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Potentials of Capillary Gas Chromatography in Toxicology Today

M. Bogusz[1], J. P. Franke[2], and R. A. de Zeeuw[2]

[1] Institute of Forensic Medicine, Academy of Medicine, Grzegorzecka 16, PL-31531 Krakow, Poland
[2] Dept. of Toxicology, State University, Antonius Deusinglaan 2, NL-9713 AW Groningen, The Netherlands

Summary. The usefulness, the applicability and the limitations of capillary gas chromatography in various types of toxicological analysis were discussed. Technical parameters of capillary gas chromatography, such as type of injector, type of column with regard to material, size, and stationary phase were assessed in view of the requirements of toxicological analysis. The main advantage of capillary gas chromatography, i.e. high separation power, is unfortunately counterbalanced by low loadability and/or speed of analysis. In the present situation capillary gas chromatography is a method of choice in drug screening despite some disadvantages, but in drug-oriented analysis the conventional chromatography on packed columns is probably more useful.

Key words: Capillary gas chromatography – Drug screening – Drug identification

Zusammenfassung. Die Benutzung, Anwendung und Beschränkungen der Kapillargaschromatographie (KGC) in der qualitativen und quantitativen toxikologischen Analytik wurden diskutiert. Technische Parameter der KGC wie Detektortyp, Art der Säule bezüglich Material, Abmessungen und stationäre Phase wurden geschätzt im Rahmen der Anforderungen in der toxikologischen Analytik. Der wichtigste Vorteil der KGC, d.h. eine hohe Trennkraft, ist unglücklicherweise verbunden mit einer niedrigen Beladung bzw. Geschwindigkeit der Analyse. KGC hat gewisse Vorteile in Screening-Verfahren, wobei aber die geringe Beladung in Betracht gezogen werden soll. Für die Arzneimittel-orientierte Analytik ist die konventionelle Chromatographie mit gepackter Säule wahrscheinlich nützlicher.

Schlüsselwörter: Kapillargaschromatographie – Arzneimittel-Screening – Arzneimittel-Identifikation

Offprint requests to: J. P. Franke, Dr. (address see above)

Considering the applicability of a particular analytical method in clinical or forensic toxicology, it might be useful to confront the toxicological disciplines with the apparent potentials and limitations of the method. Generally speaking, the toxicological analysis consists of four consecutive steps: isolation, detection, identification, and quantitation. The main advantage of gas chromatography (GC) is that all steps, or at least the last three, can be done in one operation. This is particularly useful in the search for unknown substances. The main advantage of capillary gas chromatography (CGC) is the increase of identification potentials through enhanced separation power. Therefore, CGC should be particularly useful in those types of toxicological analysis where identification is the most critical step. Detailed considerations on the theory of CGC can be found in the monographs of Jennings [1] and Freeman [2].

Each analytical method can be estimated by its *general quality parameters*, i.e. selectivity, sensitivity, accuracy, and precision. The importance of these parameters is different in various types of toxicological analysis, which will be discussed later. The general parameters are individually influenced by the *operational parameters* of a particular analytical method. In gas chromatography such parameters are, loadability (capacity with regard to sample inlet and column), selectivity (separation, resolution with regard to column), speed with regard to column, and selectivity of response with regard to detector. The operational parameters are directly related to *technical parameters*; in the case of CGC such parameters are type of sample inlet (split, splitless, cold on-column), type of column (material, length, bore size, kind of phase, film thickness) and type of detector.

