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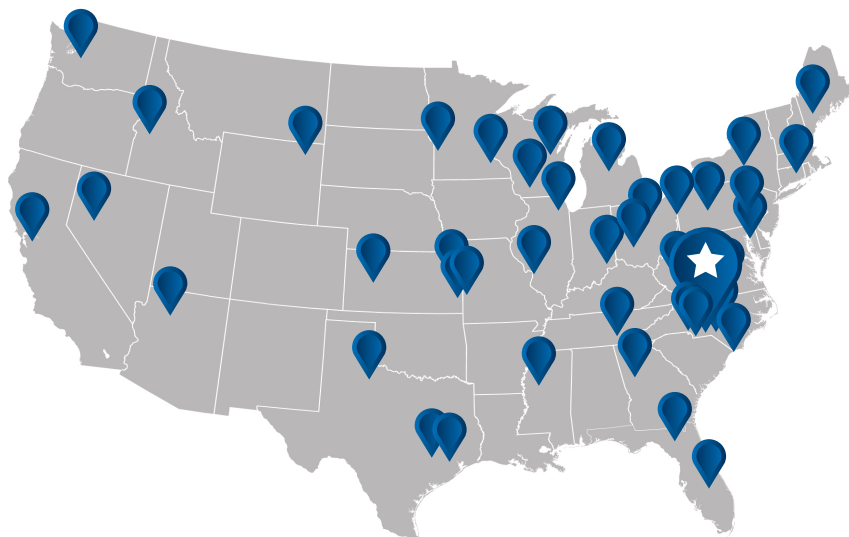
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Check out
the iWave
application
note inside.



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Notebook Section

September 2016 Volume 31 Number 9

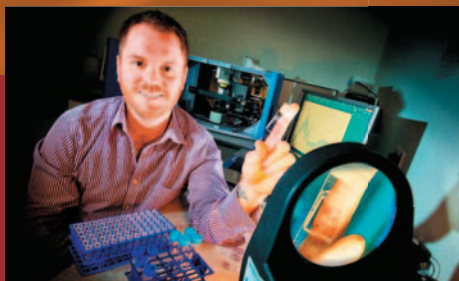
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Forensic Analysis of Bloodstains with Raman Spectroscopy

What's New with FDA's Data Integrity Guidance?

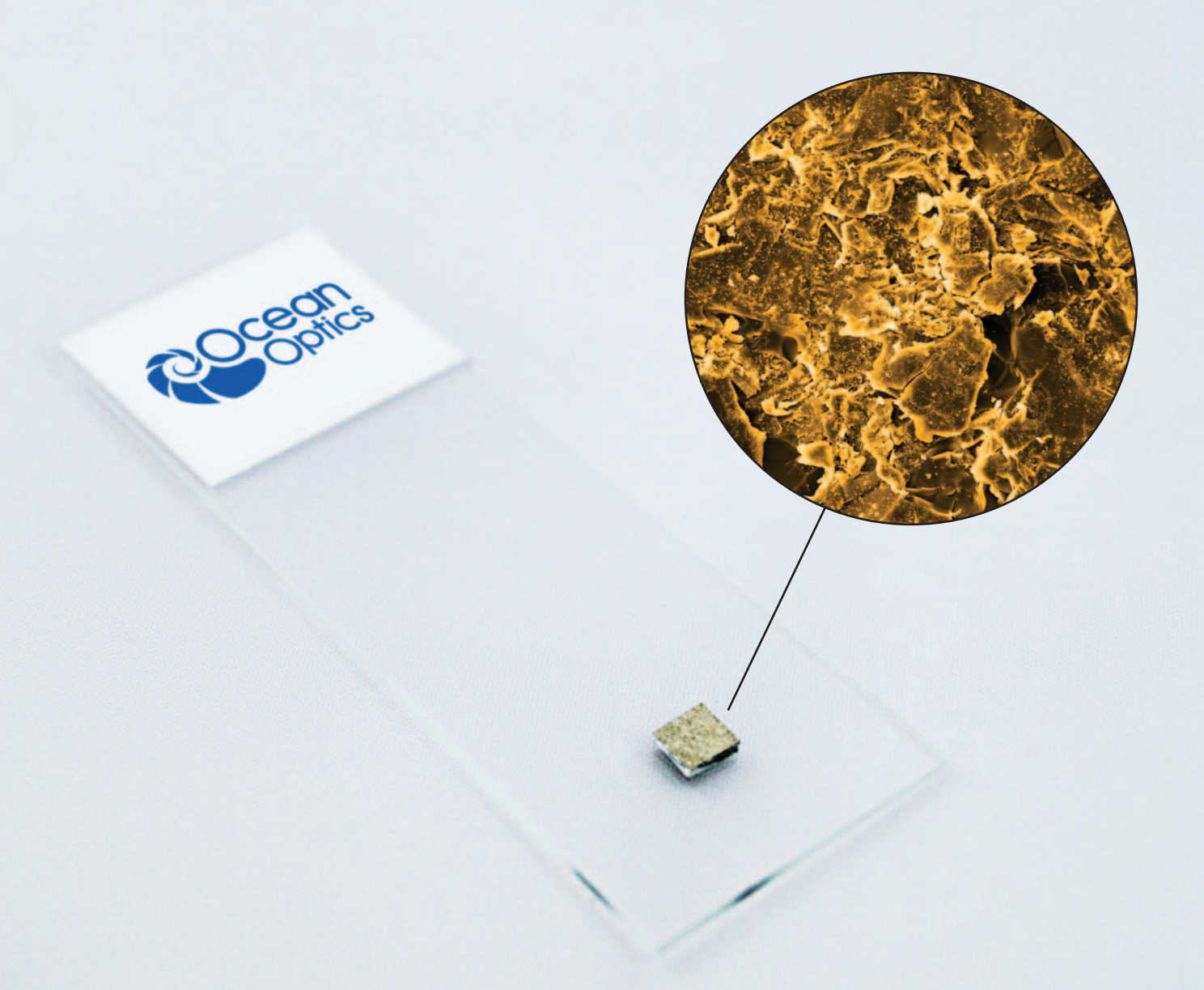
Addressing the Challenges of Process Raman Spectroscopy

FT-IR Kinetic Imaging of Epoxy Curing



2016 Emerging Leader in Molecular
Spectroscopy Award Winner

Matthew J. Baker



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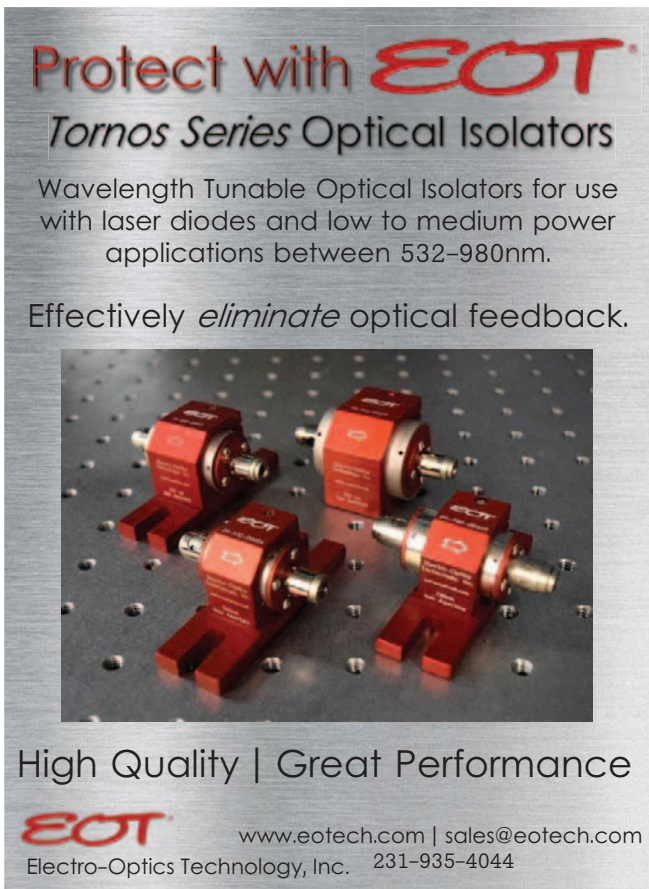
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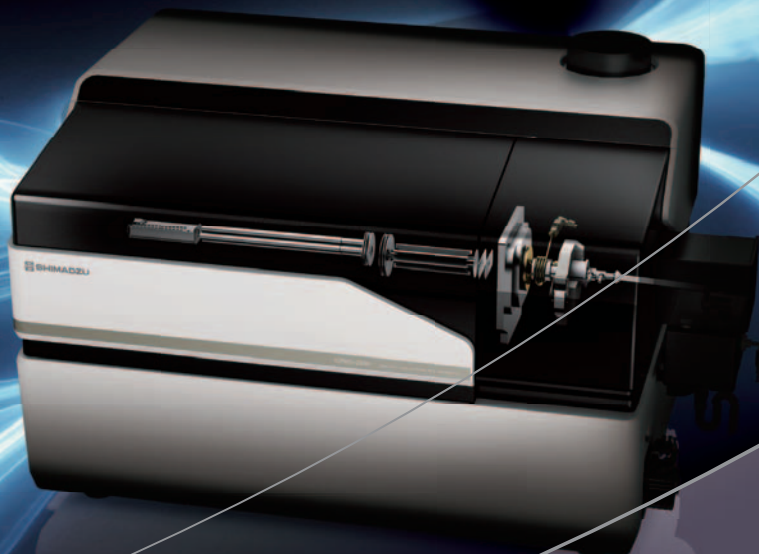
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Spectroscopy

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Volume 31 Number 9Cover image courtesy of
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ON THE WEB

QUIZ: INTERPRETING SPECTRA

Take the latest quiz!

Are your spectral interpretation skills up to par? Find out by taking the latest quiz from our "IR Spectral Interpretation Workshop" column.

See the quiz on page 33 of this issue or at:

spectroscopyonline.com/ir-spectral-interpretation-workshop-o

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A Breakthrough in IR & Raman Spectral Identification

Gregory M. Banik, Ph.D., V.S.M., Bio-Rad

Are You Sure Your ICP-MS Interferences Are Under Control?

Ed McCurdy and Steve M. Wilbur, Agilent Technologies

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Photoluminescence can provide information about the composition and solid-state structure of a material.

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R.D. McDowall

Data integrity is the currently hottest topic in regulated good practice (GxP) laboratories. Here's what you need to know about the latest guidelines, issued by the FDA in April 2016.

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The Benzene Fingers, Part II:

Let Your Fingers Do the Walking Through the Benzene Fingers

Brian C. Smith

The benzene fingers are a series of overtone and combination bands that can be used to distinguish substituted benzene rings when other methods do not work.

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Matthew J. Baker, the winner of *Spectroscopy's* inaugural Emerging Leader in Molecular Spectroscopy Award, is passionate about solving clinical problems with vibrational spectroscopy.

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Stephan Woods, Michael Bradley, and David Drapcho

By using an array detector in conjunction with ultrafast mapping, one can produce kinetic chemical imaging to monitor the curing process in a two-part epoxy resin.

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Maggie O'Connor, Kiana Jansen, Joseph Hodge, Christine O'Brien, Isaac Pence, and Anita Mahadevan-Jansen

Raman spectroscopy has the potential to accurately and nondestructively determine the age of a bloodstain for use in criminal investigations.

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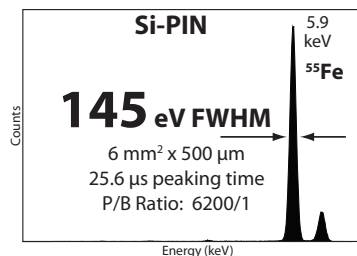
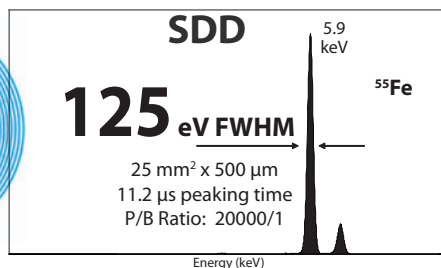
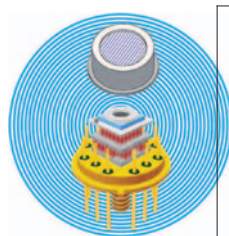
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A word cloud visualization of terms related to X-ray fluorescence (XRF) analysis. The words are arranged in various orientations and sizes, with colors ranging from dark blue to light blue. Key terms include:

- Lead**
- Nuclear teaching**
- OEM**
- research**
- fluorescence monitor**
- analysis**
- process**
- metals**
- MCA**
- handheld**
- SEM**
- Process Control**
- Space**
- Plastics**
- Verification**
- Environmental**
- Compliance**
- Non-destructive processing**
- elemental**
- Safeguards**
- detection**
- elements**
- Art**
- Archaeology**
- scintillation**
- GOLD**
- paper**
- Mining**
- Monitoring**
- EDS**
- vacuum**
- oil**
- smoke stack**
- sulfur**
- portable**
- operations**
- instruments**
- semiconductor**
- tube monitoring**
- forensics**

XRF System

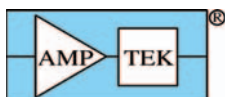
The image displays the components of an XRF system. On the left, a PX5 Digital Pulse Processor (DPP) is shown, a blue circuit board with various electronic components. In the center, an XR-100CR X-ray Detector is visible, a cylindrical component with a silver and black finish. On the right, a Min-X detector assembly is shown, featuring a green printed circuit board (PCB) with a central chip and a silver cylindrical component. A small, black, cylindrical component is also visible next to the Min-X assembly.



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MATERIALS ANALYSIS DIVISION

THE **APPLICATION** NOTEBOOK

Atomic Spectroscopy

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The advertisement features a woman in a white lab coat operating the Rigaku Supermini200 spectrometer. On the left, a graph shows X-ray fluorescence peaks for Ba-LA, Ti-KA, Ba-LB1, and Ti-KB1/Ba-LB3. The background is a periodic table of elements. The Rigaku logo and tagline 'Leading With Innovation' are at the bottom left. The bottom right contains the company name, website, email, and a QR code.

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News Spectrum

Nonprofit Brings Hands-On Laboratory Experience to Young Students to Promote STEM Careers

In the United States, a lack of qualified candidates for jobs in science, technology, engineering, and math (STEM) underscores an urgent need for educators to find ways to draw students into these areas of study. As a result, at least one concerned group has come up with a creative way to spark interest and excitement in STEM careers among young students in New Jersey.

Students 2 Science (S2S), a six-year-old program, allows middle school and high school students to get hands-on experience in scientific experimentation. The commercial-grade Technology Center, located in East Hanover, New Jersey, offers students, especially those in underrepresented school districts, the opportunity to conduct challenging experiments side-by-side with professional scientists in a real laboratory, using sophisticated laboratory instruments such as spectrophotometers and chromatographs.

With a goal of reducing the intimidation that is often associated with STEM-related learning, the program takes students out of their normal routine and brings them into a functioning laboratory work environment, connecting them with successful analytical chemists, other scientists, and engineers, and exposing them to the potential financial and social benefits of a career in a STEM-related field. The program is open to both girls and boys, addressing the gender gap in STEM, in addition to the workforce gap.

The group's work is enabled through contributions from corporations, foundations, and individuals. The roughly 5000 square feet of commercial laboratory space is equipped with more than \$3 million of analytical instrumentation to perform wet, organic, and analytical chemistry; chromatography; spectroscopy; biology; botany; biotechnology; ecology; computer science; engineering; and robotics.

In addition, in November 2015, the organization launched the Virtual Laboratory, or V-Lab, a fully interactive web-based, multilingual hybrid distance-based learning program that supports K–12 students and teachers. The V-Lab program provides a series of supplemental age-appropriate hands-on science experiments to be performed by students in their local classroom and simultaneously at the S2S Technology Center by use of high-speed video teleconferencing. S2S scientists demonstrate how to conduct each experiment and describe how the techniques are used in real-world applications. The program provides the kits, trains the teachers, and conducts a joint session using video conferencing. Each kit contains enough materials for a teacher to run the experiments again, on their own, three to four more times.

Volunteer Opportunities

For scientists who are motivated to help promote STEM education, the S2S program offers volunteer opportunities in several areas.

Program Mentors provide coaching, inspiration, and motivation while educating the students. They answer questions about the career application of the laboratory techniques being learned, and also ensure the safety of the students.

Laboratory Assistants help students to follow procedures, perform calculations using instrumentation, and offer recommendations to instructors (after students have completed the program) for modifying experimental procedures and ensuring the safety of the students.

Instructors are subject-matter experts who instruct students as they conduct each experiment. They stay at the same experimental station throughout the day, providing clear and concise information and ensuring the safety of the students.

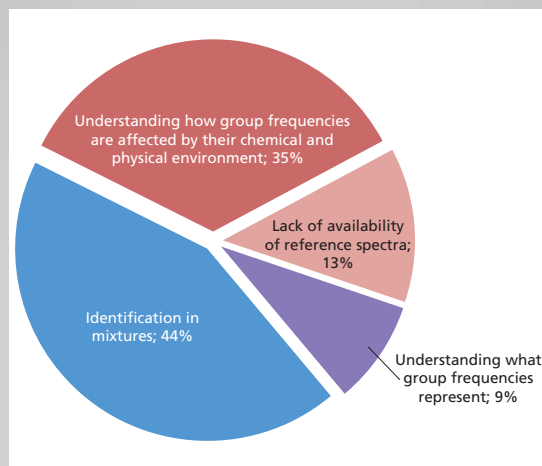
Grant Writing Assistants search corporate and foundation websites to identify and recommend specific grant opportunities.

Special Events Coordinators assist in scheduling, advertising, and coordinating board meetings, open houses and information sessions, and fund raisers.

Creative Management volunteers prepare and review collateral materials such as web pages, press releases, newsletters, solicitations, invitations, marketing, and promotional materials.

Registration for volunteers is available on-line at students2science.org.

SURVEY SAYS...



WHAT IS THE BIGGEST CHALLENGE YOU FACE IN INTERPRETING INFRARED (IR) SPECTRA?

Spectroscopy ran a poll to ask spectroscopists about their biggest challenges with interpreting IR spectra. As the figure shows, a majority of respondents found identification in mixtures a challenge. The next largest group of respondents said their biggest challenge was understanding how group frequencies are affected by their chemical and physical environment. Other respondents cited a lack of availability of reference spectra and difficulty understanding what group frequencies represent.



Molecular Spectroscopy Workbench

Photoluminescence Spectroscopy Using a Raman Spectrometer

Photoluminescence can provide information about the composition and solid-state structure of a material. The high spectral resolution of a Raman spectrometer can be useful in performing photoluminescence spectroscopy of solid-state materials, particularly when the emission spectra consist of narrow bands or even lines. Having the capability to perform photoluminescence and Raman spectroscopies simultaneously with the same instrument is advantageous, especially when studying two-dimensional (2D) crystals. When used to perform photoluminescence spectroscopy, the Raman spectrometer becomes two instruments in one.

David Tuschel

Raman scattering is a weak phenomenon and that is sometimes the reason for being unable to acquire a Raman spectrum, particularly at a low concentration or with a limited amount of sample. However, the most frequent reason for not being able to acquire a Raman spectrum is because a strong fluorescent background and the detector noise generated by it overwhelms the Raman signal. Therefore, it should be self-evident that a Raman spectrometer is ideal for performing laser-excited photoluminescence. In a recent installment of “Molecular Spectroscopy Workbench,” we examined the choice of excitation wavelength to avoid photoluminescence (1). Here we discuss the use of a Raman spectrometer with the express purpose of performing photoluminescence spectroscopy.

The light illuminating a sample must be in resonance with an electronic transition of the material for photoluminescence to occur. More specifically, the sample must absorb a photon of the incoming light to promote an electron from the ground electronic state in a molecule or valence band in a solid to the first excited molecular electronic state or conduction band in a solid, respectively. After the electron is in the excited electronic state or conduction band, it can undergo either radiationless decay or a photon can be emitted as the electron returns to the ground state or valence band. The latter emission process is called

photoluminescence because the excited state was reached through the absorption of a photon. In contrast, had the electron been promoted from the valence to the conduction band through the application of a voltage and the passage of current, the subsequent emission would be more properly described as *electroluminescence*. Photoluminescence occurs in many bulk materials that are direct band gap semiconductors and also because of impurities that absorb and emit light in an otherwise transparent medium. We discuss examples of both situations in this installment.

Chromium Impurities in Aluminum Oxide

The aluminum oxide alumina (Al_2O_3) is known as corundum in its single crystal form. Within corundum the Al-O bond is approximately 60% ionic and 40% covalent with an Al atom at the center surrounded by six O atoms to form a distorted octahedron (2). Therefore, the aluminum atoms in the crystal can be assigned a formal oxidation state of +3 with the surrounding O atoms each with a -2 formal oxidation state. Pure corundum is colorless; however, Al_2O_3 is often tinted or even deeply colored because of transition metal impurities in the crystal. Their presence at even less than 1% in the Al_2O_3 host lattice leads to the beautiful colors seen in gemstones such as ruby and sapphire. The presence of Cr^{3+} in Al_2O_3 is what gives ruby its red color, whereas sapphire,



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also a host crystal of corundum Al_2O_3 , obtains its color from titanium impurities. The electron configuration of the Cr atom is $[\text{Ar}] 3d^5 4s^1$. When occupying an Al site in the corundum crystal lattice, however, the electron configuration of Cr^{3+} is $[\text{Ar}] 3d^3$ thereby allowing $t_{2g} \rightarrow e_g$ absorption and emission electronic transitions in the 3d orbitals. These electronic transitions are affected by the crystal field of the host lattice, which are then manifest in the absorption and emission spectra.

The combination of Raman and photoluminescence spectroscopies allows one to characterize the host crystal and the transition metal impurities, respectively. Raman spectra acquired from the same location of an Al_2O_3 crystal using 532-nm and 633-nm excitation are shown in Figure 1. Both spectra consist of Raman bands from the Al_2O_3 crystal at 144, 417, 568, and 734 cm^{-1} . However, the spectrum excited with 532-nm light has no background whereas that excited at 633 nm manifests a steadily increasing

background beginning at approximately 150 cm^{-1} . Furthermore, distinct broad peaks (relative to the Raman bands) appear at approximately 640 and 870 cm^{-1} . The appearance of these two broad peaks in the 633-nm-excited spectrum and their absence in the 532-nm-excited spectrum is confirmation that they are due to photoluminescence and not Raman scattering. The use of different excitation wavelengths with the same sample is one of the best ways to differentiate photoluminescence from Raman scattering. Raman bands appear at the same position, independent of the excitation wavelength, when plotted on a Raman shift scale. However, if the bands appear at different Raman shifts, they are likely caused by photoluminescence. Now plot these same spectra on an absolute wavelength scale. If the bands appear at the same position when plotted on an absolute wavelength scale, their assignment as photoluminescent bands is confirmed.

The peaks at 640 and 870 cm^{-1}

(659.5 and 669.7 nm, respectively) of the Raman spectrum are not the only or even primary emissions from this crystal of Al_2O_3 . The photoluminescence spectra shown in Figure 2 were acquired using 405-, 532-, and 633-nm excitation. All of the spectra shown in this and other figures were acquired using a Horiba LabRAM HR Evolution spectrometer with an 800-mm focal length and 1800-gr/mm gratings. Peaks appear at 692.8 nm and 694.2 nm for all excitation wavelengths when plotted on an absolute wavelength scale. The peak at 810 nm in the spectrum excited at 405 nm is from the grating's second-order diffraction of the 405-nm laser light. The inset plot with expanded scale of the spectrum excited at 532 nm shows how well resolved the peaks are even though they are separated by only 1.4 nm. The high spectral resolution of a Raman spectrometer allows one to resolve these narrow and closely spaced emissions. This particular pair of strong emissions is quite familiar and arises from



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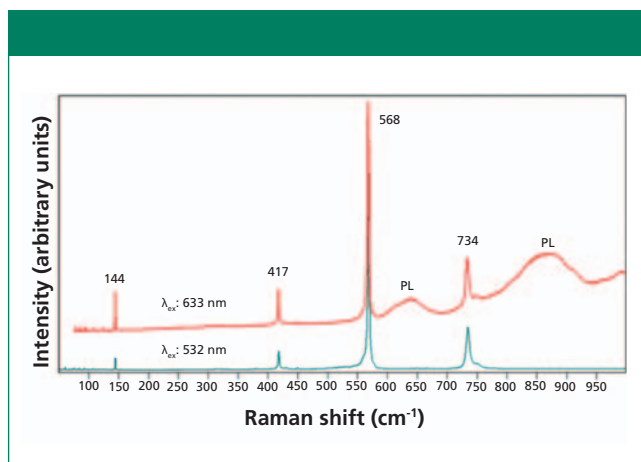


Figure 1: Raman spectra acquired from the same location of single-crystal Al_2O_3 using excitation wavelengths of 532 nm (green spectrum) and 633 nm (red spectrum). The bands marked PL are caused by photoluminescence.

Cr^{3+} impurities commonly found in Al_2O_3 . In fact, if you take almost any piece of Al_2O_3 optical flat or window and illuminate it with visible laser light, you are likely to observe these same two emissions, confirming that it is actually $\text{Al}_2\text{O}_3:\text{Cr}^{3+}$.

Without sufficient spectral resolution, the emission from $\text{Al}_2\text{O}_3:\text{Cr}^{3+}$ can sometimes appear as a single line, known as the *R line fluorescence of ruby*, in a transition from the excited ${}^2\text{E}$ energy level to the ${}^4\text{A}_2$ level. However, the ${}^2\text{E}$ level can undergo fine splitting because of distortions of the octahedral symmetry thereby producing two closely spaced emissions. These two $\text{Al}_2\text{O}_3:\text{Cr}^{3+}$ peaks are well known as R_1 (1.788 eV, 693.5 nm) and R_2 (1.791 eV, 692.3 nm) and their peak positions have been used to determine the surrounding lattice strain (2). A stress can be applied to the crystal and the induced strain can be determined by the shift in the R_1 and R_2 emissions (3,4). This phenomenon of peak shifting as a result of applied stress is known as the *piezospectroscopic effect*. Of course, the strain in the Al_2O_3 crystal induced by the applied stress can also be determined by the shifts in the Raman bands (5,6). Of the two techniques, photoluminescence may be the preferred method for determining strain in $\text{Al}_2\text{O}_3:\text{Cr}^{3+}$ because of its much greater signal-to-noise ratio.

There are several important points to take away from viewing the spectra plotted in Figure 2. The first is the high spectral resolution offered by using a spectrometer designed to resolve bands arising from vibrational modes and separated by wavenumbers (cm^{-1}). Such spectral resolution may not be necessary for typical molecular fluorescence work; however, spectral resolution can be extremely important depending upon the type of electronic transitions under study when working with solid state materials. Secondly, note that using a Raman spectrometer with charge-coupled device (CCD) detector allows a free spectral range for detection of photoluminescence covering 400 nm to 1000 nm. Depending on the type of spectroscopic or

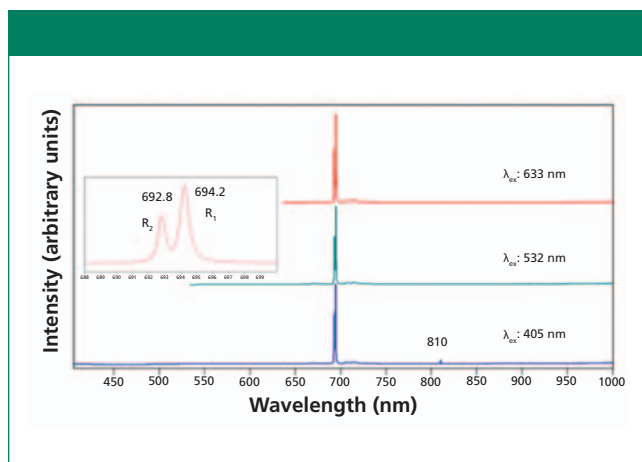


Figure 2: Photoluminescence spectra acquired from the same location of single-crystal Al_2O_3 using excitation wavelengths of 405 nm (blue spectrum), 532 nm (green spectrum), and 633 nm (red spectrum).

materials science work that you do, having a Raman spectrometer can be like having two spectrometers in one.

