

Breaking through the Stent-Coating Process
New Coating Technology to Optimize Drug-Eluting Stents and Other Medical Devices
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According to the American Heart Association, heart disease is the leading cause of death in the United States, killing almost double the number of people that cancer, car accidents and AIDS kill combined.¹ For this reason, innovative therapies and devices to treat heart disease are in high demand.

In 2003, drug-eluting stents emerged as a breakthrough solution for Acute Coronary Syndrome (ACS), one of the many causes of heart disease. This technology was anticipated to use drug therapy to address the persistence of early restenosis with bare metal stents and injury to the vessel wall associated with traditional percutaneous coronary intervention (PCI) treatments, such as balloon angioplasties. Drug-eluting stents were rapidly adopted by physicians, accounting for over \$5 billion of the biomedical device market's annual sales in 2006.²

Recently, drug-eluting stents have been plagued by concerns about long-term product safety. Although the FDA issued a statement in 2006 stating that drug-eluting stents are safe, they noted recent data suggesting a small but significant increase in the rate of death and myocardial infarction possibly due to late stent thrombosis.³

Micell Technologies, Inc. has developed a unique, proprietary, multi-layered coating technology that can create drug-eluting coatings for medical devices with better uniformity, enhanced control over drug placement, morphology and elution, and improved manufacturing process control. These improvements have the potential to provide substantial clinical benefits to the next-generation of drug-eluting stents. The company partnered with the Commercial Equipment Group of Foster-Miller to develop an automated, commercial-scale manufacturing process to incorporate the new coating technology into drug-eluting stents faster and more effectively.

Current Challenges with Drug-Eluting Stents

Patients suffering from ACS have long been treated with percutaneous coronary intervention (PCI). By inserting a stent into an occluded or narrowed coronary artery to restore blood flow to the heart, doctors avoid exposing already vulnerable heart patients to invasive open heart surgery yet achieve the same therapeutic effects. Patients benefit from reduced surgical risk, faster recovery and a less painful procedure.

While first-generation bare-metal stents virtually eliminated many of the complications associated with abrupt artery closure after balloon angioplasty, issues with restenosis (or reblocking) of the stent persisted. While restenosis can occur through several mechanisms, most importantly it is thought to result from an inflammatory cellular response in the vessel wall that induces tissue proliferation around the angioplasty site. Although the rates were somewhat lower, bare-metal stents still experienced reblocking (typically at six-months) in about 25 percent of

cases⁴, necessitating a repeat procedure. Although drug-eluting stents have been successful in eliminating early restenosis, doctors have recently become concerned about the rising number of cases of patients experiencing complications from late stent thrombosis (typically years after stent implantation) with drug-eluting stents.

A number of factors including potential polymer/drug toxicity, physician placement, off-label use, and lack of compliance with anti-platelet therapy post-stent implantation, have all been considered as contributing factors to the recent increases seen in late stent thrombosis. In September 2006, the FDA released a statement regarding their position on the public's growing concerns with drug eluting stents. At the time of the statement, they defended their approval by stating they still believe DES are safe when used in patients that fit the same anatomic features as those used in the pivotal trials.

The clinical trials for both Boston Scientific's Taxus DES and Cordis/Johnson & Johnson's Cypher DES, currently the only two approved drug eluting stents on the market, performed the trials on a certain type of patient. These patients had only one untreated blockage in a single vessel. The positive results of this treatment led to FDA approved of Taxus and Cypher for use in the situations in the clinical trials. Many cardiologists today use these devices outside of the manufacture's label guidelines called "off-label" usage. Physicians often feel the patient with the higher risk is better served by newer devices that show less restenosis (DES). As the stents were placed in these off-label patients, the incidence of late stent thrombosis has grown.

In December 2006, the FDA held a public meeting of the Circulatory System Devices Advisory Panel, where they provided recommendations and comments, including, further studies must be done to insure the safety of the products, and both approved DES are associated with a small increase in stent thrombosis compared to bare metal stents that emerges 1 year post-stent implantation.

Now that the issues associated with TAXUS and CYPHER are being publicly addressed, there is a need in the market to create new DES that are more efficient and reduce the risks of drug-eluting stents. It was thought that the DES completely prevented restenosis, when in actuality; it seems to merely delay it .. Improved technologies that address thickness and uniformity of polymer coatings, together with control over drug morphology, elution and placement within the coating, will play an important role in the ability of next generation drug-eluting stents to address the current clinical challenges.

An Improved Coating Process for Improved Patient Care

Micell Technologies has created a unique, proprietary, multi-layered coating technology that is designed for delivering advanced therapeutics to the surface of medical devices, and has the potential to create clinically superior next-generation drug-eluting stents.

First, Micell's patented process can create coatings that allow for independent placement of multiple drugs into microenvironments inside the surface coating of devices. This feature enables the drug to be "dialed-in," meaning that the distribution of the drug in the coating can be manipulated to control the elution profile.

In addition, multiple drug combinations, such as anti-restenosis and anti-coagulant therapies, can be added in a single drug-eluting stent, providing the opportunity for sequential therapies and potential improved clinical efficacy.

