Biomaterials Facilitate Medical Breakthroughs

FEATURE

by Jennifer Ouellette

Biomaterials has an exotic ring, but the design of materials suitable for use as replacements for damaged or diseased human organs or tissues has a long history of R&D. Polymeric sutures (absorbable and nonabsorbable), implant devices, polymer-based prosthetics, and metallic and ceramic implants are common applications today. And in recent years, new materials with unique properties have emerged with the potential for marked advances in areas such as artificial heart valves, controlled drug delivery, and tissue engineering.

Biocompatibility is the goal with polymers, metals, and ceramics

Most biomaterials for medical applications are based on common polymers, such as polypropylene, polycarbonates, polyurethanes, polysulphones, poly(ethylene terephthalate) and poly(ethylene ether ketone), as well as metals such as stainless steel and titanium. All these materials offer desirable properties for medical uses, including high tensile strength and stability; and polymers can be engineered for controlled biodegradation. However, such materials are not necessarily compatible with the human body. Medical catheters, guide wires, and stents are often made with materials that can cause potential complications, including bacterial infection, blood clots, and tissue trauma.

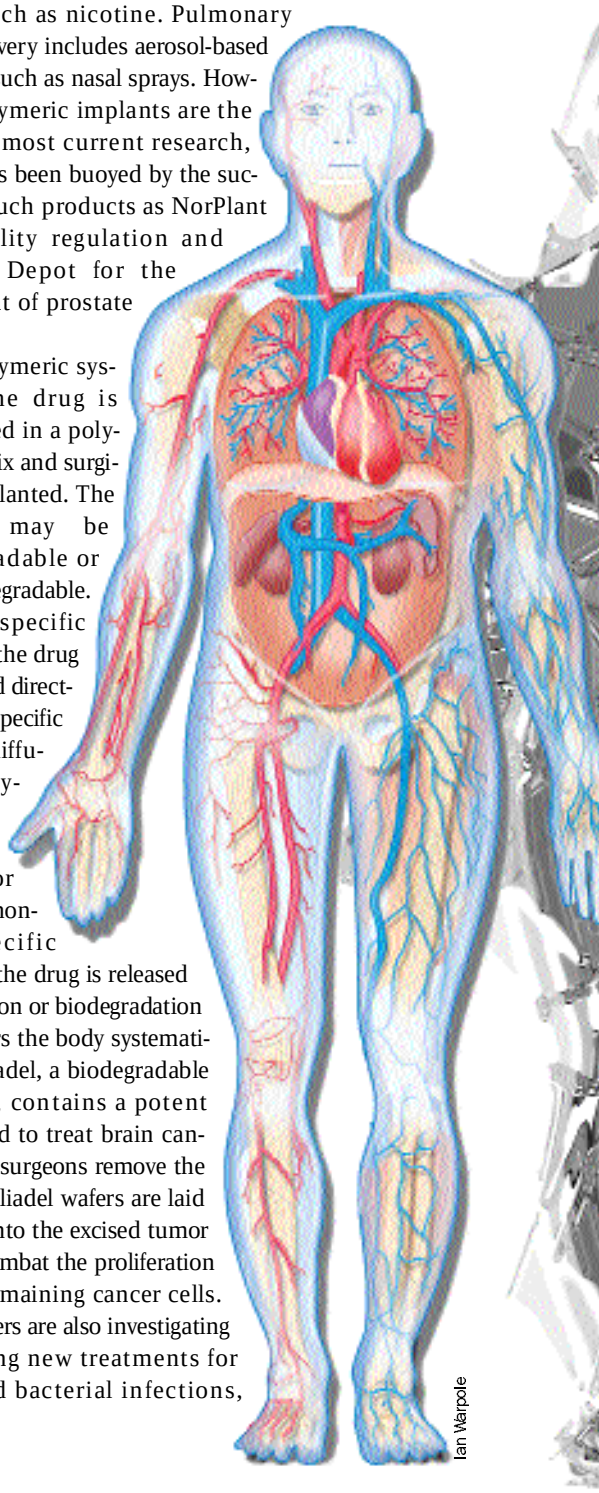
Thus, it is critical to modify material properties, through either the application of coatings or surface modification by the covalent attachment of bioactive molecules. Coatings can effectively address biocompatibility and its complications without changing the device's bulk material, says Susan Conroy, business manager of Advanced Surface Technology Products (ASTP) in Billerica, Massachusetts.

