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High-speed gas chromatography

Theoretical and practical aspects

GUY GASPAR*,[a]
Chrompack France, B.P. 20, F-91941 Les Ulis Cedex (France)

ABSTRACT

The performance of a gas chromatographic (GC) system depends mainly on the column efficiency and for fast separations, on the equipment design. A theoretical and practical study shows the importance of the various phenomena involved in the optimization of a GC system. An original approach, the performance concept, is introduced. Exact and simplified, approximate expressions are given for the calculation of the optimum practical velocity, the optimum column length and the minimum analysis time. The calculated values are in good agreement wit experimental valves from other sources. In the experimental part two cases are distinguished: fast chromatography using conventional equipment and ultra-fast chromatography requiring specially designed instrumentation. The most important considerations for the practical realization of high-speed separations are discussed in detail: column parameters, choice of working conditions and extra-column parts, such as the sampling device, detector, amplifier and data acquisition system. Some examples of extremely fast analyses (analysis times a few of seconds or less) are shown.

INTRODUCTION

Gas chromatographic (GC) analyses can potentially be performed much faster than they are practised at present. This fact was clearly understood by Desty and Goldup [1,2] soon after the introduction of open-tubular capillary columns; they published very impressive fast separations (analysis times of a few seconds) by using short, narrow-bore columns. Later, the team at the Ecole Polytechnique (France) directed by Guiochon performed systematic investigations to study instrumental contributions to the system efficiency and to the analysis time; several very rapidly obtained chromatograms (analysis time 2 s or less) were shown [3–7], these analyses being realized with a special laboratory-built equipment. These experiments were followed by studies by Cramers' research group at Eindhoven University of Technology; in particular, work by Schutjes and co-workers [8–10] showed the potential of high-speed GC for real application problems. At that time all these studies represented real technical exploits because of the lack of adequate instrumentation. Now-

[a] Present address: Fisons Instruments, 85, Av. Aristide Briand, 94 110 Arcueil, France.
Bon Anniversaire Professeur Guiochon.

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adays the great progress achieved in electronics, computer techniques, silicon micromachining and column technology (narrow-bore packed or open-tubular fused-silica columns) has allowed the construction and even the commercialization of reliable, moderate cost portable high-speed gas chromatographs; the pioneering work in this field by Microsensor Technology (Fremont, CA, USA) must be mentioned [11–13].

First we have to answer the common question of whether there is a need for very high-speed GC and what its benefits would be. The most current argument against fast chromatography is that the sample preparation itself is often a time-consuming procedure and the time saving resulting from fast analysis becomes negligible.

Naturally, the situation is simpler when there are pure samples to be injected, as in gas analyses, process measurements and field applications. A very promising application would be the continuous control of the air composition in operating rooms or of the air expired by anaesthetized patients. With complicated sample preparations the advantage of fast analyses should be interpreted differently: they allow an increase in precision or signal-to-noise ratio. If an analysis can be carried out 100 times faster, the same sample can be injected 100 times, resulting in a tenfold higher precision. Under certain conditions, it is possible to achieve extremely high reproducibility [14], and consequently the superposition of consecutive runs gives better signal-to-noise ratios; by superposing 100 runs of the same sample we obtain tenfold higher signal-to-noise ratios, resulting in tenfold lower detection limits.

This paper will focus on those aspects which are of special importance for fast (possible with conventional equipment) and for ultra-fast (requiring special instrumentation) chromatography.

THEORY

System efficiency and performance

Conventional packed columns having poor efficiency do not give a good perspective for fast separations. Although some rapid analyses with packed capillary columns have been reported [12], the most promising way seems to be the use of open-tubular columns, which have the additional advantage of much higher permeability. Consequently, we limit our discussion to the properties of these columns, which implies the use of the Golay equation to calculate the column theoretical plate height (HETP):

$$H = \frac{2D_G}{u} + \left[\frac{2k'}{3(k'+1)^2}\cdot\frac{d_f^2}{D_L} + \frac{1+6k'+11k'^2}{96(k'+1)^2}\cdot\frac{d_c^2}{D_G}\right]u \qquad (1)$$

or in its simplified form:

$$H = \frac{B}{u} + (C_L + C_G)u = \frac{B}{u} + Cu \qquad (2)$$

In order to obtain fast separations, let us assume that we are working with short columns and with hydrogen as the carrier gas; consequently, the influence of the pressure gradient on the band broadening is negligible, that is, the James–Martin and Giddings pressure drop correction factors are equal to 1. In other words, in our

equations the velocity u can be considered as the average carrier gas velocity. By derivation we can obtain from eqn. 2 the optimum velocity:

$$u_{opt} = (B/C)^{1/2} \tag{3}$$

and the minimum HETP value:

$$H_{min} = 2(BC)^{1/2} \tag{4}$$

For thin liquid films, the C_L coefficient can be neglected in comparison with C_G; hence by replacing B and C_G from eqn. 1, we obtain

$$u_{opt} = 8 \cdot \frac{D_G}{d_c}\left[\frac{3(k'+1)^2}{1+6k'+11k'^2}\right]^{1/2} = 8 \cdot \frac{D_G}{d_c} \cdot f(k') \tag{5}$$

and

$$H_{min} = d_c/f(k') \tag{6}$$

The fundamental assumption of the Golay model is that band broadening occurs only in the column. This hypothesis is valid when the column is long and the linear gas velocity is low (normal current practice). Under high-speed conditions (short columns and high velocities), the instrumental contribution becomes important. Gaspar *et al.* [6] showed the effect of extra-column parts on the system efficiency:

$$H = \frac{B}{u} + Cu + Du^2 \tag{7}$$

This equation was also proved experimentally and excellent agreement was found between measured and predicted values. In eqn. 7, the last term, proportional to the square of the gas velocity, describes all extra-column contributions (injector, connections, detector, electrometer, recording or data handling device) in the following manner:

$$D = \frac{\sigma_{EC}^2}{(k'+1)^2 L} \tag{8}$$

where σ_{EC}^2 is the sum of extra-column variances expressed in time units. The meaning of D is logical: the column is longer and the efficiency loss caused by the instrumentation is smaller; the solute is more retained and the extra-column contribution is smaller.

The existence of a quadratic term in eqn. 7 has the following consequences: (a) the minimum HETP is higher than that one given by eqn. 4, that is, the system is less efficient; and (b) the optimum velocity is smaller than the value given by eqn. 3, that is, to obtain the highest possible efficiency we are obliged to work more slowly.

