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The significance of different chromatographic methods in the European Pharmacopoeia

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Abstract

The usage frequency of chromatographic methods has been analyzed on the basis of 1008 monographs of the European Pharmacopoeia. Using this database the 'popularity-order' of the main chromatographic techniques was compared in the pharmacopoeial analyses and in the analytical literature of the world. It was established that the application order of the three leading chromatographic techniques in this somewhat special field of analyses is contrary to their position in the analytical literature of the world. The trend-analysis has shown that this discrepancy will be weakened in the future.

Keywords: Drug substances; Chromatography; Pharmacopoeia

1. Introduction

An interesting statistical analysis has been published recently about the distribution of individual instrumental analytical techniques (Braun and Zsindely, 1992). The survey is based on numerous analytical publications in the period 1980–1990. The 'popularity' order of instrumental analytical techniques, including the chromatographic methods, was established using a database containing 7500 organic compounds and 4300 chromatographic applications. The work clearly indicates that the role of chromatography is far more outstanding (approx. 61%) in the analysis of organic substances, while the second frequently used method (spectroscopy) shares only 8.8%. The article (Braun and Zsindely, 1992) also presents the usage frequency of the different chromatographic techniques.

The use of chromatography in pharmacopoeial analysis is also very significant. Thus, it seemed to be reasonable to examine the usage frequency of these methods in this somewhat special field of analysis. In the present paper the distribution of different chromatographic techniques is compared both in pharmacopoeial analysis and in the analytical literature in general.

In addition, comparing the 1995 version of the monographs with the previous ones, certain trends were established concerning the 'popularity' of chromatographic applications in the European Pharmacopoeia, 1995.

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Table 1
Number of monographs and number of monographs prescribing any chromatographic methods in the Eur. Pharm.

Classes of monographs	No. of monographs	No. of monographs containing any chromatographic prescriptions[a]	Percent of monographs containing any chromatographic prescriptions[a]
1 All monographs	1008	688	68.3
1.1 Monographs of non-uniform composition[b]	337	158	46.9
1.2 Monographs of uniform composition[c]	671	530	79.0
1.2.1 Inorganic sustances	78	1	1.3
1.2.2 Organic substances	593	529	89.2

[a]Including electrophoretic methods.
[b]Essential- and fatty oils, ointments, tablets, solutions, immunosera, etc.
[c]Chemically well-defined pharmaceutical compounds.

2. Method

The European Pharmacopoeia (Eur. Pharm.), being a regional standard, reflects the concept of experts from 22 countries. Thus, it seemed to be suitable as a representative of pharmacopoeial analysis in general.

In order to make comparison with the data of Braun and Zsindely (1992), those monographs of the Eur. Pharm. were selected which contain the testing of organic compounds with uniform composition. For this, all the monographs (1008) of the 1995 edition were treated. A database focused on methods of chromatography (part of O. Volford's Ph.D thesis) was prepared for this study. It is to be noted that the Eur. Pharm. is now available on CD-ROM as well (see Ebel, 1995).

3. Results

Monographs of the Eur. Pharm. can be classified into two basic groups: compounds of non-uniform and uniform composition. The latter is divided again into two subgroups: inorganic and organic substances. Their ratio is indicated in Table 1. The table also shows the number of monographs containing chromatography in each class.

As visible from the data, the proportion of chromatography is very significant. Some types of this method occur in as much as two-thirds of all the monographs (in 688 of 1008). It has an even greater ratio among the substances of uniform composition (1.2 group). The greatest frequency of chromatographic analysis (nearly 90%) is in the monographs of organic drug substances (class 1.2.2). Further detailed investigation of this group follows.

The application frequency of different chromatographic techniques in each of 529 monographs, representing organic substances in the Eur. Pharm., is summarized in Table 2.

Often, in the same monograph two or three different chromatographic methods are prescribed (e.g. HPLC and GC). Such monographs are considered in each of the methods. The third column in Table 2 is for the comparison with the analytical literature (Braun and Zsindely, 1992).

Table 2 shows that GC, HPLC and TLC are the most frequently used chromatographic methods both in the pharmacopoeial and in analytical literature. However, there is a considerable difference in the usage frequency of the three leading methods (Fig. 1).

The order in the analytical literature, based on data in Braun and Zsindely (1992), is: GC > HPLC > TLC; their ratio is 1:0.56:0.25.

Table 2
Usage frequency of various chromatographic methods in the Eur. Pharm. and in the analytical literature

Method	No. of prescriptions[a]	Percent of 711 prescriptions	Literature[b] percent
Gas chromatography	76	10.7	43.6[c]
High-performance liquid chromatography	145	20.4	24.2
Thin-layer chromatography	474	66.7	11.1[d]
Hyphenated chromatographic techniques[e]	–	–	7.5
Liquid chromatography	–	–	8.5
Supercritical fluid chromatography	–	–	0.8
Size-exclusion chromatography	7	1.0	2.0[f]
Ion chromatography	2	0.3	1.7
Paper chromatography	–	–	0.7
Electrophoresis[g]	7	1.0	–
Total	711	100	100

[a]In the 529 monographs (class 1.2.2, Table 1) if the same chromatographic technique (e.g. GC) in the monograph is prescribed more than once (e.g. for purity test and for assay too), the given chromatography is considered only once.
[b]Braun and Zsindely, 1992.
[c]Including gas-liquid chromatography and capillary GC.
[d]Including HPTLC.
[e]GC-MS, capillary GC-MS, LC-MS. (Not used techniques in Eur. Pharm.)
[f]In Braun and Zsindely (1992) as gel-chromatography.
[g]Including zone-, immun-, gel electrophoresis and isoelectric focusing. Not included in Table 3 of Braun and Zsindely (1992).