Most coating technologies use ultraviolet curing or solvents in the application process, which can, however, modify the material's structure and alter its properties. To address this materials problem, ASTP makes water-based, solvent-free coatings that can be customized to include drugs such as antimicrobials and blood thinners in controlled-release systems. They are also used to coat the outside of neurological catheters to improve maneuverability and reduce blood-vessel damage in the brain, and to coat intraocular lenses implanted in cataract surgery.

Drug delivery

Biomaterials for controlled drug delivery emerged in the 1970s, and there are now four basic modes. Oral delivery, the most common form, is used for many pharmaceuticals, including long-acting cold remedies. Transdermal systems deliver drugs through the skin by diffusion, although this technique is limited to small-molecule drugs such as nicotine. Pulmonary drug delivery includes aerosol-based systems such as nasal sprays. However, polymeric implants are the focus of most current research, which has been buoyed by the success of such products as NorPlant for fertility regulation and Lupron Depot for the treatment of prostate cancer.

In polymeric systems, the drug is embedded in a polymer matrix and surgically implanted. The matrix may be biodegradable or nonbiodegradable. For site-specific delivery, the drug is released directly into a specific area by diffusion, polymer degradation, or both. In non-site-specific delivery, the drug is released by diffusion or biodegradation and enters the body systematically. Gliadel, a biodegradable implant, contains a potent drug used to treat brain cancer. After surgeons remove the cancer, Gliadel wafers are laid directly into the excised tumor bed to combat the proliferation of any remaining cancer cells. Researchers are also investigating promising new treatments for viral and bacterial infections,



Ian Warpole

AIDS, birth control, and the delivery of dopamine into the brains of Parkinson's patients.

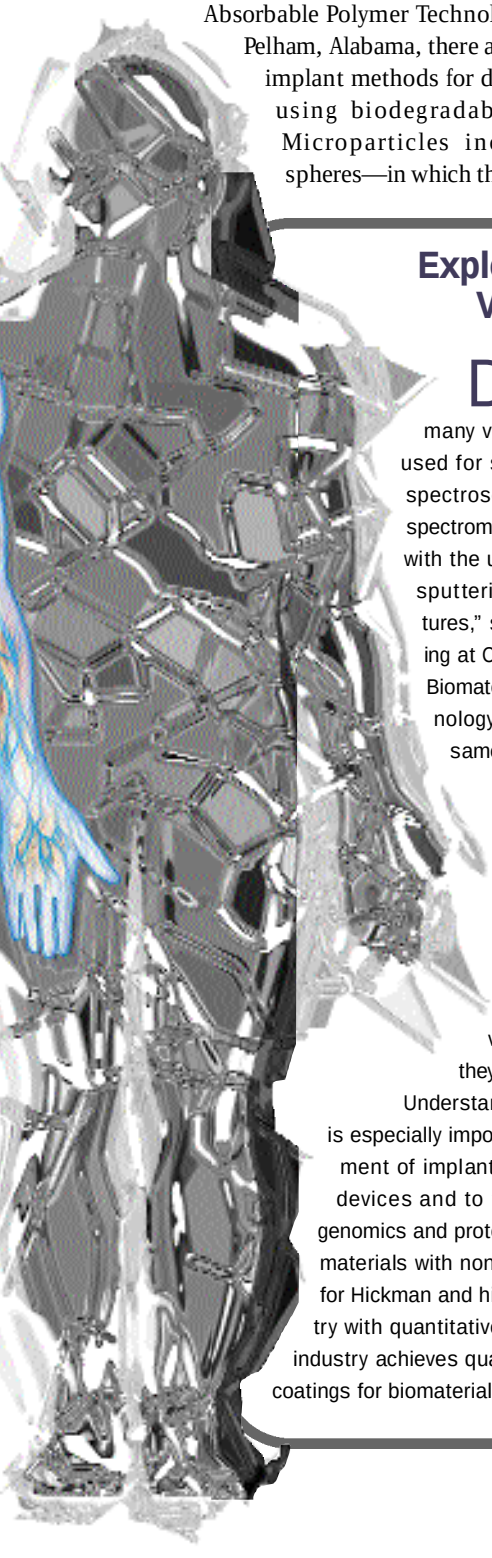
According to James English, president of Absorbable Polymer Technologies (APT) in Pelham, Alabama, there are two primary implant methods for delivering drugs using biodegradable polymers. Microparticles include microspheres—in which the drug is incorporated into a polymer matrix and released by diffusion and polymer degradation—and microcapsules, which have a controlling membrane as an outer sheath through which the drug diffuses. There are also solid implants such as Gliadel.