4f-4f Orbital Transitions in Erbium Oxide

The lanthanide element erbium has a ground-state electron configuration of $[\text{Xe}] 4f^{12} 6s^2$. With its oxidation to form the oxide Er_2O_3 the formal oxidation state of each Er atom

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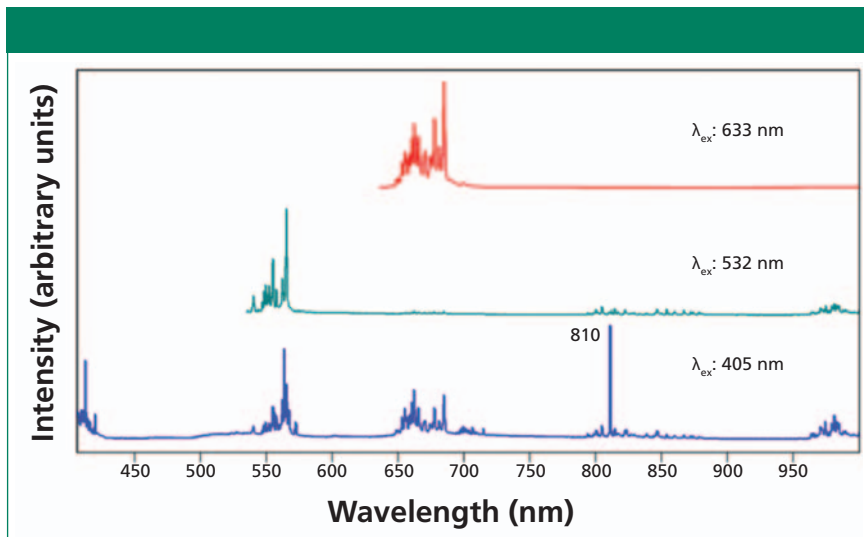


Figure 3: Photoluminescence spectra acquired from Er_2O_3 using excitation wavelengths of 405 nm (blue spectrum), 532 nm (green spectrum), and 633 nm (red spectrum).

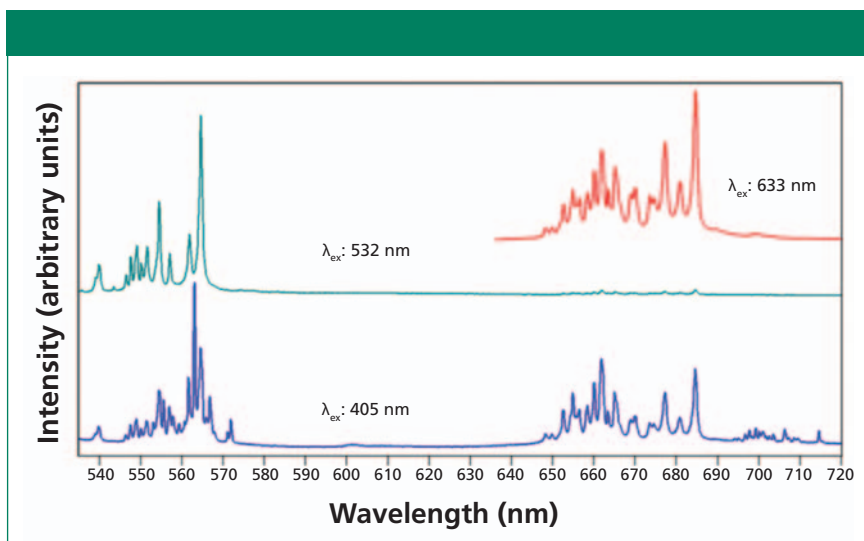


Figure 4: Photoluminescence spectra acquired from Er_2O_3 using excitation wavelengths of 405 nm (blue spectrum), 532 nm (green spectrum), and 633 nm (red spectrum).

is +3 and its electron configuration becomes $[\text{Xe}] 4f^{11}$. Thus, the highest occupied molecular orbitals of Er^{3+} are the 4f-orbitals, and they are partially filled. The 4f orbitals are nonbonding and are shielded from chemical interactions with surrounding O atoms; therefore, they do not couple strongly to the crystal lattice. The 4f-5d electronic transitions are allowed by parity selection rules. Such transitions, either absorption or emission, appear broad because of the coupling of the 5d-orbital to the surrounding crystal lattice. In contrast, 4f-4f orbital transitions are forbidden by parity selection

rules. However, the parity selection rule in Er_2O_3 is relaxed because the Er atom occupies a site lacking inversion symmetry. Under these conditions, the 4f orbitals can undergo some mixing with opposite-parity orbitals such as 5d. This phenomenon is sometimes described as the forbidden 4f-4f transition stealing intensity from the allowed 4f-5d transition. Consequently, 4f-4f electronic orbital transitions, absorption, and emission, are weakly allowed. Also, because the 4f orbitals are nonbonding and shielded from the surrounding O atoms, the absorption and emission bands appear quite sharp and narrow

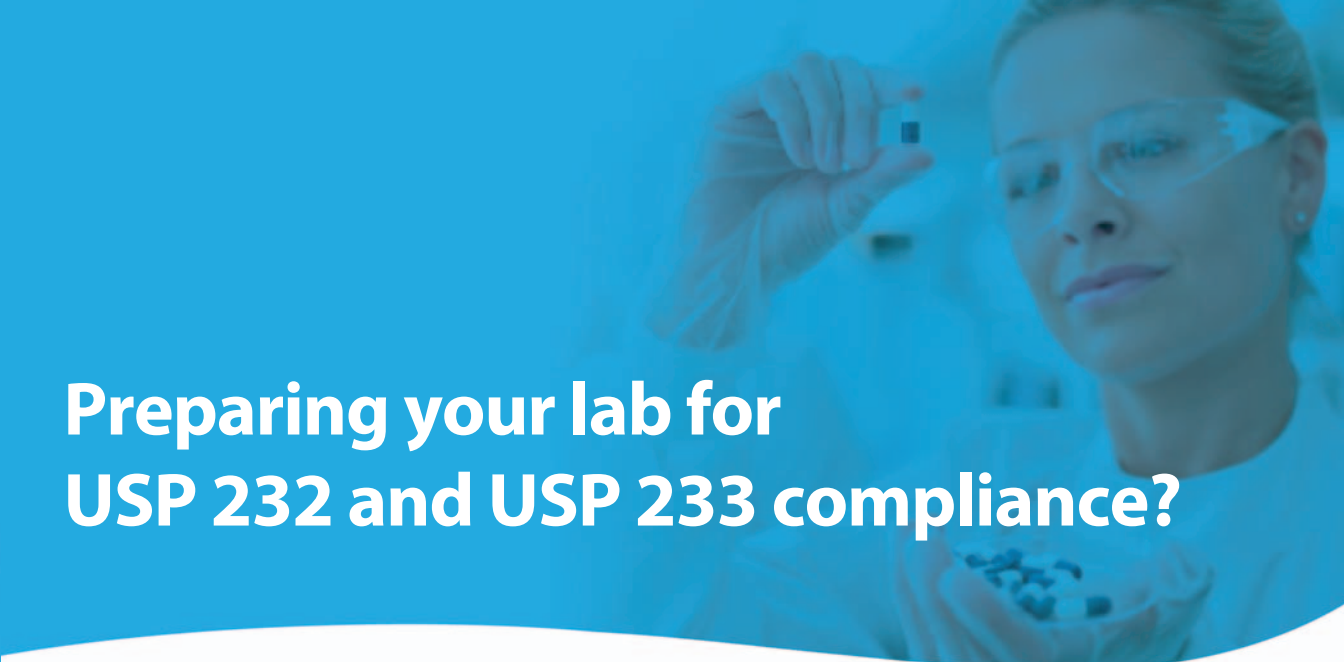
similar to those of atomic transitions.

Photoluminescence spectra of Er_2O_3 excited with 405-, 532-, and 633-nm laser light are shown in Figure 3. The emission spectra consist of five clusters of narrow bands within the range from 405 to 1000 nm. The sharp peak at 810 nm in the spectrum excited with 405-nm light is from the grating's second-order diffraction of the 405-nm laser light. The sharpness of the bands is an indication that they can all be attributed to 4f-4f orbital transitions. Also, the distribution of the emission into multiple and discrete wavelength regions is why the lanthanides are important materials in lighting and display applications (7). Note that the clusters as individual entities vary in relative intensity depending on the excitation wavelength. That variation demonstrates how the use of different excitation wavelengths allows one to generate an excitation profile depending on how closely spaced the available exciting laser lines are. Within each cluster there appear many closely spaced emission bands. A magnified plot of the spectra between 535 nm and 720 nm is shown in Figure 4. Note how the relative intensities of the closely spaced bands within each cluster vary with excitation wavelength. These narrow bands can be resolved because of the high spectral resolution of the Raman spectrometer.

Photoluminescence in Nd-Doped Glass

Another lanthanide that should be quite familiar to spectroscopists is neodymium. The element Nd has a ground-state electron configuration of $[\text{Xe}] 4f^4 6s^2$. The Nd:YAG crystal is the source of the 1064-nm laser line that functions as the excitation in Fourier transform (FT) Raman spectroscopy. Frequency doubling the 1064-nm line produces the 532-nm laser line that is so commonly used now with dispersive Raman spectrometers. Of course, there are many other electronic transitions reported for Nd and those transitions can be narrow or broad depending on the electronic orbitals involved in the transitions and the degree to which they couple to the surrounding environment (8).

The electronic transitions of Nd have been well characterized and so



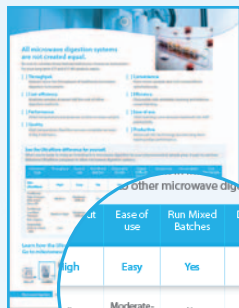
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glass doped with Nd is often used as a standard for spectral calibration. The Nd doped glass can appear faint to dark violet depending on the thickness of the glass and therefore its optical density. The violet color of the glass indicates that the Nd is very likely in the +3 oxidation state because Nd_2O_3 has the same faint violet color (9). When Nd is oxidized to form Nd_2O_3 , the formal oxidation state of the neodymium atom becomes +3 and its electron configuration is now $[\text{Xe}] 4f^3$. Consequently, $4f^3$ becomes the highest occupied molecular orbital of Nd^{3+} . Photoluminescence spectra of Nd doped glass excited with 405-, 532-, and 633-nm laser light are shown in Figure 5. The spectra appear quite barren in contrast to those of Er_2O_3 in Figures 3 and 4. The Nd-doped glass spectra are quite similar for all excitation wavelengths consisting of a weak peak at approximately 800 nm and a cluster of three partially resolved bands in the region from approximately 850 to 920 nm. The sharp peak at 810 nm in the spectrum excited with 405 nm light is from the grating's second-order diffraction of the 405-nm laser light. We can infer from the widths of these bands that the electronic transitions involved are highly coupled to the surrounding oxide environment. That is, the chemical interactions with the surrounding glass are probably similar to those of Nd_2O_3 . That interpretation would certainly be consistent with the violet color of the glass. It is likely that these transitions involve $4f$ - $5d$ orbitals of Nd^{3+} with strong coupling of the $5d$ orbital to the SiO_2 glass.

Raman Spectroscopy and Photoluminescence of 2D MoS_2

The interest in two dimensional (2D) transition metal dichalcogenides (TMD) in general and MoS_2 in particular is that a single layer of MoS_2 atoms is a direct band gap semiconductor whereas the bulk form is an indirect band gap semiconductor. Thus, single-layer MoS_2 emits light when illuminated with light whose energy is above the band gap. This property holds the promise of being able to fabricate electrooptic devices from single-layer MoS_2 or other TMDs and has therefore been

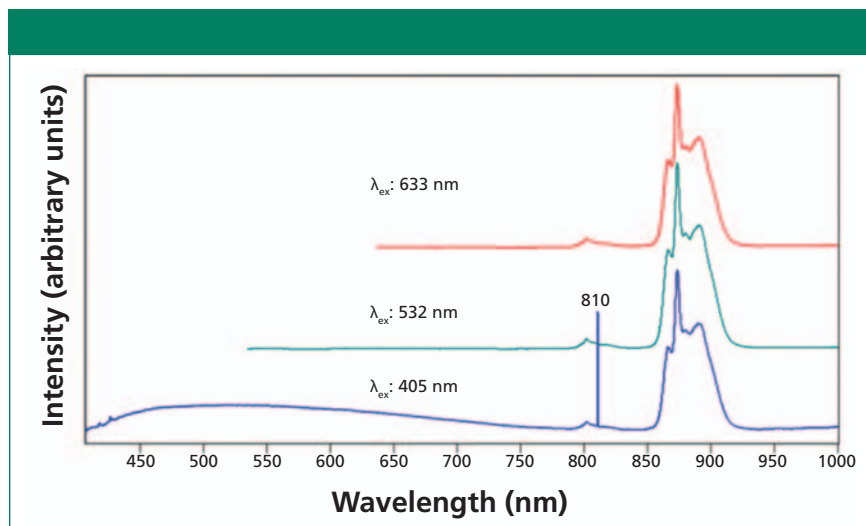


Figure 5: Photoluminescence spectra acquired from Nd doped glass using excitation wavelengths of 405 nm (blue spectrum), 532 nm (green spectrum), and 633 nm (red spectrum).

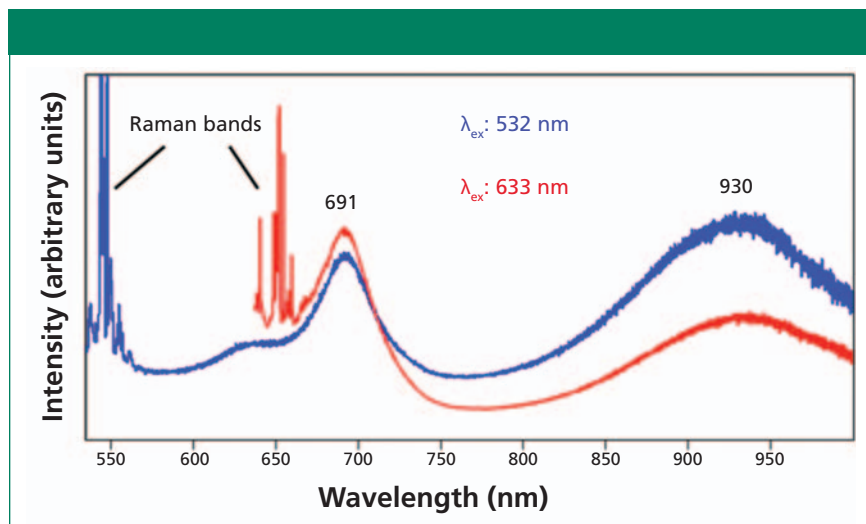


Figure 6: Photoluminescence and Raman spectra of few-layer MoS_2 flake taken at the same location with different excitation wavelengths.

the subject of intense research and development over the past few years.

The crystalline structure of 2H- MoS_2 belongs to the D_{6h} crystal class, and factor group analysis predicts one A_{1g} , one E_{1g} , and two E_{2g} Raman active modes (10–16). The symmetry assignments and corresponding Raman band positions for bulk hexagonal MoS_2 are E_{1g} (286 cm^{-1}), E_{2g}^1 (383 cm^{-1}), A_{1g} (408 cm^{-1}), and E_{2g}^2 (520 cm^{-1}). Furthermore, it is important to remember that some visible wavelengths of the laser light used to excite Raman scattering correspond to energies of MoS_2 electronic transitions. The absorption spectrum of MoS_2 reflects the band gap of 1.7 eV, but it also manifests fine structure

with narrow absorption peaks at 1.9 eV (653 nm) and 2.1 eV (590 nm) related to d-to-d orbital transitions split by spin-orbit coupling and designated A1 and B1 excitons, respectively (10,17). Consequently, one can observe an excitation wavelength dependence of the first-order Raman band intensities as well as the appearance of Raman bands assigned to harmonic and combination modes when the laser excitation is of a wavelength that couples into these excitonic transitions (10,14,16,17).

Exfoliated few-layer flakes of MoS_2 are typically heterogeneous, and so the Raman and photoluminescence spectra tend to spatially vary on the flake. The effect of excitation wavelength on

the photoluminescence spectra of few-layer MoS₂ flakes can be seen in the spectra shown in Figure 6. The spectra were acquired at the same location on the flake and are plotted on arbitrary intensity scales to better show the differences in relative strengths of both the photoluminescence and Raman signals. There are several differences to observe that relate to the electronic transitions and their coupling to the few-layer MoS₂ flake phonons. The photoluminescence excited at 532 nm is substantially weaker relative to the Raman scattering when compared to the photoluminescence/Raman strength ratio of the 632.8-nm-excited spectrum. Furthermore, the relative strengths of the 691- and 930-nm emissions are inverted for the 532- and 632.8-nm excitation wavelengths. An important aspect of this measurement is that one can simultaneously obtain a Raman spectrum and a photoluminescence spectrum from the same location. That fact holds important implications for the ability to simulta-

neously perform photoluminescence and Raman spectroscopy and imaging of few-layer MoS₂ and other TMD 2D crystals, thereby supporting the research and development of these materials to the level of electrooptic devices.

Conclusion

The high spectral resolution of a Raman spectrometer allows one to resolve narrow and closely spaced emissions from electronic transitions. Consequently, using a Raman spectrometer designed to resolve bands arising from vibrational modes and separated by wavenumbers in units of cm⁻¹ is ideal for the detection of narrow band photoluminescence. Such spectral resolution may not be necessary for typical molecular fluorescence work; however, spectral resolution can be extremely important when working with solid-state materials. The free spectral range for photoluminescence when using a Raman spectrometer and CCD detector can extend from 400 nm to 1000 nm. Having the

capability to perform photoluminescence and Raman spectroscopies simultaneously with the same instrument is advantageous, especially when studying 2D crystals. When used to perform photoluminescence spectroscopy, the Raman spectrometer becomes two instruments in one.

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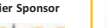
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Erratum

The October 2014 installment of “Molecular Spectroscopy Workbench” (F. Adar, *Spectroscopy* **29**[10], 14–22 [2014]) contained an error in the following paragraph: “Another metal oxide that has multiple forms is ZrO_2 . The normal stable room temperature phase is cubic, which is not Raman active because every atom sits on a symmetry site. However, for chemical or physical reasons a ceramics engineer might want to create a powder or compacted part with one of the other two phases. ZrO_2 can be stabilized in the tetragonal or monoclinic phases by alloying with a small amount of CaO or Y_2O_3 . Figure 3 shows the spectra of the tetragonal and monoclinic phases of ZrO_2 .”

The corrected text should read as follows: “Another metal oxide that has multiple forms is ZrO_2 . The high temperature phase ($>1500^\circ\text{C}$) is cubic and the first order phonons are not strictly Raman active because every atom sits on a symmetry site, although broad bands do often appear. The normal room temperature phase is monoclinic, but the ceramics engi-

neer might want to create a powder or compacted part in the tetragonal phase (that normally exists at a temperature above room temperature but lower than that of the cubic phase) by alloying with a small amount of CaO or Y_2O_3 . Figure 3 shows the spectra of the tetragonal and monoclinic phases of ZrO_2 .”

The full article, with the correction in place, can be found on our website at: www.spectroscopyonline.com/raman-spectra-metal-oxides.



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Focus on Quality

What's New with the FDA's Data Integrity Guidance?

In April 2016, the United States Food and Drug Administration (FDA) issued a draft guidance for industry called "Data Integrity and Compliance with cGMP (current good manufacturing practice)." What does this mean for a regulated laboratory?

R.D. McDowall

Data integrity is currently the hottest topic in regulated good practice (GxP) laboratories as readers of this column will know. So far, this year has seen the publication of the final version of the World Health Organization (WHO) guidance on "Good Data and Records Management Practices" (1) as well as a draft from the United States Food and Drug Administration (FDA) guidance for industry entitled "Data Integrity and Compliance with cGMP (current Good Manufacturing Practice)" (2). These publications now join the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) data integrity guidance issued in March 2015 (3). As this column was being written, the MHRA issued an update on their data integrity guidance for consultation where the overall scope is expanded to GxP (4). Not to be outdone, the European Medicines Agency (EMA) (5) and Pharmaceutical Inspection Convention/Pharmaceutical Inspection Cooperation Scheme (PIC/S) (6) also issued data integrity guidance in August as this column went to press.

A veritable cornucopia of data integrity regulatory advice and guidance is upon us! Or perhaps another perspective is a tsunami of advice from the regulators? This abundance of regulatory guidance is shown graphically in Figure 1, and you can see that the FDA has more guidance and advice for data integrity than any other regulatory source:

- Guide to the Inspection of Pharmaceutical Quality Control Laboratories (7)
- Compliance Program Guide (CPG) 7346.832 for Pre-Approval Inspections (PAI) (8)
- Level 2 guidance on the FDA website (9)
- Draft Guidance for Industry, Data Integrity, and Compliance with cGMP (2)

Although "Guide to Inspections of QC Labs" (7) is more than 20 years old, it is still worth reading because most labora-

tories have not changed their working practices greatly in the intervening time since its publication. For example, it includes the statement, "The authority to delete files and override computer systems should be thoroughly examined."

For the purposes of this column, we focus our discussion on the FDA guidance document on data integrity although the discussion will also bring up some of the other FDA guidances in Figure 1 as well as some other documents issued by the agency. This column installment is not a comprehensive review of the data integrity guidance (2)—the focus here is on those sections that impact on the regulated good manufacturing practice (GMP) laboratory. The principles discussed here can be extended to any regulated or quality laboratory.

Overview of the FDA Guidance

The FDA guidance is unlike those from the WHO and MHRA guidance documents (1,3) in that it is presented in the format of 18 questions and answers, as shown in Table I. The FDA document does not have the more encompassing scope of the MHRA and WHO guidance documents that consider topics such as data governance, the role of management, and the extension of data integrity to an organization's suppliers. Instead, the FDA guidance is complementary and is entirely focused on the interpretation of the 21 *CFR* 211 regulations for current GMP (cGMP), specifically to ensure the integrity of data generated in pharmaceutical manufacturing (10). The problem with US regulations, unlike those in the European Union, is that (with one exception) they have not been updated since 1978. As such there is no explicit reference that is specific for ensuring the integrity of laboratory data—it is the interpretation of the regulations that is key. As a result, there are multiple references to the different sections of 21 *CFR* 211 to support the 18 questions. Of particular interest is question 1e, which illustrates the

“current” in cGMP (2). Backup is now interpreted by the FDA as long-term archives for records retention rather than simply creating a copy of records on tape or disk for disaster recovery purposes.

Question 1d: Static Versus Dynamic Data

Question 1d talks about static and dynamic data, which are perhaps not the best of terms to use in describing data. *Static data* are typically discrete values such as temperature and pH that cannot be interpreted or as the guidance mentions a paper printout or image. In contrast, *dynamic data* requires human interpretation or processing, such as with chromatography or spectroscopic data files, and these types of data are of major concern to the FDA and other regulators for manipulating data and testing to pass. “Processable” data might be a better term because we typically process our data in the laboratory.

Questions 4 and 5: Access to Computerized Systems

In short, there must not be any generic or shared log-on accounts for access to a computerized system because each person must be uniquely identified and their actions within a system tracked and audit trailed. User types need to be established that separate administrator privileges from those involved with generating, processing, and reviewing data. Ideally, an independent function, typically the IT department, needs to control the administration rather than the laboratory. However, with standalone systems this independent control may be impossible to achieve and therefore as noted in the MHRA data integrity guidance (3) an alternative option may be for a laboratory user to have two user types. The first would be as an administrator with no user access rights and the second as a user with no administrator privileges.

The FDA guidance also recommends maintaining a list of authorized individuals with their access privileges. This list should cover both current and historical users of a system. In case you think this recommendation is an FDA rabbit out of the hat, it has been the stated agency position since 2007. It is contained in the guidance for industry on “Computerized Sys-

tems Used in Clinical Investigations” (11) under “Recommendations, Section E” on external security safeguards. It states, “You should maintain a cumulative record that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges.”

This is good advice because it allows quality assurance, auditors, or inspectors to see at any point in time the access privileges that any individual has had for a system, including those of trainees, analysts, and supervisors.

Questions 12 and 2: When Do Data Become a GMP Record and Can I Exclude GMP Data?

Now we come to probably the most contentious part of the FDA guidance: question 12. At the beginning of question 12 is a simple statement of fact, “When generated to satisfy a GMP requirement, all data become a GMP record.” This is simply a confirmation and restatement of the GMP requirement in 21 CFR 211.194(a) for complete data secured in the course of testing (10).

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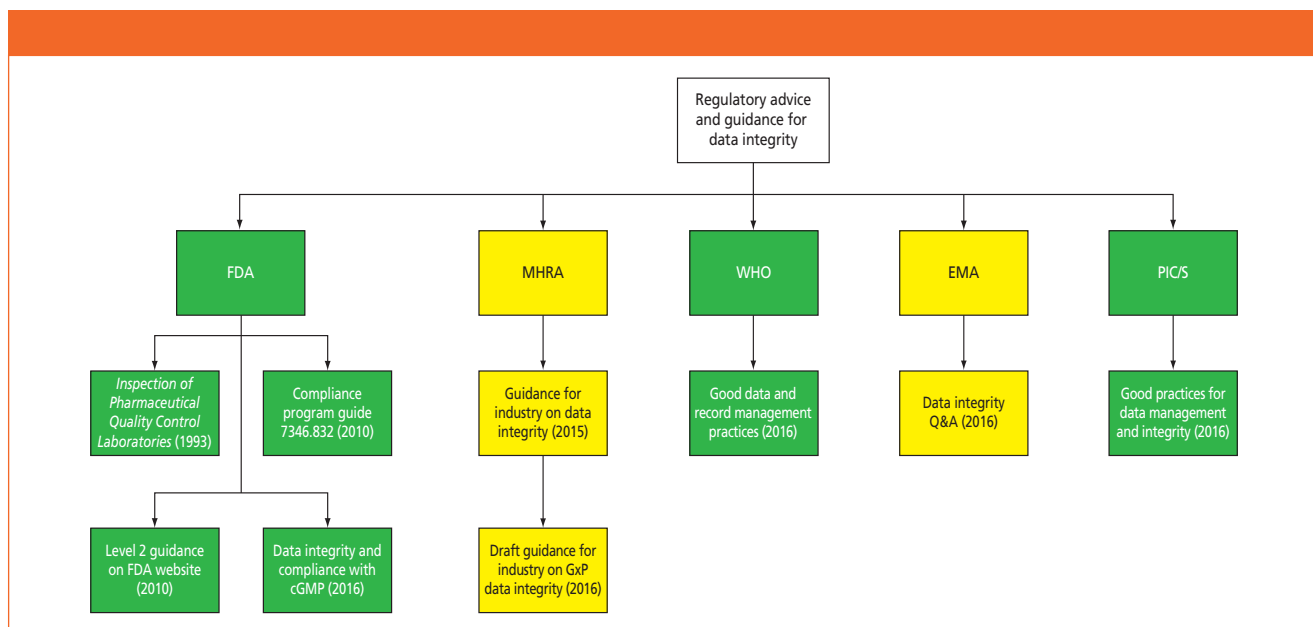


Figure 1: Data integrity guidance from regulatory sources.

