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Assessment of robustness on analysis using headspace solid-phase microextraction and comprehensive two-dimensional gas chromatography through experimental designs

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ABSTRACT

Plackett–Burman experimental design was applied for the robustness assessment of GC × GC–qMS (Comprehensive Two-Dimensional Gas Chromatography with Fast Quadrupolar Mass Spectrometric Detection) in quantitative and qualitative analysis of volatiles compounds from chocolate samples isolated by headspace solid-phase microextraction (HS-SPME). The influence of small changes around the nominal level of six factors deemed as important on peak areas (carrier gas flow rate, modulation period, temperature of ionic source, MS photomultiplier power, injector temperature and interface temperature) and of four factors considered as potentially influential on spectral quality (minimum and maximum limits of the scanned mass ranges, ions source temperature and photomultiplier power). The analytes selected for the study were 2,3,5-trimethylpyrazine, 2-octanone, octanal, 2-pentyl-furan, 2,3,5,6-tetramethylpyrazine, and 2-nonanone e nonanal. The factors pointed out as important on the robustness of the system were photomultiplier power for quantitative analysis and lower limit of mass scanning range for qualitative analysis.

1. Introduction

According to the ICH (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use) guidelines "*The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage* [1]".

In separation techniques, robustness tests have been applied in high-performance liquid chromatography (HPLC) [2–5], capillary electrophoresis (CE) [6,7] and gas chromatography (GC) [8–10]. Furthermore, to evaluate the robustness of an analytical procedure the use of experimental design is more effective than the use of one-variable-at-a-time (OVAT) procedure, since several parameters can be tested simultaneously with small number of experiments. Gaujac et al. [11] used robustness test for method validation to analyze N,N-dimethyl-tryptamine (DTM), a powerful psychoactive indole alkaloid present in a variety of South American indigenous beverages, using solid-phase microextraction (SPME)/gas chromatography ion trap mass spectrometry (GC-IT-MS). A three factor face centered design consisting of fifteen experiments was employed to evaluate the critical factors: pH of aqueous phase, time of extraction and temperature. The results showed that the obtained response remained unaffected by small changes in these parameters. Plackett–Burman experimental design was applied to robustness test for method validation of sitagliptin (STG) determination in human urine using GC–MS [12]. Six variables were assessed (analyst, column, ether, derivatization reagent, time of derivatization and temperature). The author concludes that the method was considered robust for the variations tested.

However assessment of robustness in GC × GC analyses [13] was not found in the literature until the present time. This technique employs two gas chromatographic separations in a sequential fashion. An interface, known as modulator, continuously samples primary effluent from first column and transfers to the head of the secondary one [14]. The peak capacity (maximum number of separable peaks) of a GC × GC system increases geometrically with respect to 1-D GC. Other advantages include enhanced sensitivity, as well as, structure of GC × GC chromatograms which facilitates the identification of unknowns [15–17].

Due these factors, GC × GC has been widely used to study highly complex matrices such as petroleum [18], essential oils [19], as well as, in foods such as coffee [20], honey [21] and strawberry [22]. In food analysis, GC × GC allowed classification or tracing geographical origins, through specific chemical markers [21]. Its

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use in biology has been effective, as in the work of Hantao et al. [23], where possible markers of resistance of *Eucalyptus* to fungus *Puccinia psidii* were found.

Due to the use of this technique in various types of samples, a validation procedure and consequent assessment of robustness are fundamental for its practical implementation in routine analyses. Mostafa et al. [24] described relevant aspects associated with the optimization of main operational parameters in GC × GC, but robustness was not mentioned in the manuscript.

In this work, Plackett–Burman experimental design was applied to assess the robustness in GC × GC–qMS analysis of volatiles compounds from chocolate samples. Experiments to assess the robustness of the system when used as quantitative tool (adopting peak areas of selected analytes as the monitored response) and as qualitative tool (similarity between library and experimental spectra of these compounds) were carried out.