"By controlling the delivery of the drug, you get a release profile that is continuously controlled over a prolonged period of time that is neither toxic nor ineffective," says English. "Plus, it is a lot easier to have a single injection that lasts longer instead of multiple injections."

APT is currently assisting Guilford Pharmaceuticals (Baltimore, MD), which produces Gliadel, in developing a new class of biodegradable materials known as polyphosphoesters, initially targeted for drug-delivery applications. "No single material is a panacea," says English, and the continual development of new materials opens up new realms of potential properties to meet medical needs.

Medical devices

Biodegradable polymers are now used in more than 40 medical devices, English says, including surgical adhesives, screws, and clips, as well as fixation pins and rods. Potential future applications include bone plates, ear-vent tubes, and wound dressings. Global spending for implantable medical devices is about $120 billion a year. "Metals have been the mainstay for years, and there are still going to be application areas where you can't replace them with a



Exploring Interfaces with Vacuum Technology

Drawing on lessons learned by the electronics industry, biomaterials researchers are adapting many vacuum-based technologies, particularly those used for surface analysis, including X-ray photoelectron spectroscopy, scanning electron microscopy, and mass spectrometry. "The electronics industry was very involved with the use of vacuum technologies for analysis and for sputtering processes to create very fine heterostructures," says James Hickman, a professor of bioengineering at Clemson University and a founding member of the Biomaterials Interface Group of the AVS Science & Technology Society. "We are trying to apply a lot of those same techniques to biomaterials."

As its name implies, the group's primary objective is to understand the interfaces of biomaterials through surface analysis as a way to better address issues including biocompatibility. "The human body is exquisitely sensitive to surfaces," says Hickman. "So you have to characterize the surfaces of implants before they are implanted,and then observe them interact with various fluids and tissues in the body to see how they respond."

Understanding the surface characteristics of biomaterials is especially important as the industry looks ahead to the development of implantable microelectromechanical systems (MEMS) devices and to the next generation of bioinstrumentation for genomics and proteomics,which require the interaction of biological materials with nonbiological devices. However, the immediate goal for Hickman and his colleagues is supplying the biomaterials industry with quantitative descriptions of materials interfaces. Once the industry achieves quantification, it will be easier to develop improved coatings for biomaterials-based medical devices.

biodegradable polymer because of property requirements," says English. "But polymers are moving into more and more applications each year."

One common absorbable biomaterial is polylactide, which degrades to lactic acid, a natural metabolite that is ultimately converted into carbon dioxide and water. It and other biodegradable polymers are used in screws for reattaching ligaments in the knee and for biodegradable staples to replace traditional sutures. Polylactide has helped to eliminate adverse tissue reactions that sometimes occur with metal implants, and it ends the need for a second surgery to remove a metal implant, because the polymer gradually biodegrades once it has performed its function.

Absorbable sutures, the first commercial application of biodegradable polymers, entered the market in the 1960s, and innovations continue to be made in them. In England, researchers have adapted software for automatically embroidering decorations on garments to the repair of abdominal aortic aneurysms. The software uses data gleaned from computerized tomography scans to design and make a polyester patch for the damaged artery. The ultimate goal is to use the embroidery technology to create a framework for artificial organs using the patient's own cultured tissue, thus avoiding the rejection problems associated with transplant surgery. And last year, Tissuemed Ltd. (Leeds, England) launched a new surgical adhesive—composed primarily of porcine albumin, methylene blue, glycerol, and water—designed to reduce bleeding during surgery.

For highly demanding applications, such as insulation for pacemaker leads and long-term catheter implants, the choice of materials has been limited, says Mike Skalsky, managing director of Aortech Biomaterials (formerly Elastomedic) in Sydney, Australia. Such applications require polymers with excellent biostability, good mechanical strength, and high resistance to fatigue, abrasion, and tearing. Silicone rubber has been the material of choice, with polyurethane emerging in recent years as the principal alternative. For 10 years, Aortech researchers worked to devise a material that combines the best properties of silicone and polyurethane, a difficult task because the two are not normally compatible. They succeeded, and Aortech announced Elast-Eon polymers last year.