At this point can I mention the “s” word? Sssh, whisper it softly . . . spreadsheet! How many laboratories use validated spreadsheet templates only to print but not save the completed files? This recommendation means that the completed file must be saved under a unique filename and if signed or

initialed there must be a linkage between the saved file and the signed printout to comply with 21 *CFR* 11.70 (12). Simply printing the spreadsheet to a PDF does not comply with this requirement—the original file must be saved.

The guidance then continues:

You must document at the time, or save, the data at the time of performance to create a record in compliance with GMP requirements . . . FDA expects processes to be designed so that quality data required to be created and maintained cannot be modified.

For example, chromatograms should be sent to long-term storage (archiving or permanent record) upon run completion instead of at the end of a day's runs.

There is a slight problem here: if a spectroscopy or chromatography file cannot be modified how can we interpret it? Perhaps what is meant is that the data or the computer file created cannot be changed, but the data contained within it can be interpreted?

The requirement about removing chromatograms immediately to long-term storage after each run borders on the silly side and does not reflect reality. I appreciate what the agency is trying to achieve—to ensure that electronic records generated by data systems of all types are protected, especially for standalone systems that do not have databases. This actually reflects on how instrument suppliers design and laboratories select data systems that are substandard for regulated laboratories. To put this into perspective, virtually all software currently in use in laboratories was designed before the current focus on data integrity. For too long laboratories have accepted spectroscopic applications running on standalone workstations that generate data files that are stored in directories in the operating system. Quite simply, these systems are not fit for purpose. To illustrate this point, McDowall and Burgess recently wrote a series of four papers describing the ideal chromatography data system (CDS) for regulated GxP laboratories in *LCGC North America* (13–16). Although focused on chromatography data systems, most of





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Table I: Questions from the FDA's "Guidance for Industry on Data Integrity and Compliance with cGMP"

Number	Question
1	Please clarify the following terms as they relate to cGMP records: a. What is "data integrity"? b. What is "metadata"? c. What is an "audit trail"? d. How does the FDA use the terms "static" and "dynamic" as they relate to record formats? e. How does the FDA use the term "backup" in § 211.68(b)? f. What are the "systems" in "computer or related systems" in § 211.68?
2	When is it permissible to exclude cGMP data from decision making?
3	Does each workflow on our computer system need to be validated?
4	How should access to cGMP computer systems be restricted?
5	Why is the FDA concerned with the use of shared login accounts for computer systems?
6	How should blank forms be controlled?
7	How often should audit trails be reviewed?
8	Who should review audit trails?
9	Can electronic copies be used as accurate reproductions of paper or electronic records?
10	Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as a Fourier transform infrared (FT-IR) instrument?
11	Can electronic signatures be used instead of handwritten signatures for master production and control records?
12	When does electronic data become a cGMP record?
13	Why has the FDA cited use of actual samples during "system suitability" or test, prep, or equilibration runs in warning letters?
14	Is it acceptable to only save the final results from reprocessed laboratory chromatography?
15	Can an internal tip regarding a quality issue, such as potential data falsification, be handled informally outside of the documented cGMP quality system?
16	Should personnel be trained in detecting data integrity issues as part of a routine cGMP training program?
17	Is the FDA investigator allowed to look at my electronic records?
18	How does the FDA recommend data integrity problems identified during inspections, in warning letters, or in other regulatory actions be addressed?

the principles and recommendations outlined in these papers are also applicable to spectroscopic data systems. In the part on system architecture (14), the point was made that standalone workstations and using directories in the operating system for file storage were not fit for purpose. Instead data must be acquired directly to network storage and that all data systems must use a database. In doing so, the intent of the FDA's requirement would be met but in a more practical way. Correctly designed data systems are the main way laboratories will comply with the protection of records other than implementing a scientific data management system (SDMS).

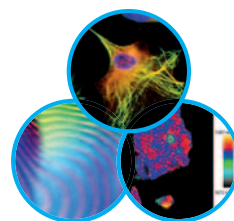
Question 12 progresses through the next statement in the document for paper records, which must have been copied verbatim from a GxP documentation class 101. However, as judging from the citations in many warning letters there appears to be an overabundance of idiots working in regulated laboratories so that the following needs to be repeated for temporary scraps of paper: "It is not acceptable to record data on pieces of paper that will be discarded after transcription into a permanent laboratory notebook."

There then follows the electronic equivalent, which is more contentious:



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Similarly, it is not acceptable to store data electronically in temporary storage, in a manner that allows for manipulation, before creating a permanent record. Electronic data that are automatically saved into temporary memory do not meet cGMP documentation or retention requirements.

This section has probably caused more discussion than any other in the whole draft data integrity guidance. Obviously the agency does not want people taking a file then interpreting it multiple times without saving it, because this is testing—or rather over-interpreting—into compliance.

I don't believe that the FDA wants keystroke loggers on all systems used for regulated analysis. The process in all data systems should be to save the data first and monitor the interpretation. However, this is where science and compliance meet, often in a head-on collision. The controls required, especially technical ones rather than procedures, need to be designed and implemented. In some systems, especially those close to the research end of research and development (R&D), may be designed with minimal regulatory compliance controls. There needs to be a fundamental rethinking by software suppliers about how their software is designed and operated in compliance with the applicable regulations. However, this process will take time as anyone will know who has seen some of the shambolic attempts to produce technically compliant Part 11 applications or are waiting now for a function to document second person review of audit trail entries for Annex 11. This step is the scientific equivalent of *Waiting for Godot*. For readers who have not seen the play, you sit through two hours and Godot never appears.

It should be noted that although this "Focus on Quality" installment is about the FDA's "Data Integrity Guidance," the recent UK MHRA guidance includes this statement, "... it is expected that GMP facilities should upgrade to an audit trailed system by the end of 2017."

It is nice to know that optimism still exists in the UK. Given the lead time for suppliers to implement these controls in software and the lack of laboratory users to press suppliers for these features means that this deadline will come and go with no change. This is the situation

with small-molecule chemistry software applications. The situation with biotechnology software is even worse—the regulatory compliance equivalent of the Wild West as it is closer to research.

Question 2 discusses if GMP data can be excluded from decision making. It notes that, "any data created as part of a GMP record must be evaluated by the quality unit as part of release criteria and maintained for GMP purposes. Electronic data generated to fulfill GMP requirements should include relevant metadata."

The answer is that data (paper, hybrid, or electronic) can only be excluded if there is a justified and documented scientific rationale—for example, an out-of-specification result following a laboratory investigation. The corollary is that data should not be deleted, even if it is excluded, because it is part of complete data collected in the course of testing under 21 CFR 211.194(a) (10). In this context, there has been an interesting publication recently entitled "18 Reasons Spelt Out by Peter J. Werth to Delete Analytical Data" (15), which range from incorrect sample preparation to plumbing problems and leaks. Perhaps this publication is an isolated view from the owner of an active pharmaceutical ingredient company, but senior management need to be aware of the issues of data integrity and comply with regulations. If they choose to ignore this advice, then as some children's TV shows warn: don't do this at home. Do not follow this advice and delete data. From the answers in questions 2 and 12 deletion of GMP data without a documented justification (2) can seriously damage your company's wealth because of noncompliance with GMP.

Question 3: Does Each Workflow on a Computer System Need Validating?

Yes, is the answer in the FDA guidance (2). If a workflow is configured or customized then it needs to be specified, built, or configured in the software and then tested for intended use. So far, so good, and I have no problem with this approach.

However, what if you have standard workflows in a system that you don't use and can't turn them off? As the question is written and answered, the data integ-

rity guidance implies that they all need to be validated, which is a compliance overhead and not in the spirit of a risk-based approach. There is also a clash of FDA guidance documents. There is the small matter of the 2002 "General Principles of Software Validation," which states in section 6.1 (18):

For example, a (device) manufacturer who chooses not to use all the vendor-supplied capabilities of the software only needs to validate those functions that will be used and for which the (device) manufacturer is dependent upon the software results as part of production or the quality system.

Or put simply, only validate those software functions you use. Note that I have added the parentheses in the quotation above because this guidance was written for medical devices. As currently written, there is a potential clash of guidance from the FDA and hopefully in the final version of the data integrity guidance there will be clarification to align the data integrity and software validation guidance documents so that there is no conflict.

Question 6: Control of Blank Forms

At the back of many procedures in regulated laboratories are blank forms designed to ensure compliance with the work contained in the standard operating procedure (SOP) and to collect the required data. Question 6 of the FDA guidance raises the question of how these blank forms should be controlled (2). The FDA wants each copy of such forms to be uniquely numbered and accounted for. Does this sound like the agency is making up rules as they go along? Actually, it is not and is simply a restatement of their position from the 1993 guidance on "Inspection of QC Laboratories" (7) as noted in section 13 on documentation: "We expect raw laboratory data to be maintained in bound (not loose or scrap sheets of paper) books or on analytical sheets for which there is accountability, such as prenumbered sheets."

The requirement for control of blank forms has also been presented in the recent MHRA and WHO guidance documents (1,3). Furthermore, this topic is also covered in some detail in the recently published EMA and PIC/S data integrity guidance documents (5,6). The rationale for this approach is

that uncontrolled blank forms present an opportunity for data falsification or testing into compliance. This is an important area that is the subject of my next "Questions of Quality" column in *Spectroscopy's* sister publication, *LCGC Europe* (19). The bottom line is that there is now an administrative burden on analytical laboratories that will, sooner or later, force organizations to move to electronic working to reduce the overhead and automate this aspect of regulatory compliance.

Importance of the Second Person Review

A problem with the FDA data integrity guidance is that there is only a focus on audit trail review with questions 7 and 8 and with question 16 on the need for personnel to be trained to detect data integrity issues (2). In my view, the draft guidance misses the point and an opportunity. If we are serious about data integrity and compliance with the regulations, surely the focus both here and in our laboratories should be on a series

of questions covering the second person review of analytical data. As currently written, the guidance is scratching the surface with simply a focus on a computerized system audit trail (if used) and a suggestion that people should be trained to detect poor data management practices. Perhaps there should be questions such as

- How should I review paper records? Here the focus could be on the objective evidence available so that the second person reviewer can check that an analytical procedure has been followed. Alternatively, if we are dealing with a color or odor test, the reviewer can go to the sample to check the observation made by the tester.
- How should hybrid records be reviewed? In this case, the reviewer needs to check that the data and all metadata have been collected and data collection SOPs have been followed. The review would also include a risk based review of the audit trail entries involved with modification (and deletion if allowed) of data. This review

would involve the data system. There would also be a check of any records outside of the system, such as sample preparation and input of data into the data system plus that the printout corresponds to the data in the application.

- How should electronic records and electronic signatures be reviewed? When a reviewer is working electronically, the review is based on the technical controls implemented to ensure that the workflow was followed and any calculations as well as the application is validated (20). When a reviewer is working electronically, with a validated workflow that enforces activities and validated calculations, the focus can be on the interpretation of the data and audit trail entries, simplifying the whole review. If the application has the functionality, the audit trail can identify which audit trail entries the reviewer should check. However, even in an electronic system as with a hybrid, samples are prepared outside of the system and data will be



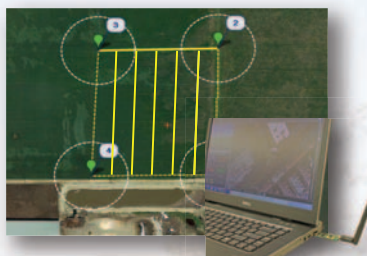
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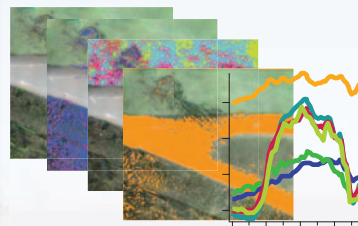
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manually input, these values also need to be checked.

- How are sample preparation activities to be recorded and, more pertinently, reviewed (for example, sample dilution and preparation)? Perhaps it's time to buy shares in video recorder companies?

These are only my suggestions, but the guidance needs to be developed further to cover this gap.

Question 10: Can I Retain Paper Printouts Rather than Electronic Records?

For simpler instruments such as an analytical balance and a pH meter, the paper printouts are the GMP record and must be retained. However, the data integrity guidance also quotes an example of a Fourier transform infrared (FT-IR) spectrometer where it is used in a GMP activity, such as identification of materials against a library. Here the electronic record is dynamic or processable, and thus paper should not be the only record because the printout may only display part of the sample spectrum. However, the argument in the draft guidance is not as well presented as the original discussion on this topic that is on the FDA's website, which poses the following question (9): "3. How do the Part 11 regulations and 'predicate rule requirements' (in 21 *CFR* Part 211) apply to the electronic records created by computerized laboratory systems and the associated printed chromatograms that are used in drug manufacturing and testing?"

In this instance, the 2010 argument began from the premise that the FDA believed that some in industry were misinterpreting Part 11 and replying on paper printouts and keeping the underlying electronic records as the raw data from an analysis. The problem is that the question begins generally talking about "computerized laboratory systems" but by mentioning "associated printed chromatograms" brings the focus of the question to a specific analytical technique. This mention of chromatography means that spectroscopists immediately turn off because the guidance is not seen as being written for them. In reality, the focus should be on the computerized laboratory system, which would include

all spectroscopic and chromatographic data systems and also, I would argue, spreadsheets. The discussion could be illustrated by FT-IR and chromatography examples, but in my view the final version of the guidance should be aimed at a wider analytical audience.

The following two sections of the GMP regulations are quoted both on the website and the guidance to support why electronic records and not paper should be the raw data:

- §211.180(d), which notes that paper printouts are not the original records or true copies of the underlying electronic records
- §211.68(b), which states that paper is not a complete and exact copy of the electronic records as the latter contain more information than printouts.

A better worded discussion that melds both the current draft guidance and the website advice together would be a better approach in this area.

What About the Part 11 Scope and Application Guidance?

It's a funny old world, isn't it? You wait for a data integrity guidance from the FDA and then you think, how does this mesh with other existing guidance documents? We have seen that, for the most part, there is consistency in the FDA's approach to blank forms and security, but what about the Part 11 "Scope and Application Guidance" (21)? A draft was issued in February 2003 with a 60-day comment period, and the final version was issued in September 2003. That was a lightning fast turnaround for an FDA guidance for industry. The guidance document is now 13 years old and the 21 *CFR* 11 regulations are nearly 20 years old. I would like to pose the following questions:

- What is the value of 21 *CFR* 11 regulations? It may appear that the sole purpose of 21 *CFR* 11 is to allow industry to use electronic signatures and software suppliers to ensure suitable technical controls are included in applications. The main means of enforcement by the FDA is via the cGMP regulations.
- Should the Part 11 guidance be retired or merged with the data integrity document? Warning letters based

on 21 *CFR* 11 regulations have been nonexistent for the past 13 years and all citations for data integrity have involved the predicate rule (21 *CFR* 211) regulations.

Furthermore, the Part 11 guidance provides enforcement discretion for:

- 11.10(a) validation – This sub clause also includes the ability of systems to discern altered records, the trigger for an audit trail entry. In the light of data integrity issues, is it still wise to have this available for anyone to read and misinterpret?
- 11.10(e) audit trails – Given the current emphasis and importance of audit trails shouldn't the enforcement discretion be lifted? The systems it refers to are probably long past their retirement date or are about to expire. Data integrity is the more important topic to focus on, and there should be statements in the final version of the data integrity guidance about how these two guidance documents interact and which takes precedence.

Summary

In this column, we looked at the elements from the draft FDA "Guidance on Data Integrity and cGMP Compliance" that have an impact on a GMP regulated laboratory. Many items are common sense and understandable, while others are less so and clash with existing guidance from the FDA. Hopefully, these unresolved issues will be addressed in the final version of the document.

Acknowledgment

I would like to thank Paul Smith for comments made in the preparation of this column.

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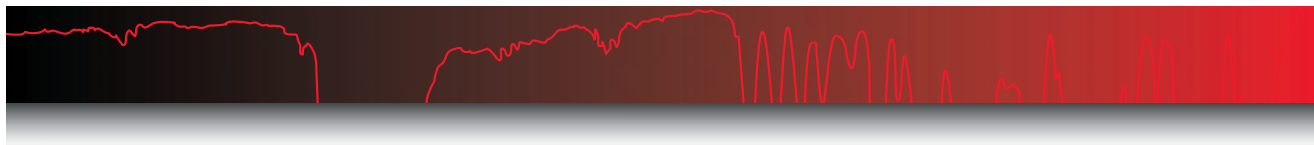
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The Benzene Fingers, Part II: Let Your Fingers Do the Walking Through the Benzene Fingers

With the theoretical background of benzene analysis laid out in part I of this series, we now know what fundamental, overtone, and combination bands look like. Here, we show that the benzene fingers are a series of overtone and combination bands that can be used to distinguish substituted benzene rings from each other when other methods do not work. We also review the benzene finger patterns for mono-, ortho-, meta-, and para-substituted benzene rings, and describe an easy mnemonic in which you use your fingers to help you remember the patterns.

Brian C. Smith

In an earlier installment (1), I introduced the chemical structures and nomenclature for mono- and disubstituted benzene rings, and showed how the presence or absence of the ring bend at $690 \pm 10 \text{ cm}^{-1}$ and the position of the out-of-plane aryl C-H wag together can be used to distinguish mono-, ortho-, meta-, and para-isomers from each other. These peak positions are summarized in Table I.

However, we discovered that under certain circumstances Table I is not sufficient to distinguish the four structures in question from each other. For example, both mono- and meta-isomers have the ring bend present and have C-H wagging peaks between 770 and 750 cm^{-1} . What then are we to do?

In part I of this series (2), we discovered that there is a series of overtone and combination bands between 2000 and 1650 cm^{-1} that I call the *benzene fingers*, that are another tool to distinguish substituted benzene rings from each other. I mentioned that the benzene fingers are a series of overtone and combination bands, and then spent the rest of the column explaining what those are.

In this final installment of the benzene fingers saga, I show the actual peak patterns for mono-, ortho-, meta-, and para-rings, and share with you a silly but effective mnemonic using your fingers to help you remember the benzene ring patterns. Hence the title of this installment.

The Benzene Finger Patterns for Mono- and Disubstituted Benzene Rings

The benzene fingers for mono- and disubstituted benzene rings are not defined by peak positions but by the number, spacing, and relative intensity of a series of peaks between 2000 and 1650 cm^{-1} . As I have stated previously, infrared (IR) spectral interpretation is not about memorizing peak positions but rather it is an exercise in pattern recognition. The benzene fingers prove this point.

In a previous column (1), we looked at the spectra of toluene and the three xylenes. If you go back to that column installment, and use a magnifying glass, you might be able to see the benzene finger patterns. These patterns have been expanded and plotted in absorbance for you in Figure 1.

The pattern for mono-substituted rings is four well separated peaks, and for ortho-substituted rings it is four peaks close together. For meta-substituted rings there are three peaks, while for para-substituted rings there are two peaks. Mono-, ortho-, meta-, para- . . . four peaks, four peaks, three peaks, two peaks . . . four, four, three, two . . . whose patterns can be remembered using your fingers as shown in Figures 2a–2d.

When I was a boy I was a member of the Cub Scouts, and when I got older the Boy Scouts. The Cub Scout salute used two fingers and the Boy Scout salute used three fingers. Another way I remember the benzene fingers for mono- and disubstituted benzene rings is four fingers, four fingers, Boy Scout salute, Cub Scout salute. This messing around with benzene and human fingers may seem silly, but I guarantee after reading this column you will never forget the benzene ring patterns for mono-, ortho-, meta-, and para-substituted benzene rings.

Table I: The C-H wag position and ring bend presence for mono- and disubstituted benzene rings

Substitution Pattern	Out-of-Plane C-H Bending	Ring Bend ($690\pm 10\text{ cm}^{-1}$)
Mono	770–710	Yes
Ortho	770–735	No
Meta	810–750	Yes
Para	860–790	No

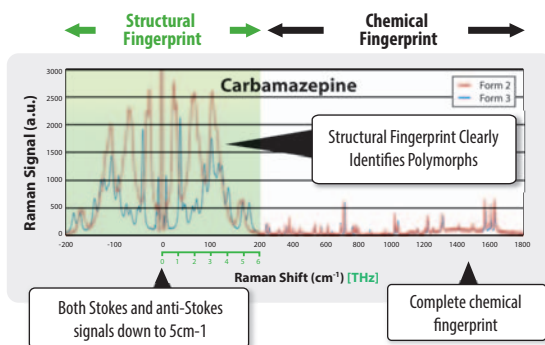
I stated above that Table I sometimes can't be used to distinguish between mono- and meta-isomers. The benzene fingers solve this problem—mono-substituted benzene has four benzene finger peaks and meta-substituted benzene has three benzene finger peaks—problem solved. In general, when I need to determine the substitution pattern around a benzene ring I use the peak positions in Table I first; if they don't work for whatever reason I will use the benzene fingers. If Table I can be used to determine a substitution pattern, I still consult the benzene fingers as a backup to my initial conclusion.

The benzene fingers are easy to

use but suffer from some problems. First of all they are inherently weak because they are a series of overtone and combination bands (2). Even in pure form these peaks can be 10 times or more smaller than the fundamental bands of a molecule. Thus, at a short pathlength, or in a mixture where the benzene ring is in low concentration, these peaks may be not big enough to see. A second problem with the benzene fingers is that they show up in a busy region of the spectrum where lots of large peaks can appear and mask their presence. Carbonyl ($\text{C}=\text{O}$) stretching peaks frequently fall between 1900 and 1600 cm^{-1} , are often intense, and have been known to

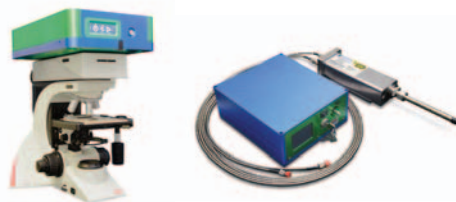
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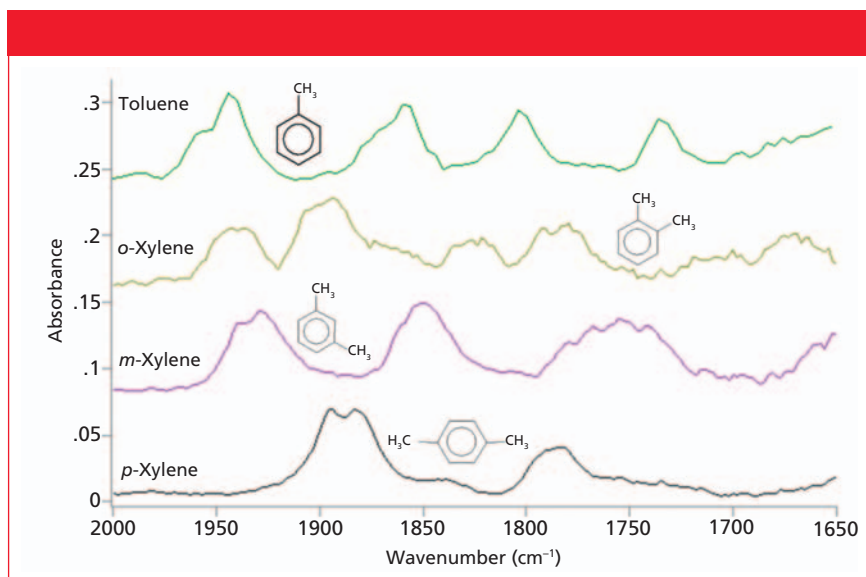


Figure 1: The benzene finger patterns for mono-, ortho-, meta-, and para-substituted benzene rings.

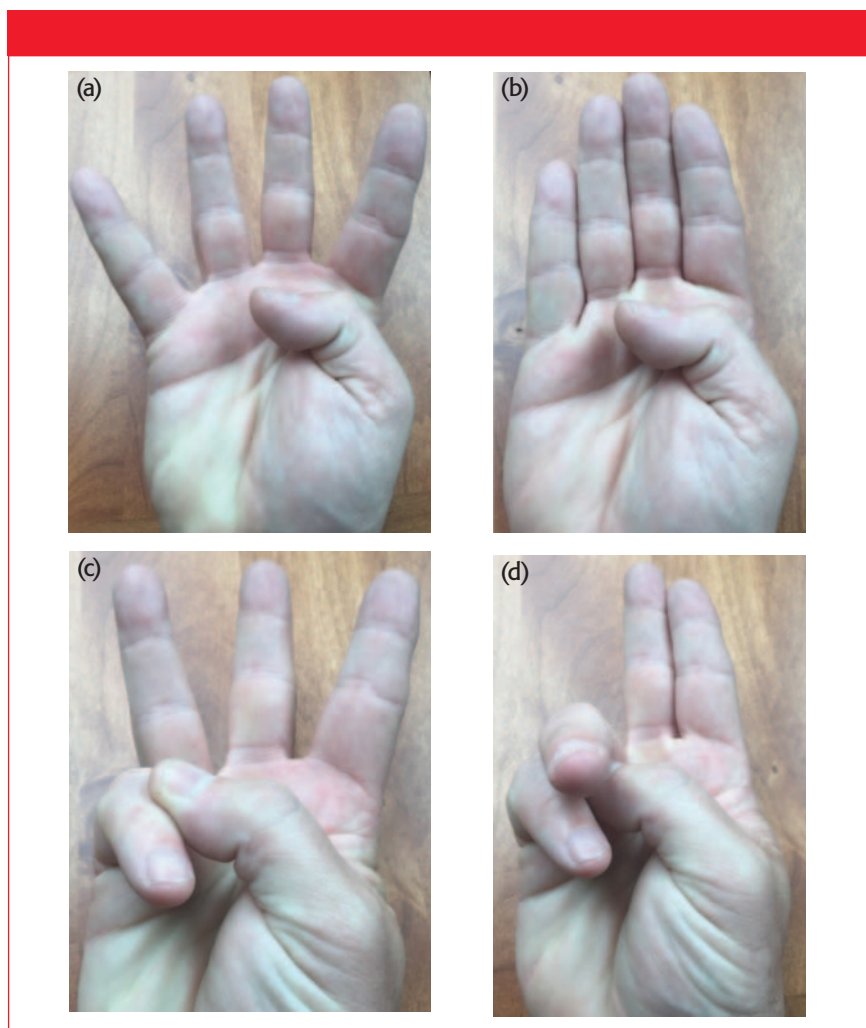


Figure 2: (a) The benzene fingers pattern for mono-substituted benzene rings, four well separated peaks. (b) The benzene fingers pattern for ortho-substituted rings, four peaks close together. (c) The benzene fingers pattern for meta-substituted rings, three peaks. (d) The benzene fingers pattern for para-substituted rings, two peaks.

mask the presence of the benzene fingers (3). Obviously, if you can't see the benzene fingers you can't use them to help determine benzene ring substitution patterns.

Other Types of Aromatic Rings

When I first introduced you to benzene rings (4) we talked about aromatic rings in general and what makes them structurally and spectroscopically unique. Since the benzene molecule contains six hydrogens, it can have up to six substituents. As discussed previously (2), the reason I limited the discussion to mono- and disubstituted benzene rings is that I believe they are the most common aromatic rings, and have the easiest to interpret spectra. The spectra of benzene rings with three, four, or five substituents display C-H stretches above 3000 cm^{-1} and ring modes like their less substituted cousins. Similarly, the presence or absence of a ring bend and the position of one or more C-H wags can be used to determine their substitution pattern. Highly substituted rings also exhibit their own unique benzene finger patterns.

