Surface Characterization:
Visualize the Invisible

POWERFUL TOOLS AND EXPERTISE FOR IMPROVED MEDICAL DEVICE COATINGS

Today's savvy medical device manufacturer realizes that improving the performance of a device through surface modification not only differentiates the device in the marketplace, but is often a requirement for market success. SurModics works together with device manufacturers to integrate the best coating onto a device and still get the coated device to the market before the competition. Application of highly sophisticated surface characterization methods helps speed up the search for the most effective coating required to meet performance criteria by providing fundamental information on the device surface, the interface between device and coating, and the coating surface. Device coating development, scale-up and production are often more easily accomplished by applying SurModics' powerful surface characterization tools.

SURMODICS SURFACE MODIFICATION TECHNOLOGY

SurModics is a leading provider of surface-modification and drug-delivery solutions to the medical device industry. SurModics' PhotoLink® surface-modification technology platform improves medical device surface characteristics such as lubricity, hemocompatibility, infection resistance, and tissue integration.

Additional coating platforms enable the time-controlled elution of drugs from device surfaces. Bravo™ and Encore™ drug-delivery polymer matrices and the Accolade™ microparticle drug-eluting system were developed by SurModics to meet the ever-increasing demand for device/drug combination products. PolyActive™ and OctoDEX™ are two biodegradable drug-eluting coatings acquired from OctoPlus.

WHAT CAN SURFACE CHARACTERIZATION DO FOR OUR CUSTOMERS?

Biomedical researchers need to know as much as possible about the structure and composition of a device surface to better understand and predict how the device will interact with the human body. Surfaces present a particular characterization challenge: extremely small amounts of material at a medical device surface can dramatically change biochemical reactions with the human body. Coatings on device surfaces are usually thin, often transparent, and difficult or impossible to see with the naked eye. Surface characterization makes visible what the eye can't see, allowing scientists to probe the physical properties, chemical composition, and spatial distribution of molecules directly at all types of surfaces. The knowledge gained allows us to see product development issues more clearly, enabling innovative solutions to technical challenges in the development of medical devices. The increased understanding of a coated device obtained through our surface characterization results in speedier problem solving and increased confidence in technical solutions.
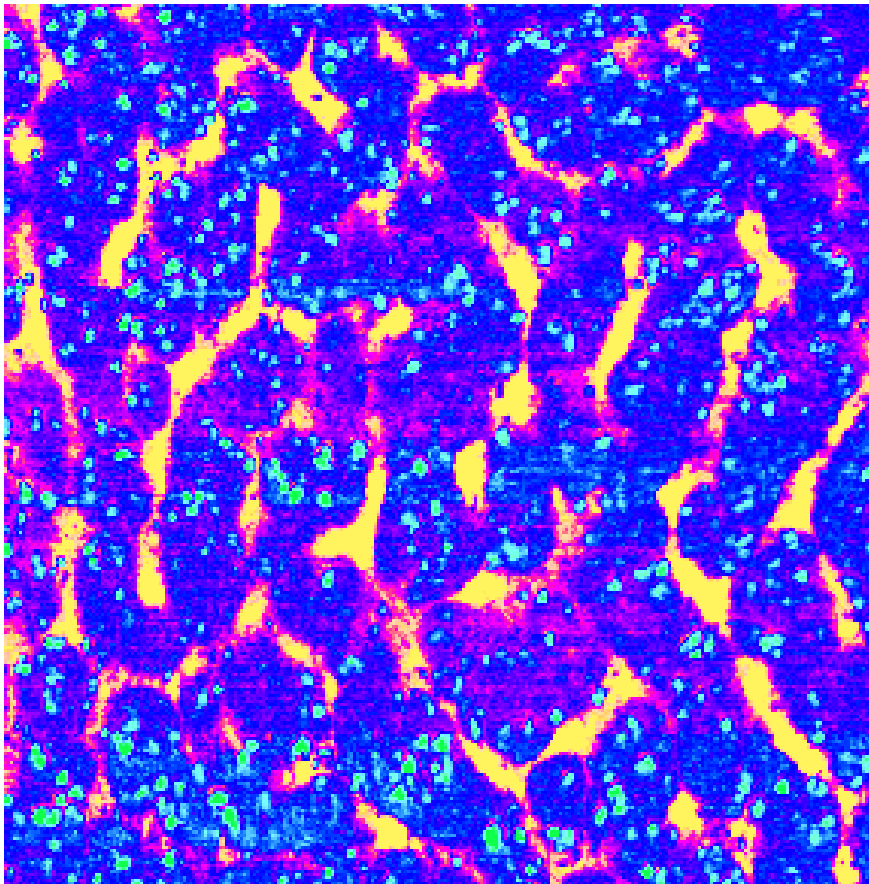

