Theoretical and Practical Aspects of Fast Gas Chromatography and Method Translation

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Abstract

Interest in the development and implementation of fast gas chromatography (GC) methods continues to increase. Fast GC method development and validation can be simplified and more successful if a few key theoretical and practical concepts are kept in mind. Key concepts such as speed-optimized flow rate, optimal temperature-program rate, sample capacity, "cut the column", and principles of method translation are discussed.

Introduction

Interest has peaked, so to speak, in optimizing the speed of routine chromatographic analyses. The interest is driven primarily by the desire to reduce cost per analysis (i.e., higher laboratory throughput, better utilization of high-cost equipment, and fewer analysts required) and the time required to get results. Other motivations such as getting results closer to where the answer is needed (e.g., at-line or online) and improving overall site efficiency (i.e., increasing chemical production yields or quality, reducing fixed and variable costs associated with the business, and saving space) add to the interest.

The interest in fast gas chromatography (GC) dates back to the period directly after the invention of capillary columns. Golay (1) outlined the theory of capillary columns at the 1958 international symposium on GC. At the following symposium in 1960, the speed-related aspects of separation were the main focus of discussions in the section concerned with the theory and application of GC (2–4). To illustrate their theoretical ideas, Desty and Goldup presented a 1-min isothermal separation of 10 peaks in a 15-m × 125-µm column with hydrogen as a carrier gas. Two years later, Desty, Goldup, and Swanton (5) demonstrated several rapid isothermal separations including the one in which more than 10 peaks were separated in less than 2 s in a 1.2-m × 34.5-µm column with hydrogen as a carrier gas (5).

Thus, it should be asked why weren't fast capillary GC methods developed for routine use early on. Actually, several issues limited the use of capillary columns in general, aside from fast GC versions. These included the complexity of installing the rigid glass capillaries, irreproducibility of column production, limited availability of columns, and the necessity to modify most GCs for capillary use. The invention of fused-silica capillaries coupled with GC instrument improvements and consistent column-manufacturing processes led to widespread migration from packed to capillary column methods. Unfortunately, initial capillary GC methods were usually not developed with speed in mind. Many of these methods became "standard" methods within organizations that now realize the gains could be made by speeding them up.

Let's consider a common environment under which many original capillary GC methods were developed. Original packed-column methods have much larger capacity and ruggedness (i.e., more immunity to injection anomalies and contamination) than capillary columns. In order to minimize the changes in hardware and method conditions, many developers of initial capillary methods chose to use large-diameter (e.g., 0.75 mm), thick-film (< 1 µm) columns. At the same time, partially because capillary column stationary phases were not as selective as those available in a packed-column format and partially because it made method development easier, developers used much longer columns than were really needed. This philosophy of "killing it with plates" was common, especially when considering that the process of migrating from packed column methods to capillary methods could be accomplished in less time. The result, however, was that many capillary methods were developed that were much slower than they needed to be. In short, analysis speed was not a primary development goal at the time.

Many of these suboptimal methods are still in use. Even though they meet the analytical need, they may no longer meet the business need. The question then becomes how can these slower capillary GC methods be converted to faster ones in the least amount of time and with the highest degree of success. It is clear that in most business settings one would

only choose to change routine methods that are either in widespread use (many will benefit from the improved method) or because speed is critical to meeting business objectives. In this study we attempt to highlight the most important theoretical concepts for the practical optimization of routine capillary GC methods.

In order to increase the speed of GC analysis, it is possible to increase the carrier gas flow rate (F), increase temperature-program heating rates, use a faster carrier gas such as hydrogen, reduce the column length (L), reduce the column diameter (d_c), reduce the thickness of the stationary phase, and use a detector that operates at a lower outlet pressure (p_o).

An inappropriate combination of these changes complicates the method development process. It is also important to keep in mind that when the separation speed is optimized, it is not for free. Separation power, sample capacity, or both must be given up (as illustrated in Figure 1). If any one attribute were to be maximized (e.g., speed), the other two would then be minimized. Therefore, any fully optimized chromatographic method is a tuned compromise between speed, capacity, and resolution (R_s). Whatever attribute gets priority or focus depends on the specific goals or requirements of the analysis.

Of course, the ability to optimize any given separation is also constrained by instrumental limitations. These include solute detectability (limited by detector sensitivity and noise level), available inlet pressure (p_i), maximum oven temperature ramp rate, maximum detector sampling rate, and sample introduction (i.e., initial bandwidth as influenced by such conditions as the injection speed, split ratios, and liner volume). Recent GC designs have incorporated improvements in many of these areas, allowing method developers to push analysis speeds much faster than those that were possible just a few years ago.

Two general approaches to fast GC method development can be followed, either start from scratch or scale a current method. The path that is taken depends on the status of the current method. Method translation yields a scaled version of the current method. If the current method meets all of the analytical needs except speed, then translation is the best way to go (especially if the analysis involves many (e.g., > 20) components). If there are deficiencies with the current method, it might be better to redevelop the method from scratch in order to better meet the overall analytical requirements.

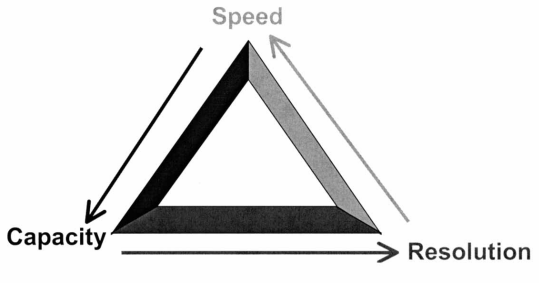

Figure 1. Optimization triangle of compromise. The apices represent maxima for each of three dependent variables and minima for the other two. Any given separation requires a combination of the three variables, with analytical goals or requirements dictating which attributes are favored over the other.

Current method deficiencies that may result in starting from scratch are: (*a*) the stationary phase is problematic (i.e., it decomposes easily, the upper temperature is too limited, it bleeds too much, and it is nonstandard and hard to get) and (*b*) sample introduction is problematic such as splitting peaks, low sensitivity, overload, discrimination, and decomposition (i.e., a sample solvent change is warranted; a change in the injection technique (cool on-column, large volume injection, programmable temperature vaporizer, splitless vs. split); a different initial temperature, time, or the addition of a retention gap; fast autoinjection versus manual injection that then requires tuning initial conditions; or the use of headspace sampling instead of liquid).

Also, when considering the merits of developing and validating a routine GC method, the total time involved with analyzing the sample must be considered. The total analysis time is the sum of the time for sample preparation, sample introduction, separation and detection, cool down and reequilibration, and reporting.

Any time that the other factors become equal to or greater than the separation itself, the benefits derived from speeding up the separation become less significant.

Isothermal analyses provide the fastest overall analysis times for simple mixtures of solutes with similar volatilities. For example, within the theoretical and experimental studies of fast GC and GC–mass spectrometry (MS) presented by Cramers et al. (9–12) are several fast isothermal analyses, including a separation of 9 peaks in approximately 0.7 s using a 30-cm × 50-µm column with helium as a carrier gas.

The framework for a theory of temperature-programmed GC was developed by Giddings (6,7) in the early 1960s. Giddings (8) also contributed to the evaluation of the influence of various components (i.e., carrier gas type, p_i, p_o, and the amount of stationary phase) of a GC method on the analysis time.