Benzene rings can also be found in structures where they are fused, with adjacent rings sharing two carbons. These are called polycyclic aromatic hydrocarbons (PAHs) (5). Some examples of simple PAHs are seen in Figure 3.

Naphthalene is the simplest PAH containing two fused benzene rings. It is the smelly ingredient commonly found in moth balls. There are two isomers possible for three benzene rings fused together, anthracene and phenanthrene, as seen in Figure 3. Because PAHs have more atoms than benzene rings, their spectra are more complicated. However, they exhibit many of the same features already discussed for benzene rings including C-H stretches above 3000 cm^{-1} , aryl C-H wags, and ring bends. As mentioned above, some of these features can be used to distinguish isomers from each other. For example, the two isomers of a mono-substituted naphthalene can be distinguished from each other by their IR spectra.

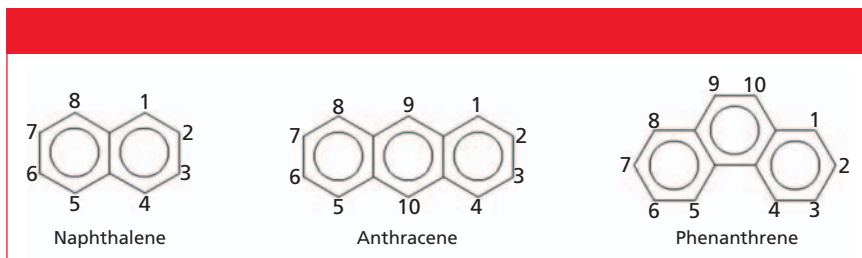


Figure 3: Some examples of polycyclic aromatic hydrocarbons. The numerals represent the carbon numbering scheme for each specific ring system.

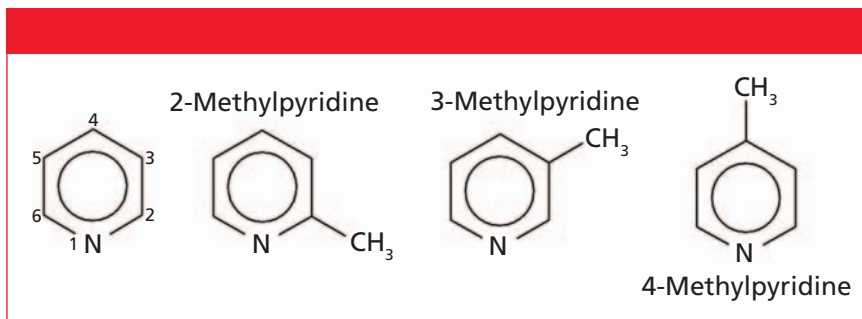


Figure 4: Pyridine and the family of mono-substituted pyridines, examples of heterocyclic aromatic hydrocarbons.

hydrocarbons. Some example structures of these are seen in Figure 4.

Like other aromatic rings, heterocyclic aromatic hydrocarbons have C-H stretches above 3000 cm^{-1} , ring modes, and aryl C-H wags. These peaks can be used, for example, to distinguish the three mono-substituted pyridines shown in Figure 4 from each other. A discussion of the IR spectra of highly substituted benzene rings, polycyclic aromatic hydrocarbons, and heterocyclic aromatic hydrocarbons will be the subjects of future columns.

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Brian C. Smith, PhD, is a Senior Infrared Product Specialist for PerkinElmer, based in San Jose, California. Before joining PerkinElmer, he ran his own FT-IR training and consulting business

for more than 20 years, and taught thousands of people around the world how to improve their FT-IR analyses and interpret infrared spectra. Dr. Smith has written three books on infrared spectroscopy: *Fundamentals of FTIR* and *Infrared Spectral Interpretation*, both published by CRC Press, and *Quantitative Spectroscopy: Theory and Practice* published by Academic Press. He has published a number of papers in peer-reviewed journals and is a co-inventor on a patent for an FT-IR method to monitor dust exposure in coal mines.

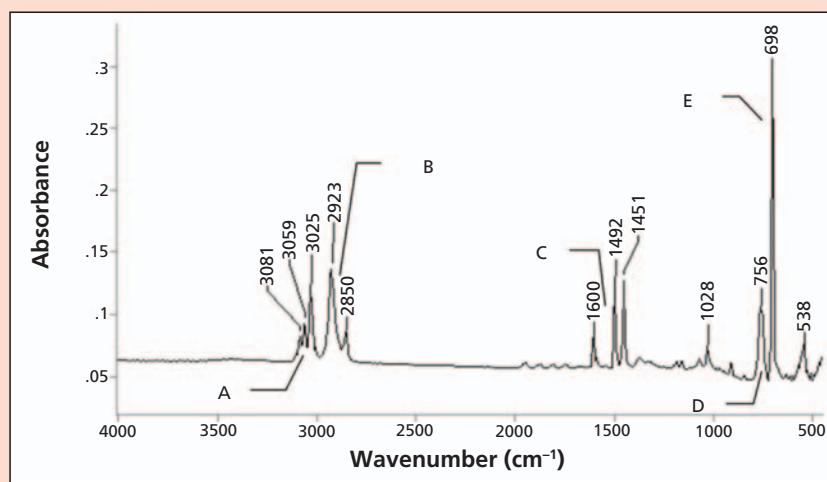
Quiz Section: A New Interpretation Challenge

New Quiz

Your latest interpretation problem is seen in the figure below. First, determine why Table I fails for this spectrum, then using only the benzene fingers; determine the substitution pattern around the benzene ring present in the molecular structure. If possible, use the rest of the spectrum to determine the complete molecular structure of the molecule.

Table: Peaks for the spectrum seen in the figure

A	3081, 3059, 3025
B	2923, 2850
C	1600, 1492
D	756
E	698



New quiz: Your next unknown spectrum. A thin film in transmission.

A heterocyclic aromatic hydrocarbon is an aromatic ring that contains a noncarbon or “heteroatom.” Examples

of heteroatoms include nitrogen and oxygen. Pyridine and substituted pyridines are heterocyclic aromatic

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SPECTROSCOPY SPOTLIGHT

Addressing the Challenges of Process Raman Spectroscopy



In recent years, Raman spectroscopy has been applied to process monitoring and control applications in a wide range of application fields, including bioprocessing, pharmaceuticals, food, oil and gas, and oceanography. Brian Marquardt, cofounder and CEO of MarqMetrix, Inc., and director and senior principal engineer with the Center for Process Analysis and Control in the Applied Physics Laboratory at the University of Washington, has more than 15 years of experience with such applications and recently spoke with us about his research.

Your research in applying Raman spectroscopy to process applications spans many fields, ranging from industrial process analysis and marine measurements to bioprocess monitoring. What do you consider to be the most challenging process application for Raman at the moment? Are you currently working on any projects that would address that challenge?

From my perspective, biotech applications of Raman are currently the most challenging because of the complex biological matrices and their associated fluorescence. We are currently working with a near-field focusing Raman immersion fiber probe (Ball-Probe, MarqMetrix) to effectively sample these systems with Raman as the optical density and the composition changes during a bioprocess. To reduce the fluorescence impact in a bioprocess application we are using a combination of unique data analysis methods and some very cleverly designed sampling interfaces. These developments allow us to look at the small-molecule initiators or products formed in the bioprocess with reduced interference from the cells or organisms, thereby greatly improving our signal-to-background ratio. I feel that Raman is an excellent tool for use in understanding bioprocessing once we mitigate the challenges due to biofluorescence.

In a recent paper (1), you demonstrated that Raman spectroscopy could provide real-time validated quantitative monitoring of continuous flow reactors (CFRs) when used in tandem with multivariate modeling. What benefits does this system and method offer compared to others?

The ability to collect in near real time (1 s) a high-resolution, quantitative Raman spec-

trum of a molecule in flow has many inherent benefits for process monitoring and quality control. We have demonstrated that the application of Raman in continuous flow reactors has many benefits. We have been using Raman as a quality assurance tool for molecule/reaction development in CFRs. The information-rich data provided by in-line Raman allows us to quickly perform complex design of experiment (DoE) studies to optimize the reaction space and conditions for production of that molecule. We have routinely used Raman as a quality assurance tool for the measurement and control of final product quality for many CFR applications in both the pharmaceutical and chemical industries.

Has the pharmaceutical industry shown interest in adopting this approach?

Yes, there has been significant interest from the pharmaceutical industry in what we have been doing with mating continuous flow reactors and Raman spectroscopy for improved process and product quality control. We have received support for some of our work in this field from a few leading pharmaceutical companies as well as from the Food and Drug Administration and the Bill and Melinda Gates Foundation.

You also presented work on a new method to detect cosmic spikes in process Raman data featuring a multistage spike recognition algorithm based on tracking sharp changes of intensity in the time domain (2). How does this method differ from previous methods for detecting cosmic spikes in process Raman data?

There are many algorithms for detecting and removing cosmic spikes from Raman

spectra. They all have significant limitations and tradeoffs, and are suitable for only a narrow range of applications or hardware. Our algorithm was designed to be universal, robust, and easy to use. It has only one variable parameter that might need to be changed and is capable of discriminating cosmic spikes from rapid intensity changes of real Raman peaks.

How did you develop the multistage spike recognition algorithm?

At the time I had a visiting student from Scotland (who later became an excellent post-doc). He had an idea and shared it with me. I found several gigabytes of process Raman data that were accumulated in my lab over a decade that would make a great test set. We sat together and worked through the data refining the algorithm, and eventually we developed a version of the algorithm that worked best with all the data sets. We had a great set of reproducible process Raman data to test the idea, and that was one of the reasons for our success.

In what situations do cosmic spikes cause the greatest difficulty in interpreting process Raman spectra?

Cosmic spikes are manageable in all practical circumstances, except for cases when measurement times are very long. We have had some challenges with cosmic spikes in applications such as Raman imaging and the determination of very low analyte concentrations that involved long integration times.

You have also been involved with fusing data from process Raman, infrared (IR), and nuclear magnetic resonance

(NMR) analyses for crude oil fractions (3). What are the advantages provided by this approach?

The primary advantage for developing data fusion algorithms is to deal with the real-world process analysis challenge: "There is no perfect analyzer that can measure all of my process problems." Therefore, we began to look at the systematic coupling of analytical tools that gave us a more complete view of the measurement challenges faced with complex processes or products. We began to couple complementary tools such as Raman and Fourier transform infrared (FT-IR) spectroscopy to fully describe the vibrational signatures of a product or process. We found that we could improve our models and better understand our process, but it was still not completely informative to describe all crude oil fractions. We required an orthogonal analytical technique to help describe variations in chemical structure of the samples that was not being captured by the vibrational methods. The addition and fusion of the NMR data into our models greatly reduced the classification and prediction errors in our system.

What are the main challenges you and your group faced in this research?

The biggest challenges were determining how to combine data sets with greatly different intensity and wavelength scales and have them represent equal weight in a process control model. We had to develop numerous algorithms to deal with scaling and weighting of both spectral data (Raman, IR, NMR, mass spectrometry, UV-vis, and so on) and univariate data (temperature, pressure, refractive index, and so forth) to build robust and effective process models using data fused inputs.

Which of your research projects have yielded the greatest step forward in process Raman spectroscopy?

I think that the development of the Raman immersion ballprobe sample interface was a huge step forward for process Raman. The ability to have a sampling interface for Raman spectroscopy that was effective for measuring many different sample types including solids, slurries, powders, liquids, and gases reproducibly was a big step forward. A stable and

reproducible sample interface facilitated the application of Raman in a variety of process applications from pharma to food to the deep ocean at high temperatures and pressures. Since then we have designed, built, and optimized many different versions of the immersion probe that are making an impact across a number of industrial and environmental application fields (for example, biotech, oceanography, food, pharma, and oil and gas).

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This interview has been edited for length and clarity. To read the full interview, please visit: www.spectroscopyonline.com/addressing-challenges-process-raman-spectroscopy ■

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The 2016 Emerging Leader in Molecular Spectroscopy Award

The winner of *Spectroscopy's* inaugural Emerging Leader in Molecular Spectroscopy Award is highlighted.

Megan L'Heureux

Matthew J. Baker, a senior lecturer in chemistry at the University of Strathclyde, in Glasgow, has won the inaugural Emerging Leader in Molecular Spectroscopy Award, which is presented by *Spectroscopy* magazine. This new annual award recognizes the achievements and aspirations of a talented young molecular spectroscopist, selected by an independent scientific committee. The award will be presented to Baker at the SciX 2016 conference in September, where he will give a plenary lecture and be honored in an award symposium.

Spectroscopy created this award as a way to recognize and encourage leaders of the next generation of molecular spectroscopists. The achievements that Baker has already made at this early stage of his career make it clear that he is indeed a standout in the field. His work also makes the future of the field look very bright.

An Early Focus on Biomedical Applications of Vibrational Spectroscopy

At Strathclyde, Baker leads interdisciplinary research rooted in fundamental studies to advance the use of analytical chemistry to real-world problems, particularly in biomedical and clinical applications. His main focus is the development of spectroscopic and spectrometric molecular pathology techniques, disease diagnosis, and detection of pathogenic bacteria and toxic chemicals.

Baker's focus on the use of vibrational spectroscopy for biomedical use was already well underway during his studies for his master's degree in chemistry, which he received in 2004 from the University of Manchester Institute of Science and Technology (UMIST). Through his research on using Fourier transform infrared (FT-IR) microspectroscopy and multivariate analysis for diagnosing prostate cancer, he was able, for the first time, to correlate FT-IR spectra with the Gleason score (a measure of the microscopic appearance of a prostate tumor) and the clinical stage of the tumor at the time of biopsy.

Peter Gardner, a professor of Analytical and Biomedical Spectroscopy at the University of Manchester, taught Baker in his first and final years at the university and was his academic advisor during his year in industry. "I supervised his final year project, so I guess I can claim to have set him off on his path to using IR spectroscopy," said Gardner. "Although I was not his PhD supervisor, he did work in my lab for a period of time and did his first work on blood serum, which now forms a major part of his research."

Baker's doctoral studies also focused on cancer diagnosis under the supervision of Dr. Nick Lockyer—in tissues and cells—but in this case using time-of-flight (TOF) secondary ion mass spectrometry (MS) combined with multivariate analysis and pattern recognition. He received his PhD from the Department of Chemical Engineering and Analytical Science at the Manchester Interdisciplinary Biocentre at the University of Manchester, and his thesis was a collaboration with the Paterson Cancer Research Institute.

In 2011, Baker received a PGCert (postgraduate certificate) in International Studies from Staffordshire University. The certification covered international relations in the 20th century and diplomacy and the global world, which helped Baker understand the international arena he was working in.

After receiving his PhD in 2007, Baker held numerous fellowships and research positions. First, he received a Life Sciences Interface fellowship from the UK's Engineering and Physical Sciences Research Council (EPSRC). This fellowship focused on biomedical applications of vibrational spectroscopy, mass spectrometry, and imaging and took him from the Manchester Interdisciplinary Biocentre in the UK, to the Robert Koch Institute in Berlin, Germany, and to Harvard Medical School in Boston, Massachusetts. During the same period, he had research fellowships at the Robert Koch Institute and at Harvard Medical School and Brigham & Women's Hospital (also in Boston). At the Robert Koch Institute, he used vibrational spectroscopy combined with multivariate analysis–pattern recognition for the analysis of prostate cancer tissue; at Harvard medical School, he focused on multi-isotope imaging MS for the analysis of prostate cancer cell lines, prostate cell lines, and stem cells.

Rohit Bhargava, a professor at the University of Illinois who is well known for his research on biomedical imaging using vibrational spectroscopy, praised Baker's early studies on prostate tissue imaging. "This careful work spanning tissues, cell culture, and modalities permitted new insight and capabilities in using spectroscopy for understanding and typing prostate cancer," he said.

Baker also had a stint as a visiting academic at the Centre for Biospectroscopy at Monash University in Melbourne, Australia, where he conducted research funded by the Royal Society of the UK to develop spectroscopic-based four-dimensional (4D) imaging molecular histopathology.

From 2010 to 2012, Baker also took on two roles with a somewhat different focus. In a position in the Detection Department at the UK's Ministry of Defense, he was responsible for the technical leadership of research areas concerning spectrometry and spectroscopy for the detection of toxins and chemical and biological agents of interest. And in a research fellowship with the Optoelectronics Research Centre at the University of Southampton, he investigated the fabrication of nanostructured surfaces for surface-enhanced Raman spectroscopy (SERS) and their combination with specific recognition elements for biological detection and trace analysis.

In 2012, Baker returned to academia, becoming a senior lecturer in toxicology and analytical chemistry with the Division of Chemistry School of Forensic and Investigative Sciences at the University of Central Lancashire. In 2014 he moved to his current role as a senior lecturer in chemistry in the Department of Pure and Applied Chemistry and Centre for Forensic Science at the University of Strathclyde. He is also currently a visiting fellow at the Université de Reims Champagne-Ardenne in France with Professor Ganesh Sockalingum, where he teaches a seminar and develops research in bacterial and disease detection for the security and defense applications.

Since June 2013, Baker has also been an honorary fellow at the Royal Preston Hospital in Lancashire, which is part of the Teaching Hospitals National Health Service (NHS) Trust and Walton Centre NHS Trust. In this position, Baker is developing novel diagnostic methods based on spectroscopy for the clinical environment. Since October 2014, he has also been a visiting academic with the School of Forensic and Investigative Sciences at the University of Central Lancashire.

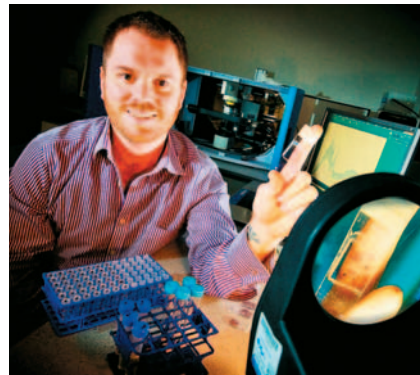
Contributions to the Field

Though young, Baker has already made significant contributions to analytical chemistry and molecular spectroscopy. In particular, Baker is doing pioneering work to advance the use of vibrational spectroscopy for clinical diagnostics. He has developed an accurate, reproducible, and repeatable method to diagnose and differentiate brain tumors via spectroscopic analysis of body fluids such as serum and plasma, and he is currently expanding this approach

using novel light sources to enable rapid, high-throughput imaging.

"Baker used attenuated total reflection (ATR) mode and conventional FT-IR spectroscopy to demonstrate that body fluids can be used as 'liquid biopsies,' which is very impressive," said Sergei Kazarian, a professor of Physical Chemistry at Imperial College London. "Differentiation of the severity of brain cancer using this approach appears very promising."

Bhargava agreed. "Baker and his group have made impressive progress in this area



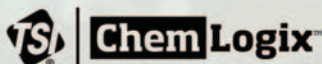
Baker in his lab holding a slice of brain tissue.

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and this is an emerging contribution that is exceptional,” he said.

“Baker probably has the largest molecular spectroscopic study at the moment on serum diagnostics,” added John Chalmers, a consultant at VS Consulting.

Nick Lockyer, who cosupervised Baker during his PhD and has collaborated on several research efforts with Baker, agreed that Baker’s greatest contribution to molecular spectroscopy so far is “developing clinical applications of vibrational spectroscopy, particularly for biofluids.”

Baker has also contributed key papers to the field; organized, chaired, and developed clinical spectroscopy sessions at the SciX conference; co-organized a Faraday Discussion of the Royal Society of Chemistry on “Advanced Vibrational Spectroscopy for Biomedical Applications;” cowritten a concise physics e-book for the Institute of Physics; and guest edited three journal issues. Baker recently joined the editorial advisory board for *The Analyst*, a journal of the Royal Society of Chemistry. To date, Baker has also published 53 papers, one book (*Vibrational Spectroscopic Diagnostics*), and given 54 conference presentations.

Recently, Baker coinstigated and co-formed the UK Clinical Infrared and Raman Spectroscopy (CLIRSPEC) network, from which the nonprofit International Society for Clinical Spectroscopy has emerged, which has the specific aim to translate promising vibrational spectroscopy methods into the clinic. He is also a member of Raman4Clinics, a European consortium focused on the use of Raman spectroscopy in the clinic. In addition, Baker developed the successful CLIRSPEC Summer School, now in its second year, to provide an interdisciplinary education to a broad range of students interested in clinical spectroscopy.

“Much of the success of the CLIRSPEC summer school was because of Baker’s enthusiasm and organizational skills,” said Kazarian, who is on the management committee of CLIRSPEC and teaches in the summer school.

Chalmers agreed. “The summer school initiative is an excellent example of Baker’s drive to engage with students in the bioarena and advance their molecular spectroscopic understandings and developments,” he said.



Baker speaking at the SPEC 2016 conference in Montreal, Canada, where he announced that he will host SPEC 2018 in Glasgow from June 10–15, 2018. Photo taken by Sergei Kazarian.

Baker is also a member of a number of professional groups including Chartered Chemist (CCChem) with the Royal Society of Chemistry, Fellow of the Royal Society of Chemistry (FRSC), International Society for Clinical Spectroscopy, Infrared and Raman Discussion Group, British Association for the Advancement of Science (BA), Evidence Base (a database of specialists organized by the Sense about Science charity), and the Chartered Society for Forensic Science (MCSFS). In 2015, Baker also developed and held the world’s first Twitter poster conference, now in its second year.

Grants, Awards, and Accolades

Baker has received significant funding for his work—54 grants so far. A few examples include the Global Exchange Programme (GEP) Award that Baker received in July 2006, which enabled him to undertake a period of study on MS imaging of model cell membranes at Pennsylvania State University. In November 2007, he received a Prostate Cancer Charity Research Grant that provided £15,000 for research with Peter Gardner of the Manchester Institute of Biotechnology into novel ways of diagnosing prostate cancer. In 2015, Baker was awarded a Royal Society International Exchanges Scheme grant for £5,990 in collaboration with Professor Rohit Bhargava for “Developing Discrete Frequency Infrared (DF-IR) Spectroscopy and Imaging.” In addition, Baker also received an Arts and Humanities Research Council (AHRC) Early Career Research Grant in collaboration with Dr. David Robinson (UCLan Archaeology) and Dr. Jennifer Perry (California State University) for £234,500



Baker on a mountain walk during the CLIRSPEC Summer School. Photo taken by Sergei Kazarian.

for research looking at portable spectroscopy for ancient Native American rock art analysis. To date, Baker has been awarded more than £1.5M in principal investigator funding and more than £3M in project team funding.

Baker also received the British Neuro Oncology Society Best Presentation Award in 2015 at the society’s annual meeting, the Departmental Physical Chemistry Prize in 2004 for the best undergraduate in physical chemistry, and a scholarship in 2000 in which he received £18,000 as a university scholarship from Universal Products Ltd. to help fund university studies.

Who Is Matthew Baker?

Baker’s friends and colleagues are impressed with more than his work.

Bhargava said that one of Baker’s most impressive qualities is his leadership. “He is working tirelessly to help the spectroscopy community. Whether it’s by organizing influential methods papers, entire conferences, or societies, his impact is already being felt,” he said. “This is truly exceptional for a young scientist. He should be commended for these contributions that go well beyond just research.”

In addition, Kazarian said, Baker has a very friendly and engaging personality. “This trait is very important in collaborative projects and in life in general too,” he said. He noted that Baker’s positive approach to his life and work extends to having a large spectroscopic tattoo on his arm that at first glance appears to be an interferogram. “As I recall, what Baker said to me is that it is a second derivative of an infrared spectrum of his blood serum,” he said. “Having a spectroscopic tattoo is an unusual but creative form of public outreach!”

Future Directions

Where is Baker headed next? Based on the accomplishments he's achieved so far in his career, the future looks very bright for Baker. His friends and colleagues agree.

"Baker's vision is to introduce serum spectroscopy for diagnosis and monitoring into clinics and outpatient departments, and he is moving toward this with multiple collaborating partners," said Michael Jenkinson. Jenkinson is a clinical senior lecturer and honorary consultant neurosurgeon at the University of Liverpool and has collaborated on various projects with Baker on brain tumor research, including developing serum monitoring of glioma response to treatment.

"Baker is an enthusiastic and talented researcher with great ambition to develop and deliver serum spectroscopy into routine clinical practice," Jenkinson added.

Gardner agreed. "Baker is going to go far. He has boundless energy," he said. "Baker will continue developing the serum IR technology. His company will expand and he hopefully will bring a product to market." Baker is currently setting up ClinSpec Diagnostic Ltd., a prospective spin out from the University of Strathclyde supported by the Scottish Enterprise High Growth Spin Out program.

Bhargava said Baker is one of the most insightful, energetic, and capable young spectroscopists in the world today. "He has a wealth of expertise and is working hard on relevant problems," said Bhargava. "If all goes well, his methods may make the transition to clinical practice, which would be very exciting."

Lockyer agreed. "Baker has always been very ambitious and has quickly developed an international reputation in his field," he said. "I have no doubt his career will go from strength to strength."

"I expect Baker to continue great research, but I also think he would develop and demonstrate his leadership in organizing and leading large research programs and I hope to collaborate with him on that," said Kazarian.

"Baker's dynamic and enthusiastic work ethic and his research and academic contributions lead me to believe he will undoubtedly gain a professorship within the next 4–5 years," added Chalmers. "Baker is truly well-deserving of this award you have honored him with and will be a shining example to future awardees."

More About Baker

An in-depth interview with Matthew Baker focused on his research, challenges, and accomplishments, will be published in the September 19, 2016 edition of our newsletter, *The Wavelength*.

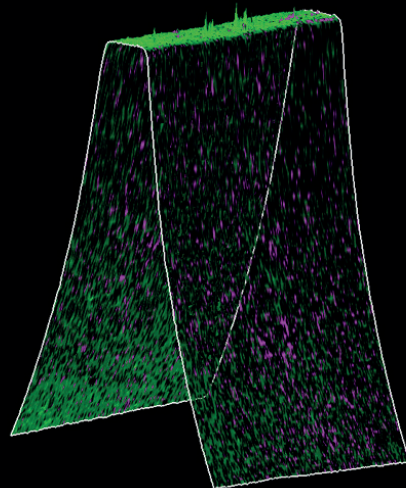
2017 Emerging Leader in Molecular Spectroscopy: Now Accepting Nominations

For information about how to nominate someone for the 2017 award, please see the call for nominations on our website: www.spectroscopyonline.com/call-nominations-2017-emerging-leader-molecular-spectroscopy.

Megan L'Heureux is the managing editor of *Spectroscopy* and *LCGC North America* magazines in Iselin, New Jersey. Direct correspondence about this article to: meg.lheureux@ubm.com ■

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Shedding New Light on Forensic Timelines

The development of novel, nondestructive technologies for rapid analysis of evidence discovered at crime scenes is pertinent to our criminal justice system to solve the millions of violent crimes that occur each year. Without a witness, establishing the precise timeline of a crime is difficult. Therefore, technologies based on sensitive, nondestructive techniques are needed to evaluate evidence and create such a timeline. We propose the use of Raman spectroscopy to analyze the age of bloodstains for potential use as a forensics tool. Previous studies have revealed Raman spectroscopy is sensitive to changes in blood analyte concentration and different oxidative states of hemoglobin. Raman spectroscopy could allow for rapid comparison of spectra from bloodstains of unknown age to spectra of known age with high temporal accuracy. Though further investigation into other substrates and biochemical components should be performed, our study reveals Raman spectroscopy has the potential to accurately and nondestructively determine the age of a bloodstain for use in criminal investigations.

