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Application of an improved column characterisation system to evaluate the within and between batch variability

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Abstract

The selection of a reversed-phase liquid chromatographic column with suitable selectivity for a particular separation is difficult if the brand name of the column is not known. A project to develop a chromatographic test procedure to characterize reversed-phase liquid chromatography C_{18} columns was started earlier and resulted in a fast, simple, repeatable and reproducible test procedure using four column parameters. Here, this procedure is used to evaluate the diversity of columns originating from the same batch as well as from different batches. The determination of one of the parameters, the retention factor of 2,2′-dipyridyl, was improved and a simplified test procedure is proposed.

Keywords: Reversed-phase liquid chromatography; Test parameters; C_{18} column

1. Introduction

When looking at the repeatability of chromatographic parameters using different batches of packings, differences may occur in column plate-count (peak-width), back-pressure, retention times and more importantly, a change of the selectivity of the separation. This can influence the specificity of the used method.

The manufacturer often provides information on physico-chemical properties of packings like particle shape, particle size, average pore size, specific surface area, nature of the bonded ligand, carbon loading, end-capping and absence of metal impurity. Among the physical properties, the specific surface area of the packing is very important, since a variation in this parameter is directly translated into a variation in retention times. An important chemical parameter is the variability of the surface coverage by the bounded phase. This is customarily expressed as μmol/m^2 of bounded phase. Many manufacturers do not provide that parameter, but give specifications for the carbon loading. The chromatographic repeatability is sometimes examined using a mixture of simple neutral compounds, such as toluene and ethylbenzene. This is not a discriminative test because the relative retention of these neutral, hydrophobic compounds is quite insensitive to variations in the quality of the packing material.

Earlier, researchers like Atwood and Goldstein studied the batch-to-batch variability of 24 batches of a commercially available reversed-phase bonded phase [1] and Smith et al. examined the batch-to-batch variability of the retention properties of a commercial silica used for the analysis of basic pharmaceutical drugs [2]. Concerning column-to-column and batch-to-batch variabilities of stationary phases, an important study was carried out by Kele and Guiochon: for different brands of commercially available C_{18} packings, the short-term and long-term repeatability of chromatographic data acquired on a single column as well as on different columns of the same batch or of different batches were examined [3–9]. The investigated parameters were characteristic for the retention, the hydrophobic interaction selectivity, the steric selectivity, the relative retention of basic and neutral compounds, the column efficiency and the peak asymmetry. They reported that the repeatability for certain silica-based C_{18}-packings is quite remarkable. They also con-

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cluded that the batch-to-batch variability of the chromatographic data is almost as good for non-monomeric stationary phases as for monomeric phases and that the RSD of the relative retention of the neutral–neutral pairs is always much lower than that of basic-neutral or basic–basic pairs.

Many chromatographic tests are dedicated to column classification in the literature [10–27]. Like for chromatographic methods, the reliability of those tests should be evaluated. Only some authors reported on the repeatability of tests, the variability introduced by either the packing or the batch of the stationary phase (corresponding to column-to-column and batch-to-batch reproducibility) and on the reproducibility of tests [28]. Regarding test reproducibility, a good approach is to perform an interlaboratory trial, as performed by Visky et al. for the test parameters used in this paper [29].

Here, an evaluation was made of the scores of columns from the same and from different batches in a column test procedure, determining four column test parameters, reflecting hydrophobicity, silanol activity, steric selectivity and metal impurity. This procedure was developed earlier to characterize and classify columns. This allows to evaluate the within and between batch variability. During the application of the test procedure, a problem was observed with the determination of the retention factor of 2,2′-dipyridyl. To improve the procedure, a buffer was added to the mobile phase. Also, a simplification of the dead volume determination was introduced.

2. Experimental

2.1. Reagents and samples

Acetonitrile was purchased from Acros Organics (Beerse, Belgium), potassium dihydrogen phosphate and phosphoric acid were from Merck (Darmstadt, Germany) and methanol HPLC grade from BDH (Poole, England). Water was purified by distillation of demineralised water.

