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products. He foresees the annual U.S. market for these systems approaching $300 million by 1991.

Another intriguing way to deliver recombinant drugs is nasally, a strategy being stressed by California Biotechnology Inc. (CBI, Mountain View, CA). The company has licensed its Nazdel™ nasal membrane permeation technology to Ortho Pharmaceutical Corp. (Raritan, NJ) for possible delivery of luteinizing-hormone-releasing-hormone. CBI has similar agreements with Hoffmann-La Roche for anti-obesity drugs and growth-hormone analogs, and with Eli Lilly (Indianapolis, IN) for recombinant human insulin. Nazdel works by coating the drug molecule with an adjuvant that allows it to penetrate the mucus membrane.

John Longenecker, senior scientist at CBI, reports that the company's major interest lies in delivering peptides that are less than 20 amino acids long. Still, the firm is looking at nasal delivery for proteins up to 20,000 molecular weight, although he is not sure what the upper limit will turn out to be. "A wide range of pharmacologically therapeutic peptides will be deliverable by the nasal route," he concludes.

One of nasal administration's major advantages is its convenience, Longenecker says. When a product must be self-injected by the patient—as is the case with insulin for diabetics—compliance becomes a serious problem. Also, adds Longenecker, nasal delivery "allows you to deliver the hormones in a pulsatory manner similar to in a healthy individual." Difficulties that CBI has overcome, he says, include formulation problems, reproducibility of dosing, and irritation of the mucus membranes. Alza's Zaffaroni criticizes nasal delivery, however, because the amount of mucus on a patient's nasal membranes might affect the uptake of drug. For this reason, Zaffaroni feels that other mucosal membranes—the mouth, rectum, and vagina—are more promising.

Even though the size of some recombinant peptides could make transdermal delivery difficult, Moleculon Inc. (formerly Moleculon Biotech, Cambridge, MA) is looking towards its Poroplastic® membrane technology to solve these problems. Containing 90–95 percent drug, the poroplastic matrix takes advantage of passive delivery to transport molecules with molecular weights as high as 5,000. According to Marsha Fanucci, director of business development at Moleculon, this means that the company is targeting hormones rather than larger biologicals like lymphokines. **—Arthur Klausner**

DRUG DELIVERY

PERFECTING POLYMERS TO RELEASE DRUGS

NEW YORK—In the future, drug release may be mediated by ultrasound. This is one of the potential advantages of the bio-erodible polymer technology for drug delivery developed by Robert Langer and his associates at MIT (Cambridge, MA). The technology, recently licensed to Nova Pharmaceutical (Baltimore, MD), augments Nova's existing license with MIT, which covers drug delivery to the brain to treat diseases such as brain cancer. Nova and Celanese (New York, NY) have formed a joint venture, NovaCel, to apply this technology to treating other cancers, infectious diseases, and cardiovascular and nervous system disorders.

Langer has developed bio-erodible polymers that degrade by surface erosion, in a nonhomogeneous manner. He says that the drawback of other types of bio-erodible polymers is that their homogeneous erosion loosens the polymer matrix; its permeability changes and the matrix eventually ends up "dumping the drug." He adds that erosion from the surface maintains the overall shape of the matrix. The incorporated drug is released at a constant rate, with zero-order kinetics.

Langer's polymers are polyanhydrides, which were originally synthesized to be used in textile fibers but were deemed unsuitable because of their hydrolytic instability. It is just this instability that makes them good candidates for drug release matrices, according to Langer. A polymer that is hydrophobic but has hydrolytically unstable linkages *will* erode heterogeneously. As it is hydrolyzed, a polyanhydride will degrade into its nontoxic acid monomers. As water is taken up, it hydrates the incorporated drug and initiates its release. The drug diffuses through pores that form as the polymer degrades. The rate of drug release can be controlled by chemical modification of the polyanhydride backbone; simple changes can alter the rate by 1,000-fold.

Langer has devised several methods to formulate the drug and polymer. The mixture can be compression- or injection-molded into small implantable cylinders or pellets; it can also be hot-melted into microspheres for injection. Langer says that injection-molding is the method of choice for controlled release because there is good correspondence between drug release and polymer degradation. This method does have a drawback: since the molding has to be done at a temperature above the polymer's melting point, it is possible that the drug will degrade or interact with the matrix. Although this is not a concern with many conventional drugs, bioengineered drugs—many of which will be polypeptides—*are* sensitive to temperature. The hot-melt method for producing microspheres suffers from the same limitations. Langer's group is now working on a system for making microspheres at temperatures around 25°C.

The polyanhydrides are biocompatable, non-mutagenic, and non-teratogenic. *In vivo* studies in rabbits and rats have confirmed *in vitro* observations that the polymers do release incorporated substances in a steady, controlled manner. Diabetic rats that received implants of insulin-containing polymer, for instance, maintained normal blood glucose levels during the implantation period.

While steady drug delivery is appropriate in many clinical situations, some conditions require "demand delivery." These include "an extra shot" of insulin to maintain a diabetic's blood glucose levels at mealtimes. Demand delivery would also be useful to control ulcers with gastric acid inhibitors and to alleviate respiratory distress with epinephrine.

Langer and co-workers have found that externally applied ultrasound can trigger drug release from these polymer matrices. Apparently, ultrasound enhances the erosion rate by causing the polymer to dissolve faster; water can enter the matrix more easily, and speed release of the drug. It may be that small bubbles form, breaking up the polymer.

Langer says that studies on the *in vivo* applications of ultrasound-mediated release are *very* preliminary, and have no clinical significance yet. Perhaps the greatest obstacle will be to determine the ultrasonic wavelength that degrades the polymer but does not destroy surrounding cells.

—Jennifer Van Brunt