SurFACTS in Biomaterials

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Greetings Fellow Biomaterial and Analytical Instrument Scientists

By Steve Goodman

This issue of SurFACTS carries some significant changes for the Surfaces in Biomaterials Foundation. These include our next BioInterface Symposium, which will be held in December rather than the more usual time of late October or early November.

The second significant change is that the Surfaces in Biomaterials Foundation contracted with Ewald Consulting in the past year for management and meeting organization services. As reported in the Fall SurFACTS issue, this occurred prior to the October 2005 meeting and it has been excellent for the Foundation as Ewald is leading us to new opportunities with their experience in association management. Finally, this is now my second chance to provide "Executive" Editorial leadership for the Foundation Newsletter. So, change is in the air, but what does this mean for the Foundation and its members?

When change is already occurring, it is the best time to make your own changes. (I am sure someone else has said this better, perhaps it was Lao-Tzu or Sun-Tzu.) Regardless, now is the time to apply your creative input into making this Foundation meet your needs. We need your input on policy

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Allan Hoffman Is Keynote Speaker for BioInterface Symposium & Workshop 2006

By Min-Shyan Sheu

Professor Allan Hoffman will be the keynote speaker in the BioInterface Symposium & Workshop 2006 in San Mateo, December 4-6. Hoffman has been a pioneer and a great mentor in biomaterials and controlled drug delivery research for almost four decades. He is well-known internationally and well respected in these fields. This article highlights some of his great achievements and his contributions to our members and SurFACTS readers.

Professor Hoffman received his B.S., M.S., and Sc.D. degrees from Massachusetts Institute of Technology (M.I.T.) in Chemical

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BioInterface 2006 – San Mateo, CA

Marriott SAN MATEO

Last year's BioInterface in Minneapolis was a resounding success, thanks to the fine work of Mark Moore, Program committee chair; Joe Chinn, Workshop chair; and Ewald Consulting, the foundation's management company. At the Foundation business meeting, Carl Turnquist of Genzyme Corporation accepted the invitation to be the program chair for BioInterface 2006. He has spearheaded a committee of dedicated members that has developed the outline for this year's symposium.

Several locations were discussed for BioInterface 2006, including returning to Minneapolis as well as East and West Coast venues. The Program Committee worked with Ewald Consulting late in 2005 to lock in a firm date and

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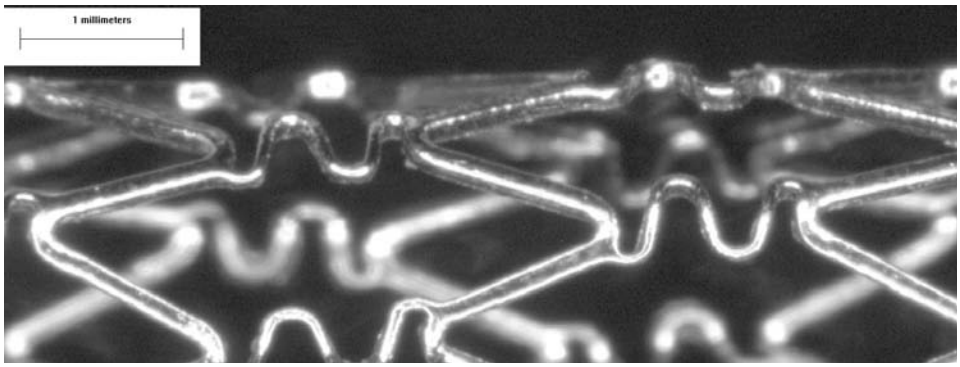
What's Inside

Characterization of Combination Products: Drug Eluting Stents

By Klaus Wormuth

Ever since I began a new job in 2001 at SurModics building capabilities in surface characterization and later taking on management of the analytical chemistry lab, combination devices have been a primary focus. In this time period, the launch of the wildly successful drug eluting stent products Cypher® (Cordis) and Taxus® (Boston Scientific) have advanced significantly in the treatment of cardiovascular disease.

Drug eluting stents combine a cylindrical steel mesh (stent) with a drug/polymer coating. The stent keeps weakened blood vessels open, while the polymer coating elutes a drug to inhibit restenosis (re-blockage of the vessel) by reducing scar tissue formation. Challenges arise in the formulation of the coating since it must be thin and conformal, incorporate a high concentration of drug, control the rate of drug release, and also withstand the severe deformations of the metal cage upon its insertion and expansion into the blood vessel.



Most research in the field of drug delivery from polymers focuses on delivery from monolithic, porous, or barrier devices. Understanding drug release from coatings presents new challenges caused by the high surface area to volume ratio created when a thin layer of material is spread over a device surface. Typically, the inherent equilibrium solubility of drug within a polymer matrix is low – on the order of a few weight percent drug in the polymer.

The blending methods used to create monolithic devices that contain high-concentration dispersions of drugs within polymer matrices cannot be applied to create thin coatings. This is because the dip and spray coating processes rely on the application of coating solutions of drug and polymer mixed with volatile solvents which rapidly evaporate and allow the polymer matrix to encapsulate drug within the polymer matrix.

For a particular drug, choice of the polymer matrix chemistry, solvent chemistry, coating processing conditions, and drying conditions strongly influence the morphology of the resulting coating. If the drug is not well encapsulated by the coating, controlled release is often difficult to achieve and coating durability often impaired. Driven by demands from regulatory agencies, along with scientific curiosity and the need to further improve drug eluting coating technology, new characterization methods have been developed to greatly advance the understanding of the morphology of coatings on stents.

