SurFACTS in Biomaterials

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Bio-Bandaids: A Natural Approach to Promoting Wound Healing

By Jessica M. Joslin, Vinod B. Damodaran, and Melissa M. Reynolds; Colorado State University

Researchers at Colorado State University (Fort Collins, Colorado) have developed a class of biodegradable materials that mimics the body's own healing process without causing a foreign-body reaction. Due to the natural therapeutic action, this material could prevent and treat localized infection and prevent platelet activation without causing systemic side effects. The first generation materials are based upon a poly(lactide-co-glycolide) (PLGH) polymer backbone functionalized with a naturally-occurring signaling agent, nitric oxide (NO) (see Figure 1).[1]

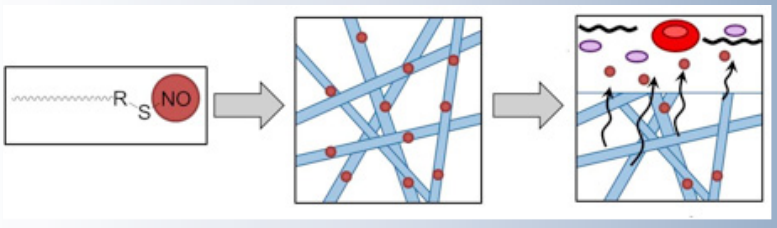

Figure 1: Polymers containing covalently attached NO donor groups are processed and release their therapeutic payload under physiological conditions, thereby affecting cells and proteins at the material-biology interface to promote biocompatibility of the device.

Advantages of Naturally Occurring Therapeutic Agents

The use of naturally-occurring therapeutic agents, such as NO, to overcome current challenges with synthetic materials is

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Inside this Issue

Members are encouraged to submit articles for future editions of SurFACTS. Please e-mail your story (with all appropriate figures and graphics) to Staff Editor Cody Zwiefelhofer at codyz@ewald.com for consideration in a future issue. Deadlines for upcoming issues are posted on surfaces.org.

From the Editor

By Joe McGonigle, Ph.D., SurModics, Inc.
SurFACTS Executive Editor

Happy new year to everyone and just a few quick announcements regarding SurFACTS. We are moving to quarterly publications in an effort to include more member-driven content in each issue. Future issues will be coming out in April, July and October. I'd also like to welcome Colin Fairman, Melissa Reynolds and Bill Theilacker as new editors to SurFACTS and thank Phil Triolo for staying on as an editor. Brief bios of all the content editors are below and I'm thankful for their help in putting this newsletter together. I think we're off to a good start in putting more and useful content into SurFACTS. This is due to the hard work of the volunteer editorial staff. I hope all the readers will enjoy what we hope is a good mix of information pertaining to both the science and business of biomaterials. We are still interested in having one additional editor to cover medical device related content and I invite anyone interested to contact me - my address is listed on the right sidebar. I also invite all interested members to submit articles for inclusion in future issues and hope you enjoy this one.

Colin Fairman, JD, PhD

Intellectual Property and Legal Editor

Colin Fairman is a senior associate with Fulbright & Jaworski L.L.P.'s intellectual property practice in the Firm's Minneapolis office. Colin focuses his practice on identification, acquisition, enforcement, prosecution and licensing of intellectual property, with an emphasis in biotechnology and nanotechnology. He has a broad range of experience within these industries including client counseling and patent prosecution in matters involving pharmaceuticals, biomedical prosthetics, medical devices, molecular biology, treatment methods, instrumentation, microscopy, lasers, optics and nanosignal acquisition. Prior to practicing law, Colin was a research scientist and chemist in the areas of molecular biology, ion channel characterization, metabolic and cardiovascular physiology and environmental toxicology.

Melissa Reynolds, PhD

Biomaterials Editor

Melissa Reynolds is a Boettcher Investigator and Assistant Professor in the Departments of Chemistry and Biomedical Engineering at Colorado State University. She received her PhD in chemistry from the University of Michigan and has over 14 years of experience designing, developing, and testing materials for use in medical devices in both industrial and academic settings. She is an inventor on 15 issued/pending patents and has received a Science Award from the National Institutes of Health in recognition of her work involving the role of nitrite in pathophysiology. Most recently, she was named Educator of the Year by the Colorado Bioscience Association. Her passion, innovation and leadership have led to the formation of multiple start-up companies. Currently, her primary research focus is on the development of therapeutic materials that

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

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multi-fold. First, since NO functions as an in situ anti-microbial and anti-platelet agent produced from the natural endothelium, a device that releases NO will serve to mimic the natural processes that occur within the body to maintain homeostasis. In fact, many biostable NO-releasing materials have been previously demonstrated to drastically reduce or altogether eliminate platelet activation and gross thrombus formation and effectively kill several strains of bacteria including Pseudomonas aeruginosa and Staphylococcus aureus.[2,3] More importantly, since NO is a gaseous radical, it readily diffuses from the material into its physiological surroundings when triggered but is short-lived. As a result, its action is truly localized to the device-biology interface where needed and does not initiate systemic effects. This allows for maximum targeted delivery of the therapeutic to the injury site.

Multi-functional Materials for Improving Performance

Biodegradable polymers are used to provide mechanical support in a range of clinical applications where a permanently implanted device is not necessary. Some examples include sutures, vascular closure devices, surgical patches, bone screws, and scaffolds. As such, the ideal materials must simultaneously have good biocompatibility, excellent mechanical strength, and controllable degradation properties. One approach to creating such an ideal material involves the incorporation of nitric oxide (NO) that is spontaneously released under physiological conditions from a polymer containing hydrolyzable groups.

Indeed, we have demonstrated that by altering the composition of the PLGH polymers, different amounts of NO can be loaded onto the polymer, allowing for tunable storage. In addition, nearly 100% of stored NO can be recovered in a time-controlled fashion depending upon the macromolecular structures employed. This allows us to tailor the total amount of NO delivered and the time course of delivery. Different amounts of NO may be required for different applications, therefore the tunability of the material properties is paramount.

Besides the ability to tailor the therapeutic storage and delivery capabilities of the material, these polymers demonstrate other desirable device properties such as expected hydrolysis degradation, non-toxic character, and surface wettability. The materials have been evaluated for toxicity via the ISO elution method and have received a score of "0" indicating that these materials would not cause adverse effects, such as cell death in vivo. Moreover, the family of biodegradable polymers we developed are characteristic with an overall moderate hydrophilic nature which enhances cell viability, attachment and biocompatibility, generally lacking characteristics with other synthetic polymers. The materials can also be processed as thin films for coatings or nanofibers (see Figure 2) while maintaining their therapeutic action. The ability to fabricate nanofibers is

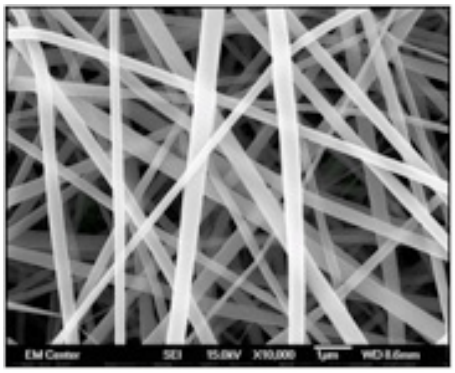

Figure 2. A representative SEM image of the material that has been electrospun to form nanofibers.

promising since nanoscaffolds have been shown to mimic the behavior of the extra cellular matrix (ECM). Preliminary cell and protein studies indicate differences in cell viability and protein adsorption, indicating that these materials do indeed have an effect on biological responses. Preliminary platelet spreading studies using human blood demonstrated a

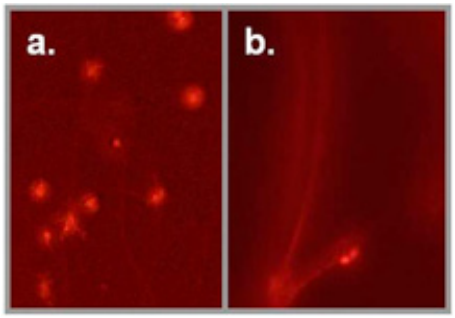

Figure 3. The NO-releasing material (b.) results in a significant decrease in adhered platelets when compared to the control material (a.) that does not release NO in the presence of collagen. Courtesy of Dr. Keith Neeves and Joanna Sylman at Colorado School of Mines.

strong platelet inhibition capability of the NO-releasing derivatives, even in presence of collagen, a known platelet aggregation agonist (see Figure 3). The biodegradable, non-toxic and processable nature of these materials indicates that these materials are practical for clinical use.

