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Novel gas-diffusion microextraction followed by gas chromatography coupled to tandem mass spectrometry methodology for the determination of fragrance allergens in cosmetic products

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ABSTRACT

An efficient sample preparation method using gas-diffusion microextraction (GDME) followed by gas chromatography coupled to tandem mass spectrometry (GC-MS/MS) is proposed for the first time to determine fragrance allergens in both aqueous and alcohol-based cosmetic products. The most significant GDME parameters were optimized, starting with extraction temperature as a preliminary experiment. Subsequently, an experimental design was performed to evaluate the influence of six parameters: acceptor solution volume, acetonitrile percentage in the acceptor solution, sample dilution, salting-out effect, extraction time, and sample volume. Under the optimized conditions, the method was validated in terms of linearity, precision, trueness, obtaining a good performance. The validated methodology was applied to twelve real cosmetic samples, demonstrating the widespread occurrence of these allergens in cosmetics. Notably, lilial, a compound prohibited by Regulation EC No 1223/2009, was detected in one cosmetic product (460 μg mL^{-1}); and the concentrations of some of the target fragrance allergens in some samples reach values above 1000 μg mL^{-1}. This methodology represents a sustainable and practical approach, supported by AGREEPrep and BAGI metrics, respectively.

1. Introduction

Fragrance substances, organic compounds characterized by their pleasant odors, are widely used in perfumes, cosmetic products, and household items such as detergents. However, some fragrances are well-known allergens. Exposure to significant amounts of these fragrances can lead to contact allergy, because they alter specific reactivity in the human immune system. Contact allergy is a lifelong condition, and once a person becomes sensitized to an allergen, a much lower concentration of that allergen can cause allergic symptoms. The Scientific Committee on Consumer Safety (SCCS) has classified 82 fragrance substances as contact allergens in humans, comprising 54 single chemicals and 28 natural extracts [1,2]. Under the European Union Regulation EC No 1223/2009 on cosmetic products, fragrance allergens in cosmetic products must be indicated on the ingredients label under the terms 'parfum' or 'aroma'. However, if the concentration of a fragrance allergen exceeds 0.001 % (10 μg mL^{-1}) in leave-on products and 0.01 % (100 μg mL^{-1}) in rinse-off products, the specific fragrance name must be listed on the label [3]. Furthermore, the International Fragrance Association (IFRA), the official representative body of the fragrance industry worldwide, whose main purpose is ensuring the safety of fragrance materials, has also restricted most of the fragrance allergens listed in the mentioned regulation [4].

The extraction of fragrance allergens from various environmental matrices, such as water and air, has been studied [5]. For water samples, techniques like ultrasound-assisted emulsification microextraction (USAEME) [6], USAEME combined with solidification of floating organic drop (SFOD) [7], solid-phase microextraction (SPME) [8–14], and dispersive solid-phase extraction (d-SPE) [15] have been employed to analyze various types of water samples, including bathwater,

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wastewater, river water, and swimming pool water. For air samples, passive sampling, along with extraction techniques such as SPME and needle-trap device (NTD), have proven to be convenient sample preparation procedures [16–18].

Regarding cosmetic products, which display significant variability, different sample preparations were applied. Pressurized liquid extraction (PLE) was selected for solid samples like creams, lotions, wipes, and baby and childcare products [19–21], alongside solid phase dispersion (MSPD) [21,22] and its miniaturized version, micro-matrix solid phase dispersion (μ-MSPD) [23]. For liquid samples, such as shampoos and lotions, and even hydroalcoholic gels, SPME was employed [24–27]. All the mentioned studies were performed using gas chromatography coupled to mass spectrometry (GC–MS), except for the mentioned SPME studies, which were conducted using gas chromatography-flame ionization detection (GC–FID).

Gas-diffusion microextraction (GDME) is an extraction technique in which the analytes are separated from the sample through a microporous gas-permeable membrane (diffusion) into a small volume of an acceptor solution. This non-exhaustive technique is based on the diffusion of the analytes, so it is typically applied to volatile and semi-volatile compounds. GDME combines membrane-assisted gas-diffusion and microextraction, offering a simple, fast, and economical alternative for extraction [28].