1.1. Theory

Robustness tests usually have been performed by two level factorial designs, such as fractional factorial (FF) or Plackett–Burman (PB) design [25–27], with examination of a relatively large number of factors with a small number of experiments [28].

In Plackett–Burman (PB) design [29], the most important feature is that it involves always $4n$ experiments, where $n=1, 2, 3\ldots$ The maximum number of factors that can be studied are $4n-1$ and then a 12-experiment design can evaluate no more than 11 factors. In Plackett–Burman designs, the first line will be always the same and it can be found in tables described in [27,29]. The second line is obtained through a cyclic permutation from the first position of the first line and the subsequent lines following the same reasoning, as shown in Fig. 1. Moreover, the last line of this design has all values in inferior level.

In this sense, factors presenting significant effect in the experimental design indicate that no robustness was verified for this factor. In an opposite way, if the studied factor does not present significant effect, robustness was proved for it.

For this kind of saturated design the factor effects are estimated as

$$\frac{E_x = \sum Y(+1) - \sum Y(-1)}{N/2} \quad (1)$$

where $\Sigma Y(+1)$ and $\Sigma Y(-1)$ represent the sums of the responses where the factor X is $(+1)$ and (-1) level and N is the number of experiments.

Generally to evaluate the factors effect a t-test approach is used and all effects that are larger or equal to $E_{critical}$ are significant [25]

$$t = \frac{|E_x|}{(SE)_e} \leftrightarrow t_{critical} \quad (2)$$

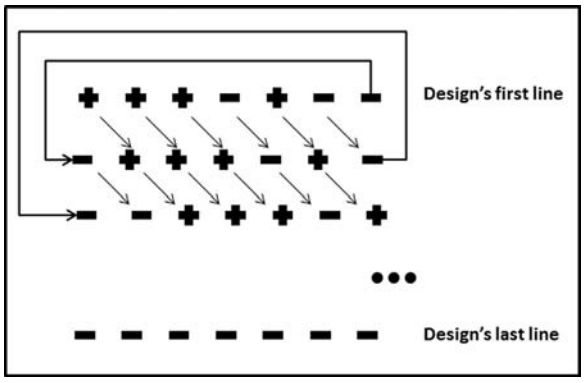

Fig. 1. Plackett–Burman design.

$$|E_x| \leftrightarrow E_{critical} = t_{critical} \times (SE)_e \quad (3)$$

The critical effect depends on the tabulated t-value ($t_{critical}$) and the estimation of the standard error of the effect $(SE)_e$. The standard error can be estimated from dummy effects (effects that are negligible)

$$(SE)_e = \sqrt{\frac{\Sigma E_{error}^2}{n_{error}}} \quad (4)$$

where ΣE_{error}^2 is the sum of squares of the n_{error} dummy effects. In this case, at least three dummy factors should be selected [27].

Another way to estimate $(SE)_e$ is the use of the algorithm of Dong [30]. In this approach, an initial estimate of the error is obtained (s_0) and from this value a final estimation of the standard error (s_1) is derived

$$s_0 = 1,5 \times \text{mean}\,|E_i| \quad (5)$$

$$s_1 = \sqrt{m^{-1} \Sigma E_j^2} \text{ forall } |E_i| \leq 2.5 s_0 \quad (6)$$

where E_i is the effect of the factor i, E_j the effect in which the absolute value is less than $2.5 \times s_0$ and m is the number of such effects.

The s_1 value is used to calculate the so called margin of error (ME), which is a critical effect

$$E_{critical} = ME = t_{(1-\alpha/2,df)} \times s_1 \quad (7)$$

The algorithm of Dong is interesting when applied in saturated designs, where there are no degrees of freedom for standard error calculation. Another strategy that can also be used is the permutation tests [31].

