SurFACTS in Biomaterials

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Nanoscale Thermo-Mechanical Analysis of Biomaterial and Polymeric Surfaces

By Steven Goodman, 10H Technology Inc.; Khoren Sahagian, Anasys Instruments Corporation; Andy Hung, Boston Scientific; Roshan Shetty, Anasys Instruments Corporation

The Anasys Instruments Corporation Vesta is a novel instrument that uniquely measures the surface thermo-mechanical materials properties of medical polymers, coatings, drugs, and devices via Local Thermal Analysis (LTA) and Transition Temperature Microscopy (TTM). LTA and TTM assess thermal materials properties similar to conventional bulk thermo-mechanical analysis (TMA), but unlike TMA or DSC (differential scanning calorimetry), measurements are obtained on any identified specific region of a device. Thus, LTA and TTM uniquely enable the spatial imaging of thermal material properties. Thermal property measurement provides information on MW, crystallinity, drug component mixing, and can provide insight into mechanisms of localized degradation, wear and/or failure of devices after testing or following clinical use.

The Vesta Instrument incorporates a micro-machined inverted pyramidal thermal probe that is fabricated on an AFM-like (atomic force microscope) cantilever. Users locate regions of interest using the Vesta's integrated optical microscope, and the Vesta then automatically engages the 30 nm radius thermal probe into contact with the sample surface. The Vesta thermal probe then rapidly heats up to a user-determined maximum temperature as high as 450°C, while monitoring the probe vertical position. This generates a Local Thermal Analysis (LTA) measurement. With most materials, as the probe

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From the Editor

I draft this a few weeks after a very successful BioInterface meeting and shortly after a midterm national election. Both may have a profound effect on our industry.

My perception of the mood of this year's BioInterface attendees was that, "while we never fell as deep as some other sectors, we are now in the beginning of a rebound." This optimism was a substantial improvement since last year's meeting. BioInterface 2010 attendees appeared to have renewed excitement about the promise of better materials and coatings for improved medical devices. They were excited about new and more powerful surface analysis instruments to develop these devices, and they were hopeful for sufficient economic stability within their companies to enable the advancement of these technologies towards commercialization and thence to patients.

But I now am concerned. Certainly the (US) national and global economic environment is not great, but it is better than it was at last years meeting, and certainly there are concerns within our industry regarding the timing of future economic recovery. However, in this regard, my concern is with the

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What's Inside

From the Editor
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By Steven L. Goodman, Ph.D., 10H Technology Corporation

uncertainty that will prevail with a divided Congress: will this lead to slower growth, both technically and economically? While I am discussing the USA, this of course has global effects.

I see the problem of uncertainty propagating from a divided congress in 3 major areas: a) Health Care Reform, b) Medical Device (FDA) Regulation, and c) Small Business Innovation Research (SBIR) development funding. I will briefly address these in turn:

Health care reform is certainly a hot issue. With a divided Congress it is not clear what will happen to the major remake of health care that is now US law, but a very complex law that has been only partially interpreted and implemented. Even before the election it was unclear how issues related to medical devices, for example, would be covered. With the implementation of health care reform now thrown into doubt, it is even less clear whether businesses will invest to bring new products and devices to market when reimbursement for these technologies is now more uncertain.

As previously reported in SurFACTS 15:3 (May-June 2010) the FDA is preparing for a substantial reform to the 510(k) regulatory path. For those who attended the final part of the BioInterface 2010 meeting held at the Georgia Institute of Technology, there was an excellent video presentation and discussion by Angela Krueger of the Office of Device Evaluation, Food and Drug Administration. Her presentation was entitled, "Recommendations for Changes to the 510(k) Program" and at least to these ears, there appears to be reasonable consensus for the need for some reform. What is not clear is if the midterm election results can or will alter any of these proposed regulatory changes. My concern is how this uncertainty with regard to regulatory changes may affect product development decisions, since it is often safer to sit and wait until the path is certain.

The third item to address is the Small Business Innovation Research or SBIR/STTR program, which I last discussed in SurFACTS 14:4 (July-August 2009). We all want job creation, and as I have previously discussed, the SBIR/STTR program has been a superb investment in creating technology job growth with 28 years of success. Well, the SBIR reauthorization bill is still stalled, having seen its **9th** continuing resolution to keep it going *only* until January 31, 2011. For most of its history, the SBIR program has received bipartisan support. However, with Congress leading to further anticipated gridlock, and with the electoral loss of one of the major proponents for reauthorization, Sen. Russ Feingold, it is not clear if stability will ever return to this program. As a reminder, the SBIR program has directly and indirectly created or supported entire segments of the medical device industry by providing seed and development grant funding. Examples include many medical device coating technologies and several analytical instruments used regularly by SurFACTS readers. Perhaps the one hope is that both political parties are talking jobs creation, and small businesses and the SBIR program certainly have an excellent track record in this area.

I close this editorial wondering about how uncertainty can produce an absence of change. Yet as an eternal optimist, I am hopeful that we can drive change in the right direction for the betterment of our industry, the economy and for patients. I will do what I can to inform and educate my representatives. I hope you will too.

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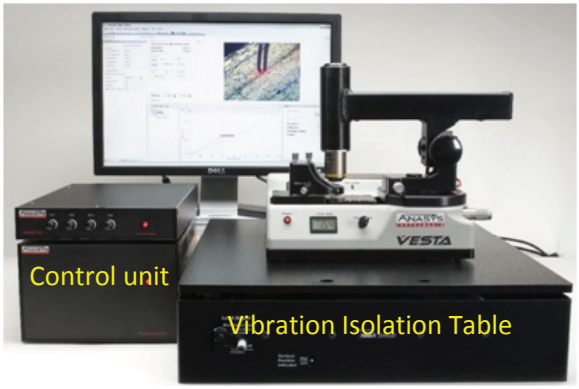
is heated the specimen first expands and moves the probe tip up. As heating continues the specimen softens at its Tg or Tm, and the tip will then begin to move into the specimen. A typical LTA temperature versus height deflection curve is shown in Figure 1. Multiple individual LTA measures may be automatically generated into a Transition Temperature Map (TTM) or micrograph of specimen areas of tens to thousands of square microns.