The initial target market for Elast-Eon is synthetic heart valves, approximately 150,000 of which are implanted annually worldwide. Existing synthetic heart valves are either mechanical, with a metal housing and carbon disks, or made from pig tissue. Although the mechanical valves are durable, patients require anticoagulants to prevent blood clots from forming around them. Tissue implants do not have this clotting problem, but they are not as durable.

"So for a long time, there has been a concerted effort to find new materials to make valves that would be both durable and not require anticoagulants," Skalsky says. The first clinical trials for a heart valve made with Elast-Eon are under way. The material is also in human testing for possible use in products such as coronary arterial grafts and orthopedic implants.

Biomaterials have already had an impact in ophthalmology, particularly in the implanting of intraocular lenses during cataract surgery. Researchers at Optobionics (Wheaton, IL) have developed implantable silicon chips for artificial retinas, which convert incident light into electrochemical signals to trigger any remaining retinal cells into processing images. Unlike other sight-saving implants, which are positioned on the retina's surface, the Optobionics chips sit behind the retina. The pin-sized chips contain about 3,500 microphotodiodes. They have been implanted into the eyes of three patients blinded by retinal disease, and plans call for three more patients to receive implants.

Looking to the future

For now, most commercial biomaterials research is focused on combining implant devices with targeted drug delivery. It would be, for example, more beneficial for patients if an adhesive or staple could both hold damaged tissue together and deliver an agent that promotes new tissue growth, or if an implanted medical device could also deliver an anti-inflammatory drug.

Coatings are a promising method for such applications. Biocompatibles, Ltd. (Surrey, England), has developed two drug-delivery/stent systems using coatings to deliver therapeutic agents to implantation sites. The technology is now in clinical trials to determine its effectiveness in fighting postimplant inflammation and other complications. NjeX Medical Systems, Inc. (Industry, CA), has achieved a technology breakthrough that may make delivering implanted devices easier. Its technique is simpler, more precise, and faster than those now used for implanting, and it requires less surgical skill. The implant is placed into a protective sealed cartridge, which is positioned at the implant site with a catheter. The cartridge then opens, releases the device, and is withdrawn, leaving the implant precisely positioned at the desired site. NjeX president James Elliott foresees the implant device as useful for emerging products such as gene-therapy implants, nanomechanical and electronic chip implants, and a variety of vascular and intraorgan stents.

Liquid-crystal elastomers are another promising class of materials for controlled drug delivery. Such materials are similar to those that form the basis of spider silk, and they combine the molecular mobility of a liquid with the solidity of a crystal. They can self-assemble into complex hierarchical structures and are also highly tunable. Their controlled degradation and good biocompatibility make them excellent candidates for the production of fine sutures, wound dressings, and woven or embroidered materials for prosthetics. According to David Knight, a zoologist at Oxford University in England, future applications of liquid-crystal elastomers include controlled drug-delivery implants, implantable biosenors, and artificial muscles. The materials can also be modified to have conducting or magnetic properties. Thus, they might one day be used as components in implantable microelectronic devices that would interface with living cells to repair the effects of nerve damage.

Tissue-engineered medical products (TEMPs) are among the most rapidly developing areas of research aimed at repairing, replacing, or restoring function to damaged or diseased soft or hard human tissue. Several such products are on the market, primarily for skin replacement. A range of TEMPs is under development, including cartilage and ligaments, heart valves, liver tissue, and insulin-producing pancreatic cells, all engineered from human tissue.

Nevertheless, the field is in its infancy, and Skalsky points out that researchers are still working to develop a deeper understanding of the cellular responses to engineered human tissue. In addition to the difficult technological and manufacturing hurdles, TEMPs face stringent regulatory barriers. Concerns over mad cow disease and tissue rejection have influenced public acceptance of animal tissue for this application. And the use of human tissue, including stem cells from embryos, is a source of considerable ethical controversy.

Larry Perry, who heads Pluris Research (Nashville, TN) sees the strongest market opportunities for biomaterials in the consumer applications, particularly in light of the high cost, long time to market, and inherent risk associated with cutting-edge R&D. "Tissue engineering, for example, is very complex, and those developments will take a very long time," says Perry. "People are now trying to take advantage of what we already know to target new consumer applications right now."