Figure 1. AFM image of the surface of a drug-eluting coating.

SurModics expertise is the ability to ask pertinent questions, choose the appropriate tools to answer these questions, know the theoretical and practical limitations of the tools, and apply the tools to more quickly understand what is happening at the surface of a device.

The goals of the surface characterization efforts at SurModics are to: (1) identify the failure modes of coatings during durability testing, (2) measure any chemical or physical changes upon shelf-life stability testing, (3) monitor the consistency of coating processes, (4) identify defects and contaminants in coatings, and (5) develop a fundamental understanding of the drug release mechanisms from coatings.

The following describes how SurModics utilizes the power of its surface characterization tools, along with extensive know-how in interpreting test results, to meet these goals.

COATING THICKNESS AND UNIFORMITY

Knowledge of the coating thickness helps in understanding device performance. For example, a coating that is too thin may not provide adequate lubricity, and a coating that is too thick may alter the geometry and affect device function. Uniformity in thickness is critical: uncoated regions impair function, and non-uniform drug delivery coatings deliver non-uniform drug dosage. Measurement of coating thickness often confounds researchers due to problems visualizing the coating and distinguishing the seemingly invisible coating from the substrate. At SurModics, a variety of methods allow accurate measurement of coating thickness and uniformity. The thickness range of the coating and the device morphology determine the method of choice.

For a round or rod-shaped device, such as a wire or catheter tube, the scanning laser micrometer accurately measures the diameter of the device by blockage of a scanning laser beam. Measurement of the change in diameter of the device at the same location before and after application of the coating yields the
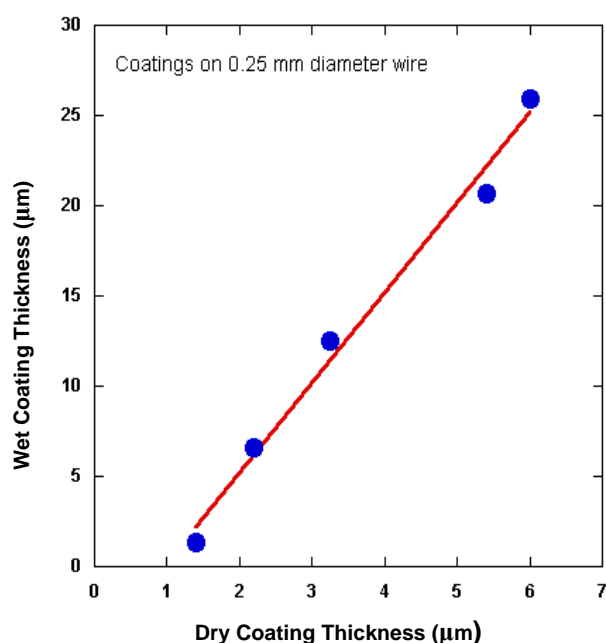
coating thickness with a resolution of about 0.5 microns. Figure 2 demonstrates the ability of the scanning laser micrometer to measure coating thickness in the dry and/or wet state (swelling) as well as the wide range of coating thickness achievable with PhotoLink technology.

For devices of other shapes, devices that exhibit variations in diameter much larger than the coating thickness, or devices that do not maintain dimensional stability upon coating, the scanning confocal Raman microscope provides an accurate measurement of coating thickness. Analogous to an infrared absorbance spectrum, the Raman spectrum provides a spectral "fingerprint" of the coating chemistry. Confocal optics give a cross-sectional image of the coating: the laser penetrates into the coating with a depth resolution of approximately 0.5 microns. A scanning table moves the sample up, down, back and forth relative to the laser spot, enabling the scanning confocal Raman microscope to produce a spatial map of the chemicals in the coating. For example, the "fingerprint" of a PhotoLink coating differs significantly in shape from the spectra of a polyurethane substrate (Figure 3).