There are several measures for the particular operational parameters. Among the *measures of loadability* the following terms can be mentioned:

$$\textit{Distribution constant } K_D = \frac{\text{Concentration of analyte in liquid phase}}{\text{Concentration of analyte in gas phase}} \qquad \text{Eq.1}$$

$$\text{therefore, } K_D = \frac{\text{Weight of analyte in liquid phase}}{\text{Weight of analyte in gas phase}} \times \frac{\text{Vol. of gas phase}}{\text{Vol. of liquid phase}} = k.\beta \qquad \text{Eq.2}$$

Partition ratio k can be related to retention time:

$$k = \frac{t_R - t_M}{t_M} = \frac{t'_R}{t_M} \qquad \text{Eq.3}$$

where t_R = total retention time
t_M = retention time of unretained compound (e.g. methane)
t'_R = adjusted retention time

Phase ratio β for open tubular columns can be calculated:

$$\beta = \frac{r}{2d_f} \qquad \text{Eq.4}$$

where r = internal column radius
d_f = film thickness of liquid phase.

Typical β values for wall-coated open tubular columns range from 50 to 500. Since K_D is constant, the k and β values are related: lowering of β (e.g. in narrow-bore columns) causes an increase of k. Therefore, the speed of analysis is inversely related to loadability.

There are several measures of column *separation power:*

Theoretical plate number

$$n = 5.54 \left(\frac{t_R}{w_{0.5}}\right)^2 \qquad \text{Eq.5}$$

where $w_{0.5}$ = peak width at half heigth

Height equivalent to a theoretical plate HETP

$$\text{HETP} = \frac{L}{n} \qquad \text{Eq.6}$$

where L = column length

Effective theoretical plate number

$$N = 5.54 \left(\frac{t'_R}{w_{0.5}}\right)^2 \qquad \text{Eq.7}$$

Height equivalent to an effective theoretical plate HEETP

$$\text{HEETP} = \frac{L}{N} \qquad \text{Eq.8}$$

Resolution

$$R_s = \frac{t_{R(b)} - t_{R(a)}}{w_{0.5(a)} + w_{0.5(b)}} \qquad \text{Eq.9}$$

where a and b are separated substances

Separation number SN or Trennzahl TZ

$$\text{TZ} = \frac{t_{R(x+1)} - t_{R(x)}}{w_{0.5(x+1)} + w_{0.5(x)}} - 1 \qquad \text{Eq.10}$$

where x and x + 1 are two consecutive members of a homologous series

TZ is approximately related to Kovats retention indices by:

$$\text{TZ} = \frac{100}{\Delta I} - 1 \qquad \text{Eq.11}$$

where ΔI is the difference between retention indices of separated substances.

TZ indicates the number of peaks, that can be accomodated, between two consecutive members of a homologous series. From Eq.11 the resolution of two components with known Kovats indices on a column with known TZ number can be predicted.

The third operational parameter, *speed of analysis*, is related to the retention time of substance. Retention time is related to the columns length, the gas

flow, the column internal diameter, the film thickness, and the distribution constant:

$$t_R = \frac{L}{\bar{\mu}}\left(1 + \frac{K_D \cdot 2d_f}{r}\right) \qquad \text{Eq.12}$$

where $\bar{\mu}$ is the average linear velocity of the carrier gas.

$$\bar{\mu} = L/t_M \qquad \text{Eq.13}$$

An increase of the internal diameter of the column with a constant phase ratio, lowers the separation power of the column, i.e. the number of theoretical plates. This decrease in N can be avoided by increasing the column length and decreasing the linear velocity of the carrier gas. Both changes have, however, a negative effect on the speed of analysis. In general, with a constant N and β, the retention time is related to the column diameter as follow:

$$t_R \sim r^z \qquad \text{Eq.14}$$

where $1 \leq z \leq 2$, depending on the column pressure drop. An increase in film thickness will have a negative influence on both the analysis speed and the theoretical plate number. The type of carrier gas influences the optimum gas velocity and the theoretical plate number: Nitrogen gas at optimum velocity gives less theoretical plates than hydrogen and helium. Furthermore, the optimum gas velocity for nitrogen is lower than for hydrogen and helium. Hence, hydrogen or helium provide shorter analysis times together with better sensitivity than does nitrogen.