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Overall, we have developed a class of biodegradable polymers that is capable of improving biological performance, including preventing platelet activation without causing local toxicity. The materials can be processed in a variety of ways, including as thin-films and nanoscaffolds. Overall, the tunable therapeutic action, biodegradation and processability of these polymers make for a versatile class of materials that promote biocompatibility and wound-healing using natural signaling agents.

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work synergistically within the body. She is also the CEO and co-founder of Diazamed, an advanced biomaterials company, with the support of CSU Ventures, the commercialization arm of Colorado State University.

Bill Theilacker, PhD

Surface Characterization and Analysis Editor

Bill Theilacker is a Senior Scientist at Medtronic, a world leader in the manufacturing of medical devices. He is an integral member of the Microscopy and Surface Analysis team, specializing in the characterization of biomaterials and biointerfaces to support business-critical issues. He has been with Medtronic for just over a year and has already been a key player in solving several materials-related issues. Prior to working at Medtronic, he obtained his PhD in Biochemistry and Chemistry from the University of Delaware in Professor Tom Beebe's group. His doctoral work focused on "Extracellular Matrix Protein Patterns and Gradients to Modulate Axonal Growth." Prior to graduate school, he worked for 5 years as a Research Associate at DuPont in the area of agrochemicals, which has some similarities with the pharmaceutical and drug delivery industries. Prior to DuPont, he double majored in Biology and Chemistry at West Virginia University.

Phil Triolo, PhD, RAC

Regulatory Editor

Phil has been the editor of SurFACTS' Regulatory Affairs column since 2008 and a member of the SIB Foundation since 1998. After working in medical product development for 15 years, he formed his own company in 1996 that provides technical and regulatory assistance to device manufacturers to assure compliance with FDA and European regulations. His company devises regulatory strategies for market introductions in the US and EU; prepares 510(k)s, IDEs, PMAs, Technical Files and Design Dossiers for implants, cardiovascular, diagnostic, and blood access devices and combination (drug/device) products; and Clinical Evaluation Reports, literature reviews, and other technical and regulatory documents, including biological safety assessments. Phil is an adjunct faculty member of the University of Utah Department of Bioengineering where he lectures on regulatory affairs issues, and past Chairperson of the Biomaterials Availability and Policy special interest group of the Society for Biomaterials.

In Memoriam: William "Bill" Katz, PhD

By Lawrence Salvati, Jr., PhD, Surfaces in Biomaterials Past President

It is with great sadness that we report on the death of one of our Surfaces in Biomaterials Foundation members. On January 7, 2012 William "Bill" Katz, PhD unexpectedly passed away at his home in Marine in St. Croix, Minnesota. Bill, who was 58, is survived by his former wife, Patti Katz, and daughter, Rachel Powers and his two beloved Airedales, Buddy and Sherlock.

Many of you will remember Bill from his most recent position as owner and President of Katz Analytical Services. Bill received his MS and his PhD in analytical chemistry from the University of Illinois at Champaign-Urbana. However, chemistry was not Bill's first career goal. Bill's initial career choice was medicine, but when he collapsed in the ER trying to stop an arterial bleed, he decided that he may fare better with chemistry. Bill completed his doctoral research investigating the effects of energetic ion bombardment and the subsequent emission of secondary ions followed by mass spectrometric detection under the guidance of Prof. Charles Evans. To supplement his chemistry knowledge, Bill elected to delve into the "dark" side by completing an MBA program at the State University of New York.

Bill started his career in 1980 at the General Electric Corporate R&D Center where he worked in the ion beam analytical group. In 1986 Bill joined Perkin-Elmer, Physical Electronics (Phi) in Eden Prairie, MN as the manager of ion beam systems. Bill later assumed the role as Laboratory Director for Phi. It was during his tenure at Physical Electronics that I first met Bill. As a matter of fact, in his role as Laboratory Director, Bill was my direct supervisor. In 1989 Bill decided to step out on his own so he teamed up with his research advisor, Charles Evans, to start Evans Central as part of the Evans Analytical Group. After directing Evans Central (which later became Katz Analytical) through 12 successful years, Bill sold the business and tried "retirement" for a brief time before returning to the corporate world. Over the next few years Bill held positions at Braun Intertec and Crane Engineering. At this juncture in his life Bill elected to take a sabbatical from science and cater to his more creative side by pursuing his interest in the culinary arts. He enrolled himself in a culinary school where he completed a degree in the culinary arts, and became well versed in the art of cooking.

When Bill realized that "man does not live on bread alone," he decided to once again return to his first passion, science. He obtained a position as the Director of Research at Lifecore Biomedical and then moved on to Surpass where he served as a pre-clinical study director. Realizing that the corporate world was not his cup of tea, Bill elected to venture back into the world of contract analysis in 2009 when he established Katz Analytical Services, which he structured to support device related preclinical studies.

Through the years, Bill established himself as a speaker, author and teacher. He authored or co-authored over 75 peer reviewed articles, and contributed or edited chapters in several reference books. Bill is also listed in "Who's Who in Science and Technology" and "Who's Who in America" and actively participated in numerous technical societies including the Surfaces in Biomaterials Foundation.

Bill's life experiences took him down many paths, but science was always his true passion. Bill had a great sense of humor, but at the same time a broad technical knowledge and he was a respected leader, scientist, and entrepreneur. He will be greatly missed.

If anyone would like to make a contribution in Bill's memory his family has asked that donations be made to the Minnesota Airedale Dog Rescue Shelters since two of Bill's best friends and companions were his Airedales, Buddy and Sherlock.

Surface Science Calendar of Events

Surfaces Webinar: The Intersection of Pharmacodynamics and Materials Biocompatibility in the Development of Combination Medical Devices
January 24, 2012
http://surfaces.org/cde.cfm?event=371897

Medical Device and Manufacturing West (MD&M West)
February 13-16, 2012
Anaheim, CA
http://www.canontradeshows.com/expo/west11/

Surfaces Webinar: The FDA's Proposed NEW de novo Process
February 23, 2012
http://surfaces.org/cde.cfm?event=374818

EuroPCR 2012
May 15-18, 2012
Paris, France
http://www.europcr.com/page/europcr/9-course-concept.html

World Biomaterials Congress
June 1-5, 2012
Chengdu, China
http://www.wbc2012.com

BIOINTERFACE 2012

BioInterface 2012
October 23-25, 2012
Dublin, Ireland
http://www.BioInterface2012Ireland.com

America Invents Act: Practical Applications of Patent Reform

By Colin Fairman, SurFACTS Intellectual Property & Legal Editor

On September 16, 2011 the America Invents Act (AIA), the first major patent reform act since 1952, was signed into law. The AIA contains several significant changes to American patent law. First, the Act changes the U.S. patent regime from a "first to invent" system to a "first to file" system corresponding with most other national regimes worldwide. Second, the Act provides for significant changes in post-grant review. The Act also results in significant additional changes in patent law affecting both patent prosecution and patent litigation. As discussed below, these changes will significantly alter the way prosecution and litigation are carried out in the U.S. However, as with all bureaucratic changes, the implications of some changes (in particular the post-grant review proceedings) will take a significant amount of time and multiple court cases to be fully understood.