Assigning a color scheme to the spectral shift allows color-coded mapping of the polyurethane (darker) and PhotoLink coating (brighter) (Figure 4). Air has no Raman signal and is assigned an intermediate (gold) color. Raman imaging not only reveals the thickness of the coating, but also shows coating uniformity along the path scanned.
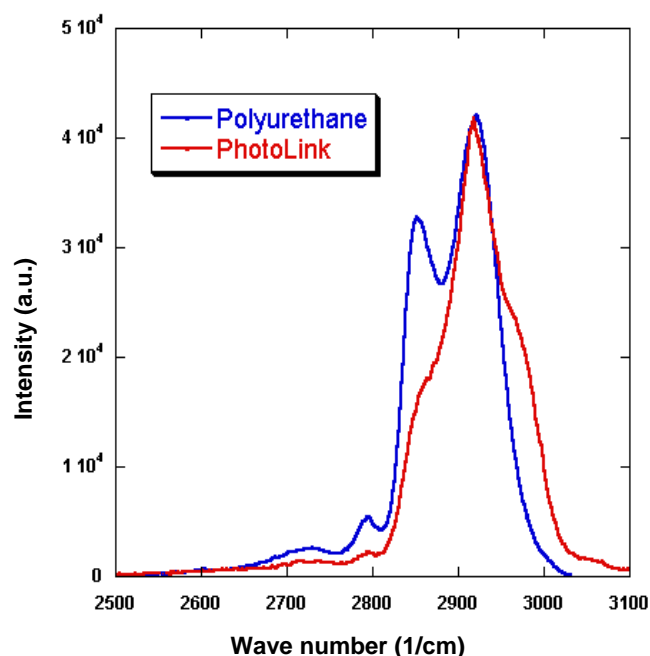

Figure 3. Raman spectrum of PhotoLink coating and polyurethane catheter.

For coatings thicker than 2 μm on reflective metal surfaces such as guidewires or stents, the optical interferometer uses the light interference fringes which appear at surfaces to map the topography and the position of the surface. By subtracting the positions of the air/coating and coating/device surfaces, a detailed color-coded map of coating uniformity over areas as large as 0.45 x 0.60 mm results (Figure 5).

The laser micrometer, Raman microscope, and optical interferometer allow non-destructive measurement of coating thickness.

Figure 2. Measurement of dry and wet coating thickness by laser micrometer.

Figure 4. Raman cross-sectional image of coating on polyurethane catheter.

Where application of these methods is not possible, destructive methods are required. If a coating is scratched, peeled, or cracked off the surface of a device, the step profile created between coated and uncoated areas can be measured with an optical microscope for thick coatings For thin coatings, an electron microscope, optical interferometer, or atomic force microscope can be used.

For especially thin coatings, the atomic force microscope (AFM) measures coating thickness with almost atomic-level resolution: 1.0 nanometer or 0.000001 millimeters! The AFM drags or taps a sharp tip across a surface, senses the force between the tip and surface, and thus measures the surface topography of a sample. Coating thickness is measured by scratching away a region of coating on a substrate and measuring the height difference between the coated and uncoated areas with the AFM (Figure 6). The AFM allows measurement of both dry and wet coatings, and thus allows measurement of the degree of swelling of thin PhotoLink coatings (Figure 7). PhotoLink gels containing more photocrosslinker swell less.

Utilization of these various techniques gives SurModics the capability to measure a wide range of coating thicknesses in both the dry and wet state and confirms that PhotoLink coatings can be applied from nanometers to several microns in thickness.
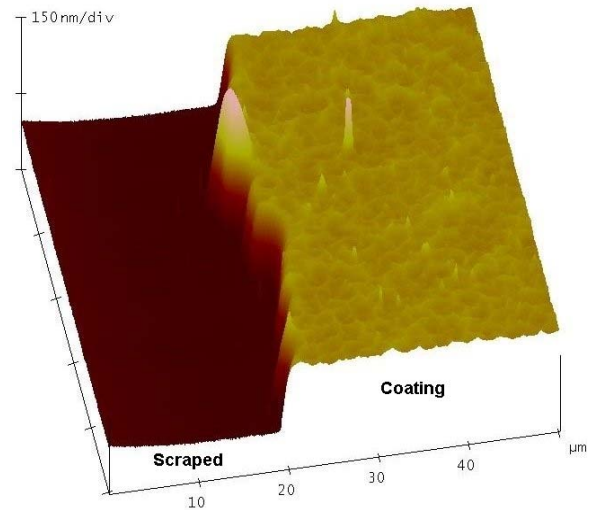

