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BioInterface 2015 Student Poster Winner

Opacification of Shape Memory Polymer Foams Using Tungsten Nanoparticles for Neurovascular Embolic Applications

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Introduction

In this work, the authors developed radiopaque composite materials using shape memory polymers (SMPs) for their use as biomedical implants. Thermally actuated shape memory polymers are a special class of materials that are capable of switching between a primary and a secondary shape upon a heat stimulus. [1-3] Previously synthesized SMP foams have proven to rapidly occlude aortic aneurysms and the resulting clot is stable up to 90 days. [4, 5] These SMP foams can further be utilized for a neurovascular occlusion device due to their ultra-low density, which allows for the material to be crimped to a small geometry and delivered to the aneurysm via catheter. [5]

X-ray visualization of the device, however, is a challenge, because the polyurethane SMP material has a density similar to soft tissue and cannot be observed during x-ray fluoroscopy. [4] Therefore delivery of the foam to the aneurysm in a safe and reliable manner is a significant challenge, as guidance by x-ray contrast cannot be used. The purpose of this work was to introduce radiopacity to the foam using heavy metal nanoparticles, which can be incorporated into the polymer using physical mixing. Tungsten has been used as a radiopaque agent previously for embolic coils with much success. [4, 6-8] Based on the established biocompatibility of tungsten, Rodriguez et al. synthesized SMP foams for embolic applications with tungsten micropar-

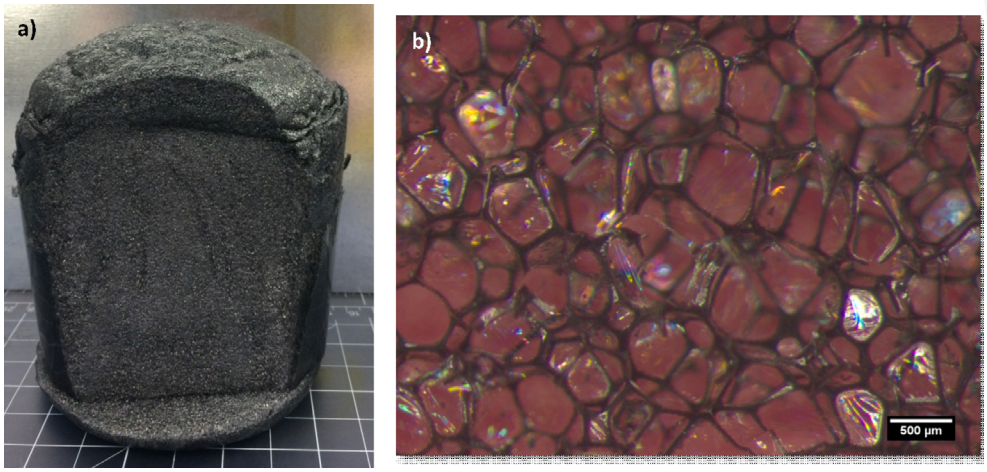

Figure 1: a) Bulk morphology of a 4% W nanocomposite. b) Microscopic image of a 4% W nanocomposite.

BioInterface 2015 Student Winner ... continues on pg. 2

INSIDE THIS ISSUE

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ticles to induce x-ray visualization and achieved sufficient opacity with foam geometries up to 6 mm diameter cylinders. [4] While the SMP microcomposites were visible under x-ray fluoroscopy, radiopacity was highly dependent on the diameter of the foam cylinders. Larger diameter cylinders would limit the accessibility of the embolic devices to peripheral blood vessels only therefore small geometry radiopaque materials need to be developed for neurovascular applications. Additionally, high filler loading disrupted foam synthesis. Previously, 4% by volume was the maximum tungsten loading that could be achieved with microparticles which would also require the use of large geometry foam cylinders for visualization. This study aims to increase filler loading by using tungsten nanoparticles, allowing for improved particle dispersion resulting in visualization of smaller geometry materials for neurovascular devices that require radiopacity through soft and hard tissue. [9]

