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# Qualitative Analysis and the Answer Box: A Perspective on Portable Raman Spectroscopy

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**Miniaturization of Raman instruments has created a new genre of devices for qualitative analysis of materials. These new devices are introducing Raman spectroscopy to a diverse range of applications.**

The game “20 Questions” has been around for a long time and has even been translated into the popular yo-yo sized 20Q toy. This game is very similar to qualitative analysis, a method that uses flow charts to identify an unknown material. Though the science of qualitative analysis dates back to alchemists, today’s challenge is to identify materials faster and more accurately. One method that can provide accurate answers is Raman spectroscopy—and Raman instruments are rapidly shrinking to a size approaching that of the 20Q toy.

Not many schools offer qualitative analysis courses anymore. I’ll never forget mine; the course consisted of identifying unknown materials based on smell, color, reactivity, melting point, and IR spectrum. The unknown from my final project was 3-methylindole—there has to be a better way to analyze 3-methylindole than using one’s olfactory senses!

Raman spectroscopy, which has evolved greatly in the past 30 years, has become a powerful tool for qualitative analysis. Years ago, collecting data on a Raman instrument involved watching an LED display and hoping that the numbers on the display went up and down. If you were lucky, you got a spectrum. To this day, the spectra are difficult to interpret. The vibrations of molecules are a complex summation of normal modes that have stymied programmers and eluded simple computational analyses. The equations are not the problem; there are simply more unknowns than observed vibrational frequencies. This problem may only be solved by substituting isotopes individually at every location in the analyte, which is completely contrary to quick determination of an unknown. In spite of the complexity of the spectra, Raman



spectroscopy is an information rich “fingerprint” technique that can be used in virtually any situation and can provide chemistry sleuths with a unique identification of materials. It has a simple sampling method founded on the concept of “if you can see the sample, you can obtain a spectrum”; anywhere a laser can shoot, a spectrum can be generated.

### RAMAN SPECTROSCOPY’S MOVE TO POPULARITY

The increasing popularity of Raman spectroscopy stems from its easy sampling methods and its specificity. Raman spectra may be obtained directly from powders or liquids or even through transparent containers. Much like the 20Q toy, the complex spectra, with the assistance of chemometrics, provide sufficient answers to questions about the sample. These features of Raman spectroscopy have been

true since its discovery in 1928, when Professor C. V. Raman used an astronomical telescope to focus sunlight onto his samples and observe the Raman scattering effect (he eventually won the Nobel Prize for his discovery).<sup>1</sup> But less than 10 years ago, Raman spectroscopy was still an esoteric technique that required large and expensive instrumentation. Two unrelated commodities have now helped elevate Raman spectroscopy above a laboratory technique: the CD player and the digital camera.

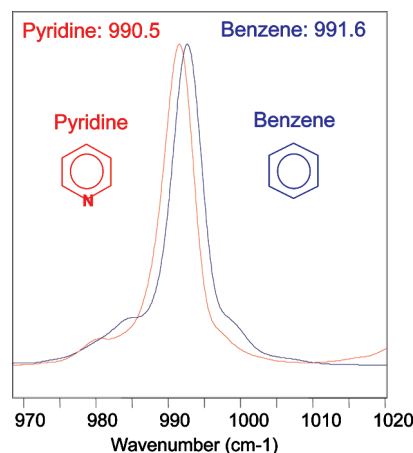
Optical data storage media such as CDs or DVDs require a tightly focused laser for maximum storage capacity. The diode lasers used in CD players meet many of the requirements of a small Raman system. However, lasers used in Raman spectroscopy require a minimum degree of laser stability for a stable spectrum in the x- and y-axis response. Under many conditions, semiconductor lasers discontinuously switch back and forth between wavelengths. This switching is called “mode-hopping”, which is caused by several factors: laser temperature, injection current into the laser, and optical feedback. Even the smallest amount of feedback into the diode laser can cause it to mode-hop. This problem has been addressed with the volume Bragg grating (VBG), which has added the final touch needed for diode lasers to act as stable laser sources for Raman spectroscopy.<sup>2</sup>

VBGs lock the laser into a single frequency to prevent mode-hopping. A VBG is inserted near the tip of a laser diode to provide strong angular selectivity feedback in transmission and reflective modes. In general, wavelength locking is achieved when the axis of a laser diode is near collimation and the VBG is positioned behind a lens to reflect some of the laser diode light back into the laser cavity. For Raman spectroscopy, the VBG allows stabilization, small, and inexpensive laser sources.