First to File (with Grace)

Prior to the AIA, the U.S. was a "first to invent" system with the date of "conception" determining the earliest priority date of an invention. With the passage of the Act, the U.S. is now a "first-to-file, with grace" regime. Conception allowed a first inventor, even if the last to file, to claim priority by "swearing behind" an earlier filed application, showing prior conception and diligent reduction to practice. The AIA now establishes priority solely on the basis of filing date, prior conception no longer providing a basis to overcome priority of an earlier filed application. This change brings the U.S. in harmony with the rest of the world's patent regimes with the exception of the "grace" proviso peculiar to U.S. patent law. The grace proviso provides for a one-year grace period granted to inventors who publish their inventive concepts prior to filing a patent application.

Importantly, it should be noted that the one-year grace period only accrues to the first inventor. Therefore, if inventor A invents and publishes an inventive discovery, he has one year from publication to file a patent application. After a year, the publication becomes prior art, which destroys the novelty of the invention. Further, if inventor B invents later and files a patent application, inventor B gets the patent. This is shown in Figures 1 and 2.

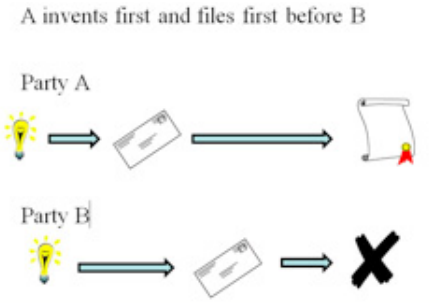

Figure 1

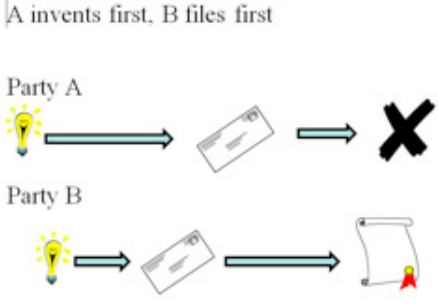

Figure 2

However, if inventor A invents first and then publishes, with inventor B inventing later and filing first, inventor A gets the patent if he files within the one year grace period. This is illustrated in Figure 3.

Figure 3

It is important to note that, as illustrated in Figure 3, while inventor A receives a one-year grace from the date of publication, publication before filing destroys the novelty of inventor A's invention in the rest of the world. In other words, although the AIA converts the U.S. a first to file regime corresponding to the rest of the world, it does not convert the U.S. to an absolute novelty regime as required by most other patent regimes.

As a practical note, the first to file with grace provision will mainly be used by academic institutions where prompt publication of scientific discoveries is an imperative that supersedes confidential development of invention disclosures. However, in those cases where publication is not imperative and where world-wide patent protection is desired, the proper filing of provisional and utility applications prior to public

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disclosure will continue to satisfy the absolute novelty requirement for protection worldwide.

As discussed above, another result of the AIA is the loss of the ability to swear behind a competitor's disclosure. In this situation inventor A invents first but is slow in filing a patent application. Inventor B invents second and promptly publishes but does not file a patent application. The result is that party B's publication destroys the novelty of party A's prior invention as shown in Figure 4 and neither inventor is eligible to receive a patent.

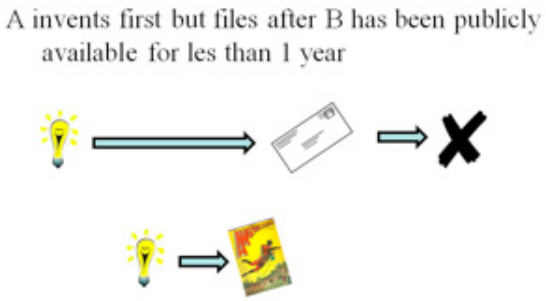

Figure 4

There are other practical implications of the change from first to invent to first to file. First, with the change to first to file, the Patent Office will no longer need to declare or conduct interference proceedings. An interference proceeding was formally declared when two patent applications were simultaneously being prosecuted and the patent office was required to determine which inventive entity had the earliest priority. A flow through result of this change is that the meticulous keeping of laboratory notebooks documenting conception and reduction to practice is no longer a significant consideration. In addition, while interference proceedings will no longer be held, the act does provide for new "derivation" proceedings meaning that the first to file must still be an inventor and not merely someone "deriving" the invention from another and racing to the patent office to file first.

Post-Grant Proceedings

The AIA provides for a radical overhaul of post-grant proceedings including opposition proceedings. The Act now provides four new post-grant opposition proceedings in addition to existing ex parte reexamination:

- Ex Parte Reexamination: an existing proceeding allowing a third party to challenge the validity of a patent grant. The AIA now precludes the ability of the patent owner to appeal the finding to the District Court. In ex parte re-exam, third party participation is not allowed and the prior art considered is limited to patents and printed publications.
- Inter Partes Reexamination: an existing proceeding to be replaced by inter partes review, inter partes reexam is an administrative proceeding taking place in the patent office and carried out by patent examiners. The proceeding allows for third party participation and the prior art considered is limited to patents and printed publications taking place within the Patent Office.
- Post-Grant Review: a new procedure that allows a third party to request review of the patent based on any ground of invalidity that could be raised in District Court, including lack of written description, nonenablement, or patent-ineligible subject matter within nine months of patent grant.
- Inter Partes Review: a new proceeding that can only be requested after the nine months period set for post-grant review (unless the post-grant review is pending). Inter partes review will be held before a new Patent and Trial Appeal Board following a quasi-judicial format of pleadings and responses between the patent owner and a third party petitioner.
- Supplemental Examination: a new proceeding that allows for patent owners (but not practitioners) to "cure" inequitable conduct by submitting information relevant to the patent grant concealed from the Patent Office during prosecution.
- Transitional Program for Business Method Patent: a new proceeding similar to Post Grant Review but without the 9 month filing window. Any covered business-method patent defined by the statute (i.e., not a technological invention) issued before, on, or after the effective date is subject to review if the petitioner is sued for infringement or charged with infringement.

Other Provisions

The AIA also institutes other significant changes to patent law. These include:

- Eliminates false patent marking as a cause for legal action. In the past a considerable industry has arisen for suits based on the marking of products with expired patent numbers. These suits have resulted in headline grabbing damages. The AIA now provides that manufacturers can use virtual marking, (e.g., providing a website on a product, instead of a patent number, that provides a list of patents, their expiration dates and the products they cover).
- Eliminates the patentability of any invention based on strategies for

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Bioinspired Multiactive Coatings for Dental Implants

By Conrado Aparicio, Minnesota Dental Research Center for Biomaterials and Biomechanics

At the Minnesota Dental Research Center for Biomaterials and Biomechanics[1] of the University of Minnesota we have developed bioinspired coatings with multiple bioactivity for dental implants. The coatings are made of synthetically-obtained biomolecules, recombinant elastin-like polymers (recombinamers) and solid-phase synthesized oligopeptides that are covalently-anchored to the metallic substrate using silane chemistry. The coatings can be made with either biomolecules that carry multiple bioactive motifs or molecules with different targeted activities specifically designed to be combined under controlled fabrication conditions. This versatile approach produces coatings with localized and long-term multi-activity, mechanical and thermochemical stability, and that are easy to fabricate.

Challenges for the Clinical Application of Dental Implants

Dental implants are made of commercially pure titanium and are becoming the treatment of choice for replacing missing teeth. 3 million patients in the U.S. have dental implants, and this number is expected to rise by 0.5 million per year with a market of $1.3 billion in 2010[2]. Most dental implants available in the market have a microrough surface with the main purpose of improving the micromechanical retention of the implant after its integration into the adjacent bone tissue[3]. As such, dental implants have a survival rate of 89%+ at 10-15 years. However, some notable obstacles still need to be overcome to expand the application of dental implants to all patients as well as to reduce morbidity and economic impact of the large number of implants failed.

On the one side, the lack of bioactivity –osseostimulative reactions– of titanium also implies that (a) it takes over 3 months after surgery for the patient to be able to normally load the implants; and (b) compromised clinical scenarios with inferior quality or loss of bone volume jeopardize the outcome. Established techniques for the enhancement of osteogenesis use modifications of surface morphology[3] and inorganic surface chemistry[4] with variable success.

