in a substantially elevated release of drugs incorporated into the polyanhydride matrix[5,6].

The ultrasonic energy can be safely applied from outside the body and can be generated with a small, portable probe. In another example, composites of thermally responsive polymers with nanoparticles that absorb in the near infrared have been shown to undergo marked phase changes in response to near-infrared light[7]. This might be useful as a drug delivery system that releases the drug upon external illumination from a light source similar in size to a laser pointer. These stimuli-responsive systems are likely to offer greater control and flexibility than systems based on inherent differences in polymer degradation, but they will also be more complicated and costly. The potential benefits of pulsatile dosing regimens for a variety of conditions should ensure a high level of interest in modulated drug delivery systems well into the future, and advances in materials science will significantly improve our capabilities in this field of drug delivery.

References

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