Table 1 shows how the technical parameters of the column influence the operational parameters. From this table the analyst can choose the optimal technical parameters, providing the requirements for analysis are known. The type of stationary phase, which is a technical parameter not mentioned in the table, will depend on the type(s) of drugs encountered in the analysis. Table 1 also shows that the increased separation power, i.e. the greatest advantage of capillary columns, is inversely related to loadability, because the latter increases with bore size and film thickness. This feature appears a very serious drawback in toxicological analysis, where often minute amounts of substance are to be detected against a background containing high concentrations of accompanying compounds, or when concentrations are not known at all. Figure 1 illustrates the capabilities of various types of columns in this context.

When the limits of loadability are exceeded, overload phenomena occur, which can be recognized by retention deviations, alterations of the peak shape and peak splitting [3, 4]. The problems of peak distortion, splitting and, particularly, alterations in retention behaviour of substances important in toxicology have been described recently, the load-related variations in retention sometimes exceeding 100 RI-units [5, 6].

The toxicologist, examining the sample containing unknown substance(s) at unknown concentration, should always be aware of these problems, which may significantly affect the identification potentials and may lead to serious errors.

Table 1. Relation between the operational and technical parameters of the column in capillary gas chromatography

	Length →	Bore size →	Film thickness →
Loadability	Ø	→	→
Separation	→	←	←
Speed	←	←	←

→ increase; ← decrease; Ø no effect

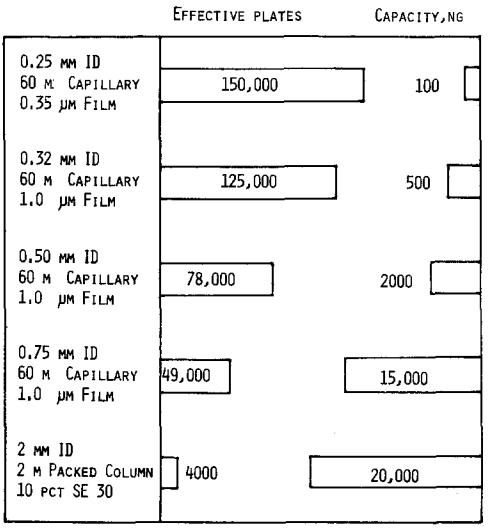

Fig. 1. Loadability and separation power of different types of GC columns, SE-30 type phases. Adapted from the Supelco Report, Vol. 1, No. 4 (1982) with the permission of the publisher

These overload phenomena cannot be noticed easily when highly automated, "intelligent" equipment is used, where all data are processed and stored as numerical values, and where nobody sees the actual chromatographic picture. In such cases the cry of young bicycle rider "Look father—no hands" followed by "Look father—no teeth" cited as a consequence of automated, "untouched by hand" analysis, may be particularly relevant [7]. It should also be kept in mind that the problems of peak distortion or peak splitting may originate not in the column but in the sample inlet [8, 9].

Injection Systems Used in Capillary Gas Chromatography

The problem of sample introduction is most critical and difficult in CGC. This is understandable in view of the conflicting requirements of high loadability and high separation power. In other words, chromatographers and constructors always face the problem how to introduce the largest possible sample to a column of lowest possible loadability? The variety of proposed techniques caused also some confusion in the terminology, the latter being recently classified by Pretorius and Bertsch [10].

From the technical point of view, three injection systems are now in use, i.e. split, splitless and on-column injection. In the splitting mode the *amount* of material entering the column is controlled and restricted. In the splitless and on-column modes the whole introduced sample is allowed on the column, and concentrated at the column head into a narrow band.