Uracil was purchased from Janssen Chimica (Geel, Belgium) and *o*-terphenyl from Aldrich (Bornem, Belgium,). Amylbenzene, benzylamine, 2,2′-dipyridyl, phenol and triphenylene were acquired from Acros Organics (Geel, Belgium).

All solvents were HPLC grade and all reagents of analytical grade.

2.2. Instrumentation and liquid chromatographic conditions

The LC apparatus consisted of a Varian (Walnut Creek, California, USA) 9010 LC pump, a 9100 autosampler equipped with a 20 μl loop and a 9050 UV–vis detector, set at 254 nm. ChromPerfect 4.4.0 software (Justice Laboratory Software, Fife, UK) was used for data acquisition. The column temperature was maintained by immersion in a water bath heated by a Julabo EC thermostat (Julabo, Seelbach, Germany) at 40 °C while the laboratory was air-conditioned at 25 °C. A set of 66 RP-LC C_{18} columns was investigated. Specifications of the different columns examined are reported in Table 1. The buffers were prepared using a Consort C831 pH meter (Consort, Turnhout, Belgium), equipped with a Hamilton (Bonaduz, Switzerland) combination glass electrode.

To characterize each column, three chromatographic methods were carried out in a defined order (A-B-C) to determine the four column parameters. The mobile phases and samples were prepared according to Tables 2 and 3. The flow rate was 1 ml/min.

3. Results and discussion

3.1. Development of a characterisation and classification system

Earlier methods for RP-LC column characterisation were reported by Steffeck et al. [10] and Engelhardt and Grüner [11]. Since, many other laboratories have published on this subject and more recently published articles were cited above [12–26].

In our laboratory, after a study of the existing literature, 36 column parameters were selected, which could be determined by performing eight chromatographic methods [30,31]. The repeatability and reproducibility of the test parameters were examined in three different laboratories. Based on the evaluation of the relative standard deviation, 24 out of the initial 36 parameters proved to be repeatable and reproducible [29].

To further reduce the number of parameters, without losing important information, principal component analysis (PCA) was applied. The 24 reproducible test parameters were classified in seven groups. A representative parameter was chosen from each group. The resulting seven test parameters and the chromatographic property they are supposed to represent were: the theoretical plate number of amylbenzene (efficiency), the retention factor of amylbenzene (hydrophobicity), the relative retention factor benzylamine/phenol at pH 2.7 (silanol activity), the relative retention factor triphenylene/*o*-terphenyl (steric selectivity), the retention factor of 2,2′-dipyridyl (silanol activity and metal impurity), the relative retention factor 2,3-dihydroxynaphtalene/2,2′-dipyridyl (metal impurity) and the relative retention factor acetylsalicylic acid/5-*p*-methylphenyl-5-phenylhydantoin (non-defined property). Even when the number of parameters was further reduced from 7 to 4, a classification of the RP-LC columns, similar to that originally based on 24 parameters, could be maintained. The finally retained parameters were: the retention factor of amylbenzene (k'_{amb}), the relative retention factor benzylamine/phenol at pH 2.7 ($rk'_{ba/ph\,2.7}$), the retention factor of 2,2′-dipyridyl ($k'_{2,2'\text{-dip}}$) and the relative retention factor triphenylene/*o*-terphenyl ($rk'_{tri/o\text{-ter}}$). It was concluded earlier that there is no guarantee that columns with similar reported properties also exhibit equivalent selectivity towards a given separation, which emphasized the need for chromatographic test parameters to characterize stationary phases [32].

A practical approach to classify RP-LC columns was introduced by using *F*-values, derived from the four selected parameters.