On the other side, the clinical efficacy of dental implants is influenced by peri-implantitis, an inflammatory response to bacteria on the implant surface, resulting in bone loss and implant failure. Infection affects up to 14% of implants after 5 years and the relevant incidence is likely higher due to poor clinical diagnosis and the short duration of reporting clinical studies[5].

Bioinspired Molecules for Improving Clinical Outcomes

Our advance strategy to potentially enhance bone regeneration directly on the surface of dental implants and provide antimicrobial properties focuses on the covalent retention to titanium of biomolecules inspired by bone matrix and/or salivary components.

Recombinamers

Our first approach consists of using elastin-like recombinamers made of repeating amino-acid motifs. We use recombinamers studied in collaboration with the University of Valladolid[6,7] that include: 1) the basic elastin five-aminoacid (VPGIG) unit; 2) one-lysine substitution of the previous one (VPGKG) to favor covalent anchoring of the polymer to the silanized metallic surface; and 3) the bioactive peptide sequence(s). The later can be the well-known cell adhesion motif RGDS present in different bone matrix proteins, the SN15A peptide, and the two of them in the same recombinamer molecule.

SN15A is a peptide inspired on a 15-aminoacid peptide present in statherin, a human salivary protein that is known to have strong affinity for calcium phosphate – the mineral that forms our hard tissues, including bone. Etched titanium implants that were coated with recombinamers containing the SN15A peptide and biomimetically mineralized using an enzimatically-controlled process resulted in a unique nanostructured calcium-phosphate surface (Fig. 1) that was able to enhance osteoblastic differentiation up to 21 days in culture[8]. Those that also included the RGDS sequence had a synergistic effect on the adhesion, proliferation, and differentiation of osteoblasts (Fig 2).

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Oligopeptides

Our second approach consists of using oligopeptides[9] that include a bioactive sequence extended with a short number of lysines to favor covalent attachment to the silanized titanium as well as a few glycines in between to give flexibility to the molecule. We designed peptides with controlled ionic potential and polarity to allow the combination of several of them in the same coating step. Some of the peptides that we have successfully tested include the GL13K antimicrobial peptide derived from the human parotid secretory protein; the P144 peptide that inhibits TGF-ß1 activity and thus, prevents the formation of soft tissues around the implant; the aforementioned SN15A and RGDS peptides, and combinations of those as well as RGDS with the synergistic PHSRN found in fibronectin, a bone matrix protein.

As an example of the potential of this approach, the surfaces coated with GL13K, a peptide developed by our collaborators at the University of Minnesota School of Dentistry[10], produced a markedly hydrophobic surface with strong mechanical and thermal stability. The coated surfaces allowed proliferation of osteoblasts and fibroblasts, and most importantly prevented the formation of p. gingivalis biolfilm (Fig 3), one of the most prevalent bacteria in peri-implant infections[11]. At this time we are obtaining encouraging preliminary results when we combine this peptide with the SN15A peptide.

Further steps for the in vivo testing of some of these coatings are already on-going, as for implants coated with the P144 peptide. This demonstrates the potential of implants produced with this versatile approach to be used by dental practitioners in the near future.

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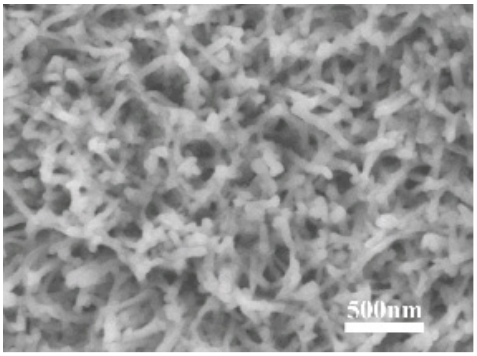

Fig 1. Calcium-phosphate coated nanorough titanium surface. The nanocoating was obtained through a biomimetic enzimatically-controlled mineralization process on a covalently-anchored elastin-like recombinamer that carried a statherin-inspired peptide (SNA15). The SNA15 peptide has strong affinity for calcium-phosphates and was able to control the overgrowth of the mineral formed.

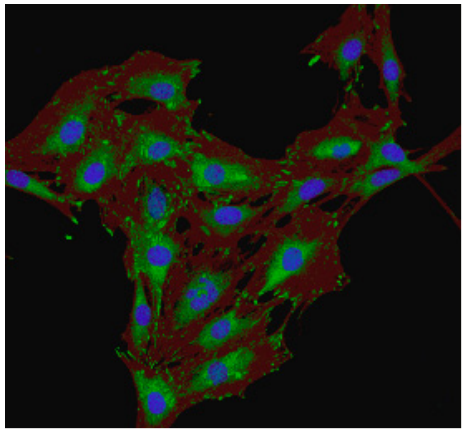

Fig 2. MC3T3-E1 murine osteoblasts had an enhanced adhesion, proliferation, and differentiation response on a titanium surface coated with elastin-like recobinamers that included both RGDS and statherin-inspired peptides.

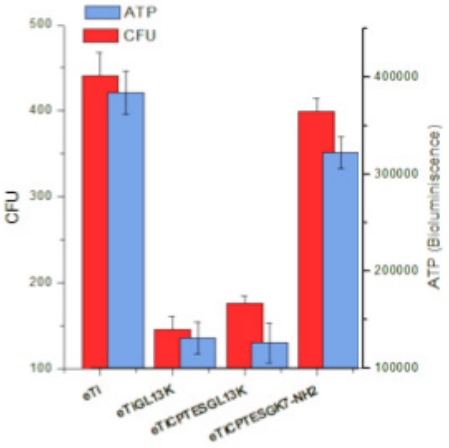

Fig 3. Titanium surfaces coated with the antimicrobial peptide GL13K significantly reduced the number (CFU) and activity (ATP) of p. gingivalis cultured for 8 days in anaerobic conditions compared to non-coated surfaces and surfaces coated with a control peptide (GK7-NH2).

Regulatory Update

By Phil Triolo, SurFACTS Regulatory Editor

Happy New Year!

If 2012 is as eventful as 2011, device manufacturers will be extremely busy just staying current with and adapting to the changing regulatory environment in the U.S. Last year the FDA announced significant changes to the 510(k) process and published a cornucopia of draft guidance documents. A few of these guidance documents that may be relevant to the surfaces community are summarized below.

Three significant draft guidance documents were published by the Office of Combination Products (OCP):

How to Write a Request for Designation (RFD)

This guidance provides an outline of the information that OCP expects to be included in an RFD. The agency is very particular in its review of RFDs, so be careful when addressing each requested item to assure that you've provided complete and unambiguous information. In addition to a list of required information, the guidance document provides very useful information on combination products and their definitions.

Classification of Products as Drugs and Devices and Additional Product Classification Issues

The Agency outlines its "current thinking" on the classification of products as devices, drugs, biologics, or combination products in this document. Particularly useful is Section III, which describes the factors the FDA considers in making its classifications and includes the statutory definitions of "drug" and "device" based on the "primary intended purpose" of the product. It is also fortunate that the Agency documents that:

"In instances where the product presented in a pending RFD appears to be a drug or device (as opposed to a combination product), if current scientific understanding may potentially lead to a different classification of that product than the Agency previously applied, the Agency generally intends to refrain from providing, within 60 days of receipt of the RFD, a 'written statement' or letter of designation concerning the requested classification or component of FDA that would regulate the product pursuant to section 563 of the FD&C Act. 21 U.S.C. § 360bbb-2. As a result, in such cases, the recommendation made by the submitter concerning the classification or Agency component would be considered a final determination by FDA of such classification or component. 21 U.S.C. § 360bbb-2(c); 21 CFR § 3.8(b)."

In other words; if, using current definitions and "thinking" expressed in its guidance documents, a product would now be classified as "device" that was previously classified as a "drug", the Agency would not formally issue a response to a RFD for the product, but would allow the sponsor's recommendation in its RFD to stand if the Agency doesn't respond to the RFD within 60 days. This allows products that were previously, and perhaps mistakenly, classified as "drugs" to be tacitly classified as "devices".