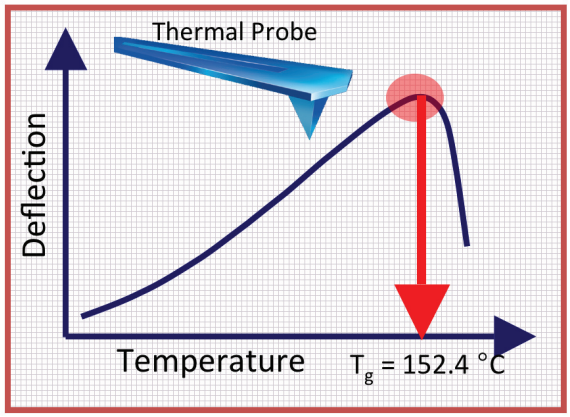


Figure 1: The photo shows the Vesta components. A drawing of the pyramidal thermal probe is shown inset into a typical LTA plot showing thermal expansion (vertical deflection) of the probe followed by probe penetration at Tg.

Example 1 – Contact Lenses

Two unused hydrogel contact lenses of the same type but differing in refraction and date of manufacture were examined following rinsing in distilled water to remove packaging salts and after air-drying. Figure 2 shows that the Tg varied significantly between the two lenses. The -3.0 and the -3.5 power lenses had respectively, mean±sd Tg of 140.2±2ºC and 144.4±1.8ºC from 10 separate LTA measures of each lens in various locations. Each lens was quite consistent in its own thermal properties, yet the two lenses did not have the same Tg.

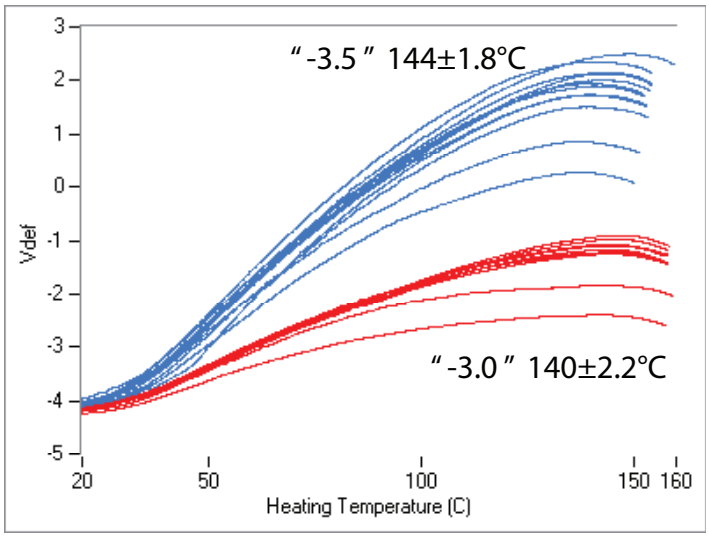


Figure 2: LTA analysis of two contact lenses differing in refractive index. LTA for the -3.0 lens (red curves) has a statistically lower Tg than the -3.5 lens (blue curves). Moreover, the (uncalibrated) thermal expansion (V def) of the -3.0 lens is also lower.

The ~4ºC difference in Tg between the lenses suggests a small difference in the MW of the polymers, other chemical components, and/or slight differences in the fabrication protocols for these two similar lenses. The relative heights (Y-axis: V def) of the two sets of LTA curves indicates that the lenses also differed in thermal expansion coefficients, albeit the level of deflection was un-calibrated in this study; hence, it is plotted as Vdef (Voltage deflection). These measurements indicate that the surface Tg and thermal expansion of two contact lenses of the same type nonetheless differed significantly, thus suggesting unexpected differences in polymer structure and/or chemistry.

Example 2 - Polyurethane Stress Corrosion Cracking

The problem of environmental stress cracking (ESC) of polyurethane pacing lead degradation due to in vivo free radical and lysozymal enzymatic remains problematic since it is difficult to predict or detect until severe surface cracking occurs or it manifests in device failure. In general, the benchmark earliest detection is made via Scanning Electron Microscopy (SEM).

In the present study, polyurethane pacemaker leads were treated in vitro to mimic environmental stress corrosion degradation. Leads were tied with a ligature that applied a steady 250 g pulling force while soaked continuously in 0.1 M CoCl2 and 20% H2O2 at 37°C for up to 1 month, with reagent me-

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Implantable Silk Metamaterials Could Advance Biomedicine, Biosensing Tufts University

From NewsRx.com

Researchers at the Tufts University School of Engineering and Boston University have fabricated and characterized the first large area metamaterial structures patterned on implantable, bio-compatible silk substrates.

The research, reported online July 21, 2010, in the journal Advanced Materials, provides a promising path towards the development of a new class of metamaterial-inspired implantable biosensors and biodetectors.

Metamaterials are artificial electromagnetic composites, typically made of highly conducting metals, whose structures respond to electromagnetic waves in ways that atoms in natural materials do not. The most futuristic metamaterials would absorb all light, to create heat to destroy cancerous tissue, or bend light completely around an object, rendering that object invisible – an imaginary delight for fans of science fiction or spy novels.

"However, the real power of metamaterials is the possibility of constructing materials with a user-designed electromagnetic response at a precisely controlled target frequency. This opens the door to novel electromagnetic behaviors such as negative refractive index, perfect lensing, perfect absorbers and invisibility cloaks," explains Tufts Professor of Biomedical Engineering Fiorenzo Omenetto, who led the research team. Omenetto also holds an appointment in the Department of Physics at Tufts School of Arts and Sciences.

The team focused on metamaterial silk composites that are resonant at the terahertz frequency. This is the frequency where many chemical and biological agents show unique "fingerprints," which could potentially be used for biosensing.

Small Antennas Act as One

The researchers sprayed gold-based metamaterial structures directly on premade silk films with micro-fabricated stencils using a shadow mask evaporation technique. Spraying the metamaterial onto the flexible silk films created a composite so pliable that it could be wrapped into small, capsule-like cylinders.

Silk films are highly transparent at THz frequencies, so metamaterial silk composites display a strong resonant electromagnetic response. Each fabricated sample was 1 square centimeter and contained 10,000 metamaterial resonators with unique resonant response at the desired frequencies.