Table 1
List of investigated C_{18} columns

No	Name	Length (mm)	Particle size (μm)	Manufacturer/Supplier	*F*-value within batch	*F*-value between batch
1	Acclaim 3 μ 150 mm	150	3	Dionex		
2	Acclaim 5 μ 250 mm	250	5	Dionex		
3	Ace 5 C18	250	5	Achrom	0.000	0.085
4	Alltima AQ	250	5	Alltech	0.006	
5	Alltima C18	250	5	Alltech	0.002	0.575
6	Alltima HP C18 5 μ	250	5	Alltech		
7	Alltima HP C18 Amide 5 μ	250	5	Alltech	0.010	
8	Brava BDS C18	250	5	Alltech	0.000	0.225
9	Brava ODS	250	5	Alltech	0.001	
10	Capcell Pak C18 ACR	250	5	Shiseido Fine Chemicals	0.000	
11	Capcell Pak C18 AQ	250	5	Shiseido Fine Chemicals	0.000	
12	Capcell Pak C18 MG	250	5	Shiseido Fine Chemicals	0.002	
13	Capcell Pak C18 UG 120	250	5	Shiseido Fine Chemicals	0.000	
14	Chromolith	100	5	Merck	0.000	0.631
15	Discovery C18	250	5	Supelco	0.000	0.369
16	Discovery HS C18	250	5	Supelco	0.003	
17	Exsil ODS 5 μm	250	5	SGE	0.002	
18	Hamilton Hx Sil C18	250	5	Hamilton	0.002	
19	Hydrospher C18	250	5	YMC	0.000	0.100
20	HyPURITY Advance	250	5	Thermo Electron Corporation	0.001	
21	HyPURITY Aquastar	250	5	Thermo Electron Corporation	0.008	
22	HyPURITY C18	250	5	Thermo Electron Corporation	0.001	
23	Inertsil ODS-2	250	5	GL Sciences Inc.	0.005	
24	Inertsil ODS-3	250	5	GL Sciences Inc.	0.001	
25	Inertsil ODS-80A	250	5	GL Sciences Inc.		
26	Inertsil ODS-P	250	5	GL Sciences Inc.	0.005	
27	Kromasil KR 100-5C18	250	5	EKA Chemicals	0.000	1.020
28	LiChrosorb RP-18	250	5	Merck	0.001	
29	LiChrospher 100 RP-18	250	5	Merck	0.001	0.026
30	MP-Gel ODS-5	250	5	YMC/OmniChrom	0.010	
31	Omnispher 5 C18	250	5	Varian	0.001	0.796
32	Platinum C18	250	5	Alltech		0.046
33	Platinum EPS C18	250	5	Alltech		
34	Polaris 5 μC18-A	250	5	Varian	0.013	
35	Prevail Amide	250	5	Alltech	0.001	
36	Prevail C18	250	5	Alltech	0.002	
37	Prevail Select C18	250	5	Alltech	0.004	
38	Prontosil 120-5-C18 AQ	250	5	Bischoff	0.000	
39	Prontosil 120-5-C18 AQ PLUS	250	5	Bischoff	0.000	
40	Prontosil 120-5-C18-ace EPS	250	5	Bischoff	0.001	
41	Prontosil 120-5-C18-H	250	5	Bischoff	0.001	
42	Prontosil 120-5-C18-SH	250	5	Bischoff	0.000	
43	Prontosil 60-5-C18 H	250	5	Bischoff	0.002	
44	Purospher RP-18e	250	5	Merck		1.748
45	Purospher Star RP-18e	250	5	Merck	0.000	1.310
46	Pursuit 5 μ C18	250	5	Varian	0.001	
47	Restek Allure C18	250	5	Restek		
48	Restek Pinnacle DB C18	250	5	Restek		
49	Restek Pinnacle II C18	250	5	Restek		
50	Restek Ultra C18	250	5	Restek		
51	Supelcosil LC-18	250	5	Supelco	0.001	0.065
52	Supelcosil LC-18 DB	250	5	Supelco	0.002	0.292
53	Superspher 100 RP-18	250	5	Merck	0.001	0.007
54	Uptisphere 5 HDO-25QS	250	5	Interchrom/Achrom	0.000	0.164
55	Uptisphere 5 ODB-25QS	250	5	Interchrom/Achrom	0.001	0.159
56	Wakosil II 5C18RS	250	5	SGE	0.000	
57	Xterra MS C18	250	5	Waters		
58	Xterra RP C18	250	5	Waters		
59	YMC-Pack Pro C18-3	250	3	YMC	0.000	0.135
60	YMC-Pack Pro C18-5	250	5	YMC	0.000	0.101
61	YMC-Pack Pro C18 RS	250	5	YMC	0.003	
62	Zirchrom -PS 3 μ	150	3	Zirchrom	0.003	
63	Zorbax Eclipse XDB-C18	250	5	Agilent	0.001	0.028
64	Zorbax Extend-C18	250	5	Agilent	0.000	0.023
65	Zorbax SB-Aq	250	5	Agilent	0.001	
66	Zorbax SB-C18	250	5	Agilent	0.000	0.149