In addition to VBG technology, high volume commodities such as digital cameras that use CCD detectors have driven down the cost and size of detectors for Raman spectroscopy; high quality CCD detectors are now available for <\$100. Improvements in optical filter technology have also made smaller Raman spectrometers possible. Traditionally, Raman spectroscopy was performed with double or even triple monochromators to reject the intense diffuse laser scattering and Rayleigh scattering. Today, very efficient dielectric or holographic filters are available. The reduction in size and price of these components has allowed instrument manufacturers to produce small and compact spectrometers.

Early skeptics suspected that portable Raman systems did not have the appropriate spectral resolution for discrimination. Resolution of a Raman spectrometer depends upon the focal length of the spectrometer, dispersion, laser collimation dimensions, aperture, and pixel density of the CCD. As systems have become smaller, high spectral resolution has become more challenging. Nonetheless, modern portable Raman systems have sustained resolution values of 8–12  $\text{cm}^{-1}$  across the full range of the spectrum; these values are more than adequate to discriminate among various substances. The natural linewidth of many solids and liquids is 5–10  $\text{cm}^{-1}$ . Although full peak separation is not attained for many materials, overlapping peaks and peak curvature can aid discrimination algorithms in material identification.

For example, the peak locations of benzene and pyridine are separated by  $\sim 1 \text{ cm}^{-1}$  (Figure 1). A correlation model was used to distinguish the materials in the truncated region of 950–1008



**Figure 1.** Raman spectra of benzene and pyridine obtained from a  $5 \text{ cm}^{-1}$  resolution instrument.

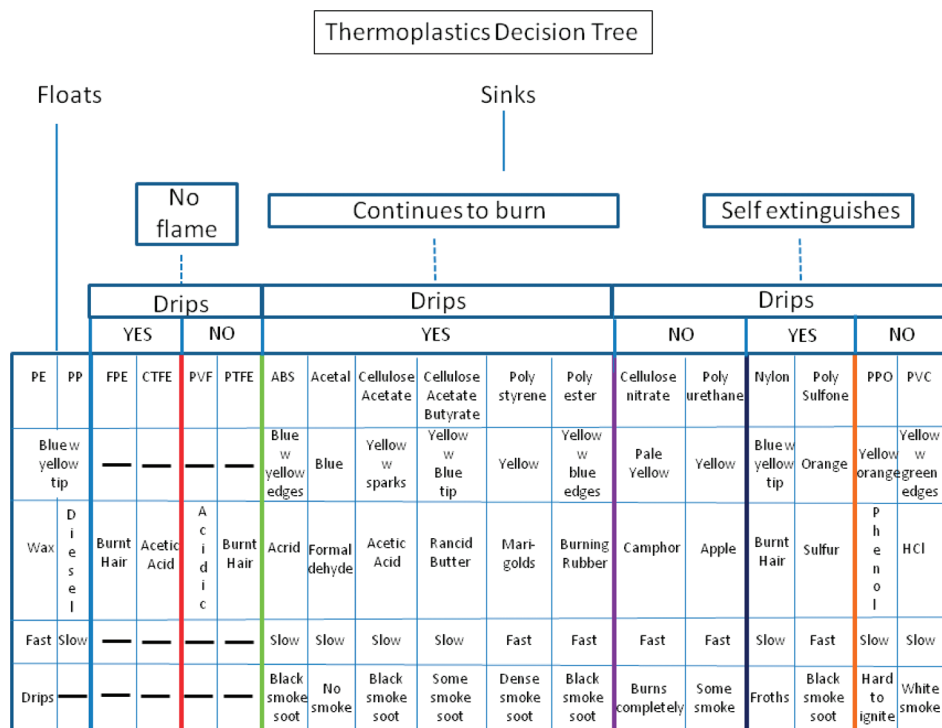
$\text{cm}^{-1}$ . A Raman spectrometer with  $\sim 5 \text{ cm}^{-1}$  resolution can easily distinguish these substances with a difference of  $\sim 0.05$  quality match index, and an instrument with  $13 \text{ cm}^{-1}$  resolution confuses the materials with only a difference of  $\sim 0.01$  quality match index between benzene and pyridine. If the full spectrum is used, then these substances are more fully discriminated. In the case of mixtures, determining the composition of materials is more challenging. Several curve fitting and mixture algorithms are commercially available to assist in discrimination.<sup>3</sup>