Interpretation of the Term "Chemical Action" in the Definition of Device Under Section 201(h) of the Federal Food, Drug, and Cosmetic Act

This guidance document paints a fairly bright line that distinguishes chemical action from other interactions that occur between a device and a patient or entity that interacts with the patient. This is important because the characteristics that differentiate a drug from a device are that a device "*does not achieve its primary intended purposes through chemical action within or on the body of man or other animals* and… is not dependent upon being metabolized for the achievement of its primary intended purposes. (emphasis added)."

Under the Agency's interpretation, a product exhibits "chemical action" for purposes of the device definition at section 201(h) of the FD&C Act if, through either chemical reaction or intermolecular forces or both, the product:

- Mediates a bodily response at the cellular or molecular level, or
- Combines with or modifies an entity so as to alter that entity's interaction with the body of man or other animals.

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For purposes of these factors, the term "chemical reaction" means the formation or breaking of covalent or ionic bonds, and "intermolecular forces" are electrostatic interactions or forces resulting from the interaction of localized, short-range electrical fields among atoms and/or molecules. Intermolecular forces include ion-dipole interactions, permanent dipole-based interactions, and induced dipole-induced dipole forces.

Further, unless the covalent bonding, ionic bonding, or intermolecular forces of a product mediate a bodily response at the cellular or molecular level or combine with or modify an entity to alter the entity's interaction with the body, the product does not exhibit "chemical action".

The guidance provides several examples of chemical action, including hydration, catalytic action, selective binding of a chemical agent to a molecular receptor, influence of molecular diffusion in liquids, neutralization, detoxification, precipitation and/or crystallization, dissolution of a solute by a solvent, and surfactant action. It's a good read for surface science geeks and other technically oriented folks who are interested in the FDA's thought processes and the logic it applies in its science-based decision making.

One draft guidance document has been published that is particularly relevant to those who are developing new low- or medium-risk devices that employ novel technologies. These devices do not have legal predicate devices on which to base "substantial equivalence" in a 510(k) premarket notification. Therefore, these new devices are automatically classified into Class III by the FDA and require submission of a Premarket Approval application (PMA). One avenue open to manufacturers of such devices is the "de novo" process. By following the de novo process, it is possible to classify the new device into Class I or II and avoid having to submit a PMA to allow its marketing in the U.S. However, the review times for devices that follow the de novo pathway have been extremely long, resulting in delayed market introductions. The FDA has targeted the process for improvement and recently published a new draft guidance document, Draft Guidance for Industry and Food and Drug Administration Staff - De Novo Classification Process (Evaluation of Automatic Class III Designation) that outlines a potentially more streamlined process.

According to the old guidance document currently in place, the de novo process could not be initiated until a 510(k) for the new device was submitted and the device was found to be "not substantially equivalent (NSE)" to a currently marketed cleared device, or device legally marketed before the implementation of the Medical Devices Amendments of 1976. The proposed guidance would allow for early submission of a pre-de novo package. Once the information in the pre-de novo package is accepted by the Agency, both a 510(k) and de novo application would be processed by the Agency with a combined total review period for both of 120 days. The draft guidance provides a more defined pathway, and essentially assures a back-end review period of 120 days by insisting that appropriate upfront information is provided in the pre-de novo package. I'll be discussing the provisions of this draft guidance in a SurFACTS Webinar in February. Details will be posted on the Surfaces in Biomaterials website.

In the next issue of SurFACTS I'll summarize the changes that the FDA has proposed for or implemented to its 510(k) process. If you have any other issues you'd like to see addressed or articles you'd like to contribute to this column, please feel free to contact me, and, if they are relevant to the surfaces community, I'll do my best to address them or have them published.

ICP/MS Analysis of Silver as an Antimicrobial Agent

By Wendy Fleming and Bill Katz, Katz Analytical Services

The precious metal silver, unlike any other metal, is a natural antimicrobial agent. It is noted that silver is effective against many different bacteria, fungi, and viruses. In fact, early civilizations such as the ancient Phoenicians who flourished around 1200BC, used silver bottles to prevent their drinking water from spoiling. The use of silver for medicinal purposes is actually documented all the way back from 750AD, with the first scientific papers published on the subject starting around 1881. The use of silver to prevent infection continued through history into the first World War until the discovery of penicillin in the 1940s. In the 1960s, silver use was revitalized in the form of AgNO3 for burn care management.

Today, with the ever increasing number of antibiotic-resistant strains of bacteria, the use of silver as an antimicrobial agent has made a resurgence in medicine and also maintains a great deal of relevance to many fields of study and industries. Because of its favorable chemical properties, natural abundance, simple and effective mechanism of action, minimal bacterial resistance, and low toxicity, silver is currently being integrated into many different applications. Today, one will find silver widely used in water filters, as a drinking water disinfectant, in wound care on bandages and dressings, in foams for surgical sutures, in topical creams for burn management, permeated into vascular and urinary catheters, and embedded as particles in microfiber cloth for surgical masks.

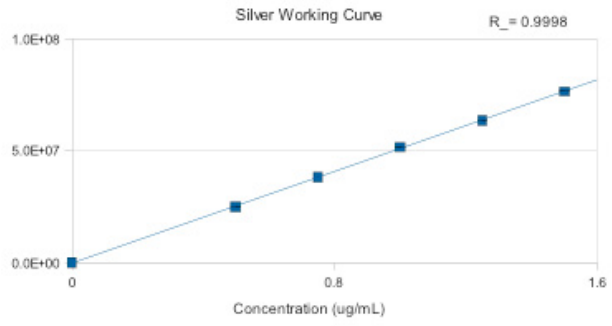
The mechanism of action of silver as an antimicrobial agent is only now being investigated and more understood. Recent studies show that silver is only effective as an antimicrobial in its ionized form, Ag+ (Lok et al., 2007; Rai et al., 2009). Because it's the Ag+ that is effective, it provides broad flexibility, in that it can be integrated in the application in its salt forms AgCl and AgNO3 for immediate Ag+ release or as silver sulfadiazine for a more controlled release that continues for a longer time period. Metallic silver coated nanoparticles also allow for that controlled release as the metallic silver slowly reacts with moisture converting it to Ag+. It is thought that silver atoms bind to thiol groups (-SH) in enzymes and subsequently cause their deactivation. Silver forms a stable S-Ag bond with thiol-containing compounds in the cell membrane that are involved in transmembrane energy generation and ion transport (Klueh et al., 2000).

Another proposed mechanism is that Ag+ enters the cell and intercalates between the purine and pyrimidine base pairs disrupting the hydrogen bonding between the two anti-parallel strands and denaturing the DNA molecule (Klueh et al., 2000). Although this has yet to be proven, it has been shown that silver ions do associate with DNA once they enter the cell (Fox and Modak, 1974).

When considering analytical techniques for determining total silver content, inductively coupled plasma-mass spectroscopy (ICP-MS) is typically the favored technique. Since silver is not ubiquitous and is easily ionized, detection limits are extremely low, generally in the part per trillion (pg/mL) range.

Following are some actual analytical values and a working curve used for the quantitative analysis of silver; note the outstanding linear correlation coefficient (0.9998) obtained for this type of study. Further, we note a limit of detection of 50 part per trillion or 50 pg/ml. The use of ICP-MS thus provides an excellent technique for the determination of silver.

- Accuracy RSD <1.0%
- Precision RSD <1.0%
- Limit of Detection: 50 ppt (pg/mL)



Main Concepts and Techniques for Contact Angle Measurements of Biomaterials

By Dehua Yang and Ryan Farel, Ebatco

Abstract

Surface characterization is important for determining appropriate material surface properties for a given application. Contact angle measurement is a widely-applied method to characterize the wettability of a solid surface. With increasing applications, contact angle measurements have been used in studies and characterization for the purposes of better understanding and control of wettability, hydrophobicity, hydrophilicity, and biocompatibility of biomaterials.

