Accepted Manuscript

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Please cite this article as: L. Rubio, L. Valverde-Som, L.A. Sarabia, M.C. Ortiz, Improvement in the identification and quantification OF UV filters and additives in sunscreen cosmetic creams by gas chromatography/mass spectrometry through three-way calibration techniques, *Talanta* (2019), doi: https://doi.org/10.1016/j.talanta.2019.120156.

IMPROVEMENT IN THE IDENTIFICATION AND QUANTIFICATION OF UV FILTERS AND ADDITIVES IN SUNSCREEN COSMETIC CREAMS BY GAS CHROMATOGRAPHY/MASS SPECTROMETRY THROUGH THREE-WAY CALIBRATION TECHNIQUES

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Abbreviations[2]

Abstract

The simultaneous determination of 2,6-di-tert-butyl-4-methyl-phenol (BHT), benzophenone (BP), benzophenone-3 (BP3) and diisobutyl phthalate (DiBP) in seven sunscreen creams was carried out by gas chromatography/mass spectrometry (GC/MS) using DiBP-d_4 as internal standard. The content of BP3, which is a UV filter, must not exceed 6% (w/w) in

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[2] 2,6-di-tert-butyl-4-methyl-phenol (BHT), benzophenone (BP), benzophenone-3 (BP3), capability of detection (CCβ), core consistency diagnostic (CORCONDIA), decision limit (CCα), diisobutyl phthalate (DiBP), electron impact (EI), elliptical joint confidence region (EJCR), gas chromatography/mass spectrometry (GC/MS), internal standard (IS), multivariate curve resolution coupled to alternating least squares (MCR-ALS), parallel factor analysis (PARAFAC), principal component analysis (PCA), probability of false positive (α), probability of false negative (β), programmed temperature vaporizer (PTV), single ion monitoring (SIM), sun protection factor (SPF), total ion chromatogram (TIC), ultraviolet (UV).

cosmetic products according to Regulation (EU) 2017/238 and the use of DiBP in cosmetic products shall be prohibited according to Regulation (EC) No 1223/2009.

The conclusions obtained with the univariate standard methodology in the identification of the analytes contained in the creams were wrong. However, a calibration based on PARAFAC or PARAFAC2 decompositions, where the samples of the prediction set were projected on the model obtained previously with the calibration set, enabled the unequivocal identification and quantification of the analytes even in the presence of interferents not considered in the calibration model. The PARAFAC2 decomposition was used to overcome the shifts in the retention time of BP and BP3. These three-way calibration techniques are needed to avoid false negative results. The method had not proportional or constant bias.

The presence of BHT was detected in the seven sunscreen creams analysed at an amount of $6.48 \cdot 10^{-2}$ %, $8.53 \cdot 10^{-2}$ %, $1.70 \cdot 10^{-4}$ %, $1.11 \cdot 10^{-4}$ %, $2.51 \cdot 10^{-3}$ %, $3.20 \cdot 10^{-5}$ % and $6.35 \cdot 10^{-3}$ %. The concentrations of DiBP found in four creams were $3.49 \cdot 10^{-2}$ %, $3.19 \cdot 10^{-2}$ %, $3.26 \cdot 10^{-2}$ % and $2.51 \cdot 10^{-2}$ %. On the other hand, BP was only detected in two of the cosmetic creams analysed at an amount of $7.84 \cdot 10^{-3}$ % and $1.04 \cdot 10^{-2}$ %. In addition, BP3 was detected in six of the creams at an amount of 4.73%, 3.49%, $4.94 \cdot 10^{-3}$ %, $1.98 \cdot 10^{-3}$ %, $6.62 \cdot 10^{-1}$ % and 1.73%. Therefore, none of the cosmetic creams contained BP3 in an amount higher than 6%.

Keywords: Benzophenone-3; PTV-GC/MS; PARAFAC; PARAFAC2; UV filter; sunscreen cream.

1. Introduction

The use of sunscreen cosmetic creams protects the skin from the negative effects of ultraviolet (UV) rays such as sunburn or skin cancer. Unfortunately, some of the additives contained in these creams could interfere in the hormone levels of the human body [1,2,3].

Regulation (EC) No 1223/2009 [4] on cosmetic products *establishes rules to be complied with by any cosmetic product made available on the market, in order to ensure the*

functioning of the internal market and a high level of protection of human health. The content of oxybenzone or benzophenone-3 (BP3), with the chemical name 2-hydroxy-4-methoxybenzophenone, was modified in Commission Regulation (EU) 2017/238 [5] and must not exceed 6% (w/w). In addition, the label of the cosmetic product must include the wording "contains benzophenone-3" when the concentration is upper than 0.5% (w/w) and it is not used for product protection purposes. This range does not pose a risk to human health, apart from its contact which could produce allergy [6].

BP3 is a sunscreen agent used to absorb UV radiation in plastics and in personal care products. In addition, it is used as a photo-stabilizer to minimize the colour and odour changes of the cosmetic product [7].

The concentration of this compound is regulated because it is harmful to human health [7] and causes allergy [8,9]. Benzophenone-type UV filters also induce endocrine disrupting effects [10,11,12]. BP3 penetrates the skin and 1-2% of the sunscreen is absorbed in humans [13,14,15]. BP3 has been detected in blood plasma [16,17], in human breast milk [18,19] and in urine since the compound is excreted [1,13,14,20]. On the other hand, most of the compounds present in creams are soluble in water so negative environmental effects appear [7] such as fish contaminations which cause the appearance of these compounds in food [21,22]. In addition, the presence of BP3 in swimming pool water could produce hazardous products by reaction with chlorine [7,23] being a problem to human health.

Other additives are added to sunscreen cosmetic creams such as benzophenone (BP) and 2,6-di-tert-butyl-4-methyl-phenol (BHT). BP is another UV filter [2,24], whereas BHT is used as antioxidant to prevent rancidity or to inhibit oxidation in cosmetic formulations [2,25]. On the other hand, the presence of phthalates such as diisobutyl phthalate (DiBP) in these creams can be due to manufacturing process or to their migration from packaging when plastic is used [26]. The control and analysis of these compounds is important because they have harmful effects on health too [27,28]. DiBP has been classified as carcinogenic, mutagenic or toxic substance to reproduction (category 1B) in [29]. Therefore, the use of this

compound in cosmetic products shall be prohibited as stated in [4]. However, the non-intended presence of a small amount of this substance shall be permitted if its presence is technically unavoidable, that is, if it comes from impurities of natural or synthetic ingredients, the manufacturing process, storage or migration from packaging.

Many analysis methods have been developed to detect these compounds [2,30]. The extraction of the analytes from the cosmetic product can be performed with organic solvents such as methanol [24,31], ethanol [32,33], among others [26,34]. The use of an ultrasonic bath or a vortex can accelerate the solubilisation of those compounds. Then, the extract could be filtered or centrifuged to extract the fraction of interest and remove the insoluble fraction of the cosmetic matrix. Other extractive approaches are based on solid phase microextraction [35], or liquid-liquid microextraction [24].

The analytical techniques employed to determine UV filters in cosmetics [30] and other additives [2] are: (i) chromatographic techniques with different detectors; (ii) spectroscopic techniques; and (iii) electrochemical techniques. The two latter have been less used than chromatographic techniques. The use of liquid chromatography with different detectors in this determination has lately increased [32,33,36]. However, gas chromatography has been less used since a derivatization step with silylating reagents is sometimes required to increase the volatility and sensitivity of the compounds [35,37,38]. The determination of phthalates and sunscreen agents in cosmetic products is carried out using a gas chromatograph coupled to a mass spectrometer detector without derivatization in [26,39].

Several three-way algorithms can be used with chromatographic signals. Previous works [40,41,42] have demonstrated the usefulness of three-way calibrations based on the PARAFAC decomposition using chromatographic data obtained with different detectors that provide multivariate signals (mass spectrometers or diode array detectors) [43]. These works highlight the advantage of using the abundances recorded at all the ions selected (or the absorbance spectrum) when quantifying or identifying the analytes according to the requirements stated in European regulations. In addition, these calibrations are useful for the

optimization and evaluation of the robustness of analytical methods [42] since the second-order property enables the identification of the analyte of interest as a single factor independently of the change in the instrumental factors, even in the presence of unknown interferents, which coelute with the analytes.

The PARAFAC2 decomposition overcomes some deviations in the chromatographic signals [43,44]. PARAFAC2 has the second-order property if the correlation between the time profiles is the same in all the samples, which is a weaker condition than the equality of chromatographic profiles imposed by the PARAFAC model. If the loss of trilinearity is important, then multivariate curve resolution techniques are a useful alternative, because their signal-related requirements are weaker than those demanded by PARAFAC or PARAFAC2. Multivariate curve resolution coupled to alternating least squares (MCR-ALS) has been widely applied in analytical chemistry and its related fields [43,45,46], and it has been used to resolve coeluted compounds. Its major limitation in identifying and quantifying an analyte is the presence of rotational ambiguities and non-unique solutions. However, the non-uniqueness problem can be alleviated or totally avoided in some cases through the intelligent use of the data structure and appropriate constraints. This problem is discussed in depth in [46].