These effects are negligible with conventional (long) capillary columns if they are properly connected and other parts (injector, detector, etc.) are also functioning normally. For instance, with conventional equipment the magnitude of the sum of all extra-column variances can be estimated as 0.001 s^2; using a 25 m × 0.25 mm I.D. column for a compound having a capacity factor of 1.5, eqns. 3 and 4 give u_{opt} =

58.7 cm/s and H_{min} = 0.170 mm, and a plate number of 146 910. By considering also the Du^2 term, these values become 57.0 cm/s, 0.172 mm and 145 027, respectively (substituting D_G = 0.25 cm^2/s in the Golay equation, corresponding to *n*-octane at room temperature with hydrogen as carrier gas). The differences are negligible. However, with a specially designed system for ultra-fast analyses (85 cm × 0.065 mm I.D. column and total extra column variance only 0.0000685 s^2, calculated from Fig. 1) extra-column effects become dramatic: the optimum velocity falls to 110 cm/s instead of 226 cm/s, the minimum HETP is 0.072 mm instead of 0.044 mm and we have only 11 834 instead of 19 211 plates; the Du^2 term will amount to 21.7% of the total HETP value calculated at u = 110 cm/s.

It would be possible to characterize simultaneously the resolution and the rapidity by a new, not yet defined, chromatographic term, which we can call "performance". We shall use it in the following manner: (a) for two chromatographic systems, that with the higher performance gives the same resolution in a shorter analysis time; or (b) the performance is higher if the system gives a higher resolution in the same time. In both instances we assume that the same mixture is injected and the same type of stationary phase is used.

Gaspar *et al.* [7] introduced the notion of the time necessary to generate a theoretical plate (*TH*), defined as

$$TH = \frac{\sigma^2}{t_R} \tag{9}$$

which gives the zone broadening as the time-based variance increase per unit time spent in the chromatographic system and which can characterize the system performance. Considering eqn. 10 also, *TH* is the inverse of the magnitude already used, *i.e.*, the number of plates generated per unit time. *TH* is an analogous quantity to HETP; while the classical theory of GC is based on the efficiency, we shall use the performance measured by *TH*. The best performing system is the one which results in the smallest increase in band time variance in a given time. By transformations, we obtain from eqn. 9

$$TH = \frac{\sigma^2}{t_R^2} \cdot t_R = \frac{t_R}{N} = (k' + 1)\frac{L}{u} \cdot \frac{H}{L} = (k' + 1)\frac{H}{u} \tag{10}$$

and from eqn. 7

$$TH = (k' + 1)\left(\frac{B}{u^2} + C + Du\right) \tag{11}$$

By derivation, we can show that *TH* has a minimum at an optimum velocity given by

$$u' = (2B/D)^{1/3} \tag{12}$$

It is easy to show that this is the velocity at which the tangent, through the origin, touches the H–u curve (*cf.*, Fig. 1). We have to understand the meaning of u' in the following way: starting from the optimum velocity (which gives the minimum HETP value) and increasing the carrier gas velocity up to u', the increase in analysis speed is

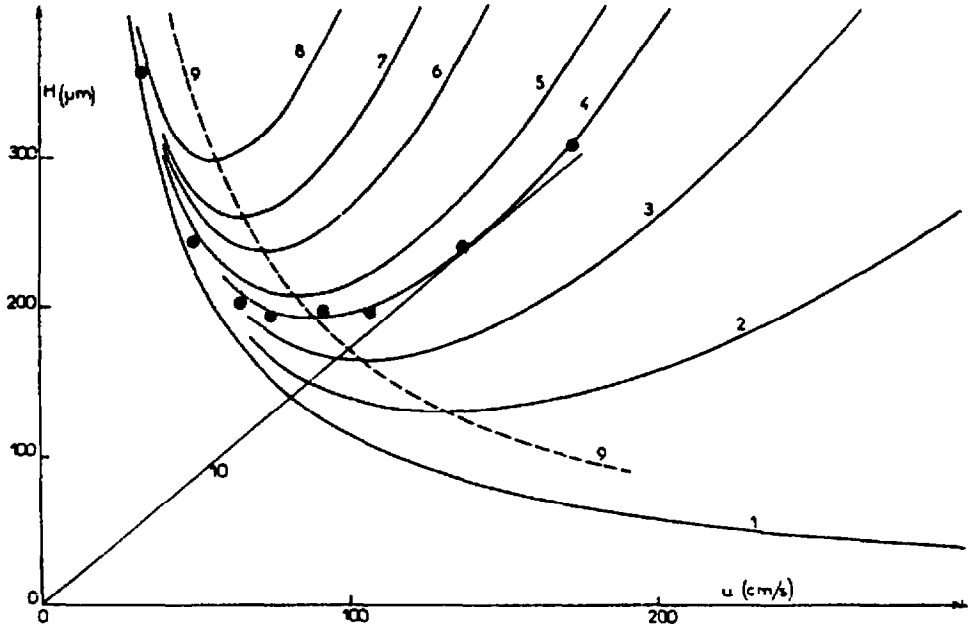

Fig. 1. Plot of HETP *versus* carrier gas velocity. Carrier gas, hydrogen; sample, methane; column, 85 cm × 65 μm I.D.; temperature, 25°C. *D*: (1) O; (2) $2.5 \cdot 10^{-7}$; (3) $5 \cdot 10^{-7}$; (4) $8.1 \cdot 10^{-7}$ with experimental points; (5) $1 \cdot 10^{-6}$; (6) $1.5 \cdot 10^{-6}$; (7) $2 \cdot 10^{-6}$; (8) $3 \cdot 10^{-6}$ s^2/cm. Curve 9 links the minima of all the $H - U$ plots. Line 10 is the tangent from the origin to curve 4, corresponding to minimum *TH*.

greater than the decrease in efficiency, but at higher gas velocities the situation is completely reversed and the efficiency decreases rapidly.

In the early days of capillary GC, Scott and Hazeldean [15] defined the optimum practical gas velocity (OPGV) as that at which H/u is minimum. It is easy to find a similarity and even an identity between OPGV and u' but, whereas the classical theory results an infinite value for the OPGV, now u' has a concrete value.

The plate height at velocity u' is

$$H' = \frac{3}{2}(2B)^{2/3} D^{1/3} + \frac{C}{D^{1/3}}(2B)^{1/3} \tag{13}$$

It is important to note that this value is not the minimum but that one which corresponds to the optimum practical gas velocity.

Analysis time

The retention time of a compound is given by the well known expression

$$t_R = (k' + 1)t_0 = (k' + 1)\frac{L}{u} = N \cdot \frac{H}{u}(k' + 1) \tag{14}$$

If we compare it with eqn. 10, we obtain the following very simple relationship:

$$t_R = N \cdot TH \tag{15}$$

The target of chromatography is to separate the components of a mixture. Therefore, in order to obtain the minimum retention time:

(1) we have to use a system without any redundancy or, in other words, the minimum necessary plate number sufficient for a given separation is

$$N_{ne} = 16R_s^2\left(\frac{\alpha}{\alpha - 1}\right)^2\left(\frac{k' + 1}{k'}\right)^2 \tag{16}$$