According to Fiorenzo Omenetto, the research team likens the concept to "a very peculiar kind of antenna-actually, a lot of small antennas that behave as one. The silk metamaterial composite is sensitive to the dielectric properties of the silk substrate and can monitor the interaction between the silk and the local environment. For example, the metamaterial might signal changes in a bioreactive silk substrate that has been doped with proteins or enzymes."

The addition of a pure biological substrate such as silk to the gold metamaterial adds immense latitude and opportunity for unforeseen applications, says Professor Richard Averitt, one of Omenetto's collaborators from Boston University and an expert on metamaterials.

The resonance response could be used as an implantable electromagnetic signature for contrast agents or biotracking applications, says co-author Hu Tao, a former Boston University graduate student who is now a postdoctoral associate in Omenetto's lab.

In Situ Bio-Sensing

To demonstrate the concept, the researchers conducted a series of in vitro experiments that examined the electromagnetic response of the silk metamaterials when implanted under thin slices of muscle tissue. They found that the metamaterials retained their novel resonance properties while implanted. The same process could be readily adapted to fabricate silk metamaterials at other frequencies, according to Tao.

"Our approach offers great promise for applications such as in situ bio-sensing with implanted medical devices and the transmission of medical information from within the human body," says Omenetto. "Imagine the benefits of monitoring the rate of drug delivery from a drug-eluting cardiac stent, making a perfect absorber that can be implanted to attack diseased tissue by heat, or wrapping an 'invisibility cloak' around an organ to examine the tissue behind it."

Synthetic Polymer Mimics Antimicrobial Properties of Host-Defense Proteins

By Bob Michaels, Medical Product Manufacturing News

Bacterial infections caused by medical implants afflict tens of thousands of patients and result in upwards of 24,000 deaths each year in the United States. While silver has emerged as the antimicrobial material of choice, the precious metal also has its detractors. Among them is PolyMedix (Radnor, PA), which is developing a family of synthetic polymer antimicrobial agents that mimics the natural defenses of the human body.

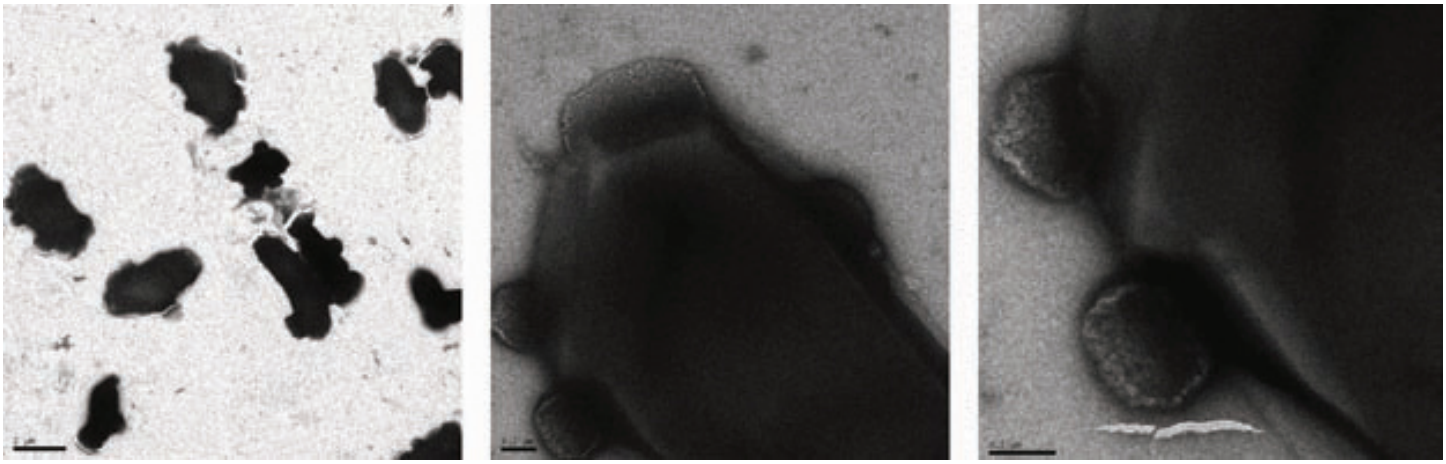
The company's PolyCide family of antimicrobial materials is active against hundreds of Gram-positive and Gram-negative drug-resistant bacteria and 399 kinds of staph bacteria, says Nicholas Landekic, PolyMedix's president, CEO, director, and founder. Consisting of fully synthetic compounds made from commercially available starting materials, the family includes three classes of agents: one-step methacrylate polymers synthesized from two commercially available prepolymers, two- or three-step polynorbornenes, and five-step phenylalkyne oligomers.

These materials mimic natural host-defense proteins, Landekic explains. Produced in all higher forms of life, host-defense proteins such as magainins and cecropins protect against bacterial infections. In humans, this role is played by defensins, amphiphilic peptides featuring both a hydrophobic and a spatially opposing hydrophilic face that can act selectively on bacterial cell membranes. It is this property that the PolyCide materials have been designed to mimic.

"Like host-defense proteins, the PolyCides can form pores in the outer layer of bacterial membranes, causing bacterial cell death by direct biophysical membrane disruption," Landekic says. "This process of direct membrane lysis is fundamentally different from most other antimicrobial mechanisms, which are biochemical in nature." This biophysical mechanism, he adds, reduces the likelihood of bacterial resistance.

The PolyCides are water soluble and heat stable to approximately 200°C. They can also be incorporated into materials by injection molding, extrusion, or solvent melt-casting processes. Capable of being mixed into a variety of materials—including PVC, polyurethane, silicone, PLGA, styrene, polysulfone, and polyester—the antimicrobials can either be incorporated into the substrate of the device structure itself or applied as a coating in a PVC, polyurethane, or similar carrier. "As long as the surface is accessible to the PolyCide polymer, the material can exert its antimicrobial activity," Landekic says.