Fabrication of SMP Foams

SMP foam synthesis was conducted using the protocol described by Hasan et al. Isocyanate (NCO) pre-polymer was first synthesized and cured for 32 hours at 50°C. TMDHI comprised the NCO pre-polymer along with 35% of alcohols (HPED and TEA). [10] W nanoparticles (40-60 nm) were dispersed in the NCO pre-polymer, prior to foam blowing, at 4% to 11% by volume. Molar equivalent of the remaining hydroxyls was added to the hydroxyl (OH) pre-polymer. The resulting OH pre-polymer was combined with the NCO-W mixture, along with catalysts, surfactants, and Enovate. [10] The foam was cured at 90°C under vacuum at -10 mmHg for 10 minutes. [10] The SMP foam was allowed to cool to room temperature before further characterization. [10] Figure 1a shows the typical morphology of a SMP nanocomposite and Figure 1b shows a microscopic image of the pore morphology.

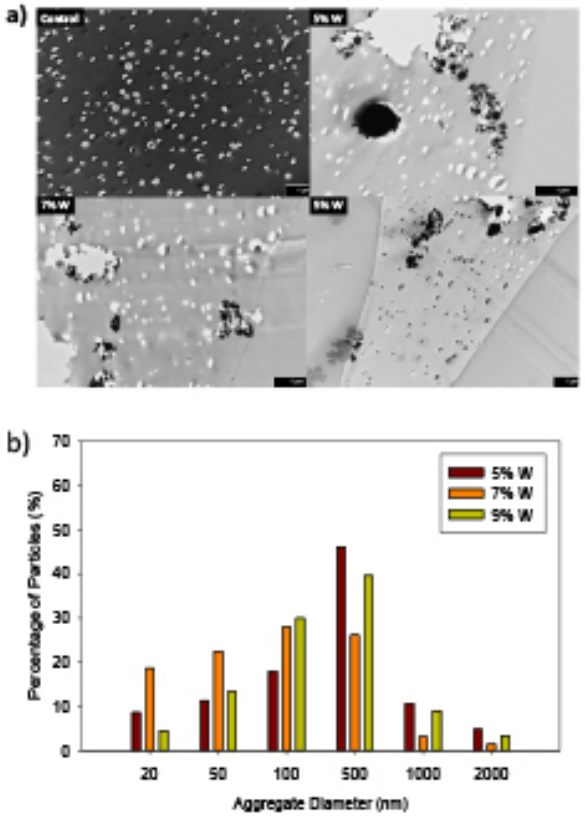

Figure 2: a) Transmission Electron Microscopy (TEM) image showing filler dispersion of various SMP nanocomposites. b) Quantification of W aggregate sizes.

Filler Dispersion

Incorporation of W nanoparticles into the SMP system resulted in aggregate formation at the nanoscale even at low concentrations, Figure 2. TEM image of the control (0%W) foam shows nanopores within the polymer struts which indicate the occurrence of these defects as a part of the foaming process rather than as a result of filler incorporation. However, 5%W, 7%W, and 9%W composites have filler aggregates in the polymer struts that imply poor dispersion of the nanoparticles with physical mixing.

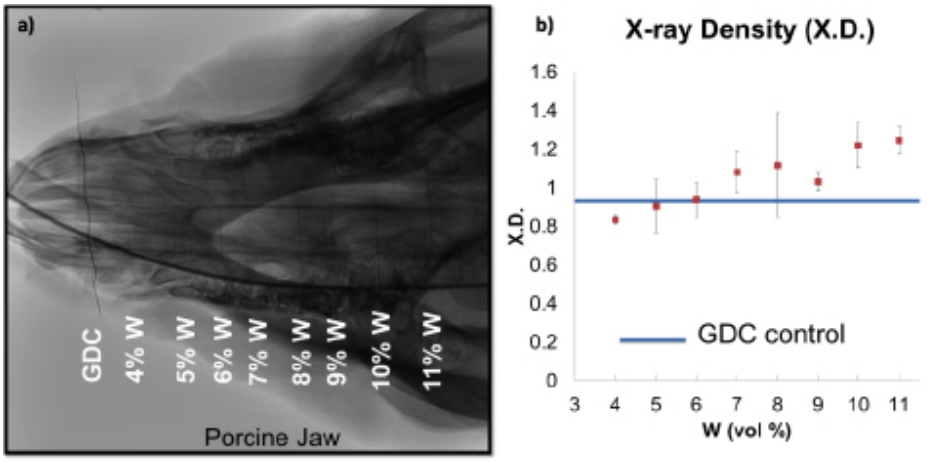

Figure 3: a) X-ray fluoroscopy images of the SMP nanocomposites under a porcine head. b) X-ray density of SMP nanocomposites.