The GDME technique was first proposed in 2010 and has been mainly applied to the determination of volatile organic compounds, such as aldehydes and vicinal diketones, particularly in alcoholic beverages like beer [28–30], wine [31,32], or both [33]; as well as in liquors [34]. Formaldehyde [35,36], with other aldehydes [37,38], have also been studied in wood-based and cork products where they are applied as preservatives and disinfectants. Additionally, the determination of lipid peroxidation products such as malondialdehyde [39], as well as acrolein and other carbonyl compounds, has gained attention in edible oils [40] and infant formulas [41] due to potential health risks. This technique was also applied to other compound families in different matrices, such as aliphatic amines in wines and beers [42], volatile corrosion inhibitors in metal parts to assess steel protection against corrosion [43], and organochloride pesticides in semi-skimmed milk [44]. Concerning the cosmetic products analyzed in this work, only the determination of formaldehyde has been previously reported [45,46].

To the best of our knowledge, this study represents the first instance of GDME being utilized for the determination of fragrance allergens. Furthermore, most applications described in the mentioned works rely on liquid chromatography, as the GDME acceptor solution is typically aqueous. In two studies, GDME was followed by GC–MS [40,44], but, in both cases, an additional step was necessary during the sample preparation in order to achieve a compatible solvent with GC–MS. In the present work, a novel approach has been introduced: the use of a combination of organic solvents as the acceptor solution, enabling the integration of GDME with GC–MS/MS without requiring additional steps. Therefore, GDME could represent a promising technique for the effective extraction of analytes from cosmetic formulations. The objective of this research is the development of a new methodology for the simultaneous determination of fifteen frequently used fragrance allergens in cosmetic samples, using the GDME as the sample preparation technique, followed by gas chromatography coupled to tandem mass spectrometry (GC–MS/MS) analysis. Once optimized and validated, the method was applied to a high number of samples from a wide variety of cosmetic products (including aqueous and alcohol-based cosmetics), demonstrating its suitability and the high concentration of fragrance allergens in these cosmetic matrices.

2. Materials and methods

2.1. Reagents and standards

Ultrapure water, methanol, and ethyl acetate were supplied by Scharlau (Barcelona, Spain), and acetonitrile and ethanol were purchased from VWR BDH Chemicals (PA, USA). The target compounds were supplied by Fluka, (pinene, PIN; geraniol, GER; α-isomethyl ionone, IMI; benzyl salicylate, BS), Aldrich (limonene, LIM; linalool, LIN; citronellol, CT; citral, CIT; methyl eugenol, MEUG; amyl cinnamaldehyde, ACA; benzyl cinnamate, BC), SAFC (methyl-2-octyonate, M2O; hexyl cinnamaldehyde, HCA), Dr. Ehrenstorfer GmbH (lilial, LIL), and Chem Service (benzyl benzoate, BB). 2,4,6-trichlorobiphenyl (PCB-30), used as the internal standard, was supplied by Dr. Ehrenstorfer (Augsburg, Germany). Individual stock standard solutions were prepared in ethanol and in acetonitrile at nominal concentrations of 10,000 μg mL^{-1}. Solutions containing all the analytes and further dilutions were made in ethanol. All these standard solutions were stored at −20 °C until use, and all solvents and reagents were of analytical grade.

2.2. Sampling and extraction procedure

Cosmetic products, including hairspray, micellar water, deodorant, sunscreen; were collected from different stores (supermarkets and drugstores) in Galicia (Northwest Spain). Samples were kept in 20 mL glass tubes at room temperature until analysis. The analyzed samples are included in **Table S1** showing the composition indicated on the label.

Fragrance allergens from cosmetic samples were extracted using a GDME module, made in-house at the Faculty of Science of the University of Porto, Portugal. A schematic of the GDME apparatus is displayed in Fig. 1.

The sample (500 μL) was added to a glass flask and diluted 1:20 v/*v* with ultrapure water (final volume: 10 mL). In the case of aqueous samples, 500 μL of ethanol were also added, ensuring the same water-to-ethanol ratio for both types of samples (aqueous and alcohol-based samples).The flask was covered with a cap adapted to support a GDME device operating in headspace mode, which included a polytetrafluoroethylene (PTFE) membrane with a 5 μm pore size and a 13 mm diameter (CHMLAB Group, Terrasa – Barcelona, Spain). Inside the GDME module, supported by the membrane, the acceptor solution, consisting of a mixture of 300 μL of ethyl acetate/acetonitrile (50/50, *v*/*v*) containing the internal standard (PCB-30), was placed, and an aluminum foil cap covered the GDME module. PCB-30 was added in order to correct the possible acceptor solution volume variability. Once the flask was capped, the GDME system was placed in a water bath at 50 °C for 15 min, and magnetic stirring was applied. Afterward, 50 μL of the acceptor solution was collected and diluted 1:1 (final volume: 100 μL) in ethyl acetate (ethyl acetate/acetonitrile, 75/25, *v*/*v*). Finally, 1 μL of the extract was injected into the GC–MS/MS system.