In this work, the simultaneous determination of BHT, BP, BP3 and DiBP in seven sunscreen cosmetic creams, using DiBP-d_4 as internal standard (IS), was carried out by means of gas chromatography/mass spectrometry (GC/MS) with a single quadrupole mass analyser in selected ion monitoring (SIM) mode. Parallel factor analysis (PARAFAC) or PARAFAC2 decomposition methods were used to discover if a coeluent that shares ions with the analyte of interest is present [47,48] and to identify unequivocally the compounds present by their chromatographic and spectral profiles following the criteria established in Decision 2002/657/EC for residues of veterinary medicinal products [49] which are stricter than other official regulations and guidelines [49,50,51]. In this case, at least a minimum of 3 identification points is needed for the confirmation of each compound; in this work 5 ions

were selected. The PARAFAC2 decomposition overcome the shifts in the retention time of BP and BP3 in the samples and the analytes were unequivocally identified although the shift of the retention time is limited in regulated analyses. The results of the identification were compared with the ones obtained with the univariate standard methodology. The determination of the compounds in the sunscreen creams analysed was performed through the projection of the samples of the prediction set on the corresponding PARAFAC or PARAFAC2 model.

Other advantages of this work with respect to analytical methods previously reported are the determination of different compounds, that affect human health, in sunscreen cosmetic creams and the determination of BP3 by GC/MS without a derivatization reaction, which is not very usual.

2. Material and methods

2.1. Chemicals

Benzophenone (CAS no. 119-61-9, purified by sublimation, ≥ 99% purity), 2-hydroxy-4-methoxybenzophenone (benzophenone-3, CAS no. 131-57-7, 98% purity), 2,6-di-tert-butyl-4-methyl-phenol (CAS no. 128-37-0, ≥ 99% purity), diisobutyl phthalate (CAS no. 84-69-5, 99% purity) and diisobutyl phthalate-3,4,5,6-d_4 (CAS no. 358730-88-8, analytical standard, 99.7% purity) were purchased from Sigma-Aldrich (Steinheim, Germany).

Ethanol (96% vol., CAS no. 64-17-5, HiPerSolv CHROMANORM®, gradient grade for HPLC) was supplied by VWR International (Radnor, Pennsylvania, USA). N-hexane (CAS no. 110-54-3) and acetone (CAS no. 67-64-1) for liquid chromatography Lichrosolv® were from Merck KGaA (Darmstadt, Germany).

2.2. Standard solutions

Stock solutions of BHT at 1 g L^{-1}, of BP at 5 g L^{-1}, of DiBP at 2 g L^{-1}, and of DiBP-d$_4$ at 0.45 g L^{-1} were prepared individually in hexane. Intermediate solutions were prepared from the former ones by dilution in the same solvent.

A stock solution of BP3 at 30.5 g L^{-1} were prepared in ethanol and intermediate solutions at concentrations of 1, 5, 7.5, 10, 15, 20 and 25 g L^{-1} were prepared from that stock solution in ethanol. All those solutions of BP3 were diluted 25000 times to prepare the corresponding calibration standards in hexane. The stock and intermediate solutions of BP3 were stable for 15 days. The rest of the solutions of this analyte were prepared daily since this compound was not stable.

All the stock and intermediate solutions, which weight was controlled to verify that the solvent had not evaporated, were stored in crimp vials at 4ºC and protected from light. The laboratory glassware used was thorough cleaned and plastic consumables were avoided as far as possible.

The number and type of the samples analysed together with the concentration ranges of the solvent standards (analyte standards prepared in solvent) for each analyte in each stage are collected in Table S1 in the Supplementary Material.

2.3. Sunscreen cream samples

Seven different sunscreen creams were purchased at local stores and pharmacies (Burgos, Spain). These cosmetic products were: i) cream 1 (sun protection factor (SPF) 50+), ii) cream 2 (SPF 30), iii) cream 3 (SPF 50+), iv) cream 4 (SPF 30), v) cream 5 (SPF 30), vi) cream 6 (SPF 50+), and vii) cream 7 (SPF 15). Cream 1 and 2 belong to the same cosmetic brand, whereas cream 4 and 7 belong to another one. The sunscreen product's label of cream 1, 2 and 7 specified that BP3 was contained in their formulation and the label of cream 1, 2, 5 and 7 specified that BHT was one of their ingredients.

2.4. Sample preparation method

For each cream, 2 g of the cosmetic product was weighted in a 50-mL polypropylene tube and 10 mL of ethanol was added. Then, the mixture was stirred in a vortex mixer for 2 min and left to settle for 10 min. The supernatant of the extract was clarified through a 0.45-μm nylon filter and stored in a crimp vial at 4ºC for 24 hours. Next, the final extract was clarified through a 0.20-μm nylon filter. A blank extract was also prepared following the same procedure detailed previously.

The extracts were diluted using hexane prior to their measurement in the GC/MS system: cream 1, 2 and 3 were diluted 10000 times, cream 4 was diluted 1300 times, cream 5 was diluted 1000 times, cream 6 was diluted 8000 times and cream 7 was diluted 3000 times. In addition, the extract obtained from cream 3, 4, 5 and 6 was also diluted 10 times. The blank extract was diluted in all those proportions using hexane.

2.5. Instrumental

A vortex stirrer LBX Instruments V05 series (Barcelona, Spain), with speed control, was used. The filters used were Minisart® NY 25 (0.45 μm pore size) and Minisart® NY 15 (0.20 μm pore size) syringe filters which were obtained from Sartorius Stedim Biotech GmbH (Goettingen, Germany).

An Agilent 7890A gas chromatograph coupled to an Agilent 5975C mass spectrometer detector (Agilent Technologies, Santa Clara, CA, USA) were used to perform the analyses. The injection system consisted of a septumless head CIS 6 and a programmed temperature vaporizer (PTV) inlet equipped with a straight-with-notch quartz glass liner from GERSTEL GmbH & Co. KG (Mülheim an der Ruhr, Germany). The injections were performed using a 10 μL syringe and the MultiPurpose Sampler MPS2XL from GERSTEL. The gas chromatograph was equipped with an Agilent HP-5MS Ultra Inert column (30 m × 0.25 mm i.d., 0.25 μm film thickness).

2.6. GC/MS conditions

The PTV inlet operated in the cold splitless mode. Helium (99.999% purity, ALPHAGAZ[TM] 1, Air Liquide, Madrid, Spain) was used as the carrier gas at a flow rate of 1.3 mL min^{-1} and the initial pressure was set at 10.121 psi. Two washings of the syringe with acetone and other two washings with hexane were performed before and after each injection. A volume of 1 μL was injected at a controlled speed of 1 μL s^{-1}. The injection penetration was set at 40 mm, whereas the vial penetration was 30 mm. During the injection and for 0.1 min afterwards, the inlet temperature was 55ºC and then ramped at 12ºC s^{-1} up to 270ºC, which was held for 15 min. The septum purge flow rate was 3 mL min^{-1} while the purge flow rate through the split vent was fixed at 30 mL min^{-1} (from 0.6 min to 2 min). After 2 min, that rate was set at 20 mL min^{-1}.

The oven temperature was 40ºC for 0.6 min after injection and then was increased at 20ºC min^{-1} to 250ºC, which was held for 1 min. That temperature was ramped again at 20ºC min^{-1} to 290ºC, which was held for 1 min. The run time was 15.1 min and a post-run step was carried out at 300ºC for 4 min.

The mass spectrometer operated in the electron impact (EI) ionization mode at 70 eV. The transfer line temperature was set at 300℃, the ion source at 230℃ and the quadrupole at 150℃. After a solvent delay of 7.5 min, data were acquired in single ion monitoring (SIM) mode using four acquisition windows: i) for BHT peak (start time: 7.5 min, ion dwell time: 30 ms), the diagnostic ions were 91, 145, 177, 205 and 220; ii) for BP peak (start time: 8.80 min, ion dwell time: 30 ms) the m/z ratios recorded were 51, 77, 105, 152 and 182; iii) for DiBP and DiBP-d$_4$ peaks (start time: 9.80 min, ion dwell time: 10 ms), the diagnostic ions for DiBP were 104, 149, 167, 205 and 223, whereas the m/z ratios selected for DiBP-d$_4$ were 80, 153, 171, 209 and 227; and iv) for BP3 peak (start time: 10.80 min, ion dwell time: 30 ms), the m/z ratios recorded were 77, 105, 151, 227 and 228.

