



Connections

Gas chromatography (GC) separations at higher speeds have received much attention in recent publications. In this month's "GC Connections" column, John Hinshaw examines the reality of GC at high speeds in light of the potential for rapid separations and the speed limits imposed by the practicalities of instrumentation and other considerations external to the instruments themselves.

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How Fast Is Fast Enough?

Pioneers in open-tubular or capillary column gas chromatography (GC) recognized the potential for high-speed separations from the outset. Indeed, some of the earliest capillary GC chromatograms obtained by Golay in 1956–1957 presented separations of four to eight peaks in less than 20 s (1), which was very fast compared with the routine packed-column separations of that time, let alone with today's routine capillary chromatograms. In August 1957 at the Instrument Society of America symposium in East Lansing, Michigan, Golay presented a series of three chromatograms that illustrated the gains in resolution or speed that chromatographers could obtain with open-tubular columns (2).

The chromatograms, which showed the separation of only three peaks, were labeled "Standard Packed-Column Run," "High-Resolution Capillary Column Run," and "High-Speed Capillary Column Run." Performed using a 30 m × 0.25 mm column, the 4-min, high-speed run was eight times faster than the other runs, and it effectively demonstrated possibilities for high-speed separations unattainable with conventional packed-column technology.

A few years later, Desty (3) investigated separations at speeds much higher than those generally used today in conventional instruments. He obtained near-baseline separation of 15 hydrocarbons and isomers in less than 2 s using a 120 cm × 0.035 mm squalane-coated column and hydrogen carrier gas at a 200-psig inlet pressure (4). Desty understood the technical difficulties of operating at such high inlet pressures: His description of using a hammer to depress the syringe plunger rapidly is one of the best-known anecdotes in GC.

These early examples, which are taken from many that predate the recent resurgence in high-speed GC, demonstrate the potential for high-speed GC separations, and they show that chromatographers have been familiar with this potential since capillary GC's beginnings. Why have most of today's chromatographers failed to take advantage of the very rapid separations pro-

vided by capillary columns operated at their fastest potential speeds? The answer lies in the difficulties inherent in developing the new capillary column technology — as Desty's hammer shows. High-speed GC required new inlet and detection systems. Chromatographers needed to investigate various tubing materials, invent new methods for capillary column production, characterize new and existing stationary phases, and apply their results to new applications and myriad existing separations. Because of these simultaneous multiple technical challenges, most applications, columns, and instrumentation were better served by the much less rapid but vastly more practical separation speeds that were available for widespread use.

It was not increased speed so much as improved separations that gradually led chromatographers to adopt capillary GC over packed-column GC during the past several decades. As capillary columns and instrumentation improved, these columns rapidly outstripped packed-column performance in speed, resolution, sensitivity, and inertness. By the 1980s, capillary GC was becoming dominant as a routine analytical technique but not at its highest analysis speeds. Significantly faster separations remained an experimental curiosity. Today, this situation is beginning to change.

As a nonstandard technique, very rapid capillary GC separations require additional justification beyond a mere perceived need for speed before they can gain widespread acceptance. In conventional laboratories, high-speed instrumentation may be able to separate and analyze samples at rates that outstrip the available or desirable rate of sample preparation. Increased sample preparation rates require additional equipment and modifications to laboratory procedures, which further complicate transition to faster analyses. Because of its specialized equipment and dedicated columns, high-speed capillary GC does not fit well in laboratories that must deal with many different samples and make frequent column and equipment changes. In many respects, rapid GC analysis matches better

with specialty applications such as at-line or on-line analysis than with conventional laboratory sample work flow.

An often overlooked option for rapid GC analysis is the accumulation of multiple analyses for a single sample followed by statistical treatment of the data for improved results reliability, a process that is made less time-consuming by faster analyses. Using multidimensional techniques with two or more high-speed columns in series or parallel is another possibility. These systems have attracted renewed attention recently in the form of comprehensive two-dimensional GC separations (5,6) and as tunable coupled-column systems (7). At this time, however, the engineering complexities of these multiseparations make them impractical for use in routine GC separations.

High-speed capillary GC today appears to be in a state similar to that of now-conventional capillary GC 20 years ago. The lack of proven applications and a large installed base of existing instrumentation inhibit rapid and widespread adoption. Unlike routine GC, the newer technology requires very experienced personnel, often at the Ph.D. level, for successful deploy-

ment. The instrumentation itself is in a state of flux as new ideas and technologies find their way into products.