As an example, work by Ranade et al. applies atomic force microscopy (AFM) to the surface of the Taxus® stent to reveal not only the nano-scale surface morphology of the SIBS (styrene-isobutylene-styrene) copolymer, but also show that the paclitaxel drug is dispersed as nanoparticles on the surface of the stent coating (Ranade, et al.). After elution of the particles, nanopores remain. In another paper, Verhoeven et al. of Medtronic use dynamic secondary ion mass spectroscopy (DSIMS) to monitor

Characterization, continued on page 7

SurFACTS in Biomaterials is the offical publication of thefoundation and is dedicated to serving industrial engineers, research scientists, and academicians working in the field of biomaterials, biomedical devices, or diagnostic research.

Amendments to the Medical Devices Directive Will Likely Increase Clinical Data Requirements

An update on clinical data requirements and review of technical documentation for combination products

By Phil Triolo

SUMMARY

Forthcoming changes to the Medical Devices Directive, the regulation that governs marketing of medical devices in the European Union, will effectively increase clinical data requirements. All manufacturers of CE-Marked devices will be affected by the changes, especially those who manufacture hip, knee, and shoulder prostheses. These prosthetic devices will be upgraded to Class III, requiring the submission of design dossiers to notified bodies which meet the revised requirements for clinical data. Additionally, the proposed amendments clarify the role of notified bodies, competent authorities, and the European Agency for the Evaluation of Medicinal Products (EMEA) in the assessment of products considered "combination products" in the United States. The clarifications codify recommendations currently in place and are particularly discouraging for manufacturers of device/biologic combination products. The amendments will require lengthy EMEA review of the safety and quality of the biologic components of these products.

BACKGROUND

A final proposal for amending Council Directive 93/42/EEC on Medical Devices (MDD), as well as directive 90/385/EEC for Active Implantable Medical Devices (AIMDD) and 98/8/EEC for Biocides, was published on the 22nd of December, 2005. (1) The amended Directives have to be transposed (translated and incorporated into national legislation) by all EU Member States, and will most probably come into force, that is, become legal requirements for CE Marking, some time between 2007 and 2010.

The changes that have the greatest overall effect on medical device manufacturers are those pertaining to requirements for clinical data that need to be included in technical documentation. Section 1.1 of Annex X, Clinical Evaluation, of the current version of the MDD indicates that "the acceptability of the benefit/risk ratio ... must be based on clinical data in particular in the case of implantable devices and devices in Class III." The proposed amendment eliminates the phrase that particularly singles out implantable and Class III devices, effectively requiring that technical documentation for all classes of devices must include a benefit/risk assessment based on clinical data. The change has been made because of differences in interpretation of the notified bodies with respect to what was required to meet clinical data requirements, and a finding that, in general, clinical data are lacking in technical files. (2)

There are several guidance documents that help clarify what information can constitute clinical data. Clinical data can consist of a documented critical review of the scientific literature for the device or a similar marketed device, or a clinical evaluation of the new device. (1,3,4) Reference 3 provides guidance on when a clinical evaluation is necessary; reference 4 suggests what information is necessary in order to use a critical review of the literature to supplement clinical evaluation of the new product or to serve as the lone source of clinical data. In addition, Annex A of EN ISO 14155-1:2003 Clinical investigation of medical devices for human subjects - Part 1: General requirements, has a detailed description of how to conduct a literature review for purposes of the review serving as clinical data. (5)

Retrospective validation of the clinical acceptability of devices that are already CE-Marked will be required in many cases. Review of internal complaint, vigilance, and Medical Device Report files for the device in question and review of the FDA's MAUDE (Manufacturer and User Facility Device Experience) data base for similar devices will be required. In addition, a critical review of the clinical and technical literature by a qualified, independent individual, a discussion of state-of-the-art technologies, and an overall benefit/ risk analysis based on the clinical risk assessment for the device will be required in most instances. (4)

Some changes that have been proposed to the MDD are particularly relevant to products identified in the United States as "combination products." Determination of "principal mode of action" is now the documented means by which a decision can be made on whether the requirements of the MDD or of the Medicinal Products Directive, 2001/83/EC (6), will be the primary document used to determine if the product can be CE Marked. This aligns the European Union (EU) closer to the US, where assignment of an FDA Center for primary jurisdiction of a combination product is based on the product's "primary mode of action", and will eliminate" intended purpose of the product" as one of the criteria identified in MEDDEV 2.1/3 rev.2 that could be used to distinguish whether the product was to be regulated primarily as a medicinal product or medical device. (7)

Under the existing MDD, the role of the notified body (NB) and competent authority (CA) in reviewing medical devices that incorporate "as an integral part, a substance which, if used separately, may be considered to be a medicinal product, and which is liable to act upon the body with action ancillary to that of the device," were not clearly identified. MEDDEV 2.1/3 helped to delineate responsibilities,

Amendments, continued on page 9 ➤➤➤

SurModics and Donaldson Company Partner to Create a New Cell Culture Platform

By Muhammad Lodhi, Ph.D., SurModics, Inc.

SurModics, Inc. and Donaldson Company, Inc., two well-established companies based in Minnesota, have entered a joint partnership arrangement to create a new cell culture platform. SurModics is a global leader in surface modification and drug delivery technologies for biomedical applications. Donaldson is a global leader in industrial filtration solutions.