To assist scientists and engineers who have interests in contact angle measurements but yet to become more familiar with the subject, this paper will introduce a few major concepts and techniques about contact angle measurements with examples of applications on biomaterials. The concepts include static contact angle, advancing and receding angle, contact angle hysteresis, hydrophobicity, hydrophilicity, surface tension, surface free energy, wettability. The techniques touched on here encompass sessile drop method, extension and contraction method, sliding angle method, surface free energy analysis, and more. Biomaterials used for exemplification of these techniques include polymer catheters and gelatin capsules.

Introduction

According to NIH, a biomaterial is defined as any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body[1]. It is obvious that functional biomaterials will be in close contact with biological tissues and bodily fluids. Therefore biocompatibility will be an extremely important issue for biomaterials. One of the critical factors that could influence biocompatibility of the biomaterials is the surface, its hydrophilicity, hydrophobicity and wettability, since the surface will be in contact and possibly interact with biological tissues and bodily fluids. Contact angle as a digital index of wettability is thus considered and employed in characterization of biomaterial surfaces. Publications and reviews have been conducted to understand the impact of contact angle on the biocompatibility of biomaterials[2]. In this paper, contact angle measurement related techniques and their applications on biomaterials are introduced and discussed in the following sessions.

Contact Angle, Wettability, Hydrophilicity and Hydrophobicity

When a liquid encounters a solid surface, the interaction between the interfacial tensions forms a droplet shape. The Young Equation *(1)* governs the shape of the droplet assuming that the liquid is in contact with a uniformly flat and a rigid surface. The interfacial tension forces are balanced at the three phase interface point of vapor (under the most of circumstances air), liquid and solid as shown in Figure 1. Where θ is the contact angle, γS the solid surface tension or sometimes referred as interfacial tension between solid and vapor phases, γL the liquid surface tension or sometimes referred as interfacial tension between the liquid and vapor phases, and γSL the solid-liquid interfacial tension. *(1)*

$$\gamma_S = \gamma_L \cos\theta + \gamma_{SL}$$

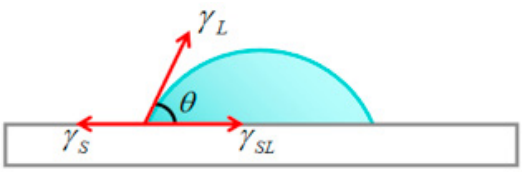


Figure 1. Interfacial tension components and contact angle of a liquid droplet on a solid surface.

The contact angle is a measure or a digital index of a surface's wettability. The term wettability refers to the quality or degree of a solid surface being wet by a liquid. Complete wetting is achieved when a continuous layer of liquid is spread over and stuck on the solid surface or the liquid has a zero contact angle with the solid. Partial wetting is achieved when the liquid would not form a continuous layer and contact angle has a non-zero value. When a material has a contact angle with water greater than 90°, that material is hydrophobic or water fearing. When a material has a contact angle with water less than 90°, that material is hydrophilic or water loving. A special case for a hydrophobic material occurs when the contact angle is greater than 150°. When this occurs, that material is

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called superhydrophobic. In nature, lotus leaves are superhydrophobic. These leaves repel water and maintain cleanness by easily removing dirt from their surfaces with assistance from rain drops. This phenomenon is named the Lotus Effect and has been enthusiastically mimicked for possible industrial applications[3,4].

Advancing Angle, Receding Angle and Contact Angle Hysteresis

The contact angle discussed above is of static nature or equilibrium contact angle between a liquid and a solid. In a dynamic process when liquid volume is modified the contact angles measured are called dynamic contact angles. When adding more liquid to the droplet, the contact angle at the time when the liquid contact area starts to increase or the liquid advances is called the advancing angle. The advancing angle is the maximum contact angle the liquid and the solid may have. When reducing the volume of the droplet, the contact angle at the time when the liquid contact area starts to decrease or the liquid recedes is called the receding angle. The receding angle is the minimum contact angle between the liquid and the solid. The difference between the advancing and receding angle is the contact angle hysteresis as shown in Equation *(2)*.

$$\theta_H = \theta_A - \theta_R$$

Where θH is the contact angle hysteresis, θA is the advancing angle and θR is the receding angle. These two contact angles are the dynamic contact angles which are useful parameters when studying dynamic processes such as the ones in spin coating, cleaning and drying. The static contact angle typically falls between the advancing and receding angles. Surface roughness, surface heterogeneity, overturning of molecular segments at the surface, interdiffusion, and/or surface deformation are possible reasons for the contact angle hysteresis[5].

Surface Free Energy and Surface Tension

Contact angle measurement is a simple and quick way to quantify a surface's wettability. Contact angle measurements on a solid surface using liquids with known surface tension components may determine the surface free energy of a solid surface. Surface tension of a liquid or surface free energy of a solid surface, sometimes interchangeably used, is the excessive energy existing on the surface of a liquid or a solid due to imbalanced intermolecular forces at the surface of the matter. The surface free energy analysis provides a more in-depth characterization of a surface chemically and energetically. The analysis is of significance to numerous applications such as wetting, cleaning, adhesion and wear. Besides, surface free energy analysis of solids using contact angle technique is quite popular and essential because it is easy to perform and it can yield highly accurate results[6].

The basis for surface free energy analysis consists of three components: A. the Young-Dupré Equation as shown in Equation *(3)*, B. assumption that surface tension or surface free energy can be divided into components, C. theories about expression of work of adhesion, WSL. Different components B and C exist based on several models or theories. Five of the more popular theories are acid-base, Kitazaki-Hata, Owens-Wendt, Kaelble-Uy and Wu theories. *(3)*

$$W_{SL} = \gamma_L(1+\cos\theta)$$

The acid-base theory splits the surface free energy into long range Lifshitz-van der Waals and short range Lewis acid-base components. The Kitazaki-Hata theory divides the surface free energy into dispersion, polar and hydrogen-bond components. The Owens-Wendt theory only utilizes the dispersion and hydrogen-bond components to express the surface free energy. The Kaelble-Uy theory assigns dispersion and polar components for the surface free energy. The Wu theory uses dispersion and polar components. Except for the Wu theory that uses a harmonic mean computational model for the work of adhesion, other theories all are adhered to geometric means expression. Equations *(4)* and *(5)* are mathematical descriptions of the most popular Owens-Wendt theory.

$$\gamma = \gamma^d + \gamma^h$$

$$W_{SL} = 2\sqrt{\gamma_S^d \gamma_L^d} + 2\sqrt{\gamma_S^h \gamma_L^h}$$

Where superscripts d and h are for dispersion and hydrogen component respectively; subscripts S and L are for solid and liquid respectively. Combining Equation *(3)* and *(5)*, one can get Equation *(6)*.

$$2\sqrt{\gamma_S^d \gamma_L^d} + 2\sqrt{\gamma_S^h \gamma_L^h} = \gamma_L(1+\cos\theta)$$

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Using Equation ***(6)*** and 2 probe liquids with known surface tension components and their two measured contact angles one can solve the two simultaneous equations to derive the two components for the solid surface free energy.

It is interesting to point out that because each theory has its own assumptions and limitations, there is not one theory that can be universally applicable to all solid surfaces and liquids. Sometimes a particular model will yield useful data and other times it will not based on the combination of probe liquids chosen. Scientists and engineers may need to work with more than one theory in practice. In spite of this, surface free energy analysis through contact angle measurement remains a popular choice for its component level analysis capability and ease of operation. A protocol for determining the surface free energy of dental materials using the Acid-Base theory provide a guide on how to select the probe liquids and process the data to obtain more meaningful results[6].

In addition to measuring total surface free energy and its components, it is possible to extract other useful information from the same data obtained for surface free energy analysis. By applying the Young-Dupré Equation ***(3)***, the work of adhesion between liquid and solid; and by applying the Young Equation ***(1)***, interfacial tension between liquid and solid can be calculated out as well. If surface free energy analyses are conducted using multiple probe liquids and on several solid samples, work of adhesion and interfacial tension may be found for any combinations of solid-solid, solid-liquid and liquid-liquid interfaces. These kinds of analytical abilities make the surface free energy analysis a very powerful technique in analyzing adhesion strength between adhesives and bonding surfaces.