(2) we have to set the velocity u' (see eqn. 12) giving the minimum value of TH:

$$TH' = (k' + 1)\left[\frac{3}{2}(2B)^{1/3} D^{2/3} + C\right] \tag{17}$$

(3) the previous conditions involve using the shortest column, its length being

$$L' = N_{ne}H' \tag{18}$$

However, eqns. 12, 15 and 18 are not valid for calculations because they depend on the column length via D. As Gaspar *et al.* [7] have shown, by introducing a quantity $\mathscr{D}$ independent of the column length:

$$\mathscr{D} = DL = \frac{\sigma_{EC}^2}{(k' + 1)^2} \tag{19}$$

the shortest column length will be

$$L' = \frac{7.35\mathscr{D}B^{1/2}}{\left[\left(C^2 + \frac{6\mathscr{D}}{N_{ne}}\right)^{1/2} - C\right]^{3/2}} \tag{20}$$

and now the following form of the optimum practical gas velocity is also independent of L:

$$u' = \left[\frac{6B}{\left(C^2 + \frac{6\mathscr{D}}{N_{ne}}\right)^{1/2} - C}\right]^{1/2} \tag{21}$$

It is interesting that contrary to eqn. 12, this velocity is independent of column length, but it is a function of the necessary plate number. Finally, the retention time is

$$t_R' = N_{ne}TH' = 0.5(k' + 1)N_{ne}\left[C + \left(C^2 + \frac{6\mathscr{D}}{N_{ne}}\right)^{1/2}\right] \tag{22}$$

If the "critical pair" to be separated is the last one in the chromatogram, eqn. 22 gives the minimum analysis time. If there are other peaks eluted after the critical pair, we can use another expression which resembles eqn. 22:

$$t_{A,min} = 0.5(nk' + 1)N_{ne}\left[C + \left(C^2 + \frac{6\mathscr{S}}{N_{ne}}\right)^{1/2}\right] \quad (23)$$

where n is the ratio of the column capacity factor of the last compound and the k' value of the second peak of the critical pair.

Eqns. 22 and 23 give a direct correlation between the analysis time and equipment contribution. These results are not surprising: the decrease in the coefficients of plate-height equation increases the system efficiency and also the "performance", that is, the analysis speed.

When we have a simple separation to do (requiring a few thousand plates or less) and if we use very efficient columns (narrow bore and very thin films), it is possible to show that

$$\frac{6\mathscr{S}}{N_{ne}} \gg C^2 \quad (24)$$

Combination of eqns. 19, 22 and 24 leads to a simpler form of the analysis time:

$$t_R = 0.5(k' + 1)CN_{ne} + 1.23\sqrt{\sigma^2_{EC}\,N_{ne}} \quad (25)$$

assuming always that we are working at the optimum practical gas velocity and with the minimum column length. This expression gives smaller values than eqn. 22; the error is less than 1% for small k' values (0.5–4), but it increases up to 4–8% in the k' range 10–15 using a narrow (0.05 mm I.D.) column.

As an example it will be interesting to replace real data in the analysis time equation (eqn. 25) with the following values: $d_c = 50$ μm, $d_f = 0.05$ μm, $D_G = 0.25$ cm^2/s and $D_L = 9 \times 10^{-7}$ cm^2/s (which correspond to n-octane at room temperature in hydrogen as carrier gas and on a squalane-type stationary phase and gives roughly $k' = 2$. Further, by using $6.85 \cdot 10^{-5}$ s^2 as the extra-column variance, one obtains for the plate height coefficients: $C = 8.65 \cdot 10^{-6}$ s and $\mathscr{S} = 9.6 \cdot 10^{-6}$ s^2.

With a simple analysis requiring only $N_{ne} = 10\,000$ plates, we obtain for the analysis time 1.14 s. The exact expression eqn. 22 would give 1.15 s; these values are in good agreement with analysis times reported by several workers under similar conditions. The numerical value of the first term $[0.5(k' + 1)CN_{ne}]$ is equal to 0.13 s, corresponding only to 11% of the total time. If the necessary plate number were only 3000, the first term would be 6% of the analysis time. This result means also that by using very efficient columns most of the zone broadening occurs in the extra-column part of the chromatographic system; on the other, hand for very simple separations, in addition to eqn. 24 the following condition is also valid:

$$\left(\frac{6\mathscr{S}}{N_{ne}}\right)^{1/2} \gg C \quad (26)$$

TABLE I

ANALOGOUS MAGNITUDES

	Efficiency concept		Performance concept		
E 1	Length-based zone variance	${}_L\sigma^2$	Time-based zone variance	σ^2	P 1
E 2	Height equivalent to a theoretical plate	$H = {}_L\sigma^2/L$	Time necessary to generate a theoretical plate	$TH = \sigma^2/t_R$	P 2
E 3	Theoretical plate number	$N = L^2/{}_L\sigma^2$	Theoretical plate number	$N = t_R^2/\sigma^2$	P 3
E 4	Column length	$L = N \cdot H$	Retention time	$t_R = N \cdot TH$	P 4
1st degree optimization					
E 5	Column length	$L = N_{ne} \cdot H$	Retention time	$t_R = N_{ne} \cdot TH$	P 5
2nd degree optimization					
E 6	Column length	$L = N_{ne} \cdot H_{min}$	Retention time	$t'_R = N_{ne} \cdot TH'$	P 6

which allows further simplifications both for the optimum column length:

$$L' = 1.92\left(\frac{\sigma_{EC}^2 B^2 N_{ne}^3}{(k'+1)^2}\right)^{1/4} \tag{27}$$

and also for the optimum practical velocity:

$$u' = 1.56\left[\frac{B^2 N_{ne}(k'+1)^2}{\sigma_{EC}^2}\right]^{1/4} \tag{28}$$

It is important to note that the above expressions are only approximate, allowing a rapid estimation of the column length and velocity, respectively; the exact equations are eqns. 20 and 21. These approximate equations lead to smaller values than the exact values, with errors of 15–50% for the optimum length and 5–20% for the optimum velocity (depending on the k' range), using always narrow columns (0.05 mm I.D.). For columns with I.D. = 0.15 mm or larger, the errors are much more important because condition 26 is no longer valid.

"Efficiency" and "performance" concepts

During the progress of GC, most efforts were dedicated to the development of very efficient columns (or GC systems), and the main goal of optimization approaches or theories was to find operating optimum conditions giving the highest efficiency (minimum HETP), the analysis speed being of only secondary or no interest. Many papers (even this one) show H/u plots, which indicates a kind of myth around the notion of HETP. Hence it is easy to understand that the starting point of all theoretical arguments was the efficiency concept.

When process control or routine analyses are to be performed, it is also important to optimize the analysis speed, which gives a supplementary advantage in sensitivity (see Figs. 2 and 7). Naturally, the chromatographic system always has to effect the required separation, and no concessions are admitted here, so the analysis time optimization must not be self-contained. As we have shown above, the "performance" concept is more extended, involving both efficiency and speed. Table I offers a comparison of the classical efficiency and the more extended performance concepts.

Some remarks can be made about Table I:

(1) Band broadenings are characterized by their length- or time-based variance.

(2) The plate number notion is interpreted in the same way in both concepts.

(3) HETP and TH in addition to column length and retention time are symmetrical in the two concepts.

(4) The values σ^2, ${}_L\sigma^2$, H, TH, N, L and t_R are specific for a given compounds and for a given chromatographic system working under given operating conditions.