2.3. GC–MS/MS instrumentation and working conditions

The chromatographic separation of fragrance allergens was performed on a Thermo Trace 1310 gas chromatograph equipped with an autosampler AI 1310 (Thermo Scientific, San Jose, CA, USA) and coupled to a triple quadrupole mass spectrometer TSQ 8000 Evo. The separation was performed on a Zebron ZB-Semivolatiles column (30 m × 0.25 mm × 0.25 μm) obtained from Phenomenex (Torrance, CA, USA).

Helium (purity 99.999 %) was employed as the carrier gas at a constant flow rate of 1.0 mL min^{-1}. The temperature program for the gas chromatography oven was as follows: 0.00–1.00 min, hold at 60 °C; 1.00–6.00 min, increase from 60 to 100 °C (8 °C min^{-1}); 6.00–8.5 min, increase from 100 °C to 150 °C (20 °C min^{-1}); 8.5–10.50 min, increase from 150 °C to 200 °C (25 °C min^{-1}); 10.50–15.50 min, hold at 200 °C; 15.50–18.00 min, increase from 200 to 220 °C (8 °C min^{-1}); 18.00–20.33 min; increase from 220 to 290 °C (30 °C min^{-1}); 20.33–21.83 min, hold at 290 °C. The total run time was less than 22 min. The injection volume was 1 μL, with the injector temperature set to 260 °C. A pulsed splitless mode at 200 kPa, maintained for 1.2 min, was employed for injection.

The mass spectrometer detector was operated in the electron impact (EI) ionization positive mode (+70 eV). The ion source and transfer line

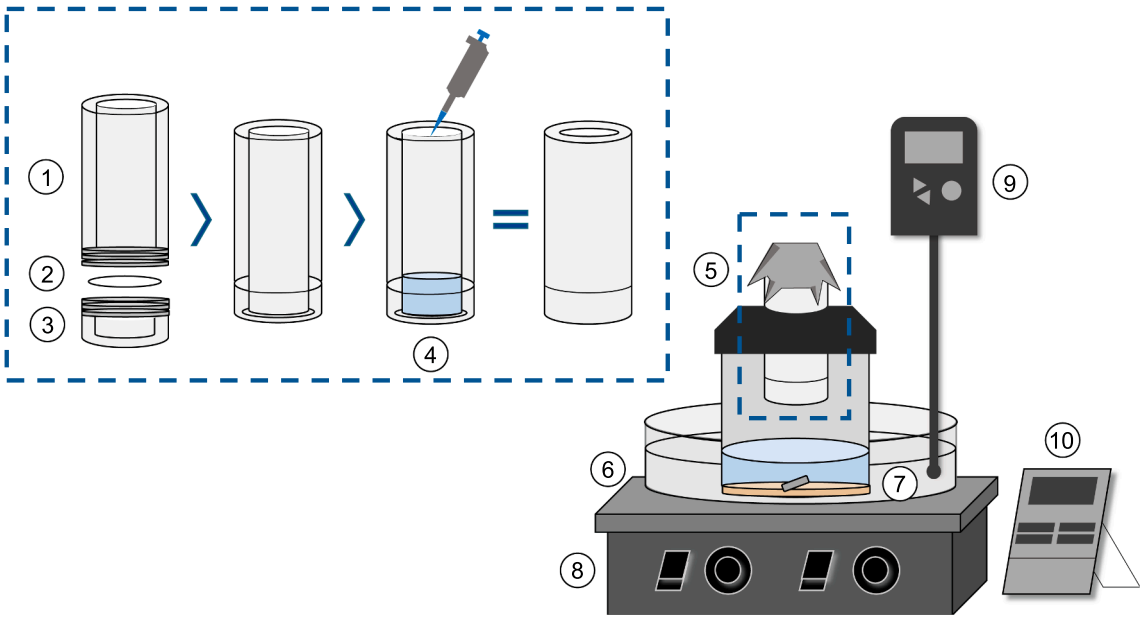

Fig. 1. Schematic representation of the GDME extraction apparatus: 1 – GDME unit upper piece, 2 – PTFE membrane, 3 – GDME unit lower piece, 4 – acceptor solution, 5 – aluminum foil cap, 6 – water bath, 7 – sample, 8 – heating and magnetic stirring, 9 – thermometer, 10 – chronometer.

temperature were set at 350 and 290 °C, respectively; the filament current was set at 25 μA, and the multiplier voltage was 2300 V. The mass spectral data were acquired in selected reaction monitoring (SRM) mode in positive ion mode, and both quadrupoles, Q1 and Q3, operated at unit mass resolution. Instrument control and GC–MS/MS data analysis were carried out using Xcalibur 2.2 and Trace Finder™ 3.2 software. **Table S2** shows the SRM transitions for each fragrance allergen used for quantification and confirmation purposes, with their corresponding collision energies (V) in the employed GC–MS/MS method.

