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The Column

the interactive e-publication for the global separation science industry

Cover Story

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Analytical Quality by Design

What benefits can it offer chromatographers?

UBM

Cover Story

Features

Regulars

New Year's Resolution(s)

A new year means a fresh start. Incognito suggests some resolutions to help chromatographers succeed in 2018.

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As I said in 2011 when I wrote the first New Year's Resolution(s) piece (1), please forgive the pun!

In that first piece, I described several of my own resolutions for the coming year, including improving my preparation for meetings and conferences, investigating new stationary phases, using digital literature more effectively, and investigating the use of quality by design approaches to method validation. Some of these were achieved and, like many New Year's resolutions, some fell by the wayside. However, the mere act of starting a new year by drawing up a list of what we might want to improve allows us to reflect on what is good and what is not so good about our science and our working lives in the laboratory. It's an ideal time of year to do this, when the pressures of work are perhaps less onerous and we have the past year as a neat "unit" of time on which to focus our recollections.

Of course, the most difficult part of the reflective process is getting started with ideas on what we might like or need to improve. This time around I'd like to make some suggestions on areas of concern or opportunities for improvement that most often crop up when I'm working with external clients, in the hope that this inspires you to recognize these issues in your own workplace and act as an accelerant for your own resolutions.

One final tip before I get going on the list: Don't restrict your ideas because you believe things cannot be changed or are "above your pay grade"—this will demotivate you. Instead, look to include some changes that are "blue sky" or seemingly unachievable and, if nothing else, the mere act of contemplating these goals may begin the process of making them real.

Know Your Analyte Structure: I've written on this subject previously (2), but there are many folks who undertake analyses much like following a recipe, never knowing the chemical structure of the analytes they are separating. I can see that this is tempting where methods are written in prescriptive SOPs, and instrument acquisition and data analysis methods are pre-programmed into computer data systems. Whilst things are going well this may not be an issue, but if problems with the separation occur, then knowing the chemistry of the analyte is a big advantage. For those of you who develop methods, I would propose that it's not possible to develop good methods without considering the analyte chemistry. Make it your aim in the new year to find out more about the chemistry of your analytes; you will be amazed how quickly your insight

and understanding of chromatography improves.

Know Your Analyte Physicochemical Properties: Properties such as Log P, Log D, p*K*a, boiling point, and vapour pressure can be vital to chromatographic behaviour of analytes. Knowing this data will help you to better understand retention, selectivity, and robustness of methods and will again assist with developing and troubleshooting methods. Undertaking a desktop evaluation of your analytes prior to method development will without doubt lead to a more efficient development process. For those of you working with analytes whose structures are in the public domain, websites such as ChemSpider, Chemicalize, and PubChem are great resources and for those whose analytes are proprietary, there are various commercial programs available for parameter estimation. A great free resource is ChemAxon MarvinSketch, which has a fairly reliable plug-in for p*K*a and LogP estimation (https://www.chemaxon.com/products/marvin) and allows structures to be drawn and properties estimated.

Redevelop an Old Method: If you are using a 15- or 25-cm high performance liquid chromatography (HPLC) column with 5-mm particles, there may be better technology out there to save you time and improve your separations. If you use triethylamine or dibutylamine in your mobile phase, it may be time for a rethink. If you are using packed gas chromatography (GC) columns or if you are regularly undertaking liquid–liquid extractions, then newer technologies may have major benefits in terms of separation speed and quality. Seek advice from your column or instrument vendors to explore how methods may be improved, bearing in mind that changes to regulated methods are restricted and re-validation will be necessary under certain circumstances. Those following pharmacopeial methods may have some scope for change, but advice should be sought on the scope of allowable changes. Even if you consider that your capacity to change methods is limited, assess what is possible and then weigh this up against the time, effort, and cost to change.

Improve Your Knowledge of Stationary Phases: We all have our favourite HPLC and GC phases and manufacturers, but don't restrict yourself to a narrow universe of selectivity. Take some time this year to learn about different types of phase and understand the chemistry of both the bonded phase and the underlying support material. Aim to better understand what drives retention and selectivity and why more esoteric aspects such as deactivation and bonding chemistry might affect the column properties. Many manufacturers produce C18 HPLC columns or 5% phenylmethyl polysiloxane GC columns, but how do they differ? Which is the most "extreme" pentafluorophenyl (PFP) stationary phase? Who has the most inert

GC phase for your application? Which types of application are polar embedded stationary phases most suitable for? These are the types of questions that you need to be asking to push your understanding of stationary phases and improve your ability to make good column choices for method development or understand why your separation is going wrong.

Improve Your Understanding of Instrument Acquisition and Data Analysis Parameters: Print out the whole method from your data system, including the more "esoteric" parameters not usually considered during routine method setup. Whilst some method parameters are less critical than others, this does not mean that they are not important and I often see "drift" in methods, where old methods are used as "templates" for new ones and these "secondary" parameters are not considered. This is a dangerous approach because these variables can be application specific, or at least application sensitive. The more you learn about and understand secondary instrument variables, the more insight you will have when optimizing or fixing your chromatography.

Improve Your Preventative Maintenance Regime: Prevention is always better than cure, yet there are many laboratories where I see even the most basic preventative measures being ignored or undertaken too infrequently. If your work involves any element of preventative maintenance—from monitoring the status of gas filters in GC to calibrating an ultraviolet (UV) detector—make a promise to yourself that you will be as diligent as possible to keep with the programme. If you have regular instrument breakdowns, ask yourself why this might be and if there is anything that can be done to improve the preventative maintenance schedule that you are following. Your instrument manufacturers will be pleased to supply you with a maintenance schedule if you are not sure what is required.

Learn How to Properly Tune Your LC–MS or GC–MS: The auto-tune routines built in to any mass spectrometric (MS) detector are there to achieve a "reasonable" performance from the instrument. However, by learning a little more about how the ion source and mass filters work, then it is possible to tune them to give a more optimized response for the analytes with which you work. Don't be worried that the element of consistency will be lost from work; most instruments offer the ability to save tune "target" files to aim for the optimized output that you have achieved and which can be used by your co-workers. At the very least, in the coming year, strive to understand the various numbers generated by your auto-tune reports and gain a deeper understanding of how your MS detector works.

Improve Your Sample Preparation: I see modern sample preparation as a "race for the bottom". That is, everyone seems to want to do as little sample preparation as possible in the

interests of throughput. I believe in many cases this can be false economy and that with some diligence in this area we can develop methods more easily and will suffer less failed batches of analyses and reduce instrument down time. Simplest is not always best, and if you have the option to employ a more selective sample preparation technique (solid-phase extraction or support assisted liquid–liquid extraction instead of dilute-and-shoot or protein precipitation for example), take some time to contemplate what life might be like with a cleaner and simpler analyte solution when you get to the chromatography step.