(5) The necessary plate number N_{ne} calculated by eqn. 16 is a value determined by the analytical problem and it is independent of the chromatographic system itself.

(6) Consequently, if $N \gg N_{ne}$, the system has a redundancy, and the column length and analysis time are larger than is strictly necessary.

(7) The first-degree optimization means shortening the column to obtain sufficient (but not more) plate numbers. Consequently, we can also save analysis time.

(8) The second-degree optimization is intended to optimize the operating conditions (gas velocity); in the efficiency concept to choose the optimum velocity giving the minimum HETP and in the performance concept another velocity to obtain the minimum TH (TH'; see eqn. 17). We have to interpret these results very carefully: expression E6 in Table I gives the shortest column of all, whereas expression P6 gives the smallest analysis time of all, but not by using the same column length as given by E6. Expression P6 assumes we use the column length given by eqn. 22 and we set the gas velocity given by eqn. 21. Both are larger than the minimum column length and optimum gas velocity determined by the efficiency concept, but all together they give a shorter analysis time. This is in complete harmony with what was pointed out by Scott and Hazeldean [15], *i.e.*, a longer column operated at a higher velocity gives a more rapid analysis than a shorter column operated at the optimum velocity for minimum HETP, with equivalent resolution. This statement was later confirmed experimentally by Villalobos and Annino [21].

PRACTICAL ASPECTS

In most of following discussions we shall distinguish two cases:

(a) "pseudo" fast analyses, which can be performed by means of conventional equipment; in this case, the typical analysis times are of the order of minutes and separations can be carried out by respecting some simple rules;

(b) truly high-speed analyses, which need specially designed instrumentation in order to achieve analysis times of a few seconds. In this latter instance, it is assumed that we are working with simple sample mixtures (5–10 compounds or quantification of some key compounds only).

Column parameters

Column inside diameter. As eqn. 3 shows, the optimum gas velocity is inversely proportional to the inner diameter. This velocity increases as the inner diameter decreases, so that a shorter analysis time can be obtained by using columns with a smaller diameter. Another phenomenon is that the minimum HETP decreases with decreasing column radius (see eqn. 4) so that, with a short, narrow-bore column, the same separation can be obtained as with a long, wider bore column, which increases the analysis speed even more (*cf.*, Fig. 2).

Nowadays, there are no technical limitations to the manufacture of (fused-silica) columns with diameters of 50 μm or less, but the construction of commercially available gas chromatographs prevents unlimited miniaturization. Sample introduction in particular raises problems with diameters smaller than 100 μm. The use of 150 μm (0.15 mm) columns seems to be the best compromise, as they can easily be installed in any capillary gas chromatograph and are completely compatible with the split injection technique. Fig. 3 shows a chromatogram obtained using such a column.

Really fast analyses can only carried out by using narrow columns (I.D. < 0.1 mm), but special equipment is needed in order to reduce instrumental contributions (*cf.*, Figs. 4 and 5).

As an interesting approach, Lee *et al.* [12] used packed capillary columns to analyse natural gas (Fig. 6).

Film thickness. The stationary phase film thickness influences the column effi-

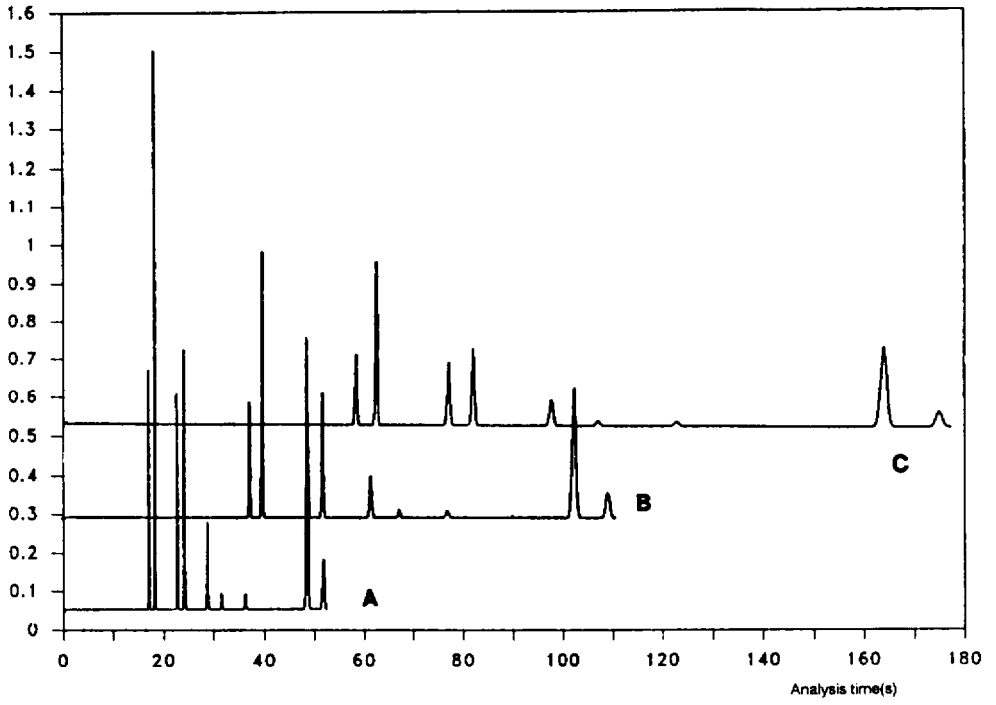

Fig. 2. Effect of column diameter peak height and analysis time. Columns: A = 10 m × 0.15 mm; B = 16 m × 0.25 mm; C = 21 m × 0.32 mm. Columns have the same phase ratio (same capacity factor) and plate number (same resolution). (Reprinted from Chrompack brochure.)

ciency directly (see the Golay equation), and indirectly via k' values because of the well known relationship

$$k' = \frac{4Kd_f}{d_c} \tag{29}$$

An increase in liquid film thickness has several complicated effects. As a first approximation, the result is a loss of efficiency because of increases in C_L. This effect is negligible as far as the condition $C_L \ll C_G$ can be respected. Most of the fast applications were carried out with a film thickness inferior to 0.1 μm, that is on very efficient columns. Exceptions are when very volatile compounds are to be separated (see Fig. 3).

Column length. For really short analyses, very short columns (0.15–4 m) are used in order to obain analysis times of a few seconds or less. Eqns. 20 and 27 permit the calculation of the column length necessary for a given analytical problem, assuming we set the optimum practical gas velocity at a value calculated by eqn. 21 or 28. To obtain these expressions we neglected the gas compressibility effect; therefore, in practice it is better to use 10–15% longer columns and 10–15% smaller values for the optimum velocity, which together give 20–30% longer analysis times.

Using the same values as above (see *Analysis time*), eqn. 20 gives 86 cm for the column length, which is also in good agreement with literature data.