2.7. Software

MSD ChemStation version E.02.01.1177 (Agilent Technologies, Inc.) with Data Analysis

software was used for acquiring and processing data. PARAFAC and PARAFAC2

decompositions were performed with the PLS_Toolbox [52] used under MATLAB

environment [53]. The regression models were fitted and validated using STATGRAPHICS

Centurion XVI [54]. Decision limit (CCα) and capability of detection (CCβ) were calculated

using the DETARCHI program [55].

3. Results and discussion

The characteristics of the seven different sunscreen creams analysed are specified in

Section 2.3. The extracts of each cream and the corresponding dilutions were prepared

following the procedure detailed in Section 2.4.

Nine calibration standards were prepared within the concentration ranges detailed in Table

S1 in the Supplementary Material (sixth row, columns 3-7) and analysed in triplicate (at the

beginning, in the middle and at the end of the analytical sequence to check the behaviour of

the GC/MS system over time). Two of these standards were also measured again after the

first calibration batch. Fig. S1 (a) in the Supplementary Material shows the total ion

chromatogram (TIC) of the standard at the highest concentration.

The extracts diluted 10 times of cream 3, 4, 5 and 6 were injected only once after the third

calibration batch because these extracts were too dirty. Therefore, the chromatograms

obtained from these samples had abundant peaks, as can be seen in Fig. S1 (b) in the

Supplementary Material. However, the rest of the diluted extracts were injected after the first

calibration batch and a replicate of all of them after the second calibration batch. By way of

example, Fig. S1 (c) in the Supplementary Material shows the TIC obtained from the injection

of the extract of cream 1 diluted 10000 times. The blank extract was diluted similarly to the

creams, and the latter were injected in duplicate. In addition, a solvent blank (only hexane)

was measured after the injection of each extract of cream to check if the GC/MS was clean

prior to the next injection (see Fig. S1 (d) in the Supplementary Material as an example). For

that same reason, four system blanks (empty vials without solvent) were also measured throughout the analytical sequence. Table S1 in the Supplementary Material (row 4 to 8) shows a summary of the number of each type of sample analysed in this analysis.

3.1. Identification

3.1.1. Univariate standard methodology

Three reference standards at low, intermediate and high concentration level of the analytes were prepared within the concentration ranges shown in Table S1 in the Supplementary Material (third row). By way of example, the tolerance intervals for the relative abundances of the *m/z* ratios 104, 167, 205 and 223 for DiBP (being the *m/z* ratio 149 the base peak) were estimated at the retention time of this analyte with its reference standard. The relative abundances were also calculated using the univariate standard methodology in four creams. Fig. S1 (e) in the Supplementary Material shows a part of the chromatogram of the window of DiBP obtained from the extract of one of those creams. A peak appears that could be assigned as DiBP or an interferent may coelute with this analyte. As can be seen in Fig. 1, the relative abundances for the *m/z* ratio 104 obtained with the four creams were within the permitted tolerance intervals, whereas the relative abundances for the rest of the *m/z* ratios calculated with these creams were outside the tolerance intervals in many of the cases. For the extract obtained from cream 1 diluted 10000 times and the extract obtained from cream 6 diluted 8000 times, only three *m/z* ratios met the identification criteria established in [49] considering at least one of the tolerance intervals calculated for each *m/z* ratio. On the other hand, less than three *m/z* ratios met the identification criteria in the other two creams. Therefore, it would be concluded that there can be no assurance that DiBP was present in the creams.

3.1.2. Multi-way analysis of interferents

The extracts of the creams may contain some interferents that coelute with the analytes so there could be a problem in the identification of the analytes in those samples.

PARAFAC can be used as a data analysis technique that enables the visualization of the compounds present in the samples as new factors in the model. Some details about PARAFAC decomposition can be seen in [48,56,57]. The PARAFAC2 decomposition is used to overcome the shifts in the retention time of the analytes from sample to sample that appear in the chromatogram [58,59].

Therefore, the PARAFAC or PARAFAC2 decompositions were carried out using a three-way array that contained all the samples of the analysis together. Some interferents were present in the extracts of the creams and appeared as new factors. Two interferents coeluted with BHT (see Fig. 2 (a)), whereas only one interferent coeluted with DiBP (see Fig. 2 (b)) and another one was present in the PARAFAC2 model for BP3 (see Fig. 2 (c)). In the case of BP3, only the first 39 scans were considered to obtain a model coherent with the experimental knowledge. There was a great difference in the abundance between the analytes and the interferents present in the extracts of the creams.

There was only a peak in the retention time of DiBP in Fig. S1 (e) in the Supplementary Material but three compounds (IS, DiBP and an interferent) were really present as can be seen in Fig. 2 (b) when the PARAFAC decomposition was carried out. That interferent also shared *m/z* ratios with DiBP. Therefore, DiBP was present in that cream so the conclusion obtained in Section 3.1.1 with the univariate standard methodology was wrong. This problem can be solved using three-way techniques which perform a mathematical separation of the signal.

3.1.3. Identification using three-way techniques

The steps followed to perform the analysis of the creams were:

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i) For each sample, record the matrix of abundances of J m/z ratios acquired at I elution times for each chromatographic peak.

ii) Estimate the corresponding tolerance intervals for the relative retention time and for the relative ion abundances with the loadings of the chromatographic and spectral profiles obtained from the PARAFAC (or PARAFAC2) decomposition of an array, $\underline{\mathbf{X}}_0$, that contained some K_0 reference samples.

iii) Build the three-way array, $\underline{\mathbf{X}}_1$, made up by the K_1 samples of the calibration set.

iv) Perform the PARAFAC (or PARAFAC2) decomposition of that array which provides the chromatographic and spectral profiles of the different compounds present in those samples.

v) Use the Q residuals and Hotelling's T^2 statistics to check if there is any outlier.

vi) Identify the factor of the model which corresponds to the analyte of interest unequivocally using the tolerance intervals previously calculated.

vii) Build another three-way array, $\underline{\mathbf{X}}_2$, made up by the K_2 samples of the prediction set.

viii) Project the prediction samples on the PARAFAC or PARAFAC2 model obtained previously and the sample loadings of the new samples are estimated.

ix) The sample loadings of each analyte are standardized by dividing each of them by the corresponding of its internal standard.

x) A calibration model "standardized sample loading *versus* true concentration" using the calibration standards ($\underline{\mathbf{X}}_1$) is fitted and validated.

xi) Determine the concentration of the analyte in the prediction samples ($\underline{\mathbf{X}}_2$) through the standardized sample loading of these samples with the calibration model of the step before.

The dimension of the three-way arrays was $I \times J \times K$. In the case of the PARAFAC decompositions, a change in the order of the dimension of the arrays for the calibration and prediction sets respect to the one explained above was performed to carry out the projection of the samples on the model. In this case, the first dimension of the three-way array was the

number of samples, while the second and third ones were the number of scans and ions, respectively.

3.1.3.1. Tolerance intervals (step ii)

To estimate the tolerance intervals, the reference standards measured in Section 3.1.1 were used. In addition, three reference standards that contained the IS at three concentration levels and the analytes at a fixed intermediate concentration (see Table S1 in the Supplementary Material, third row) were also considered.

The chromatograms of all these samples were equally fragmented around the retention time of each analyte after a baseline correction. The resulting data matrices were arranged in a three-way array, $\underline{\mathbf{X}}_0$, for each analyte except for DiBP and DiBP-d_4 peaks for which a joint array was considered for both compounds. The dimension of the four three-way arrays built are given in the second row of Table 1, whereas the samples included in those arrays are detailed in rows 1 to 3 of Table S1 in the Supplementary Material. The first dimension corresponds to the number of scans considered, the second one refers to the number of ions recorded and the third one is the number of samples. Then, a PARAFAC decomposition was performed for each of the arrays. Table 1 (rows 1-7) also contains the features of the models obtained in each case. The core consistency diagnostic (CORCONDIA) [60] measures the trilinearity degree of the experimental three-way array when there are more than 2 factors in the model. If the array is trilinear, then the maximum CORCONDIA value of 100 is found.

For BP and BP3, a PARAFAC2 decomposition was carried out since there were shifts in the retention time of those analytes in the samples. In addition, the variance explained by these PARAFAC2 models was higher than the one obtained with a PARAFAC model. The PARAFAC model for DiBP and DiBP-d_4 required three factors where the third one was related to an interferent (characteristic m/z ratio: 223) that eluted before DiBP-d_4.