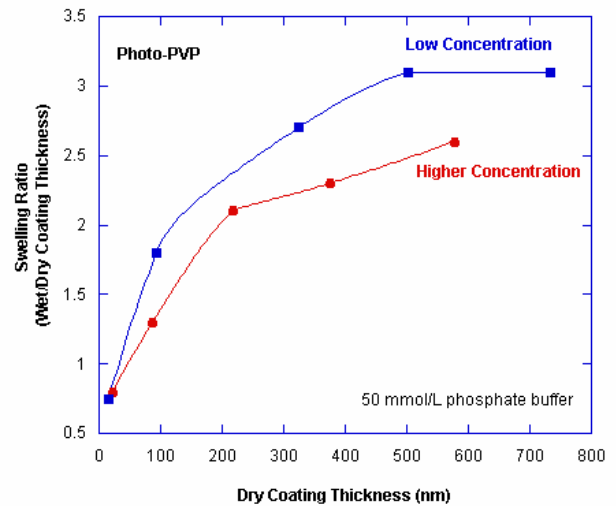**Figure 6. Atomic force microscope measurement of coating thickness.**

Figure 7. AFM measure of swelling of PhotoLink coatings. (Effect of photocrosslinker concentration.)
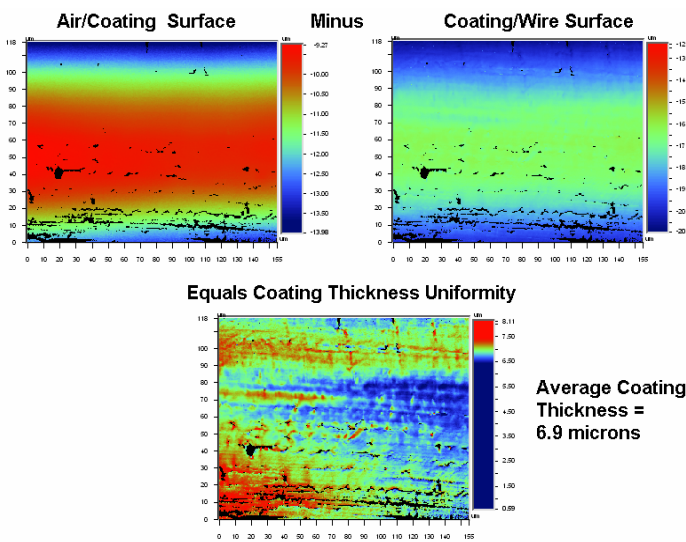

Figure 5. Optical interferometry of a PhotoLink coating on a guidewire. Red areas are higher/thicker, blue areas lower/thinner, and an overall average thickness is measured.
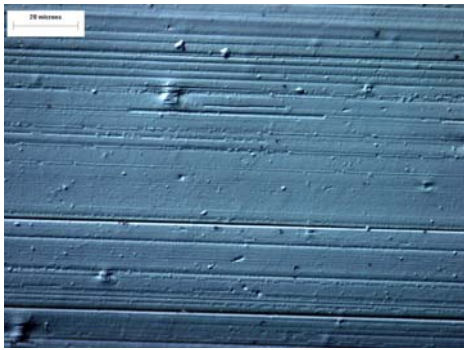
SURFACE ROUGHNESS AND UNIFORMITY

The roughness of a device surface and the uniformity of the coating also play critical roles in the surface functionality and biocompatibility of devices. High-resolution light microscopy allows visualization of coatings for a qualitative assessment of roughness and uniformity. Four contrast methods, brightfield, darkfield, polarized, and differential interference contrast (DIC), yield four types of images and sometimes four different pieces of information. For example, the DIC mode highlights surface roughness, and the die-lines of an extruded polyurethane device become clearly visible (Figure 8a). Application of a PhotoLink coating to the same device covers up the rough features and die-lines, and yields a smooth device surface (Figure 8b). Figure 8c illustrates a rough coating caused by surface contamination. Skilled use of a high-resolution light microscope facilitates quick determination of the quality of coatings and provides critical information on coating uniformity and roughness.