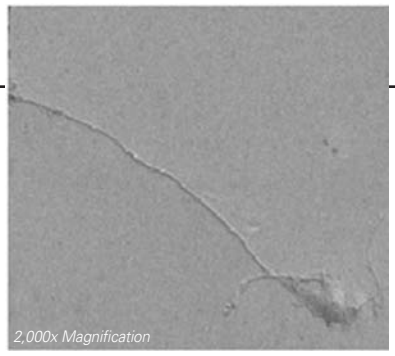


Figure 1a. *SEM image of PC12 cell growing on uncoated polystyrene.*

In 2002, Dr. Melvin Schindler from Michigan State University noted that the nanofibers in Donaldson's synthetic filters resembled the surface of the extracellular matrix (ECM)/basement membrane of mammalian cells. Also, Dr. Schindler, in collaboration with Dr. Sally Meiners from the Robert Wood Johnson Medical School demonstrated in vivo-like cell morphology and growth on Donaldson's nanofiber media.

Figure 1b. *SEM image of PC12 cell growing on Ultra-Web Synthetic ECM with surface modification. Note the in vivo-like morphology of the cell compared to the cell growing on polystyrene.*

This scientific serendipity led to the development of Donaldson's nanofibers for cell culture applications and to the formation of a partnership between Donaldson and SurModics to jointly develop the technology.

The result of this partnership is the Ultra-Web® Synthetic ECM platform. The Ultra-Web Synthetic ECM – a nanofibrillar cell growth surface – is a synthetic, stable and scalable platform that provides a more in vivo-like cell culture environment with its biomimetic extracellular matrix structure. This technology provides consistent, reproducible, and biologically meaningful results in an easy-to-use, cost-effective, and time-efficient manner for cell research and cell-related applications.

ECM is the dynamic network composed of proteins and glycosaminoglycans that is present throughout the bodies of multicellular organisms. It is the pivotal regulator and controller of cellular functions such as adhesion, migration, morphogenesis, apoptosis, proliferation, and differentiation. ECM provides the appropriate multi-dimensional architecture and structural support for cell attachment, cell-cell interaction, biomechanical and biochemical signaling.

The absence of the nanofibrillar geometry for in vitro cell culture results in cellular morphology oftentimes very different from that of cells grown naturally inside the body (Figures 1a and 1b). In addition, cellular function and gene expression vary markedly on conventional cell culture systems, which may have a profound effect on the interpretation of cell culture data and developing therapies based on these data.

Several strategies have been devised to mimic the natural microenvironment for cell growth such as the use of animal-derived ECM protein(s), surface modifications based on self-assembling biomolecules, and the use of chemical reagents. All of these approaches have their drawbacks, and some methods are undesirable because of regulatory, storage, ease-of-use, and performance issues. The ultimate goal in developing the ideal, biomimetic cell culture system is to construct a completely synthetic system capable of providing the necessary geometry and surface chemistry for more in vivo-like cell growth.

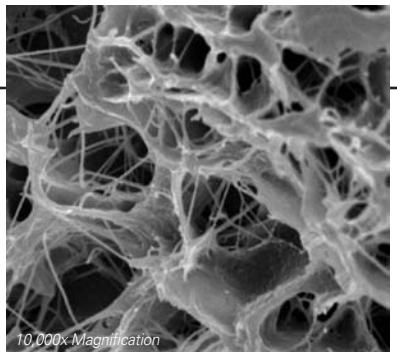


Figure 2a. *SEM image of natural collagen matrix.*

The Donaldson-SurModics Ultra-Web Synthetic ECM technology is specifically designed to address the key challenges and unmet needs of in vitro cell culture studies. The Ultra-Web nanofiber matrix provides a nanofibrillar cell culture surface that mimics the nanofibrillar architecture of the body's own Basement Membrane (Figures 2a and 2b).

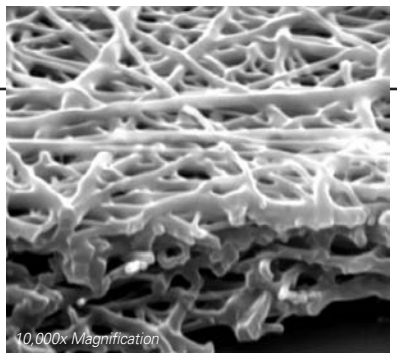


Figure 2b. *SEM image of Ultra-Web Synthetic ECM.*

By further tailoring the nanofiber surface using nanolayer surface modification and engineering, a Surface-Activated Nanofiber cell culture system

New Platform, continued on page 5 ➤➤➤

Call for Nominations To The Board of Directors

The Surfaces in Biomaterials Foundation is now accepting nominations to the Board of Directors. Board officers serve one-year terms. The current officers of the foundation are: Dan Ammon, President; Daniel Hook, Secretary; Lise Duran, Treasurer; Jim Brauker, Past President; Victoria Carr-Brendel, President-Elect; Joe Chinn, Vice President.

According to the by-laws of the Foundation, the president-elect automatically becomes president and the president assumes the office of past president. The offices of secretary, treasurer, president-elect and vice president will be filled at the annual meeting to be held at BioInterface 2006 in December. Duties of the open offices are described below:

President-Elect shall assist the president with scientific program details as requested and shall automatically become president at the annual business meeting.

Vice President shall assist the president and president-elect with scientific program details as requested.

Treasurer shall have guard and custody of and be responsible for all funds and securities of the corporation; receive and give receipts for moneys due and payable to the corporation and deposit all such moneys due and payable to the corporation.