Undertake Some Training, But Give of Yourself: Take some personal time (if necessary) to improve your understanding of a technique or piece of instrumentation by carefully selecting some key webcasts and taking time to watch, and, crucially, to understand what is being conveyed. There are many webcasts that deliver a true learning experience and will help you to understand the science and technology behind new or even well-established techniques. Most webcasts are available on demand to suit your workload.

Learn About Newer Technologies: Obviously everyone will have a different list of possibilities for new technology, however, my own list for this year includes:

2D-HPLC—especially for complex mixtures containing analytes with widely varying Log P values;

Ion Mobility Spectrometry—with respect to the separation of analytes where isobaric interferences are an issue;

Atmospheric Ionization Techniques and New Modalities for MS detectors—I'm interested to see what techniques such as desorption electrospray ionization (DESI), resin-embedded multicycle imaging (REMI), and selected ion flow tube (SIFT) technologies can do for our work.

In conclusion to this long list, I'd suggest that if you see an opportunity for personal or work-based improvements, communicate your thoughts upwards and explore with your management team. As the Chinese philosopher Laozi said in the *Tao Te Ching*, "a journey of a thousand miles begins with a single step".

I wish you all a very successful and highly resolved 2018.

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Tackling Chagas Disease With Proteomics and LC–MS/MS

Researchers have developed a proteomics-based approach, using liquid chromatography tandem mass spectrometry (LC–MS/MS), to identify the food sources of the Chagas disease vector Triatominae insects (1).

Vector-borne diseases have complex transmission dynamics and fully understanding these are critical for the creation of evidence-based vector control programmes. In the case of Chagas disease—a parasitic disease endemic in many parts of Latin America—its transmission dynamics focus largely around the 140~ species across the Americas capable of acting as a vector. Occurring primarily in communities with limited resources and traditional houses made of natural materials, Chagas disease claims the lives of an estimated 12,500 people annually, with 8–10 million infected and over 60 million at risk of infection (2–4). It can take up to 20 years to develop diagnosable symptoms once infected with one-third of the infected developing life-threatening illnesses.

Unfortunately, despite large numbers at risk, treatment options for the disease are currently limited because there is no effective vaccine, and the drugs that are available are accompanied by considerable side effects. This places prevention at the heart of any strategy to reduce the disease's prevalence, and an effective prevention strategy relies heavily on vector control. However, to effectively reduce the bug vectors of this parasite, the transmission dynamics must be well understood, including the blood meal sources they feed on. A complete understanding of this can be challenging for many reasons, and the techniques currently employed for studies can be stretched. DNA sequencing is regularly used, however, the technique works best with high-quality DNA, which is not always available, and although amplification steps can alleviate this strain, it can also lead to false positives from contaminating DNA not derived from the blood meal itself.

To address these issues researchers turned to LC–MS/MS and the identification of the highly stable haemoglobin proteins, which are some of the most abundant proteins in any blood meal. The high precision of the technique can accurately identify haemoglobin peptide sequences, many of which are unique to specific vertebrate classes, orders, families, genera, and even species (1). Furthermore, the technique does not rely on the creation of spectral libraries, instead using publically available DNA and protein sequences.

The results of the study indicated that the approach could be used as a valuable tool when attempting to understanding the sources of blood meals in vector control strategies. The method provided data on the species the blood meal derived from effectively and demonstrated proof-of principle. "We were happily surprised at how well the technique works," said Lori Stevens, University of Vermont, USA. "We are currently working on a second paper reporting some of those details," continued Stevens. The researchers highlighted the upfront costs of LC–MS/MS platforms as a potential stumbling block for this technique's widespread use, but running a sample is relatively inexpensive following the initial purchase. Despite this, the sensitivity of LC–MS/MS reinforces its position as a valuable methodology when identifying the source of triatomine insect vector blood meals. — L.B.

For more information on Chagas Disease, please visit: www.chagasecohealth.com

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Biotage Acquires Horizon Technology

Biotage AB (Uppsala, Sweden) has agreed a deal to purchase all outstanding shares in Horizon Technology Inc. for $18.4 million.

Based in New Hampshire, USA, Horizon Technology is a provider of separation systems and consumables in areas such as water purification, food safety, biofuels, agriculture, pharmaceuticals, and the petrochemical industry. The purchase of Horizon Technology will strengthen Biotage's position within environmental applications and food safety and allow Biotage to offer a more comprehensive portfolio of products.

"The acquisition of Horizon is in line with our strategy to grow our separation business through expansion into new application areas," said Torben Jörgensen, CEO of Biotage. "This transaction enables Horizon's existing products to reach a larger global market through Biotage's direct sales channels, at the same time as Biotage's existing products get access to customers in industries where Biotage historically has not been as active."

"We are excited to partner with Biotage for the next phase of Horizon's development," said Robert S. Johnson, co-founder and CEO of Horizon. "This combination will allow Horizon's product offering to continue to expand its global footprint and open up new opportunities for developing and bringing our innovative products to the market," he continued.

For more information, please visit: **ww.biotage.com**

Combatting Antimicrobial Resistance Through VOC Analysis of RTIs

Researchers from the Liverpool School of Tropical Medicine and the University of Warwick have conducted a pilot study to assess the viability of a gas-capillary column ion mobility spectrometer (GC–IMS) for the analysis of volatile organic compounds (VOCs) in exhaled breath for the diagnosis of bacterial respiratory tract infections (RTIs) in hospital patients (1).

Antimicrobial resistance represents one of the greatest challenges of the coming decades as mass overprescription of antibiotics raises the possibility of a post-antibiotic health care era. This situation has been compounded by a tendency to prescribe antibiotics for viral infections, such as with respiratory tract infections, a very common form of infection especially within health institutions and hospitals. One study in America estimated that of the 40 million antibiotics prescribed for respiratory tract infections, around 23 million were unnecessary because the infection was in fact viral (2). However, because respiratory tract infections remain one of the leading causes of mortality and morbidity, worldwide antibiotics will continue to be used in cases of suspected RTIs as a safeguard by concerned health professionals without accurate data. There is therefore a need for accurate and rapid diagnosis of RTI infections that can be performed at the bedside during primary care.

Research into the viability of VOCs as a diagnostic marker has been demonstrated in a number of studies across various diseases, including cancers [3¬–5],inflammatory bowel disease (6), cystic fibrosis (7), and for the diagnosis of ventilator-associated pneumonia (VAP) (8), among many others. However, no research had been conducted on their viability as an RTI diagnostic marker with the capability of differentiating bacterial from viral RTIs.

Researchers used a gas-capillary column ion mobility spectrometer (GC–IMS) on patients diagnosed with an RTI at the Royal Liverpool University Hospital, Liverpool, UK.

Results demonstrated the feasibility of VOC analysis as a diagnostic tool, however, there were a number of limitations with the study because of its exploratory nature and small sample size. The researchers responsible for the study indicated they are currently putting together a larger scale study.