The previously mentioned references (as well as myriad others) helped to identify the influence of different method parameters (such as column dimensions, carrier gas type and pneumatic conditions, stationary phase type and thickness, and heating rate in a temperature program) on the separation/speed tradeoff. However, until recently, the quantitative evaluation of the contribution of each particular factor to the separation/speed tradeoff remained unclear, especially in the case of temperature-programmed GC. This omission made it difficult to efficiently search for the optimum conditions for the best separation/speed tradeoff. One of the reasons for this problem was the perception that changing almost any parameter usually leads to many interdependent and contradictory changes in the chromatographic results. Shortening the column generally leads to a reduction in the analysis time and a loss of R_s. However, if all other method parameters (including F and the temperature program) remain constant, the change in L could actually cause separation improvement in some peak pairs and loss of separation or even a reversal of the peak elution order in others. In general, results from shortening L in order to reduce the analysis time had not been totally pre-

dictable. The discovery of GC method translation (13,14) helped to eliminate these uncertainties and provide a predictable means of evaluating method tradeoffs.

According to the concept of GC method translation, all changes in chromatographic conditions can be divided into two groups: translatable and nontranslatable changes (15). Changes in column dimensions and a carrier gas's type and its pneumatic conditions (i.e., p_i, p_o, and F) are translatable ones. Also translatable are proportional changes in the heating rates and the durations of temperature plateaus of a temperature program. Nontranslatable are the changes in stationary phase types and phase ratio (16). Also nontranslatable are the initial temperature and plateau temperatures in the temperature program.

The concept of the GC method translation is based on the fact that void time (t_M) can be viewed as the fundamental time unit in chromatography that can be used to express time-related components in all chromatographic metrics. Thus, in a normalized temperature program (15) (as shown in Figure 2), durations of all of the temperature plateaus and heating rates are expressed in units of t_M measured at the same temperature. Two methods are mutually translatable if they have identical nontranslatable parameters and the same normalized temperature program.

A version of method translation software is available free of charge from the internet (17). It computes translations of temperature programs and head pressures for any change in column dimensions, carrier gas type, pneumatic condition, or a combination of the three. The actual setpoints in Figure 2 were calculated using this software.

Mutually translatable methods have an important feature, they yield the same peak elution order (15). As a result, the retention times of the peaks corresponding with the same solute in two mutually translatable methods (e.g., 1 and 2) are proportional to the ratio:

$$G = t_{M1} / t_{M2} \qquad \text{Eq. 1}$$

of the void times t_{M1} and t_{M2} in these methods (13,15). Quantity G is known as the speed gain of method 2 in relation to method 1 (15). Method translation also results in the same reduction or increase in the resolutions R_{s1} and R_{s2} of any peak pair corresponding with the same pair of solutes in two methods. The ratio of R_{s1} and R_{s2} can be found as (15):

$$R_{s2} / R_{s1} = \sqrt{(N_2 / N_1)} \qquad \text{Eq. 2}$$

The previously mentioned properties of method translation allow for the finding of simple dependencies between the changes in the separation and the analysis time resulting from any translatable change in a method parameter and from a combination of such changes (15,18–21).

The use of method translation principles for the analysis of optimum chromatographic conditions helped to define both a generally optimal heating rate (approximately $10°C/t_M$) (21) for temperature-programmed GC and a speed-optimized flow (SOF) (18,20) for both isothermal and temperature-programmed GC. SOF (which will be discussed in more detail) is the F value that corresponds with the shortest analysis time for a given plate number (N) in a column of a given d_c.

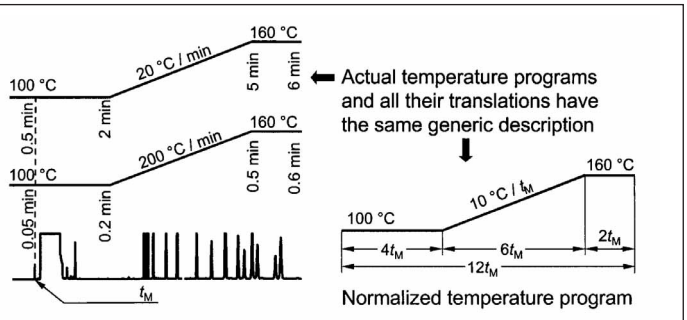

Figure 2. Two actual temperature programs and their normalized equivalent.

Discussion

In this study it is assumed that a somewhat familiar knowledge of the general process of separation in capillary GC is known. The following definitive publications for descriptions of flow through open-tubular columns (22–25) and mathematical descriptions of the separation process (1,18,20,23,26–30) are suggested.

What is "Fast GC"?

The definition of "fast GC" has been debated for some time. Concepts relating fast GC to run times clearly indicate the bottom-line need of getting analytical results faster. However, definitions based solely on run time miss the important aspects of peak separation and peak capacity. In other words, a poor separation of three peaks in 1 min is inferior to the baseline separation of 15 peaks in the same minute. Although the analyses both end in 1 min, the second case provides more separation power per time. Therefore, it is important to use a definition that is representative of separation per time. Thus, a definition based on peak width seems reasonable.

Table I lists hypothetical peak widths as a function of d_c to illustrate the benefit of smaller-diameter columns for fast GC. In this example, the total column efficiency (plate count) was held constant. Calculations were performed by assuming that a solute had a retention factor of 1, eluted at 100°C, and had helium as the carrier gas at SOF.

From the comparison in Table I, it is apparent that moving from a 530-µm-i.d. column to a 100-µm column can generate approximately 9 times narrower peaks with the same R_s and peak capacity. This then corresponds with 9 times faster analysis with no loss in separation. This approach allows for the comparison of separations based on the quality of the separation as well as the absolute speed.

Column dimensions

Two general approaches to fast GC method development can be followed: start from scratch or translate the current method. The path that is taken depends on the

status of the current method. Method translation yields a scaled version of the current method. If the current method meets all analytical needs except speed, then translation is the best way to go, especially if the analysis involves many (e.g., > 20) components. If there are deficiencies with the current method, then it might be better to redevelop the method from scratch in order to better meet overall analytical requirements.

Table II compares the relative speed, separation power, and capacity of various common d_c values. It is clear from this comparison that smaller-diameter columns have a lot to offer as a means of speeding up analyses.

By reducing the d_c, a higher efficiency per L is produced (a shorter column can be used to affect the same separation). When the d_c is reduced, optimal average linear velocity (u_{opt}) is also faster. Both results lead to a shorter t_M and a proportionally shorter analysis time at the same separation power. The penalties to be paid are a much lower sample capacity and much higher carrier gas pressures required to perform a run. Therefore, one must remember to reduce the amount of solute reaching the column proportional to the decrease in the stationary phase in order to maintain a similar peak fidelity to the original method that used a larger inner-diameter column.

Table I. Typical Peak Widths (Area-Over-Height) Shown as a Function of the Column Inner Diameter*

Column inner diameter (µm)	Peak width (s)
530	2.6
320	1.2
250	0.85
200	0.64
100	0.29
50	0.14

* The inherent speed of a given separation is best defined by the width of peaks. Typical peak widths (area-over-height) are shown as a function of the column inner diameter for the peaks eluting with k = 1 at 100°C. All columns have equivalent separation power (i.e., the same $N_o = L/d_c$ = 100,000).

A useful relationship to keep in mind when migrating to faster separations is that column efficiency is related to the ratio of L to d_c. Therefore, if one wished to maintain separation power while increasing the analysis speed by using a smaller inner-diameter column, then the maintaining of the L/d_c ratio would be ensured. For example, if the original method were developed on a 25-m × 250-µm-i.d. column, a 10-m × 100-µm-i.d. column would be chosen in order to get the same separation.

For a number of reasons (e.g., sample capacity, p_i values required, and translated temperature-programmed rates), 100-µm-i.d. columns seem to represent the current limit for routine use. L values up to 40 m have been used on a routine basis with very good results. It might be possible to meet method requirements for a few applications using 50-µm-i.d. columns (< 10 m), but these columns operate at the extremes of even the most current instrument designs and are, therefore, usually too problematic for routine use.