Physical Properties of SMP Nanocomposites

Foam density increased markedly, from 0.013 to 0.060 g·cm^{-3}, with greater W incorporation due to the added mass within the foam struts per block, Table 1. All compositions, however, maintained low densities, indicative of the foams retaining high surface area to volume ratios. Porosity calculations (Table 1) showed high porosity (> 98%) for all compositions with low standard deviation, indicating cell uniformity throughout the bulk foam.

Thermal characterization of the foams revealed increasing transition temperatures with greater W loading (Table 1). Nanoparticle incorporation restricted polymer mobility at the molecular level and increased the number of physical crosslinks within the SMP network.

BioInterface 2015 Student Winner ... continues on pg. 3

The addition of these physical cross-links requires greater heat input for the polymer to transition from the glassy to the rubbery state therefore shifting the T_g towards higher temperatures.

x-ray more effectively, increasing from 0.8 to 1.2 at 45 KV.

Actuation Profiles

Nanoparticle addition altered passive actuation kinetics of SMP foams at physiological temperature (Figure 4).

W (vol %)	ρ_{foam} (g·cm^{-3})	Porosity (%)	Dry T_g (°C)	Wet T_g (°C)
Control (0% W)	0.013 ± 0.001	99 ± 0.1	58 ± 2	34 ± 1
4% W	0.033 ± 0.004	98 ± 0.2	63 ± 1	28 ± 1
5% W	0.041 ± 0.000	98 ± 0.0	65 ± 1	35 ± 0
6% W	0.045 ± 0.002	98 ± 0.1	67 ± 0	38 ± 1
7% W	0.045 ± 0.004	98 ± 0.2	66 ± 1	39 ± 1
8% W	0.054 ± 0.009	98 ± 0.4	67 ± 1	41 ± 0
9% W	0.060 ± 0.011	98 ± 0.4	66 ± 1	41 ± 1
10% W	0.048 ± 0.003	98 ± 0.1	68 ± 1	41 ± 1

Table 1: Physical properties of SMP nanocomposites.