"We are looking to recruit around 2200 patients into the study from six centres across the UK. [In] both primary and secondary care settings," said James Covington, University of Warwick. Results from the study are tentatively expected in 2019, while the full commercialization of a dedicated product is still far away. "The unit we are using is commercially available already," explained Covington. "However, it is likely that a dedicated unit would be developed for this purpose at a lower cost point. But it is hard to say exactly when this would reach the market." — L.B.

For more information on the study and product, please visit: www.breathspec.com

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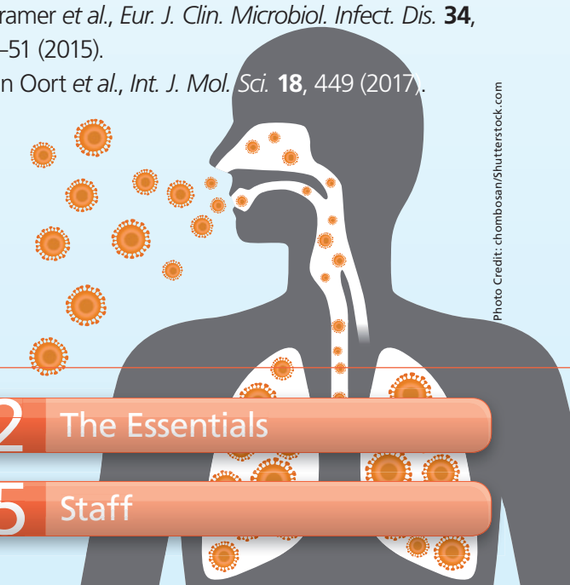

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LCGC TV Highlights

***LCGC* TV: Peter Schoenmakers on a Microfluidic Device for 3D LC Samples**
Peter Schoenmakers from the University of Amsterdam talks through his group's designs for a microfluidic device for 3D LC and the challenges that had to be overcome.
Watch Here>>

***LCGC* TV: Paola Dugo on 2D LC: Continuous-Flow vs Stop-Flow Mode**
Paola Dugo from the University of Messina discusses when online comprehensive 2D LC should be operated in either continuous-flow or stop-flow mode.
Watch Here>>

Peaks of the Week

The *LCGC* Blog: Ditch Your Mundane HPLC Methods and Supercharge Your Chromatography—It's very easy to be comfortable with what you have. It's only when we realize what could be, that we become interested in changing things. **Read Here>>**

GC: The State of the Art—In this extended special feature to celebrate the 30th anniversary edition of *LCGC Europe*, leading figures from the separation science community explore contemporary trends in separation science and identify possible future developments. We asked key opinion leaders in the field to discuss the current state of the art in gas chromatography, **Read Here>>**

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The Role of Mass Spectrometry in Biopharmaceutical Drug Discovery and Development—The discovery and development of biopharmaceuticals that target specific diseases can be transformative for people living with illness. However, bringing a new therapy to market is a prolonged and costly process mired in uncertainty. **Read Here>>**

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News In Brief

Concept Life Sciences has invested a further £250,000 in new equipment at its East Kilbride site on the outskirts of Glasgow, UK, doubling the facilities capacity across many areas, including gas chromatography and mass spectrometry. This follows an initial £250,000 sum invested in the facility in 2016, which expanded the analytical instrumentation available at the site.
www.conceptlifesciences.com

Research published in the *Journal of the American Oil Chemist's Society* has detailed the phospholipid (PLs) profiles of oleaginous pressed cakes from different sources using NMR and gas chromatography. The by-product of the oil removal process, pressed cakes have a wide variety of uses across many industries and understanding PL diversities could allow a wider range of PL sources to be utilized.
DOI: 10.1007/s11746-017-3022-y

Researchers from the University of Córdoba and the University of Valencia, Spain, have developed a novel method of extracting nonsteroidal anti-inflammatory drugs (NSAIDs) from human urine samples using a copolymer prepared from glycidyl methacrylate, ethylene glycol dimethacrylate, and oxidized single-walled carbon nanohorns via photo-polymerization and centrifugation. Their research has been published in the journal *Microchimica Acta*.
DOI: 10.1007/s00604-017-2203-6

The Benefits of AQbD

The benefits of an analytical quality by design (AQbD) approach to method development cannot be underestimated. *The Column* spoke to Changqin Hu and Xia Zhang from the National Institutes for Food Drug Control, in Beijing, China, about their work developing a dual-gradient elution stability-indicating method for cloxacillin within an AQbD framework.

—Interview by Kate Mosford

Q. Your group published a study on the development of a dual-gradient elution stability-indicating method for cloxacillin within an AQbD framework (1). What led your group to begin this study?

A: Cloxacillin represents a large number of drugs that are easily degraded and can produce many degradation-related impurities (DRIs) with variable polarities. It is often a challenge to develop selective and robust high performance liquid chromatography (HPLC) methods for these drugs to separate all DRIs effectively. Thus, the development of a stability-indicating method for impurity determination requires an in-depth understanding of the method. In this context, the concept of analytical quality by design (AQbD) is thought of as a tool for regulatory flexibility and robust analytics, and so it was applied to develop the stability-indicating method for cloxacillin.

Q. What benefits does this approach offer to chromatographers?

A: An AQbD approach provides the ability to assess robustness throughout the development process and to perform quality risk management when the method is transferred or the experiment variables are changed. It ensures a controlled risk-based development of the methods where quality assurance will be guaranteed and represents an advantageous alternative approach to the traditional quality by testing (QbT) approach or a one-factor-at-a-time (OFAT) process.

Q. Are there any misconceptions surrounding the role of AQbD in relation to chromatography?

A: We want to emphasize the importance of gathering prior knowledge and analyzing the results of preliminary experiments because they can provide significant information for the following steps. Some beginners often perform design of experiments (DoE) at the beginning, and they often get unsatisfactory results after the time-consuming implementation of the experiment runs. Such failures are often caused by a lack of prior knowledge and preliminary experiments.

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Q. What advice can you offer to other scientists thinking of implementing AQbD in their research?

A: When we apply the AQbD approach to develop a chromatographic method, it is very important to implement the experiments step by step. The AQbD workflow begins with an understanding of the analytical samples, followed by selection of the initial chromatographic parameters, definition of the analytical target profile (ATP) and critical quality attributes (CQAs), risk assessments, screening of the experimental risk factors, and optimization of the experiment parameters. The end result is a robust analytical method with a well understood design space (DS) and method control strategy. Analysts should not copy another's workflow completely, and they must understand the objective of each step to decide whether this step is needed in their experiment. If one step is omitted, analysts should be able to justify it.