The x-axis stability of portable systems merits particular attention because high-resolution analysis is only effective when coupled with a high accuracy of calibration among spectrometers and with high precision (reproducibility and repeatability) under various environmental conditions. The VBG has helped achieve stability, but other factors such as the detector and electronic components must be controlled and monitored to minimize x-axis drift in portable systems. Periodic noise and drift can be characterized under various environmental conditions, including variations in temperature<sup>4</sup> and humidity. For effective discrimination of materials, a goal is to maintain the wavelength accuracy and precision of a spectrometer at less than the apparent peak separation. Many commercially available portable Raman systems have accuracy of the frequency less than  $\pm 2 \text{ cm}^{-1}$  to assist in library transfer among systems. Portable spectrometer precision is commonly  $< 0.05 \text{ cm}^{-1}$ .

## LOOKING FOR ANSWERS, NOT SPECTRA

In order for portable Raman devices to be placed in the hands of the layman, they must be accessible in a so called “answer box” format—perhaps not displaying spectra at all. Further improvements in spectral preprocessing methods and library search algorithms have assisted in achieving this goal.

Spectral preprocessing methods reduce noise in the Raman spectrum, and other techniques assist in reducing spurious baseline fluctuations.<sup>5</sup> One difficulty for automatic material identification with Raman spectroscopy is the problem of fluorescence excited by the illuminating laser, which appears in the spectrum as a broad background hump. This fluorescence background is not usually diagnostic as to the type of material. Instead, it can

**Table 1. Plastic Identification Decision Tree**


interfere with identification because the shape of the fluorescence background can differ between samples of the same material.

A common method of reducing fluorescence background is baseline correction such as manual point correction, derivatives, and subtraction methods.<sup>5,6</sup> Derivatives and subtraction methods are the most popular for automated baseline correction. In a subtraction routine, peaks are eliminated by heavily smoothing the Raman spectrum. The background is subtracted from the raw spectrum leaving only the peaks. One of the advantages of this procedure is that the direction and general shape of the Raman peaks are preserved with the exception of small adjacent sidelobe dips that become more pronounced near sharply sloped peaks. More advanced methods can be employed to assist in removing sidelobes and dips in the spectra to improve matching results among samples.<sup>7</sup>

Preprocessing the raw data diminishes the noise in the spectrum, ensures a constant baseline, and reduces the fluorescence. Several chemometric matching algorithms are now available to improve the library search result. The most widespread search algorithm is a correlation algorithm.<sup>8,9</sup> This algorithm is popular because it searches a large number of spectra in a short period of time, resulting in excellent "hit" or correlation quality. For example, McCreery, et al. found this simple approach could identify pharmaceuticals through USP vials.<sup>10</sup> The disadvantage of this approach is that materials with common spectral features are not as easily discriminated.