Besides having different structures and mechanisms, silver-based antimicrobial agents and the PolyCide materials differ in several other respects. For example, while silver compounds require approximately 24 hours to kill bacteria, the PolyCides can accomplish this task in less than one minute, Landekic states. He adds that while silver acts poorly on biofilms, the PolyCides act rapidly in both disrupting



Scanning electron microscopy images show how PolyMedix's synthetic polymer antimicrobial agents disrupt the membrane of E. coli bacteria.

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Titanium Foams Replace Injured Bones

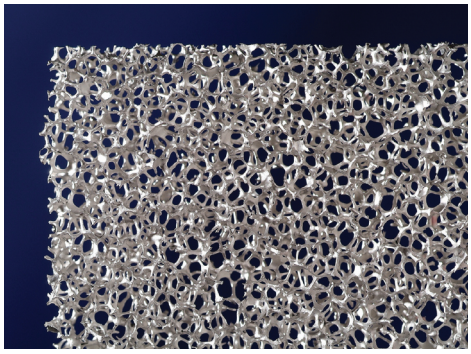
From ScienceDaily

Flexible yet rigid like a human bone, and immediately capable of bearing loads – a new kind of implant, made of titanium foam, resembles the inside of a bone in terms of its structural configuration. Not only does this make it less stiff than conventional massive implants, but it also promotes ingrowth into surrounding bones.

The greater one's responsibilities, the more a person grows. The same principle applies to the human bone: the greater the forces it bears, the thicker the tissue it develops. Those parts of the human skeleton subject to lesser strains tend to have lesser bone density. The force of stress stimulates the growth of the matrix. Medical professionals will soon be able to utilize this effect more efficiently, so that implants bond to their patients' bones on more sustained and stable basis. To do so, however, the bone replacement must be shaped in a manner that fosters ingrowth – featuring pores and channels into which blood vessels and bone cells can grow unimpeded. Among implants, the titanium alloy Ti6Al4V is the material of choice. It is durable, stable, resilient, and well tolerated by the body. However, it is somewhat difficult to manufacture; titanium reacts with oxygen, nitrogen, and carbon at high temperatures, for example, making it brittle and breakable.

There are still no established processes that can be used to produce complex internal structures. This is why massive titanium implants are primarily used for defects in load-bearing bones. Admittedly, many of these possess structured surfaces that provide bone cells with firm support, but the resulting bond remains delicate. Moreover, the traits of massive implants are different from those of the human skeleton: they are substantially stiffer, and, thus, carry higher loads. "The adjacent bone bears hardly any load any more, and even deteriorates in the worst case. Then the implant becomes loose and has to be replaced," explains Dr.-Ing. Peter Quadbeck of the Fraunhofer Institute for Manufacturing and Advanced Materials IFAM in Dresden. Quadbeck coordinates the "TiFoam" Project, which yielded a titanium-based substance for a new generation of implants. The foam-like structure of the substance resembles the spongiosa found inside the bone.

The titanium foam is the result of a powder metallurgy-based molding process that has already proven its value in the industrial production of ceramic filters for aluminum casting. Open-cell polyurethane (PU) foams are saturated with a solution consisting of a binding medium and a fine titanium powder. The powder cleaves to the cellular structures of the foams. The PU and binding agents are then vaporized. What remains is a semblance of the foam structures, which is ultimately sintered. "The mechanical properties of titanium foams made this way closely approach those of the human bone," reports Quadbeck. "This applies foremost to the balance between extreme



durability and minimal rigidity." The former is an important precondition for its use on bones, which have to sustain the forces of both weight and motion. Bone-like rigidity allows for stress forces to be transmitted; with the new formation of bone cells, it also fosters healing of the implant. Consequently, stress can and should be applied to the implant immediately after insertion.

In the "TiFoam" project, the research partners concentrated on demonstrating the viability of titanium foam for replacement of defective vertebral bodies. The foam is equally suitable for "repairing" other severely stressed bones. In addition to the materials scientists from the Fraunhofer institutes IFAM and IKTS – the Institute for Ceramic Technologies and Systems in Dresden – physicians from the medical center at the Technical University of Dresden and from several companies were involved in developing the titanium foam. Project partner InnoTERE already announced that it would soon develop and manufacture "TiFoam"-based bone implants.

Heal and Run – A New Stent M.O.

By Shana Leonard, Medical Product Manufacturing News

Now you see stents; soon you won't. That could be the case, at least, if bioabsorbable stents live up to their hype.

Since the first bare-metal stent was approved for use in the United States 15 years ago, stent manufacturers have been plagued by the problem of stent thrombosis. Potentially fatal, stent thrombosis occurs when a clot forms inside the stent—an adverse event for which the likelihood increases exponentially with implant duration. However, some researchers think that fully bioabsorbable stents could be the solution, especially to late stent thrombosis. The rationale: a stent can't cause clots if it no longer exists.

Recent drug-eluting stent designs have included a biodegradable polymer matrix that houses the therapeutic agent and degrades over time. Building on this concept—not to mention the success of resorbable sutures—researchers are developing drug-eluting stents that are fully metabolized and then absorbed into the body after serving their designated purpose.

Leading the charge is Abbott Vascular. About to expand into Phase II clinical trials, the company's Absorb coronary stent features a bioabsorbable polylactic acid backbone coated with an absorbable layer of everolimus drug. Although several other companies are working on the development of fully biodegradable or bioabsorbable stents, Abbott claims to be the only one that has long-term patient data. In its initial phase of clinical trials, the Absorb stent demonstrated efficacy in treating coronary artery disease and was fully absorbed by patients' bodies within two years. Furthermore, the study showed that there were zero instances of stent thrombosis two years after stent implantation and no new major adverse cardiac events.

"A fully bioabsorbable stent solves many of the challenges of metal stents. There is no metal left in the body that would impede future medical procedures—for example, if a new stent had to be inserted, there would be no metal in the artery blocking the way," notes Jonathon Hamilton, Abbott Vascular public affairs. "Also, when a metal stent is put in an artery, the stented portion remains rigid and immovable. Our two-year data in patients shows that our stent fully absorbs, and it leaves the vessel to expand and contract as if it never had a stent, allowing healthy, normal movement."