In permutation test, the significance of a particular effect is not derived from tables of statistical values, but from the distribution of the test statistic generated by randomization of the data in different ways. An advantage in this case is that it is not necessary to assume normality of the data [31]. The permutation test is based on the randomization values of the vector of responses ($\mathbf{y}$), but maintaining constant the order of the experimental design. A test is calculated to each effect (and for iterations) through the equation:

$$t = \left| \bar{y}\left(\frac{N}{2}\right)_1 - \bar{y}\left(\frac{N}{2}\right)_2 \right| \quad (8)$$

where $\bar{y}(N/2)_1$ is the average of half-responses, relative to high level $(+)$, and $\bar{y}(N/2)_1$ is the average of the another half, relative to low level $(-)$ for each factor effect. To identify significant effects, from hundreds or thousands of permutations, a p-value is determined (in proportion) by the number of times that the t-values are greater than or equal to the original effect. When a p-value is lesser than or equal to 0.01 or 0.05, the effect is considered significant at $\alpha=0.01$ or 0.05, respectively.

2. Material and methods

2.1. Sample and SPME materials

A single batch of commercial dark chocolate labeled as containing 65% cocoa was used throughout this study. The volatile fraction of the sample was isolated from (1.000 ± 0.005 g) aliquots of chocolate by HS-SPME using a 50/30 μm divinylbenzene/carboxen/polydimethylsiloxane (DVB/CAR/PDMS) fiber. The general extraction procedure was the same as adopted previously for similar samples [32,33] with some experimental conditions adjusted in preliminary optimization studies not described here: sample/headspace equilibration time=5 min, fiber/headspace equilibration time=50 min, extraction temperature=60 °C and desorption time=5 min.

2.2. GC × GC–qMS

GC × GC analyses were carried out on a prototype based on a Shimadzu QP2010+ GC–MS, fitted with a lab-designed and made compact 4-jet cryogenic modulator, already described elsewhere [23]. The column set consisted on a 30 m × 0.25 mm × 0.25 μm HP-5 capillary column (Agilent Technologies, Wilmington, DE) connected by a pressfit connector to a 0.80 m × 0.1 mm × 0.1 μm Solgel Wax (SGE Analytical Science, Ringwood, Victoria, Australia). The modulation period was set to 6.0 s. The split-splitless injector was operated on splitless mode at 260 °C. The column oven temperature was programmed as follows: 60–70 °C at 3 °C min^{-1} (staying during 6 min at this temperature), 70–110 °C at 3 °C min^{-1} and 110–240 °C at 10 °C min^{-1}. High purity (99.9999%) hydrogen at 0.6 mL min^{-1} was used as carrier gas. The MS interface temperature was 260 °C and photomultiplier power was set to 0.8 kV until 10 min run and then at 0.9 kV. The scanned mass range was set from m/z=40–340 D, which resulted on a data collection frequency of 25 spectra s^{-1}. Peaks on the GC × GC–qMS chromatograms were identified by combinations of MS data library searches on GCImage software (Zoex Corp., Houston, TX, USA) fitted with the NIST 2010 spectra library and by co-injection of authentic standards, when available.

2.3. Plackett–Burman designed experiments

Two separated studies planned out according to a Plackett–Burman design were carried out, to assess the effect of variations of relevant GC × GC–qMS operational parameters on the intensity of the chromatographic signals (and, therefore, on the performance of the system on quantitative chemical analyses) and on the quality of the matching of the obtained mass spectra to a standard MS library (which, on its turn, can be associated to the ability of the system to perform as qualitative tool).

2.3.1. Effect of variation on GC × GC–qMS operational parameters on quantitative performance

This study comprised 12 experiments, where general GC × GC–qMS parameters—including chromatographic- and MS-related variables were varied. Table 1 describes the evaluated variables, their nominal levels and corresponding ranges. The response was defined as the sum of the normalized peak areas corresponding to the following compounds: 2,3,5- trimethylpyrazine, 2-octanone, octanal, 2-pentyl-furan, 2,3,5,6-tetramethylpyrazine, 2-nonanone e nonanal. These specific compounds were selected for being representative of the diverse chemical functionalities and structures present on the chocolate volatile fraction, as well as because they were detected in all chromatograms. Five dummy variables were used to calculate the standard error.

Table 1
General GC × GC–qMS experimental parameter evaluated.