Carrier gas choice

The carrier gas choice can have a substantial influence on analysis speed. This influence depends on the column pressure drop (p_d) (18,29,31).

When p_d is low compared with the p_o (e.g., 530-µm-i.d. columns and short 320-µm-i.d. columns), the u_{opt} (whether optimized for the best efficiency or the shortest analysis time) and thus the speed of analysis is proportional to the molecular diffusivity (D) of a solute in the gas (18,29). The ratio of the D values for a given solute in different gases is typically independent of the solute and depends only on the type of gas (31–34). Relative speeds of analysis based on the published D data (33) for the typical carrier gases are listed in Table III.

When p_d is high compared with the p_o (e.g., for long 320-µm-i.d. columns and all typical columns with a 200-µm or smaller inner diameter), the u_{opt} (whether optimal for the best efficiency or shortest analysis time (18,29)) and the speed of analysis are proportional to the quantity $\sqrt{(D/\eta)}$, where η is the viscosity of the carrier gas (18,29,31). The ratio of $\sqrt{(D/\eta)}$ values for a given solute in different gases is typically independent of the solute and depends only on the type of gas (31–35). Relative speeds of analysis based on the published D

Table II. Column Parameters as Functions of the Internal Diameter (d_c) at the Same Separation Efficiency* and Phase Ratio†,‡

Internal diameter (µm)	L (m)	SOF (mL/min)	t_M (min)	Relative speed	Relative sample capacity	Head pressure (psi)
530	53	4.24	2.72	1	100	6.7
320	32	2.56	1.25	2.18	22	14.9
250	25	2	0.89	3.05	10.5	21.3
200	20	1.6	0.67	4.06	5.4	28.9
100	10	0.8	0.3	8.97	0.67	68.7
50	5	0.4	0.15	18.5	0.084	150.2

* L/d_c = 100,000.
† d_c/d_f = 1000.
‡ The carrier gas was He at SOF (20), and the column temperature was 100°C.

and η data (33,35) for the typical carrier gases are listed in Table IV.

A comparison of the relative speeds in Tables III and IV reveals the following facts. At a low p_d (short wide-bore columns), helium is approximately 20% slower than hydrogen (i.e., the difference between these two gases is not very large). However, both hydrogen and helium are substantially (3 to 5 times) faster compared with nitrogen and argon. At a high p_d (narrow-bore columns, precisely those in which the speed is an important aspect of the overall performance of the separation), a 40% speed disadvantage of helium over hydrogen is more pronounced compared with that at the low p_d. However, the advantage of helium over nitrogen and argon is less pronounced compared with that at the low p_d. It can be conclude that when the speed of analysis is an important factor, hydrogen is substantially (70%) faster than all other types of carrier gases.

Although H_2 is clearly the best carrier gas for the fastest analysis speed, some laboratories are uncomfortable using H_2 as a carrier gas because of safety concerns. There are means (e.g., accurate safety information, safety interlocks, H_2 generators with limited capacity, and inherently safe instrument designs) of satisfying safety requirements and concerns within most organizations. If H_2 carrier gas use is not allowed, helium is a good second choice.

Carrier gas flow rate

In the previous section, we used the average velocity ($u = t_M/L$) of a carrier gas to compare the speed-related properties of several carrier gas types. There are many other useful applications of this quantity. However, one widely accepted practical application of $\bar{u}$ (i.e., its use as a control parameter for the pneumatic optimization of a column) is a source of many unnecessary errors and confusions (29) that can be avoided if F (25) was used instead of $\bar{u}$ (20). There is a widely held perception that Van Deemter/Golay equations (1,26), typically described in the form:

$$H = \frac{b}{\bar{u}} + c\bar{u} \quad \text{or} \quad H = \frac{b}{\bar{u}} + (c_1 + c_2)\bar{u} \qquad \text{Eq. 3}$$

are valid descriptions of the column plate height (H) regardless of the p_d ($p_i - p_o$) across the column. The fact is, however, that the original theories assumed only low p_d ($p_i - p_o << p_o$) situations. Golay, for example, explicitly stated (1) that his theory was based on the assumption that "the input to exit pressure ratio is nearly unity". However, no one ever has proven theoretically or experimentally that equation 3 is valid for high p_d ($p_i >> p_o$). Furthermore, it has been recently shown that when the column pressure is high, the dependence of H on $\bar{u}$ can be better described as (29):

$$H = \frac{B}{\bar{u}^2} + C_1\bar{u}^2 + C_2\bar{u} \qquad \text{Eq. 4}$$

As same as the coefficients b, c_1, and c_2 in equation 3, their counterparts B, C_1, and C_2 are independent of $\bar{u}$ (coefficients b and c_1 represent, respectively, the resistance to the axial mass transfer in the mobile and the stationary phase, and c_2 represents the resistance to the radial mass transfer in the stationary phase; the coefficients B, C_1, and C_2 reflect respective properties). However, C_2 is only equal to c_2 when B and C_1 in equation 4 are totally different from their counterparts b and c_1 in equation 3. The difference between equations 3 and 4 is a result of the compressibility of a carrier gas and has the following two practically important implications.

First, the dependence of H on $\bar{u}$ in equation 4 is substantially sharper compared with that in equation 3 (Figure 3). This means that at the high p_d it is much more important to correctly predict and maintain the value of $\bar{u}$ that corresponds with the minimum in H (H_{min}) ($\bar{u}_H$) compared with low-p_d situations. Traditionally, $\bar{u}_H$ is referred to as $\bar{u}_{opt}$. In this study, we avoid this terminology and notation because H_{min} is not optimal for the best separation/speed tradeoff (18).

Second, for capillary columns, coefficient c_1 in equation 3 depends on d_c, but neither coefficient in equation 3 depends on L nor η (1). As a result, $\bar{u}_H$ at a low p_d depends on d_c, but is independent of L. However, coefficients B and C_1 in equation 4

Table III. Relative Speeds of Analysis for Several Types of Carrier Gases at a Low p_d*,†

Gas	Relative speed
Hydrogen	1
Helium	0.78
Nitrogen	0.24
Argon	0.21

* $p_i - p_o << p_o$.
† The run time is inversely proportional to the speed.

Table IV. Relative Values of the Speed-Related Parameters for Several Types of Carrier Gases at a High p_d*

Gas	Relative diffusivity†	Relative viscocity‡	Relative speed§
Hydrogen	1	1	1
Helium	0.78	2.23	0.59
Nitrogen	0.24	2.03	0.34
Argon	0.21	2.61	0.28

* $p_i >> p_o$.
† $D/D_{hydrogen}$.
‡ $\eta/\eta_{hydrogen}$.
§ $\sqrt{(D/\eta)}/\sqrt{(D_{hydrogen}/\eta_{hydrogen})}$.

are completely different from their counterparts in equation 3 as well as their dependence on d_c. Both depend on L and η. As a result, in addition to the dependence on d_c, $\bar{u}_H$ at the high p_d in columns with the same inner diameter substantially depends on L (as shown in Figures 4 and 5).

Clearly, it makes little sense to perform a run at flows slower than $\bar{u}_H$. To do so would increase the run time and decrease analysis quality by creating wider peaks. In contrast, there can be an advantage to running higher-than-optimum F values. In fact, several authors have recommended using longer columns at higher-than-optimum F values in order to achieve more separation power per time (plates/min). However, in high p_d conditions, this approach leads to a loss in separation power per time. One must, therefore, be careful not to overgeneralize this concept.