2.4. Statistical analysis: method optimization and validation

The statistical software Statgraphics Centurion XVIII (Manugistics, Rockville, MD, USA) was employed to generate the experimental design and to analyze the experimental data. An irregular fractional factorial design $2^{6\cdot\frac{8}{3}}$ was applied to optimize several factors affecting GDME procedure, with a total of 24 experiments performed. An analysis of variance (ANOVA) was conducted to evaluate the GDME parameters, providing insights into how each factor and their interactions influence the variance of the obtained responses. The F-ratios quantify the impact of each factor and interaction on response variability, while the p-values assess their statistical significance at a 95 % confidence level ($p < 0.05$ indicates statistical significance). Several graphical tools available in the software were used in the optimization process, including Pareto charts, in which the bar length is proportional to the effect of the corresponding factor or interaction, and a vertical line represents the significance limit at the 95 % confidence level. Additionally, main effects plots were used to illustrate the variation in responses when moving from the low to the high level of each factor: the steeper the slope of the line, the greater the effect of the factor. Interaction plots were visualized using interaction charts, which illustrate the variation in responses when one factor is affected by the level of other factor, helping in the identification of the most favorable conditions. All graphs were generated using Microsoft Office 365 and the aforementioned software.

Regarding the validation of the developed analytical method, standard solutions were prepared using the completed experimental procedure in water containing 500 μL of ethanol (see *Section 2.2.*), covering a concentration range from 0.1 to 50 μg mL^{-1} in duplicates and triplicates (see specific ranges for each target compound in Table 1).

Recoveries were initially calculated by comparing the response obtained from an alcohol-based standard (prepared in 500 μL of ethanol as the sample) with an aqueous standard (prepared in 500 μL of ultrapure water as the sample), at two concentration levels (5 and 20 μg mL^{-1}), based on the calibration curve. Subsequently, trueness was evaluated using two real cosmetic samples, fortified with the target fragrance allergens at two concentrations (5 and 20 μg mL^{-1}). For each fragrance allergen, recovery was calculated by quantifying the fortified sample and dividing the result by the added concentration.

Repeatability (intra-day precision) was calculated as the relative standard deviations (RSD, %) of three extracts at 20 μg mL^{-1} analyzed on the same day ($n = 3$), while reproducibility (inter-day precision, RSD, %) was determined at 5 μg mL^{-1} over four days ($n = 4$). The limits of detection (LOD) and quantification (LOQ) were determined based on the concentration of the analyte that resulted in a signal-to-noise ratio of 3 and 10, respectively.

3. Results and discussion

3.1. Optimization of the GDME parameters

The gas chromatographic behavior of these compounds, using a Zebron ZB-Semivolatiles column, has already been studied by our research group [12,13,23,26,27]. The results demonstrated that ethyl acetate is the optimal solvent for achieving a good chromatography performance, particularly in terms of peak shape and chromatographic resolution, for all target compounds. Although ethyl acetate was effective as an injection solvent, its permeability through the GDME membrane made it unsuitable as the GDME acceptor solution. Alternative solvents (acetonitrile, isooctane, and hexane) were tested as acceptor solutions, with acetonitrile being the only solvent retained by the GDME membrane. This retention may occur because acetonitrile is a polar solvent and has a stronger dissolution capability for hydrophilic/polar regions of membranes. However, PTFE is a hydrophobic membrane, so acetonitrile's dissolution ability in a nonpolar structure is weak, leading a low permeability for polar solvents. Furthermore, another study indicated that acetonitrile exhibits low permeability through PTFE membranes due to its limited diffusion capacity in this glassy polymer [47,48]. However, acetonitrile presented poor chromatography for the target compounds, causing poor peak shape in some cases, peak