Using benign supercritical fluids, Micell's technology provides a more gentle coating process that does not expose drugs to harsh environments. Entirely dry and solvent-free, Micell's technology uses moderate temperatures to retain the structure, morphology and potency of therapeutic agents. Additionally, more uniform, flexible and adherent polymer coatings can be created using Micell's solvent-free system due to the elimination of lengthy drying times and lack of exposure to harsh solvents.

Lastly, Micell's unique process reduces exposure to potential solvent hazards and minimizes disposal issues related to hazardous waste.

Keeping Manufacturing in Mind

While the features of Micell's stent-coating process were designed to facilitate improved clinical efficacy and safety in the next-generation of drug-eluting stents, a feasible manufacturing process was essential to enable commercialization of this technology. For this reason, Micell partnered with the design and engineering firm Foster-Miller early in the development process so that manufacturing needs would be considered from the initial stages of the project.

Combining Micell's expertise with Foster-Miller's engineering, materials and manufacturing know-how created a powerful team and a wealth of information about regulatory and quality standards, emerging technologies and manufacturability. This reduced the risk of designing an unmanufacturable device, or one doomed to regulatory failure, and facilitated the development of an efficient, novel process.

Foster-Miller capitalized on several unique features of Micell's technology to design a proprietary manufacturing process that can coat one or more stents in less than five minutes. The homogenous, unidirectional process developed by the Foster-Miller – Micell team decreases production time and streamlines operations, accelerating product time-to-market and offering advantages in terms of manufacturing throughput and associated costs.

Process control is also enhanced in this proprietary system, allowing the coating process to be monitored and measured at multiple points. The drug dosage can be metered in real-time to maximize the quality and consistency of drug placement.

The companies' partnership created a seamless transition from design to manufacturing, moving the project from the laboratory to a process platform that could support pre-clinical and clinical trials, and ultimately commercial product manufacturing. Foster-Miller also helped its partner secure intellectual property protection by assigning Micell all rights to the manufacturing process.

Looking to the Future

Preliminary data suggest that Micell's unique drug-eluting stent technology may provide improved clinical benefits to ACS patients. Although coronary drug-eluting stents has been targeted as the first application for Micell's proprietary technology, the process' flexibility promises future applications. The technology can be applied to a variety of combination devices, and is compatible with numerous drugs and a wide range of durable and bioabsorbable polymers. Small molecules, peptides, proteins, hormones and other heat sensitive agents can be used with Micell's proprietary process, providing new therapeutic options for drug-eluting coatings. The next applications may include drug-eluting orthopedic devices and novel drug-delivery systems.

In the competitive medical market, drug coating will continue to be an important part of creating more effective, safer medical devices. Micell's unique coating process offers significant advances in technology and has the potential to redefine surface modification of medical devices using drug-eluting coatings.

About the Authors

Robert R. Andrews is medical division manager for the commercial group at Foster-Miller Inc., a QinetiQ North America company. He has 30 years of medical device experience managing product development and operations. He has 11 issued U.S. medical device patents. He received an MBA from Bryant College and Bachelor's and Master's degrees in plastics engineering from The University of Lowell. He can be contacted at (781) 684-4639 or randrews@foster-miller.com.

James B. McClain serves as Chief Technology Officer and is one of the co-founders of Micell Technologies. Jim has been recognized for his work with supercritical fluids with prestigious awards including a 2000 International Messer Innovation Award, the 1997 Presidential Green Chemistry Challenge Award with Micell co-founder Joseph DeSimone and the 1998 and 2006 R&D 100 Awards in collaboration with scientists at Pacific Northwest National Laboratory, managed by Battelle. He has published many articles in leading scientific journals including Science, Nature, and the Journal of the American Chemical Society, and is listed as author on more than fifty U.S. patents.

Jim holds a B.S. in Chemical Engineering from Lehigh University in Bethlehem, Pennsylvania, specializing in Polymeric Materials Engineering. He also attended the University of North Carolina at Chapel Hill, North Carolina, receiving his Ph.D. in Chemistry on the characterization of polymeric materials and surfactants dissolved in supercritical fluids. He can be contacted at (919) 313-2111 or jmclain@micell.com.

About Foster-Miller

Foster-Miller, Inc. is a technology and product development company with an international reputation for delivering and supporting innovative products and systems that perform under the most demanding conditions. The firm was founded in 1956 by three graduates of MIT who believed there was a need for a company that could solve clients' difficult technical problems through first-class analysis and design. Today, after thousands of successful programs, Foster-Miller continues to meet the most challenging needs of its military, government and commercial

clients. Foster-Miller is certified to Aerospace Quality Management Standard AS9100 and ISO 9001. The commercial Equipment and Eletronics and Electrical Engineering groups are certified for ISO 13485. Foster Miller also has SW-CMM Level 3 software certification from the Software Engineering Institute at Carnegie Mellon University. In November 2004, Foster-Miller became an independent, wholly owned subsidiary of QinetiQ North America part of QinetiQ Group plc, one of the world's leading defense and security technology companies. For more information, please visit www.QinetiQ-NA.com or www.foster-miller.com.

About Micell

Micell Technologies is a privately held, early-stage biomedical company dedicated to applying its unique surface and polymer modification technologies for improved patient benefits and accelerated product development for medical device and drug delivery applications. The Company's patented processes and methods for medical device surface modification using supercritical fluids are focused on improvements to current polymer based drug-eluting technologies. To learn more, please visit www.micell.com.

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