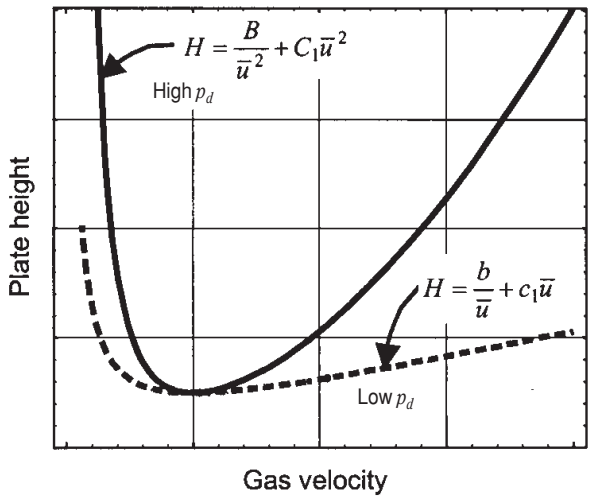

Figure 3. H versus $\bar{u}$ in a thin film column (in equation 2, C_2 = 0). In both cases, the curves are normalized such that their minima coincide.

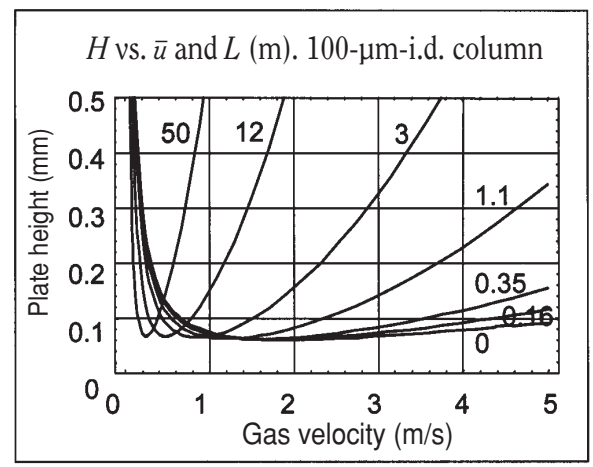

Figure 4. H versus $\bar{u}$ for several L values in meters of a 100-µm-i.d. column (He, 100°C, 1 atm outlet, k = 1) (reprinted from reference 29). Equation 1 yields the curve corresponding with $L = 0$ regardless of the actual L. For the long columns ($L \geq 3$ m) this curve shows substantially higher $\bar{u}_H$ than actual $\bar{u}_H$. This indicates that, using equation 1 to find $\bar{u}_H$ can lead to a substantial loss in the efficiency of a long column.

The ordinate of van Deemter curves is often misrepresented by $\bar{u}$ when it is most accurate to use instantaneous outlet velocity or outlet F. At a low p_d, $\bar{u}$ and $\bar{u}_{opt}$ are directly proportional, whereas at a high p_d they are not. Optimal outlet F for a given d_c and carrier gas type does not change with temperature or L, but $\bar{u}$ (as commonly misused on van Deemter plots) does. This is because gases are compressible. As d_c decreases or L increases, higher p_i values are required to force the carrier gas through the column. The higher the p_i, the more compressed is the gas, the slower is the instantaneous linear velocity at the inlet, and the larger is the difference between the inlet and outlet velocities. This then leads to exaggerated losses in efficiency as a deviation from optimal F values occurs.

Figure 4 illustrates the effect of increasing the p_d on the shape of the height equivalent to theoretical plate versus $\bar{u}$ curve. There was quite a difference in $\bar{u}_H$ for the different L values of 100-µm-i.d. columns. It should be noticed that the $\bar{u}_H$ decreased and became narrower as L increased (p_i increases). Smaller inner-diameter columns tend to exaggerate this phenomenon because of the high p_i values required.

As shown in Figure 5, even though there was a notable loss in efficiency when $\bar{u}$ was doubled for the 530-µm column, it was not as dramatic as the loss incurred by doubling the $\bar{u}$ for the 100-µm column because of the higher p_d.

A high p_d is required in virtually all practical cases in which narrow-bore columns ($d_c \leq 250$ µm) are used (i.e., for all practical cases in which the speed of analysis is important) as well as GC–MS configurations in which the column outlet is under vacuum. Although in all these cases it is especially important to correctly predict $\bar{u}_H$, it is exactly in these cases that equation 3 leads to substantial error in predicting $\bar{u}_H$.

These problems can be avoided by the proper use of equations 3 and 4. However, it can be noticed that there are some practical difficulties. In order to use these equations for the optimization of column pneumatics, it needs to be known beforehand what the working pressure requirement will be in order to know which equation to use. The rules for the calculation of $\bar{u}_H$ are different depending on the pressure region.

Fortunately, although $\bar{u}$ can play a key role in theoretical studies of separation/speed tradeoff (18), it does not have to be used as a pneumatic control parameter in method development practice. The rules of the column pneumatic optimization become substantially more simple if F (measured at predetermined conditions, typically 1 atm and 0°C or 25°C) rather than $\bar{u}$ was used as a pneumatic control parameter in the method development practice. There are several reasons for this.

As was mentioned previously, the conditions corresponding with H_{min} are not the best for the best separation/speed tradeoff. The tradeoff is the most favorable at the minimum (Q_{min}) in the plate duration (Q), which is defined as:

$$Q = H / \bar{u} \qquad \text{Eq. 5}$$

As this definition indicates, Q is the average time that it takes for the carrier gas to migrate along the distance equal to H. The inverse of Q ($1/Q$) is the time per plate.

The prominent role of quantity $H/\bar{u}$ in studies of the speed-related aspects of separation was first described by Purnel

(4,36,37), the same role of $H/\bar{u}$ was also explored by Cramers and Leclercq (11,38). A definitive theory of the role of Q in the separation/speed tradeoff was described in references 18 and 20, in which the term "plate duration" was proposed. It has been shown (18) that Q_{min} corresponds with the shortest analysis time (isothermal or temperature programmed) for N in a column with d_c. This means that, if the analysis time is important, the column should be run at Q_{min} by choosing the L value that is just enough for the required N. This way, the required separation power will be achieved in the shortest time. It would, in fact, take longer to achieve the same separation with the corresponding column at its H_{min} (18,20).

Not only does running a column at Q_{min} lead to a better separation/speed tradeoff, but also the conditions corresponding with Q_{min} are much easier to predict than those corresponding with H_{min}. In fact, the SOF that was discussed earlier corresponds with Q_{min}. As a function of F, Q can be expressed as (18,20):

$$\frac{Q}{Q_{min}} \approx \frac{4\delta}{3} + \left(\frac{SOF}{F}\right)^2 \left(\frac{1 + 2(F/SOF)^2}{3}\right)^{3/2} \qquad \text{Eq. 6}$$

where the quantity δ represents the contribution of the stationary phase to Q. It can be verified that equation 6 has a minimum when F equals SOF (Figure 6). The relationship between SOF and F corresponding with the H_{min} (F_H), depends on the film thickness (d_f) (20). For thin-film columns, SOF equals $F_H\sqrt{2}$, otherwise SOF is greater than $F_H\sqrt{2}$ (20).

It is remarkable that of the four relevant pneumatic parameters ($\bar{u}_H$, $\bar{u}_Q$ ($\bar{u}$ corresponding with Q_{min}), F_H (F corresponding with H_{min}), or SOF (which, in line with the notations for its counterparts, can be denoted as F_Q)) only SOF does not depend on L or d_f.

These simplifications facilitated the development of a simple formula (20) for the default SOF ($SOF_{default}$) for general use in all practical fast GC cases.

$$SOF_{default} = SOF_{100\ \mu m} \times 0.01 \times \text{diameter (μm)} \qquad \text{Eq. 7}$$

In this formula, $SOF_{100\ \mu m}$ represents the SOF in a 100-μm column that only slightly depends on the column temperature and solute retention (39). The recommended values (20) of $SOF_{100\ \mu m}$ for typical carrier gas types are listed in Table V.