Variables	Minimum level	Maximum level	Nominal level
Carrier gas flow rate (ml min^{-1})	0.5	0.7	0.6
Modulation period (s)	5	7	6
Ion source temperature (°C)	240	260	250
Photomultiplier power (kV)	0.79–0.89	0.81–0.91	0.80–0.90
Injector temperature (°C)	250	270	260
MS interface temperature (°C)	250	270	260

Table 2
Specific MS parameters evaluated.

Variables	Minimum level	Maximum level	Nominal level
Ion source temperature (°C)	240	260	250
Photomultiplier power (kV)	0.79–0.89	0.81–0.91	0.80–0.90
Minimum scanned m/z	35	45	40
Maximum scanned m/z	315	325	320

2.3.2. Effect of variation on GC × GC–qMS operational parameters on qualitative performance

Following the initial quantitative study, other independent Plackett–Burman design study with eight experiments was applied to the MS detector parameters which could affect the reliability of spectral identification of chromatographic peaks. Table 2 describes the evaluated parameters, their nominal levels and ranges. The responses here were defined as the sum of spectral similarities between the experimental and NIST08 library spectra for the same compounds abovementioned. In this case, three dummy variables were used to calculate the standard error.

For interpretation of the effects on both studies, half-normal probability plots [34], statistical interpretation based on dummies variables [25] or Dong algorithm [30] and permutation tests [31] were employed.

3. Results and discussion

Fig. 2 shows a typical GC × GC–qMS chromatogram obtained. The peak corresponding to the selected model compounds is assigned in this figure. Tables 3 and 4 show the results from the Plackett–Burman experiments described above.

Several approaches were applied and compared to assess the significance of these results and to determine which parameters are really relevant on the robustness of the analytical system. The first and more straightforward of them was the examination of half-normal plots generated for each experiment (Fig. 3a and b below). Effects that can be fitted in a straight line can be considered not significant (normal distribution around zero).

According to these plots, variations on carrier gas flow rate (**a**) and photomultiplier power (**k**) can affect significantly the performance of GC × GC–qMS as quantitative tool and only changes on the lower limit of the m/z scanned range (**a**) can affect the quality of fitting between library and experimental mass spectra. However, in some cases half-normal or normal plots can leave to an inconclusive evaluation of the significant effects. In this way, statistical interpretation, when it is given enough degrees of freedom, provides a numerical limit value that allows the definition, in a less subjective way than the visual one, the significance of the effects [27]. This limit value is usually derived from the t-test statistic and it is necessary to estimate the experimental error.

For the following evaluations, experimental error was calculated by two ways: through the use of dummy variables and by the Dong algorithm. For the study of the robustness of GC × GC–qMS as quantitative tool, five dummies variables were used; in this case the standard error (SE) was estimated as 6.75 which resulted on a t-test value of 2.57 (for α=0.05) and $t_{critical}$ (calculated using Eq. (3)) of 17.3. As for the qualitative robustness of the GC × GC–qMS system, the SE was 0.38 and the $t_{critical}$ value was found to be 1.20. When these limiting values are applied to the data in Tables 3 and 4, it is possible to verify that the results are consistent with the evaluation of significance through half-normal plots: variations on the same operational parameters for both experiments (carrier gas flow and the photomultiplier voltage for the quantitative