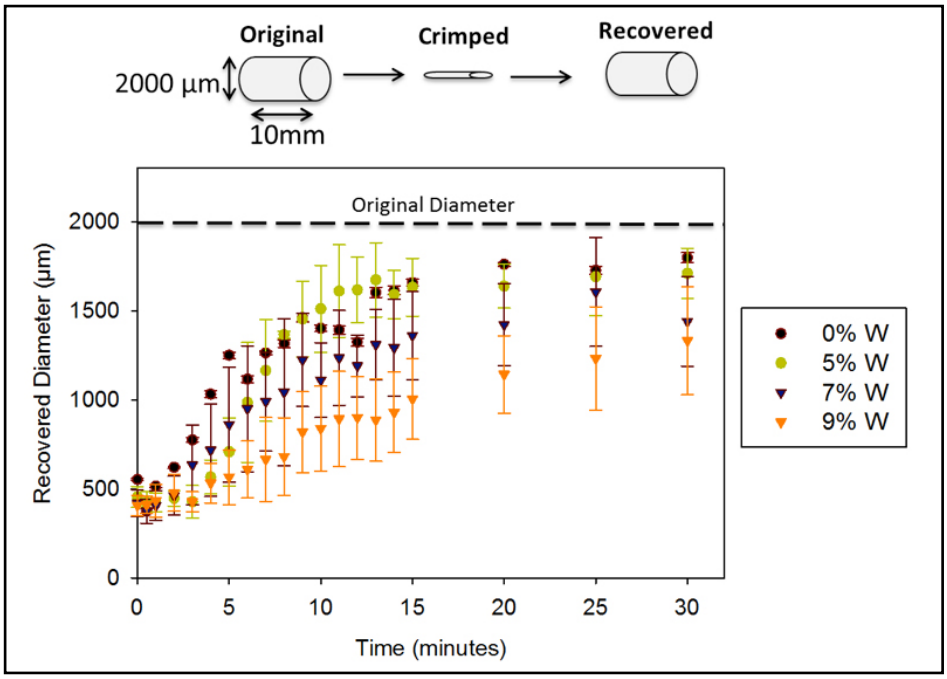

Figure 4: Actuation profiles of SMP nanocomposites.

X-ray Visibility of SMP Foams

Sufficient x-ray visibility, compared to Guglielmi Detachable Coils (GDC), was achieved for SMP nanocomposites with W loading greater than 6%, Figure 3a. Crimped foams attenuated x-rays through soft and hard tissue of the porcine head at various locations, suggesting acceptable visibility through qualitative analysis. Furthermore, quantitative evaluation of foam visibility was conducted via X.D. analysis (Figure 3b). With increasing W loading, the crimped SMP attenuates

The control foam actuated within 4 minutes. However, with increasing W loading the SMP experienced longer actuation times of 6, 8, and 10 minutes for 5% W, 7%W, and 9% W foams, respectively, which is reasonable given their increasing thermal transitions.

Conclusions

The new SMP nanocomposites provide greater control over device visibility and actuation kinetics compared to the previously developed systems. Nanoparticles afforded uniform filler dispersion and minimal foam destabilization compared to microparticles. The SMP foams have comparable radiopacity to current GDC coils and variable thermo-mechanical properties that make them optimal for use as embolic agents for neurovascular applications.

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Member News

BioInterface 2016 is scheduled for Oct. 3–5 in Minneapolis. Sessions and a call for abstracts will be announced shortly. We are looking for nominations for the **Surface Science Award Winner**. Please send any nominations to Joe McGonigle at mcgonigle@gmail.com.

Medtronic launched the VenaSeal Closure system for treatment of symptomatic venous reflux in November. The device uses an adhesive to close superficial veins in the lower extremities. The company also announced FDA approval of the MyCareLinkSmart™ Monitor. This is the first app-based remote monitoring system for patients with pacemakers. Medtronic acquired Aircraft Medical in a $110 million cash transaction to gain access to its affordable, high-quality video laryngoscopes used in patient intubation. This is expected to reduce the risk of respiratory compromise, the second most frequent safety adverse event in hospitals.

Medtronic and Samsung announced an expanded alliance for digital health solutions for chronic pain, movement disorders, incontinence and other conditions associated with neuromodulation therapy. In January, the company received CE Mark for the use of the IN.PACT® Admiral® drug eluting balloon in maintaining AV access for patients undergoing hemodialysis. Also in the dialysis space, Medtronic acquired Bellco a pioneer in hemodialysis treatment solutions and will add the company's products to its Renal Care Solutions business.

Carmeda announced enrollment of the first patients in the Gore RELINE MAX clinical study to evaluate the heparin-coated Viabahn endoprosthesis for treatment of in-stent restenosis in the superficial femoral artery. This study will enroll more than 100 patients in one of the most difficult populations with lower limb disease.

W.L. Gore received FDA 510K clearance of a unique biomaterial for hernia repair. The Gore®SYNECOR biomaterial is a combination of PTFE, the Gore®Bio-A® degradable scaffold and a film to prevent adhesions. This new material reduces the compromise surgeons must make when choosing materials for complex cases. The company also published a study on the use of the BIO-A® material in complex ventral hernia repair in the Annals of Surgery in January.

SurModics made two acquisitions to increase its expertise in device development and manufacturing, and continue its transition to becoming a whole-product solution provider. The first, Creagh Medical, is an Irish company that develops and builds balloon catheters. The second is NorMedix, a design and development company with expertise in thin-walled, minimally invasive catheter technologies. Both companies are expected to complement the company's hydrophilic coating technologies and drug-coated balloon platforms.