Table VI lists the results of applying Eq. 7 to common columns and carrier gases. The F values presented represent outlet F value rates at standard conditions (1 atm and 25°C) as they would be measured exiting from a detector at room temperature. Most recent GCs allow for the setting of outlet F values such as those presented and then calculate the corresponding head pressure based on column dimensions and oven temperature. Alternately, separate software tools (17) or chromatographic data systems can be used to provide corresponding head pressures.

The importance of using SOF at a high p_d is illustrated in Figure 7. For Figure 7A, the column used was a 0.1-μm HP-5 column (10-m × 100-μm i.d.), and the oven program began at 70°C for 0.4 min, ramped to 150°C at 40°C/min for 0.4 min, ramped to 200°C at 15°C/min, and then ramped to 300°C at 25°C/min for 2 min. The carrier gas was H_2 at 44.6 psi constant pressure. Also used was an Agilent 6890 GC with a pillow insert and flame ionization detection. The sample used was 1 μL of a 10-ppm pesticide mix in acetone (split 5:1). For Figure 7B, the oven program began at 70°C for 0.2 min, ramped to 150°C at 80°C/min for 0.2 min, ramped to 200°C at 30°C/min, and then ramped to 300°C at 50°C/min for 1 min. The carrier gas was H_2 at 95.0 psi. Figure 7C shows the results of translated conditions for a 5-m × 100-μm-i.d., 0.1-μm HP-5 column. The

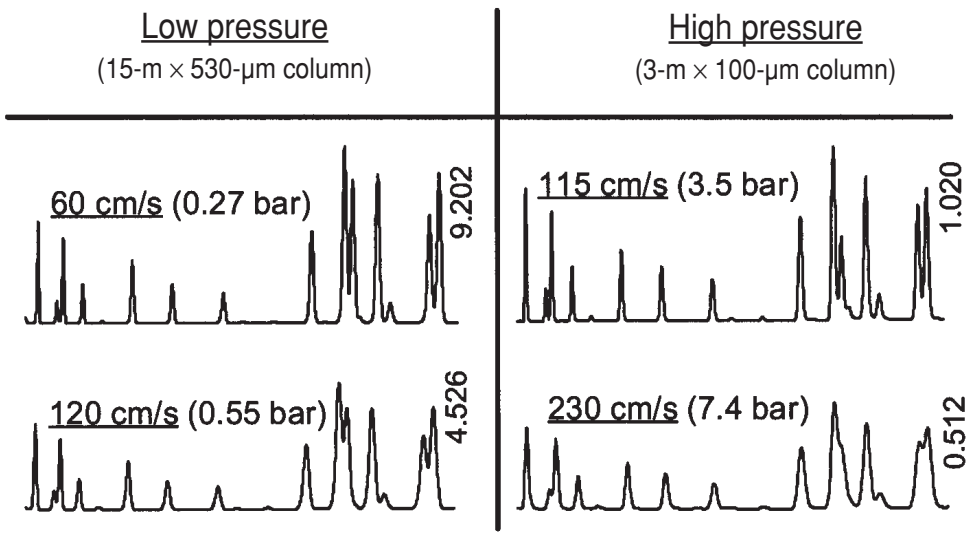

Figure 5. Effect of $\bar{u}$ on the separation efficiency of two columns with the same efficiency at slightly higher SOF conditions. In all cases, the p_o was ambient pressure (approximately 1 bar). Shown in parentheses for each chromatogram are the p_d values. Under original conditions in a 530-μm column p_d is significantly less than p_o, but for the 100-μm column p_d is significantly greater than p_o. As a result, the latter is much more sensitive to efficiency losses because of an F increase (further from optimum $\bar{u}$) than the former. Conditions were translated to maintain the relative retention order.

oven program began at 70°C for 0.15 min, ramped to 150°C at 106°C/min for 0.15 min, ramped to 200°C at 40°C/min, and then ramped to 300°C at 66°C/min for 0.75 min. The carrier gas was H_2 at 44.6 psi. At a high p_d, a reduction in the column efficiency in favor of reduction in the analysis time can be done more effectively by reducing L than by increasing F beyond SOF. If, in the case of a temperature-programmed analysis, each approach is accompanied by method translation, then neither change affects the peak elution pattern and they equally affect R_s values of all of the peak pairs in the chromatogram. Figure 7 shows that, although both approaches lead to a reduction in the analysis time (t_a), increasing F beyond SOF leads to a much smaller reduction in t_a compared with that resulting from a reduction in L.

Table V. $SOF_{100\ \mu m}$ for Common Carrier Gases in 100-µm-i.d. Columns

Gas	$SOF_{100\ \mu m}$
Hydrogen	1.0
Helium	0.8
Nitrogen	0.25
Argon	0.22

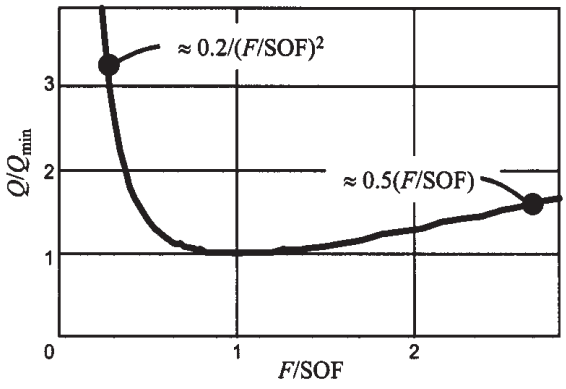

Figure 6. Q values relative to Q_{min} plotted as a function of flow relative to SOF (shown in equation 3). Q_{opt} coincides with SOF.

It has been shown elsewhere (21) that at a high p_d a translatable change in t_a resulting from a change in L at a fixed F (e.g., at SOF) is proportional to R_s^3 (i.e., $t_a \approx R_s^3$ (variable L, fixed F)).

For example, a translatable reduction in the R_s of all peak pairs by a factor of 2 leads to an 8-fold reduction in the analysis time. However, when increasing the flow for a given column in that F exceeds the SOF, the increase in F yields a reduction in t_a that is only proportional to the reduction in R_s (i.e., $t_a - R_s$ (variable F, fixed L)).

The significance of this concept is in the separation power (R_s) versus speed tradeoff. Let's say that we wished to reduce the analysis time of a current method (e.g., Figure 7A) approximately twofold (the original method in this example was performed at the column's SOF rate (1.0 mL/min) to yield the best separation power per time). It could be possible to simply translate the conditions (p_i and ramp rate) of the current method to achieve a twofold speed gain (e.g., Figure 7B), or it is possible to use a column of half the length run at its SOF rate. Figure 7C illustrates that using a shorter column at its SOF rate yields the better separation in less time. As supported by most prior examples in the literature, the same experiment repeated for large inner-diameter columns (low p_d) would likely show better separation for the twofold speedup of the long column rather than for one-half its length at SOF.

Therefore, when high-p_d columns are used to trade separation power for analysis speed, the most effective approach is to "cut the column" and use SOF.

Temperature-program rate

An optimal temperature-program rate for fast GC is that which renders the best separation in the least time. If it is the intention to migrate a current method to a faster one, then following method translation principles is highly recommended. If the goal is to start to develop a method from scratch, then a few general concepts are helpful to keep in mind.

It is important to remember that the relative retention (including elution order) of solutes depends on temperature. Figure 8 shows how relative retention can change as a function of temperature. Although Figure 8 is an isothermal analysis, changes in the retention order can also occur if changing the temperature-program rate independently from F.