The tolerance intervals for the relative retention time (see Table 2A, fourth column) and for the relative ion abundances (see Table 2B, fifth column) were estimated from the loadings of the chromatographic and spectral profiles, respectively, of the PARAFAC or PARAFAC2 models. These two intervals were built following the requirements established in [49] and were used as reference for the unequivocal identification of the analytes. PARAFAC decompositions provide a unique chromatographic profile for each compound that is common to all the samples, whereas PARAFAC2 decompositions provide a chromatographic profile of each compound for every sample. When a PARAFAC2 decomposition was considered, the median of the retention times of the analyte obtained from the chromatographic profile was used to calculate the relative retention time (the ratio of the chromatographic retention time of the analyte to that of the internal standard). Table 2A contains the retention times (second column of this table) and relative retention times (third column of this table) for each analyte obtained from the models estimated with the array that contained the reference standards. The tolerance intervals for the relative retention time were built with a tolerance margin of ± 0.5% as [49] established. It has also been checked that the relative retention times of BP and BP3 in all the samples obtained through the PARAFAC2 decomposition were within the tolerance intervals estimated with the retention times of these analytes in each sample. Therefore, the use of the median to estimate a representative retention time for BP and BP3 was adequate. On the other hand, PARAFAC and PARAFAC2 decompositions provide a unique spectral profile for each compound common to all the samples. The relative ion abundances of each *m/z* ratio used to determine the tolerance intervals according to ref. [49] were calculated with the corresponding spectral loading (see Table 2B, third column) with respect to the one of the corresponding base peak of the analyte.

3.1.3.2. Calibration models and projection (steps iii to viii)

Then, a three-way data array was built for the calibration set ($\underline{\mathbf{X}}_1$) and another one for the prediction set ($\underline{\mathbf{X}}_2$) for each analyte, except for DiBP and DiBP-d_4 peaks for which a joint array was considered again in both cases. The samples that made up the calibration set were: four system blanks (empty vials without solvent), the first solvent blank measured, the first calibration batch together with the two replicates injected after it and two calibration standards of the second and of the third calibration batches. The prediction set was constituted with the rest of the samples (the rest of the calibration standards, solvent blanks, blank extracts and the diluted extracts of the creams). Some calibration standards were included in the prediction set to guarantee the feasibility of the projection of the samples. The dimension of $\underline{\mathbf{X}}_1$ and $\underline{\mathbf{X}}_2$ is included in Table 1 (rows 9 and 15, respectively).

Then, PARAFAC decompositions (or PARAFAC2 decompositions in the case of BP and BP3) were performed with the three-way array that contained the calibration set. When a PARAFAC decomposition was carried out, a change in the order of the dimension of the three-way arrays for the calibration and prediction sets was carried out (see Table 1). In the case of the array of DiBP and DiBP-d_4, some additional solvent standards were added as can be seen in Table 1 since both compounds were completely overlapped and the abundance of DiBP-d_4 was much lower than the abundance of DiBP, so PARAFAC needs a greater variation of DiBP-d_4. Therefore, a standard containing all the analytes and a higher amount of DiBP-d_4 (100 µg L^{-1}) together with two standards that only contained 100 µg L^{-1} of DiBP-d_4 were added to that three-way array.

The characteristics of the PARAFAC and PARAFAC2 models obtained in each case are listed in Table 1 (rows 8-15, columns 2-5). An unconstrained one-factor model was needed for BHT, BP and BP3, whereas the decomposition of the common array for DiBP and DiBP-d_4 needed three factors (CORCONDIA index of 100%).

Once these models were obtained, the samples of the prediction set were projected on the corresponding model. The extract obtained from cream 6 diluted 10 times exceeded the threshold value of the Q and Hotelling's T^2 statistics at the 95% confidence level when it was

projected on the PARAFAC2 model for BP3. Therefore, it was considered an outlier and removed from the three-way array that contained the samples of the prediction set (see the dimension of this array in Table 1). Fig. 3 shows the chromatographic, spectral and sample profiles of the one-factor PARAFAC2 model obtained for BP3. As can be seen in Fig. 3 (c), the sample loadings of BP3 were zero in the solvent blanks measured after the injection of each extract of cream (samples number 23, 25, 27, 30, 33, 36, 39, 49, 51, 53, 56, 59, 62 and 65) so the cleanliness of the GC/MS system was guaranteed.

By way of example, the loadings of the three-factor PARAFAC model for DiBP and DiBP-d_4 are shown in Fig. 4. The sample loadings for the factor corresponding to DiBP Fig. 4 (a)) increased with the concentration of the calibration standards as expected and the replicates were similar. The sample loadings of this analyte in the extracts of cream 3 and 4 diluted 10 times were outside the calibration range (samples number 80 and 82 not shown in that figure) so the amount of DiBP in those dilutions could not be quantified. The loadings of the sample profile for the factor associated to the internal standard (Fig. 4 (b)) were zero in the solvent and system blanks, whereas they remained nearly constant in the rest of the samples except for the additional samples added to the three-way array where the loadings were higher as expected. On the other hand, the sample loadings for the third factor (Fig. 4 (c)) were very high in the extracts of cream 3 and 4 diluted 10 times. Some of the *m/z* recorded for DiBP were shared with this factor being 223 its most characteristic *m/z* (see Fig. 4 (d)). This factor was attributed to an unidentified interferent eluting near the beginning of the DiBP-d_4 peak as can be seen in red in Fig. 4 (e).

The analytes were unequivocally identified since the relative retention times (see Table 2A, fifth column) and the relative ion abundances (see Table 2B, sixth column) estimated from the loadings of the chromatographic and spectral profiles obtained in this analysis, respectively, were within their corresponding tolerance intervals (see Table 2A (fourth column) and Table 2B (fifth column), respectively). As can be seen in Fig. 1, the relative abundances estimated from the spectral PARAFAC loadings of DiBP obtained were within

the tolerance intervals for all the *m/z* ratios. Therefore, the conclusion that DiBP was not present in the creams stated in Section 3.1.1 was wrong since a coeluting interferent (see Fig. 2 (b)) present in those samples shared some *m/z* ratios with DiBP. This interferent did not appear in the PARAFAC model considered (see Table 1) since it was not present in the samples of the calibration set and the extracts of the creams were projected on the model obtained with the calibration set. Therefore, there was no problem in the identification of DiBP using PARAFAC. It is important to bear in mind that one of the advantages of the PARAFAC decomposition over the univariate standard methodology is that this three-way technique provides a unique spectral profile for each analyte that is common to all the samples.

The results of the steps *ix*, *x* and *xi* of the procedure will be shown in the following section although many approaches can be used to perform a calibration based on PARAFAC or PARAFAC2 decompositions [61].

3.2. Quantification using three-way techniques

The sample loadings of each analyte were numerically high since they came from the first mode of a PARAFAC decomposition or from the third mode of a PARAFAC2 decomposition and these modes are not normalized in the decomposition. Therefore, they were manually normalized prior to standardization. Once the sample loadings for each analyte were standardized by dividing each of them by that of the internal standard, calibration models "standardized sample loading *versus* true concentration" using the standards contained in the calibration set were fitted and validated. The parameters of the regression models estimated for each analyte are included in Table S2 in the Supplementary Material. A quadratic regression model was considered for all the analytes except for DiBP. One outlier was detected in the calibration models for BP and BP3 since these data had a studentized residual greater than 3 in absolute value. Therefore, those outliers were removed, and a new fitting was carried out with the remaining data in both cases (see the calibration models

obtained in Table S2 in the Supplementary Material). The lowest mean of the absolute value of the relative errors in calibration was 1.97% (n = 11) for BP, whereas the highest value was 6.86% (n = 8) for BP3 when the samples with predicted concentration lower than the corresponding CCβ had been excluded. In addition, the mean of the absolute value of the relative errors in prediction for the second and third calibration batches were calculated. Taking these values into account, it was concluded that BP3 was not stable over time since the errors increased from the second calibration batch to the third one. Therefore, the solutions were prepared daily.

Table S2 in the Supplementary Material also contains the parameters of the corresponding accuracy lines built with the calibration standards, that is the regressions "predicted concentration *versus* true concentration". The elliptical joint confidence region (EJCR) test was computed and Fig. S2 in the Supplementary Material shows the confidence ellipses, at a 95% confidence level, for the slope and the intercept of the accuracy line estimated for each analyte. All the confidence ellipses contained the point (0,1). In addition, Table S2 in the Supplementary Material contains the p-values of this test. These p-values were higher than 0.05 (0.973 for BHT, 0.960 for BP, 1.000 for DiBP and 0.123 for BP3) so the intercept and the slope were significantly not different from 0 and 1, respectively. Therefore, the method had not constant or proportional bias at a 95% confidence level.