Maggie O'Connor, Kiana Jansen, Joseph Hodge, Christine O'Brien, Isaac Pence, and Anita Mahadevan-Jansen

In recent years, forensic investigation has undergone a surge in popularity among scientists and researchers. Focus has shifted to developing novel, nondestructive techniques for rapid analysis of evidence discovered at crime scenes. This technology is pertinent to our criminal justice system as nearly 1.2 million violent crimes are committed in the United States each year (1). Oftentimes, without a witness, it is difficult to determine the time a crime occurred and the time of injury to or death of an individual. This specific time is paramount in a police investigation to confirm or reject a suspect's alibi. Of the techniques that currently exist to enable formation of this timeline, most require a body. These techniques are also prone to error because of environmental conditions and variability of skill among investigators (2). Therefore, there exists a need for a sensitive, nondestructive technique to quickly and accurately determine the time a crime occurred.

The analysis of blood discovered at a crime scene can provide authorities with pertinent information regarding the crime and those involved, including blood type and DNA. Further analysis, however, has the potential to reveal other valuable information including the age of the bloodstain. The "age" is considered to be the amount of time the blood has been outside of the body and exposed to air. Prior research by Bremmer and colleagues used diffuse reflectance spectroscopy to determine the age of a bloodstain (3). Changes in oxyhe-

moglobin, methemoglobin, and hemichrome profiles were analyzed to predict the bloodstain's age. Methemoglobin is produced through the auto-oxidation of oxyhemoglobin, while hemichrome is the result of the denaturation of methemoglobin. Though this technique proved to be highly accurate over the first 20 days, it had limited accuracy as the blood continued to age over an extended period of time. Diffuse reflectance spectroscopy is also sensitive to environmental factors, potentially affecting the accuracy of the age estimation. Other work has looked at RNA degradation (4), electron paramagnetic resonance spectroscopy (5), oxygen electrodes (6), and atomic force microscopy (7) to determine a bloodstain's age. The accuracy of each of these techniques has temporal limitations. Therefore, in an effort to strengthen temporal accuracy, we present the use of Raman spectroscopy as a possible technique to determine the age of a bloodstain.

Raman spectroscopy is an inelastic scattering technique, requiring monochromatic light. The laser light is used to excite a substance and cause alterations to the vibrational modes of its constituent molecules. Each of the molecules requires a specific amount of energy to vibrate, producing a shift in the output laser energy. Raman spectroscopy allows for the detection of the biochemical signatures specific to the molecule's vibrational modes, which results in the determination of a substance's constituent components. Because of its non-

destructive nature, ability to take rapid measurements, and extreme sensitivity, Raman spectroscopy has the potential to correlate changes in blood's biochemistry with time.

Analysis of Blood Using Raman Spectroscopy

Numerous studies have revealed the ability of Raman spectroscopy to analyze blood components. Two studies, in particular, analyzed hemoglobin and deoxygenated red blood cells (RBCs) (8,9). These studies revealed the effect of excitation wavelength on the resultant spectral signal. Wood and colleagues used 488-, 514-, 568-, 633-, and 785-nm excitation wavelengths to analyze deoxygenated RBCs (8). The results showed variances in peak intensities with differing excitation wavelength. Similar changes in peak intensity occurred when Wood and colleagues analyzed human hemoglobin with 632.8-, 780-, and 1064-nm excitation wavelengths (9).

Sikirzhytski and colleagues found that as blood dries, it becomes more heterogeneous, altering the Raman spectral signal compared to that of fresh, liquid blood (10). The components that contribute most to the Raman signal in its various states of drying were determined through principal component analysis (PCA). They concluded that the two major components of dried blood, based on the location of spectral peaks, were hemoglobin and fibrin. According to Sikirzhytski and colleagues, this result was to be expected because the literature states hemoglobin and its derivatives are the primary components remaining when red blood cells dry out. Fibrin appears as part of the blood coagulation process. It is believed that this process contributes to the spectral differences of liquid and dried blood. Knowing how the contribution of fibrin and hemoglobin change as blood dries and coagulates could allow for an age estimation of an unknown sample of dried blood.

Berger and colleagues used Raman spectroscopy to look at blood analytes, focusing specifically on glucose, cholesterol, triglycerides, urea, total protein, and albumin (11). Using partial least squares (PLS), they determined that each of these analytes had its own contribu-

tion to the overall Raman signature of both whole blood and serum. The extent to which each analyte contributed is proportional to its concentration. During this experiment, each sample of blood was only analyzed once; therefore, an evaluation of blood analyte concentration as a function of time could aid in the determination of blood age.

The studies performed by Bremmer and colleagues revealed diffuse reflectance spectroscopy to be sensitive to differences in hemoglobin in its vari-

ous states including methemoglobin, oxyhemoglobin, and hemichrome (3). Dasgupta and colleagues demonstrated that Raman spectroscopy is also sensitive to these states (12). They concluded that RBCs can be monitored for their oxygen-carrying capacity because of the conformational changes that occur when oxygen binds or dissociates from the heme molecule.

Because of the decreased sensitivity of diffuse reflectance spectroscopy for bloodstain evaluation across extended

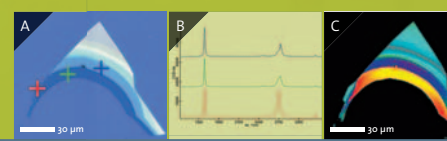
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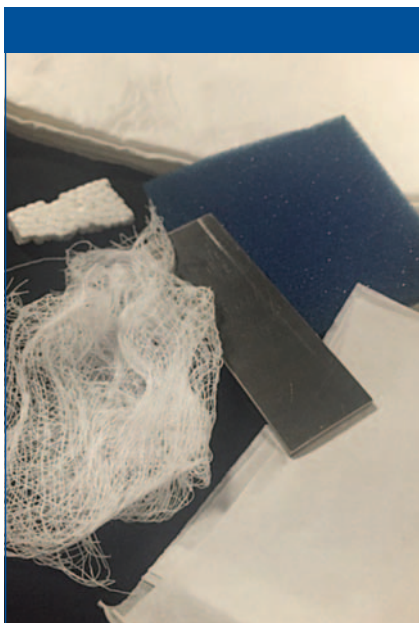


Figure 1: Material substrates investigated with Raman spectral measurement for blood stain age.

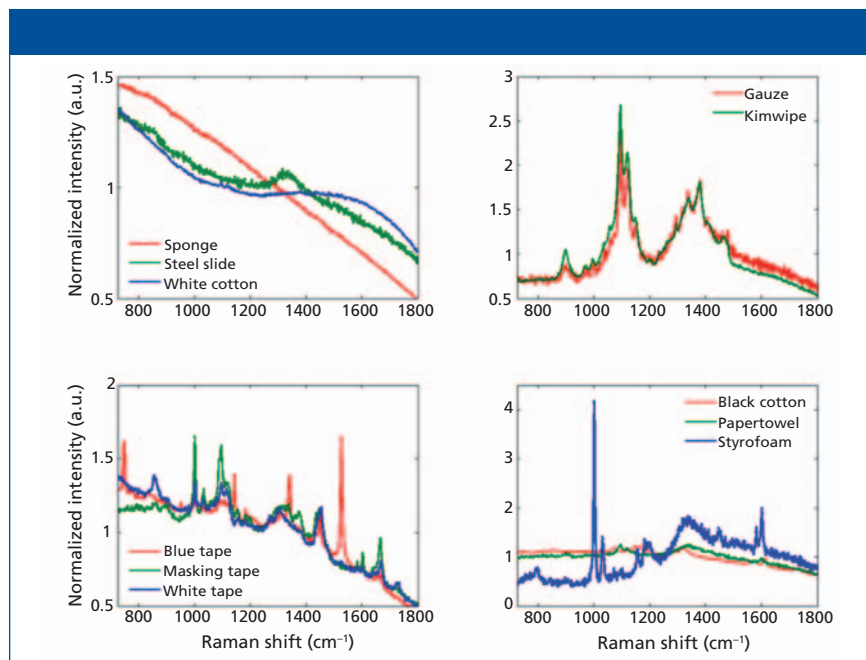


Figure 2: Raman spectral signals of the 11 substrates.

time periods and the need for a rapid, nondestructive technique to analyze bloodstains for forensic purposes, we propose the use of Raman spectroscopy as an ideal technique to predict the age of a bloodstain. As can be seen through previous research, various components of blood are altered as it ages *ex vivo* that may be useful in determining how old a bloodstain is. One of these components is fibrin, which appears because of blood coagulation. Other components are hemoglobin derivatives such as oxyhemoglobin, methemoglobin, and hemichrome. Based on the sensitivity of Raman spectroscopy to the presence and concentration of these constituents, along with various blood analytes, a timeline could be formed for rapid comparison of the Raman spectrum of an unknown blood sample to the Raman spectra of blood samples of known ages with high temporal accuracy. This timeline would allow for the prediction a bloodstain's age without destruction to forensic evidence.

Materials and Methods

Fresh blood samples were obtained from three healthy adult volunteers, two males and one female (IRB-151532). The blood samples were placed on various substrates and allowed to air dry at room

temperature as measurements were acquired. Spectral measurements were obtained using an inVia confocal Raman microscope (Renishaw). The microscope was chosen for its high spatial resolution because of the degree of confocality it offers. A 785-nm diode laser (Innovative Photonic Solutions) was used to excite the samples. The blood samples were viewed in the microscope using a 50× objective. Measurements were taken at several integration times, laser powers, and various spatial locations in an effort to obtain the greatest possible signal-to-noise ratio while preventing damage to the sample. Data were collected as a time course, with measurements taken every 3–5 min for fresh blood and then daily at various time points up to 63 days.

Spectral measurements were normalized against the 520 cm^{-1} peak intensity of silicon to account for daily fluctuations in the setup. Spectra also underwent fluorescence subtraction using a fifth-order polynomial fit to extract the Raman signature.

Following data collection, a linear least squares model was developed to evaluate the contributions of various biochemical constituents over time. Nine pure components, commercially purchased from Sigma Aldrich, were measured using the same system. These

components are albumin, biliverdin, cholesterol, fibrin, fibrinogen, globulins, glucose 6-phosphate, glutathione, and human hemoglobin A_0 . The model holds two basic assumptions. The first assumption is that the Raman spectrum is a linear combination of its component spectra. The second is that the intensity of the signal is linearly related to the constituent's concentration in the blood (11).

Raman Signatures from Aging Blood Samples

For this experiment to be effective, two practical considerations needed to be addressed. These considerations included the substrate used to measure the blood and photoinduced changes from the laser.

Practical Considerations: Substrate

Crime scenes can have bloodstains present on any number of materials, which can complicate signal detection. Depicted in Figure 1, a variety of substrates were tested for their efficacy in obtaining spectral measurements for our purposes. Two main concerns about the substrates were addressed during testing. The first was that the substrate's spectrum should be of low-intensity and featureless in shape, such that its

contribution to the measured blood spectrum is minimized to prevent confounding factors. The second concern we addressed was to choose a substrate that would allow us to focus specifically on the bloodstain under the microscope objective and not the substrate.

Next, 11 substrates were tested for their compatibility with these concerns. Displayed in Figure 2 are the Raman spectral signals of these substrates. The tested substrates included black cotton, blue sponge, blue tape, gauze, laboratory tissue (KimWipes, Kimberly-Clark), masking tape, paper towel, stainless steel, polystyrene foam (Styrofoam), white cotton, and white tape. Of these substrates, all had intense Raman signals with distinct peaks except for the blue sponge, stainless steel, and white cotton. Because interference from the substrate's spectral signal is of concern, the other eight substrates were eliminated as options to carry out this experiment.

Further testing was performed on the white cotton, blue sponge, and stainless steel. Fresh blood samples

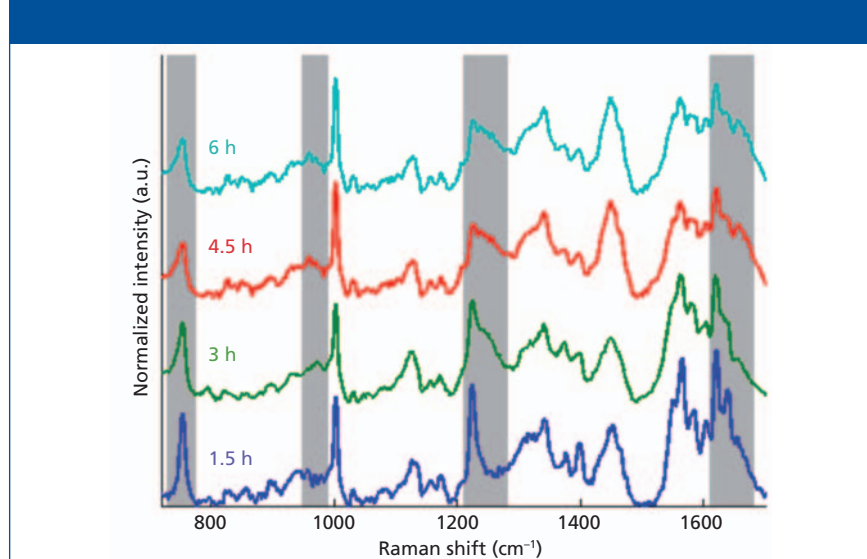


Figure 3: Raman spectral signal of a single sample during the first 6 h. Gray regions depict distinct signal changes over time.

were placed on these substrates and the Raman spectral data was collected. The heterogeneity of the white cotton and blue sponge on the microscopic level made it difficult to focus on the bloodstain. Focus was disrupted by the

intricate network of fibers that compose these substrates. Though we did our best to focus between fibers and on the blood, when the spectral signals were analyzed, they appeared identical to the pure cotton and sponge spectra.

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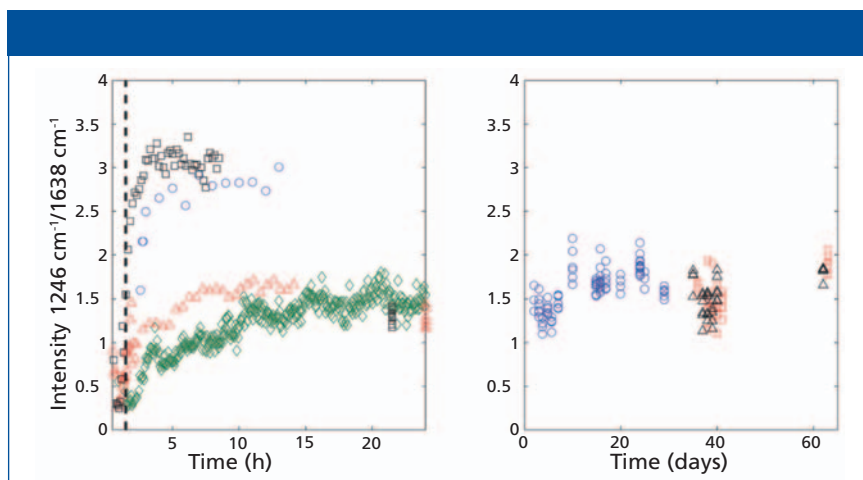


Figure 4: Peak ratio of $1246\text{ cm}^{-1}/1638\text{ cm}^{-1}$ over 24 h (left panel) and 63 days (right panel). Each distinct color-shape combination represents measurements taken from various wells.

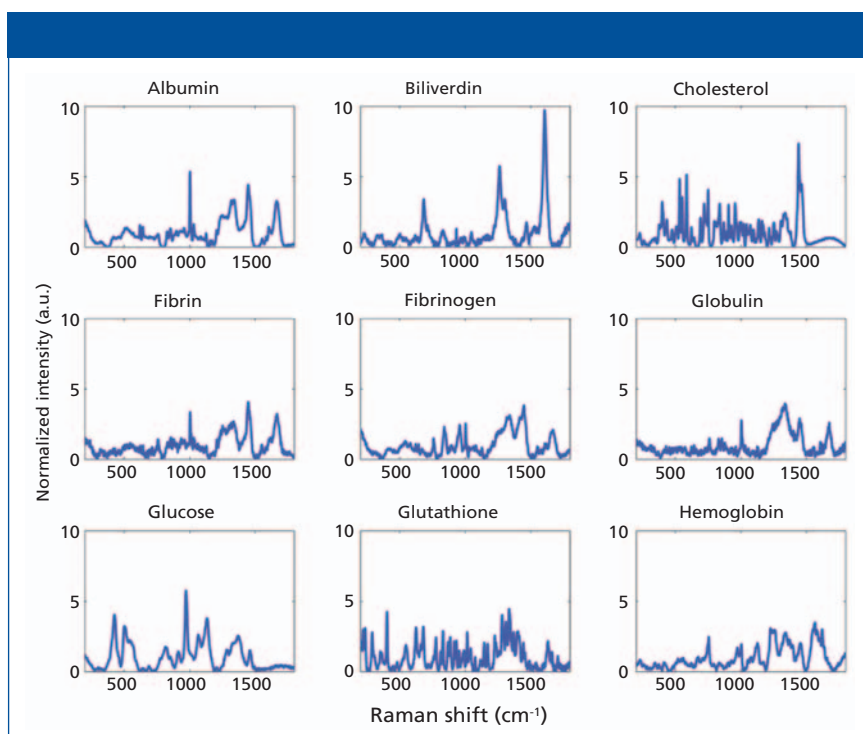


Figure 5: Raman spectra of biochemical constituents used to create the linear least squares model.

However, when the blood sample was placed on stainless steel, we were able to focus on the blood instead of the substrate. The resultant spectra were distinct from that of stainless steel and were similar to the Raman spectra of blood found in literature.

Because it was the only substrate that allowed us to focus on the blood without imparting its own spectral signal, the stainless steel was used for further testing. Shortly thereafter, however, a problem was encountered. As the blood dried, it began to flake off the stain-

less steel, preventing long term measurements. To avoid this problem with future samples, a small well, holding approximately $10\text{ }\mu\text{L}$ of blood, was drilled into the $75\text{ mm} \times 25\text{ mm}$ slide. The experiment was repeated in the same manner with fresh blood in the well. Again, we were able to focus solely on the blood. This time, though, the blood was held in place by the well and did not easily flake off the stainless steel. For this reason, we chose to continue using stainless steel in our analysis of photoinduced changes to the sample.

Practical Considerations: Photoinduced Changes

Several publications address the effect of photoinduced changes to a sample because of the laser power. Wood and colleagues attributed an increase in signal-to-noise ratio of RBC measurements to heme aggregates that formed as a result of protein degradation from exposure to intense laser power and increased temperatures (8). Dasgupta and colleagues used optical tweezers to analyze how RBCs were affected by prolonged exposure to laser light (12). They found spectral changes occurred even with the laser power at a few milliwatts and also attributed these changes to aggregation of heme.

In an effort to combat effects from the laser, we experimented with a variety of integration times and laser powers to minimize irradiance to the sample while maintaining a good signal-to-noise ratio. We first addressed the laser power reaching the sample. By using a combination of pinhole aperture and neutral density filters, we were able to reduce the amount of scattered light focused on a $1.5\text{-}\mu\text{m}$ spot on the sample. This drastically reduces the power of the laser that reaches the sample, which in this case, was beneficial. Ultimately, the sample received 1.5 mW of power.

Though we chose a minimal laser power, long exposure times or even short exposure times to the same spot have the potential to cause unwanted destruction of the sample. Initially, we believed an exposure time of 15 s and five accumulations was acceptable; however, further experimentation revealed that was too long. Spectral changes that had previously been attributed to photodamage were seen in our spectra. Therefore, the parameters were adjusted to a 10 s integration time with two accumulations. Measurements were also acquired at different spatial locations to prevent photodamage to the sample at individual measurement spots. Secondly, this also accounts for effects of spatial variability in the sample as it allows measurements across the sample to be averaged at a single time.

Figure 3 displays spectral signals across the first 6 h for a single sample, separated for clarity. Obvious changes in the signal can be observed, even after eliminating

potential photoinduced alterations from the laser. Among these changes are the appearance of peaks known to be associated with fibrin at 970 cm^{-1} and 1246 cm^{-1} and the disappearance of a peak associated with hemoglobin at 1639 cm^{-1} (13). Because of the careful measures taken to prevent photoinduced changes to the sample, these figures suggest the observed transformations are because of chemical alterations in the sample as it dries—that is, oxidation and coagulation, rather than changes caused by the laser. It is possible, therefore, that observing peak ratios over time may provide an indicator of blood age. Figure 4 reveals consistent trends among peak ratios ($1246\text{ cm}^{-1}/1639\text{ cm}^{-1}$) of samples over the first 24 h (Figure 4a). Over the first 5 h, a drastic increase in the ratio occurs, implying a large increase in the presence of fibrin in the sample during this time. Consistent patterns are lost, however, as the samples become days to months old (Figure 4b). Expanding the data size may help to reveal and establish meaningful trends in the aging process.

Despite the changes observed in several peak ratios, the determination of a timeline is complicated because of the variability that occurs even within a single time point. This warrants further investigation into intradonor variability and the heterogeneity of the blood sample. Additionally, nonlinear trends, as seen in the peak ratios, in the aging process complicate the quantitative estimation of an appropriate timeline, thus requiring the use of component coefficients from the linear least squares model to obtain new quantitative metrics.

Figure 5 displays the Raman spectral signals of the nine components used in the linear least squares model. The modeled summation of these components at 1.5 h is displayed in the right panel of Figure 6, along with the true spectrum on the left. The difference between the true spectrum and the modeled spectrum is the residual, also displayed. The obvious features that remain in the residual, primarily at 970 , 1225 , and 1638 cm^{-1} , reveal that our model is missing some of the constituents that account for the spectral changes we are seeing at these same locations. Potential constituents that might increase the accuracy of our model will be investigated fur-

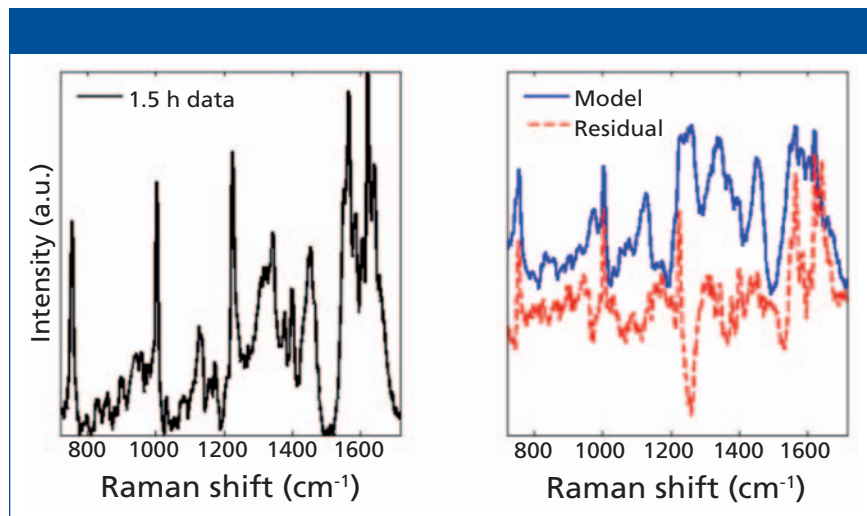


Figure 6: Raman spectrum of a blood sample at 1.5 h (left). Spectra of linear least squares model and the residual, obtained from subtracting the model spectrum from the spectrum taken at 1.5 h.

ther, the inclusion of which may improve the clarity of trends as a function of time.

Conclusions

Raman spectroscopy is sensitive to changes in blood as a function of time and therefore, has the potential to aid in creating a forensic timeline of blood age. There are a variety of complications, however, which prevent this from being a simple process. Primarily, caution needs to be taken to ensure the sample is not being damaged and the aging process is not being altered by the laser. Consistent changes, based on peak ratios, occur in the sample over the first 24 h. This consistency is lost as the sample continues to age. Despite this, an increased sample size and multivariate statistical models have the potential to enable accurate age prediction. Our use of a stainless steel substrate does not mimic likely conditions at a crime scene, yet absorbent materials may affect the ability to obtain an accurate spectral signal. Further investigation into other substrates is underway to combat these problems. By addressing issues with the substrate, increasing sample size, and having consistent measurement parameters, we can demonstrate the feasibility of using Raman spectroscopy to determine the age of a bloodstain for use in criminal investigations.

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Kinetic Imaging of Epoxy Curing

Adhesives are materials that are found extensively in manufacturing and production industries and are of great interest for quality control and failure analysis. This article discusses the use of an array detector in conjunction with ultrafast mapping to produce kinetic chemical imaging to monitor the curing process in a two-part epoxy resin. This technique allows for simultaneous analysis of both the kinetics of the epoxy reaction along with the spatial information of the reaction. This kinetico-spatial information gives insight about localized domains that form when the epoxy is mixed and how the reaction progresses.

Stephan Woods, Michael Bradley, and David Drapcho

Many industries use adhesives for bonding materials when other, standard connections (welding, fasteners, or tapes) are either unreliable, too expensive, or difficult to implement (1). For instance, in the automotive industry a major source of improved efficiency (for example, fuel economy) involves incorporating lightweight materials. Beams and struts attached with adhesives are far lighter than those attached with standard connections, but there is concern over their durability and safety.

There is a need for a wide range of adhesives that can bond to many different materials. Rapid advances in materials based on carbon fibers, aluminum, and other metals and polymers require specific adhesive properties (1). Application under water or in the vacuum of space and on a wide range of materials requires different bonding techniques that maintain strength even when managing differing thermal expansion properties. These requirements can be further complicated by surface treatments, including nonstick coatings. Common uses include bonding plastic to plastic or plastic to metal, devising fillers for repairs, potting electronics, and setting optics (2,3). The field of dental adhesives alone is enormous, with the additional requirements of nontoxic vapors and exposure to a range of solvents and acids.

Two-part epoxies generally consist of a resin and a hardener. Mixing initiates a reaction that forms linkages, a process known as *curing*. Cure times can be controlled by adjusting the concentrations of components, and epoxy types vary from the common 5-min epoxies to ones needing hours (4,5). Being able to monitor the reaction at both the macro- and microscales is of great importance to understanding the curing process (1,5).

Probing adhesives at the bulk level requires measuring the viscoelastic properties, which are typically measured using devices like a rotating disk viscometer. These properties and the bond strength are controlled at a molecular level, however, as bonds form and cross-linking of chains occurs. Infrared and Raman spectroscopy can be used to probe the molecular nature of these changes, tying the bulk property to a molecular source. Fourier transform infrared (FT-IR) spectroscopy in particular has long been used in this application (1).

Standard FT-IR can supply a general view of a curing epoxy (2,4,6). However, the analysis spot size is typically a few millime-

ters in size, so the experiment is viewing a relatively large zone. The spectral information is effectively averaged over the area. FT-IR microspectroscopy provides users with the chemical analysis but also adds a spatial component to the chemical information. This area of information can be gathered by point-by-point mapping or imaging using a multielement detector. With fast-setting epoxies, using FT-IR mapping to cover an area would generally be slow, which does not lend itself to kinetics analysis. Studying a 5-min epoxy requires the data to be collected in seconds over the full area (4,5,7). This article shows how rapid FT-IR microspectroscopy can be used to carry out this work, identify localized domains, and follow the kinetics in a two-part epoxy.

Experimental

To set our microspectroscopy parameters, we first studied a two-part epoxy using a standard FT-IR. A Thermo Scientific Nicolet iS50 FT-IR spectrometer with a built-in iS50 attenuated total reflectance (ATR) accessory was used. This ATR unit uses a monolithic diamond crystal, which provided excellent spectra and also enabled aggressive cleaning after the epoxy cured.