Table VI. Recommended *F* Values* (SOF) for Common Column Sizes and Carrier Gas Types

Column inner diameter (µm)	H_2 (mL/min)	He (mL/min)	N_2 (mL/min)
50	0.5	0.4	0.12
100	1.0	0.8	0.25
200	2.0	1.6	0.5
250	2.5	2.0	0.62
320	3.2	2.6	0.8
530	5.3	4.2	1.3

* F values represent normal flow, such as those that would be measured coming out of the end of the column at 25°C and 1 atm.

If the peaks of interest do respond differently to temperature or temperature ramp (independent of *F*), then an adjustment of plateau temperatures and ramp rates can provide powerful levers in optimizing conditions for the best separation in the least time. However, once these conditions have been painstakingly optimized, it then becomes extremely important to follow method translation principles when scaling the method or else the relative retention will be affected.

Unfortunately, a common approach to speeding up previous methods in the past has been to "crank up" the temperature-program rate. The burden of identifying the elution order and identity of peaks after such a change can then became a serious time synchronization for methods involving many peaks (e.g., > 15).

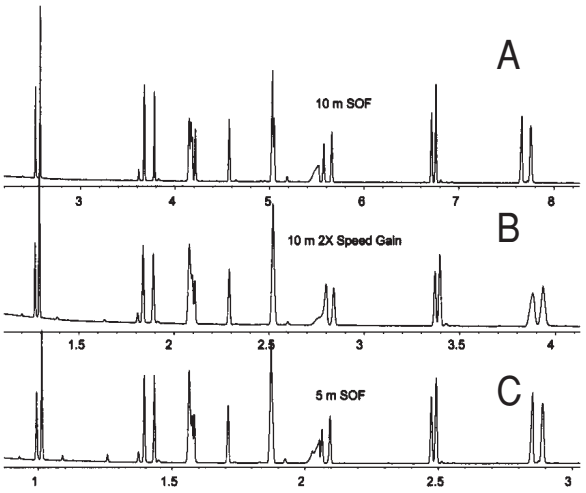

Figure 7. Trading separation power for speed at a high p_d by increasing *F* (Figure 7B) or reducing *L* (Figure 7C). A twofold translation of the original is shown in Figure 7B. SOF with the shorter column yields a greater than twofold speedup of Figure 7A (i.e., 2.6 time more) with better efficiency than Figure 7B.

Changes in the relative retention or elution order can also arise from increasing the column *F* without changing the temperature ramp rate proportionally (i.e., not adhering to method translation principles). Figure 9 illustrates the change in the relative retention as the head pressure (and thus t_M) is changed while the temperature-program rate remains constant. The optimum *F* for this column under the experimental conditions used corresponds with a head pressure of approximately 50 psi He (Figure 9A). In this case, somewhat counterintuitive, as *F* became faster, the separation of the indicated pair of peaks became better. This is because the two solutes are chemically different and their individual retention versus column temperature relationships are different. Clearly, the effort required to identify peaks after the relative retention has changed can be quite burdensome, especially for methods involving many peaks.

Therefore, again, the point is that once an effective temperature program–*F* combination has been determined, method translation principles for all further scaling of the method should be strictly followed.

When developing a temperature-programmed capillary GC method involving a large number of components (> 20) from scratch, global optimization procedures for temperature programs become more complex, more time consuming, and ultimately result in limited success. The more target analytes in a sample, the more likely will there be competing phenomena that counterbalance each other (when some solutes become better separated, others become worse). In these cases, it is worthwhile to consider using a generally optimal temperature ramp rate that yields a good compromise between peak capacity, separation power, and analysis time. A recent study recommends such a ramp rate: $10°C/t_M$ (21). The ramp rate is stated in terms of t_M because of the relationships previously presented. Ramp rates significantly faster than this will in effect not allow for a sufficient partitioning time in the stationary phase for the effective use of the column (solutes will experience significant partitioning along only a fraction of *L*). If solutes are so different that separation is satisfactory with

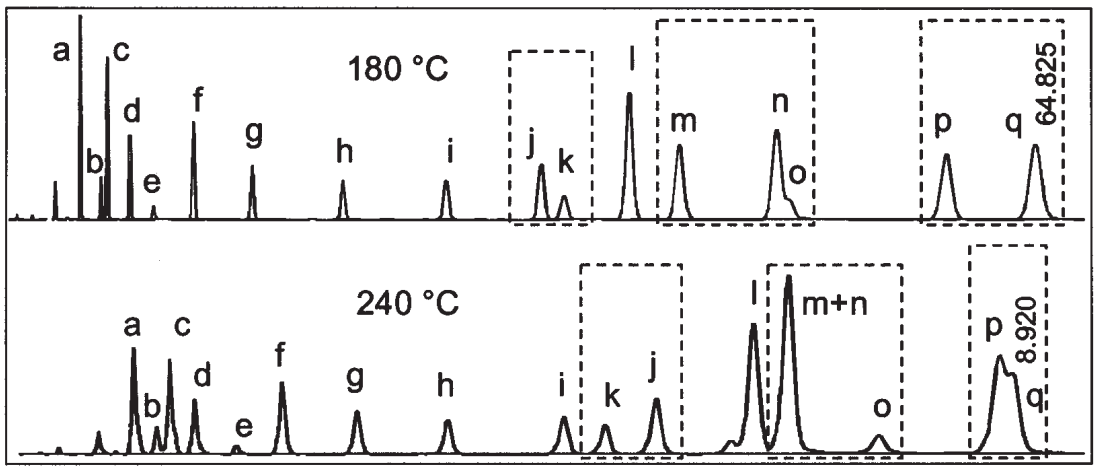

Figure 8. An isothermal analysis of an EPA-608 mix on a 30-m × 530-µm × 0.88-µm HP-5 column with a 4-mLn/min outlet flow of He, illustrating that a change in temperature can dramatically change the peak elution pattern.

ramp rates significantly greater than $10°C/t_M$, then even faster analysis is possible by using a shorter column at its SOF or the same column with a higher F and the same absolute temperature ramp such that its reduced ramp rate is closer to $10°C/t_M$.

For the case in which the current method has generally met all of the analytical requirements except for speed, then applying the concepts of method translation to scale the method is the most direct and efficient approach to developing a fast GC method. An example is shown in Figure 10 in which the initial analysis provided more separation than required as well as took too long. One constraint of speeding up the

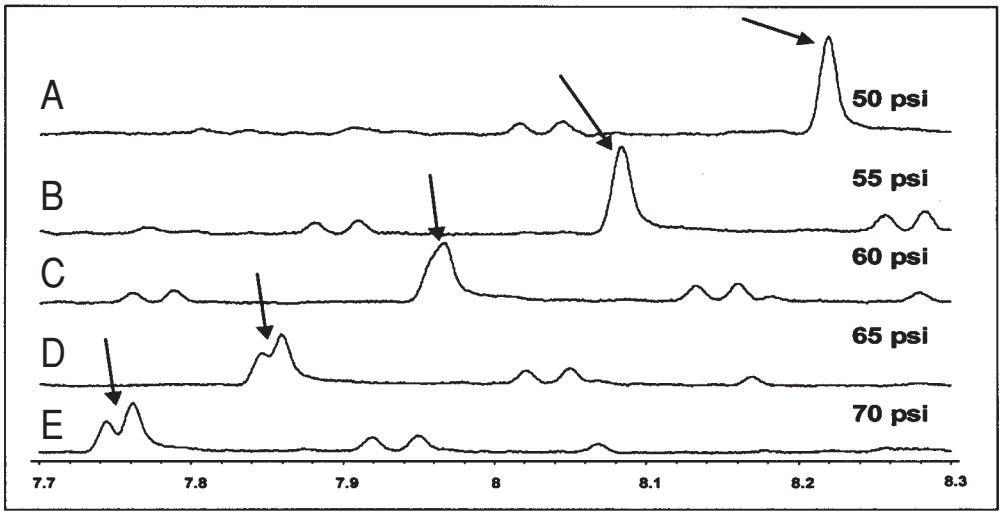

Figure 9. Orange oil extract separated on a 100-µm × 0.1-µm × 10-m HP wax column. The relative retention changes as the head pressure is changed with a constant temperature-program rate. The temperature change and flow are not synchronized.