The values of decision limit (CCα) and capability of detection (CCβ) for each analyte with the probabilities of false positive (α) and false negative (β) fixed at 0.05 are listed in the first two rows of Table 3. The blank extract contained DiBP in all its dilutions except for the one diluted 8000 and 10000 times, whereas the amount of the rest of the analytes in the blank extract was below the corresponding CCα values. The amount of each analyte found in the sunscreen creams together with the corresponding 95% confidence interval are detailed in Table 3. The label of cream 1, 2, 5 and 7 specified that BHT was contained in their formulation but BHT was detected in the seven creams analysed. On the other hand, BP3 was found in all the sunscreen creams except for cream 4 since the confidence interval for

that analyte in that cream contained zero and the values were below CCα as can be seen in Table 3. The creams 1, 2, 6 and 7 were the ones which contained a concentration of BP3 between 0.5% and 6%. However, only the product's label of creams 1, 2 and 7 specified that BP3 was one of their ingredients as required in [5]. In addition, DiBP and BP were only detected in four and two cosmetic creams, respectively. The amount found of DiBP (below 0.035%) may come from impurities of natural or synthetic ingredients, the manufacturing process, storage or migration from packaging of the cosmetic product.

4. Conclusions

The projection of the samples of the prediction set on the corresponding PARAFAC or PARAFAC2 model enabled the determination of BHT, BP, DiBP and BP3 in the sunscreen cosmetic creams analysed even in the presence of interferents not considered in the calibration model. PARAFAC2 decomposition overcame the problems due to the shifts in the retention time of BP and BP3.

In addition, the unequivocal identification and quantification of each analyte according to the requirements established by EU regulations were possible using a PARAFAC or PARAFAC2 decomposition despite some of the m/z ratios of a coeluting interferent were shared with DiBP. In fact, the unequivocal identification of this analyte could never have been achieved from the mass spectrum recorded at its retention time due to the presence of a coeluting interferent present in the sunscreen creams analysed. The presence of BHT was detected in the seven sunscreen creams analysed, whereas BP3, DiBP and BP were detected in some of these creams. None of the cosmetic creams contained BP3 in an amount higher than 6% as established in Regulation 2017/238 [5].

5. Acknowledgments

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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FIGURE CAPTIONS

Fig. 1   Tolerance intervals for the relative ion abundances of DiBP estimated for each
m/z ratio with three reference samples that contained a different concentration
level of DiBP: 25 µg L^{-1} (in blue), 75 µg L^{-1} (in red) and 125 µg L^{-1} (in green).
Relative abundance for each *m/z* ratio obtained with: the PARAFAC models
obtained with the reference samples (light blue circles) and with all the samples
of the analysis of the creams (black cross), the extract obtained from cream 1
diluted 10000 times (pink triangle), the extract obtained from cream 2 diluted
10000 times (purple diamond), the extract obtained from cream 3 diluted 10000
times (red square) and the extract obtained from cream 6 diluted 8000 times
(light green star). (For interpretation of the references to colour in this figure
legend, the reader is referred to the web version of the article).

Fig. 2   Chromatographic profiles of the PARAFAC models obtained with the three-way
arrays that contained the calibration and predictions sets together in the same
array for: (a) BHT, (b) DiBP and DiBP-d$_4$, (c) BP3 (a PARAFAC2 decomposition
of the array was carried out in this last case).

Fig. 3   One-factor PARAFAC2 model obtained with the three-way array that contained
the calibration set for BP3. Loadings of the: (a) chromatographic profile, (b)
spectral profile and (c) sample profile. The sample loadings of the 20 samples of
the calibration set are represented by grey circles, whereas the sample loadings
of the 62 samples of the prediction set, which have been projected on the
PARAFAC2 model, are represented by red diamonds. (For interpretation of the
references to colour in this figure legend, the reader is referred to the web
version of the article).

Fig. 4   Loadings of the sample profile for: a) factor 1 (DiBP), b) factor 2 (DiBP-d_4) and c)

factor 3 (unknown interferent) of the three-factor PARAFAC model fitted with the

common three-way array for DiBP and DiBP-d_4 that only contained the calibration

set. The sample loadings of the 24 samples of the calibration set are represented

by grey circles, whereas the ones of the 63 samples of the prediction set, which

have been projected on the model, are represented by red diamonds. d)

Loadings of the spectral profile and e) loadings of the chromatographic profile. In

figures (d-e), factor 1 (DiBP) is in light blue, factor 2 (DiBP-d_4) is in light green,

while factor 3 (interferent) is in red. (For interpretation of the references to colour

in this figure legend, the reader is referred to the web version of the article).

Table 1 Dimensions (scans × ions × samples) of the three-way arrays built for every analyte in each experimental stage and characteristics of the PARAFAC or PARAFAC2 models (number of factors, constraints imposed, explained variance and CORCONDIA index) obtained from the decomposition of each array.

Analytical stage	BHT	BP	DiBP and DiBP-d_4	BP3
Tolerance intervals				
Dimension of $\underline{X}_0$	21 × 5 × 9	49 × 5 × 9	41 × 10 × 9	56 × 5 × 9
Model	PARAFAC	PARAFAC2	PARAFAC	PARAFAC2
# Factors	1	1	3	1
Non-negativity constraints	None	None	In modes 1 and 2	None
Expl. Var (%)	99.71	99.88	99.45	99.79
CORCONDIA (%)[a]	---	---	100	---
Analysis of the sunscreen creams				
Dimension of $\underline{X}_1$ (calibration set)	20 × 21 × 5 [b]	49 × 5 × 20	24 × 41 × 10 [b]	56 × 5 × 20
Model	PARAFAC	PARAFAC2	PARAFAC	PARAFAC2
# Factors	1	1	3	1
Non-negativity constraints	None	None	In the three modes	None
Expl. Var (%)	99.74	99.87	99.08	99.82
CORCONDIA (%)[a]	---	---	100	---
Dimension of $\underline{X}_2$ (prediction set)	63 × 21 × 5 [b]	49 × 5 × 63	63 × 41 × 10 [b]	56 × 5 × 62

Expl. Var.: Explained variance by the model.

[a] The CORCONDIA index cannot be calculated in the PARAFAC or PARAFAC2 decomposition with only one factor.

[b] In this case, the dimension of the array corresponds to the number of samples × scans × ions.

Table 2 Tolerance intervals for: A) the relative retention time and for B) the relative ion abundances estimated from the loadings of the chromatographic and spectral profiles, respectively. Identification of every analyte in the analysis of sunscreen creams. In the case of BP and BP3, the median of the retention times obtained in the corresponding PARAFAC2 decomposition was considered.

A) Retention time

Analyte	t_R (min)	Relative t_R	Tolerance interval	Identification in the analysis of the creams
				Relative t_R
BHT	8.229	0.806	(0.802-0.810)	0.806
BP	9.016	0.883	(0.879-0.887)	0.883
DiBP-d_4	10.211	1.000	(0.995-1.005)	1.000
DiBP	10.220	1.001	(0.996-1.006)	1.001
BP3	11.120	1.089	(1.083-1.094)	1.089

B) Diagnostic ions

| Analyte	m/z ratio	Spectral loading	Relative abundance (%)	Tolerance interval (%)[b]	Identification in the analysis of the creams
					Relative abundance (%)
BHT	91	$6.85 \cdot 10^{-2}$	7.13	(3.57-10.70)	7.08
	145	$1.15 \cdot 10^{-1}$	11.94	(9.55-14.33)	11.94
	177	$7.67 \cdot 10^{-2}$	7.98	(3.99-11.97)	8.03
	205[a]	$9.61 \cdot 10^{-1}$	100	-	100
	220	$2.29 \cdot 10^{-1}$	23.81	(20.24-27.38)	23.94
BP	51	$1.37 \cdot 10^{-1}$	17.75	(14.20-21.30)	17.42
	77	$4.38 \cdot 10^{-1}$	56.77	(51.09-62.45)	56.63
	105[a]	$7.71 \cdot 10^{-1}$	100	-	100
	152	$3.27 \cdot 10^{-2}$	4.24	(2.12-6.36)	4.34
	182	$4.40 \cdot 10^{-1}$	57.05	(51.35-62.76)	57.61
DiBP-d_4	80	$5.65 \cdot 10^{-2}$	5.68	(2.84-8.52)	5.70
	153[a]	$9.94 \cdot 10^{-1}$	100	-	100
	171	$2.48 \cdot 10^{-2}$	2.50	(1.25-3.75)	2.57
	209	$1.17 \cdot 10^{-2}$	1.18	(0.59-1.77)	1.23
	227	$4.95 \cdot 10^{-2}$	4.98	(2.49-7.47)	5.14
DiBP	104	$7.82 \cdot 10^{-2}$	7.86	(3.93-11.79)	7.66
	149[a]	$9.95 \cdot 10^{-1}$	100	-	100
	167	$2.75 \cdot 10^{-2}$	2.76	(1.38-4.14)	2.75
	205	$1.37 \cdot 10^{-2}$	1.38	(0.69-2.07)	1.39
	223	$5.24 \cdot 10^{-2}$	5.27	(2.64-7.91)	5.27
BP3	77	$1.56 \cdot 10^{-1}$	22.86	(19.43-26.29)	22.33
	105	$8.16 \cdot 10^{-2}$	11.99	(9.59-14.39)	11.74
	151	$5.73 \cdot 10^{-1}$	84.19	(75.77-92.61)	83.43
	227[a]	$6.81 \cdot 10^{-1}$	100	-	100
	228	$4.21 \cdot 10^{-1}$	61.86	(55.67-68.05)	61.80

[a] Base peak.
[b] According to ref. [42], the estimation of the tolerance interval is different depending on the value of the relative abundance of the corresponding m/z ratio. The tolerance margin was ±50% for relative intensities lower or equal to 10%, a ± 20% for relative intensities from 10% to 20%, a ± 15% for relative intensities from 20% to 50% and ± 10% for relative intensities higher than 50%.