Q. Were there any particular challenges that you faced during this research?

A: Yes. After the mix-process design was performed, no design spaces were obtained in which all the selected CQAs were satisfied. We were frustrated at first, but after an attentive analysis, we found that the CQAs could be classified into two groups according to their retention time: one included the separation factors for early eluted peaks B1/2, B2/3, and B3/A0, and the other included the later eluted peaks A3/1, A1/2, A2/M1, M1/M, and M1/2. Each group of CQAs could be satisfied in two different optimum regions. For peak pairs in Group 1, the optimum region was located in the region (a) where pH was close to 5.0 and the mixture composition covered a relatively wide range; for Group 2, it was located in the region (b) where both the acetonitrile content and pH were higher. This was also validated by performing two different chromatographic conditions in the region (a) and (b). This led us to use the dual gradient elution, which allowed the two optimum regions to be satisfied in the same chromatographic method by changing acetonitrile content and pH simultaneously. The dual gradient elution is therefore the key to building the design space for a cloxacillin stability-indicating method.

Q. Could this workflow be applied to other stability-indicating methods?

A: The AQbD approach and dual gradient elution method can be very powerful tools when developing HPLC methods for complex ionic samples. The AQbD workflow described in our paper could be advantageously applied to the development and improvement of any stability-indicating method. Based on our study, the following points are important when developing a stability-indicating HPLC

method for other easily degraded drugs, such as penicillins:

- Gradient elution is more suitable to ensure the best retention of all penicillin DRIs than isocratic elution because both highly polar and nonpolar impurities are produced.
- For ion samples, such as penicillins DRIs, the most effective ways to vary separation selectivity are adjusting the pH or solvent type.

Q. What is your group working on at the moment?

A: We are applying the AQbD approach to the development of determination methods for other kinds of penicillins and cephalosporins to try to find the common rules for the satisfactory HPLC methods of these drugs whose structures and impurities are similar. We want to summarize a general workflow for the method development of penicillins and cephalosporins so that the suitable HPLC conditions for other similar penicillins and cephalosporins can be found quickly according to these common rules.

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Changqin Hu is a full professor at the National Institutes for Food and Drug Control (NIFDC) in Beijing, China. Prof. Hu is in charge of more than 20 projects and his research interests lie in the development of a drug impurity profiling analytical platform, drug crystal forms analysis, the development and application of fast detection technologies in drugs, and the microbiological analysis of drugs. Prof. Hu has authored or coauthored more than 200 peer-reviewed papers and more than 10 books.

Xia Zhang received her Ph.D. as a joint training student of NIFDC and Peking Union Medical College in 2017. Her research work includes the selection of HPLC columns, the development of chromatographic methods, and theoretical calculations.

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Five Things You May Not Know About GC

Five top tips for improving your gas chromatography (GC) methods.

These five tips for gas chromatography (GC) could improve your methods.

Hydrogen Is the Best Carrier Gas

Hydrogen can provide increased analysis speed by increasing carrier gas linear velocity without losing too much efficiency, allowing for shorter run times and thereby increasing throughput. Lower temperature separations are another benefit; at faster elution times, it may not be necessary to increase the column temperature ramp rate. It may even be possible to lower the maximum temperature needed for the analysis, which will reduce the reequilibration time too. The use of lower temperatures leads to less column bleed, which in turn can mean a longer column life. Hydrogen is readily available through the electrolysis of water and, with gas generators, it can be generated safely on demand. Hydrogen gas is already used in the laboratory for a variety of purposes; it is the fuel gas for the most commonly used GC detector, the flame ionization detector.

GC–MS Columns for GC Methods

Analytical sensitivity and detection limits are ultimately a function of the signal-to-noise ratio (S/N). A decrease in noise increases sensitivity. All GC columns bleed, although polar phases and thicker films are more prone to bleed. This normal degradation of the stationary phase polymer results in increased baseline noise. Degradation is accelerated when excess oxygen is present and at higher temperatures; hence the elevated baseline that is seen as the temperature rises to the column's upper limit. Columns designated for gas chromatography–mass spectrometry (GC–MS) have been designed to exhibit reduced bleed and high inertness at elevated temperatures, which ultimately increases S/N. Many detectors are sensitive to contamination from bleed products and require less maintenance when using low-bleed columns. For GC–MS applications, low-bleed stationary phases reduce column contribution to background noise, resulting in improved mass spectral purity and more-accurate library identification.

Advantages of Highly Inert Columns

Manufacturers have developed new ways of deactivating GC columns in recent years, which provides improved sensitivity because they exhibit low bleed and low silanol activity. Decreased silanol activity is particularly pertinent when analyzing bases or polar compounds, or for certain specialist applications, such as pesticide, food, environmental, or drug analyses, all of which require ever decreasing detection limits. Active

silanol species in the column can interact with bases or polar compounds and cause peak tailing that impacts sensitivity (via reduced peak heights relative to baseline noise) and makes integration (and hence quantitation) more challenging and less reproducible. The benefit of highly deactivated columns can only be fully realized in conjunction with a system that has an inert flow path (that is, inlet liner and packing, column, ion source, and so forth). Any advantages from low silanol activity in only the column will be mitigated if peak tailing occurs in the inlet. Most manufacturers provide highly inert consumables, including liners and packing, as well as deactivated inlets.

A Little Bit of Split

Splitless injection is used for low-concentration samples to provide optimum sensitivity. Sample vapour transfer from the inlet is much slower compared with split injection, resulting in band broadening; therefore, sample vapours must be trapped at the head of the column by using a low initial oven temperature. If some sensitivity can be sacrificed, it may be better to use a little bit of split, for the following reasons:

- Better peak shape: the liner is cleared more quickly, which introduces the analytes onto the column in a narrower band.
- No need for cryo-cooling: the analytes are being introduced in a narrower band; hence, the oven temperature does not need to be lowered to allow for focusing at the head of the column.
- Shorter run times: analyses can be started at higher initial oven temperatures, which decreases run and oven reequilibration times.
- Use of isothermal methods: with no need for low initial oven temperatures, isothermal methods that start at higher temperatures can be used. These methods are particularly good for samples that contain higher boiling point components.

A split of 1:10 is good for balancing sensitivity with the benefits of split injection.

The Wonder of Gas-Saver Mode

Gas-saver mode can be used during split injection to change the split ratio at a specified time after sample injection, which reduces carrier gas consumption. For example, if the split flow rate is reduced from 150 mL/min to 25 mL/min 1 min after sample injection (ensure all the sample and solvent vapours have been transferred to column prior to using the gas saver), the reduced split flow rate can be maintained throughout the analytical run until the next analysis. Under these conditions, that is a 79% gas saving per analysis: analysis time: 20 min; split ratio: 100:1; gas saver mode: split ratio 15 after 1 min; column temperature: 100 °C; column: 30 m × 0.25 mm, 0.25-µm.

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Sampling Volatiles From Fragranced Consumer Products Using High-Capacity Sorptive Extraction

Lara Kelly and David Barden, Markes International, Llantrisant, UK

This study describes the analysis of fragranced washing detergent and washing powder using probe-based headspace and immersive sorptive extraction, in conjunction with analysis by thermal desorption–gas chromatography–mass spectrometry (TD–GC–MS). As well as discussing the differences between the two samples, the analyte ranges covered by headspace and immersive sampling are compared.