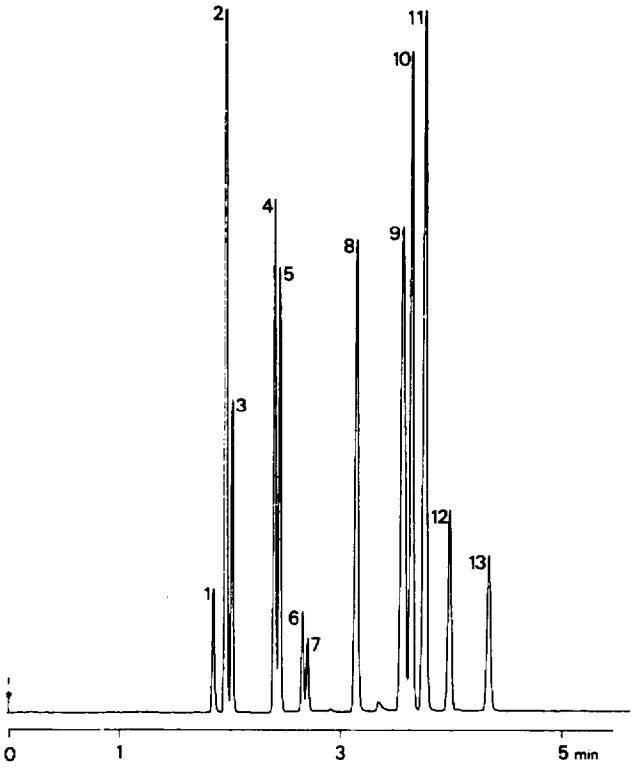

Fig. 3. Separation of C_1–C_4 hydrocarbons. Column, 25 m × 0.15 mm I.D., coated with CP-Sil 5 CB (1.2 μm); temperature, 25°C; carrier gas, hydrogen; flow-rate 53 cm/s; split injection with slitting ratio 133; flame ionization detector. Peaks: 1 = methane; 2 = ethene; 3 = ethane, ethyne; 4 = propene; 5 = propane; 6 = propadiene; 7 = propyne; 8 = isobutane; 9 = isobutene, 1-butene; 10 = 1,3-butadiene; 11 = *n*-butane; 12 = *trans*-2-butene; 13 = *cis*-2-butene. (Reprinted from Chrompack brochure.)

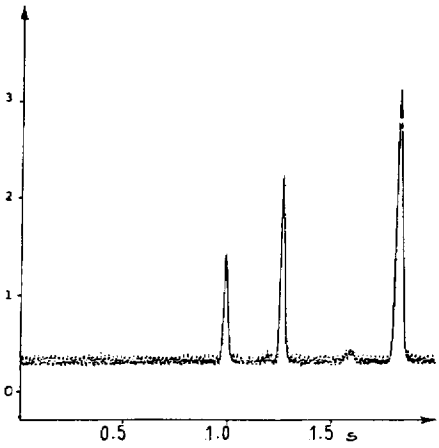

Fig. 4. High-speed chromatogram 1. Column, 120 cm × 0.065 mm I.D., coated with squalane (0.03 μm); temperature 20°C; carrier gas, hydrogen; flow-rate, 121 cm/s; fluidic logic gate injector; digital reconstruction of chromatogram. Compounds in their elution order: methane, *n*-heptane, *n*-octane.

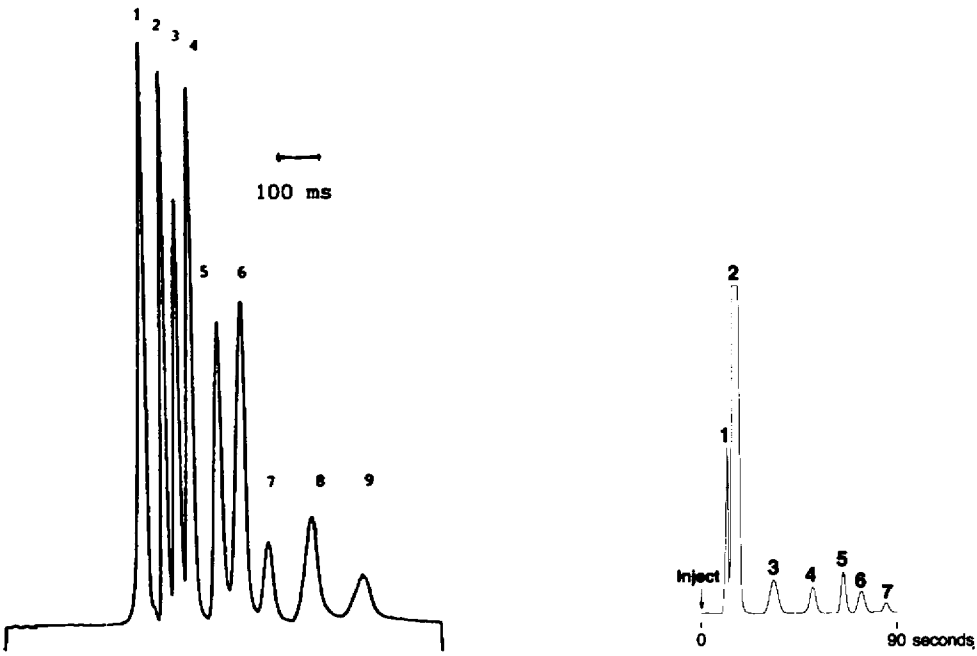

Fig. 5. High-speed chromatogram 2. Column, 30 cm × 0.050 mm I.D. coated with squalane; temperature, 72°C; carrier gas, helium; flow-rate, 470 cm/s; on-column cold-trap injector. Peaks: 1 = n-C_6; 2 = cyclohexane; 3 = n-C_7; 4 = methylcyclohexane; 5 = toluene; 6 = n-C_8; 7 = 1,2-dimethylhexane; 8 = ethylhexane; 9 = n-C_9. (Reproduced from ref. 16 with permission).

Fig. 6 Analysis of natural gas. Column, 25 cm × 0.5 mm I.D. PLOT Molsieve 5A column packed with 100–120-mesh HayeSep A; silicon microvalve injector; thermal conductivity detector. Peaks: 1 = air; 2 = methane; 3 = carbon dioxide; 4 = ethane; 5 = carbonyl sulphide; 6 = hydrogen sulphide; 7 = propane. (Reproduced with permission of Microsensor Technology).

It is interesting to observe that L', as given by eqn. 20, has a minimum of the function $\mathscr{D}$. It is easier to explain the increase in L' with the increase in $\mathscr{D}$: the system efficiency becomes lower and we must compensate for this loss by using a longer column, but it also increases with decreasing $\mathscr{D}$ at small values of $\mathscr{D}$. The reason is that we must now operate the column at a very high velocity (*cf.* eqn. 21) and again, but for a different reason (large velocity allowed by small extra-column contributions; we must not forget that this velocity is not the one giving the highest efficiency, but the minimum of the ratio H/u), the column length must become large. As pointed out by Grant [17], "...the fastest analysis possible will always be at OPGV provided that column length is increased to compensate for the theoretical plate loss...". It is important to note that this is by no means the shortest analysis time. The shortest analysis time is always that given by eqn. 22, this phenomenon being of only mathematical and secondary interest. The simplified form eqn. 27, of the column length is unambiguous.