Secretary shall keep the minutes of the meetings of the board of directors; see that all notices are duly given in accordance with the provisions of the by-laws or as prescribed by law and be custodian of the corporate records.

All supporting members and academic members in good standing may nominate candidates for the board. Applications can be found on the website at www.surfaces.org (under Awards & Nominations). Please fill out the application and a letter of recommendation for the person you are nominating. Nominees must be employed by a supporting member in good standing.

Supporting members of the Surfaces in Biomaterials Foundation are:

Abbott Laboratories
Angiotech BioCoatings
Bacterin International, Inc.
Bausch & Lomb
BioCoat, Inc.
Boston Scientific
Carbomedics
Carmeda-BDSM
CIBA Vision Corporation
DePuy Orthopaedics
Dexcom
Evans Analytical Group
Genzyme Corporation
Harland Medical Systems
Lindquist & Vennum
Medical Device Evaluation Center
Medtronic
Physical Electronics
Surface Solutions Lab, Inc.
SurModics
Terumo Medical Corporation
W.L. Gore & Associates
University of Arizona
University of Minnesota
University of Washington

➤➤➤➤ *New Platform, continued from page 4*

can be created. For example, by covalently attaching ECM peptides and proteins to the nanofiber surface, designer ECM-like surface biochemistry can be produced that further enhances cell attachment, growth, maintenance, and differentiation, thus creating a more cell-friendly environment for more sensitive and harder-to-culture cells such as neurons, hepatocytes, and stem cells.

An Effective and Versatile Platform

The technology provides many advantages. These include:

- A more in vivo-like cell growth surface for biologically meaningful results
- Consistent and reproducible results
- A synthetic, stable, and scalable platform that is easy to use, cost-effective, and time-efficient
- Optical clarity of the nanofiber discs enables microscopic imaging
- Better cell adhesion on the nanofibrillar surfaces
- Prolonged maintenance of cells grown on the nanofibrillar surfaces
- Potential to reduce the use of animal-derived products
- Suitability for specialized applications such as bioreactors and high-throughput screening (HTS)

Applications

The Ultra-Web Synthetic ECM holds high promise as a cell culture platform for drug development, drug screening and optimization, stem cell maintenance, proliferation and differentiation, and toxicity testing. The technology is particularly attractive for cell culture studies with more sensitive and harder-to-culture cells.

Consequently, the Ultra-Web Synthetic ECM has immediate applications in neurobioscience, stem cell and hepatocyte research and applications, as well as oncology research. For example, early work from several groups has shown the potential of long-term culture viability of functional hepatocytes, which could prove to be very valuable for pharmaceutical companies in their drug screening and toxicity testing.

Both internal and external cell research work has been carried out on several primary cultures. The results to date clearly demonstrate that this new technology platform provides significant advantages in effecting biologically meaningful, in vivo-like cell morphology, organization, and function.

Call for Papers!

For BioInterface 2006.

Check the website at www.Surfaces.org in late April for Abstract submission information

Surface Solution Labs Is a Leader in Water-Based Coatings

When someone mentions coatings for medical devices, what do you think of? Twenty years ago you probably thought of silicone and Surgilube™. Ten years ago hydrophilics were the rage. Today most medical device engineers think of stent coatings and drug delivery systems as the most evolved applications for coatings on medical devices.

In the everyday world at least 90 percent of all articles we contact are coated to improve their appearance, durability or functionality. Consider automotive, architectural, industrial, recreational, textile and personal products. Almost every product has some surface modification. We even coat our bodies with UV protection and moisturizing products and beautify our skin and hair with personal care "coatings." So why limit the surfaces of devices to only surface bioactive and hydrophilic types of coatings?

Surface Solutions Labs Inc (SSL) was incorporated in 1995 to provide easy to use, eco-friendly, water-based coatings. With more than 18 years of experience in the medical industry, SSL technologies have been able to meet a myriad of coating needs beyond, and including, those typical for medical devices.

Adhesion and wetting are achieved with proper formulations. Pretreatments with plasma, corona and/or primers can be used, if needed, to provide durable adherent coatings on difficult-to-wet or low-energy plastics. Solvent stress crazing of polycarbonate and acrylic plastics is avoided by the use of aqueous coatings.

Custom formulation and coating design of environmentally friendly water systems keeps handling, disposal and manufacturing costs and hassles to a minimum. These technologies are suited for dip, pad, roll or spray applications and may be dried and cured at ambient or slightly elevated temperature, usually without hoods, eliminating the cost for conditioned and static explosion concerns related to solvent-based coatings. An FDA master file supports the biocompatibility and can be accessed by a device manufacturer in their filings to help assure FDA of the safety of the coatings.

Many project managers in the medical device field are mechanical engineers, who are not trained in polymers and coatings. The prospect of developing a messy coating process for their devices can be daunting. Thoughts of hazardous coating solvents, controlled environments and tricky processes that ensure adhesion, function and aging consistency, are often sufficient to derail a coating as a possible product enhancement. As a result, SSL has custom engineering to support design and development of versatile coatings and forgiving processes for those who are on short time-tables or are uncertain as to the best options.

Photo Courtesy of Advanced Polymers Inc. Copyright 1999 Used with Permission. Coatings for stent retention and balloon protection allow safe stent delivery and deployment with high pressure balloons.

Coatings, Continued on page 7 ➤➤➤

➤➤➤ *Hotel, continued from page 1*

location and settled on the San Francisco Bay area for Dec. 4-6, as the symposium's traditional meeting dates in late October were already reserved by other meetings.