Table 3 Decision limit (CCα), capability of detection (CCβ) at $x_0 = 0$ and concentration of each analyte found in the sunscreen creams together with the corresponding confidence intervals for the predicted concentration at a 95% confidence level.

	BHT	BP	DiBP	BP3
CCα ($x_0 = 0$) (µg L^{-1})	4.03	6.32	5.93	142.67
CCβ ($x_0 = 0$) (µg L^{-1}) [a]	7.93	12.40	11.65	279.80
Sunscreen cream 1				
Concentration (% w/w)	$6.48 \cdot 10^{-2}$	< CCα [b]	$3.49 \cdot 10^{-2}$	4.73
Interval at a 95% confidence level (% w/w)	$(4.62 \cdot 10^{-2}, 8.21 \cdot 10^{-2})$ [b]		$(6.75 \cdot 10^{-3}, 6.20 \cdot 10^{-2})$ [b]	$(4.17, 5.52)$ [b]
Sunscreen cream 2				
Concentration (% w/w)	$8.53 \cdot 10^{-2}$	< CCα [b]	$3.19 \cdot 10^{-2}$	3.49
Interval at a 95% confidence level (% w/w)	$(6.70 \cdot 10^{-2}, 1.02 \cdot 10^{-1})$ [b]		$(3.75 \cdot 10^{-3}, 5.91 \cdot 10^{-2})$ [b]	$(2.90, 4.17)$ [b]
Sunscreen cream 3				
Concentration (% w/w)	$1.70 \cdot 10^{-4}$	< CCα [b]	$3.26 \cdot 10^{-2}$	$4.94 \cdot 10^{-3}$
Interval at a 95% confidence level (% w/w)	$(1.46 \cdot 10^{-4}, 1.92 \cdot 10^{-4})$ [c]		$(4.50 \cdot 10^{-3}, 5.98 \cdot 10^{-2})$ [b]	$(4.17 \cdot 10^{-3}, 5.95 \cdot 10^{-3})$ [c]
Sunscreen cream 4				
Concentration (% w/w)	$1.11 \cdot 10^{-4}$	$7.84 \cdot 10^{-3}$	< CCα [d]	$8.41 \cdot 10^{-4}$
Interval at a 95% confidence level (% w/w)	$(8.68 \cdot 10^{-5}, 1.34 \cdot 10^{-4})$ [c]	$(3.92 \cdot 10^{-3}, 1.14 \cdot 10^{-2})$ [d]		$(-1.56 \cdot 10^{-4}, 1.56 \cdot 10^{-3})$ [c]
Sunscreen cream 5				
Concentration (% w/w)	$2.51 \cdot 10^{-3}$	$1.04 \cdot 10^{-2}$	< CCα [e]	$1.98 \cdot 10^{-3}$
Interval at a 95% confidence level (% w/w)	$(5.75 \cdot 10^{-4}, 4.27 \cdot 10^{-3})$ [e]	$(7.49 \cdot 10^{-3}, 1.31 \cdot 10^{-2})$ [e]		$(1.08 \cdot 10^{-3}, 2.75 \cdot 10^{-3})$ [c]
Sunscreen cream 6				
Concentration (% w/w)	$3.20 \cdot 10^{-5}$	< CCα [f]	$2.51 \cdot 10^{-2}$	$6.62 \cdot 10^{-1}$
Interval at a 95% confidence level (% w/w)	$(6.87 \cdot 10^{-6}, 5.56 \cdot 10^{-5})$ [c]		$(2.40 \cdot 10^{-3}, 4.67 \cdot 10^{-2})$ [f]	$(3.84 \cdot 10^{-2}, 1.06)$ [f]
Sunscreen cream 7				
Concentration (% w/w)	$6.35 \cdot 10^{-3}$	< CCα [g]	< CCα [g]	1.73
Interval at a 95% confidence level (% w/w)	$(5.40 \cdot 10^{-4}, 1.17 \cdot 10^{-2})$ [g]			$(1.56, 2.00)$ [g]

[a] $\alpha = \beta = 0.05$.
[b] The concentration value was calculated using the extract diluted 10000 times (n = 2).
[c] The concentration value was calculated using the extract diluted 10 times (n = 1).
[d] The concentration value was calculated using the extract diluted 1300 times (n = 2).
[e] The concentration value was calculated using the extract diluted 1000 times (n = 2).
[f] The concentration value was calculated using the extract diluted 8000 times (n = 2).
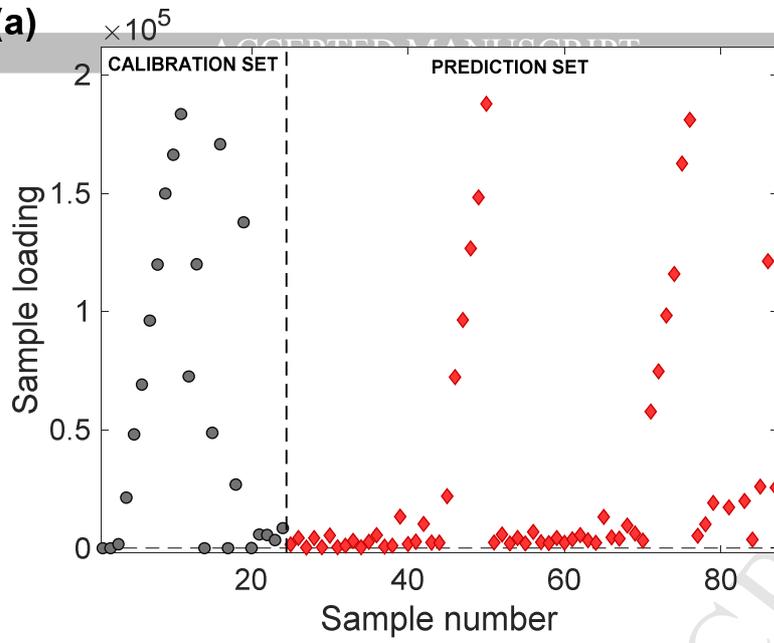[g] The concentration value was calculated using the extract diluted 3000 times (n = 2).
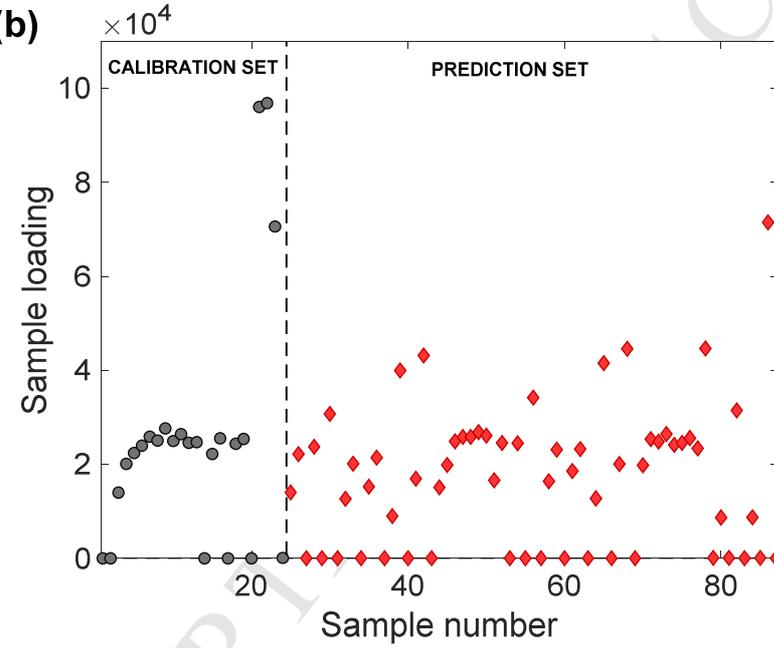
Fig. 1

(a)

(b)

(c)

Fig. 2

(a)

(b)