Optimizing for Speed

Researchers have written hundreds of articles, books, and reports about capillary GC potential. This topic is well understood, and little controversy exists over its limits and parameters. Ultimately, only two independent variables are significant: resolution (R) and speed (t_R). Answers to the questions *How high?* and *How fast?* provide related sets of values for all other separation parameters as determined by choices of columns, stationary phases, and instrumentation. Usually, multiple combinations of columns and elution conditions can yield a desired separation, if users can establish some basis for selectivity. Today's available technologies cannot create the required conditions for all possible parameter sets, so the set of useful columns and elution conditions comprises fewer possibilities. At significantly elevated speeds, capillary GC separations may require operating parameter sets that conventional instrumentation cannot recreate and therefore may require different instrumentation for success.

A capillary GC column — or any chromatographic column, for that matter — delivers a degree of solute resolution in a defined time span. A good operating minimum resolution is 2.0, which slightly over-resolves peaks and accommodates the possibility of resolution loss during the lifetime of the column and the likely advent of unanticipated sample or instrumental problems with extended use. Resolution, in turn, depends on the separation factor (α) for the solutes on the chosen stationary phase, the number of available theoretical plates (N), and the ratio of time spent in the stationary phase relative to the time spent in the mobile phase — the retention factor (k). Larger values of α and N produce greater resolution. Larger retention factors improve resolution, but retention factors higher than 3–5 produce little resolution improvement. A number of column parameters, including the column dimensions and temperature, directly influence all of the above variables. Solute-related variables, including diffusion and thermodynamic coefficients, also determine theoretical plates, the separation factor, and the retention factor.

All of these interrelationships make for a dauntingly complex picture of what occurs in a capillary GC separation. Fortunately for practicing chromatographers, the theoretical basis for modeling these separations is well understood. In the case of capillary GC, the theory yields predictions that usually are close to reality, if users know accurate thermodynamic and diffusion coefficients. This theory forms the basis for much of the available separation prediction software, and it allows analysts to predetermine the possibilities that various separation parameter sets offer for high-speed analysis.

If I set a minimum resolution level for the closest-eluted solute pair in a run, then the column dimensions and elution conditions determine the speed of analysis for any particular stationary phase. Speed of analysis, as measured by the retention time of the last peak of interest, is related directly to the retention factor and the unretained peak time (t_M), so GC users can influence the speed of analysis by controlling these parameters. Lower retention factors or unretained peak times will produce correspondingly faster separations. However, simply reducing the retention factor by increasing the temperature or decreasing the stationary-phase film thickness can

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adversely affect resolution. Operating the column at significantly higher than optimum carrier-gas velocities will bring peaks out more quickly but also may yield less resolution because of the availability of fewer theoretical plates at elevated velocities. Alternatively, reducing the column length while maintaining the same carrier-gas velocity increases speed of analysis proportionately, but it also reduces the number of theoretical plates in a similar manner (8).

If all the peaks in an existing GC run are eluted with large amounts of empty space between them — with excess resolution — then the strategies described above should produce faster analysis times and bring the excessive resolution to a minimum level. Shorter column lengths, faster linear velocities, and higher temperatures or program rates will have this effect, although higher temperatures or program rates also can shift peaks relative to one another and could increase or decrease resolution for each peak pair. Chromatographers often use those in-column modifications, when practical, because they can avoid using columns with different diameters, film thicknesses, or stationary phases.

If one or more peak pairs are eluted with baseline or only slightly better resolution, then chromatographers must take a different approach to increased speed. In many cases, careful optimization of the column temperature or the temperature program can improve speed by using resulting shifts in separation factors to reduce theoretical plate requirements and open the way for faster linear velocities or shorter columns. If those efforts fail, changing to a different stationary phase can produce larger separation factors for the critical peaks with correspondingly higher resolution that again

permits optimization for speed. On different stationary phases or with different temperature conditions, however, the closest-eluted solute pair may be a different pair of peaks than those observed with the original stationary phase or temperatures. In these cases, analysts should identify each peak carefully at its new retention time by mass spectroscopy (MS) or by a series of individual solute injections.