If you've visited the Surfaces in Biomaterials Foundation website – www.surfaces.org – you know that BioInterface 2006 will be at the San Mateo Marriott San Francisco Airport where Ewald Consulting has negotiated an excellent rate of $139 per night. BioInterface 2006 will comprise the one-day Workshop on Monday, Dec. 4, followed by general sessions on Tuesday and Wednesday, Dec. 5-6. The two full days of program sessions also include the student poster contest and awards.

Be sure to make your hotel reservations early to ensure that you receive the special rates. Register directly through Marriott reservations at 1-800-556-8972 and be sure to ask for the Surfaces in Biomaterials Foundation rate. For those who want to extend their stay, the special rates will be honored up to five days before and five days after the Workshop and Symposium dates.

At last year's Symposium in Minneapolis there was some confusion about rates and some attendees may have spent more than they should have. Be sure to reserve your room(s) – and register for the Symposium – early.

The Program Committee is looking forward to giving each of you a warm welcome and top-notch technical program in San Francisco Dec. 4-6. Mark your calendars and check the website for meeting updates. The call for papers and session titles will be posted soon.

➤➤➤ *Coatings, Continued from page 6*

SSL's first patented application was a major success for stent delivery catheters. Patented water-based technology used a soft, "sticky" polymer to retain the stent on the balloon until it was deployed. The coating also contains a scratch-protective feature that prevented premature catastrophic balloon failure due to scratching by, or scissoring of, the stent in handling, or vascular calcifications in deployment. SSL also provides the typical coatings such as hydrophilics, antithrombogenic and antimicrobial, and drug delivery. SSL has licensed hydrophilic coatings to AST, that have become the LubilAST product line.

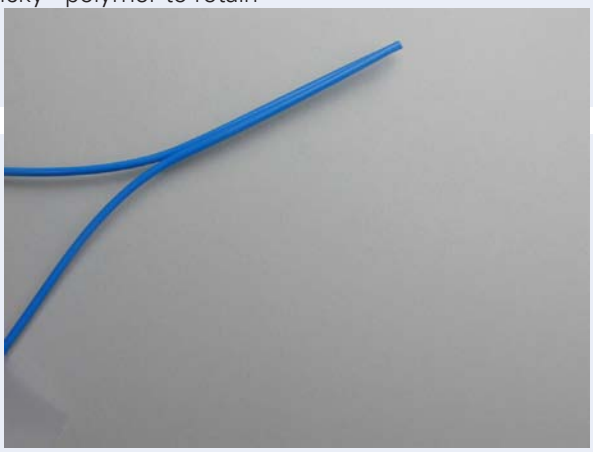


Photo courtesy of Surface Solutions Labs Inc Copyright 2005

Attachment and sustained release of some materials is required in blood and tissue contact. A patented system of attaching bioactives has been developed for use with various therapies. Attachment of Heparin and Hyaluronic Acid has shown promise as biomimetic surface coatings. Even after six months in PBS at body temperature, the Heparin and Hyaluronic Acid films still exhibit characteristic surface activity.

A frothed film of hydrophilic, antimicrobial containing polymer has hydrogel attributes and shows good potential for wound care products. Other bioactives such as analgesics or gene therapies may compliment these systems. (Takahashi et al. GENE THERAPY(2003) 0, 1-8 Nature Publishing Group)

Many industrial coatings prevent surfaces from sticking to each other. This characteristic is called block- resistance. Such coatings have been developed that allow medical products made of soft durometer plastics such as balloons and catheters to be hard at the surface. This block-resistant coating prevents sticking of the device to itself or its neighbors, or to other devices being deployed through them.

Soft, tacky surfaces may cause adhesion and yield failures and often tearing. Surface hardening with a coating can eliminate this "stickiness."

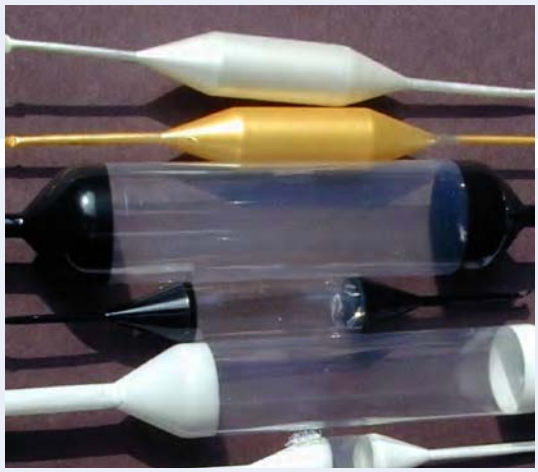


Photo Ccourtesy of Advanced Polymers and Surface Solutions Labs Copyright 2004 Used with Permission. Light absorbing and reflecting coatings on balloons of various sizes.

Other coatings modify appearance and allow for reflective and absorbing capabilities. Aesthetic considerations for novel colors and effects, as well as the ability to focus, contain and direct light energy to where it is needed may be useful in light activation or visualization in vivo. Need a color or glow-in-the-dark treatment for low-light operation or hospital rooms?

Think outside the box when you encounter a surface need. There is most likely a simple-to-apply coating or adhesive to solve the problem!