DSM Biomedical announced a partnership with Vention Medical to provide a single-source solution for catheters and coatings. Customers having catheters manufactured by Vention now have the option to integrate DSM's ComfortCoat® lubricious coating into the process. This offers many benefits including a streamlined supply chain and improved quality control. DSM also announced FDA clearance of the Dyneema Purity® radiopaque cerclage cable for orthopedic trauma treatment. This is the first device fully designed by DSM's polyethylene group to receive 510K clearance. This is the only polymeric cerclage cable on the market that is also radiopaque. The company also announced that Christophe Dardel will be stepping down as president and will be replaced by Gerard de Reuver on an interim basis.

Bausch&Lomb announced the acquisition of Alden Optical Laboratories, a manufacturer of specialty and custom contact lenses. This addition will allow the company to address serious visual challenges including irregular corneas.

ExThera Medical announced initiation of clinical trials of its Seraph® Microbind® affinity blood filter after receiving approval of the CE mark clinical trial protocol in Germany. The device will be used to treat dialysis patients with bloodstream infections. ExThera also was selected to participate in a Phase IV subcontract as part of the DARPA Dialysis-Like Therapeutics program. This selection was made after the device performed well during in vivo testing of MRSA removal.

CooperVision announced the initial rollout of Biofinity® XR contact lenses. This extended range toric lens is the only silicone hydrogel lens from a major manufacturer designed for prescriptions outside the traditional range. The lenses should be widely available in April.

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Device Coatings: FDA Update

Phil Triolo PhD, RAC

The FDA recently issued a warning about the potential for coatings to separate from their substrates (Lubricious Coating Separation from Intravascular Medical Devices: FDA Safety Communication) as well as documented its recommendations for information to include on coatings applied to implanted hemodialysis catheters in a guidance document (Implanted Blood Access Devices for Hemodialysis - Guidance for Industry and Food and Drug Administration Staff).

The guidance document includes FDA's recommendations for information to include in 510ks for implanted hemodialysis catheters with coatings or additives in Section H (2), which recommends that the premarket notification includes:

"a. A description and material characterization of the coating or additive material, the purpose of the coating or additive, duration of effectiveness, and how and where the coating is applied (21 CFR 876.5540(b)(1)(vii)(A)).

"b. An identification in the labeling of any coatings or additives and a summary of the results of performance testing for any coating or material with special characteristics, such as decreased thrombus formation or antimicrobial properties (21 CFR 876.5540(b)(1)(vii)(B)).

"c. A Warning Statement in the labeling for potential allergic reactions including anaphylaxis if the coating or additive contains known allergens (21 CFR 876.5540(b)(1)(vii)(C)).

"d. Performance data must demonstrate efficacy of the coating or additive and the duration of effectiveness (21 CFR 876.5540(b)(1)(vii)(D))."

The FDA further recommends that, if there is a clinical benefit for such coatings, that the results of a clinical study be provided in the labeling in support of these benefits. "Antimicrobial coatings generally require a clinical study to demonstrate a clinically and statistically significant decrease in the rate of infection or microbial colonization compared to an uncoated catheter." However, FDA adds that coatings identical to previously cleared coatings for similar indications may not need new supportive clinical data, but could, instead, rely on a comparison of the new with the existing coatings present on already cleared devices. The comparison should include a comparison of the chemical formulation, concentration, physical specifications (particle size, surface texture, etc.), elution profile, and manufacturing methods.

These requirements are not new and have been addressed elsewhere in more detail (See, e.g. published in 2005, Surface-Modified Devices and CDRH and Using Risk Analysis to Develop Coated Medical Devices ...) The relatively new recommendation addresses the potential for the development of microbial resistance to the coating:

"Because antimicrobial coatings may lead to the development of microorganisms that are resistant to the antimicrobial in the coating as well as other antimicrobial products, the 510(k) submission should address the potential for the coating to lead to antimicrobial resistance, and if necessary, include testing to demonstrate that the coating does not lead to the induction of resistant microorganisms."