Operating conditions

First, we should point out that really fast analyses can only be carried out under isothermal conditions; with temperature-programmed runs the cooling time and the system stabilization period would be too long, and consequently the main benefit would be lost. Possibly further developments in micromachining technology ("cartridge" chromatographs, injector, column and detector integrated on a low heat capacity wafer; the chromatograph itself becomes a consumable part of the whole system) and adoption of Peltier elements as heating and cooling devices will allow temperature-programmed high-speed separations also to be performed. Until that time we have to consider only two parameters as degrees of freedom: the carrier gas velocity and the column temperature. In addition, we shall discuss briefly how to choose the carrier gas.

Choice of carrier gas. According to eqn. 5, the best carrier gas for fast analyses is the one in which the diffusion coefficient of the component is the highest. Hydrogen is obviously the best choice. In helium it is slightly smaller, and this gas could be a secondary choice, but as its viscosity is high the pressure gradients would be too large.

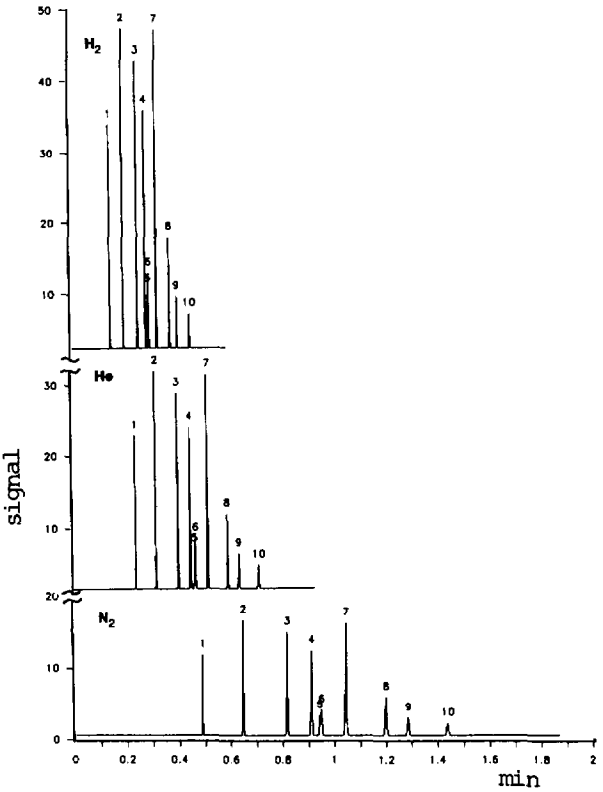

Fig. 7. Separation of aromatic hydrocarbons with different carrier gases. Column, 50 m × 0.32 mm I.D., coated with CP-Sil 5CB, film thickness 1.20 μm; temperature 100°C; optimum gas velocities, hydrogen 47 cm/s, helium 30 cm cm/s and nitrogen 15 cm/s. Peaks: 1 = benzene; 2 = toluene; 3 = vinylcyclohexane; 4 = ethylbenzene; 5 = *m*-xylene; 6 = *p*-xylene; 7 = styrene; 8 = isopropylbenzene; 9 = benzaldehyde; 10 = *n*-propylbenzene. (Reprinted from Chrompack brochure).

Other gases giving small diffusion coefficients are approximately three times slower than hydrogen (see Fig. 7).

Carrier gas velocity. Eqn. 21 or 28 permits the calculation of the optimum practical velocity as a function of instrumental variance and of the necessary plate number for a given analytical problem. As was mentioned above, slightly smaller values are recommended because of gas compressibility effects.

According to eqn. 21, the smaller the amount of all the extra-column variances, the higher is the optimum velocity. Using again the same values as above (analysis time calculation), we obtain 224 cm/s for the carrier gas velocity.

Column temperature. Temperature changes influence the values of the diffusion coefficients D_G and D_L and mainly the partition constant K, which is directly related to the column capacity factor k' (see eqn. 29). We shall focus only on the temperature dependence of k', which is the strongest. In other words, we have to examine how the column length and the optimum practical velocity depend on the capacity factor. These dependences are complicated because the necessary plate number (N_{ne}) and the plate-height coefficients C and D depend on k'.

We are interested in optimization of the analysis time with a satisfactory resolution between the two critical components of the sample mixture. We therefore have to look for the minimum analysis time. Two completely different cases will prove to give similar results (*cf.*, Fig. 8). In both instances, the analytical problem is the same: separation of these components with a resolution factor of 1.3 (baseline separation) and a liquid-phase selectivity of 1.1. In the first instance, let us assume that we use a specially designed fast chromatographic system, with the same parameters as in the above calculations. In the second instance, let us assume that we use conventional equipment with a split injector and a 0.15 mm I.D. column.

On examining Fig. 8A–D, several features may seem surprising or even contradictory:

(a) Under certain conditions (low initial values of k'), a temperature decrease (k' increasing) accelerates the analysis speed (Fig. 8B). We must not forget that we want to optimize the system using eqns. 16, 20, 21 and 22. Thus, the reason is simple: the necessary plate number is smaller at higher k' values (Fig. 8A), a shorter column is

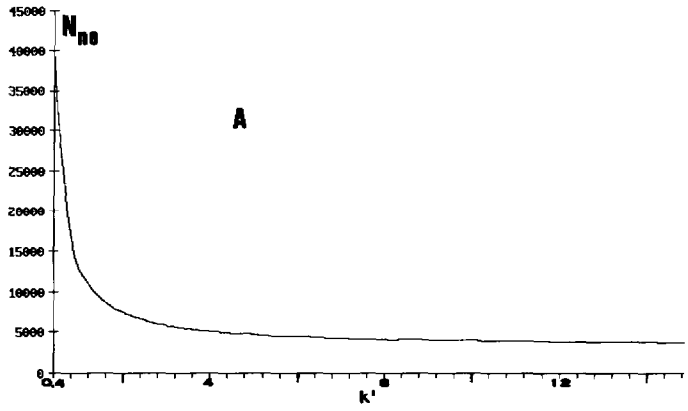

Fig. 8.