Call SSL if you think we can help.
SSL Contact Informtaion:

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www.SurfaceSolutionsLabs.com
www.Coatings2Go.com

2006 NESAC/BIO Surface Characterization Workshop

August 23-35, 2006

The 2006 NESAC/BIO Surface Characterization Workshop will be held at the University of Washington August 23-25, 2006. Learn to characterize the surface composition and structure of biomaterials. The workshop includes lectures and surface analysis demonstrations on NESAC/BIO instruments. Attendees will be taught the capabilities of surface analysis methods and how to review data received from surface analysis laboratories. When you register for both the UWEB Summer Symposium and NESAC/BIO Surface Characterization Workshop you will receive a discount. For more information, contact nesacbio@u.washington.edu.

➤➤➤ *Characterization, continued from page 2*

the distribution of the drug cytochalasin D within a polymer coating as the drug is eluted from the coating, and find that initially the drug is depleted from the outer layer of the coating (Verhoeven et al).

These AFM and DSIMS methods provide information on the chemical and morphological state of the surface of the drug eluting coatings, information which is critical to understanding the complex interaction of the stent coating surface with vascular tissue and blood: the "biointerface." I look forward to keeping you informed on new developments in the characterization field.

➤➤➤ Hoffman, Continued from page 1

Engineering between 1953 and 1957. He also taught on the faculty of M.I.T. Chemical Engineering Department for a total of 10 years, including a graduate course in Surface and Colloid Chemistry that he taught several times. Since 1970, he has been a Professor of Bioengineering and Chemical Engineering at the University of Washington in Seattle, Wash., where he also has taught principles of surfaces and non-fouling surfaces in many lectures.

With the additions of Professors Tom Horbett and Buddy Ratner, who joined Hoffman first in the early 1970s as Post-doctoral Fellows and later became life-long collaborators, the Biomaterials group at the University of Washington was formed and cultivated. One of the byproducts of this UW Biomaterials group is Ratner's National Science Foundation Engineering Research

Min-Shyan Sheu and Professor Hoffman

Center called University of Washington Engineered Biomaterials (UWEB). This center brings together a cross-disciplinary team of scientists, biologists, engineers, researchers and physicians, as well as industry leaders, to exploit specific biological mechanisms in the development of medical innovations in the 21st century.

The seed Hoffman planted 36 years ago at the University of Washington has grown into a large forest and continues to spread seeds and influences worldwide across academia and in the industry among those who are working on Biomaterials research and development. One important contribution to this field is the widely renowned textbook, "Biomaterials Science" from Elsevier/Aca-

Hoffman, Continued on page 10 ➤➤➤

➤➤➤ *Amendments, continued from page 3*

and identifies the notified body as the ultimate decision maker in the process.

The amended MDD clearly gives the NB responsibility for deciding whether or not the device with integral, ancillary drug/substance can be placed on the market. However, "the notified body shall, having verified the usefulness of the substances as part of the medical device and taking account of the intended purposes of the device, seek a scientific opinion from the EMEA [or one of the competent authorities designated by the Member States in accordance with Directive 2001/83/EC] on the quality and safety of the substance." (1)

Thus, the usefulness of the substance in achieving the intended purpose of the device will have already been verified by the NB before a request is made for the review of its quality and safety. The "usefulness" of the medicinal product/ substance is not evaluated by the competent authority (CA) or European Agency for the Evaluation of Medicinal Products (EMEA). Determining "Usefulness," as used in the EU, is not as rigorous as determining "efficacy" for FDA purposes. (Note: A brief discussion of "usefulness" is provided in reference 7.)

An opinion on the safety and quality of the substance shall be made by either the CA or EMEA, depending on the nature of the substance. Regardless of which body is responsible for issuing its opinion, "the concerned competent authority [or EMEA] shall take into account the manufacturing process and the data related to the incorporation of the substance into the device."

The EMEA is responsible for review of the quality and safety of some classes of ancillary substances. The quality and safety of medicinal products that were granted Community marketing authorization, human blood derivatives, and those medicinal substances identified in Annex I to EU Regulation 726/2004 (including medicinal products developed by means of specific biotechnological processes and medicines used to treat AIDS, cancer, neurodegenerative disorders, or diabetes) will be reviewed by the EMEA. (8)

In addition, human tissue engineered products (HTEPs) incorporated as an integral part of a device which are liable to act upon the body with action that is ancillary to that of the device are subject to assessment and authorization in accordance with the MDD. Previously, HTEPs were excluded from consideration under the MDD. HTEPs, themselves, are subject to proposed legislation (9) which would define them as Medicinal Products subject to regulation under the Medicinal Products Directive and Regulation EC 726/2004, the so-called "centralized procedure" (8). As such, review of the safety and quality of HTEPs would be made by the EMEA.

Unfortunately, the EMEA has been notoriously slow in issuing its opinions. The "centralized procedure" defined in EU Regulation 726/2004 requires that all EU Member States be given the opportunity to review and comment on marketing authorization decisions, which could be problematic given the number of members, the time it could take all of them to respond, and the time required to resolve any issues. For other substances, including most drugs, a CA will offer its opinion on the substance's safety and quality. Although more responsive than the EMEA, competent authorities are not usually familiar with the use of small quantities of medicinal substances to enhance the safety or performance of a device. The time it takes to complete a review can be long, and CA focus on concerns that are more typical for systemically administered drugs can be problematic.

The good news is that roles of the NB and CA or EMEA are clearly defined, and HTEPs will now be governed by community-wide regulation. The bad news is that the "centralized process" is not an expedient one, and will lead to delays in the issuing of market authorization of "combination products."

References (All accessed on April 10, 2006)

1. Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on amending Council Directives 90/385/EEC and 93/42/EEC and Directive 98/8/EC of the European Parliament and the Council as regards the review of the medical device directives. Download a pdf of the proposal here.