The order in the pharmacopoeial analysis based on the Eur. Pharm. is: TLC ≫ HPLC > GC, which means a reverse sequence. Here the ratio is 1:0.31:0.16.

In a pharmacopoeial monograph there are three fundamental application fields of chromatography, i.e. identification, purity control and assay. Data in Table 3 demonstrate the main application field of the three leading chromatographic techniques. It can be clearly seen that the main role of all three methods is in purity control. Here again, TLC dominates; this method is prescribed in (106

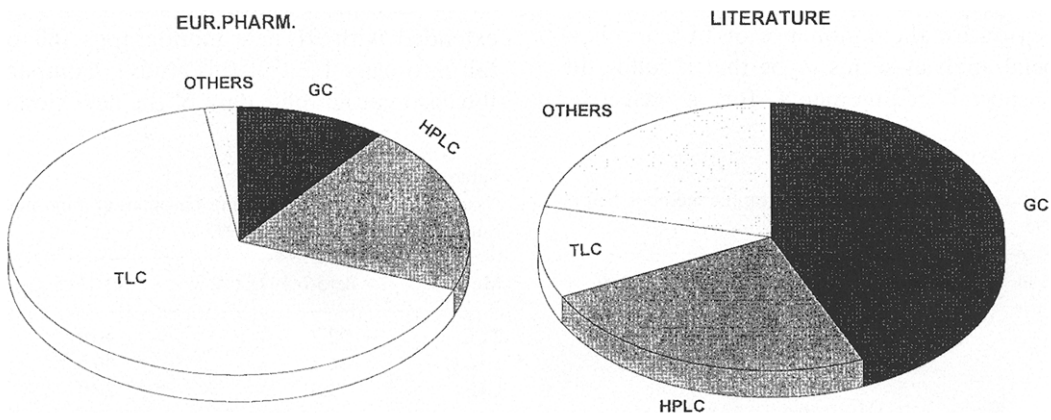

Fig. 1. The ratio of the three leading chromatographic techniques.

Table 3
The applications of the three main chromatographic techniques in the monographs of organic pharmaceutical chemicals (I, identification; P, purity; A, assay)

	I	P	A	I + P	I + A	P + A	I + P + A	Total
TLC	129	106		239			–	474
HPLC	1	93	12	5	3	21	10	145
GC	1	62	4	4	2	3		76

+ 239 =) 345 monographs. The dominance of TLC in identification is also evident; however, it has no role in assay at all.

4. Discussion

The dominant role of chromatography in pharmacopoeial analysis is not surprising and is in accordance with its significant role in the analytical literature of the world (Tables 1 and 2). However, the outstanding role of TLC among the chromatographic techniques may be astonishing and is contrary to its position in the analytical literature (Table 2 and Fig. 1).

This shift in the 'popularity' toward TLC is not exceptional for the Eur. Pharm., as supported by previously published statistics (Hubert, 1989) based on the United States Pharmacopeia. Distribution of the methods according to Hubert (1989) shows: TLC 66.6%, HPLC 15.2% and GLC 13.4%. (It has to be noted that these data were calculated in a somewhat different way.)

The reason for the dominance of TLC in pharmacopoeial analysis seems to be that it fulfils the pharmacopoeial requirements for a selective, semi-quantitative analytical method with efficacy and economy.

Similarly, the inferior role of the other important separation technique, electrophoresis, may be unexpected. But this is only characteristic for the analysis of class 1.2 (Table 1). In the 158 monographs of class 1.1, including the mixtures of biological macromolecules (immunosera, vaccines, etc.), electrophoresis is used in 36 cases.

Note that monographs of pharmacopoeias are standard-operating-procedures. Standards require settled analytical methods. Thus, the new techniques always appear in the pharmacopoeias with a certain delay. It can be expected that the proportion of chromatographics shown above will be shifted toward HPLC and GC (see below), and that the spectacularly developing technique of capillary electrophoresis will also enter into pharmacopoeial analysis in the future.

4.1. Trend-analysis

The European Pharmacopoeia (1995) has been extended with 91 new monographs (60 of them fall into class 1.2.2 of this study). Comparison of the chromatographic data of the new monographs

Table 4
Monographs containing any chromatographic methods before and in 1995

Classes as in Table 1	Before 1995 (%)	In 1995 (%)
1	67.3	79.1
1.1	47.0	52.0
1.2	77.9	89.4
1.2.1	1.4	0
1.2.2	88.2	98.3

Table 5
Usage frequency of the leading chromatographic methods in Eur. Pharm. before and in 1995

Method	Before 1995 (%)	In 1995 (%)
TLC	72.2	50.0
HPLC	16.8	40.0
GC	11.0	10.0
Total	100	100

(1995) with those of the 1994 edition of the Eur. Pharm. shows the establishment of certain trends.

Table 4 shows that application of the chromatographic techniques was further enhanced in the new monographs of the Eur. Pharm. relative to the 1994 edition (the only exception is class 1.2.1). It is noteworthy that nearly 100% of the new organic substances (class 1.2.2) contain a chromatographic prescription (in 59 of the 60 monographs).

Table 5 compares the distribution of the three leading chromatographic techniques in the new (1995) monographs with that in the 1994 version of the Eur. Pharm. The relative expansion of HPLC prescriptions is considerable. The 16.8% usage frequency of HPLC in the 1994 edition of the Eur. Pharm. was enhanced to 20.4% in the 1995 edition. The 'popularity' of GC is unchanged, while the number of TLC prescriptions decreases in the new monographs. However, if our statement in the third paragraph of the Discussion is true, it can be expected that TLC will also keep its dominance in the future. The application of HPLC in purity control seems to be reasonable where either the pharmacopoeial requirements are more rigorous than usual or semi-quantitative evaluation is not sufficient.

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