In many systems, the correlation is the first step in the library search, then second and third tier algorithms may be used to further discriminate similar materials or mixtures. These multitier algorithms improve matches by selecting spectral regions where materials differ. Peak ratios, principal component analysis (PCA),

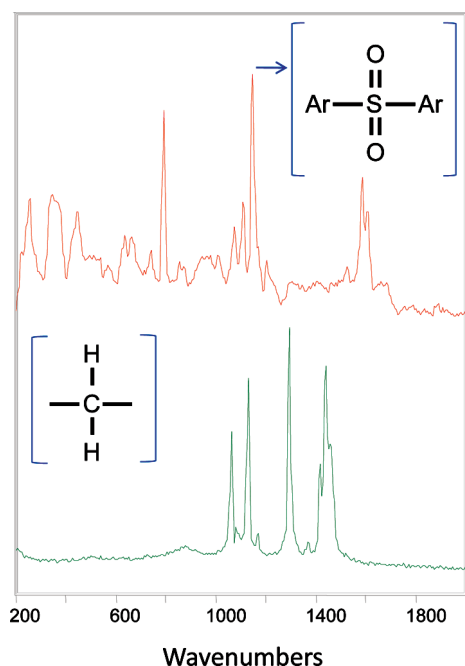
standard deviations, or further correlation can be employed in discrete spectral regions to improve the hit quality index.<sup>3,11</sup>

Multitier algorithms have been developed for mixture analysis based upon matching a residual spectrum to the search library. A residual spectrum is created by subtracting the top match spectrum from the unknown material. The challenge is determining the proper number of subtraction factors to subtract the unknown spectrum from the top library match. One such automated routine has been used by Ethegoin, Galloway, et al. to select the proper number of factors for subtraction.<sup>12</sup>

## APPLICATIONS

The proliferation and improvement of these devices in the last five years is caused by the demand for identification of materials in a variety of applications and markets. Areas most in need of materials identification are industrial plastics, medical diagnostics, pharmaceuticals, law enforcement, military, hazmat, geology, and archeology, among others. Below, we will discuss a few of these applications and how these miniature systems may be tailored for various applications.

**Identification of Plastics.** Plastics are a challenge for quick identification because they often have a similar appearance. In the common method of analysis, called "burn and sniff",<sup>13</sup> a complex chart is used as a decision tree for identifying plastics. This method is an excellent parallel to the 20Q toy (Table 1). The identification is based on several tests that lead to different branches of a decision tree. These tests include whether the plastic floats in water and, when burned, whether it drips or self extinguishes, the color of the flame, the odor, and the speed of burning. This method has the specificity to identify many unknown plastics correctly but is not very practical.

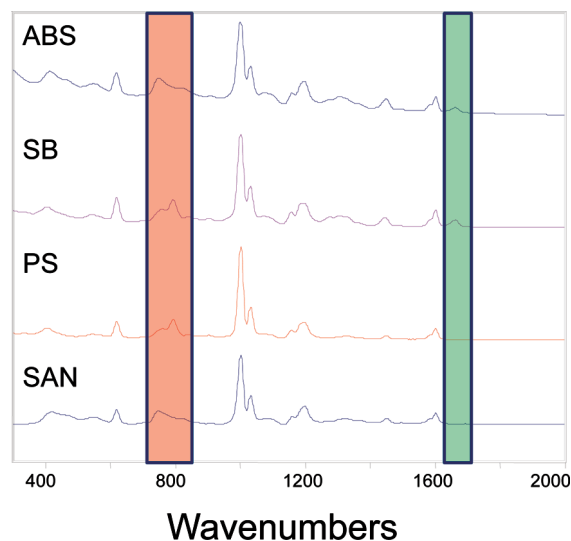


**Figure 2.** Raman spectra of polysulfone (red) and polyethylene (green).

Our goal is to replace burning and sniffing of plastics and observations of their density as compared to water with both a rapid turn-key spectroscopic measurement and powerful algorithm for a computed decision making process. A Raman spectrum has characteristic frequencies that relate to specific chemical groups; the flame color and odors generated when a material is burned are also caused by these groups. For example, a polysulfone plastic will produce a sulfur odor when burned. Figure 2 illustrates the Raman spectra used to identify two plastics: polysulfone and polyethylene. The Raman spectroscopic signature equivalent to the odor is the  $1148\text{ cm}^{-1}$  peak due to  $\text{O}=\text{S}=\text{O}$  symmetric sulfone stretching. This demonstrates how a Raman spectrum, just like the sniff test, provides answers to correctly identify a material.