Table 2
Chromatographic test methods

Method	Mobile phase	Column parameter
A	Methanol–water–0.2 M potassium phosphate buffer pH 2.7 (34:90:10, w/w/w)	$rk'_{\text{benzylamine/phenol}}$
B	Methanol–water (34:100, w/w)	$k'_{2,2'\text{-dipyridyl}}$
B′	Methanol–water–0.2 M potassium phosphate buffer pH 6.5 (34:90:10, w/w/w)	$k'_{2,2'\text{-dipyridyl}}$
C	Methanol–water (317:100, w/w)	$k'_{\text{amylbenzene}}$ $rk'_{\text{triphenylene}/o\text{-terphenyl}}$

$$F = (k'_{\text{amb, ref}} - k'_{\text{amb, }i})^2 + (rk'_{\text{ba/ph 2.7, ref}} - rk'_{\text{ba/ph 2.7, }i})^2 + (k'_{2,2'\text{-dip, ref}} - k'_{2,2'\text{-dip, }i})^2 + (rk'_{\text{tri}/o\text{-ter, ref}} - rk'_{\text{tri}/o\text{-ter, }i})^2 \quad (1)$$

The F-value of a column i equals the sum of squares of the differences between each parameter value of a freely chosen reference column and of column i. The smaller the F-value, the more similar is column i to the reference column. In order to have the same weighing of each parameter in this equation, the parameters are autoscaled using formula (2) before being introduced in Eq. (1):

$$\frac{x_{ij} - \bar{x}_j}{s_j} \quad (2)$$

where x_{ij} is the value of parameter j on column i, $\bar{x}_j$ the mean of parameter j on all tested columns and s_j is the standard deviation on the mean parameter value. With this F-value, a ranking of all columns is obtained; low F-values correspond to ranking close to a selected reference column [33,34].

Later, pharmaceutical analyses were performed in order to study the correlation between the column classification system and performance in real separations (acetylsalicylic acid, clindamycin hydrochloride, buflomedil hydrochloride, chloramphenicol sodium succinate, nimesulide, phenoxymethylpenicillin, dihydrostreptomycin sulphate and vancomycin) [35–37].

3.2. Application to pairs of columns of the same and different batches of brands

In this paper, the F-value is used to compare only two columns with each other. For clarity, it will be denoted as F. Only column types, of which two columns from the same or different batch were present in this study, could result in a F-value.

Table 3
Sample composition

Method	Sample composition
A	5 mg of benzylamine and 5 mg of phenol in 10 ml of mobile phase A
B	0.1 mg of uracil and 3 mg 2,2′-dipyridyl in 10 ml of mobile phase B
B′	3 mg 2,2′-dipyridyl in 10 ml of mobile phase B′
C	0.1 mg uracil, 7 mg amylbenzene, 0.2 mg o-terphenyl and 0.02 mg triphenylene in 10 ml of mobile phase C

All test parameters were determined on two columns from the same batch, which allows to evaluate the change of properties within a batch. For a number of brands two batches were examined, to compare between batches, and the average of the two columns originating from a same batch was calculated for each of the four parameters. The F-value, described above, was determined between two sets of four parameters from the same batch or from different batches. These results for columns from the same batch are shown in Table 1. Results for Platinum C_{18}, Platinum EPS C_{18} and Purospher RP-18e are not reported since a problem occurred during determination of the retention factor of 2,2′-dipyridyl. Of the latter columns, one column from each pair did not gave a value for $k'_{2,2'\text{-dip}}$, making the calculation of the above-mentioned F-value impossible.

The obtained F-values are in the range of 0–0.013, indicating that the differences between columns from the same batch are small. This also implies that no difference in ranking will be observed if columns from the same batch are interchanged in the complete database of columns.