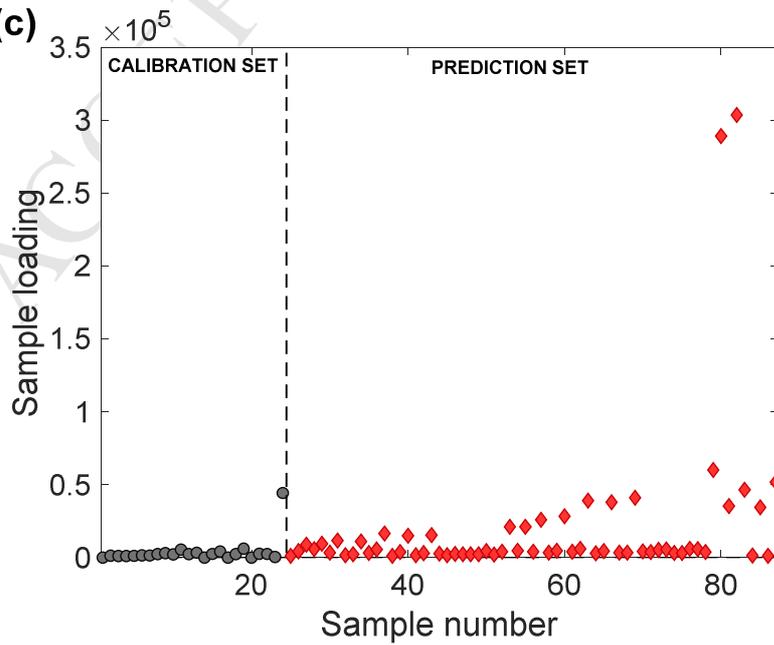
(c)
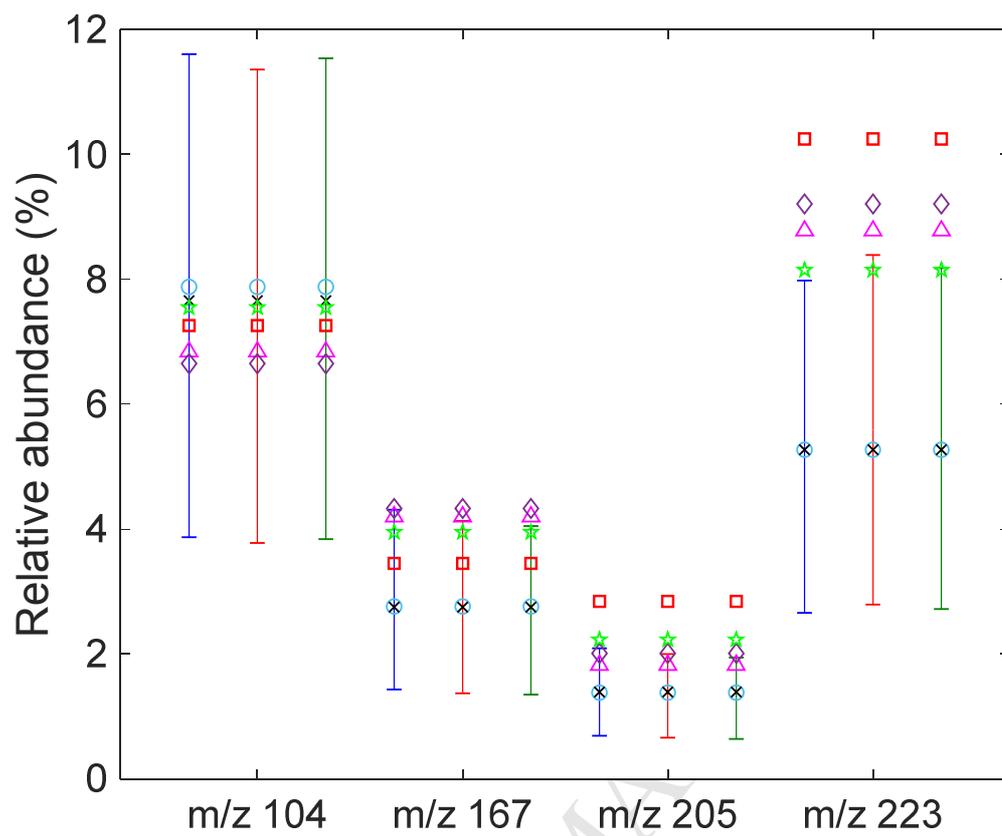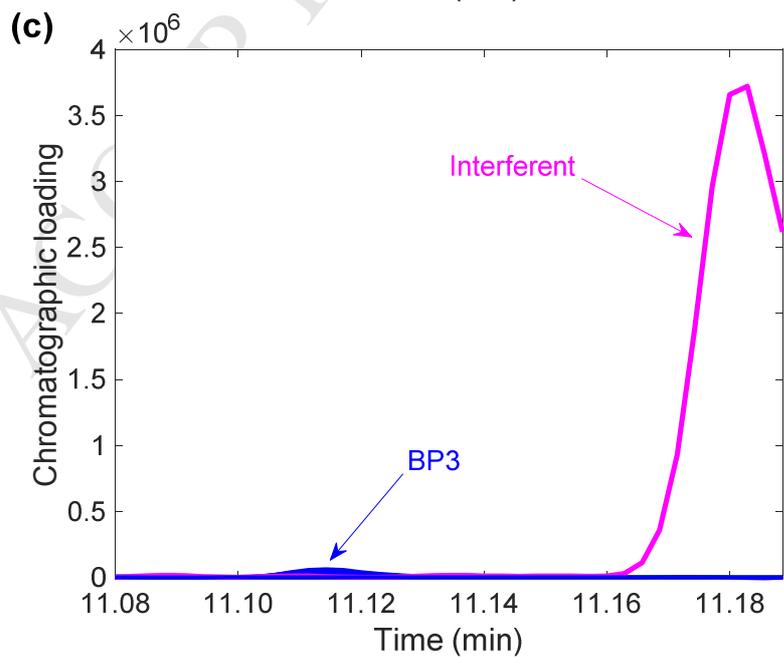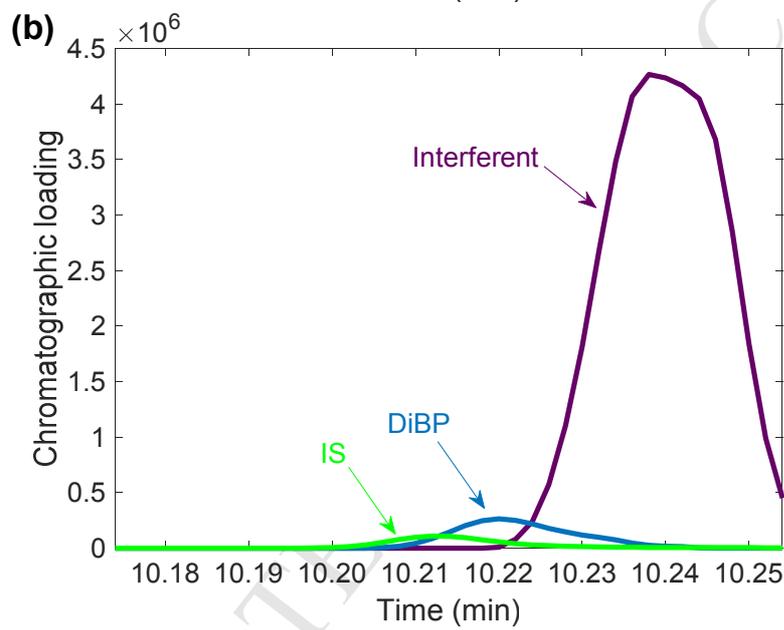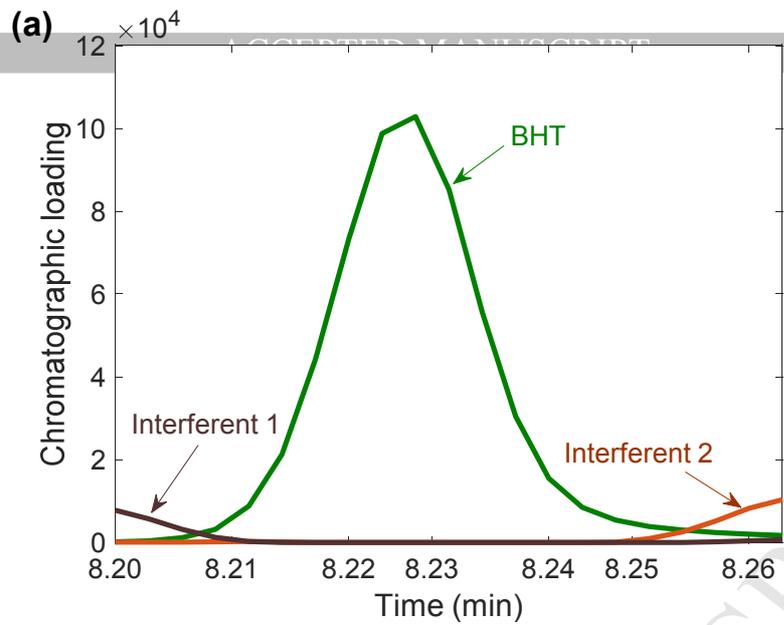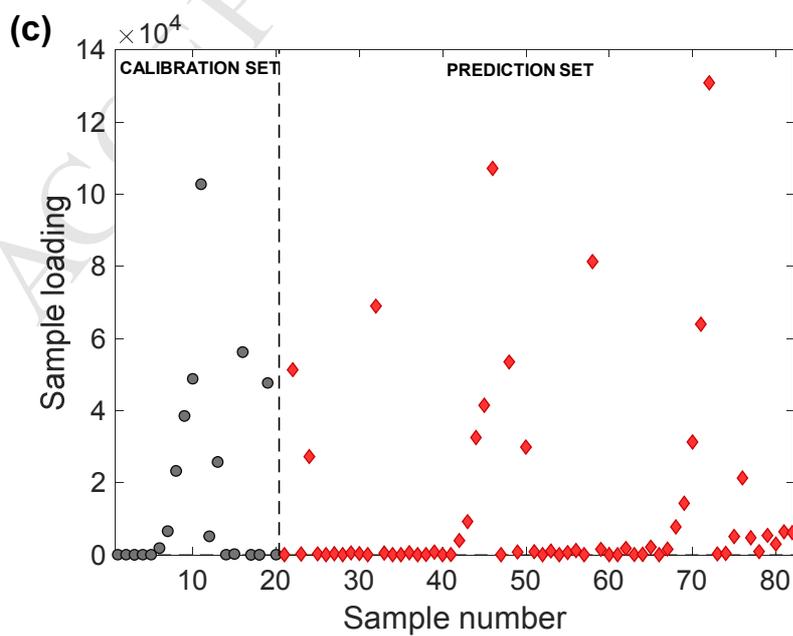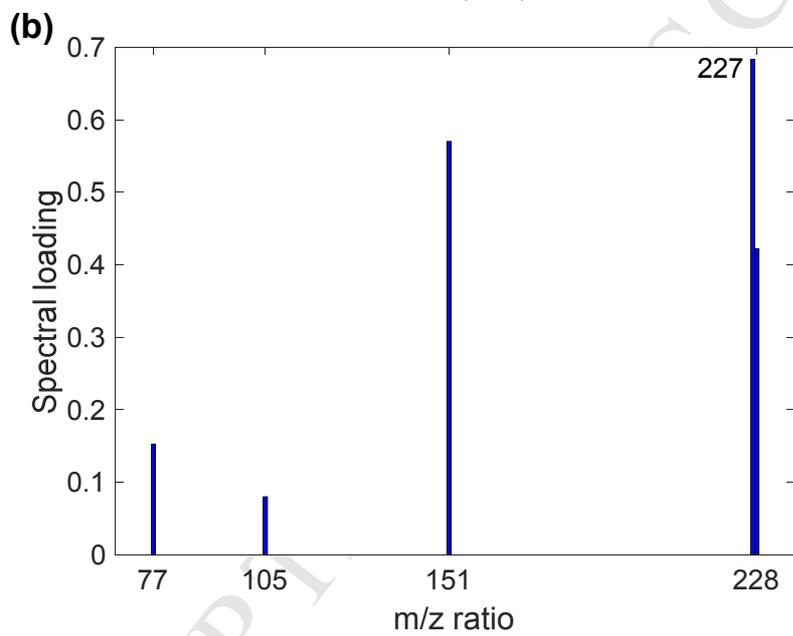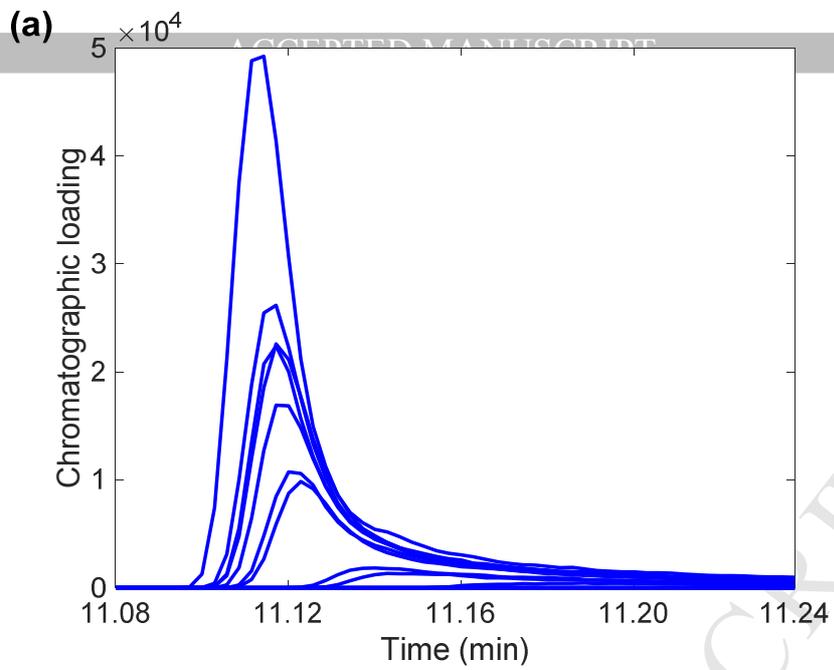
Fig. 3