The success of many personal care and household cleaning products has long depended on the precise mix of aroma-active compounds that they release. For example, manufacturers are continuously developing new formulations that offer different (or longer-lasting) fragrances, while consumers loyal to a well-established brand can notice even the slightest variation in fragrance quality. In addition, there has been increasing concern over the presence of potentially harmful compounds—such as allergens—in fragrance formulations. These factors have led to an ongoing need to monitor the volatile and semivolatile organic compounds (VOCs and SVOCs) released by fragranced consumer products.

Sampling and analyzing VOCs and SVOCs from a wide range of products and materials has long been performed using gas chromatography (GC), enhanced by preconcentration using thermal desorption (TD). TD provides a versatile

and high-sensitivity alternative to traditional sample preparation methods for GC, such as solvent extraction, solid-phase micro-extraction (SPME), or static headspace, and involves minimal manual sample handling while being applicable to the widest possible range of GC-compatible analytes. In the field of consumer products, TD has generally been associated with sampling vapours released from solid samples, but recent developments in sorptive extraction have extended the applicability of TD preconcentration technology to aqueous samples (1).

This study aims to demonstrate the use of headspace and immersive sorptive extraction probes for the analysis of VOCs and SVOCs in a liquid washing detergent and washing powder solution.

Experimental

Samples: Two fragranced household products were analyzed: (1) liquid washing detergent; (2) washing powder solution (prepared by dissolving 1 g of powder in 18.5 mL water).

Headspace Sorptive Extraction: Sample: 10 mL sample in 20 mL headspace vial, sealed with a HiSorb septum seal and cap. Sampler: Short-length, inert HiSorb-P1 probe (Markes International part no. H1-AXABC-5). TD tube: Empty (Markes International part no. C0-AXXX-0000). Sample incubation: HiSorb Agitator (Markes International). Sampling temp.: 40 °C. Agitation speed: 300 rpm. Sampling time: 90 min.

Immersive Sorptive Extraction: Sample: 18.5 mL sample in 20 mL headspace vial, sealed with a HiSorb septum seal and cap. Sampler: Standard-length, inert HiSorb-P1 probe (Markes International part no. H1-AXAAC-5).

Figure 1: Sampling setup for headspace sorptive extraction. For immersive sorptive extraction, the liquid level is raised to above the level of the PDMS.

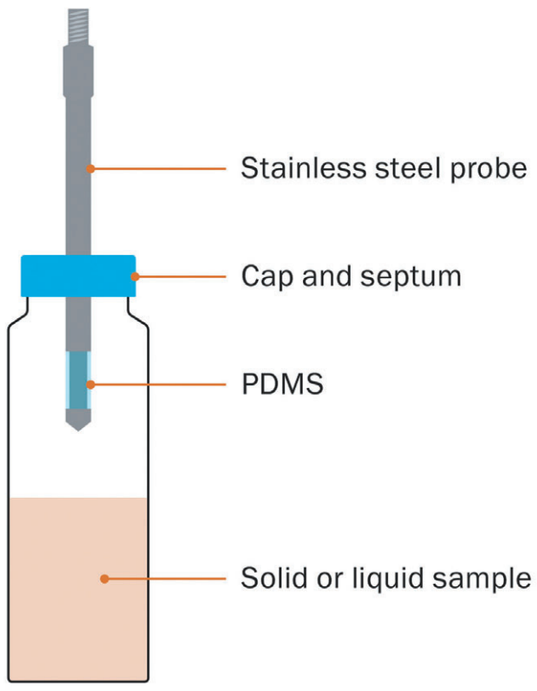


Table 1: Major analytes identified in the washing detergent and washing powder by a search against a 407-component library of fragrance compounds

No.	Compound	Washing Detergent		Washing Powder	
		Headspace	Immersive	Headspace	Immersive
1	1,4-Dioxane	—	1.97E+07	—	—
2	n-Butyl acetate	3.41E+07	1.13E+07	—	—
3	Ethyl 2-methylbutanoate	2.60E+07	6.95E+06	—	—
4	Hexan-1-ol	—	—	1.21E+07	1.20E+07
5	Citronellene	4.29E+08	—	—	—
6	n-Hexyl acetate	2.19E+08	1.28E+08	2.72E+07	3.20E+06
7	Limonene	4.03E+07	7.02E+06	9.79E+06	—
8	p-Methylanisole	4.60E+07	2.46E+07	—	—
9	Eucalyptol	—	—	8.60E+06	2.26E+06
10	Dihydromyrcenol	2.96E+08	3.59E+08	1.24E+05	4.98E+07
11	Tetrahydrolinalool	—	—	3.16E+05	3.94E+07
12	Linalool	7.81E+07	7.72E+07	1.20E+06	7.72E+07
13	Phenylethyl alcohol	—	—	1.15E+06	4.06E+07
14	Gardeniol	3.56E+07	1.12E+08	—	—
15	β-Citronellol	1.49E+07	7.48E+07	1.88E+06	2.05E+07
16	Citronellyl nitrile	—	—	—	1.64E+06
17	β-Phenylethyl acetate	3.59E+07	1.13E+08	—	—
18	Undecan-2-one	3.15E+07	5.86E+07	—	—
19	4-*tert*-Butylcyclohexyl acetate	5.37E+06	7.33E+06	—	—
20	Anisaldehyde	—	—	1.04E+06	5.16E+07
21	n-Tetradecane	4.94E+07	1.42E+08	—	—
22	2-Methylundecanal	2.35E+07	2.82E+07	—	—
23	Methyl cinnamate	—	—	—	1.46E+07
24	Diphenyl ether	2.85E+07	8.54E+07	—	—
25	Tricyclodec-5-enyl acetate	—	—	1.63E+07	2.01E+06
26	Indan-1,3-diol monopropanoate	—	—	2.46E+07	3.96E+07
27	Amyl salicylate	1.51E+07	1.82E+08	—	—
28	Methyl dihydrojasmonate	—	—	—	4.87E+07
29	n-Hexyl salicylate	2.86E+07	4.49E+08	—	1.27E+07
30	β-Methylionone	—	1.67E+08	—	—
31	Pentadecan-1-ol	—	1.03E+08	—	—
32	n-Hexyl cinnamaldehyde	—	—	—	1.21E+07

Other conditions as for headspace sorptive extraction.

TD: Instrument: TD100-xr (Markes International). Cold trap: Tenax TA (Markes International part no. U-T9TNX-2S). Desorption time: 10 min. Desorption temp.: 280 °C. Trap low temp.: 25 °C. Heating rate: Max. Trap high temp.: 290 °C. Trap hold time: 1.5 min. Outlet split: 100 mL/min. Split ratio: 51:1. Flow path temp.: 180 °C.

GC: Column: 60 m × 0.32 mm, 1.8-µm VF-624ms (Agilent Corporation). Oven: 40 °C (3 min), then 6 °C/min to 230 °C (15 min). Inlet: 180 °C. Carrier gas: Helium, 2.0 mL/min. Septum purge: 3.0 mL/min. MS transfer line: 240 °C.