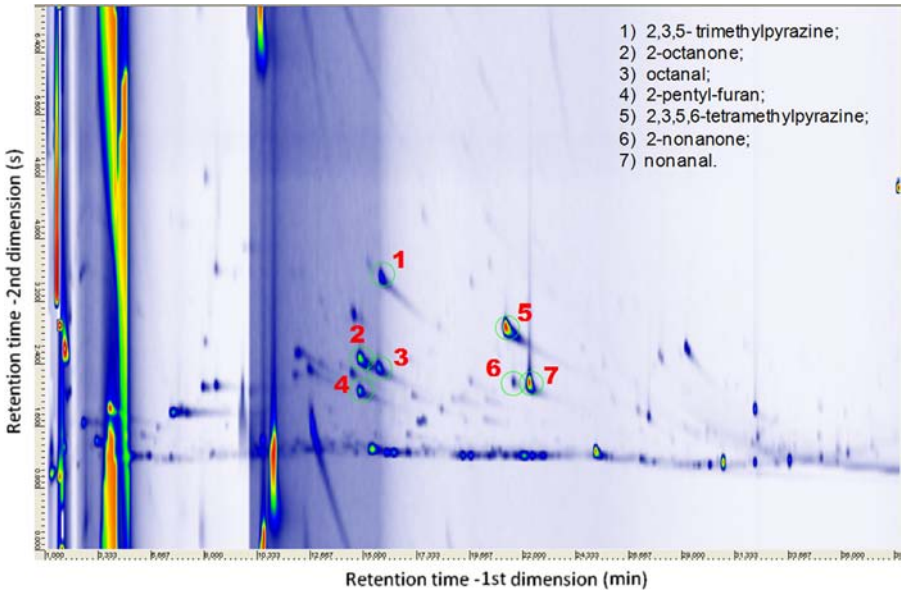

Fig. 2. GC × GC surface of a chocolate sample and selected compounds for design evaluation.

Table 3
Effects estimated from Plankett–Burman study for general GC × GC–qMS operational parameters.

Parameter	Effect
a. Carrier gas flow rate	−20.6
b. Dummy	−4.2
c. Modulation period	1.2
d. Dummy	2.1
e. MS interface temperature	5.6
f. Dummy	5.6
g. Dummy	6.9
h. Dummy	11.3
i. Ion source temperature	14.1
j. Injector temperature	16.1
k. Photomultiplier power	30.7

Table 4
Effects estimated from Plankett–Burman study for specific qMS operational parameters.

Parameter	Effect
a. Minimum scanned m/z	−1.50
b. Ion source temperature	−0.44
c. Dummy	−0.37
d. Dummy	−0.19
e. Maximum scanned m/z	−0.06
f. Photomultiplier power	0.31
g. Dummy	0.50

assessment and lower limit of mass scanned range for the qualitative study) were deemed as important on the robustness of the system.

The Dong algorithm is useful when saturated design is applied and the number of degrees of freedom is not enough for reliable standard error calculation. For both experiments, s_0 and s_1 values were calculated to allow determination of margins of error (*ME*), as discussed above. The calculated *ME* (α=0.05) was 23.8 (10 degrees of freedom) and 0.85 (6 degrees of freedom), for the quantitative and qualitative studies, respectively. The comparison of these values with the effects shown in Tables 3 and 4 points out that variations on the photomultiplier power and on the minimum scanned *m*/*z* were relevant to the robustness of the GC × GC–qMS system for quantitative and qualitative analysis, respectively—which agrees with the previous results. However, according to this approach variations on the carrier gas flow rate have no significant impact on the robustness when the system is applied to quantitative analysis.

A further evaluation was carried out through permutation tests: for this strategy, if a *p*-value obtained through data randomization under different conditions is smaller than an adopted level of significance; its influence on the robustness can be considered as significant. Fig. 4a and b shows *p*-values and confidence limits for both studies; the number of permutations utilized was 100.000 and α=0.05 was adopted as the significance level. It is possible to verify that the significant effects obtained with permutation tests method were consistent with the results from Dong algorithm.

Finally, Table 5 summarizes the results obtained from all strategies for the evaluation of the relevance of GC × GC–qMS operational parameters on its robustness.

It can be seen that the use of different strategies to analyze the effects leads to slightly different conclusions: variations on the carrier gas flow rate were pointed out as significant on the quantitative robustness of the GC × GC–qMS system according to half-normal plots and confidence limits calculated through dummy variables, where results from Dong algorithm and permutation tests say that this parameter does not affect the quantitative robustness. For other parameters, all strategies agree that only photomultiplier power (for quantitative analysis) and lower limit of mass scanning range (for qualitative analysis) can be impacted upon robustness.