Lastly, the FDA warns, that, if the coating incorporates a drug that is not already incorporated onto a cleared device with the same intended use, or claims for the coated device differ from those made for already cleared devices, the coated device may be considered a "combination product" and the FDA recommends that a pre-submission meeting be held with the FDA to discuss the requirements for the new coated device.

With respect to the FDA's warning that the separation of coatings on intravascular medical devices has the potential to cause serious injuries to patients, FDA informed health care providers that patients could be at risk if the hydrophilic and/or hydrophobic coatings separate (e.g., peel, flake, shed, delaminate, slough off) from devices such as intravascular catheters, guidewires, balloon angioplasty catheters, delivery sheaths, and implant delivery systems commonly used during minimally invasive procedures in the cerebrovascular, cardiovascular and peripheral vascular systems. The agency has not concluded that any specific manufacturer or brand of devices or coating is associated with higher risks than others.

The basis for this warning is that the FDA reports that since 1 January 2014 it has received roughly 500 MDRs (medical device reports) that describe coating separations, including 9 that it concluded resulted in patient deaths due to the occlusion of blood vessels by occluding particles/ coating fragments.

FDA noted that, "It may be difficult for clinicians to associate these adverse events with malfunction of the coating; instead, they may mistakenly attribute the adverse events to other procedural complications or patient

Device Coatings: FDA Update ... continues on pg. 7

Surface Roughness and Morphological Analysis through Scanning Probe Microscopy

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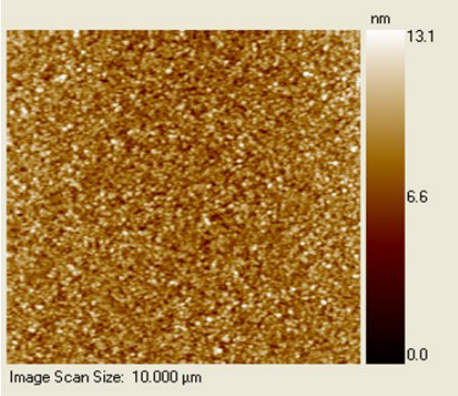
Surfaces play a critical role in numerous material applications. In many cases, surfaces are the very first place to show signs of failure or breakdown. Examples of surface changes may include detachment of coating particles, cracks caused by fatigue, grinding damage due to friction, and phase separation appearing on the surface. Therefore, observing and monitoring surface morphology are of practical significance in industries so as to prevent catastrophic breakdowns and interruptions by detecting signs of failure at its early stages. Controlling surface roughness is also very important in applications such as precision position controls, semiconductors, and manufacturing. One good example is with combustion engines. The engine cylinder surface requires a certain surface roughness in order to hold lubricants in between the parts under compression while not too rough to induce metal-metal contact. It is evident that characterizing surface roughness and surface features is essential for quality control, work condition monitoring, failure analysis, and design improvement.

Surface roughness is usually characterized by several parameters such as average surface roughness (Sa), root mean squared, RMS, surface roughness (Sq), maximum peak height (Sp), maximum valley depth (Sv) and Peak-to-Valley Height (Sz). According to ASME B46.1, Sa is the arithmetic average of the absolute values of surface height deviations from the defined mean surface. Sq is the root mean square average of the surface height deviation from the defined mean surface. Sa and Sq are the most often used parameters to characterize the surface roughness based on the same measurement results of surface peaks and valleys. However, the Sq is influenced more by isolated large peaks or valleys.