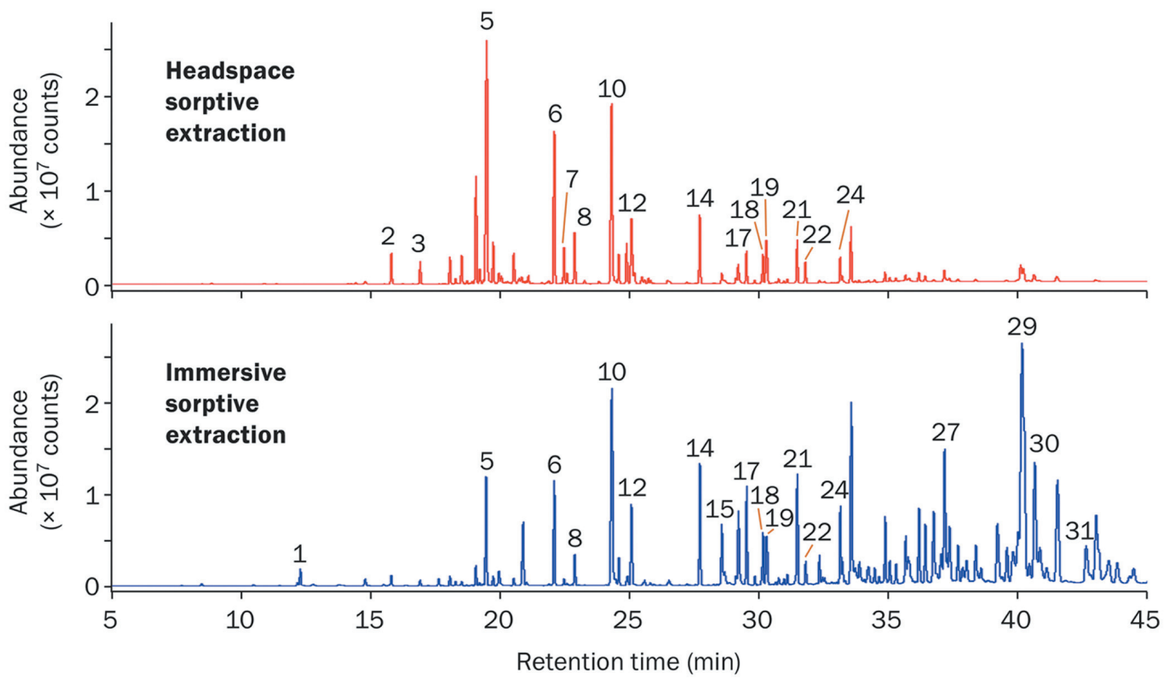
MS: Ion source: 230 °C. Quadrupole: 150 °C. Mass range: *m/z* 35–450.

Data Analysis: TargetView GC–MS software (Markes International) was used to selectively remove unwanted background noise from the chromatograms, carry out automated comparison against a 407-component fragrance-compound target library, and generate peak-area information.

Results and Discussion

Sampler Design and Operation: The high-capacity sorptive extraction probes used in this study consist of a short section of poly(dimethylsiloxane) (PDMS) located at the end of a stainless-steel probe, which is either immersed in the sample or suspended above it (Figure 1). Agitation and gentle heating is then sufficient to ensure that analytes are effectively absorbed into the sorbent volume in a reasonable time frame. A key consideration is the relatively large sorbent volume (65 µL compared to 0.5 µL for SPME), which, combined with GC preconcentration by TD, results in higher sample loadings and therefore greater sensitivity across a wide analyte range.

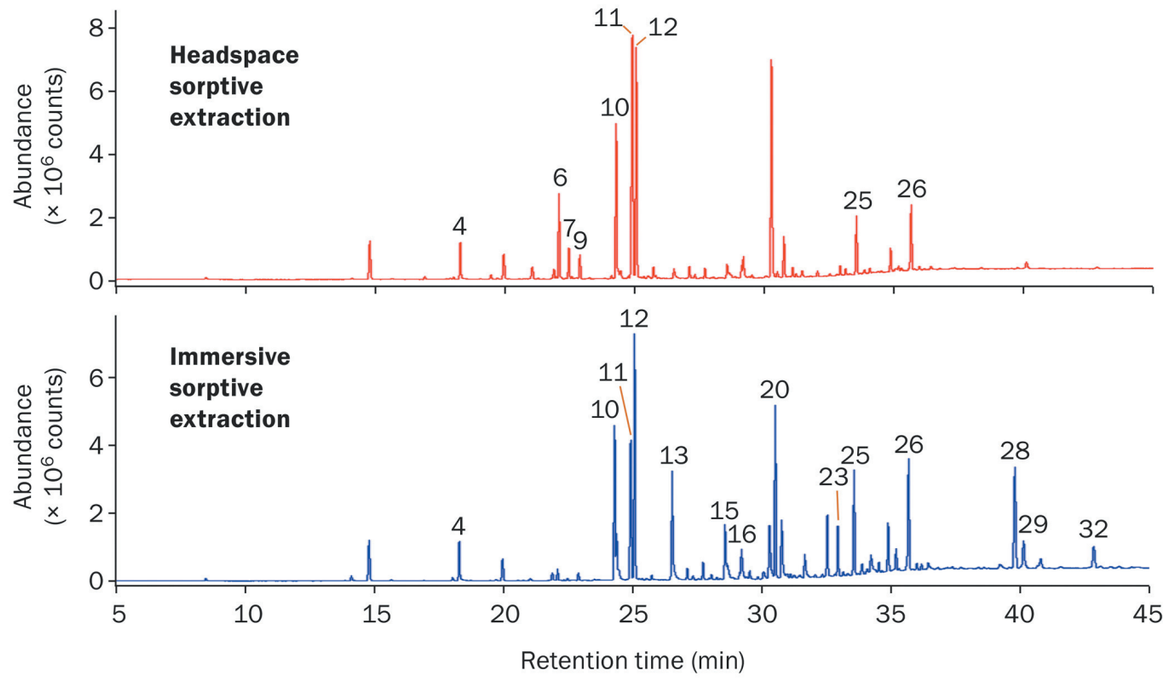
Figure 2: TD–GC–MS analysis of washing detergent using headspace and immersive sorptive extraction. Major peaks are labelled (see Table 1).



Comparison of Overall Fragrance Profiles: The fragrance profiles of the washing detergent and washing powder (using both sampling techniques) are shown in Figures 2 and 3, respectively, with major components being labelled and listed in Table 1. It is reasonable to expect that the washing detergent would be more heavily fragranced than the washing powder, and indeed this is apparent from the chromatogram, which shows a more complex profile. However, only n-hexyl acetate (#6), dihydromyrcenol (#10), linalool (#12), and β-citronellol (#15) are present at substantial levels in both samples.