Abbott is currently hoping for a 2012 or 2013 product launch, although it has not yet specified a U.S. time frame. As with all devices, though, it's now a wait-and-see game as Abbott (and its competitors) awaits the more definitive answers to be gained in expanded clinical trials. There's no doubt that challenges lie ahead for the Absorb, like reducing absorption time and proving its worth against existing stents. However, if Abbott's bioabsorbable stent gets to market with the current statistics, it could be a game-changer for stent manufacturers and patients alike. Let's face it, a bioabsorbable stent is a disappearing act that has the potential to please any crowd.

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existing biofilms and in preventing the formation of new ones. Also, while silver compounds must leach into the bacterial cell, the PolyCides act on the cell surface. Finally, silver ions exhibit cytotoxicity that accumulates in body tissue. In contrast, the PolyCides are highly selective toward bacterial versus human cells, according to Landekic.

"Many types of medical devices—such as surgical sutures, catheters, intravenous tubing, implantable joints, bandages, and wound dressings—could benefit from our antimicrobial material," Landekic says. Like host-defense proteins, which have developed resistance to bacteria over hundreds of millions of years, the PolyCides offer broad resistance against bacteria, as evidenced by 18 sets of serial passage experiments and single-point mutation assays. Landekic concludes, "PolyMedix has thus learned from nature to mimic one of the oldest and most effective immune system defenses against bacterial infection."

NanoInk Releases Two New Nanoscale Applications in Biology for The NLP 2000 System

NanoInk, Inc.®, a global leader in nanolithography, announced today that it expanded the range of nanoscale applications for biology with the recent launch of two new Application Notes. NanoInk's NanoFabrication Systems Division instruments, most notably the NLP 2000 System, have now been proven to enable applications related to micropatterning of polyethylene glycol (PEG)-based hydrogel and UV-curable polymer. These new capabilities broaden even further the applicability of the NLP 2000 System for biological sciences. Earlier Application Notes described the benefits of using NanoInk's platform to functionalize biosensors, pattern functional hydrogels and print multiplexed protein arrays.

Launched in 2009 as a tool for bioscience research, the NLP 2000 System is a simple, user-friendly desktop nanolithography platform. The system leverages patented Dip Pen Nanolithography® (DPN®) technology to deposit sub-cellular-scale features of a wide variety of materials with nanoscale registry, all under ambient conditions. With the addition of two new Application Notes to its portfolio of biological research support materials, NanoInk continues to serve as a true partner to the life science community.

"The first of the new Application Notes demonstrates successful use of the NLP 2000 System for micropatterning PEG-based hydrogels," said Tom Warwick, NanoInk's general manager of sales and marketing. "Hydrogels are three-dimensional cross-linked polymer networks that have physical characteristics similar to those of natural tissues. The versatility of PEG chemistry and the excellent biocompatibility of PEG-based hydrogels have been instrumental in hydrogel advances related to controlled material release, directed cellular function, tissue engineering, and regenerative medicine applications. NanoInk has developed a consistent and reproducible methodology for directly depositing hydrogel precursors at defined locations on a surface and subsequently polymerizing these precursors to form PEG-based hydrogels."

The second new bioscience Application Note validates the utility of the NLP 2000 System for printing UV-curable polymers. Features generated by the NLP 2000 System have sub-cellular dimensions, so polymer arrays can be used to study cell/substrate interactions at the single cell level. Micro-patterned polymers are also useful in tissue engineering, lab-on-a-chip, flexible circuit and microlens applications. With DPN's ability to generate arrays that cover millimeter-scale areas with nanometer resolution and precision, the NLP 2000 System has been proven to print homogeneous and highly reliable polymer patterns onto smooth substrates like glass and silicon wafers.

NanoInk is dedicated to developing and supporting a wide range of biological applications for the NLP 2000 System. The latest two Application Notes further confirm this commitment. A full list of applications notes is available at: www.nanoink.net/biomaterials/literature.html#notes.

Zimmer Looks to Silver-Based Antimicrobial Technology to Thwart Biofilm Formation on Implants

Accentus Medical, a leading UK medical technology company that supplies advanced coatings and surface treatments to the medical device industry, announced today that it has signed a Licence and Services Agreement with Zimmer Holdings, Inc., a global market leader in musculoskeletal care. This agreement will enable the use of Accentus Medical's Agluna® anti-infective technology on a potentially broad range of Zimmer products.

Under the terms of the agreement, Zimmer will acquire exclusive global rights to utilize Agluna for joint reconstruction and trauma products. In addition, the company will have an 18-month option to acquire additional exclusive rights for spinal devices, dental implants and sports medicine products. As part of the agreement, there will be an initial period of further development of Agluna. Accentus and Zimmer will collaborate to secure regulatory approval for products treated with the Agluna technology in both the E.U. and U.S. Financial details of the agreement were not disclosed.

Agluna is a novel, patented surface modification technology applied to medical devices manufactured from titanium and its various alloys. The goal of the

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Medtronic Advances Research on Drug-Eluting Balloons for Coronary and Peripheral Artery Disease

Advancing research on drug-eluting balloons for the treatment of coronary and peripheral artery disease, Medtronic, Inc. (NYSE: MDT), today announced the latest results from the IN.PACT drug-eluting balloon (DEB) clinical program presented last week at the Transcatheter Cardiovascular Therapeutics (TCT) 2010 conference. The company also announced the start of a key clinical study of the IN.PACT Admiral (DEB) for the treatment of superficial femoral artery (SFA) disease.

During TCT's Drug-Eluting Stent (DES) Summit session on "Next Generation DES, Bioabsorbable Stents, and Drug-Eluting Balloons," interventional cardiologist Bruno Scheller, M.D., professor of internal medicine and cardiology at the University of Saarland in Homburg/Saar, Germany, presented six-month final results of the investigator-initiated IN.PACT CORO ISR study on coronary in-stent restenosis. Prof. Scheller also presented an overview of the FreePac technology and interim findings from the larger IN.PACT clinical program, which includes studies of both coronary and peripheral applications of the IN.PACT family of drug-eluting balloons.