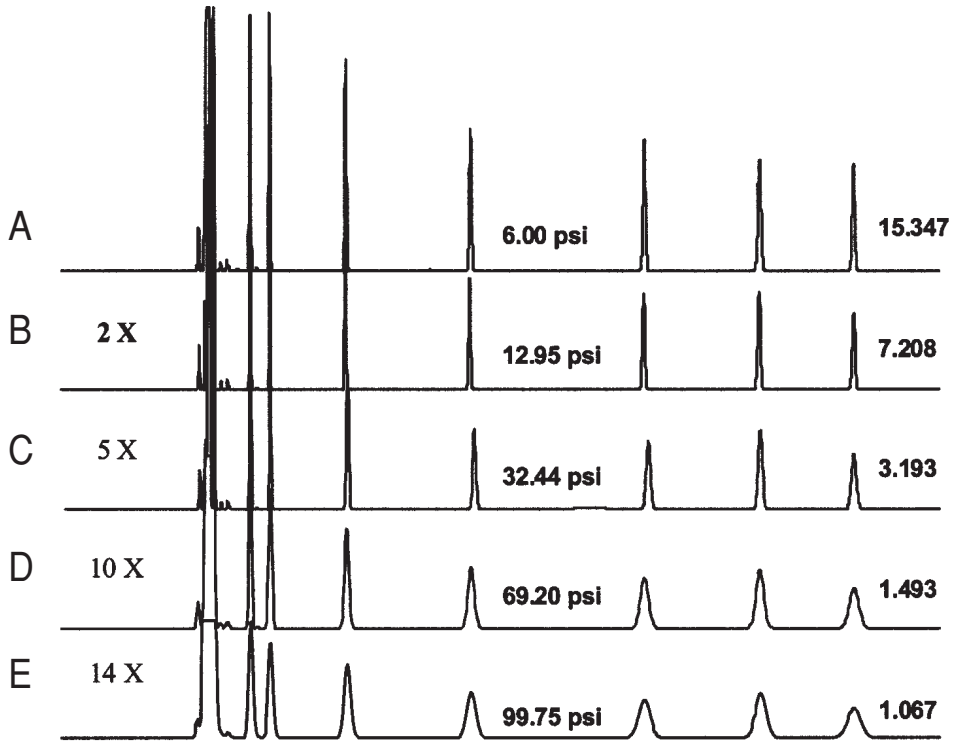

Figure 10. An original and several translations of the original up to 14 times faster. The same column (30-m × 320-mm × 0.5-mm HP1) was used at increasing speeds via method translation. The retention time of the last peak is listed along with the corresponding He p_i.

method was that the same column had to be used because of other methods that were being run on the instrument. Therefore, "cutting the column" was not an option, nor was substituting one that had different dimensions. Thus, the only parameters available were flow and temperature-program rates.

Figure 10 illustrates speeding up the original method by increasing the flow (decreasing t_M) and temperature-program rate in a proportional manner following the concepts of method translation. In this case we traded excess R_s for speed improvement. The eventual limitation to speeding up this method even further was an instrumental one; the maximum instrument pressure (100 psi) was reached at the fourteen-fold speedup, and its corresponding temperature ramp rate was at the limit of the instrument being used.

In order to best illustrate the point that relative retention remained constant (proportionally scaled), each chromatogram was stretched such that the last peaks would line up each other. The test of maintaining relative retention was performed to see if all the peaks in the chromatogram were aligned. This visualization is the same as multiplying the "speed gain factor" at the left of each chromatogram to all retention times. As can be seen from the alignment, method translation ensured that relative retention remained constant.

Figure 11 illustrates this point further by superimposing scaled temperature programs and their resulting chromatograms.

The concept of using t_M as the fundamental time unit is illustrated by the identical normalized ramp rates listed under the curves, even though the absolute ramps on the top of the curves are quite different. It should be noticed that the elution order (relative retention) was maintained.

Figure 12 shows several additional translations of the original method presented in Figure 11. It should be noticed that the relative retention was maintained, the 100-µm × 10-m column had similar efficiency to the 530-µm × 30-m column, and cutting the 100-µm column and running it close to optimal F yielded much higher separation power and speed gain compared with running the 530-µm column at a faster F.

Capacity and injection consideration

As mentioned in the Introduction section, one of the tradeoffs of moving to faster columns with a smaller diameter is lower sample capacity. Figure 13 illustrates what can happen if a smaller diameter column is migrated to without proportionally reducing the amount of solute reaching the column. It should be noticed that the peak for the overloaded component is more distorted for the same amount injected into smaller inner-diameter columns because of the corresponding higher sample loading per amount of stationary phase as d_c decreases.

Figure 14 shows that peak shape can be maintained (in this case the peak shape maintained was overloaded for demonstration purposes) if the amount of solute reaching the column is scaled proportionally to the amount of stationary phase. It should be noted that one of the penalties paid for injecting less sample is poorer signal to noise (S/N), because there is less solute to be detected. This is somewhat compensated for because faster chromatography on narrower-bore columns yields narrower peaks and thus higher signal per amount injected. However, the increased H per amount does not fully make up for the lower amount reaching the detector, thus there is a net decrease in S/N. One can only go so far in reducing the injection amount before detector (or system) noise dominates the signal.

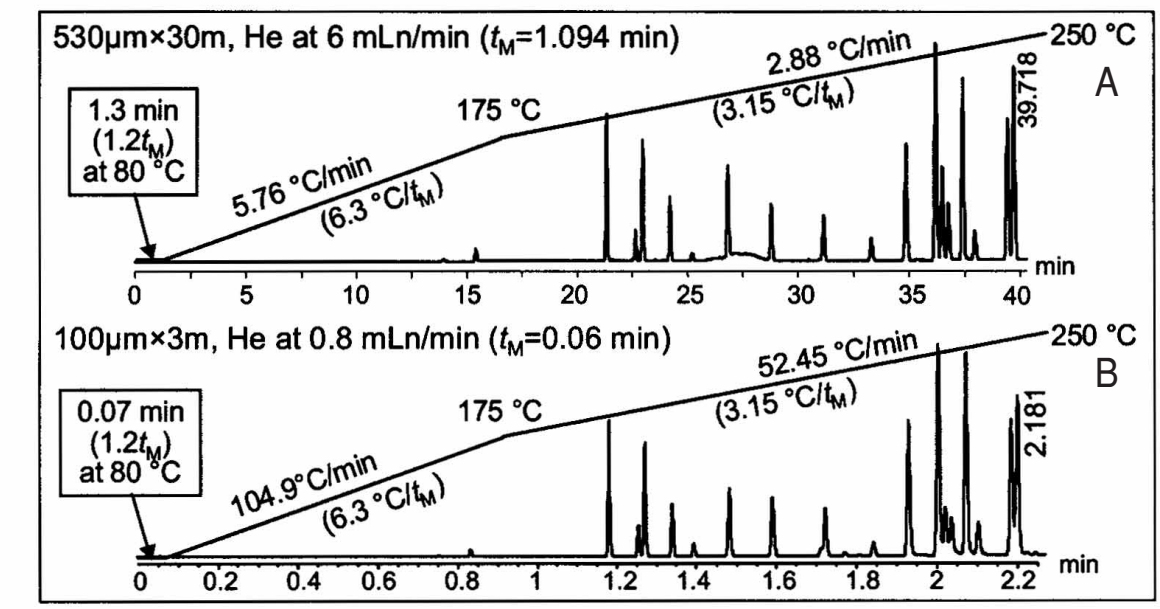

Figure 11. Resulting chromatograms from superimposed scaled temperature programs. The process of method translation scales hold times and ramp rates proportional to t_M values. The relative retention (elution order) is maintained, although efficiency is a function of column dimensions and individual F values relative to the optima for those columns. In this example, the 100-µm column has approximately half the theoretical plate count of the longer 530-µm column.