Comparison of Immersive Sorptive Extraction with Headspace Sorptive Extraction: For both samples, although there remains a considerable degree of overlap in analyte range between the

Figure 3: TD–GC–MS analysis of washing powder solution using headspace and immersive sorptive extraction. Major peaks are labelled (see Table 1).



headspace and immersive approaches, it is clear that the immersive approach is better at sampling the less volatile compounds. As a result, many of the later eluting compounds identified using immersive sorptive extraction are not fragrance compounds—but they are nevertheless important constituents of the formulation that may have an effect on the overall product quality. Immersive sorptive extraction therefore provides a useful complement to the headspace techniques by allowing a more comprehensive understanding of the compounds present to be obtained. For example, it is interesting that although amyl salicylate (#27) is presumably added to the washing detergent formulation in substantial quantity (because of its significant presence in the immersive profile), it is nearly absent from the headspace profile.

Conclusions

In this study, we have shown that high-capacity sorptive extraction can be used in conjunction with TD–GC–MS analysis to provide valuable information on the volatile profiles of fragranced consumer products.

A key benefit of this approach is versatility, with the same approach being compatible with both headspace and immersive sampling of liquids or solids. The immersive approach, while sampling the vast majority of analytes found in the headspace, preferentially samples the less volatile compounds, therefore delivering a more comprehensive profile including compounds that would not typically contribute to the fragrance. As well as being robust and easy to handle, the probes avoid the interference effect that can occur with SPME when liquid rising up into the SPME fibre casing remains there during the next sampling run, which can result in poor reproducibility.

These factors make this approach highly suitable for analyzing a range of sample types—not just fragranced consumer products, but also foods, beverages, and biological samples. Potential applications include routine quality control, product comparison, troubleshooting customer complaints, product development, and advanced research—a diverse range of uses that reflects the versatility of this technology.

Reference

1. For examples, see Markes International Application Notes 120 (milk), 122 (filter coffee), 123 (herbal infusions), 124 (alcoholic spirits), and 125 (premium teas), available at http://chem.markes.com/l/129721/2016-10-31/24vx7m

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The *LCGC* Blog: Potential for Use of Stable Isotope–Labelled Internal Standards in Gas Chromatography–Vacuum Ultraviolet Spectroscopy Methods

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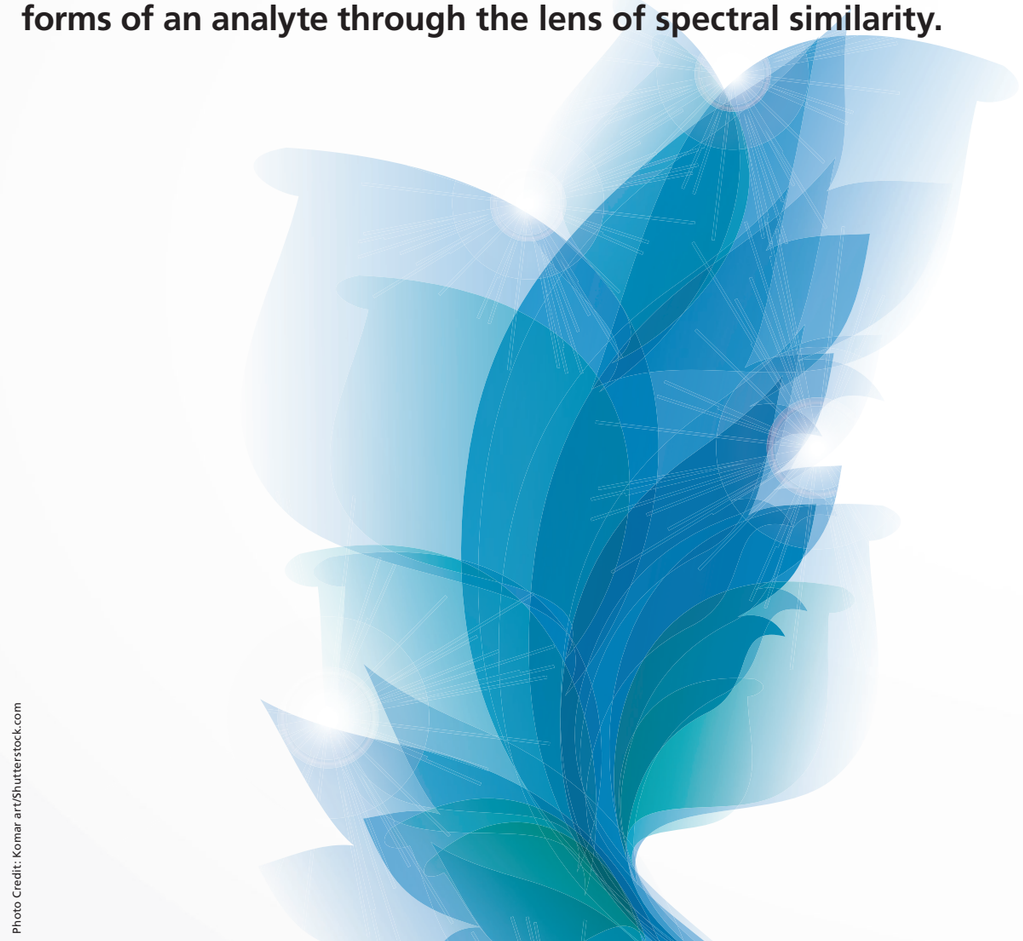
Evaluating the ability of gas chromatography–vacuum ultraviolet detection (GC–VUV) to distinguish and correctly identify various isomer and isotopologue forms of an analyte through the lens of spectral similarity.



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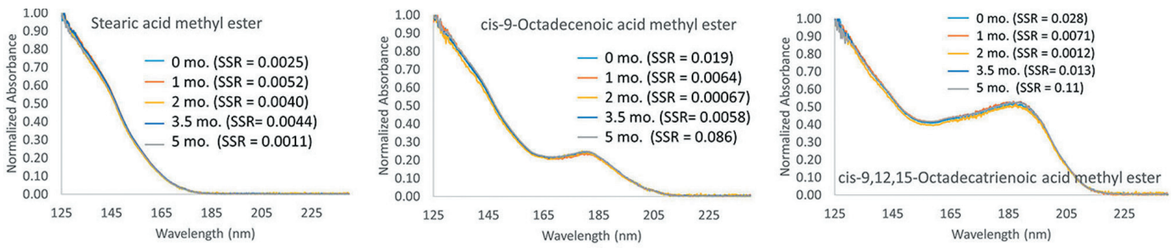
Internal standards (IS) are commonly incorporated into quantitative methods to increase accuracy and precision. An IS is a compound that is different than the analyte of interest, has similar physicochemical properties to the analyte, and is added to samples, calibration standards, and quality control samples in a known quantity. It should not be present in the sample, it should be available in high purity, and it should be easily differentiable from the analyte of interest.