Figure 8a. Optical micrograph of an uncoated polyurethane device.

Figure 8b. Optical micrograph of a smooth Photo-Link coating on a device. Note the coating defect in the upper left-hand corner.
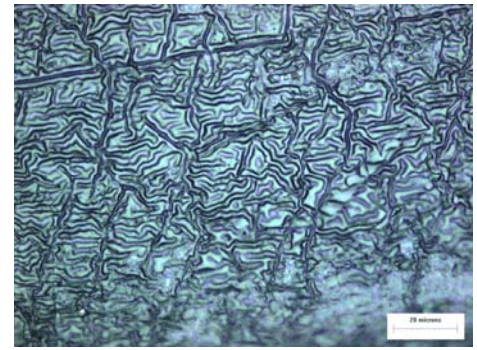

Figure 8c. Optical micrograph of a poor coating on a surface-contaminated device.

Figure 9. Scanning electron micrograph (SEM) of a drug elution coated stent.

The scanning electron microscope (SEM) takes over where the optical microscope leaves off, allowing both high depth-of-field imaging around the coated surfaces of a complicated geometry such as a stent (Figure 9), and high magnification imaging of tiny features such as small crystals of drug sprouting out of the surface of a drug eluting coating (Figure 10).

While light microscope and SEM allow visualization of coating roughness and uniformity, the optical interferometer and AFM techniques quantitatively measure surface roughness with nano-meter-level resolution over large- and small-sized regions respectively. The surface profile of a drug-eluting coating on stent taken with the optical interferometer reveals some waviness in the coating, along with a lower region in the middle of the area examined (Figure 11). As shown in Figure 12a, the AFM reveals that a seemingly smooth uncoated Pebax® rod exhibits a high level of roughness on the 200 nm scale. A thin PhotoLink coating covers up the small-scale roughness but leaves the larger-scale roughness, exhibiting a "sand-dune-like" topography (Figure 12b). Application of a thicker coating covers up all of the roughness and leaves a very smooth surface (Figure 12c). Even at the nanometer scale, PhotoLink coatings uniformly cover rough device surfaces and make them extremely smooth.

SURFACE AND COATING CHEMISTRY
The physical properties of coatings and surfaces – thickness and roughness – yield important information about coating quality.
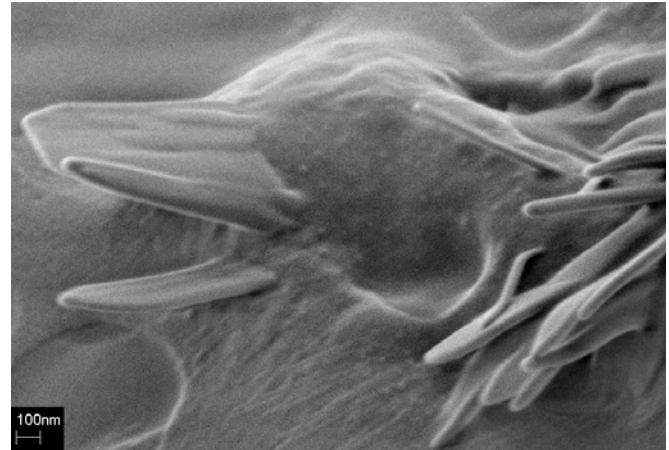

Figure 10. SEM of drug crystals on the surface of a coating.

Critical and complimentary is chemical information: both the chemistry right at the surface, and for coatings which are blends of ingredients such as the drug eluting coatings, the chemical morphology throughout the coating.