When assessing the types of sample inlet against the requirements of toxicological analysis it can be stated that the split injection is of limited use in toxicology. With split injection only a small fraction of the sample is introduced onto the column. Therefore, the substance of interest has to be present in the sample at a rather high concentration. More promising for toxicologists are on-column and splitless injections. The principle of cold on-column injection, introduced by Grob and Neukom [11], is the deposition of a liquid sample directly in the column with a special syringe. At the moment of injection the temperature in the oven is kept below the boiling point of the solvent, and the inlet part of column is flooded with solvent. The film of solvent evaporates exclusively at the rear (inlet-oriented) end of the column, moving gradually to the front. The solute moves also with the solvent, becoming more and more concentrated, and is finally deposited as a small zone when the last portion of solvent evaporates. This is the "solvent-trapping effect" described by Grob [12, 13]. The advantages of cold on-column injection were summarized by Knauss et al. [14] as elimination of thermal discrimination in the sample; elimination of thermal or catalytic decomposition of sample; high analytical precision; excellent quantitation of individual solutes and the easy implementation into routine practice. On the other hand, this mode of injection reveals also some drawbacks, as indicated by Poy et al. [15]: the choice of column bore is restricted (at least 0.32 mm); the preparation of the first 6 cm of glass column is difficult; non-volatile compounds in the sample can contaminate the column inlet part; a very special delicate syringe is required; the retention values are not reproducible; only diluted sample can be introduced; automatic injection is in its infancy. Therefore, it may be stated that cold on-column injection is a very promising technique, but at the present still too vulnerable for routine toxicological work.

Another widely used type of injector is the splitless injection system of Grob and Grob [16]. In this type the injected sample is rapidly vapourized in the heated liner and transported to the inlet part of the column. The column temperature is kept below the boiling point of the solvent, which causes recondensation of the sample and flooding of the inlet part of column. In the next step, the sample is evaporated by rapid temperature programming. In this injection system the "solvent-trapping effect" occurs also. The main advantages of splitless injection over on-column injection are little or no contamination of the column head by non-volatile components (they remain in the liner) and the possibility of automation, and therefore, ease of use. Some thermolabile samples, however, may decompose in the injection part of this system. Poy et al. [15] developed a universal injection system called Programmed Temperature Vaporizer (PTV). The system is claimed to overcome the problems associated with cold on-column injection. The injection of the sample on a capillary column is often associated with peak distortion known as band broadening. Two types of this phenomenon can be distinguished, i.e. band broadening in

time and band broadening in space, which have completely different mechanisms. For more detailed description the reader is referred to the papers by Grob [8, 9, 12, 13].

Types of Columns Used in Capillary Gas Chromatography

Analytical toxicologist today can choose between glass and fused silica capillaries. Jennings [17] presented a critical comparison of these two materials: each has its own advantages and drawbacks. The main advantage of glass capillary columns is in the fact that it can be manufactured relatively easily by the analyst himself, using a rather simple glass drawing machine. Also, modification of internal surface of glass is possible, to make "whiskered" or "etched" columns. This can enhance the wetability by a wider variety of stationary phases. Glass columns, however, have serious drawbacks as well. Most important among them is the relatively high activity of the glass surface, due to the presence of metals or silanol (hydroxyl) groups. This can cause a significant reactivity of exposed (i.e. not covered with stationary phase) column wall. Some compounds, analyzed on such columns, may be adsorbed and never reach the detector. The deactivation of a glass surface is tedious and requires time-consuming, skillful operations. Glass capillaries are also fragile and non-flexible, which can cause a particular problem, especially for beginners. The fused-silica columns, introduced by Dandeneau and Zerenner [18], have in fact only one questionable drawback in comparison with glass columns: the process of its manufacturing is highly sophisticated; therefore, such columns cannot be produced "at home". However, they reveal a lot of advantages, which argue for the superiority of these columns over glass ones. First, the activity of fused silica is very low due to the extremely low (below one ppm) metal content. Fused silica, contrary to glass, contains no metal atoms in the lattice. Also, the content of silanol groups can be controlled. Saito [19] described fused silica capillaries containing less than 1 ppm of both silanol groups and metal oxides. These columns required no deactivation procedures and showed excellent inertness and stability. Such material, however, is rather unusual since silanol groups occur regulary in silica lattices and, therefore, they are to be inactivated, for which different techniques have been described [20]. The second advantage of fused silica columns is their thin wall and, consequently, their low thermal mass. This is very important for the reproducibility of retention behaviour in temperature-programmed operations. Last but not least, silica columns are very flexible, inherently straight and mechanically resistant; therefore, the handling is easy and safe, also for unskilled personnel. The lenght of capillaries does not require much discussion; usually, two lenghts are used (24–30 m or 50–60 m), which are chosen according to particular needs. For rapid analysis some authors [21] advocate the use of short (5–10 m) capillaries. It should be noted, however, that such columns lose the most important feature of capillaries, i.e. high separation power.