As samples and standards are analyzed, the response of the analyte is normalized by the response of the known amount of IS. The IS is ideally subjected to the same discrimination processes throughout the method as the analyte; thus, by normalization, systematic errors are reduced. An IS should be chosen to properly ensure that all potential discrimination processes can be corrected. Random error is also generally reduced using an internal standard calibration method.

In mass spectrometry (MS)-based quantitative methods, the ideal IS a stable isotope–labelled version of the analyte. This is an analyte form where some or all of its stable (non-dissociable) hydrogens are switched to deuterium atoms, carbon-12 atoms are switched for carbon-13 atoms, or nitrogen-14 atoms are switched for nitrogen-15 atoms. With each one of these switches, a new compound is formed that has an incrementally higher molecular weight, but virtually the same physicochemical properties of the analyte. A stable isotope–labelled internal standard (SIL-IS), which is added to the sample before processing, will track together through the entire sample preparation and analysis process with the analyte, and then be

Figure 1: Demonstration of the reproducibility of three fatty acids over a period of five months. SSR values are relative to the recorded library spectrum for each analyte.



differentially detected by the mass difference, evinced by MS.

Many gas chromatography–mass spectrometry (GC–MS) methods feature SIL-ISs. In our research using the vacuum ultraviolet detector for gas chromatography (GC–VUV) (1,2), it has been an unanswered question whether the use of SIL-IS methodology would be a viable thing to consider. Although GC–VUV can distinguish positional isomers (dimethylnaphthalenes) (3), constitutional isomers (designer drugs) (4), and stereoisomers (mono-, di-, and trisaccharides) (5) to a significant degree, it was unclear whether the addition of neutrons into atoms would affect significant changes to the electronic absorption spectra for the heavy forms of the molecules, relative to the natural form. We decided it was time to answer that question (6).

Before I discuss that research, I think it is important to address a couple of points. First, to largely evaluate the ability to distinguish two chemical compounds based on their gas-phase absorption profile in the 125–240 nm wavelength range, we can calculate a sum of squared residuals (SSR) value for any pair of spectra we are interested in comparing. The larger the SSR between them, the easier they are to distinguish from one another—the more dissimilar are the spectra.

If a pair of compounds with a high SSR between them (for example, SSR > 100) were coeluted chromatographically, then their individual contributions to the summed signal observed could still be easily determined (a process we call *deconvolution*), even if they were present at as much as three or more

orders of magnitude difference in relative abundance (assuming similar absortivities and that the minor component was still above the detection limit). If two compounds were coeluted that have an SSR ~ 10 between them, then they could likely still be reliably deconvolved at a relative abundance of around 100:1. As spectral similarity increases (that is, SSR decreases), it becomes less possible to deconvolve two overlapping signals having different relative abundances. An SSR = 1 might accommodate a 10:1 difference. With an SSR < 0.1 it might be still possible to deconvolve two compounds overlapping in a 1:1 relative abundance, but not much more than that; additionally, at that level, if the spectra for two compounds are that similar, then a library search initiated from an experimental spectrum of one or the other compounds would certainly also return a high match.

To draw the lines here, remember that to use a SIL-IS, we need to incorporate it into all samples and standards at a single known amount. If the SSR value = 1 between the spectra of the analyte and its SIL-IS form, then the widest range of calibration you might expect to accommodate in your method is just two orders of magnitude (that is, if we prepare the samples so that the SIL-IS amount is in the middle of the calibration range, then we can expect to detect one order higher and lower from this with the analyte concentration).

Another important thing to keep in mind is that the VUV spectra are highly reproducible. This attribute is extremely important for library searching. If a high-quality library spectrum has been recorded into the library, and then another high-quality spectrum is generated experimentally and compared to the library spectrum, SSR values below 0.01 can be routinely observed. Since many of the isomer pairs we have tested exhibited SSR values above this level, the correct library match would be selected most of the time. However, if a noisy experimental spectrum was generated (for example, from a low-abundance compound), some ambiguity might be present in the library search results. But, even in that case, the search results will still more often than not indicate the correct class of compounds.

Figure 1 provides some additional data regarding reproducibility of normalized spectra for a series of fatty acid methyl ester compounds. The figure shows the normalized spectra recorded for three different compounds over a period of approximately five months, as well as the SSR values relative to the recorded library spectrum for each compound. In this case, some of these library spectra were recorded more than two or three years ago. Thus, we can see that gas-phase electronic absorption spectra are highly reproducible—peak maxima do not shift and ratios of absorptivities at different wavelengths remain fixed and constant.

It is only because of this reproducibility, stability, and resolution that we can even consider that it might be possible to distinguish the absorption spectrum for the natural form of an analyte from its deuterated counterpart.

We systematically evaluated the spectral similarity between different labelled and unlabelled analytes (6). For benzene, we evaluated both spectral similarity and absolute absorptivity, but we focus here only on the former (pair-wise SSR values), and what it potentially means for creating a SIL-IS–based quantitation method using GC–VUV.

We found that as you add deuterium atoms sequentially to benzene, a linear increase in SSR value (from 0.4 for benzene/benzene-d_1 to 1.7 for benzene/benzene-d_6). Interestingly, the spectrum for an all-carbon-13 form of benzene was very similar to the natural form (SSR = 0.06). For other more diverse compound types, the change in SSR with degree of deuteration was less predictable (and only one deuterated form for each of the analyte/SIL-IS pair was obtained and evaluated). A general increasing trend in SSR value was found as the degree of deuteration increased, relative to the size of the molecule. For codeine/codeine-d_3, SSR = 0.06, a very high degree of spectral similarity. For benzo[a]pyrene/benzo[a]pyrene-d_{12}, SSR = 2.4, which was the highest degree of dissimilarity we measured in the study.

Again, to place some perspective, searching an experimental spectrum for codeine against the library could very possibly return codeine-d_3 as the top hit. On the contrary, searching a good-quality benzo[a]pyrene spectrum against the library would very rarely if ever return the isotopologue as the top hit. Even more importantly, for benzo[a]pyrene and its d_{12}-isotopologue, it would be conceivable to create a SIL-IS–based quantitative GC–VUV method, which would span close to three orders of magnitude. Of course, that is just a guess based on the measured SSR value; it would have to be determined experimentally.

In summary, through the lens of spectral similarity (that is, SSR values), we can evaluate the ability for GC–VUV to distinguish and correctly identify various isomer and isotopologue forms of an analyte. If a pair of isomers or isotopologues are coeluted, then spectral similarity will control over what range of relative abundance it would be possible to determine the individual compounds. For SIL-IS–based GC–VUV quantitative methods,

the spectral similarity would control the calibration range, which could be possibly accommodated. Overall, the strategy would seem to be to try to use the most highly deuterated form of the analyte possible as the SIL-IS, if this was necessary. That said, most GC detection methods are not generally subject to a large degree of matrix effects. It may be fine to just simply use another similar compound, which can be chromatographically resolved as an IS. Even so, it was still an interesting question to evaluate.

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