The scanning confocal Raman microscope provides a chemical "fingerprint" of the coating ingredients within a coating with a spatial resolution of about 0.5 μm. Not only can the Raman method determine coating thickness and uniformity as shown above, but if the coating is a mixture of ingredients, the degree of mixing or segregation of the ingredients within the coating can be determined. The example shown in Figure 13 gives the mapping of a mixture of drug in a polymer matrix on a stent, where the drug is not uniformly mixed, but appears as particles
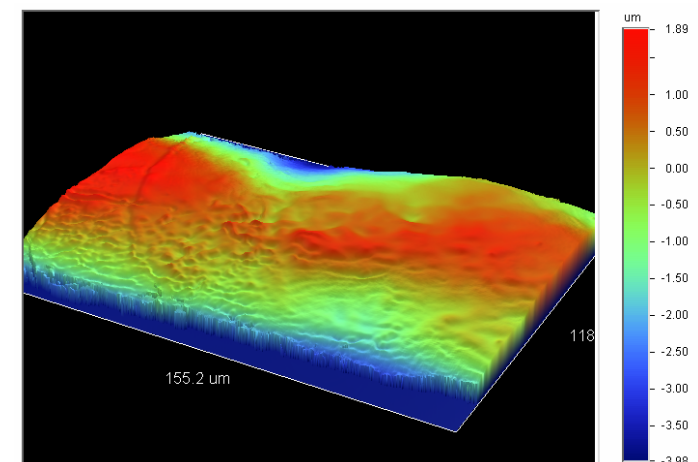

Figure 11. Profile of coating on a stent by optical interferometry.
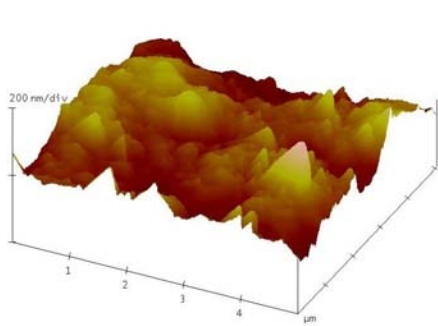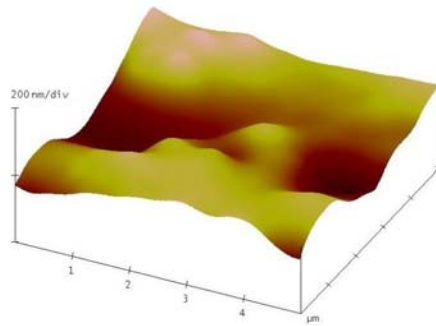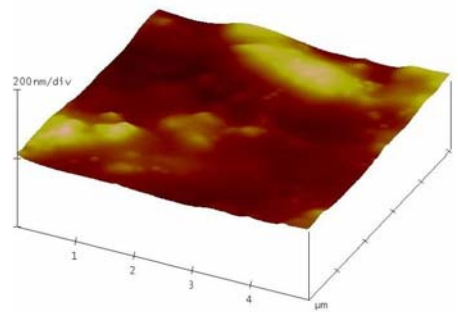
Figure 12a. AFM image of uncoated Pebax substrate.

12b. AFM image of thin PhotoLink coating on Pebax.

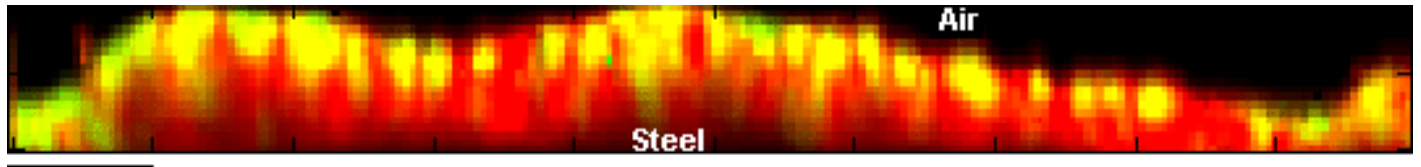12c. AFM image of thicker PhotoLink coating on Pebax.

Figure 13. Raman cross-sectional images of coating on a stent. Polymer (red), drug (green), and polymer + drug (yellow). Bar = 10 microns.

within the coating. Overlaying the images of polymer (red) with drug (green) shows regions where drug and polymer mix (yellow), and highlight that some regions of drug (green) are near the surface and not covered by polymer. Note that if multiple coating layers of different chemical composition are applied, and the layers are thicker than 0.5 µm, the Raman method can image the thickness and intermixing of each layer.