(Continued on p. 346)

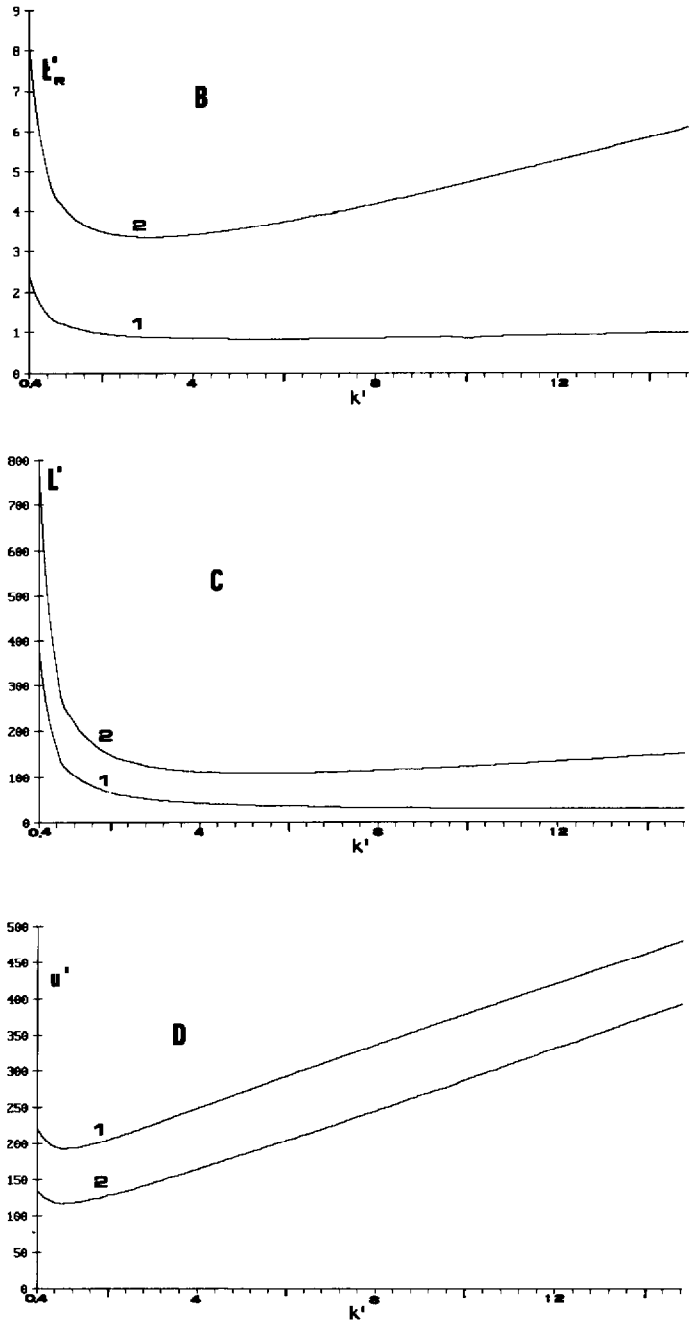

Fig. 8. Effect of column capacity factor (A) necessary plate number, (B) minimum analysis time (s), (C) minimum column length (cm) and (D) optimum practical velocity (cm/s). Phase selectivity = 1.3; required resolution factor = 1.3. Curves 1: column I.D. = 0.05 mm, film thickness = 0.05 μm, equipment variance = 0.0000685 s^2. Curves 2: column I.D. = 0.15 mm, film thickness = 0.1 μm, equipment variance = 0.000625 s^2, corresponding to well designed conventional equipment.

required (Fig. 8C) and a higher gas velocity is allowed (Fig. 8D). On the other hand, an increase in k' also has a beneficial effect on the D term, as is shown by eqn. 8, and the system efficiency also increases.

(b) The analysis time has a minimum as a function of k'. After the decrease mentioned above, the necessary plate number becomes virtually constant and the increase in the $(k' + 1)$ term is stronger than the decrease in the H/u ratio (see eqn. 14). The k' dependence of D (eqn. 19) also becomes negligible. This minimum is less marked when specially designed equipment is used (lower curve in Fig. 8B); with very efficient columns, conditions 24 and even 26 are valid and the contribution of the first term of eqn. 25 is slight compared with the second term.

(c) The carrier gas velocity has a minimum as a function of k'. The coefficient C has a very marked maximum as a function of k'. For large k' values, the gas velocity becomes infinite according to the classical OPGV concept (D becomes negligible).

From all these results, we can conclude that the optimum working k' range is roughly 1–10. For simple sample mixtures, it seems convenient to set the column temperature so that the chromatogram is placed in the k' range 1–5 (the classical theory gives $k' = 2$ as the optimum value to obtain the minimum analysis time).

Equipment

It was shown above that using very efficient, narrow-bore, short columns, zone broadening occurs mainly in the extra-column parts of the chromatographic system. Usually, the contributions of the various parts of the equipment (injector, connections, detector, electrometer, even the data acquisition and handling system) are independent of each other [18]. Thus, the equipment constant σ^2_{EC} can be broken down and expressed as the sum of individual contributions from different parts of the equipment:

$$\sigma^2_{EC} = \sum\sigma_i^2 = \sum\lambda_i\tau_i^2 \tag{30}$$

where τ_i are characteristic time (*e.g.*, time constant) and λ_i are factors depending on the choice of the characteristic times and on their profile. As examples, for a rectangular profile $\lambda = 1/12$ if τ is its width and for a Gaussian profile $\lambda = 1$ if $\tau = \sigma$. The contributions of different profiles were discussed in detail by Sternberg [18]. Below we give a review from a practical point of view.

Sample injection. The first fast injector was realized by Desty and Goldup [1,2] achieved by hitting a syringe with a hammer; with this technique, and injection duration of a few tens of milliseconds was achieved and very spectacular fast chromatograms were obtained; syringe consumption was not reported!

Conventional, commercially available capillary sample introduction systems can hardly be used to perform fast analyses because of their well known limitations (band broadening in space or in time). Only the split injector seems to allow "pseudo-fast" separations (*cf.*, Fig. 3). The contribution to band broadening of this type of injector can be estimated by the following expression:

$$\sigma_I = \tau_I = \frac{V_v}{F} \tag{31}$$

where V_v is the volume occupied by the sample in the vapour phase in the injector chamber at the injector temperature and at the inlet pressure, and F is the total flow-rate in the injector chamber. Estimating $V_v = 50$ μl (injecting 0.1 μl of liquid sample) and $F = 120$ ml/min, we obtain $\tau_I = 25$ ms as a charateristic time ($\lambda_I = 1$), which means that the injector contribution to the σ^2_{EC} equipment constant should be $6.25 \cdot 10^{-4}$ s^2. If other extra-column contributions are negligible ($\sigma^2_{EC} \approx \sigma^2_I$) and assuming $N_{ne} = 10\,000$ plates, the second term of eqn. 25 gives 2.77 s as the ultimate lower limit of the analysis time.

Gaspar and co-workers [4,5] described a fast sampling device (injection profiles of a few milliseconds) based on a fluidic logic gate; this injector was inspired by the idea of Wade and Cram [19]. Fluidic logic elements are pneumatic devices without moving parts, which allows fast operations with switching times less than 1 ms. They were developed for automation and process control because of their resistance to high temperatures and electromagnetic fields. The essential component is an inhibited OR/NOR gate. The fluidic injector is extremely reliable and stable; owing to its exceptional reproducibility, it was used later to study peak distortion profiles in non-linear chromatography [20].