As concerns bore size, two opposite approaches can be noted: Schutjes et al. [22] recommend the use of super-narrow bore columns (ID 30–50 μm). They

gave theoretical evidence, supported with experimental data, that such columns are very efficient and enable a considerable decrease in analysis time. The loadability of these columns was, however, very small; for instance for a ID 50 μm column a working range of 0.02–2 ng was recommended. On the other hand, super-wide bore glass columns have been introduced, with ID 750 μm, which can accept up to 15,000 ng of sample [23]. Between these two extremes there is a broad space, but usually three bore sizes are offered: 250 μm ID (narrow bore), 320 μm ID (medium), and 500 m ID (wide bore) columns. The relation between loadability and bore size is depicted in Fig. 1.

The film thickness of the stationary phase can be divided into three categories: thin (0.1–0.2 μm), medium (0.2–0.8 m) and thick (0.8–1.2 μm). The choise of the film thickness is dependent on the sample size: a thin film, assuring a high separation power, can accept only small amounts of sample; medium and thick films can withstand higher loads, but at the expense of resolution.

The choice of the type of stationary phase in CGC is as broad as in the case of packed columns and covers the whole range of phase selectivity. Therefore, the analyst can select the most appropriate phase for the particular analysis, when the target compound is known. In the case of toxicological screening, however, the situation is rather complex at the moment. For packed columns, SE-30 or OV-1 phases are to be recommended, according to the Committee of Systematic Toxicological Analysis of the International Association of Forensic Toxicologists [24]. These phases assure good discrimination power, are generally available, and the reference data bank obtained on this phase is quite large [24–26]. However, various authors have reported differences between RI-values of substances determined on packed and capillary columns with SE-30, OV-1 or similar dimethylsilicone stationary phases (*vide infra*). Furthermore, RI-values on capillary columns may strongly depend on the concentrations used [5, 6].

The introduction of phases which are not coated, but chemically bonded to the column wall, seems to bring a substantial progress in the applicability of CGC. Chemically bonded phases are highly resistant to solvent action; therefore, they are particularly useful when the splitless or cold on-column injection is applied. Moreover, these columns, when contaminated with deposits from e.g., biological material, can be easily rinsed with the solvent without damage of liquid phase. Therefore, the columns with bonded phases seem promising for the analysis of biological samples. Also, it remains to be seen in how far RI-values in chemically bonded CGC may be compared to RI-values in packed GC on similar phases, and whether concentration dependence of RI-values occurs.

Application of Capillary Gas Chromatography in Modern Toxicological Analysis

Toxicological analyses can be divided into several types:

Therapeutic Drug Monitoring (TDM)—detection and quantitation of known substances present in biological fluids, usually plasma, of medicated patients at low therapeutic levels.