Complementary to the confocal Raman microscope, the infrared microscope in the grazing angle mode allows measurement of the chemical spectrum of extremely thin coatings, down to one monolayer of molecules. Figure 14 shows the infrared spectrum of a monolayer thin PhotoLink coating before (blue) and after (red) adsorption of BSA protein.
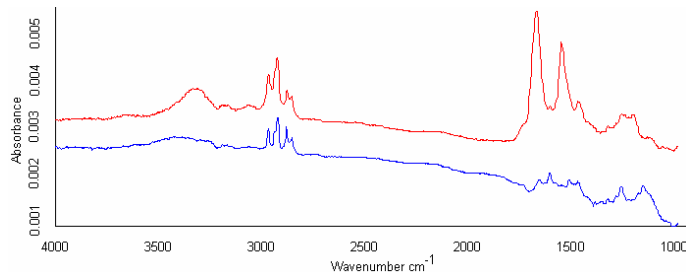

Figure 14. Infrared spectrum of PhotoLink monolayer-type coating without adsorbed protein (blue) and with adsorbed protein (red).

In an indirect way, the AFM also yields chemical information at a surface. In a mixture of two polymers of different hardness along with drug, and using the AFM in the "phase-contrast" mode, the relative hardness of materials at the surface of a drug eluting coating is measured (Figures 1 & 15). In Figure 15, the darkest (brownish) colors correspond to the softest material (polymer 1), the intermediate (greenish) colors correspond to the harder polymer 2, and the hardest material, small crystals of drug, appear pinkish-white in color. Note that the drug crystals are only about 100 nm in diameter. If the AFM tip is chemically modified with known functional groups, more specific chemical sensing is possible.

Surface chemistry of the uncoated medical device plays a critical role in adhesion of the coating to the device surface, and surface chemistry of the coating plays a critical role in the biocompatibility of the coated device in the human body. X-ray photoelectron spectroscopy (XPS, a.k.a. ESCA), and time-of-flight secondary ion mass spectroscopy (TOF-SIMS) are two methods which are surface specific and exclude signal from the bulk of the coating: the beam probes only the top-most layers (nanometers) of molecules on a surface, unable to penetrate deeper. In XPS, a beam of X-rays impinges upon the sample, and a detector senses the energy of the photoelectrons ejected from the first 2 to 20 nm of the surface. XPS measures the relative concentration of elements at the surface, and detects impurities down to concentrations of 0.01%. The XPS spectrum of a
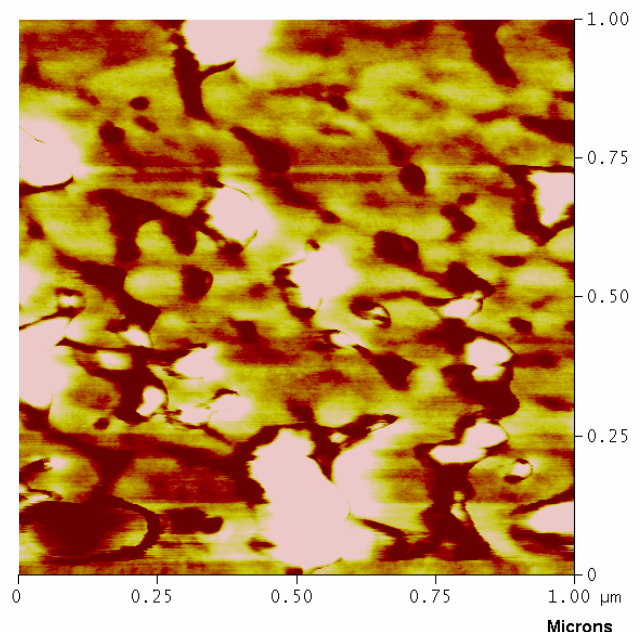

Figure 15. AFM image of the surface of a drug-eluting coating.

PhotoLink coating surface reveals the chemistry directly at the surface (Figure 16).