To overcome the limitations of conventional equipment, Van Es *et al.* [16] had the clever idea of using an on-column cold-trap reinjection system to obtain very narrow input bands (1.1 ms), and they performed high-speed separations using very short, narrow-bore columns (*cf.*, Fig. 5). They installed a 10-cm long external aluminium-caoted fused-silica column (cold trap) between the on-column injector and the short (10–35 cm) analytical column, *ca.* 2 cm of the trap being cooled to -70°C with nitrogen. The injected sample can be liberated (reinjected) from the cold trap by a fast thermal desorption step made by means of high-power electrical heating in the form of short pulses. This reinjection device allows conventional equipment to be used.

A revolutionary approach was described by Lee *et al.* [12]. Silicon micromachining technology permits the integration (Fig. 9) of low-dead-volume (4-nl) microvalves and sample loops (internal volume *ca.* 25–250 nl). A typical switching time is *ca.* 1.5 ms; the injection valve can be opened from 5 to 255 ms, this duration being controlled by a microprocessor. The input band of such a valve can be considered to be rectangular, the characteristic time τ is the pulse width and λ is equal to 1/12; consequently, for a 10-ms pulse, the extra-column contribution σ^2_I is only $8.3 \cdot 10^{-6}$ s^2, which is extremely low.

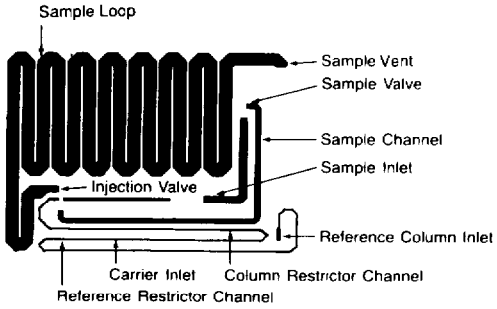

Fig. 9. Silicon wafer injection pattern. (Reproduced with permission of Microsensor Technology).

Detector. The detector time constant can have two origins: (a) purging time of internal volume given by the ratio V/F and (b) time constant arising from the principle of operation.

The flame ionization detector seems potentially to be the best detector for fast analyses. The column can be installed directly in the burner tip; the dead volume between the column outlet and the flame is estimated to be *ca.* 500–1000 nl. This volume is flushed at a relatively high flow-rate (carrier gas + hydrogen, 30–40 ml/min) and the characteristic time is about 1 ms ($\lambda = 1$). Characteristic times of the process taking place in the flame itself are a few microseconds, which is negligible compared with the previous value.

For a long time the thermal conductivity detector was disregarded from the point of view of sensitivity and rapidity. Recent developments [12] by the Microsensor Technology R & D group have given a completely new horizon for this type of detector: the Microsensor thermal conductivity detector has a dead volume of only 2 nl. Considering 0.6 ml/min as a typical flow-rate through the cell (optimum flow-rate for 0.15 mm I.D. columns), the flushing time constant is about 2 ms. Usually thermal characteristic times are much larger; however, advances in silicon technology allow a very compact, low heat capacity geometry to be realized and the total time constant remains less than 10 ms.

Amplifier (electrometer). When speaking about the amplifier we mean the electrometer (typical for flame ionization detection) and all other electronic devices for signal amplification. The contribution of the amplifier to band broadening was studied by Gaspar *et al.* [6] and later by Villalobos and Annino [21,22]. As the latter workers showed, an electrometer time constant larger than 20 ms (the usual value for modern commercially available chromatographs) results in a perceptible peak broadening even when using columns with conventional dimensions (10 m × 0.25 mm I.D.). For truly fast analyses, a specially designed preamplifier installed directly on the detector is recommended. Only in this way is it possible to achieve small enough time constants (1 ms or less); otherwise, the capacity of the input cable results in large time constants, mainly when high sensitivities (high input impedance) are required.

Data acquisition system. For truly fast analyses, ordinary chart recorders are far too slow, and only high-speed UV recorders or storage oscilloscopes can be used. The best way is to use digital data acquisition devices; here two important aspect must be considered:

(a) Choice of the A/D converter: an 8-bit A/D converter can resolve 1 part in 256 (which is not sufficient), a 12-bit converter 1 part in 4096 and a 16-bit converter 1 part in 65 536. The best compromise (considering cost) seems to be to use a 12-bit converter, considering also that the linear dynamic range of amplifiers usually does not exceed three orders of magnitude.

(b) Sampling time set-up: on increasing the sampling time (decreasing sampling frequency), two things happen: the signal-to-noise ratio increases, this ratio being proportional to the square root of the sampling period; with too high a sampling frequency undersirable baseline noise will be detected and measured; and over a certain limit decrease in accuracy occurs.

Integrator manufacturers suggest a practical rule for optimum data bunching, *i.e.* 10–20 bunches per peak half-width; thus, when working with peak standard deviations, we obtain the following relationship:

$$\frac{\sigma}{4.31} > T_s > \frac{\sigma}{8.62} \tag{32}$$

Truly fast chromatograms have standard deviations of 5–10 ms, which means that a sampling time of 1–2 ms gives the best compromise for sufficient accuracy and efficient numerical filtering.

CONCLUSIONS

Fast separations (analyses lasting a few minutes) can be carried out by means of conventional equipment, using commercially available narrow-bore (0.15 mm I.D.) columns and by respecting some simple rules, such as (a) choice of carrier gas (hydrogen), (b) setting the column temperature to optimize the capacity factor range (1–5), (c) choice of injection technique (split preferred, or cold trapping and thermaldesorption) and (d) the use of modern, sophisticated instrumentation having low time constants.

The realization of extremely fast analyses (a few seconds) is no longer a dream, the existing state of fused-silica column technology, of micromachining and of the microcomputer field giving real possibilities for manufacture specially designed high-speed chromatographs. The expressions given for analysis time, for optimum practical velocity and for optimum column length permit the best performance of such a chromatograph to be exploited.

SYMBOLS

B	coefficient of HETP equation
C_G	coefficient of HETP equation (gas phase)
C_L	coefficient of HETP equation (liquid phase)
C	Sum of C_G and C_L
D	coefficient of modified HETP equation
$\mathscr{D}$	product of D by column length
d_c	column inner diameter
d_f	liquid film thickness
F	flow-rate
H	height equivalent to a theoretical plate (HETP)
H_{min}	minimum value of HETP
H'	value of HETP at velocity u'
K	partition constant
k'	column capacity factor
L	column length
N	theoretical plate number
N_{ne}	number of theoretical plates necessary to resolve two compounds
R_s	resolution factor
T_s	sampling period time for digital data acquisition
TH	time necessary to generate a theoretical plate
TH'	minimum value of TH
t_R	retention time
u	average carrier gas velocity
u_{opt}	optimum velocity to obtain a minimum HETP
u'	optimum practical velocity to obtain a minimum TH

V	volume
α	liquid-phase selectivity
σ	time-based peak standard deviation
${}_{\mathrm{L}}\sigma^2$	length-based peak variance
σ^2	time-based peak variance
σ_i^2	time-based variance of an extra-column device
σ_{EC}^2	sum of extra-column variance (time-based)
λ	multiplication factor
τ	characteristic time of an extra-column device

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