While the Raman spectra of some plastics are easily distinguished with a common correlation algorithm, materials with similar repeating units require more complex searching algorithms for automated identification of materials. Consider the four styrenic plastics: polystyrene (PS), styrene butadiene (SB), styrene acrylonitrile (SAN), and acrylonitrile butadiene styrene (ABS). The Raman spectra of these four materials are shown in Figure 3. All four materials exhibit similar Raman signatures due to a common styrenic functional group shared among the polymers. Though less intense than the styrenic regions, the highlighted regions at  $715\text{--}825\text{ cm}^{-1}$  (red) and  $1625\text{--}1700\text{ cm}^{-1}$  (blue) illustrate the differences among the materials. For example, the single peak observed in the blue region for ABS and SB is caused by the butadiene carbon-carbon double bond.

Though a simple correlation algorithm is able to distinguish these styrenic polymers from other families of plastics, it will not completely narrow down the true identity within the styrenics group. The Raman spectra of styrenics are so similar that they cross-correlate with quality index match values  $>0.93$  correlation when the full spectral regions are used to distinguish among the



**Figure 3.** Raman spectra of styrenic polymers: acrylonitrile butadiene styrene (ABS), styrene-butadiene (SB), polystyrene (PS), and styrene acrylonitrile (SAN).

**Table 2. Correlation Matching Based on Spectral Regions for Styrenic Compounds. Highlighted Green Regions are Possible Matches and Highlighted Red Regions are Excluded from the Group as Possible Matches. Acrylonitrile Butadiene Styrene (ABS), Styrene-Butadiene (SB), Polystyrene (PS), Styrene Acrylonitrile (SAN)**

	Entire Region Matching					Block Matching-Region Red					Block Matching-Region Blue				
	ABS	SB	PS	SAN		ABS	SB	PS	SAN		ABS	SB	PS	SAN	
ABS	1	0.96	0.93	0.98		1	0.24	0.18	0.92		1				0.28
SB		1	0.98	0.96			1	0.99	0.29			1	0.53		
PS			1	0.96				1	0.24				1		
SAN				1					1					1	

materials. More precise identification requires second and third tier correlation matching based upon the discrete spectral regions where large differences among the samples occur (Table 2). Second and third tier iterations to this decision tree algorithm are based on correlation. In the second tier, four of the match possibilities are eliminated, and in the third tier, two possibilities are eliminated. Finally, there is no case in which two samples will cross-correlate based on the data in the discrete regions. This is an example of discrimination based upon multi-tier correlation algorithms; however, several other types of discrimination algorithms may be utilized, e.g. PCA, standard deviations, peak ratios, etc.

**Inorganic Analysis.** Small X-ray sources have made it possible to design handheld, field-based X-ray fluorometers to determine elemental composition of inorganic materials. Beyond these devices, inorganic qualitative analysis once again becomes a 20Q process based on physical observations. For example, minerals are identified through characteristics like hardness, luster, specific gravity, and acid reactivity.

A mineral's crystal structure and symmetry play a large role in determining its Raman spectrum. Molecular structure and 3D lattice structure combine to produce spectral information that correlates to elemental analysis, molecular composition, and crystal structure. Vibrational frequency is mass dependent; as the



mass of the elemental components increases, vibrational frequencies shift lower. The smaller molecules that form inorganic materials typically have high symmetries that form characteristic Raman spectra. When 3D crystals form, collective vibrations and crystal groups further differentiate Raman spectra.