2. Medical Devices Experts Group, Report on the functioning of the Medical Devices Directive. For more information, download a pdf here.

3. Recommendation NB-MED/2.7/Rec1, Guidance on clinicals. For more information, download a pdf here.

4. Recommendation NB-MED/2.7/Rec3, Evaluation of clinical data: a guide for manufacturers and notified bodies. For more information, download a pdf here.

5. EN ISO 14155-1:2003 Clinical investigation of medical devices for human subjects - Part 1: General requirements

6. Directive 2001/83/EC of the European parliament and of the council of 6 November 2001 on the Community code relating to medicinal products for human use. For a pdf of this directive, click here.

7. MEDDEV 2.1/3 rev.2 Interface with other directives - Medical devices/medicinal products. For a pdf of this, click here.

8. Regulation (EC) No 726/2004 of the European parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Click here to dowload a pdf of the regulation.

9. Proposal for a regulation of the European parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Click here to download a pdf of the proposal.

➤➤➤ *Hoffman, Continued from page 8*

demic Press, which is co-authored by Hoffman and Ratner. The first edition has sold out and the second edition (2004) has been highly successful around the world.

Professor Hoffman's astonishing creativity and pioneering work have stimulated developments in many Biomaterials research. His major research interests and contributions listed below include:

- Biomedical hydrogels
- Mechanics of natural tissue
- Education on surface science modification by many different techniques
- Covalent immobilization of biomolecules
- Non-fouling surfaces
- Drug delivery
- Stimuli-sensitive (smart) polymers
- Immunoassays
- Biomolecular Separations
- Smart polymer bioconjugates
- Novel polymeric carriers for gene delivery
- Tissue engineering
- Nanotechnology

Hoffman has been published in more than 350 publications and is on the editorial advisory boards of six journals, including two American Chemical Society journals (Bioconjugate Chemistry and Biomacromolecules).

As Professor Ratner described Allan at his 70th birthday celebration symposium, "Allan Hoffman has profoundly influenced current ideas in biomaterials such that, without his guiding light, many ideas we take for granted would not be with us today and biomaterials would be a different and, most likely, intellectually poorer endeavor."

Hoffman's contributions to Biomaterials research and education have resulted in numerous recognitions and awards. In 2005, he was elected to the National Academy of Engineering for his "pioneering work on the medical uses of polymer materials." Some of his professional activities and awards are highlighted below:

- Chairman, Gordon Conference on Biomaterials, 1977
- President, Society for Biomaterials, 1983-1984
- Clemson Award, Society for Biomaterials, 1984
- Biomaterials Science Prize, Japanese Biomaterials Society, 1990
- Board of Governors, Controlled Release Society, 1991-1994
- Founders' Award of the Society for Biomaterials, 2000
- Two symposia in honor of his 60th (1992) and 70th (2002) birthdays
- Elected to the National Academy of Engineering, 2005
- International Award from the Society for Polymer Science, Japan, 2006

Please join us at the BioInterface Symposium & Workshop 2006 to meet Professor Allan Hoffman. The title of his keynote speech at the Symposium will be announced in the next issue of SurFACTS.

➤➤➤ *Greetings, continued from page 1*

and meeting organization issues for the Foundation. We need your ideas on symposia and workshops and speakers for the next meeting(s). We need your nominations for the Foundation Board of Directors. (Calls for symposia and for nominations are in this issue.) Don't be shy. And we need you to let the world know about this Foundation and its leadership in Biomaterials, Surfaces, and Characterization.

Speaking of getting the word out, this past November and February I had the opportunity to do just that. I was invited to speak on the Microscopy of Biomaterials at half-day workshops on Surface Characterization for Medical Devices at the Medical Device and Manufacturing expositions in Minneapolis and Anaheim, respectively. In my earlier career as a cloistered academic, I had not previously had the opportunity to attend this HUGE trade show that encompasses the entire world of medical devices including, or perhaps especially, manufacturing and packaging. This was a wonderful opportunity to learn much more about aspects of "our" industry that we simply don't see at our BioInterface meetings, or the Society for Biomaterials, or at clinical meetings, or at any others that are listed in the SurFACTS calendar. Consequently, I spent long days walking the huge exposition floor. There were 1,400 suppliers at MDM West in Anaheim!

Of course, I also saw this as an opportunity to educate this community about what it is that we do, but first I needed to learn more. In my discussions with vendors and attendees, I tried to learn about their products and services. I especially wanted to learn about their use and knowledge of novel materials and coatings, and their needs and sophistication with respect to materials characterization and biocompatibility. Do these attendees and vendors have characterization issues? Do they have materials issues? Do they have biocompatibility issues? And, do they have coating issues? Absolutely! (I'm sure none of you is surprised.)

I also learned that they have issues related to the characterization of their packaging materials and issues related to contamination of their devices (biomaterials) by packaging, and issues related to the coatings on their packaging materials. Are these topics where the Surfaces in Biomaterials Foundation could offer guidance? Is this a market opportunity for our membership? Of course. However, during dozens of discussions with professionals in the field, at most only one or two individuals were aware of our Foundation! Many were very interested, but had never heard of us. This was even true with the technical leadership at several small but "mainstream" biomaterials and biomaterials coatings companies on the exhibit floor.

Recall the words of that great American philosopher Yogi Berra who said in one of his more lucid moments, "The future ain't what it used to be." The future (of this Society) will be what you make it. Clearly, we have to get out more.

Thank You to Our Members!