(a)

(b)

(c)

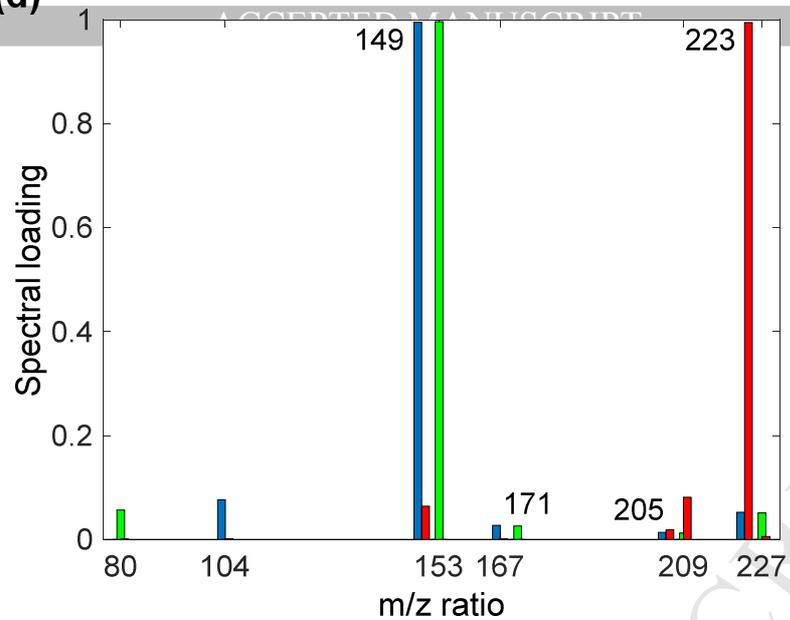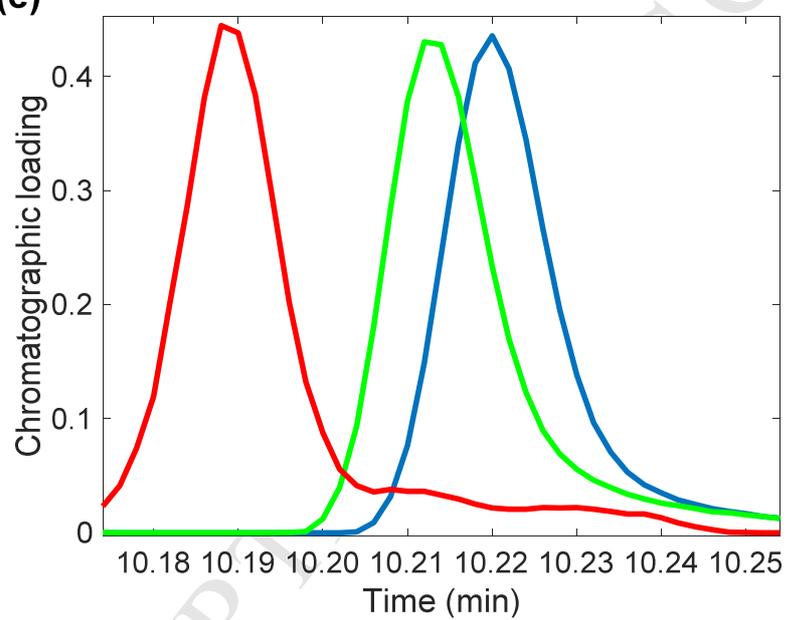**(d)**

(e)

Fig. 4

HIGHLIGHTS

Advantage of PARAFAC or PARAFAC2 models over the unequivocal identification

BHT was detected in all the creams while BP, DiBP and BP3 were found in some of them

None of the seven cosmetic creams analysed contained BP3 in an amount higher than 6%

PARAFAC2 overcame the shifts in the retention times of BP and BP3