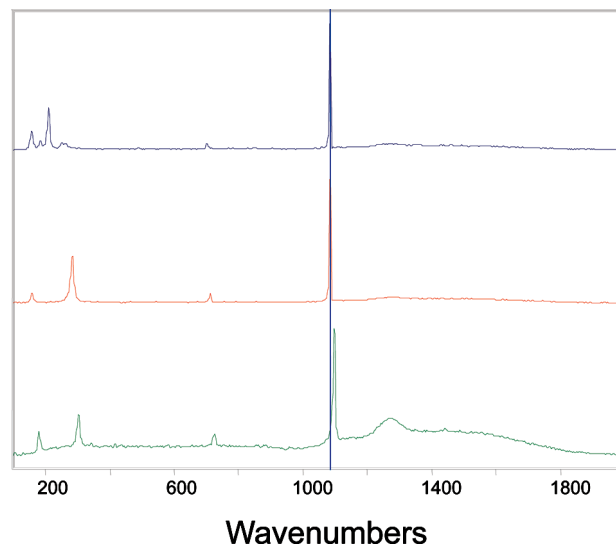
Raman spectroscopy can provide information about crystalline structure of elemental materials (allotropes) and, more generally, any kind of crystalline polymorph. It can also determine the degree of crystallinity; for example, Raman spectroscopy is very sensitive to the amorphicity of Si in solar cells. The allotropes of elements such as silicon, sulfur, and carbon are readily identified by their Raman spectrum. For example, the Raman spectrum of diamond is completely different from that of amorphous carbon. Raman signatures are obtainable for several inorganic ions such as oxanionic minerals (e.g.,  $\text{SO}_4^{2-}$ ,  $\text{CO}_3^{2-}$ ,  $\text{PO}_4^{3-}$ , silicates), oxide and sulfide minerals (e.g., hematite, pyrrhotite), cation mole fractions in  $\text{Ca}^{+2}$ ,  $\text{Mg}^{+2}$ , and  $\text{Fe}^{+2}$ , cyanide ( $\text{CN}^-$ ), and nitrates and nitrites ( $\text{NO}_3^-$ ,  $\text{NO}_2^-$ ). Examples of applications using portable Raman for qualitative inorganic identification can be found in geology,<sup>8,14</sup> planetary exploration,<sup>15</sup> gemology,<sup>16,17</sup> archeology, and art.<sup>17–19</sup>

Mineral identification techniques taught in undergraduate geology curricula have changed little in the last century. Rocks and minerals exhibit an array of diagnostic properties, which include color, luster, hardness, specific gravity, acid response, more involved optical properties, and magnetism. Raman spectroscopy will never completely replace all of these mineral diagnostic tests. Nevertheless, it is an excellent method that can assist the field geologist in rapid field identification of rocks and minerals.

Many rocks and minerals are difficult to distinguish using classical methods without various levels of expertise and training, and many types of materials require bench top laboratory equipment for identification. One of the big advantages of a portable Raman system is that it can rapidly delineate the location of mineral beds and columns in the field. The purpose of a mineral survey is to map the location of a site so that it can be evaluated as a resource. Onsite mineral identification for a geological survey can save the geologist extensive time and laboratory backload and can provide additional mapping points to increase the resolution of data. A lightweight portable Raman system can also be used on outcrops to identify and map sedimentary effects. Raman can be applied to minerals in various ways; the speciation of carbonates is an example of this powerful discrimination method.

Figure 4 displays the Raman spectra of carbonate minerals. Aragonite and calcite are the two most common polymorphs of calcium carbonate. These polymorphs share the same chemistry, but aragonite's crystal lattice is in an orthorhombic pattern, whereas that of calcite is trigonal-rhombohedral. The CO stretching band at  $1086\text{ cm}^{-1}$  is common to each polymorph; however, the lower frequency regions vary based on symmetry of the carbonate ion. The CO stretching band of dolomite, which is composed of calcium magnesium carbonate, is shifted to  $1096\text{ cm}^{-1}$ . The Raman spectra of these carbonates provide a powerful example of discrimination between closely-related minerals of different polymorphs and stoichiometries.

**Forensics, Law Enforcement, and Hazmat.** IR systems were the first portable spectroscopy devices to be accepted by forensics



**Figure 4.** Raman spectra for calcite (blue), aragonite (red), and dolomite (green).

scientists and first responders. The demand in the forensics field was driven by the need for a portable device to identify narcotics and explosives at crime scenes. First responders later used portable IR systems to identify spills, clandestine lab chemicals, and other hazardous substances requiring environmental cleanup. Though portable Raman systems are rapidly emerging in these markets, Raman spectroscopy is not likely to supplant IR technology because of the unique fundamental properties of each technique. Raman has always been considered complementary to IR; pairing these two technologies provides a “total vibrational” solution by coupling software, hardware, sampling, spectra, and other information from the two technologies to identify unknown materials.