A number of available software packages can optimize separations by modeling the effects of changing the column dimensions and elution conditions when given the results of two or three example runs (9). These tools can save a lot of time when analysts are looking for the conditions and dimensions that produce the fastest speeds. Speed is not everything, however. Each instrument, in effect, imposes speed limits that should be obeyed for the best possible results.

Requirements for High-Speed Capillary GC

As part of discussing requirements for high-speed capillary GC, I need to define it. The appellation *high speed* does not have the same meaning in all situations, just as it doesn't mean the same thing to automobile-driving commuters and race car drivers. From an instrument-oriented point of view, separation systems must traverse several distinct levels as the speed of analysis increases (Table I). These categories are my own description, and they represent one of several ways to define requirements for high-speed capillary GC.

Level 1: Routine capillary columns, for which the bulk of conventional GC instruments are designed, are what most chromatographers would consider the first level. These columns span lengths from

10 to 100 m and inner diameters from 0.18 to 0.53 mm in a variety of stationary phases and film thicknesses. Analysts expect that modern GC instruments, when equipped with appropriate capillary inlet systems, would operate most of these columns at carrier-gas velocities of 20–60 cm/s or higher and accurately generate oven programmed-temperature rates as high as 40–75 °C/min, depending on the oven temperature. Detectors on these instruments should track eluted peaks with greater than 0.5-s widths at half height at greater than 95% fidelity, and they will respond to the full dynamic range of solute amounts that the columns can pass without overloading. Conventional inlet systems — such as split–splitless, programmed-temperature vaporizing, and on-column inlets — are compatible with nearly all these columns when operated under those conventional velocities and temperature conditions. Today, those instruments and columns have become commodities that analytical laboratories purchase by specification for routine application areas, and workers expect to experience little difficulty with installation or operation. These instruments require a minimal level of technician training.

Level 2: At the second level, chromatographers use conventional instruments at higher speeds. These schemes can yield significant speed increases when the initial analysis uses little of the already existent resolution potential. For example, a separation on a 50 m × 0.53 mm column that resolves all peaks with *R* greater than 3 could be optimized for three- to eightfold faster separation by increasing the linear velocity, reducing the column length, or running at higher temperature or program rates.

Table I: Four levels of capillary GC

Level	Description	Relative Speed of Analysis	Column Dimensions	Inlet Pressure (psig)	Injector	Detector
1	Conventional capillary GC	1	10–100 m × 0.18–0.53 mm	2–100	Conventional	Conventional
2	Rapid capillary GC on conventional instruments	3–5	5–50 m × 0.18–0.53 mm	2–100	Conventional, programmed-temperature vaporizing cold trapping	Conventional, sampling rates as fast as 50 Hz
3	High-speed capillary GC on modified conventional instruments or components	5–10	2–25 m × 0.10–0.25 mm	10–150 or higher	Rapid heating	Conventional, sampling rates as fast as 200 Hz
4	Very-high-speed capillary GC on specialized instruments	10–50	2–10 m × 0.03–0.10 mm	20–200 or higher	Specialized, high speed	High sensitivity, high speed

If no resolution overhead is present, then a less impressive two- to threefold speed improvement might be obtained by choosing a 25 m \times 0.25 mm column, which would generate approximately the same theoretical plate number in approximately half the time. However, a narrow-bore column might be incompatible with an inlet for 0.53-mm i.d. columns, so an analyst could incur some additional cost for another inlet.

With conventional instrumentation at this level, the oven cooldown rate quickly becomes a limiting factor. Faster temperature program rates are implied by higher carrier-gas velocities to keep peaks moving through the column and to produce the best resolution. At conventional analysis times of 20–60 min, oven cooldown times of 4–8 min represent a small fraction of the total time between injections. As the oven-heating time decreases, the portion of the overall analysis time attributable to cooldown can become significant. For example, a temperature-programmed run from 100 to 300 °C at 75 °C/min takes 2.67 min, but the oven may need twice that long just to cool down and get ready for the next run.

