GC and LC: Getting small in non-life science markets

Angelo DePalma

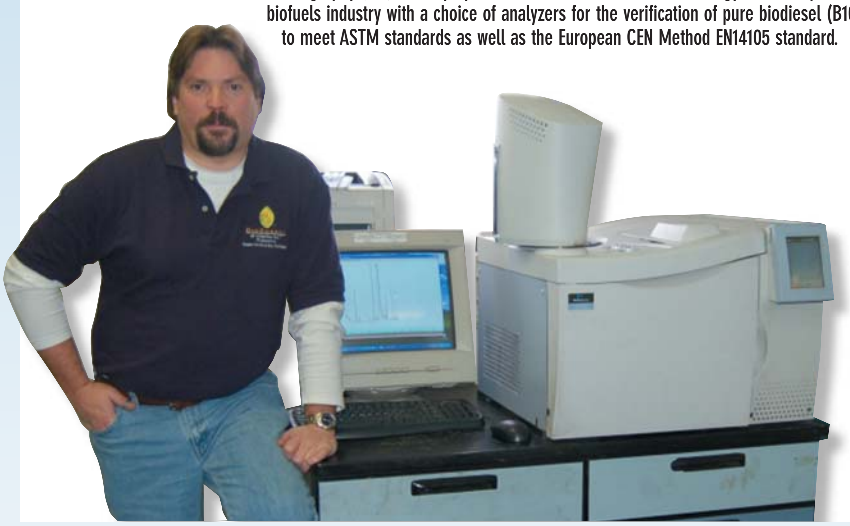
Chromatography continues to evolve towards greater capability, versatility, and usability as instrument designers draw on innovations in materials, miniaturization, and computers/software. While the life sciences continue to drive markets for gas chromatography (GC) and high-performance liquid chromatography (HPLC), applications outside of healthcare and biology are growing briskly.

According to Alessandro Baldi, Ph.D., chromatography business manager at PerkinElmer (Waltham, MA), customers are snapping up GC and LC instruments in food, environmental, industrial safety, forensics, and materials testing markets. Industry wide, about half of HPLCs and nearly 70% of GC sales go to non-life science markets. PerkinElmer's figures are somewhat higher than the industry norm.

Food analysis is driven by safety and QA/QC — rapidly growing areas due to growth in dietary supplements and concerns of contamination in foods and personal care products. Spurred by the explosion in workplace and environmental regulation, interest in analyzing air, water, and soil is similarly robust. On the materials front, HPLC's "big molecule" capabilities make it the preferred method for measuring monomer residues and molecular weight distribution within polymers. "Ultimately, these are quality measures," Dr. Baldi says. GC and GC-MS retain their dominance for analyzing small molecules, particularly polymer out-gassing.

Biofuels represent an up-and-coming market for GC and LC, where engineers need to control raw material and product quality for fats (biodiesel) and ethanol. In these applications, real-time monitoring is far ahead of standard practice in drug-making.

PerkinElmer's Biodiesel Gas Chromatography (GC) Turnkey Systems, shown here in use at BioEnergy America, provide the biofuels industry with a choice of analyzers for the verification of pure biodiesel (B100) to meet ASTM standards as well as the European CEN Method EN14105 standard.



The question of "GC or LC?" used to be answered straightforwardly along the lines of molecular weight and charge. Today, with both techniques broadened in scope and coupled with exotic detectors, application lines have somewhat-blurred. Large charged molecules remain the domain of LC, but investigators turn to it for greater sensitivity as well. For example, pesticides and their residues are generally small, uncharged, GC-worthy species, but present at ppb levels, thus making them suitable for LC.

Environmentalism and forensics have upped the ante for sample preparation, which is the greatest source of error in chromatographic analysis. For volatile organics, even at very low concentrations, users are turning to headspace sample prep, which exploits the vapor pressure of a soluble organic molecule above the sample volume. Headspace sampling is the technique of choice for measuring worker or driver alcohol consumption directly from blood. Accurate measurements require normalizing the GC or LC response as well as adjusting for vapor pressure. The reward for this extra effort is virtual elimination of sample preparation.

One significant trend among the chromatography user base is greater interest in turn-key systems for specific tasks. PerkinElmer offers a wide variety of such systems that include instrumentation, columns, and methods for applications as diverse as hydrocarbon testing, blood analysis, and organic solvents.

Conservative approach

Shimadzu Scientific Instruments (Columbia, MD) prides itself in being a "company of engineers and chemists" who dabble in innovative technologies. "But bringing those technologies to market as one-offs without a proven track record is not something we do," says Terry Adams, marketing manager.

An example is the hype surrounding miniaturization for traditional LC/GC markets. Ultra-miniaturized chromatography works best, Mr. Adams notes, for defined tasks, where analytes are known and the instrument is operating as a detector rather than an instrument. Exceptions exist, of course. Photovac's (Waltham, MA) portable gas chromatographs for environmental applications come to mind. Interestingly, Photovac is looking into microchanneled columns to deliver even greater portability.

Microchanneled GC and LC columns are not well-suited for universal chromatography instrumentation. Issues of clogging, sample carry-over, reproducibility, durability, cost, and ergonomics need to be thought out, as troubleshooting microfabricated analyzers is next to impossible.

Ultra-miniaturization makes the most sense for disposable detectors that can be produced cheaply, used several times, and thrown away. Typically, such devices will focus on a narrow range of analytes, say hydrocarbons or contaminants in drinking water, and give a "yes-no" answer. "It might even be possible, using silicon etching techniques, to have quantitation and to build a robust instrument platform around these devices," Mr. Adams adds. Agilent, for example, offers numerous products based on microfluidics.

"But you need to consider the human element," adds Mr. Adams. "You don't want to market an instrument that takes a Ph.D. to run. Today, everyone in a lab needs access to chromatography instruments."