Table 2. Requirements of various types of toxicological analysis in regard to general analytical parameters

	Selectivity	Sensitivity	Accuracy	Precision
TDM	++	+++	+++	+++
SEDS	+++	++	++	++
DOFA	++	+	++	++
STFA	+++	++	++	++

+ less important; ++ important; +++ highly important

Table 3. Requirements of various types of toxicological analysis with regard to operational parameters of sample inlet and column

	Loadability	Separation	Speed
TDM	+	++	++
SEDS	+++	+++	+++
DOFA	++	++	+
STFA	+++	+++	+

+ less important; ++ important; +++ highly important

Systematic Emergency Drug Screening (SEDS)—detection, identification and quantitation of unknown substance(s) in biological fluids taken from intoxicated patients and present at various levels.

Drug-oriented Forensic Analysis (DOFA)–detection and quantitation of known substances present in autopsy material, such as body fluids and organs, at high levels.

Systematic Toxicological Forensic Analysis (STFA)—detection, identification and quantitation of unknown substance(s) present in autopsy material at various levels.

Obviously, each of these types of analysis has its own requirements and critical points. It is therefore necessary to consider the following questions:

- is capillary gas chromatography more useful for a particular type of analysis than conventional chromatography on packed columns?
- if so, which operational and technical parameters assure this superiority?
- which limitations of capillary gas chromatography appear critical in various types of toxicological analysis?

It is established that the main advantage of CGC is high separation power, i.e. high identification potentials. Therefore, CGC should be particularly useful in SEDS and STFA, where the toxic substance is to be identified. On the other hand, the speed of analysis appears critical in TDM and SEDS, i.e. in analyses applied to living subjects. Yet, it should be kept in mind that speed and separation power require conditions that are in conflict with loadability. The individual requirements of various types of toxicological analysis with regard to the general and operational parameters are shown in Tables 2 and 3. In Table 2 it should be realized that selectivity and (in part) sensitivity is related to the type of detector, whereas the accuracy and precision depend on sample inlet and

Table 4. Choice of technical parameters of column in various types of toxicological analysis

	First choice	Second choice
TDM	Packed column	CGC—medium bore medium film medium length
SEDS	CGC—medium bore medium film medium length	Packed column
DOFA	Packed column	CGC—medium bore medium film medium length
STFA	CGC—wide bore thick film long length	Packed column

Table 5. Choice of technical parameters of sample inlet and detector in various types of toxicological analysis using CGC

	Sample inlet	Detector
TDM	Splitless	Specific to target
SEDS	Splitless or split	Universal (FID) and/or directed towards certain groups (TID, ECD)
DOFA	Split	Specific to target
STFA	Splitless or split	Universal (FID) and/or directed towards certain groups (TID, ECD)

column type. Table 4 presents suggestions of column choice in various types of toxicological analysis. As most toxicologists will not be in a position to acquire a large selection of column sizes and types, a medium bore capillary column (± 300 μm ID) with a medium film (± 0.5 μm) and medium length (± 25 m) may be considered a good compromise between separation power and loadability. Table 5 shows a choice of injection and detector system. In each case, the splitless or split system is recommended. The cold on-column injection, although potentially very interesting, is hardly applicable for routine use at the present state of technical development. This situation, however, can change due to a rapid progress on this field. CGC is increasingly applied in modern toxicological analysis. For general reviews, the reader is referred to [27–29]. As concerns the individual groups of toxicologically relevant substances, CGC has been used for detection of volatiles [30–32], hypnotic and antiepileptic drugs [33–36], basic drugs, particularly narcotics [37–44], and environmental pollutants [45].

Particularly in clinical and forensic drug screening, unequivocal identification of substances is very important. For this purpose, Kovats' retention index values (RI) are very useful. However, most of the available reference lists of RI data for various drugs were obtained on packed columns [24–26]. Therefore,