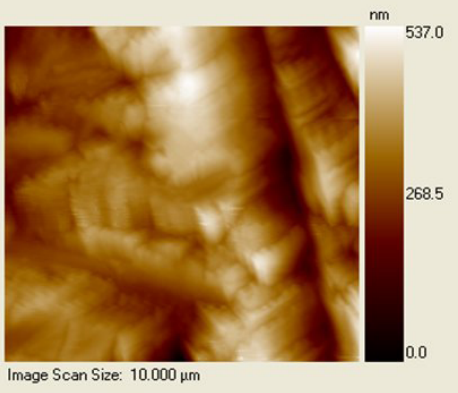
Surface roughness may be measured by either contact methods or non-contact methods. For the contact methods, a component of the measurement instrument contacts the surface during the measurement. Such methods include mechanical stylus profilometry and scanning probe microscopy. Contact methods can provide high resolution measurements in both vertical and lateral directions. However, a sharp stylus tip may cause unwanted damage to a soft sample surface. Then a non-contact method may be used instead of contact method. The non-contact methods are based on optical profilometry techniques such as interferometry, confocal microscopy, and chromatic aberration. A major advantage of the non-contact methods is the ability to rapidly produce three-dimensional measurements without contact to potentially damage or alter the surfaces. Nonetheless, if the surface has varying optical properties, is transparent or has extremely low reflectivity, optical profilometry may lead to inaccurate results. It is understandable that the contact and non-contact methods for surface roughness and topography analysis are complementary and could be selected to suit the application's needs.

Presented here are two surface roughness and morphological analyses: one for a coating on a wafer substrate and one for a stainless steel sample puck. Both surfaces were scanned through in-situ scanning probe microscopy on a Hysitron TriboIndenter system. Both images have a scan size of 10 × 10 µm. The statistical results of the surface roughness were obtained using the software for SPM image processing, Gwyddion. The Sa, Sq and Sz roughness parameters of each surface were given in the corresponding tables. It can be seen that the coated wafer surface is very smooth and uniform, and the steel puck has a higher surface roughness with large peaks and valleys as a machined surface would have.



Sa (nm)	Sq (nm)	Sz (nm)
1.05	1.32	13.01

Figure 1. Surface roughness analysis and morphology for a coated wafer surface.



Sa (nm)	Sq (nm)	Sz (nm)
64.20	80.46	537.47

Figure 2. Surface roughness analysis and morphology for a stainless steel puck surface.

Device Coatings: FDA Update ... continued from pg. 5

co-morbidities." It then provided advice for clinicians to follow to minimize the potential for coating separations:

- *Be aware that many devices are designed, labeled and indicated for specific uses. For example, the coating and performance of a device meant to be used in the peripheral vasculature may be different than a device meant to be used in the cerebral vasculature.*
- *Follow manufacturer's instructions for proper device storage (e.g., shelf life, temperature, exposure to light, etc.) as improper storage can impact the integrity of the coating.*
- *When using two devices together (e.g., catheter and introducer sheath), ensure there is sufficient room for one to pass safely within the other, taking into consideration the features of the device (e.g., curved tip), and that some coatings may swell during use. For example, consider using a slightly larger French size for the introducer sheath than the catheter so there is sufficient room between the devices. Review the device labeling or consult the device manufacturer for further information.*
- *Follow the manufacturer's recommended preconditioning steps (if applicable) for the device. Preconditioning activates the lubricious properties of some device coatings for optimal use.*
    - *During preconditioning of the coating, use only the recommended solution (e.g., normal saline, heparinized saline, sterile water, etc.). Solutions may not be interchangeable and may affect the hydrophilic and/or hydrophobic coatings differently.*
    - *Avoid using alcohol, antiseptic solutions, or other solvents to pretreat the device because this may cause unpredictable changes in the coating which could affect the device safety and performance.*
    - *Avoid pre-soaking devices for longer than instructed, as this may impact the coating performance.*
    - *Avoid wiping the device with dry gauze as this may damage the device coating.*
- *Use caution when manipulating, advancing and/or withdrawing these devices through needles, metal cannulas, stents, or other devices with sharp edges, or through tortuous or calcified blood vessels. Manipulation, advancement and/or withdrawal past sharp or beveled edges may result in destruction and/or separation of the outer coating which may lead to clinical adverse events.*
- *Be aware that attempting to alter the shape of devices by bending, twisting, or similar methods may compromise the coating integrity and that damage to the coating may not always be noticeable to the naked eye.*
- *Consider replacing a device if it does not move freely, is visibly kinked or otherwise damaged, or does not perform as expected.*

For further information on how to use a device safely, consult the labeling or contact the device manufacturer.

The bottom line is that medical device coatings are a concern to the FDA, so expect more intense scrutiny of any applications sent to the agency for coated devices or MDRs for coating separation.

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