Caliper's LabChip 3000 system provides a quality approach to enzymatic and cell-based screening and kinase profiling.

Shimadzu's conservatism is, above all else, user-centric. The company was reticent about marketing a liquid chromatography system with an ion-trap time-of-flight mass detector until the marketplace had carved out applications and the company identified a strong user base for the instrument. Similarly, the company has been talking up a microscope-MS device at scientific meetings, but has not yet introduced it as a product.

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Adams mentions the capillary electrophoresis (CE) craze of 15 to 20 years ago as an example of over-hyped, too-early technology. Many experts believed that CE would eventually replace HPLC, as several users told Mr. Adams at Pittcon in the late 1980s. "Not many CE companies are around anymore."

Parallel evolution

LCs have evolved in parallel within healthcare and non-healthcare markets. Richard Friday, chromatography marketing director at GE Healthcare (Uppsala, Sweden), notes that the multi-disciplinary nature of scientific work has caused hardware and software vendors to adapt their products to researchers who are not necessarily chromatography experts. As its name implies, GE sells its LC instruments almost exclusively into life science markets, for purification of proteins from microgram to gram quantities.

"Units must be easy to get up and running, as users demand results without needing to understand an instrument's intricacies," he says. This puts a premium on simplification, on getting samples through the "black box."

Mainstream LC instruments are becoming more compact, but biologists value systems that allow sample recovery. This is probably the most consequential difference, with respect to miniaturization, between biologists and chemists. Ultra-small systems do not permit recovery because injected samples are minuscule.

GE got into the miniaturized chromatography marketplace in the early 1990s with its SMART chromatography systems. However, its leading chromatography system remains the EKTA line of HPLC instruments, which claims 100,000 users worldwide.

Regardless of the market, mass detection has probably been the most significant trend in HPLC and GC over the past decade. Together, chromatographs and mass detectors allow hookup to compound databases for confirmatory analysis of any molecule that gets through the column, from VOCs to proteins.

GC/MS and LC/MS have been made possible by mass spec vendors, who within fifteen years have shrunk their instruments from room-sized to desktop-sized. "They've done a great job of bringing mass spec to the masses," says Mr. Friday, "almost to the point where almost any lab can have a mass spectrometer."

Getting small

Caliper Life Sciences (Hopkinton, MA), a lab-on-a-chip pioneer, has kept pace among instrument makers by adapting to the need for higher throughput and automation. Caliper was awarded a U.S. Environmental Protection Agency grant to develop new approaches to identifying potentially toxic environmental chemicals through the company's microfluidic analyzers.

As its technology platform, Caliper is relying on its LabChip 3000 product. Primarily used for drug discovery, the LabChip miniaturizes and automates enzyme assays integrated with a microchanneled electrophoresis pathway. At this scale — channels are narrower than a human hair — distinctions between chromatography and electrophoresis fade. "This is a form of chromatography," says Dave Manyak, Ph.D., executive VP at the company. Fluid and sample are forced through channels through either pressure or electric current.

Caliper's identification scheme is based on enzyme assays — biological activity — rather than direct detection. LabChip utilizes activity/inhibition assays for kinases, phosphatases, proteases, lipid-modifying enzymes, and G-coupled protein receptors. Environmental pollutants interfere with these proteins, making this a functional assay. The readout is a fluorescent event associated with normal enzyme or protein functioning.

The EPA currently performs environmental toxicology using laboratory test rats, a slow and cumbersome process that has left the agency with a nearly 30,000-compound backlog. With new chemicals being introduced weekly, it is unlikely to catch up. The Caliper assay system takes just a few minutes to set up and run and is easily run in replicate.

Note that this project seeks not "detection" of unknowns but quantification and prediction of the toxicology of previously untested, off-the-shelf chemicals.

Caliper's work with the EPA is part of a larger framework, EPA's "ToxCast" initiative. ToxCast seeks, among other objectives, to predict toxicology through innovative techniques borrowed from the chemical and life sciences, including high-throughput screening methods. According to Dr. Manyak, Caliper's participation could at some point lead to a field instrument for detecting chemicals directly in air, water, and soil.

Conclusion

Chromatography markets, particularly for GC and LC, combine mature technology and innovation in ways that few other instruments do. While the attendant separations principles remain the same, instrument makers continue to provide greater value per instrument dollar. At the same time, ultra-miniaturization, which has promised much for the last fifteen years, has entered the mainstream for LC (and related electrophoresis methods) but not for GC. Nevertheless, miniaturization will continue to influence how LC and GC formats evolve. ■

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A GC-Chip?

Interest in ultra-miniaturized chromatography systems has waxed and waned since the early lab-on-a-chip days of the late 1980s and early 1990s. Most pioneering devices were based on electro-osmotic driving mechanisms rather than more familiar gas or liquid pressure. In addition, these systems were poorly integrated with heating elements and detectors, and lacked true stationary phases.

Somenath Mitra, a professor at New Jersey Institute of Technology, was recently awarded a patent on a microchanneled GC, about the size of a penny, that holds a traditional (although greatly scaled-down) column, stationary phase, and detector. The "business" side of the device is etched silicon (column, stationary phase) bonded to an aluminum substrate that serves as a heater, and a glass cover on top. Dr. Mitra fills the channel with conventional stationary phases, for example, the siloxane polymer OV-1, and mass produces hundreds from a six-inch silicon wafer.

The device is not quite a GC yet, but it suggests the direction in which tomorrow's ultra-miniature field instruments are heading. "It contains all the technology that can lead to a fully-functional GC-on-a-chip," he says. Today, Mitra uses the device as a concentrator to prepare volatile organic molecules for analysis by conventional GC or another GC-chip.