"Based on a growing body of clinical data and while results of randomized trials are awaited, IN.PACT drug-eluting balloons show great promise for the treatment of both coronary and peripheral arterial disease," Prof. Scheller said. "The best potential applications appear to be in atherosclerotic leg vessels and for previously stented coronary arteries that have restenosed. Drug-eluting balloons may very well become the fourth therapeutic platform for cardiovascular interventions, joining traditional balloon angioplasty, bare-metal stents and drug-eluting stents."

IN.PACT drug-eluting balloons feature a proprietary, hydrophilic coating called FreePac that frees and separates paclitaxel molecules, facilitating their absorption into the vessel wall to mitigate re-narrowing of the artery over time. The IN.PACT clinical program consists of studies on the treatment of de-novo coronary lesions and coronary in-stent restenosis, as well as below-the-knee (BTK) and superficial femoral artery (SFA) disease. A combination of company-sponsored and physician-initiated studies, it will enroll a total of approximately 1,500 patients.

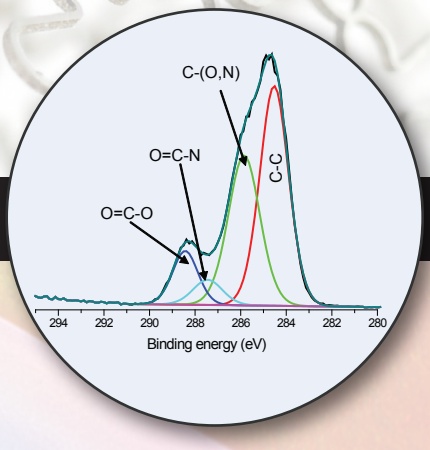
As part of his TCT presentation, Prof. Scheller highlighted IN.PACT CORO ISR, a single-center, single-arm confirmatory study of the IN.PACT Falcon DEB for the treatment of coronary in-stent restenosis conducted in 23 consecutive patients with a total of 26 lesions. The primary endpoint was late lumen loss measured by angiographic follow-up at six months. In the study, in-stent late lumen loss with the IN.PACT Falcon DEB was just 0.07 mm at six months, indicating a minimal degree of tissue growth inside the stented segment of the treated vessel.

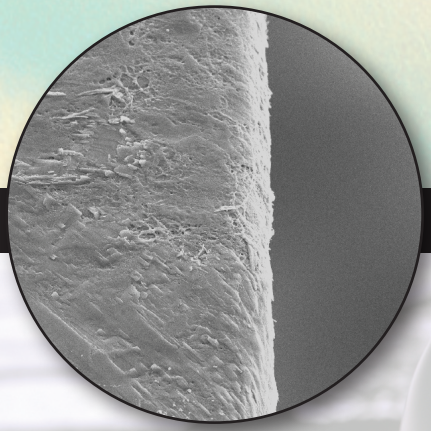
The newly-initiated IN.PACT SFA I trial is investigating the safety and efficacy of the IN.PACT Admiral paclitaxel-eluting percutaneous transluminal angioplasty (PTA) balloon catheter in the SFA compared to treatment with a standard PTA balloon. It will enroll 150 patients at up to 20 sites in Europe. The primary endpoint is clinically-driven target lesion revascularization (TLR, the need for repeat procedures) or restenosis (the re-clogging of an artery) at 12 months. Prof. Gunnar Tepe, M.D., chief of radiology at Klinikum Rosenheim in Germany, is the principal investigator. The first patient in the IN.PACT SFA I trial was treated earlier this month by Prof. Marianne Brodmann, M.D., and her team in the department of angiology at the University of Graz in Austria.

Data from this trial may be combined with those from the IN.PACT SFA II trial, which will be performed in the United States, to file for approval by the U.S. Food and Drug Administration (FDA). The IN.PACT Admiral DEB and the IN.PACT Falcon DEB received the CE (Conformité Européenne) mark in 2009 and are available in more than 100 countries around the world. They are not available in Canada, Japan and the United States.

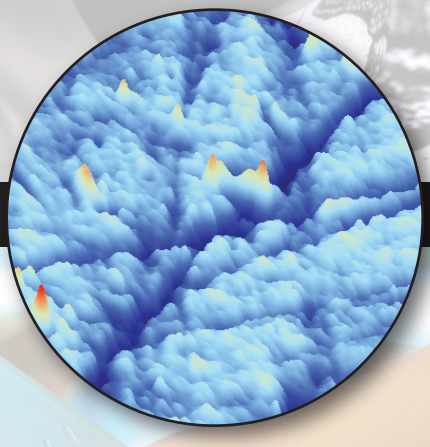
Specialists in Materials Characterization

XPS Spectrum of Hydrophilic Polymer Coating





SEM of Polymer Coated Stent



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DSM and DuPont Announce Joint Venture in Surgical Biomedical Materials

Royal DSM N.V. and DuPont have announced an agreement to form a joint venture to develop, manufacture, and commercialize advanced surgical biomedical materials. The agreement is pending European Union regulatory approval. The joint venture will be named Actamax Surgical Materials LLC. Under the joint venture agreement, DSM and DuPont will each share a 50 percent interest.

The joint venture, set to develop next-generation materials, will address the market for surgical sealants, adhesion barriers, and tissue adhesives. According to the companies, this is a large and underserved market of more than 100 million annual surgical procedures worldwide.

Actamax Surgical Materials LLC will build a comprehensive biomedical product portfolio based on several patent-protected biodegradable hydrogel technologies. The early technology development was completed utilizing DuPont materials science and biotechnology capabilities. Commercialization will rely on the medical polymer processing and manufacturing capabilities of DSM.

According to a joint release, the activities of the joint venture fit with the DSM biomedical materials portfolio in which the company, through its DSM Biomedical unit, has rapidly built a leading position in the past few years. Actamax Surgical Materials LLC is a strategic component of the DuPont Applied BioSciences business, which integrates biotechnology with other sciences to create products that can transform large, addressable markets. The joint venture will focus on the clinical validation of the products and technology, and commercialization will include manufacture and sale of proprietary products as well as the establishment of joint development relationships with leading device companies.

"The cooperation with DuPont is a great way to furthear boost our activities in the biomedical field," said Christophe J. Dardel, president DSM Biomedical. "In line with our open innovation strategy, this will allow us to combine the strengths of two leading companies to develop solutions to better address patient needs through material innovations."