Complementary information comes from time-of-flight secondary ion mass spectroscopy (TOF-SIMS). In the TOF-SIMS experiment, a beam of gallium ions causes the break-up and ionization of the molecules at the outermost layer of a surface (about 1 nm). TOF-SIMS "fingerprints" the molecular composition of the surface of a PhotoLink coating (Figure 17), and the mass spectrometer senses impurities at the parts per million (ppm) level. The methods for measurement of surface chemistry complement each other, with advantages and disadvantages to each method (see Table I).

BENEFITS OF THE SURFACE CHARACTERIZATION CAPABILITIES AT SURMODICS

In summary, SurModics utilizes various surface characterization methodologies as powerful tools to "visualize the invisible." We have shown here how SurModics can measure the important physical and chemical properties of coatings and surfaces. With the skillful application of these powerful surface characterization tools and our extensive know-how in coating chemistry and processes, SurModics can help medical device manufacturers speed the development and facilitate the scale-up and production of coatings for medical devices. These capabilities, combined with SurModics' extensive surface modification expertise and regulatory experience, provide our customers with a complete solution — bringing innovation together to generate successful products.
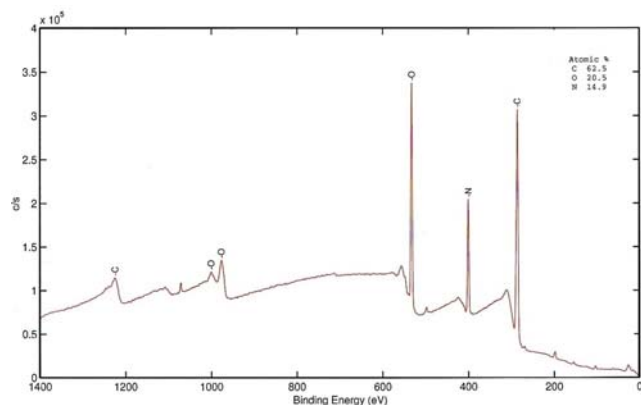

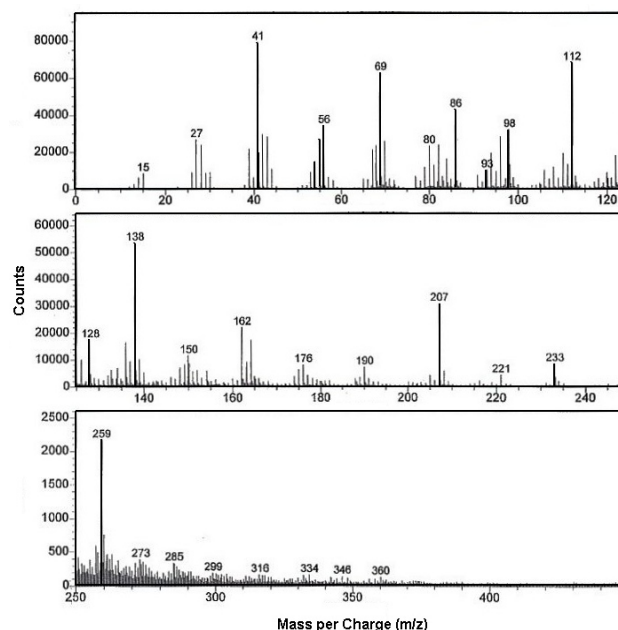Figure 16. XPS spectrum of surface of polyacrylamide PhotoLink coating.

Figure 17. TOF-SIMS spectrum of the surface of a polyvinylpyrrolidone PhotoLink coating.

Table I. Comparison of Surfaces and Coating Chemical Analysis Methods

	RAMAN MICROSCOPE	INFRARED MICROSCOPE	XPS	TOF-SIMS
TYPE OF INFORMATION	Chemical bonds	Chemical bonds	Elemental, Chemical	Molecular groups
QUANTIFICATION	Semi-quantitative	Semi-quantitative	Quantitative	Semi-quantitative
DEPTH RESOLUTION	500 nm	Monolayer	2-20 nm	1-3 nm
LATERAL RESOLUTION	500 nm	25 μm	80 μm	1 μm
DETECTION LIMITS	1%	1%	0.01%	ppm
ENVIRONMENT	Atmospheric/Wet	Atmospheric	High vacuum	High vacuum