Contact Angle Measurement Related Techniques

Contact angle measurements offer numerous advantages over other surface analysis techniques. Different methods of contact angle measurements can help to provide a better understanding of surface properties. Contact angle measurements have monolayer-detecting sensitivity and do not require a vacuum environment. Comparatively, the instrumentation used for contact angle analysis is less costly than many other surface analysis instruments. Figure 2 shows a fully automatic contact angle meter with sliding angle measurement capability.

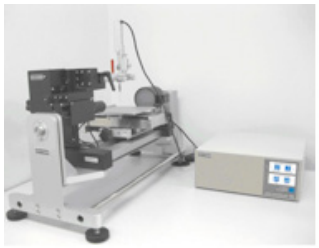

Figure 2. Fully automatic contact angle meter Model DM-701 made by Kyowa Interface Science Co. Ltd.

Sessile Drop Method

The technique used for static contact angle measurements is the Sessile Drop method. A contact angle meter or a goniometer first creates a droplet of a desired size through a liquid dispenser. Instrument automatically deposits the droplet onto the sample surface to form a sessile drop. High-speed camera captures a picture of the sessile drop resting on the sample surface and computer software then fits and analyzes the drop shape to determine the contact angle. Figure 3 is a typical image of a sessile drop on a reflective surface for contact angle measurement.

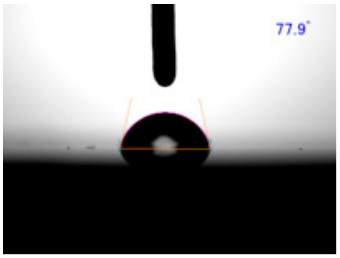

Figure 3. A typical image of a sessile drop on a reflective surface for contact angle measurement; pink color line is fitted with a circle fitting routine; the measured contact angle is 77.9 degree.

Catheters serve as a means to transport liquid into or out of the human body or as a carrier for other implantable devices such as lead or guide wires, stents or balloons. Since the outer surface of catheters will be in contact with bodily fluids during the insertion or removal processes, understanding the surface wettability can better improve their performance in field applications. Table 1 presents contact angle measurement results on 3 kinds of extrusion polymer catheters with distilled water. It can be known that Catheter A and C are hydrophobic as extruded. In order to reduce insertion resistance or to make the surface more lubricious the current

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industrial trend is to have the two kinds of catheters undergo hydrophilic coating or surface treatment.

Polymer Catheter	Contact Angle (in degrees)
A	106.2
B	78.6
C	98.3

Table 1: Contact angle measurement results for extruded polymer catheters with distilled water.

Extension and Contraction Method, and Sliding Angle Method

Several methods exist to measure the dynamic contact angles. Two such methods are the extension and contraction method and the sliding angle method.

For the extension and contraction method, during the extension portion, a droplet is deposited onto the solid surface first. With the dispenser tip inside the droplet, additional liquid is added to allow the contact angle to reache a maximum. Then the contact base of the droplet expands outward. During the contraction portion, instead of adding liquid, liquid is removed from the droplet until the contact angle reaches a minimum. Then the contact base of the droplet decreases towards the center. A high-speed camera is necessary to capture the changing drop shape. Figure 4 and 5 are the optical images and contact angle measurement data obtained on a polymer catheter for advancing and receding angle analysis using the extension and contraction method. For the sliding angle method, after depositing a droplet onto a solid surface, the instrument rotates the solid surface relative to the horizontal

Figure 4. Images captured during advancing (top) and receding (bottom) angle measurements on a polymer catheter surface.

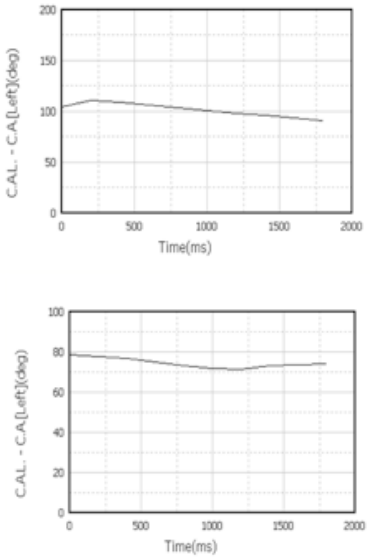

Figure 5. Contact angles measured over time through extension and contraction methods for advancing (top) and receding (bottom) angle determination of a polymer catheter.

plane until the droplet moves under gravity influence. The advancing and receding angles are the liquid drop front and rear end contact angles respectively at the drop slide starting point.

The sliding angle method provides extra data in addition to the advancing and receding angles. The tilt angle at which the deposited droplet slides from its original position is the sliding angle or the roll-off angle. Sliding angle has its own practical meaning and usefulness. Its simply conceivable applications are in windshield and building roof designs. The slope and material choices in designs ought to be in favor of rain drops' rolling off. The angles of the surfaces relative to the ground should be at least larger than the water sliding angles on the surfaces of the windshield and roofing materials. It is possible that sliding angle could be a useful parameter for the biomaterials for applications where liquid flow under gravity is of interest.

Table 2 lists the water advancing angle, receding angle and sliding angle measurement results on the polymer catheters using a sliding method.

Surface Free Energy Analysis

Surface free energy analysis of a solid surface requires a contact angle meter to measure the contact angles of at least two probe liquids with known surface tension components and a software program to process the data based on an established theory. The

Polymer Catheter	Sliding Angle (in degrees)	Advancing Angle (in degrees)	Receding Angle (in degrees)	Hysteresis (in degrees)
A	31.0	115.3	96.4	18.9
B	46.3	95.4	75.0	20.3
C	38.5	104.9	84.2	20.7

Table 2: Water advancing angle, receding angle, and sliding angle of polymer catheters.

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instrument shown in Figure 1 comes with a software program that has the ability to apply five theories to the surface free energy analysis. The software also comes with features that can use the choice of probe liquids to determine which theories are applicable and functional based on their requirements and assumptions.

Gelatin capsules are used in food and pharmaceutical industries as shells for holding drug and nutrient ingredients. There are two easily-understandable reasons for surface free energy analysis of gelatin capsules: to ensure an easy flow when being swallowed with water and to avoid capsules sticking to each other when being stored in a container. The probe liquids water, a polar liquid, and methylene iodide (diiodomethane), a non-polar liquid, were selected for the surface free energy analysis of two kinds of gelatin capsules. Table 3 shows the surface free energy components of the two probe liquids according to theories of Owens-Wendt, Kaelble-Uy and Wu.

With the components of each liquid known for the desired theories, the surface free energy are calculated based on the measured contact angle formed with each liquid.

As can be seen from Table 3, the surface free energy components used by the three different theories vary although the total surface free energy is the same value for each probe liquid. Because of these differences in models it is for the best to consider multiple theories when determining the surface free energy. Table 4 shows the surface free energy of two gelatin capsule specimens based on the Owens-Wendt, Kaelble-Uy and Wu theories. Even though each theory calculates the surface free energy differently for each gelatin sample, they are not drastically different from each other. All theories have measured lower total surface free energy values for gelatin type 1 than type 2.

Theory of Energy Analysis	***Owens-Wendt***			***Kaelble-Uy***			***Wu***		
Probe Liquid	SFE (mJ/m^2)			SFE (mJ/m^2)			SFE (mJ/m^2)		
	d	h	Total	d	p	Total	d	p	Total
Water	21.8	51.0	72.8	21.8	51.0	72.8	22.1	50.7	72.8
Methylene Iodide	49.5	1.3	50.8	48.5	2.3	50.8	44.1	6.7	50.8

Table 3: Surface free energy components of two probe liquids.
d = dispersion component, h = hydrogen-bond component, p = polar component.

Other Contact Angle Measurement Related Techniques

In addition to the above mentioned contact angle measurement techniques, a few other related techniques that are used less often are good for special applications or are just emerging. They are briefly discussed in this section.