The resin and hardener were mixed thoroughly according to the manufacturer's recommendations. A drop of the mixture was deposited onto the diamond. Infrared spectra were collected continuously for 15 min using the Thermo Scientific Omnic Series time-based software. This produced a Gram-Schmidt plot, shown in Figure 1, that shows the overall signal change. The Gram-Schmidt profile levels out after about 7.5 min, which we took as the approximate cure time for our microscope experiments.

For the FT-IR microspectroscopy, the same resin and hardener were mixed per the instructions. The blending step produced a mixture that had some bubbles, but that appeared to be homogeneous. The mixture was deposited on a gold-mirrored slide and spread out to produce a thin film. Data were collected using reflection-absorption spectroscopy (IRRAS) in which the IR beam passed through the sample, reflected off the mirror, and then passed the sample again.

Data were collected using a Thermo Scientific Nicolet iN10 FT-IR microscope equipped with an array detector and ultrafast mapping capability. An area of $500 \times 550 \mu\text{m}$ was selected, and

the spatial resolution within the maps was set to 25 μm per pixel. With this combination, each map was collected in about 2.2 s. About 23 images were collected over a span of 8 min (as determined by the earlier experiments), which proved to be enough to see the changing chemistry.

We will not delve into the specific chemistry of this epoxy, although the FT-IR data enable that analysis. Instead, we produced correlation maps that show the spatial distribution of specific components as identified from their individual spectra. Spectra collected on the ATR unit of the unmixed resin, hardener, and from the cured epoxy provided the reference spectra for the correlations. In the maps shown in Figures 2 and 3, red indicates a high correlation, meaning the component is present at that location, and blue represents the absence of the specified component. Figure 2 shows snapshots at particular times, while Figure 3 shows a time sequence for the reacted epoxy as time passed.

Results

The Gram-Schmidt profile (Figure 1), which records the change of the IR spectrum over time, indicates that the epoxy cured to its hold point in about 7.5 min, followed by a period of much slower curing thereafter. On this basis, we used 8 min as a boundary condition for the microscopy, basically assuming the epoxy had cured sufficiently.

Infrared correlation images of the uncured mix collected as soon after mixing as possible are shown in Figure 2. As noted above, these images represent how strongly a spectrum at a point in space correlated to the reference spectrum of either the resin, the hardener, or the mixture.

In Figure 2, domains of high resin concentration, high hardener concentration, and mixed domains are clear. If you overlay the images, the resin and hardener regions are almost opposites, whereas the mixture traces the boundaries in many cases. Given the vigorous mixing applied, it seems surprising that the images show a high degree of inhomogeneity at the microscale. This can be attributed to the high initial viscosity of the two components which makes the mixing difficult.

Figure 2 shows spectra from the same location for the sample 8 min after application (roughly 10 min after initial mix-

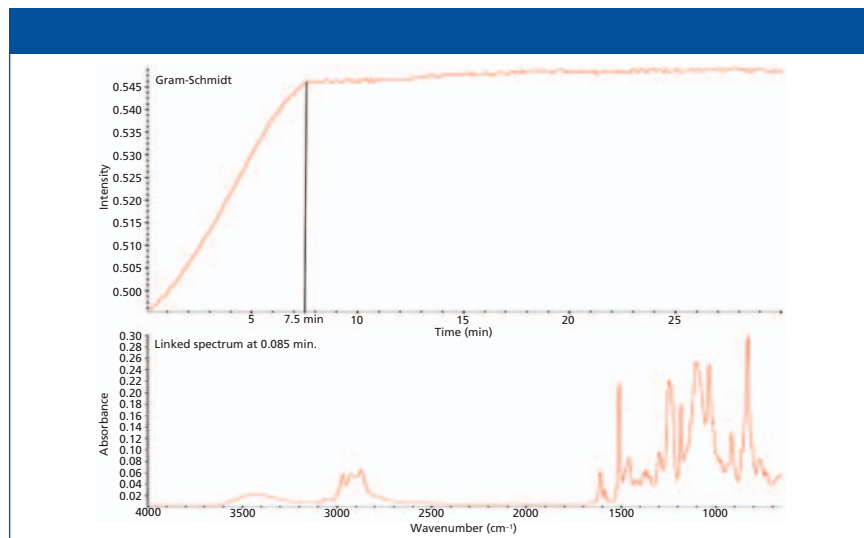


Figure 1: Gram-Schmidt plot for curing epoxy.

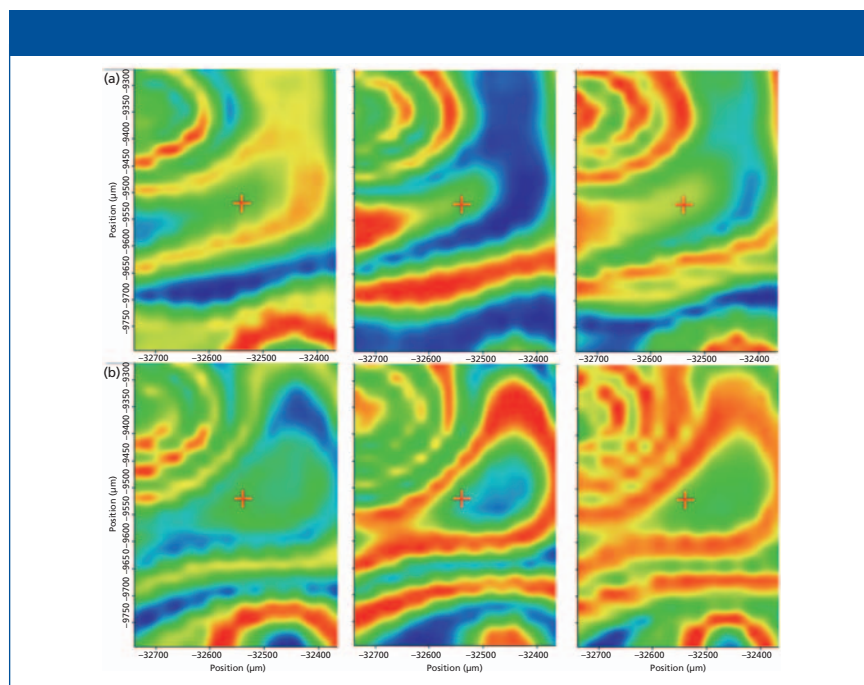


Figure 2: Correlation maps comparing the (a) first and (b) 23rd map for the resin (left), hardener (center), and mixture (right).

ing). The heterogeneous structure of the material is still present—the reaction has not proceeded equally through the entire mixture—as shown by the strong swirl marks generated during the application of the epoxy. Both the resin and the hardener are showing less red (except for the strong swirl), as expected for the reactants. Figure 3 shows the evolution of the sample.

Figure 3 shows color normalized correlation images using a spectrum of the cured material (taken on the ATR system). Initially, there is almost no trace of the product. As time proceeds, domains of cured epoxy appear and these begin to overlap with one

another. Even so, the cured material shows some localization and there are sizeable domains of unreacted resin and hardener present. Clearly, in these microdomains, set times vary and the cure is not uniform.

From our analysis, it appears after 8 min that this material is only about 50–60% cured. The continued slow evolution seen in the series data is likely because of the continued slow reaction of the material in regions where the mixing was poor. From a quality control perspective, the lack of general cure could mean this adhesive needs a longer cure time, which we note from the manufacturer's instructions when they say

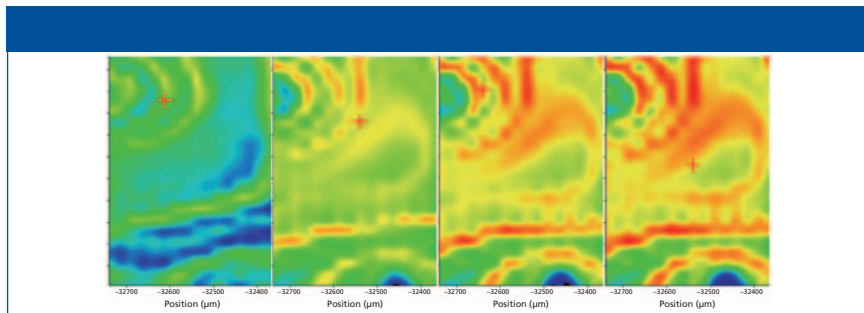


Figure 3: Infrared correlation images of the curing mix, correlated to a reference spectrum of the cured mix, from the first image ($t = 0$) to the 23rd image ($t = 8$ min), on a constant color scale red indicates areas of high correlation, blue of low correlation, with the cured mix reference spectrum.

“full strength curing occurs in 8–10 hours.” In critical alignment operations, this would mean bonded parts might slip or move during the slow final cure time.

Conclusions

FT-IR microspectroscopy has been shown effective in studying the curing of an epoxy. The appearance of microdomains clearly related to the mixing process would provide clues for process quality control. We did not follow the slower, long time cure, but we expect in this time the reaction

would proceed in the poorly mixed areas. If this were a critical process, we would advise better mixing of the hardener and resin.

Though not done in this work, other work reported by our team coupling rheometry and infrared or Raman spectroscopy in epoxy studies allows the correlation of viscoelastic properties to the bulk chemical properties can be visualized. Combining that information with the microscopic domain picture as outlined here would provide a full view—molecular, microdomains, and bulk—for adhesives analysis.

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Preparation of Mixed Food Samples Using Microwave Acid Digestion with Novel iWave Contactless In-Situ Temperature Measuring Technology

Michael Howe and Elaine Hasty, CEM Corporation

With the continued globalization of trade, it has become increasingly important in recent years to ensure the safety of the food supply, as there have been numerous instances of metals contamination. This has led to increased demand for better analytical techniques and lower detection limits for elements of interest. Food samples require some form of sample preparation prior to final analysis and in most cases a complete digestion of solid samples is required. As spectroscopic instrumentation has improved resulting in lowered detection limits, CEM has made advances in microwave sample preparation technology to simplify the technique and ensure complete digestions. The latest of these innovations is iWave™.

iWave utilizes Light Emitting Technology™ (LET) that renders the vessel transparent. This allows for a temperature measurement of every sample in real time. For the last 25 years, the fiber optic probe has been considered the gold standard for temperature measurement in microwave acid digestion. Now, iWave has the accuracy of a fiber optic probe without the time consuming set up and considerable consumable cost.

In order to highlight the benefits of this new technology, several types of food samples were prepared in a single run using standard IR and MARS 6™ with iWave. These samples were then prepared for elemental analysis.

Instrumentation

The samples were digested using a CEM MARS 6, with iWave contactless in-situ temperature sensing, in 75-mL MARSSXpress™ vessels, on the 40-position turntable.

Method Details

Four different retail products (American cheese slices, ground sausage, granola bars, and milk powder) were digested in the MARS 6 with standard IR and iWave. Samples of 0.5 g were digested with 10 mL of HNO₃, ramped to 210 °C for 20 min and held at that temperature for 15 min.

Results

All of the digested samples were clear and particle free upon dilution. The samples digested using iWave resulted in a more complete digestion of all the samples in this mixed food study. Figure 2 highlights the increased precision of the power over time. This ability to fine adjust the power control allows MARS 6 with iWave to analyze a greater variety of sample types in a single run.

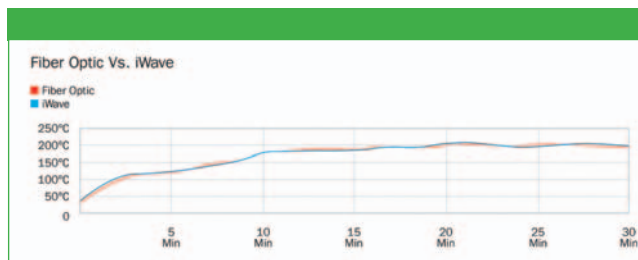


Figure 1: iWave's contactless temperature measurements track perfectly with the fiber optic probe.

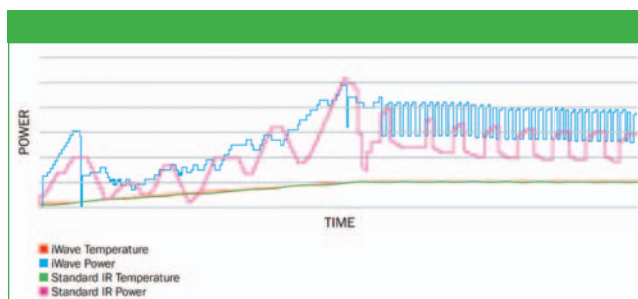


Figure 2: Using iWave, the power response is much tighter than the standard IR sensor, resulting in greater control of the reaction.

Conclusion

Based on this mixed food study, the benefits of using microwave acid digestion with iWave technology include:

- The ability to run more diverse types of mixed foods, such as high fat sausage and high carbohydrate granola, in the same batch.
- Additional control over the sample reaction, generating a better digestion that delivers the optimum analytical results.
- A new straightforward standard for temperature measurement in microwave acid digestion.

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A Simple, Low-Cost Approach to Improving ICP Productivity

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Glass Expansion has partnered with Inorganic Ventures, the well-known certified reference material (CRM) manufacturer, to investigate a simple, low cost approach to improving ICP productivity. The benefits of Glass Expansion's redesigned Niagara CM Rapid Rinse accessory were evaluated.

Most ICP systems incorporate an autosampler. With these systems there is a significant delay between the time when the autosampler probe enters the sample and the time when the sample reaches the nebulizer. There is similar delay between the time when the probe enters the rinse and the time when the rinse reaches the nebulizer. If these delays could be eliminated, the analysis time per sample would be reduced.

This is exactly what the Niagara CM Rapid Rinse (referred to as Niagara henceforth) achieves, by rinsing the nebulizer and spray chamber the instant the sample measurement is completed and continuing to rinse until the next sample has reached the nebulizer. Thus the rinse is carried out during the time it takes for the sample and the rinse solutions to flow from the autosampler probe to the

nebulizer. Typical time saved with the Niagara is around 30% and since the valve switches immediately after the read is complete, you also minimize the amount of sample introduced to the ICP. This feature drastically reduces consumables costs and frequency of cleaning, particularly for challenging sample matrices.

Niagara Updates

Since the original Niagara was introduced in January 2005 (2), Glass Expansion's line of enhanced productivity accessories have been continuously evolving to keep up with the demands of ICP analyses. Most recently, in 2013 the Control Module (CM) was introduced adding the suffix CM to denote this (3).

We now introduce a new software version, called NRRV2, which includes a redesigned Method Wizard featuring an Uptake Delay Calculator, Rinse Tubing Calculator, and Time in Sample (TIS) Calculator. The addition of these calculators greatly simplifies method development.

The Uptake Delay Time is the time required for the sample to reach the valve and pass through to waste. Once the Uptake Delay Time has finished, the Niagara actuator will switch from Rinse to the

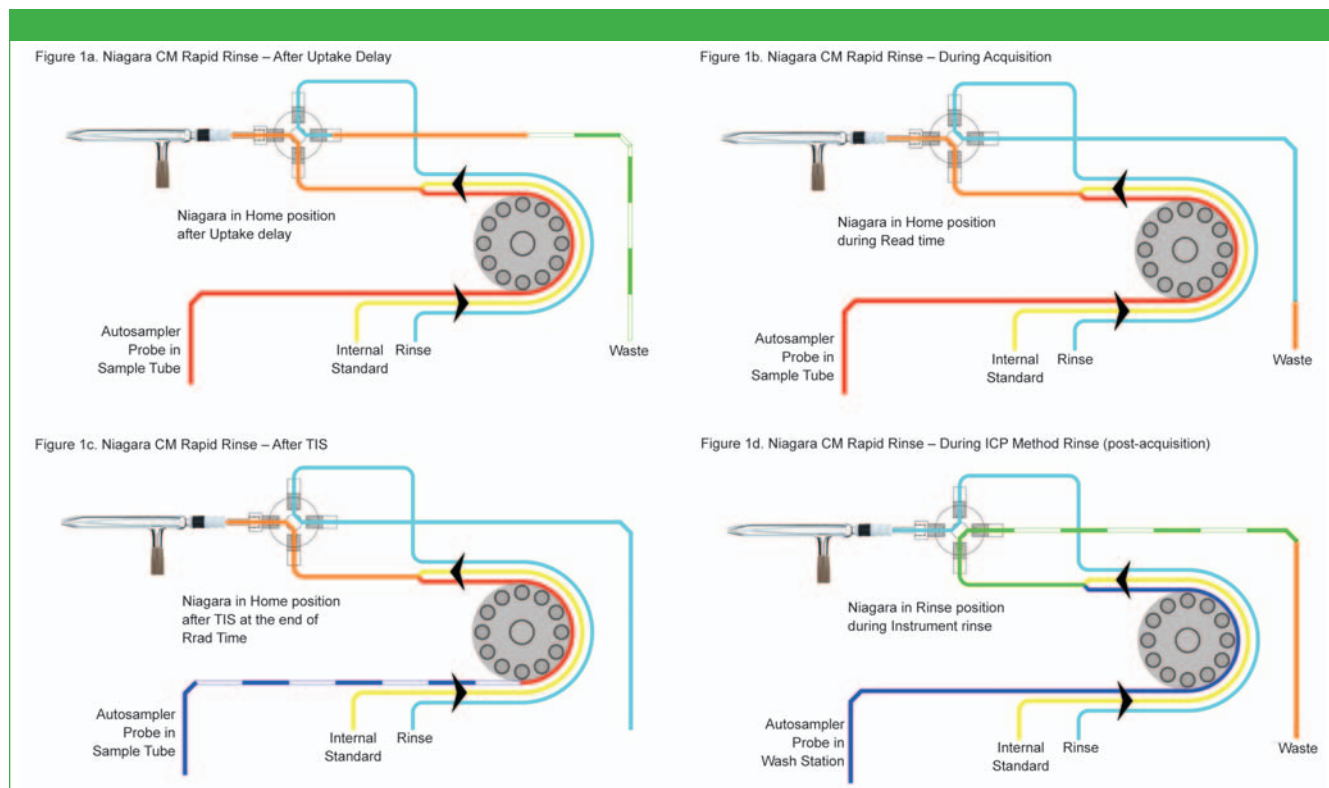


Figure 1: a: Niagara CM Rapid Rinse—after uptake delay; b: Niagara CM Rapid Rinse—during acquisition; c: Niagara CM Rapid Rinse—after TIS; d: Niagara CM Rapid Rinse—during ICP method rinse (post-acquisition).



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Figure 2: Niagara CM Rapid Rinse.

Home position, directing the sample to the nebulizer (Figure 1a). The Uptake Delay Time is calculated based on the ID and length of the autosampler probe, peristaltic pump tubing ID and length, and RPM of the peristaltic pump. The Rinse Tubing Calculator calculates the optimum peristaltic pump tubing to be used in order to achieve the same flow rate that is used during analysis while using a fast pump during the uptake and post-acquisition rinsing steps of the analysis, thereby maximizing stability. TIS is the time required for the autosampler probe to remain in the sample tube during the acquisition (Figure 1b). The TIS is based the total read time, RPM of the peristaltic pump and dimensions of the uptake tubing referenced previously.

It is well known that adding a series of bubbles can help “scrub” the uptake line. However, air bubbles introduced into the plasma can lead to instability and require longer stabilization delay times. With this latest Niagara update, we can easily add a series of air bubbles with a post wash command without the worry of introducing any air or extra argon into the plasma (Figure 1c). Once the ICP method rinse begins the air bubbles and any excess sample are directed to waste while rinse solution is directed to the nebulizer (Figure 1d).

Experimental

The speed and performance of Inorganic Venture’s single element CRM ICP-OES certification analysis was compared with and without the use of the Niagara. For these certification experiments a Spectro Arcos EOP (Axial) ICP-OES instrument was used in combination with two Glass Expansion sample introduction systems. For samples without HF, the SeaSpray DC nebulizer was used with the Twister spray chamber. The HF-resistant package consisted of the DuraMist DC nebulizer, Tracey PTFE spray chamber and fully ceramic D-Torch (3).

The Niagara (Figure 2), consists of an electronically controlled switching valve, Control Module and tubing kit. For maximum chemical resistance the valve is made entirely of Teflon and PEEK. The method timings for the Niagara were calculated using the newly developed Method Wizard (4).

Results

The Niagara allowed Inorganic Ventures to reduce their certification analysis time by 71 s per sample, roughly a 35% improvement. This allows Inorganic Ventures to run an additional 10 samples per hour with the Niagara. The performance of the ICP is

Table I: Washout experiments after analyzing 1000 ppm Tl

Sample ID	Standard Setup 30 sec Rinse	Standard Setup 1 sec Rinse	Niagara 10 sec Rinse	Niagara with Bubbles 1 sec Rinse
Blank-1 (2% HNO_3)	0.07 ppm Tl	0.48 ppm Tl	0.05 ppm Tl	0.04 ppm Tl
Blank-2 (2% HNO_3)	0.02 ppm Tl	0.06 ppm Tl	0.01 ppm Tl	0.01 ppm Tl
Blank-3 (2% HNO_3)	0.02 ppm Tl	0.04 ppm Tl	0.01 ppm Tl	0.00 ppm Tl
Sample to Sample Time	71 (sec)	41 (sec)	49 (sec)	38 (sec)

unaffected by the Niagara, as an average RSD of less than 0.5% was achieved with both sample introduction systems (4).

In addition to reducing analysis time, the Niagara also improved washout. Thallium (Tl) is known to be a “sticky” element that can necessitate long wash times. For this reason a 1000 ppm Tl solution was chosen to compare washout with and without the Niagara. Table I contains values in ppm Tl for three consecutive 2% HNO_3 blank solutions that were run after a 1000 ppm Tl sample. With only a 10 s rinse, the Niagara achieved a better washout compared to a 30 s rinse without the Niagara, saving a considerable amount of time (31%). Adding bubbles reduced carryover even further, giving better than 4 orders of magnitude washout with a 46% savings in time compared to the standard setup.

Conclusions

The Niagara CM Rapid Rinse provides a simple, low cost approach to improving ICP productivity. Typical time saved with the Niagara is approximately 30%, with little to no changes to the current ICP method settings and no degradation in performance. The new NRRV2 software with Method Wizard facilitates easy optimization and self-installation. A unique post wash adding a series of bubbles significantly improves washout and reduces rinse time. Also noteworthy, the initial financial investment of the Niagara is 60% to 70% less than other commercially available switching valve systems.

References

- (1) Glass Expansion October 2013 Newsletter, “How to Achieve High Accuracy with Difficult Samples.”
- (2) Glass Expansion October 2005 Newsletter, “Increasing the Productivity of ICP Analyses.”
- (3) Glass Expansion February 2013 Newsletter, “Latest Developments in Enhanced Productivity Products.”
- (4) Glass Expansion June 2016 Newsletter, “A Simple, Low Cost Approach to Improving ICP Productivity.”

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SRC Microwave Digestion

Tim Michel, Milestone, Inc.

Single reaction chamber (SRC) microwave digestion offers multiple benefits over traditional dry ashing for the sample preparation of heavy crude oils for trace metals analysis. These include increased sample throughput, reduced risk of contamination, more complete digestion and retention of volatile analytes.

The digestion of heavy crude oil samples prior to trace metal analysis by ICP-OES has traditionally been performed by dry ashing in a muffle furnace. The oil is burned off over a burner prior to ashing in a muffle furnace. This process takes several hours and requires continual operator attention. Loss of sample and cross contamination can occur due to foaming and splashing. Additionally, volatile analytes are lost and cannot be measured. While closed vessel microwave digestion offers several advantages over dry ashing, the max sample weight of ~0.2 g is considered too small for representative analysis. Single reaction chamber (SRC) microwave digestion, however, can digest higher sample weights, enabling microwave digestion to be applied to the sample preparation of heavy oils.

Instrumentation

Milestone's new UltraWAVE SRC benchtop digestion system can digest up to five heavy oil samples at a time, max 300 °C and 199 bar pressure. Its high temperature and pressure capability enables the complete digestion of heavy oils, which makes sample introduction to the ICP-OES easier and more routine. The Ultra-WAVE can digest 0.75 g of heavy oil (up to five samples simultaneously)—more than 3x higher sample weight than closed vessel digestion. Samples are simply digested in disposable glass vials: unlike dry ashing, there are no crucibles to clean. The system is fully automated: the sample is weighed into a vial, 10 mL HNO₃ added and loaded into the UltraWAVE. Its walk away operation means labor costs are significantly reduced over dry ashing. The reaction chamber is pre-pressurized with N₂, which eliminates cross contamination or loss of volatiles.

Conclusion

Sample digestion requires about one hour, including cool down time with the Milestone UltraWAVE. The digestion of heavy oils in the amounts described were sufficient for the application with increased sample throughput and reduced labor costs compared to dry ashing. Risk of contamination and loss of volatile elements is eliminated and the superior digestion quality allows for easier analysis by ICP-OES.

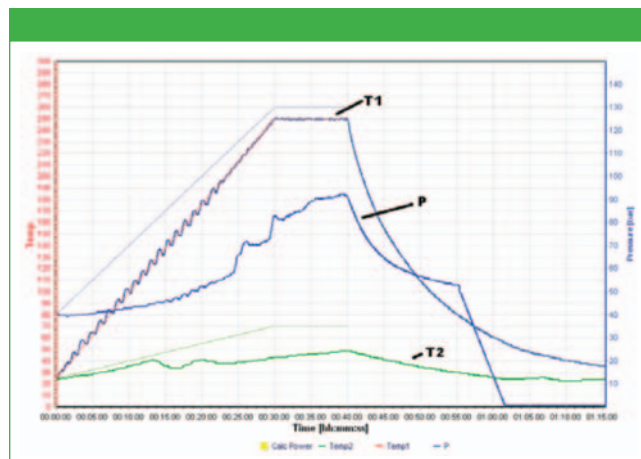


Figure 1: UltraWAVE digestion program with 5 × 0.75 g heavy oil: ramp to 250 °C over 30 min and hold for 10 min. The line T1 shows the actual digestion temperature achieved. The applied microwave power is automatically controlled by the system so the actual digestion temperature precisely follows the programmed temperature profile. The outer temperature of the reaction chamber is also monitored (T2). Note that pressure (P) reached almost 100 bar during the run. This is due to the high weight and high organic content of the samples, which generates NO_x and CO₂. Pressure was released automatically at 55 min.

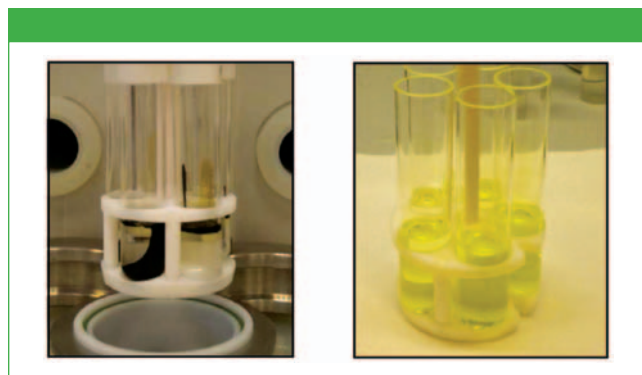


Figure 2: Sample rack being loaded and samples after digestion.

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RoHS Polyethylene (PE) Rapid Screening by XRF

Scott Fess, Applied Rigaku Technologies, Inc.

The measurement of Cr, Hg, Pb, Br, and Cd in polyethylene (PE) is demonstrated for RoHS rapid screening by XRF.