As for the parameters deemed as relevant upon the robustness of the GC × GC–qMs system by all data evaluation strategies, results are consistent with which would be expected. On a conventional quadrupole mass spectrometer, the level of current amplification is highly dependent on the power applied to the photomultiplier which detects the ionized analyte fragments: the anode output of a typical photomultiplier varies with the 6th–10th power of any variation on the applied high voltage [35]. The intensity of the chromatographic signal—and, therefore, the peak areas—should therefore be highly dependent on the photomultiplier power: a slight increase on the power would increase the

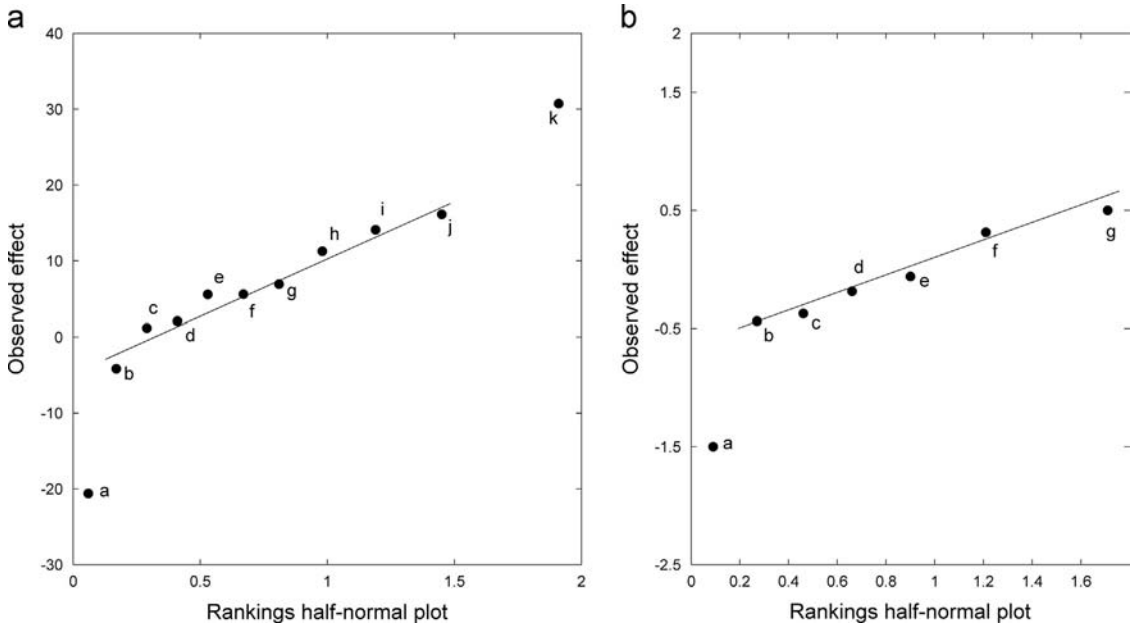

Fig. 3. Half-normal plots for the Plankett–Burman effects corresponding to: (a) general chromatographic operational variables (Table 3) and (b) MS detector only parameters (Table 4). Labels in the figures are equivalent to those in Tables 3 and 4.