Fundamentally, molecules that produce a dipole moment change when excited by IR frequencies exhibit an IR spectrum. Similarly, some of these molecules may exhibit a change in polarization when excited by radiation to produce a Raman spectrum. Often what is strong in the Raman spectra is weak in the IR and vice versa; further, when there is a center of symmetry in the molecule, no vibrational band will appear simultaneously in the two types of spectra. The ability to measure both types of spectra provides more information about a sample. A stitched spectral combination of IR and Raman spectra can provide much better library matches than either individual spectrum. Large laboratory systems that merge mid-IR and Raman technologies have become available in the past few years.<sup>20</sup>

Recently, portable Raman systems have gained a strong foothold in this market by addressing some of the shortcomings of portable mid-IR instruments. In particular, portable Raman systems have superior sampling qualities compared to mid-IR. Like near-IR, Raman readily samples through glass containers, and the Raman signal is not as sensitive to the presence of water in the sample. However, in terms of spectral structure, a Raman system produces very fine spectral features that are similar to those produced by mid-IR, whereas near-IR bands are broad and have overlapping overtones and combination modes.

One last benefit of commercially-available portable Raman systems over commercially-available portable mid-IR systems is size. Portable Raman systems tend to be smaller (<12 oz) than

portable mid-IR systems (>3 lb). One portable Raman system is palm-sized and can be operated with one hand, as required in hazmat situations.

Applications within the forensics, law enforcement, and hazmat fields for portable Raman include identification of illicit drugs,<sup>3,21–23</sup> explosives,<sup>24,25</sup> chemical and biological warfare agents,<sup>26,27</sup> trace evidence (e.g., paint chips, fibers), and a plethora of unidentified powders and liquids.<sup>28</sup> Civilian and military first responders may encounter thousands of different types of hazardous materials, and portable Raman spectrometers are one of the many sensors available in their arsenal to identify threats.

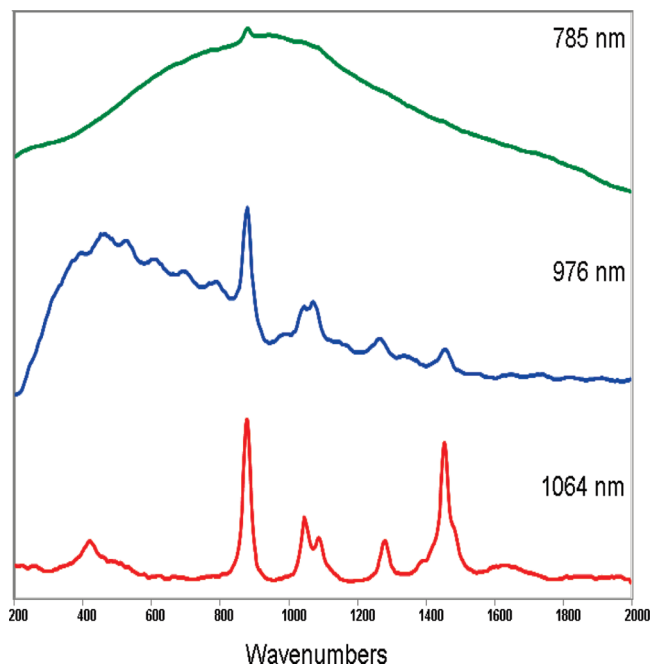
Large spectral libraries, which are required because of the great number of different substances to be identified, and fast search engines are rapidly evolving to meet the demands of these users. Though correlation is the most popular library search algorithm, variations of this have also been used. Coupling the correlation algorithm with other methods for second and third tier searches is becoming more common to distinguish like substances. Further, many unknown substances are comprised of more than one component. Cutting agents used in illicit drug manufacture are typically a blend of common household ingredients, and the portable Raman spectrometer must be able to identify the illicit substance in a mixture without false positive or false negative identification.