Table 1 also shows the F-values of 22 pairs of columns each from two different batches. For Platinum EPS C_{18}, no result could be reported because of the impossibility to measure $k'_{2,2'\text{-dip}}$. For the 22 reported stationary phases, the F-values ranged from 0.001 to 1.748, and 80% of the values showed a value below 0.64. Logically, this number is higher than observed for columns from the same batch. Therefore, when classifying columns from different batches in the general ranking system, more or less different positions may be observed, depending upon the brand.

3.3. Adaptation of the column classification system

During the determination of $k'_{2,2'\text{-dip}}$, it was sometimes observed that the 2,2′-dipyridyl peak showed a poor peak shape, that it was not eluted at all or that a high retention time was obtained, as shown in Fig. 1a. This was already mentioned previously [32], but now, it was observed that for some brands even columns from the same batch or from different batches behaved differently, in so far that for one column a value was obtained, while for the other column of the pair no value could be determined. This leads to missing or outlying values, with data points so far from the other data that they severely distort the results. A possible solution is “Winsorizing”, which means that extreme results are given a value closer to the mean [38]. Up to now, the missing and/or outlying data in our column classification study were replaced by plausible values, differing by 10% from the most extreme value measured on the other columns. A similar situation can be observed in the column classification study of Olsen and Sullivan, where sometimes arbitrary values were used also [39].

The same problem with the determination of $k'_{2,2'\text{-dip}}$ was encountered when the parameter was determined again on a column on which several analyses had been performed after a first testing. When 69 columns were retested, 33% gave no result for $k'_{2,2'\text{-dip}}$, as compared to 10% of the columns during a first testing. The parameter is determined based on retention times of uracil and 2,2′-dipyridyl, using a mobile phase consisting of methanol

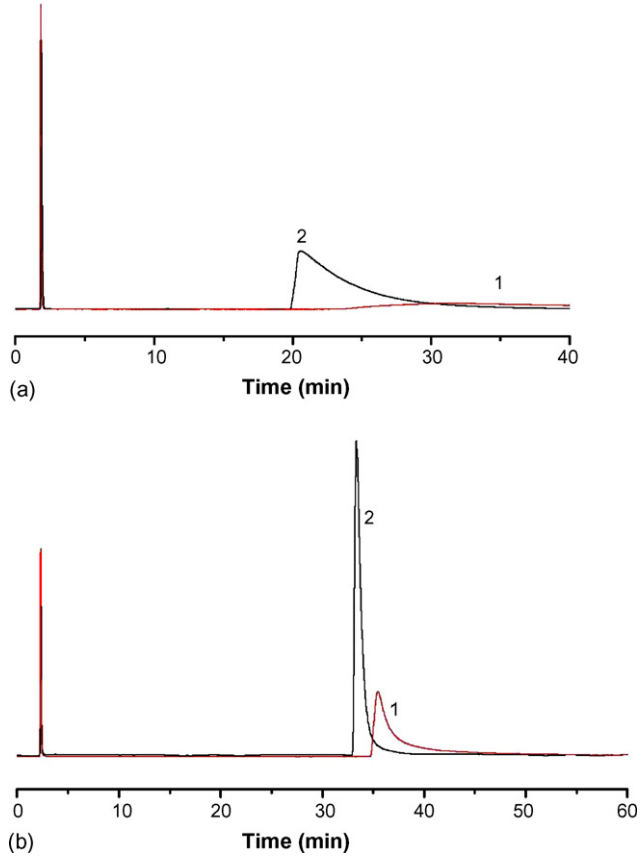

Fig. 1. (a) Column: Platinum EPS (150 mm × 4.6 mm, 3 μm); this chromatogram shows uracil with a 2,2-dipyridyl peak 1 that is troublesome to integrate. This is solved with the buffered method, giving peak 2. (b) Column: Restek Allure C18, (250 mm × 4.6 mm, 5 μm); this chromatogram shows the improvement of the buffered method (peak 2) to the non-buffered method for 2,2′-dipyridyl peak 1.

and water. To overcome the above-mentioned problem, different solutions such as change of organic modifier, change of concentration of the compounds in the mobile phase and addition of a buffer at different pH values were investigated. The best improvement was obtained by adding a phosphate buffer of pH 6.5, resulting in a mobile phase of methanol–water–0.2 M phosphate buffer pH 6.5 (34:90:10, w/w/w), as shown in Fig. 1b. There was not only an influence on the retention time, but also the peak shape was much better.