"Our platform of technologies will offer physicians and patients improved outcomes of surgery that will prevent postoperative complications while reducing health care costs," said John Ranieri, vice president DuPont Applied BioSciences. "Actamax will deliver a number of products that can be optimized for different surgical situations and clinical needs. The success DSM has had in the biomedical materials market makes them an ideal strategic partner for us to commercialize our technology portfolio."

Antimicrobial Technology Continued from Page 8

technology is to reduce infection rates following surgical procedures. Medical device materials have been shown to be susceptible to rapid colonisation by bacteria, which then produce a plaque or biofilm as protection against the body's defences. Implants treated with Agluna technology have been shown to remain clear of such biofilm formation. In vitro testing has demonstrated that Agluna surface technology has bactericidal effects against bacteria known to cause post-operative, device-related infection, including drug-resistant strains.

Philip Agg, Chief Executive of Accentus Medical, said, "This agreement represents a significant step forward for Accentus Medical, and we are very pleased to be working with a company as prestigious as Zimmer. Having invested significant resources in developing the technology and in generating a large amount of evidence supporting its safety and efficacy, Accentus Medical is now in a position to fully commercialise and exploit the Agluna technology."

Martin Pickford, Senior Vice-President of Business Development for Accentus Medical, said, "One of the most intransigent problems with orthopaedic implants is infection. It can be very difficult, costly and time consuming to treat these cases. The most effective approach is to ensure that infections do not occur in the first place. All of our data to-date demonstrates that treating orthopaedic implants with the Agluna process can contribute towards achieving this goal. If successful in the long term, Agluna will help significantly reduce the estimated $5 billion in annual costs associated with infections resulting from primary joint replacement."

Thermo-Mechanical Analysis Continued from Page 3

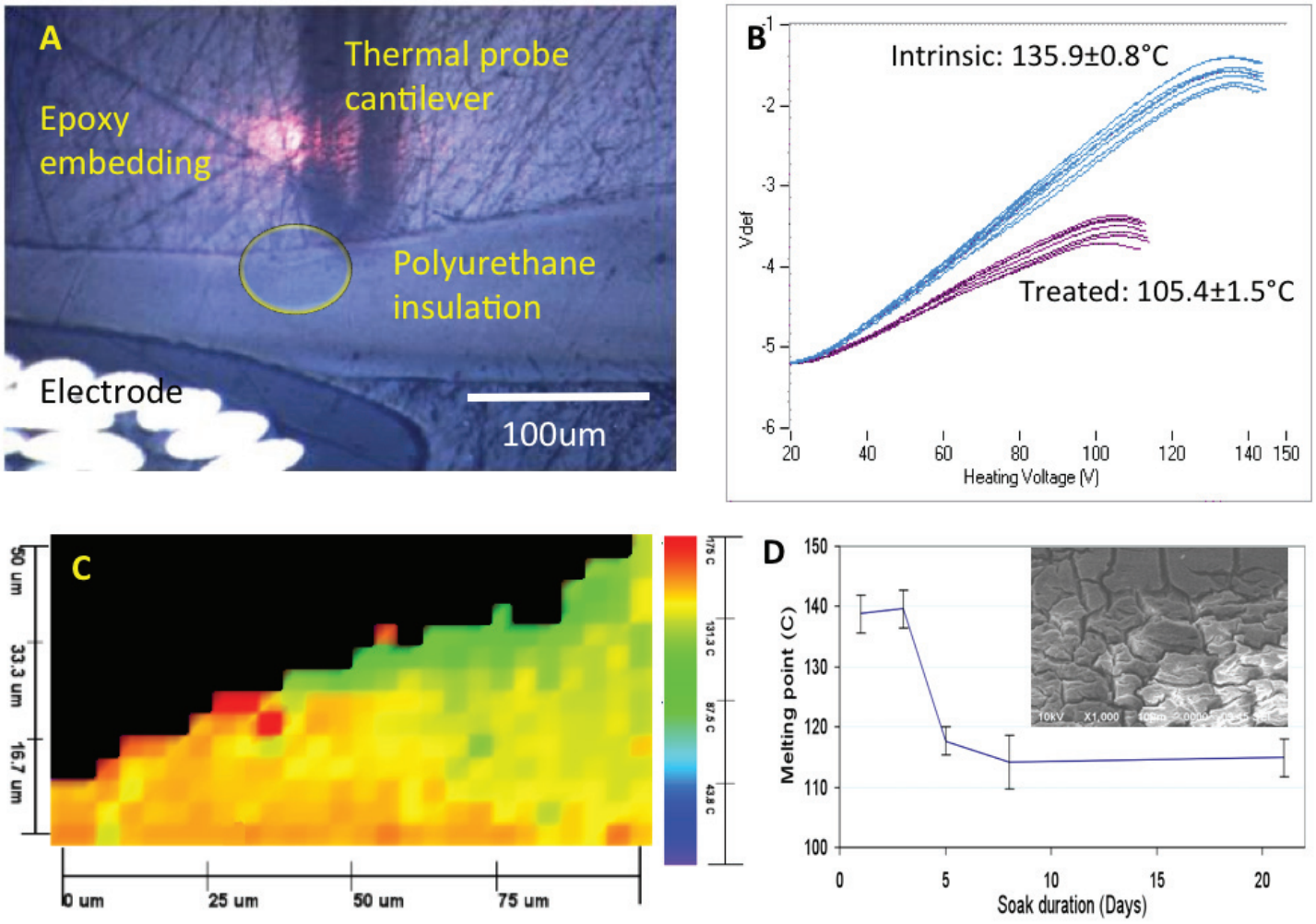


Figure 3: A cross-section through a treated pacemaker lead is shown (A). The thermal probe cantilever is above the sample and hence out of focus. LTA plots (B) obtained away from the physically stressed regions have an average Tm of 135.9°C, whereas the stressed regions have an average Tm of ~ 105.4°C in this 30 day old treated specimen. The TTM (C) of the oval marked region (A) shows substantially lower Tm at the location of the stress point (green regions), with the remainder of the polyurethane showing consistently higher Tm. (The black region is where the embedding epoxy was probed, and is not the specimen.) Figure 3D shows the mean decrease in average Tm in the stressed regions of multiple treated samples over time. (D) The inset SEM micrograph shows the first imaged appearance of ESC at 8 days.

dia changed 3 times per week. Control samples were stored unstressed in air. Samples were then removed periodically, embedded in epoxy, and then sectioned to expose a cross-section of the lead for Vesta analysis. Multiple LTA measures and TTM maps were then obtained across the bulk and surface regions of the electrode insulation as shown in Figure 3.