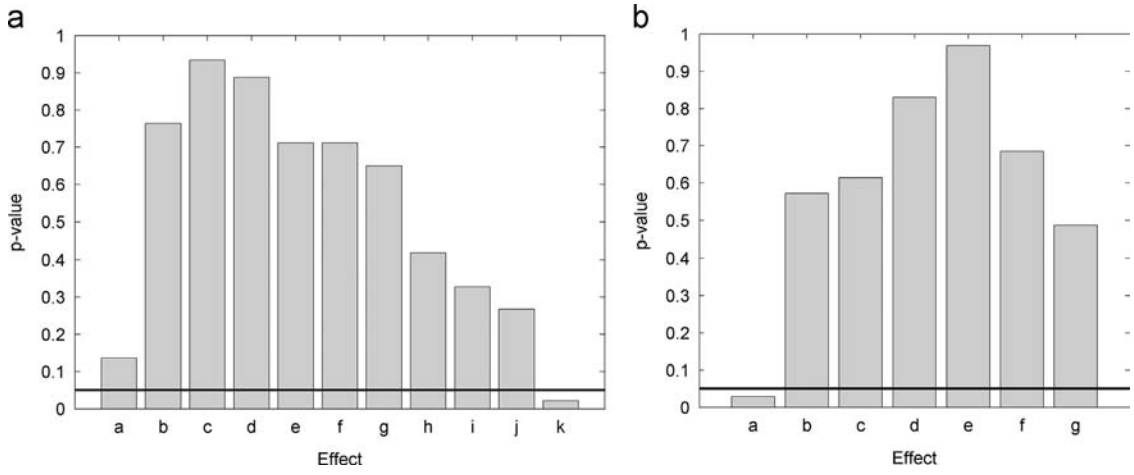

Fig. 4. Results from permutation tests for the assessment of the robustness of the GC × GC–qMS system as (a) quantitative and (b) qualititative tool.

Table 5
Significant effects for the designs considering the methodology of evaluation.

Strategy	Quantitative		Qualitative
	Carrier gas flow rate	Photomultiplier voltage	Lower limit of mass scanned range
Half-normal plot	significant	significant	significant
Statistical *t*-test	significant	significant	significant
Dong algorithm	*not significant*	significant	significant
Permutation test	*not significant*	significant	significant

peak areas, which accounts for the positive signal of the related effect.

The factor lower limit of the mass scanning range was consistently found to be significant towards robustness of qualitative analysis by GC × GC–qMS, being the effect negative: the similarity between library and experimental mass spectra decreases when the starting m/z scanned is increased. This result also could be considered as expected; the region between m/z=35 and 45 D corresponds to simple ionic fragments from aliphatic and aromatic organic compounds such as $C_3H_3^+$, CH_2CN^+, $C_3H_5^+$, $C_3H_6^+$, etc—which are present in virtually all pertinent mass spectra in great abundance. Therefore, the suppression of regions corresponding to these fragments reduces the amount of information contained on the spectra; any outlying signals on the experimental spectra or minor discrepancies with library spectra will have a higher effect on the similarity values (which are defined as the correlation coefficient between library and experimental spectra).

As for the effect of carrier gas flow rate upon both quantitative (and qualitative) performance of GC × GC–qMS systems, in a first examination its effect would be thought as being marginal. Variations on this parameter would affect the efficiency of the chromatographic system (*i.e.*, the height equivalent to a theoretical plate **h**), both related to the 1st and 2nd dimension columns—resulting in variations on peak width on both dimensions. MS can be considered as a mass-dependent and not concentration-dependent detector and therefore small variations on the width of the chromatographic band would not affect the magnitude of its signal. Perhaps only a change on the efficiency large enough to result on a chromatographic band to be modulated on more or less

modulation periods could produce measurable impact on the MS signal and therefore variations on carrier gas flow would not be important to the robustness of the system. However, two of the significance tests pointed out this parameter as relevant for the determination of the system robustness. A speculation about these discrepant results for the significance of the effect can be formulated based on the calculated values of the effect and the limits for this factor. The calculated effect was -20.6 and the limits to accept it as significant was ± 17.3 using the error calculated from the dummies variables and ± 23.8 using the Dong algorithm. These values are so close and little variation in the error estimation can change the results. This behavior can also be found in the *p*-values calculated from permutation test. The *p*-value for the column flow was 0.13 that is smaller than other *p*-values and closer to the adopted level of significance.

4. Conclusions

The Plackett–Burman design has easy implementation and experimental set-up, being a viable alternative to perform robustness studies. Furthermore, with this design it was possible to evaluate the robustness of a GC × GC–qMS system that is a fundamental step for the analytical methodology implementation. The factors considered significant to the system robustness were photomultiplier power and lower limit of mass scanning range, indicating that these factors need to be monitored with special attention, little variation can result in significant alterations on the results. Also, the effects interpretation using different strategies to find the significant factors provides an additional security and reliable conclusions.

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