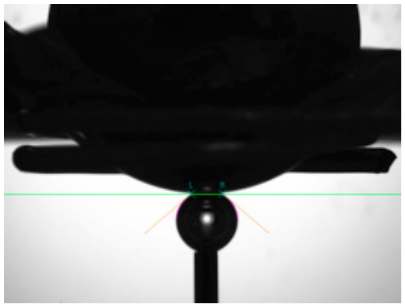

Figure 6. An optical image used for contact angle measurement of a hydrogel contact lens in contact lens solution using the captive bubble method.

Captive Bubble Method

Captive bubble method is very useful when biomaterials have dehydration concern if they would be tested in an ambient air environment. To measure contact angle using the captive bubble method, instead of a straight liquid dispensing tip, an inverted needle is employed, and samples are submerged in the testing liquid in a container with an appropriate sample support. A captive air bubble is made using the inverted needle to create an air, liquid and solid three phase interface at the sample surface. The static contact angle at equilibrium, or receding angle and advancing angle when air bubble expands or retracts can be measured. Figure 6 depicts an image used in hydrogel contact lens contact angle measurement in contact lens solution using the captive bubble method. As for the Sessile drop method, in order to measure correct contact

Theory of Energy Analysis			***Owens-Wendt***			***Kaelble-Uy***			***Wu***		
Sample	C.A. (deg)		SFE (mJ/m^2)			SFE (mJ/m^2)			SFE (mJ/m^2)		
	Water	Methylene Iodide	d	h	Total	d	p	Total	d	p	Total
Gelatin 1	87.5	57.5	27.5	3.6	31.1	26.9	3.7	30.6	24.5	8.6	33.1
Gelatin 2	73.3	59.5	24.0	11.3	35.3	22.5	12.0	34.5	21.3	16.7	38.0

Table 4: Surface Free Energy Analysis of Two Gelatin Samples.

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angle a curvature correction routine is necessary for determining the right contact angle when working with a curved surface such as the hydrogel contact lens shown below.

Microscopic Contact Angle Measurement

Contact angle measurement at microscale is an emerging technique to study surface properties of single particles, filaments, fibers, medical lead and guide wires, patterned organic light emitting display, microcircuits, microfluidic channels, micro-patterned surfaces, lotus effect, and high-speed ink-jet printing. The instrument is equipped with a unique capillary liquid dispensing system that has an inner diameter of 5-50μm, for making a liquid drop <30μm in size and picoliter to nanoliter in volume. In addition, the instrument comes with high power orthogonal vertical and horizontal optics for accurately placing and measuring such small drops on micrometer features, and CCD cameras with capturing speeds of up to 100,000 frames per second for studying dynamic characteristics of interaction between micron-sized liquid droplets and solid surfaces. For more information about this technique and about measuring wettability of biosurfaces at the microscale please refer to reference[7].

Pendant Drop Method

In general, low surface tension liquids have better surface wetting properties. High surface tension liquids have a higher tendency to form droplets. Surface and interfacial tension have infinite numbers of industrial applications where liquids, liquid to liquid interface, or liquid to solid interface are of interest. One of the most known applications could be in surfactant. Surfactant is a surface active agent to reduce surface tension of a liquid in order to increase the solution's wettability to surfaces or increase cleaning efficiency.

Any liquids that can be expelled through the dispenser tip of a contact angle meter can be measured by the so called Pendant Drop method. For conducting the measurement, the largest possible droplet is created on the end of the needle of liquid dispenser on a contact angle meter. Using the Young-Laplace analysis routine, the surface and interfacial tension of the liquid is found. The liquids that can be analyzed include aqueous solutions, beverages, chemicals, cosmetic creams, food pastes, inks, oils, paints, surfactant solutions, tooth pastes, etc. To accurately measure the surface tension, the droplet has to reach equilibrium. Most liquids will reach an equilibrium point quickly. Thicker fluids may take a bit longer to reach equilibrium.

Wilhelmy Balance Method

Wilhelmy balance method is an alternative contact angle measurement technique to the one performed on a contact angle meter. It is conducted on a precision electronic balance designed for surface tension measurement of liquids and most often referred to as a surface tensiometer. Surface tensiometers utilize a thin Wilhelmy plate to measure liquid surface tension. Based on the same principle shown in Equation *(7)* for surface tension measurement, the surface tensiometers can be engaged in contact angle measurements of plates, fibers, wires or rods if the liquid surface tension is known. *(7)*
Where F is the meniscus force acting

$$F = L\gamma_L \cos\theta$$

on the sample, L the peripheral length of the sample, γL the liquid surface tension, and θ the contact angle. The contact angles determined through Wilhelmy balance method are of dynamic nature. When the sample is being dropped into the liquid advancing angle is measured, when the sample is being pulled out the liquid receding angle is obtained.

Powder Contact Angle

Depending on the powder sizes, the contact angle of an individual powder particle can be measured using the micro contact angle meter if its size is more than tens of microns. The contact angle of fine powders may be measured based on Washburn equation using a surface tensiometer equipped with a powder measurement kit. First, the powder to be measured is packed into a column tube with a filter base. This tube is suspended vertically on the electronic balance of the surface tensiometer. When the tube is lowered to contact the liquid, the liquid infiltrates into the voids between powder particles. The infiltration rate of the liquid into the bulk powder is measured by recording the weight gain as a function of time, which may then be used to solve the Washburn equation for contact angle determination.

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Zisman Plot

Zisman plot is used to determine the so called critical surface tension of a solid surface, originally developed by Zisman in the 1950s[8]. The critical surface tension is the value of surface tension of a liquid, below which the liquid will spread on a solid or wet a solid completely. The determination of the critical surface tension is carried out by measuring the contact angles of liquids with different surface tension values, plotting the cosine values of the contact angles vs. the liquid surface tensions, and finding the surface tension corresponding to the extrapolated point with zero contact angle on the plot. The critical surface tension is not the total surface free energy of a solid and may be an approximate to the dispersive component[6]. At present, Zisman plot is not commonly applied, mainly because of insufficient theoretical justification and time-consuming investigation procedures[9].

Conclusive Remarks

Contact angle based techniques have been used in characterization of a variety of biomaterials for accurate results, ease of use, extremely high sensitivity and low cost of operation. The properties that contact angle measurement may be of significance include biocompatibility, surface wetting properties, hydrophobicity, hydrophilicity, surface cleanliness and contamination detection, liquid absorption and permeability, coating adhesion, and solid surface free energy, etc. We hope this brief introduction and overview could assist scientists and engineers to better understand and grasp these promising and useful techniques for biomaterial applications.

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America Invents Act Continued from Page 8

minimizing or deferring tax liability.

- Allows for filing of patent applications by entities other than the inventor (e.g., by the owner/assignee).
- Eliminates the "best mode" requirement as a cause rendering a patent invalid or unenforceable.
- Provides for prior user rights in the case of a trade secret being indecently invented and patented by another.
- Creates a micro-entity status for an independent inventor with a yearly gross income of than three times the national median household income who has previously filed no more than four non-provisional patent applications, not including those the inventor was obligated to assign to an employer. The micro-entity is entitled to a 75% reduction in patent fees.
- Allows for confidential sales of products without triggering a "one-year grace period." However, such sales will still eliminate patentability in most other patent regimes throughout the world.

Readers should appreciate that the AIA is a complex bill totaling over 150 pages of complex language. The practical implications of some provisions of the law will take years and many court cases to be understood and appreciated. Further, certain aspects of the law may affect some inventors more than others and have a greater impact on some technologies compared to others. Thus, while I did not review finer points and nuances of the law, the above discussion represents a very brief synopsis of some of the main changes included in the America Invents Act.

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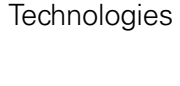

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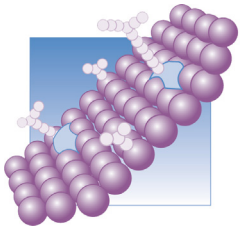

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