The peroxide treatment significantly decreased the melting point from an untreated value of 135.9°C down to 105.4°C in one specimen (Figures 3A, B, C). Control samples retained an average melting point of 128.4°C (not shown). Melting points at stressed regions showed significant reduction after soaking for only 5 days is shown in Figure 3. However, visible stress corrosion was not detected with Scanning Electron Microscopy until day 8 (Figure 3D inset). Thus, LTA and TTM analysis revealed corrosive MW degradation substantially in advance of SEM.

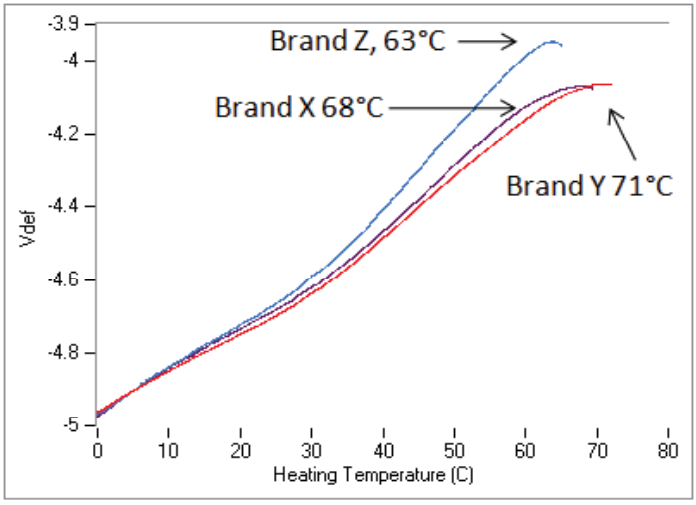
Example 3 - Drug coated cardiovascular stents

The distribution of a drug in polymer matrix, the crystallinity of the drug, and the MW and crystallinity of the polymer matrix can have substantial effects on drug release kinetics,

Thermo-Mechanical Analysis Continued on Page 13

Thermo-Mechanical Analysis Continued from Page 12

which in turn can greatly alter biological responses. Until now, no known method could directly measure the crystallinity or phase mixing of the thin drug and polymer matrix coatings on metallic stents. This is possible with the submicron spatial resolution of the Vesta as it probes only the drug coating. In this study, several drug-coated cardiovascular stents composed of poly-DL-lactic acid (PDLLA) polymer matrixes were examined. Stent sources and compositions are not provided.



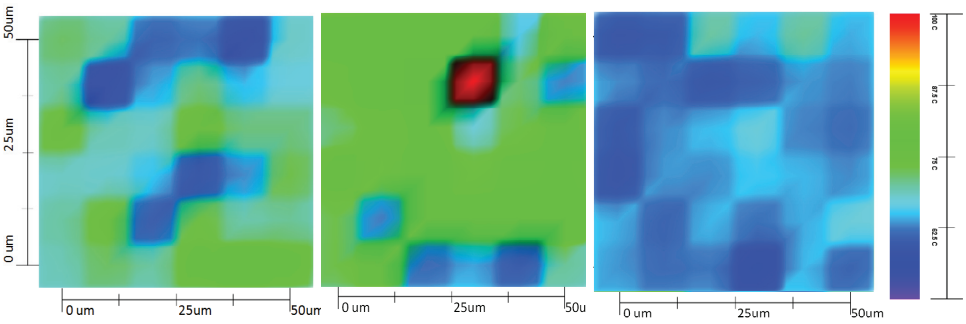


Figure 4: A typical LTA curve is shown for each stent (A) while TTM shows variations in the uniformity of the LTA peak in different regions of each stent (B) for Brand X, Y and Z (left to right). Each TTM diagrams 36 separate LTA measurements obtained at 10 um spatial intervals for a 60 x 60 um regions of the stent surface.

An LTA curve is shown for three different drug coated stents (Figure 3) where the average Tg transitions for each of the three stents ranged from 63 to 71ºC. These transitions are somewhat higher than the typical 50-60ºC Tg of pure PDLLA, which may be a function of MW, crystallinity or due to the inclusion of the drug. Transition Temperature Mapping (TTM) shows substantial differences in the uniformity and pattern of the Tg onset for the three stents. Since the drugs have substantially higher transition temperatures than the PDLLA matrix, this indicates that there were substantial differences in the local content of the drug in each of the ~30 nm regions that were thermally analyzed. For example, the Brand Y stent showed a single region of very high drug content surrounded by relatively uniform composition (Tg). In contrast, there was a very small range of drug content in Brand Z and an intermediate range in Brand X. TTM enabled the detection of differences in the thermal properties and morphological character between the three stents, including substantial differences in the mixing of the drug in the matrix.

Conclusions

The Anasys Vesta enables powerful analyses of thermal transition properties of the surface of experimental and commercial medical polymers and devices. Vesta enabled local thermal analyses (LTA) and transition temperature mapping (TTM) reveal underling structural and compositional details that are not apparent from visual inspection or from conventional or spectroscopic microscopy. The Vesta analyses provide insight into drug coating structure and function, polymeric molecular degradation, and product uniformity on functional manufactured devices, explanted devices and on experimental materials (Additional examples of applications at http://anasysinstruments.com/Medical_Devices.pdf). Due to the rapid analyses and the minimal need for specimen preparation, the Vesta can be readily utilized for applications that include R&D, Quality Control, Quality Assurance, and Failure Analysis.

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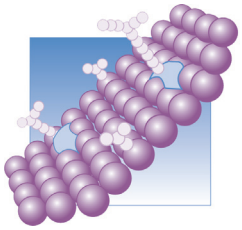

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