The Restriction on Hazardous Substances initiative (RoHS) limits the allowable amounts of the toxic elements chromium, mercury, lead, bromine, and cadmium in plastics and consumer goods. energy dispersive X-ray fluorescence (EDXRF) is an accepted analysis technique for the rapid screening by XRF and quantification of the hazardous element according to RoHS norms. To meet the industry needs, Rigaku offers the NEX DE VS analyzer with automatic collimators and camera for sample positioning and sample image, giving QA/QC technicians the means for fast and simple screening and analysis of materials that must conform to RoHS and similar directives.

Experimental Conditions

INSTRUMENTATION

Model: Rigaku NEX DE VS - Small Spot energy dispersive X-ray fluorescence analyzer

X-ray tube: 12 W 60 kV Ag-anode

Detector: High Throughput SDD

500,000+ cps

Collimators: 10, 3, and 1 mm spot size, automatic switching

Camera: High resolution for sample positioning and automatic capture of sample image

Safety Film: Mylar 6 um

Analysis Time: 90–300 s depending on usage

Environment: Air

Detection limits (LLD – lower limit of detection)					
Collimator	Cr ppm	Hg ppm	Pb ppm	Br ppm	Cd ppm
10 mm	1	0.4	0.4	0.2	0.6
3 mm	1.5	0.5	0.5	0.3	1.8
1 mm	1.8	1.8	2.2	0.6	6.7

CALIBRATION

Empirical calibration was performed using the thin certified standards available from Sumika Chemical Services, Ltd. and thick certified standards from ASI Standards. An automatic correction was used to compensate for variations in sample thickness. In this way separate methods or user input is not required for the measurement of samples having different thicknesses.

CALIBRATION VALIDATION

Ten repeat measurements of ASI Standards QC check sample were measured to validate the calibration.

SENSITIVITY VALIDATION

Ten repeat measurements of ERM-680k were measured to validate sensitivity at low levels.

USER DEFINABLE RoHS REPORT FIELDS

The flexible Rigaku software allows users to design RoHS report field headers to suite specific reporting needs. Headers to report Sample Name and Analyzed By are automatically set by default and the user simply enters up to six additional report memo headers as desired.

Results

RoHS REPORT

RoHS report is automatically generated that includes the user defined fields, sample image, and element judgment.

Conclusions

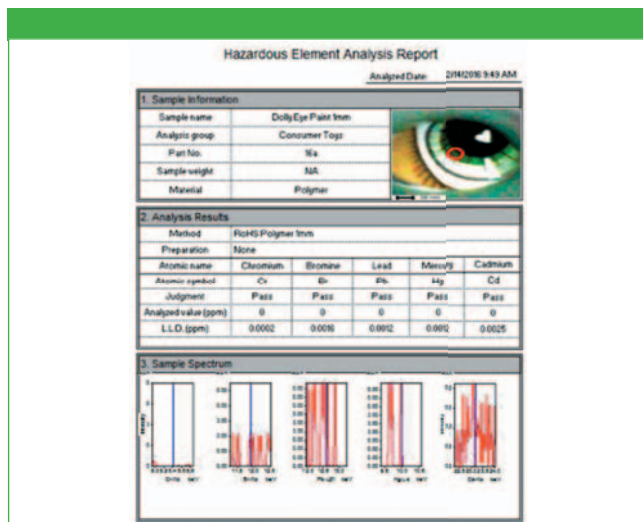
The NEX DE VS with automatic collimators and camera provides excellent sensitivity and reliable precision for RoHS rapid screening by XRF down to 1 mm spot size. Simple Point Analysis Screen allows operators to easily enter report information as designed using customizable report headers and automatically generates an RoHS report complete with sample image, analysis results and Pass/Unsure/Fail judgment.

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Performance Characteristics of a PFA Cyclonic Spray Chamber with HR ICP-MS

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The SavilleX PFA cyclonic spray chamber was used with a Thermo ElementXR HR-ICP-MS for the measurement of trace element/calcium ratios in foraminiferal calcite. The signal stability and washout (particularly for boron which is a “sticky” element) were studied. The spray chamber was found to have excellent sensitivity, good short and long term stability, and fast washout (60 s for B), making it well suited to the application.

Elemental ratio determinations in foraminiferal calcite require the measurement of trace levels of Na, Mg, Sr, and ultra-trace levels of Li, B, Ba, Cd, Mn, U in a calcium rich matrix and ratioed to calcium. Samples are run in an 0.1 M HNO₃/0.3 M HF matrix to prevent boron carryover between samples, so an inert sample introduction system is required. PTFE and PFA inert spray chambers generally have inferior performance to quartz spray chambers. We evaluated the recently introduced SavilleX PFA cyclonic spray chamber to see if advancements in technology have improved the performance of inert sample introduction systems for ICP-MS. A Thermo ElementXR HR-ICP-MS was fitted with a SavilleX inert kit comprising of an inert torch with platinum injector, PFA cyclonic spray chamber (no surface treatment) with baffle, and a C100 PFA concentric nebulizer.

An acid blank and three standards (standards 0, 4, and 8) containing 10 ppm Ca and varying ppt–ppb levels of trace elements were run. After the initial data acquisition for all standards, the



Figure 1: SavilleX PFA cyclonic spray chamber.

blank, standard 0, and standard 8 were measured 17 times each in sequence, to check for reproducibility and drift. The spray chamber was found to have good short-term stability with RSDs of 0.5–1%, and good long-term reproducibility RSDs of 1.5–2.9% over 4 h. No drift correction was applied. Washout of B from the high standard (0.74 ppb) to blank levels took <60 s, demonstrating the good washout characteristics of the spray chamber.

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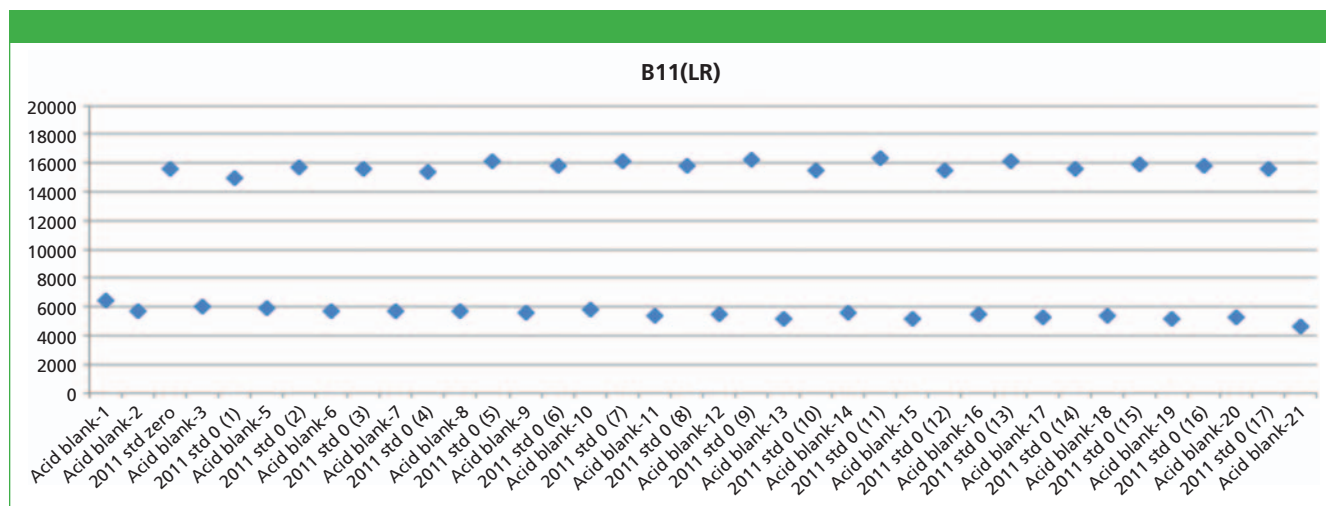


Figure 2: Boron signal over 5 h—acid blank and standard 0 (2 ppt B in 10 ppm Ca), showing excellent sensitivity and washout (the higher standards in between have been excluded for clarity). For full details visit www.savilleX.com/ICP.

Pharmaceutical Ingredient Uniformity Determination Using LIBS

Dr. Steve Buckley, TSI, Inc.

The uniform blending of active pharmaceutical ingredients (API) and excipients is critical to product quality. The homogeneity of ingredients within a batch or tablet must often be rapidly determined with minimal sample modification.

In this experiment, laser-induced breakdown spectroscopy (LIBS) analysis was used to rapidly monitor batch powder and tablet homogeneity. The distribution of pharmaceutical ingredients as a function of mixing time was monitored using the percent relative standard deviation (%RSD) of LIBS spectra. In addition, drug distribution within a non-uniformly blended tablet was assessed using LIBS spatial mapping.

Samples

Magnesium stearate, which acts as a lubricant, and croscarmellose sodium, a disintegrant, were used as pharmaceutical additives. Chlorpheniramine maleate, a pharmaceutical with antihistamine activities, was used as the API.

The API and excipients were mixed using a rotary blender, and analyzed using LIBS.

Results

Table I: Pharmaceutical batch composition

Ingredient	Concentration (w/w)	Matrix	Element Analyzed
Magnesium stearate	0.5%	50:50 lactose:cellulose	Magnesium (Mg)
Croscarmellose sodium	3.0%	50:50 lactose:cellulose	Sodium (Na)
Chlorpheniramine maleate	10%	50:50 lactose:cellulose	Chlorine (Cl)

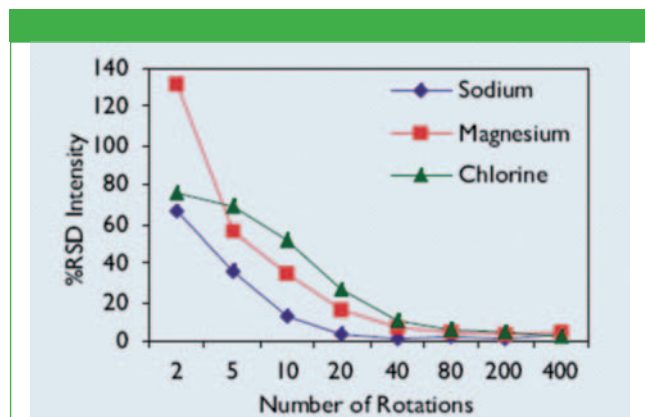


Figure 1: LIBS analysis of pharmaceutical blend uniformity.

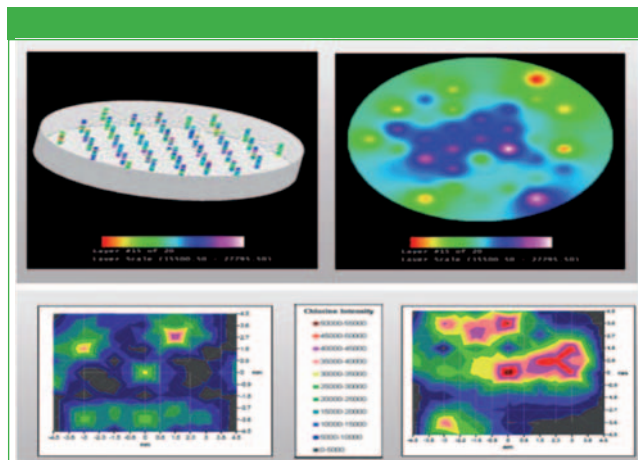


Figure 2: LIBS analysis of drug distribution in non-uniformly blended tablets.

In Figure 1, samples (Table I) were mixed in a low shear blender at 38 rpm. After a specific number of rotations, five samples were collected from different locations of the batch and analyzed with LIBS.

The results from Figure 1 show that the percent relative standard deviation (% RSD) of spectral signal is a useful indicator of sample uniformity. Prior to about 80 rotations, it can be seen that there is still some non-uniformity in the blend, whereas more than 80 rotations showed %RSDs which stabilized—indicating uniformity.

Several factors impact blend uniformity, including particle size and shape, electrostatic interactions, moisture content and particle surface characteristics. Uniformity analyses should be conducted routinely on blends to ensure quality—and with LIBS, this is rapidly and easily accomplished.

In Figure 2, Chlorpheniramine maleate (Cl) was analyzed throughout two non-uniformly blended tablets by monitoring 43 separate locations. A surface plot of chlorine intensity collected after 13 pulses is displayed in the XY plane to show the degree of ingredient variation within a tablet.

The results in Figure 2 demonstrate the ease with which final tablets can be monitored with LIBS to show API spatial uniformity.

Conclusions

LIBS was shown to readily determine the minimum rotations or blend time required to produce a homogenous batch, and hence can improve production efficiency for pharmaceutical blending. Monitoring % RSD of LIBS spectra can also be used for quality assurance and blend control, as a RSD value below 5% indicates homogenous blends. Analysis of drug distribution on a tablet could also be determined using LIBS, which is useful for end-of-line product quality assurance checks.

References

- Y. Mouget, M. Tourigny, P. Gosselin, and S. Bechard, "Three Dimensional Representation of Tablet Content Uniformity by LIBS," presented at Pittcon, 2002.
- Y. Mouget, M. Tourigny, P. Gosselin, and S. Bechard, Eastern Analytical Symposium, (2001).

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Tunable Mid-IR Lasers Set to Shrink Trace Gas Analysis Systems Using the PAS Technique

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The ultimate instrumentation for trace gas analysis would be one that can simultaneously provide a sensitive, selective, and fast, multi-gas measurement with wide dynamic range all in a compact and robust system. One of the few such promising technologies that can deliver these requirements is laser based photoacoustic spectroscopy (PAS). In this application note, the PAS technique is presented using the Cobolt Odin™ tunable mid-IR laser.

Mid-IR Lasers

Recent developments in technologies for mid-IR light sources allow cantilever-enhanced (CE) PAS instruments to now run with monochromatic and tunable wavelengths, broad spectral selectivity, and high output powers bringing sensitivity and selectivity with sub ppb levels. There are a number of laser technologies now available on the market capable of providing spectrally flexible narrow-band emission in the mid IR spectral range; quantum cascade lasers (QCLs), inter-band cascade lasers (ICLs), DFB diode lasers, and optical parametric oscillators (OPOs).

In many aspects the OPO technology is the most ideal choice for driving CE-PAS instruments due to the broad spectral selectivity and tuning capability within the 2.8–3.6 μm range. This wavelength region is not readily reachable with QCLs and the available power levels of DFBs and ICLs are comparatively low. Advancements in OPO design and laser packaging technology mean the traditional drawbacks for OPOs of bulkiness and complexity has now been removed.

Cobolt Odin™

The Cobolt Odin™ is a compact pulsed OPO with center wavelength between 2–5 μm and tunable >60 nm where the linewidth can be



Figure 1: Cobolt Odin™. Complete OPO system with all-integrated laser head (pump and OPO) and driver unit.

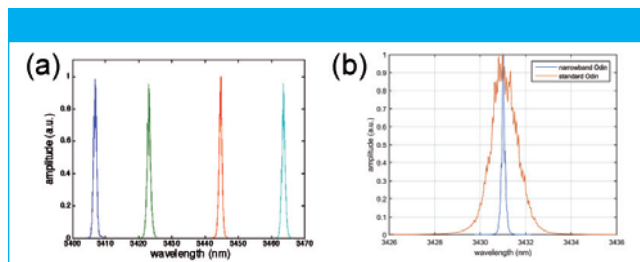


Figure 2: (a) Continuous spectral tuning of the Cobolt Odin™ over 60 nm, (b) typical linewidth.

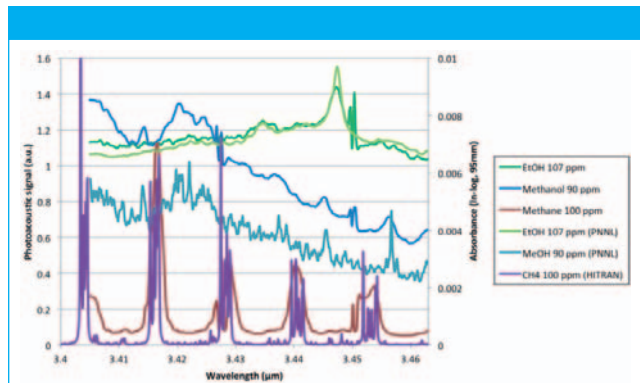


Figure 3: OPO/CE-PAS measurement of EtOH, MeOH and CH₄.

tailored from <1.5 nm to <0.2 nm, depending on the selectivity and dynamic range requirements. The proprietary HTCure™ manufacturing technology ensures reliability and robustness and means the laser is essentially insensitive to varying ambient conditions (for example, resistant to 60 G shocks and exposure to -20 C to +70 C cycling) bringing reliability and ease-of-use to instrumentation for in-field trace gas detection.

PPB Sensitivity

Experimental demonstration of the OPO/CE-PAS capability was performed using the Cobolt Odin™ operating between 3405–3463 nm (110 mW, 10 kHz). The OPO was coupled into one of Gasera's commercially available PA201 research photoacoustic detector for laser sources to measure ethanol, methanol, and methane.

Respective univariate detection limits obtained were (at 2x rms, with 1s CIT): for EtOH 7.7 ppb, for MeOH 11.4 ppb and for CH₄ 35 ppb. The total response time of the system was about 30 s, including the automatic gas exchange and the signal processing for a reduced tuning range.

The compact design and high mid-IR output power from the Cobolt Odin™, combined with Gasera's novel cantilever enhanced photoacoustic measurement technology, allow the OPO/CE-PAS technology to offer extreme sensitivity and selectivity for compact, reliable, industrial gas analysis and monitoring.

Reference

- 1) J. Peltola, M. Vainio, T. Hieta, J. Uotila, S. Sinisalo, M. Metsälä, et al. *Optics Express* **21**(8), 10240 (2013), doi:10.1364/OE.21.010240.

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A Heated ATR Single Reflection Diamond ATR Study of an Aqueous Sugar Slurry

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ATR is the most widely used FT-IR sampling technique, and is frequently used for quantitative, qualitative, and kinetic studies. New high-throughput accessories are expanding the scope of experiments by providing improved signal-to-noise performance. This application note demonstrates the potential of using a new high-throughput single-reflection diamond ATR accessory to study reaction kinetics by examining the heating of an aqueous sugar slurry.

Experimental

Infrared spectra were collected on an FT-IR spectrometer equipped with the Harrick DiaMaxATR™ single-reflection diamond ATR accessory with its Temperature Controlled Liquid Cell (Figure 1), Temperature Controller, and TempLink Software. The system was purged to remove water vapor and CO₂. Spectra were collected at 8 cm⁻¹ resolution and signal-averaged over 32 scans. A background spectrum was collected at ambient temperature. Confectioner's sugar was mixed with a small amount of water to generate a slurry and injected into the liquid cell. A sample spectrum was collected at ambient temperature. Then the cell was heated to 100 °C and additional sample spectra were collected at 2 min intervals.



Figure 1: The DiaMaxATR™ with its Temperature Controlled Liquid Cell and associated Temperature Controller.

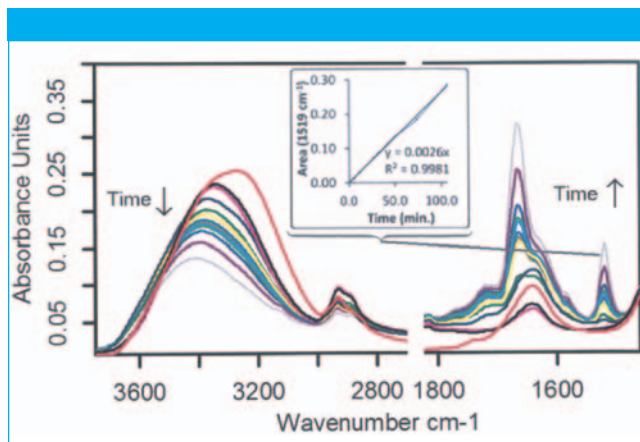


Figure 2: ATR spectra of sugar slurry over time at 100 °C, including plot of peak area versus time at 1519 cm⁻¹.

Results and Discussion

Figure 2 shows the resulting spectra. Initially, there is a broad band centered around 3276 cm⁻¹ and another at 1640 cm⁻¹, both of which are attributable primarily to water with a smaller component from the O-H stretches in confectioner's sugar, which is mainly sucrose. There are also bands in the 900–1150 cm⁻¹ region from the C-O and C-C stretches and bands in the 1400–1200 cm⁻¹ region due to the O-C-H, C-C-H, and C-O-H bends in the sugars, as expected.

Upon heating, the bands attributable to the O-H stretch and H-O-H bend both change shape, as the water evaporates and the primary contribution comes from the bound hydroxyl groups. The bands in the 900–1200 cm⁻¹ region also change, as the sucrose breaks down into glucose and fructose which in turn react to become small aromatic compounds and a brown-colored polymer.

The band at 1519 cm⁻¹ is attributed to aromatic compounds and grows as a function of time. The rate of formation of the aromatic compounds can be determined by plotting the peak area over time. Fitting the curve gives a linear relationship, where the peak area = 0.0026 x (time in minutes) with an R² of 0.9981. Given the complexity of the reaction, it is somewhat surprising that the data could be fit easily with a linear curve but this may be due to the time scale and temperature used for the measurements.

Conclusion

As seen herein, high-throughput, single-reflection ATR is valuable for examining thermally induced changes in materials. In the case of the heating an aqueous sugar slurry, it can be used to extract information about the kinetics of the reaction. Further analysis is possible to obtain more rigorous identification of the heat-induced structural changes.

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Free Space Coupling and Spectrometer Performance

Ocean Optics

In free space optics, light energy is collected from open beams and surfaces and sent on to the spectrometer. Free space optics can be used in various spectroscopy applications and are best deployed when the geometry between the light source and the spectrometer is defined and when these components are held in a rigid mechanical structure. Understanding how free space optics function within the spectrometer setup will help users to optimize experiments and obtain best results.

Imaging Spectrometer

Ocean Optics spectrometers are designed to project a spectrally convolved image of the input slit plane onto the detector (Figure 1). For example, if a light source comprising three monochromatic lines is projected onto the slit (aperture), then three distinct images of the slit would be seen at the detector plane. The images would be separated from each other by an amount determined by the wavelength dispersion of the system.

Free Space Optics

In free space coupling, an image of the subject is projected onto the slit. The details of the image projected onto the slit do matter. For example, if the image of a circular object is projected and greatly demagnified onto the slit, the image of the object may be lesser in size than the slit and produce an effect similar to having a fiber smaller than the slit. In this case, the experimenter has to be careful with horizontal alignment of the image projected onto the slit. Horizontal shift will appear as a peak wavelength shift; however, the shift can never exceed the slit's original FWHM (full width at half maximum, an expression of spectrometer resolution).

Moving the image vertically from the center of the slit will cause

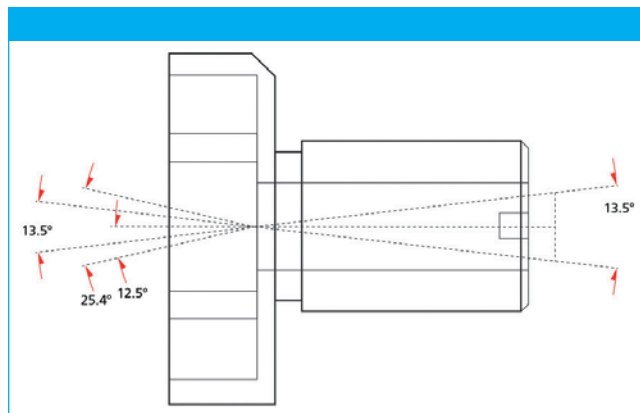


Figure 2: An aperture in the spectrometer's SMA bulkhead restricts the angle of light entering the bench.

the apparent amplitude to change. Light entering the vertical center of the slit is most efficiently coupled through the system. Light entering at the top or bottom of the slit will not be routed to the detector as efficiently.

Also, changing the angle of input causes the apparent intensity to change due to vignetting in the spectrometer. Light entering at 0° to the normal has the highest efficiency. To minimize these effects, ensure that the horizontal and vertical offsets, as well as horizontal and vertical angles, are fixed throughout the experiment.

All of these alignment issues are greatly reduced if the projected image overfills the slit and overfills the numerical aperture of the spectrometer. This spatial and angular overfilling allows small angle changes and small offset changes to be irrelevant. If the image projected onto the slit plane is not properly focused then the field of view is not a well-defined region and will instead have fuzzy edges.

SMA Bulkhead

The SMA bulkhead has an aperture that has been sized to restrict the angle of light entering the spectrometer (Figure 2). This has been designed to optimally fill the optical elements without overfilling, which would increase stray light. The full angle defined by a ray from the slit to the aperture is roughly 13.5° . The full angle defined by a ray from the opening of the SMA to the slit is greater than the 13.5° . This means that in a free space optical setup that is properly focused on the slit, the SMA connector is not restricting any light.

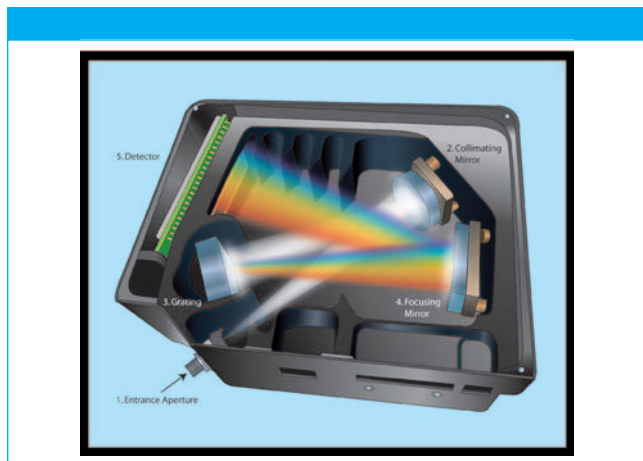


Figure 1: Light enters the spectrometer at its entrance aperture.

Ocean Optics

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Website: www.OceanOptics.com



Predictive Modeling of SiO₂ Film Thickness on Aluminum

Anna Clausen and Andrew Herian, PIKE Technologies

Reflectivity of a thin layer of SiO₂ applied to Al-coated glass was measured using the 10Spec, a near-normal specular reflection accessory. The reflection spectrum served as input data for FilmStar™ software to calculate SiO₂ thickness.

Many applications in the optics industry require highly reflective surfaces to maintain laser intensity throughout the beam path. Aluminum is an optimal material in the visible spectrum (400–800 nm) for these applications. However, due to the softness of Al, proper maintenance of the surface requires an abrasion-resistant overcoat to allow for periodic cleaning of the optical surface.

SiO₂ can protect Al while retaining a reflective surface. Previous work indicates SiO₂ provides a barrier against abrasion (1,2). Based on testing outlined in MIL-C-48497, a minimum thickness of 200 nm is recommended.

Experimental Conditions

At the PIKE Technologies facility (Madison, WI), Al-coated glass substrate was pre-cleaned via ion assist with Ar gas for 10 min at a chamber pressure of approximately 1×10^{-4} Torr. Immediately following the Ar pre-cleaning, a thin SiO₂ film was deposited onto the substrate at approximately 200 °C via electron beam physical vapor deposition.