The adapted method, as well as the original non-buffered system to determine $k'_{2,2'\text{-dip}}$, were applied onto a set of 119 new columns supplied by manufacturers. Using the method without buffer, some columns gave problems whereas with the buffered method, $k'_{2,2'\text{-dip}}$ could always be determined. A classification based on F-values was obtained with either the non-buffered or the buffered method results. The respective ranking number of the columns was plotted against each other, as seen in Fig. 2 and the correlation was examined. It shows that no outlying data point is present and the R^2 value of the trendline was 0.92. So, it can be concluded that both methods are well correlated while the new method B′ avoids (or at least seriously reduces) the occurrence of missing data.

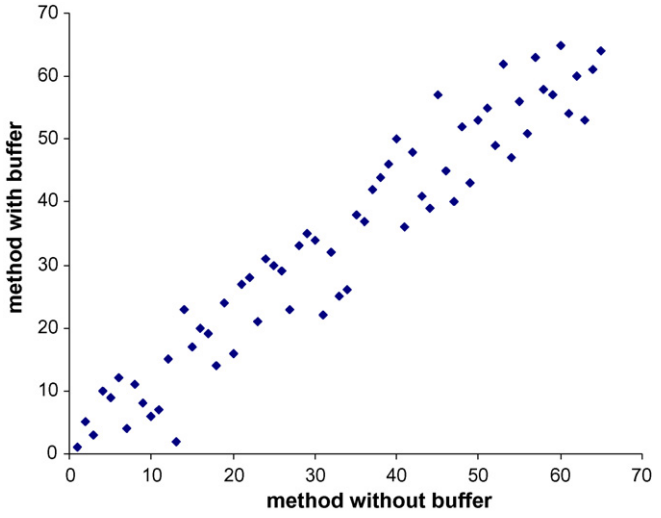

Fig. 2. A graph representing the respective positions of the columns towards a chosen ACE reference column.

Moreover, it was noticed that the retention time of uracil in method C was lower in comparison with methods B and B′, so it was considered a better indication for the dead volume. When the retention time of uracil from methods B and B′ were used, the $rk'_{\text{ba/ph 2.7}}$ gave in several cases a negative value, this being an indication that the uracil retention time obtained by methods B and B′ was too high. It was therefore decided to use in all calculations the retention time for uracil as obtained in method C.

The column ranking system is freely accessible on our website: http://www.pharm.kuleuven.be/pharmchem/columnclassification and contains over 80 different types of RP-LC C_{18} columns. New types are being characterized in our laboratory at this moment. Analysts can either classify all columns from the database with regard to a freely chosen reference column from the list or they can fill in four parameter values, determined on their own column. The latter allows them to rank columns that are available in their lab, but not included in the database. Also a second set of parameters can be added, for comparison with an original first parameter set.

4. Conclusion

A simple, repeatable and reproducible test procedure for column characterisation study was developed earlier. It implies the determination of four column parameters; the retention factor of amylbenzene, k'_{amb}, the relative retention factor benzylamine/phenol at pH 2.7, $rk'_{\text{ba/ph 2.7}}$, the retention factor of 2,2′-dipyridyl, $k'_{2,2'\text{-dip}}$ and the relative retention factor triphenylene/*o*-terphenyl, $rk'_{\text{tri}/o\text{-ter}}$. When this test procedure was applied onto columns from the same batch, small differences were seen whereas the differences between columns from different batches were somewhat bigger as could be expected. The differences were very much brand dependent.

One of the parameters, $k'_{2,2'\text{-dip}}$, could not always be properly determined. To solve this issue, a phosphate buffer of pH 6.5 was added to the mobile phase and the determination of the

dead volume by the retention time of uracil was simplified. The changes facilitated considerably the determination of this test parameter.

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