In cases where the illicit substance is in low concentration, a residual subtraction algorithm can assist in identifying all of the components in the mixture. When subtracting the unknown component from the top library match, the proper number of factors must be selected in the subtraction process to minimize spectral artifacts and spurious baseline effects. Automated techniques can be used to determine the proper number of factors. A more modern method uses the standard deviation of the residuals to determine this value.<sup>12</sup>

**Life Science and Medical.** Portable Raman systems are also gaining ground in pharmaceutical and medical diagnostic applications. Raman systems have the ability to identify materials that near-IR and mid-IR devices cannot. For example, the superior sampling and size characteristics of portable Raman systems makes them ideal tools to test for counterfeit and adulterated pharmaceutical products.<sup>29</sup>

These markets require stringent compliance and testing documentation before a device is accepted for use in a manufacturing plant or by a consumer. For instance, pharmaceutical manufacturing facilities track product development, production, and release of a drug through process analytical technologies (PAT). Portable Raman devices have to be compatible with various PAT compliance processes that are specified by the manufacturing plant and federal regulators. Communication and authentication protocols are built into the devices to help satisfy regulations.

One application in this industry is compelled by the need for on-site inspection of excipients (e.g., diluents, binders, lubricants, disintegrants, colors, and sweeteners) and active pharmaceutical ingredients. A more recent application is field testing for the active ingredient artesunate in anti-malaria tablets;<sup>30</sup> analysis through blister packs allows identification without compromising the packaging. The small size of commercially available Raman systems allows inspectors to easily transport the instruments long distances and conceal them for use in undercover operations.



**Figure 5.** Comparison of dark rum at excitations of 785, 976, and 1064 nm. The detectors were silicon CCD (at 0 °C), InGaAsP EB-CCD (at 0 °C), and InGaAs Eb-CCD (at –40 °C), respectively.

Application of portable Raman to medical areas such as point-of-care testing or surgical procedures is rapidly growing. An integral part of a point-of-care device is a consumable testing strip or probe that is based on a reporter molecule or a surface enhanced Raman scattering (SERS) substrate. One recent application is in vivo detection of tumors in live animals by targeting SERS tags to the cancerous tissue.<sup>31</sup> A healthy nude mouse received PEGylated SERS nanoparticles administered at two locations: subcutaneous injection (1–2 mm under skin) and deep muscular injection (1 cm under the skin). SERS spectra were obtained in a noncontact and noninvasive manner with a portable Raman system. Investigations and development of inexpensive, compact, and portable Raman instrumentation for the diagnosis of diseases such as cancer,<sup>32</sup> tuberculosis,<sup>33</sup> West Nile virus,<sup>34</sup> and diabetes<sup>35</sup> are growing rapidly.

## WHERE DO WE GO FROM HERE?

In spite of its ideal sampling capabilities, emission due to fluorescent materials or impurities in samples limits Raman spectroscopy. This limitation is being addressed through detectors with high quantum efficiency and low noise characteristics at longer wavelengths. The number of accessible electronic states in a sample decreases with the frequency of light. Detector sensitivity also decreases because of increases in dark noise due to thermal promotion of electrons with a typical Boltzmann distribution.

Highly cooled InGaAs detectors can reduce fluorescence.<sup>36</sup> However, the packaging and power requirements for the extensive cooling system prohibits their use in small portable systems. The amount of thermal noise is proportional to the wavelength range of the detector material's quantum efficiency curve, as well as the area under the curve. InGaAs and InGaAsP provide detection for fluorescence-reduced Raman spectra at excitation wavelengths >1  $\mu\text{m}$ . The smaller area and long wavelength range of the InGaAsP

curve means much lower thermal noise and makes it a potential candidate for a handheld Raman detector. The benefit of longer wavelength excitation is demonstrated in Figure 5. Caramelized sugars create significant fluorescence problems in samples of dark rum. A sample excited at 785 nm barely shows the 870  $\text{cm}^{-1}$  ethanol peak in the rum. Moving out to 976 nm excitation reduces the fluorescence emission. At 1064 nm excitation, all of the background fluorescence is gone, resulting in a clean spectrum of the ethanol in the rum. The stage is now set to move portable instruments to longer wavelengths and transform Raman spectroscopy into a universal detection method for identification of materials.

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