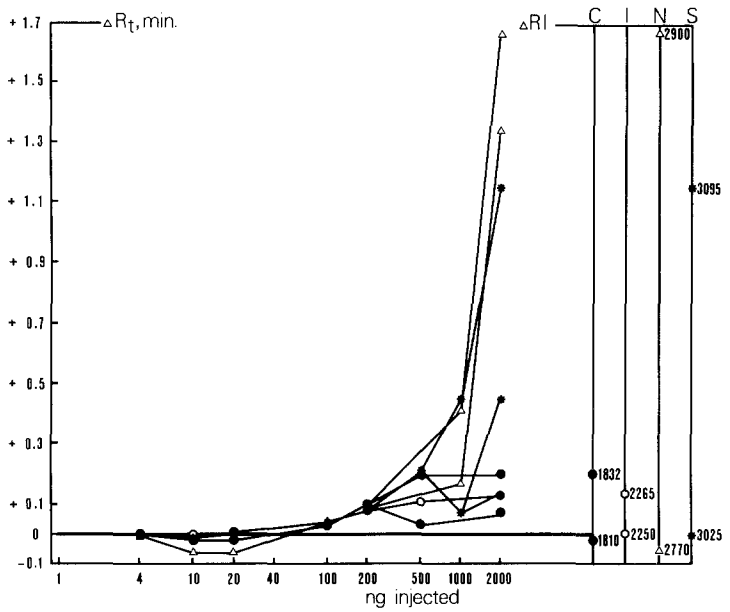

Fig. 2. Concentration-dependent retention behaviour of drugs on a narrow-bore fused silica capillary column. ● caffeine; ○ imipramine; △ nitrazepam; ✻ strychnine; □ fluphenazine. *Left* Retention time differences in minutes with lowest concentration taken as arbitrary zero point. *Right* Retention index differences between highest and lowest retentions observed. Reproduced from the Journal of Analytical Toxicology [6] by permission of Preston Publications, Inc.

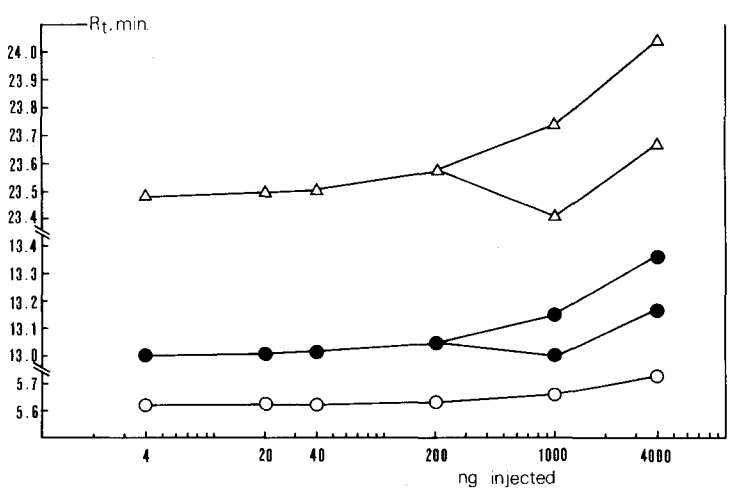

Fig. 3. Concentration-dependent retention behaviour of alkanes on a narrow-bore fused silica capillary column. ○ C_{12}; ● C_{22}; △ C_{32}. Reproduced from the Journal of Analytical Toxicology [6] by permission of Preston Publications, Inc.

there is a strong need to check the validity of these data for capillary columns. Evidence obtained so far indicates that large discrepancies can occur between RI-values for packed and capillary columns [44, 46]. Moreover, it has been shown (Figs. 2, 3) that in CGC the RI-values for various drugs are concentration-dependent, i.e. higher RI-values were obtained for higher concentrations of substance [5, 6].

These findings should warn the potential user against the non-critical application of capillary columns for identification purposes.

Conclusion

At the present, CGC, if properly used, can be a very powerful method of drug detection and quantitation. The identification step, however, should always be treated with special caution, and the retention data should be confirmed by a second analysis with a lower amount of sample and/or by packed-column GC. Therefore, the presumption mentioned at the beginning of this review that CGC should be particularly useful in analyses where identification is of prime importance, is still not totally fulfilled.

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