Meeting/Conference/Trade Show Calendar

Meeting/Conference/Trade Show	Place	Dates	Web Address
Design of Medical Devices Conference	Minneapolis, MN	04/19/06 – 04/21/06	http://www.me.umn.edu/dmd/
AIChE Spring National Meeting	Orlando, FL	04/23/06 – 04/27/06	http://www.aiche.org/conferences/spring/index.htm
Regenerate World Congress on Tissue Engineering and Regenerative Technologies	Pittsburgh, PA	04/24/06 – 04/27/06	http://www.regenerate-online.com/
Society for Biomaterials	Pittsburgh, PA	04/26/06 – 04/29/06	www.biomaterials.org
"Tutorial — Advances in Surface Characterization Methods." "Workshop — Microscopy: Basic Principles and Applications for Biomaterial Analysis."			
7th Annual Conference on Arteriosclerosis, Thrombosis and Vascular Biology	Denver, CO	04/27/06 – 04/29/06	http://www.americanheart.org/presenter.jhtml?identifier=3033071 www.aats.org
American Association for Thoracic Surgery (AATS)	Philadelphia, PA	04/29/06 – 05/03/06	www.aats.org
Association for Research in Vision and Ophthalmology Annual Meeting (ARVO)	Fort Lauderdale, FL	04/30/06 – 05/04/06	http://www.arvo.org/root/index.asp
Hearth Rhythm Society, 27th Annual Session	Boston, MA	05/17/06 – 05/20/06	http://www.heartrhythm2006.org/
Arthroscopy Assn. of North America (AANA)	Hollywood, FL	05/18/06 – 05/21/06	www.aana.org
American Thoracic Society, International Conf. (ATS)	San Diego, CA	05/19/06 – 05/24/06	www.thoracic.org
American Urological Association (AUA)	Atlanta, GA	05/20/06 – 05/25/06	www.auanet.org
Medical Design & Manufacturing East (MD & M East)	New York, NY	06/06/06 – 06/08/06	http://www.devicelink.com/expo/east05/
American Society for Artificial Internal Organs	Chicago, IL	06/08/06 – 06/10/06	www.asaio.org
33rd Annual Meeting of the Controlled Release Society	Vienna, Austria	07/22/06 – 07/26/06	http://www.controlledrelease.org/meetings/index.cgi
Microscopy and Microanalysis	Chicago, IL	07/30/06 – 08/03/06	http://mm2006.microscopy.org/
UWEB Wound Healing Technology	Seattle, WA	08/28/06 – 08/31/06	http://www.uweb.engr.washington.edu/about/news.html#shortcourse
ICEM XVI International (International Congress on Electron Microscopy)	Sapporo, Japan	09/3/06 – 09/08/06	
American Society of Retina Specialists	Cannes, France	09/09/06 – 09/13/06	http://www.retinaspecialists.org/
Transcatheter Cardiovascular Therapeutics (TCT)	Washington, DC	10/22/06 – 10/27/06	www.tctmd.com
Medical Design & Manufacturing Minneapolis (MD & M Minneapolis)	Minneapolis, MN	10/25/06 – 10/26/06	http://www.devicelink.com/expo/minn05/
AVS 52nd International Symposium on Biomaterials Science	New Brunswick, NJ	10/30/06 – 11/04/06	http://www2.avs.org/symposium/boston/meetingsevent.html
8th New Jersey Symposium on Biomaterials Science	New Brunswick, NJ	11/08/06 – 11/10/06	http://www.njbiomaterials.org/web/index.php?p=news-events&s=7794 www.aao.org
American Association of Ophthalmology (AAO)	Las Vegas, NV	11/11/06 – 11/14/06	http://www.aao.org/
American Vacuum Society (AVS)	San Francisco, CA	11/12/06 – 11/17/06	http://www.avs.org/
American Institute of Chemical Engineers (AIChE) Annual Meeting	San Francisco, CA	11/12/06 – 11/17/06	http://www.aiche.org/conferences/spring/index.htm
BioInterface 2006	**San Francisco, CA**	**12/4/06 – 12/6/06**	**www.surfaces.org**

Volunteers Wanted:

If you would like to contribute your talents to the Surfaces in Biomaterials Foundation, we'd love to have you. Let us know if you'd like to help with membership recruitment, writing or editing articles for the SurFACTS newsletter, adding content and interest to the website or other areas where your talents could be put to good use. If interested please contact Bill Monn at billm@ewald.com or call 651-290-6295.

Wanted: Members

To be leaders in the surface science community

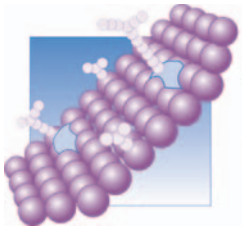
- Join a forum that fosters discussion and sharing of surface and interfacial information
- Have your voice heard and your interests represented within the surface science and biomedical community
- Help shape workshops and symposia that further the world-wide education of surface science
- Promote understanding of interfacial issues common to researchers, bio-medical engineers and material scientists.

Benefits of Membership:

- Discounted registration at BioInterface, the annual symposium of the Surfaces in Biomaterials Foundation.
- Your logo and a link to your website in the member directory on the official website of the Foundation, www.surfaces.org.
- Complimentary full page ad in surFACTS, the Foundation's newsletter and discounts on all advertising.

Join the Foundation that connects the academic, industrial, and regulatory committees within the surface science/biomedical communities!

Visit the Foundation at www.surfaces.org for a membership application or call 651-290-6267.



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