Specular reflectance of the sample was measured between 400–800 nm using the 10Spec specular reflection accessory (PIKE Technologies,

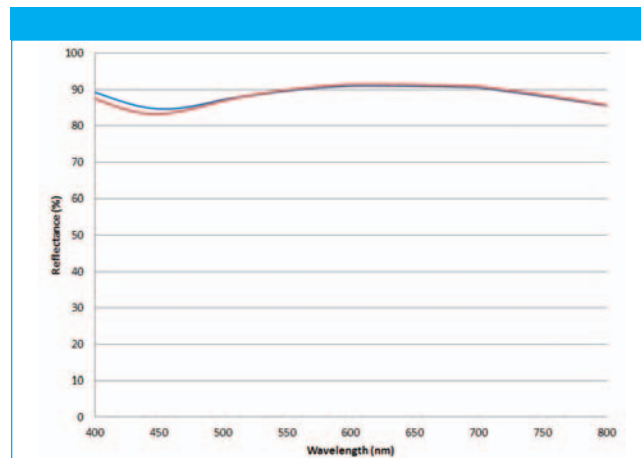


Figure 2: Reflectivity of the FilmStar modeled SiO₂ coating (blue) and the measured visible spectrum from the deposited SiO₂ coating on an Al-coated glass substrate (red).

Madison, WI) in a research-grade spectrophotometer. The accessory has a 10 degree fixed angle of incidence (Figure 1). Its optics condition a focused beam into a collimated beam, creating a uniform 10 degrees striking the sample. All reflective optics allow spectral measurements from the UV to the far IR.

FilmStar software (Princeton, NJ) was used to model the reflectance of SiO₂ over the visible region. To maximize the optical properties of the coating, FilmStar's index-solving algorithm along with additional optimization features were used to model an ideal protective coating over Al assuming the refractive index of SiO₂ to be $n = 1.46$ at 550 nm.

Results

The SiO₂ coating exhibited uniform measured reflectance over the wavelength range (Figure 2). Using the visible reflection spectrum in conjunction with FilmStar's damped least squares optimization feature, the coating thickness was determined to be 220 nm (3). When compared to the FilmStar model, the reflectivity of our SiO₂ coating is very similar. The modeled reflectance in FilmStar is fairly uniform over the wavelength range and greater than 83%, which is acceptable for most applications. A small discrepancy can be seen at approximately 450 nm due to a slightly different absorption, or k-value, utilized by FilmStar.

Conclusion

The 10Spec specular reflection accessory is used to make near-normal measurements. Spectra obtained may be used as input and verification data for FilmStar and other optical measurement modeling software.

References

- (1) U. Schulz, S. Jakobs, and N. Kaiser, *Proc. SPIE* **2776**, 169–174 (1996).
- (2) M. Mazur, D. Wojcieszak, J. Domaradzki, D. Kaczmarek, S. Song, and F. Placido, *Opto-Elec. Rev.* **21**(2), 233–238 (2013).
- (3) F. Goldstein, *Proc. SPIE* **7101**, 710105 (2008).

PIKE Technologies

6125 Cottonwood Drive, Madison, WI 53719
tel. (608) 274-2721, fax (608) 274-0103
Website: www.piketech.com



Figure 1: 10Spec near-normal specular reflection accessory.

Diamond Anti-Reflection Coating

Spectral Systems

Diamond is an important material choice for sampling optical elements in Fourier transform-infrared (FT-IR) spectroscopy. The multi-phonon absorption in the mid-infrared, although temperature dependent, is weak for thin optical elements and can be referenced to an empty cell background. However, the cost of diamond optics requires the sampling area to be very small. As a result, the signal-to-noise ratio (SNR) advantages of the FT-IR systems are frequently stretched to the limit and more energy throughput is usually quite helpful.

Frequently the sampling technique of choice is attenuated total reflection (ATR) for its benefits of ease of analysis. ATR elements can be manufactured from most optical materials of relatively high refractive index. Ge, Si, ZnSe, ZnS, KRS-5, and diamond is often used for this application. For most of these materials, a broad band anti-reflection (BBAR) coating can be applied to both surfaces of a window or the entrance and exit facets of an ATR element and can significantly increase the energy throughput of the sampling accessory or system.

Since diamond and ZnSe have similar refractive indexes a similar BBAR can be used on Diamond once the binding layers of the coating are appropriately modified.

Spectral Systems has developed its Diamond XP-BBAR™ coating with spectral performance as shown in Figure 1.

It is seen in Figure 1 that the energy and thus the SNR is about 30% better through most of the analysis region of a typical FT-IR instrument.

Since there are no suitable coating materials for the very long wavelength portion of the spectrum the coated element is not as good, but still usable, below 600 cm^{-1} . If a liquid nitrogen cooled MCT detector is used, this portion of the spectrum is usually not recorded by the spectrometer.

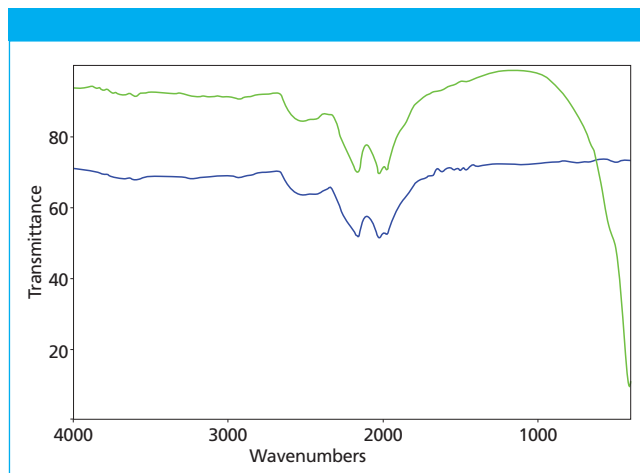


Figure 1: Transmission spectrum of uncoated Diamond window shown in blue. Transmission spectrum of Diamond XP-BBAR coating on both sides of a Diamond window shown in green.

Spectral Systems

35 Corporate Park Drive, Hopewell Junction, NY 12533
tel. (845) 896-2200, fax (845) 896-2203
Website: www.spectral-systems.com

Low-Dimensional WS₂ Characterization with Correlative Microscopy

WITec GmbH

Transition metal dichalcogenides (TMDs) display physical characteristics that hold great promise for applications in nano- and optoelectronics. These properties are strongly influenced by thickness, edge structures, lattice point defects, and functionalization of the material. For comprehensive structural and chemical characterization of low-dimensional TMDs, more than one technique is required. Here we present an analysis of WS₂ flakes using correlative confocal Raman imaging and AFM.

Using a confocal Raman-AFM microscope of the new WITec alpha300 microscope series, Raman spectra and the photoluminescence of CVD-grown WS₂ flakes on Si/SiO₂ were analyzed. AFM unambiguously revealed the numbers of atomic layers by

measuring the height of the material (Figure 1a). However, this can also be determined by the material's Raman spectra with an excitation wavelength of 532 nm. Using a RayShield coupler, several peaks could be identified and were used for analysis (Figure 1b). The low frequency Raman signal at 8.5 relative wavenumbers (cm⁻¹) assessed as being specific for single-layer (1L) structures. This band corresponded perfectly with the 1L WS₂ in the AFM image and decreased with the number of layers (Figure 1c). The peak at 416 relative wavenumbers (cm⁻¹) increased incrementally with the number of layers (not shown).

Another direct indicator of the physical and morphological features of TMDs is their photoluminescence (PL) that results from the recombination of carriers generated by photoexcitation. Its intensity and position are functions of the bandgap and thus depend on the layer count, because only the direct bandgap present in 1L WS₂ allows for direct recombination of electrons and holes. Therefore PL intensity is strongest in TMD monolayers. WS₂ shows strong PL around 639 nm wavelength (not shown). In the microscope image the highest PL intensity correlated perfectly with the AFM and Raman data of the monolayer flake (Figure 1d).

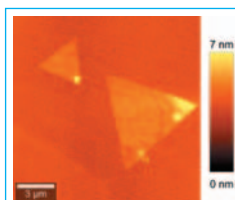


Figure 1a: High resolution AFM image of CVD-grown WS₂ flakes on a Si/SiO₂ substrate with varying numbers (1, 2, >2) of layers and a total height of up to 7 nm.

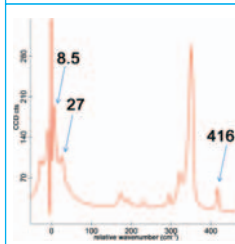


Figure 1b: Raman bands at low wavenumbers detected with RayShield technology. Excitation wavelength = 532 nm.

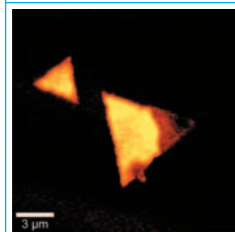


Figure 1c: The peak intensity map of the WS₂ Raman signal at 8.5 relative wavenumbers (cm⁻¹) corresponds well with the 1L WS₂ in the AFM image. The signal decreases with the number of layers.

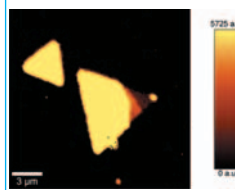


Figure 1d: The intensity of the PL at about 635 nm after excitation at 532 nm matches well to the thickness of the material. The fewer the layers the stronger is the PL. This can be explained by the transition of a direct bandgap in 1L WS₂ to an indirect bandgap in multilayer material. The upper left 1L WS₂ triangle shows strong and uniform PL.

Conclusion

In the case of low-dimensional TMDs, photoluminescence can serve as an effective method for investigating the electronic band structure as well as the local chemical structure of the material. Uniform PL at 8.5 relative wavenumbers (cm⁻¹) detected with WITec RayShield technology provides clear evidence of high quality 1L WS₂ crystals, whereas intensity shifts indicate structural inconsistencies and local modifications. The correlation of PL data with Raman imaging and AFM yields a comprehensive picture of the material.

Sample courtesy of Ting Yu, Nanyang Technological University, Singapore.

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PRODUCTS & RESOURCES

Handheld Raman spectrometer

B&W Tek's NanoRam handheld Raman spectrometer is designed for nondestructive identification and verification of materials such as active pharmaceutical ingredients, excipients, and intermediates. According to the company, the instrument's software has new updates that include e-signing of reports, improved library searching, expanded mixture analysis, Korean language support, and data archiving.

B&W Tek, Newark, DE; www.bwtek.com



Spectrometers

BaySpec's SuperGamut spectrometers are designed with holographic volume phase gratings (VPG) and back-thinned charge-coupled device or thermoelectrically cooled InGaAs array detectors. According to the company, the spectrometers have no moving parts, VPGs are manufactured in-house, and the spectrometers can be customized for any spectral range from 200 to 2500 nm and for the desired spectral resolution.

BaySpec, Inc., San Jose, CA; www.bayspec.com



Microwave acid digestion temperature sensor

CEM's MARS 6 sample preparation system now includes the contactless in situ iWave temperature sensor. According to the company, using light emitting technology, the sensor renders the vessel transparent, enabling the determination of the temperature of the actual sample in real time. The sensor reportedly can measure the sample temperature of each vessel without the need for a control vessel, fiber-optic probes, or wires.

CEM Corporation, Matthews, NC; www.cem.com



785-nm lasers

Compact, narrow linewidth 785-nm frequency-stabilized diode lasers from Cobolt are designed with an output power of up to 500 mW, and include an integrated optical isolator. According to the company, integrated electronics allow for easy incorporation into high-end Raman-based systems or other analytical instrumentation.

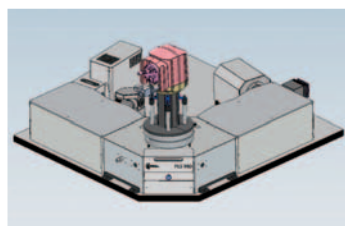
Cobolt AB, Stolna, Sweden; www.cobolt.se



Fluorescence spectrometer

The FLS980 fluorescence spectrometer from Edinburgh Instruments is designed to make measurements at temperatures ranging from <3 K to 300 K, without the need for cryogenic liquids. The spectrometer reportedly includes the Optistat Dry optical cryostat from Oxford Instruments, which uses a Gifford-McMahon cooler with a helium gas closed circuit.

Edinburgh Instruments, Livingston, UK; www.edinst.com



ICP-OES system

The Avio 200 inductively coupled plasma-optical emission spectrometry (ICP-OES) system from PerkinElmer is designed for multielemental inorganic analysis. According to the company, the spectrometer has the matrix tolerance to handle a variety of samples and to test across applications such as nutrients analysis for nutritional labeling, compliance with the RoHS Directive, analysis of soil micronutrients, determination of trace elements in water, and evaluation of metal levels in toys.

PerkinElmer, Waltham, MA; www.perkinelmer.com



UV-vis diffuse reflectance accessory

The UV-vis DiffusIR diffuse reflectance accessory from PIKE is designed for research and routine measurements. According to the company, the accessory's base is completely enclosed to shield against environmental light, and the standard configuration offers a two-position sample slide.

PIKE Technologies, Madison, WI; www.piketech.com



EDXRF spectrometer

Rigaku's NexQC+ Quant EZ benchtop energy dispersive X-ray fluorescence (EDXRF) elemental spectrometer is designed for heavy industrial use. According to the company, the spectrometer has Windows-based QuantEZ software that provides all the functions required for calibration and routine operation.

Rigaku, The Woodlands, TX; www.rigaku.com/en/products/xrf/nexqcp-quantez



Sample preparation press

Specac's hydraulic Atlas Autotouch press is designed for use in both modern laboratories and heavy industrial environments. According to the company, the benchtop press has power-assisted hydraulics and is programmable, microprocessor-controlled, and compatible with the company's pellet die assemblies and other sample preparation accessories for XRF and FT-IR pelleting applications.

Specac Inc., London, UK and Philadelphia, PA;
www.specac.com



Portable Raman spectroscopy system

The portable StellarCASE-Raman system from StellarNet is designed for material identification and composition analysis using Raman spectroscopy, and is suitable for applications in forensics, anti-counterfeiting, and enhanced Raman spectroscopy. According to the company, the system uses free SpectraWiz ID software to build and search a library for any application.

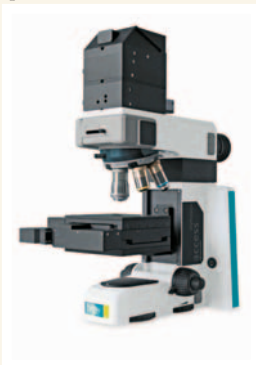
StellarNet, Inc.,
Tampa, FL;
www.StellarNet.us



Confocal micro-Raman system

WITec's alpha300 access confocal micro-Raman system is designed for submicrometer chemical analysis. According to the company, the system can be used for single-spot analysis or Raman mapping and can be upgraded to perform confocal 3D Raman imaging, atomic force microscopy, or scanning near-field optical microscopy.

WITec GmbH,
Ulm, Germany;
www.witec.de



Optical isolators

EOT's Tornos Series optical isolators are designed to eliminate frequency instability in single-frequency laser diodes and parasitic oscillations due to amplified spontaneous emission in amplified laser systems. According to the company, Faraday rotators and optical isolators for low-to-medium power applications between 532 nm and 980 nm are available.

Electro-Optics Technology, Inc.,
Traverse City, MI;
www.eotech.com



Terahertz Raman modules

Terahertz Raman spectroscopy modules from Ondax are designed to simultaneously capture low-frequency and chemical fingerprint signals. According to the company, the TR-Probe and TR-Bench modules deliver both chemical composition and molecular structural analysis in a single measurement for any process or laboratory environment.

Ondax, Inc.,
Monrovia, CA;
www.ondax.com



Spectrofluorometer

The PTI QuantaMaster 8000 spectrofluorometer from HORIBA is designed with a signal-to-noise ratio of 30,000:1 RMS for water Raman. According to the company, the research-grade spectrometer can accommodate up to four excitation sources and six detection channels, and triple-grating turrets for extended wavelength range, and it can be used with single or double monochromators for stray light rejection.

HORIBA Scientific,
Edison, NJ; horiba.com
www.quantamaster.com



Raman analyzer

The RamanRXN2 Multichannel analyzer from Kaiser is designed to provide high-resolution, research-grade Raman spectra on a portable platform for process development monitoring and control. According to the company, a single analyzer can collect Raman data from four channels, addressable by fiber-optic probes capable of direct in situ liquid or solid measurements in applications ranging from raw materials identification to process control in a manufacturing environment.

Kaiser Optical Systems, Inc.,
Ann Arbor, MI;
www.kosi.com



ULF Raman filters

BragGrate Raman filters from OptiGrate are designed to enable access to Stokes and anti-Stokes Raman bands in the ultralow terahertz frequency range down to 5 cm⁻¹. According to the company, laser line cleaning and light rejection notch filters are provided, and the filter production line is extended to cover many standard and custom laser wavelengths from 405 nm to 1550 nm.

OptiGrate,
Oviedo, FL;
www.optigrate.com



Confocal Raman microscope

Renishaw's inVia Qontor Raman microscope is designed with LiveTrack, which reportedly enables users to analyze samples with uneven, curved, or rough surfaces. According to the company, optimum focus is maintained in real time during spectral acquisitions and white light imaging, eliminating the need for manual focusing, pre-scanning, or extensive sample preparation.

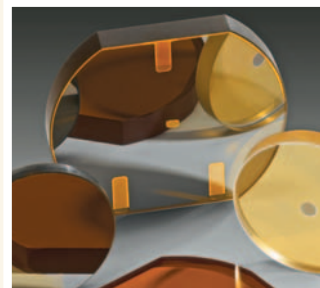
Renishaw,
Hoffman Estates, IL;
www.renishaw.com/Raman



Infrared beamsplitters

Photon Pro infrared beamsplitters from Spectral Systems are designed for use in the analysis of hazardous materials, environmental control, process control, and material recognition on the manufacturing floor. According to the company, the beamsplitters simultaneously transmit and reflect 50% of the incident beam between two optical elements.

Spectral Systems LLC, Hopewell Junction, NY;
www.spectral-systems.com



NIR neutral density filters

NIR Metal-on-Quartz neutral density filters from Starna are certified reference materials designed to enhance and extend the capability to qualify the full range of transmittance scale of a UV-vis-NIR spectrophotometer. According to the company, the filters are protected from oxidation, physical degradation, or contamination by a novel cover plate that is optically bonded to the surface.

Starna Cells, Inc.,
Atascadero CA;
www.starnacells.com



Laser metals analyzer

The handheld ChemLite laser metals analyzer from TSI reportedly is based on laser-induced breakdown spectroscopy. According to the company, the analyzer is suitable for sorting scrap metal, including light elements, and providing measurements in PMI efforts.

TSI, Inc.,
Shoreview, MN;
www.tsi.com/ChemLite



ICP-MS system

The Agilent 8900 triple-quadrupole inductively coupled plasma-mass spectrometry (ICP-MS) system is designed to provide low detection limits for difficult elements such as sulfur, silicon, and phosphorus. According to the company, the system has MS/MS capability for interference removal in reaction mode.

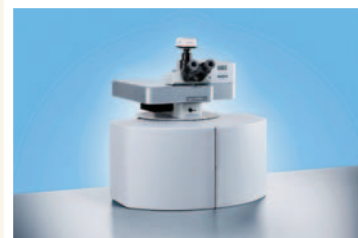
Agilent Technologies, Santa Clara, CA;
www.agilent.com



Raman microscope

The Senterra II compact, confocal multilaser Raman microscope from Bruker Optics is designed to use different acquisition modes to optimize data acquisition on spectral recording rates or lateral resolution. According to the company, the research-grade microscope is suitable for advanced Raman microscopic applications.

Bruker Corporation,
Billerica, MA;
www.bruker.com



Reflectance probe

Ocean Optics' DR-Probe 45° diffuse reflectance probe is designed with an integrated tungsten halogen light source for reflectance measurements. According to the company, the probe includes a 40-mm standoff accessory for maintaining a consistent focal length between the probe and the sample.

Ocean Optics,
Dunedin, FL;
www.oceanoptics.com



Infrared spectrometer

Thermo Fisher's Delta Ray isotope ratio infrared spectrometer (IRIS) is designed to facilitate interfacing with samples available in amounts as little as 80 µg of CO₂, as in vials, syringes, or bags. According to the company, the spectrometer extends the continuous measurement of isotope ratios and concentrations of CO₂ in air to discrete samples in applications such as dissolved inorganic carbon measurement, carbonate isotope ratio determination, and microbiology labeling experiments.

Thermo Fisher Scientific, San Jose, CA;
www.thermoscientific.com



THE APPLICATION NOTEBOOK

Call for Application Notes

Spectroscopy is planning to publish the next issue of *The Application Notebook* in December. As always, the publication will include paid position vendor application notes that describe techniques and applications of all forms of spectroscopy that are of immediate interest to users in industry, academia, and government. If your company is interested in participating in this special supplement, contact:

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It is important that each company's material fits within the allotted space. The editors cannot be responsible for substantial editing or handling of application notes that deviate from the following guidelines:

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- **Title:** short, specific, and clear
- **Abstract:** brief, one- or two-sentence abstract
- **Introduction**
- **Experimental Conditions**
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- **Conclusions**
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- **Two graphic elements:** one is the company logo; the other may be a sample spectrum, figure, or table
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All text will be published in accordance with *Spectroscopy's* style to maintain uniformity throughout the book. It also will be checked for grammatical accuracy, although the content will not be edited. Text should be sent in electronic format, preferably using Microsoft Word.

Figures

Refer to photographs, line drawings, and graphs in the text using arabic numerals in consecutive order (Figure 1, etc.). Company logos, line drawings, graphs, and charts must be professionally rendered and submitted as .TIF or .EPS files with a minimum resolution of 300 dpi. Lines of spectra must be heavy enough to remain legible after re-

duction. Provide labels and identification. Provide figure captions as part of the text, each identified by its proper number and title. If you wish to submit a figure or spectrum, please follow the format of the sample provided below.

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Each table should be typed as part of the main text document. Refer to tables in the text by Roman numerals in consecutive order (Table I, etc.). Every table and each column within the table must have an appropriate heading. Table number and title must be placed in a continuous heading above the data presented. If you wish to submit a table, please follow the format of the sample provided below.

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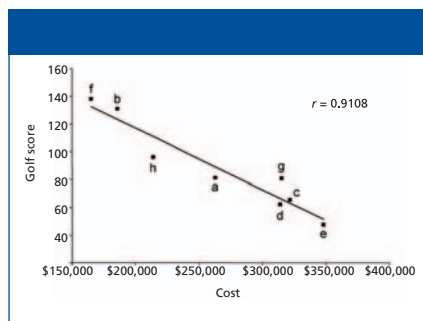


Figure 1: The ion suppression trace is shown on the bottom. Column: 75 mm × 4.6 mm ODS-3; mobile-phase A: 0.05% heptafluorobutyric acid in water; mobile-phase B: 0.05% heptafluorobutyric acid in acetonitrile; gradient: 5–30% B in 4 min. Peaks: 1 = metabolite, 2 = internal standard, 3 = parent drug.

Table I: Factor levels used in the designs

Factor	Nominal Value	Lower Level (–1)	Upper Level (+1)
Gradient profile	1	0	2
Buffer concentration	40	36	44
Mobile-phase buffer pH	5	4.8	5.2
Detection wavelength (nm)	446	441	451
Triethylamine (%)	0.23	0.21	0.25
Dimethylformamide	10	9.5	10.5

For more information, contact:

Mike Tessalone at (732) 346-3016, Ed Fantuzzi at (732) 346-3015, Stephanie Shaffer at (774) 249-1890, or Lizzy Thomas at (574) 276-2941.

Materials Due: October 31, 2016

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METROHM HANDHELD RAMAN ANALYZER:

Identify. Screen. Confirm.

Metrohm's new handheld Raman product (Mira) brings an increased level of confidence to identification, screening and confirmation measurements. Mira integrates seamlessly at all phases of the manufacturing process. Eliminating the need for sample transfer and measurement in a separate laboratory setting, Mira brings the analysis to the sample.



Key features:

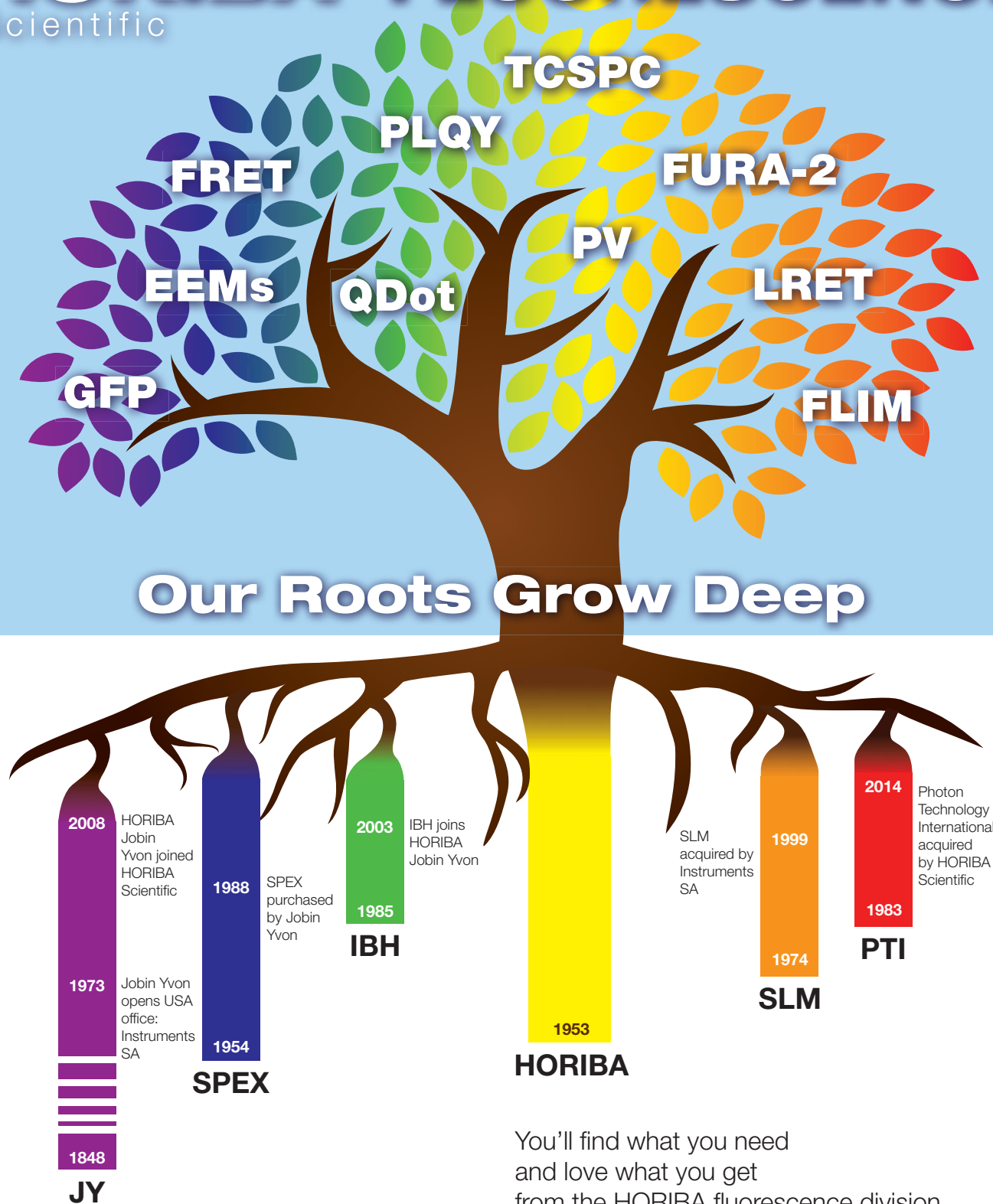
- No sample preparation
- Brings QA/QC lab measurements for identification and confirmation to the process line
- Unmatched sampling options increase accuracy and reliability
- Build your own library or use one of our application-specific libraries for analysis
- Class I laser safety means safety glasses are not required

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