Level 3: As chromatographers try to obtain a minimum resolution level in less time, the requirements imposed on inlets, ovens, and detectors become more stringent. At the third level, the narrowest peaks have widths less than 0.5 s at half height, and column diameters drop to as little as 0.10 mm. Modified programmed-temperature inlets that use rapid resistive heating can generate somewhat narrower injection profiles, but solute cold trapping at the column head followed by oven temperature-programmed elution is the most common scenario for placing narrow-enough solute bands on the column at this level. Generating temperature program rates greater than 75 °C/min requires oven modifications with high-power heaters or add-on dedicated flash heating modules. Add-on column modules have an advantage of providing a much more rapid cooldown time, as well as significantly faster heating rates than can be obtained merely by increasing the heater power dissipation of a conventional oven. At this level, some GC detectors fall short of recording peak profiles with better than 95% fidelity, which requires a sampling

rate of 100 Hz or faster for the narrowest peaks.

As column diameters shrink to less than 0.18 mm and as chromatographers push the linear velocity to new heights, inlet-pressure requirements can skyrocket beyond 100 psig. Hydrogen carrier gas reduces the pressure requirements by almost half, and it has the added advantage of producing more theoretical plates than helium as the linear velocity increases above optimum. Some manufacturers of conventional GC instruments offer a high-pressure option for the pneumatics that provides an extra 50% boost to the available inlet pressure for high-speed, high-pressure conditions.

This third level is where most dedicated high-speed GC instrumentation operates today. With analysis times as low as 60–90 s, column diameters as small as 0.10 mm, and temperature program rates as high as 100–1200 °C/min, these systems bring significant speeds to the hands of chromatographers who understand the requirements and limitations of applying the systems to existing or new GC separation challenges.

Level 4: The third level still does not tap the potential that the physics of capillary GC implies. For analysis times shorter than 60 s, experimenters have entered a fourth level using columns with lengths of 2–10 m and diameters of 0.030–0.050 mm. Those columns generate almost as many theoretical plates as conventional 0.2–0.5 mm i.d. columns with lengths of 25–100 m. At conventional carrier-gas velocities of 30–60 cm/s, those columns have unrestrained peak times from 4 to 30 s, so peaks with retention factors of 2–10 would be eluted in 8–300 s. For elevated velocities, the times become proportionately shorter. Remember, however, that Desty and others demonstrated these possibilities very early in the development of capillary GC.

These micro-GC columns have a number of significant limitations. The inlet pressures quickly become prohibitively high: A 10 m \times 0.03 mm column requires just more than 200 psig of hydrogen carrier gas to achieve a velocity of 30 cm/s at 100 °C. The injected bandwidths required for full utilization of the available theoretical plates become vanishingly small, and the eluted peak widths are 10–100 ms.

Inlets and detectors used on conventional or modified instrumentation at Levels 1–3 do not meet the new requirements imposed by such extreme operating factors.

As the inner diameter drops, the column sample capacity also decreases. Thinner

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stationary-phase films are concomitant with narrower diameters as well. Both of these factors cause the sample capacity of very narrow-bore columns to drop quickly to within two or four times the noise level of conventional detectors.

I once made an experimental 0.035-mm i.d. column that was roughly 2 m long. With some trial and tribulation, I measured its sample capacity at approximately 10 pg, which compares with flame ionization detectors' minimum detectable limit of roughly 2–4 pg. Larger sample amounts on the column caused significant peak-shape distortion, and I realized that my detector's sensitivity limited the lower end of the system's dynamic range so much that it seemed pointless to pursue using the column further. Possibilities exist for high-speed, high-sensitivity detection systems in micromachined thermal-conductivity detectors, as well as in time-of-flight MS detectors, but the combination of micro-GC columns with those detectors and appropriate inlets remains an elusive goal to practicing chromatographers who want to obtain analysis results much more rapidly.

Conclusion

High-speed capillary GC is not a new technique. The potential and possibilities for these analyses were demonstrated at the beginning of capillary GC's development. That the full potential has yet to be put into practice, 45 years later in 2001, is the result of the directions that capillary instrument and application development took and the lack of appropriate technologies to bring the full potential into routine practice. Today the incursion of high-speed capillary GC separations into everyday analyses resembles the state of conventional capillary GC separations in the 1970s. The potential is known and the principle has been adequately demonstrated, but the techniques are not in the hands of average chromatographers. Application development goes hand in hand with available technologies, and the impetus to apply new technologies is driven by the need for improved applications and for higher analysis speeds in this case. Perhaps the analytical community will see some truly remarkable developments in this area in the next few years that will bring high-speed capillary GC closer to becoming the routine analytical technique that it could be.

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