It should be noted that although the distorted peak in Figure 14 was well-resolved from neighboring peaks, it would be reasonable to accept some (or even more) peak distortion in order to get better S/N if quantitation at a low solute concentration were important. For those cases in which the solute of interest is overloaded at the injected levels necessary for detection and elutes close to other solutes, analysis speed may not be as far. In these cases, a thicker film, larger inner-diameter column (i.e., not so fast column), or both might be required to accommodate a large enough sample loading to detect the solute.

Conclusion

Fast GC brings with it the promise of providing faster, more cost-effective analytical answers. The effort required to migrate current methods to faster ones can be minimized by understanding the underlying relationships involved, some of which run counter to commonly applied tenets (especially for high-pressure conditions).

The concept of translatable versus nontranslatable method parameters allows for the migration of current methods to faster ones in a very predictable way. Concepts of SOFs and

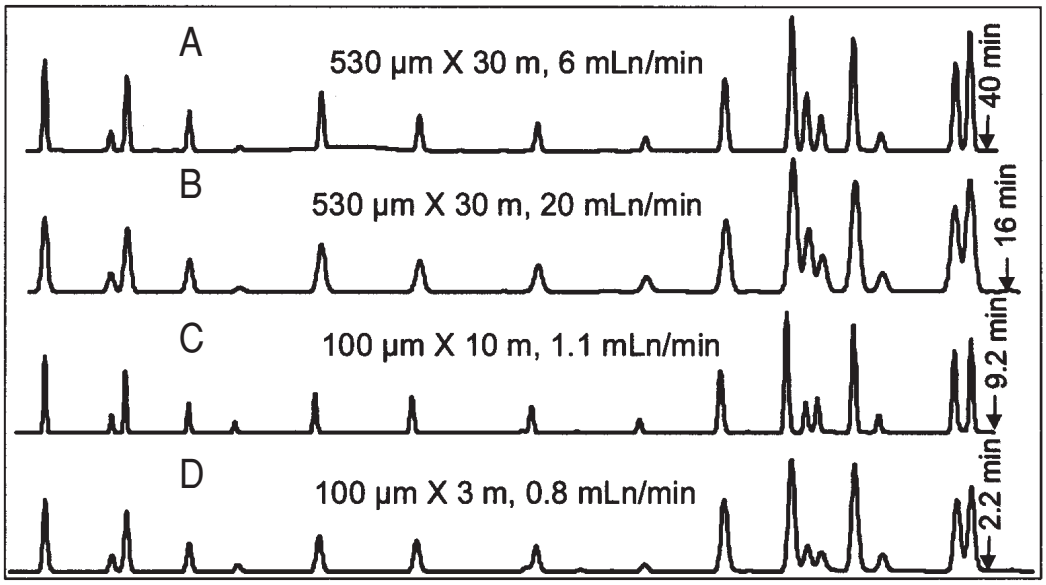

Figure 12. Several translations in the method parameters shown in Figure 11. The separation of EPA-608 organochlorine pesticides is shown on three HP-5 columns. All temperature programs are translations of the original 530-mm column conditions (Figure 11A).

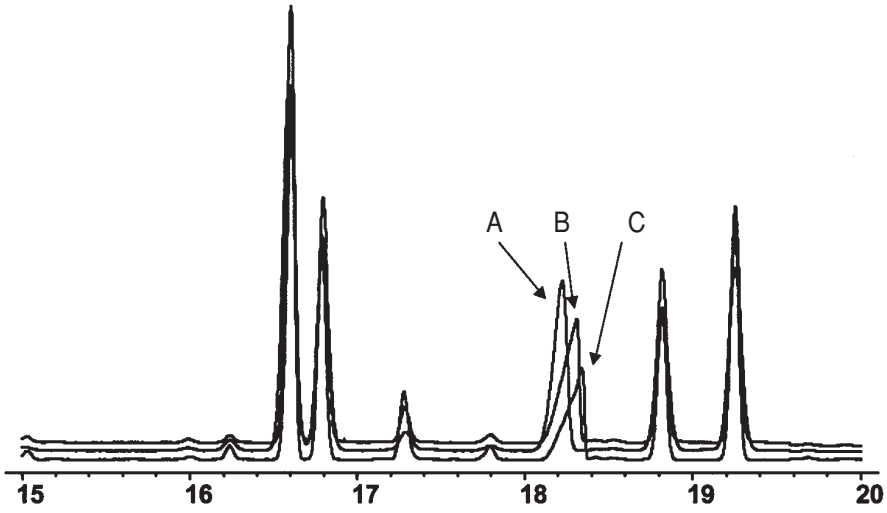

Figure 13. Identical injected amounts of orange oil separated on three different HP-5MS columns: (A) 530 µm × 0.53 µm × 30 m, (B) 320 µm × 0.32 µm × 30 m, and (C) 250 µm × 0.25 µm × 30 m. Oven temperature programs and head pressures were translated and locked to achieve identical retention times for easier comparison. Because smaller inner-diameter columns have less sample capacity, peak distortion increases because of overload.

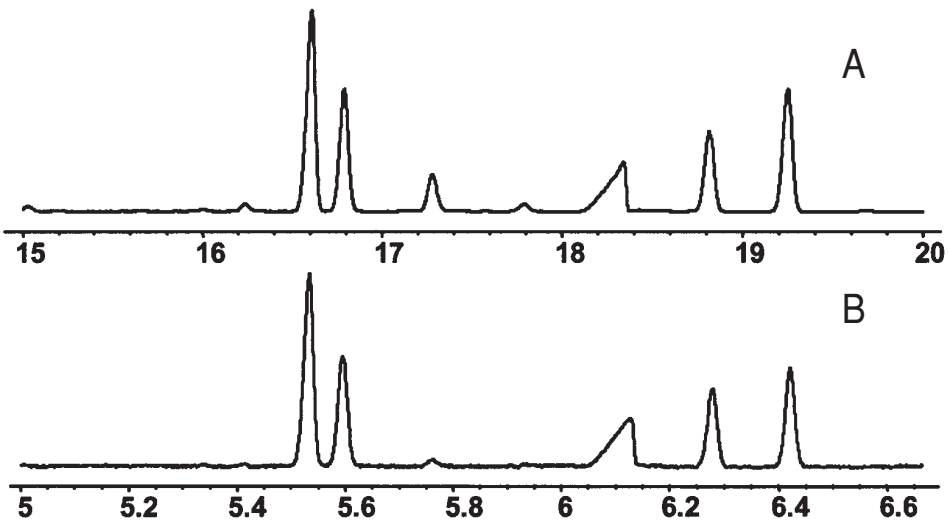

Figure 14. The maintaining of peak shapes by adjusting the injection amount in proportion to column capacity. If injection amount is adjusted in proportion to column capacity (as it was in this figure), then peak shape attributes of the original method can be maintained. The original analysis (A) used a 250-µm × 0.25-mm × 30-m column into which 1 µL was injected with a 25:1 split ratio. For the translated method using the smaller 100 µm × 0.1-mm × 10-m column (B), 1 µL was injected with a split ratio of 444:1, because the smaller column had approximately 17 times less capacity than the original.

optimal temperature-program rates help minimize the time required to create methods that give the best overall separation in the least amount of time.

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