splitting, and reduced resolution. To improve this situation, solvent mixtures were tested. A 50/50 *v/v* mixture of acetonitrile and ethyl acetate was not permeable through the GDME membrane but still caused peak splitting. An increase in the ethyl acetate content led to permeability issues despite improving chromatographic peak shape and resolution. To address these challenges, a compromise between the GDME membrane compatibility and optimal chromatographic peak shape and resolution, was achieved. After performing the GDME technique, the extract of the acceptor solution (ethyl acetate/acetonitrile, 50/50 *v/v*) was diluted 1:1 in ethyl acetate, resulting in a final solvent proportion of ethyl acetate/acetonitrile, 75/25 *v/v*. This approach provided satisfactory chromatographic peaks while addressing permeability and peak splitting issues. **Figure S1** shows the chromatographic peak shape comparison for LIN and IMI at 200 μg mL^{-1}. For LIN, **Figure S1A, S1B**, and **S1C** show the peak shape in ethyl acetate/acetonitrile 50/50 (*v/v*), ethyl acetate/acetonitrile 75/25 (*v/v*), and ethyl acetate, respectively. For IMI, **Figure S1D, S1E**, and **S1F** correspond to the same solvent conditions: ethyl acetate/acetonitrile 50/50 (*v/v*), ethyl acetate/acetonitrile 75/25 (*v/v*), and pure ethyl acetate. The satisfactory peak resolution achieved with the ethyl acetate/acetonitrile 75/25 (*v/v*) can be seen.

Conversely, the extraction temperature is one of the most significant parameters to be evaluated, as the extraction technique is based on the compounds' volatility [28]. Therefore, a study was conducted using samples spiked with the analytes at 2 μg mL^{-1} in duplicate for each extraction temperature to determine the optimal extraction temperature, with the following temperatures tested: 30 °C, 40 °C, and 50 °C. The GDME extraction was performed using 300 μL of acceptor solution, a sample dilution ratio of 1:10 with ultrapure water, and an extraction time of 15 min with magnetic stirring. Higher temperatures were not studied because, as observed experimentally, when the temperature exceeded 50 °C, the amount of acceptor solution (ethyl acetate/acetonitrile 50/50 *v/v*) collected was considerably reduced. Based on Fig. 2, it was concluded that the most favorable extraction temperature is 50 °C, which yielded a much higher signal compared to lower temperatures.

3.2. Experimental design

Once the extraction temperature was set, other parameters affecting the GDME extraction technique were included in the experimental design to optimize sample preparation conditions. In all experiments, magnetic stirring and the height of the GDME device above the sample were kept constant. As mentioned in Section 2.4., an irregular fractional factorial design $2^{6-\frac{8}{3}}$ was applied to study six factors at two levels. These factors included the volume of the acceptor solution (A) at 300 and 500 μL; percentage of acetonitrile in the acceptor solution (B) at 50 and 100 %; sample dilution ratio (C) at 1:5 and 1:10; salting-out effect by adding sodium chloride (NaCl) (D) at 0 and 20 % (*w/v*); extraction time (E) at 5 and 15 min; and sample volume (F) at 100 and 1000 μL. A total of 24 experiments were performed in random order to avoid systematic error. A real aqueous cosmetic spray sample was used for the experimental design, which contained some of the target compounds (PIN, LIM, LIN, M2O, CT, GER, CIT, IMI, BB, and BS). This made possible to perform method optimization without spiking the compounds in the sample and, in this way, evaluate the real interactions between the analytes and the sample. The design resolution of V allows the evaluation of individual main effects of each factor and two-factor interactions.

The ANOVA results for each compound are summarized in **Table S3**. This table shows the F and p-values for the main factors and two-factor interactions; p-values lower than 0.05 are considered statistically significant (see Section 2.4.) Among the evaluated parameters, acceptor solution volume was significant for eight out of the ten compounds (PIN, LIN, M2O, CT, GER, CIT, IMI, BB, and BS). Extraction time was significant for six (LIN, M2O, CT, GER, IMI, and BB). The percentage of acetonitrile (acetonitrile content) was significant for four compounds (LIM, LIN, CIT, and BB), while the salting-out effect was significant for three compounds (PIN, M2O, and IMI). Sample volume was only significant for PIN, while the dilution sample was not significant for any analyte. Regarding two-factor interactions, six out of fifteen interactions (AE, AF, CE, CF, DF, and EF) were significant for, at least, one compound. These results are depicted in Fig. 3 and **Figure S2**, which display the Pareto charts, main effects plots, and two-factor interaction plots.

According to the optimal conditions, the low level of acceptor solution volume (300 μL) and the high level of extraction time (15 min) were the most favorable for all the compounds. Additionally, their interaction AE (acceptor solution volume – extraction time) also proved that the low levels were the best conditions for seven out of the ten compounds where it was significant, as can be seen in Fig. 3**C** for the three compounds displayed (LIM, LIN, and M2O). For the percentage of acetonitrile in the acceptor solution, it was concluded that 50 % acetonitrile and 50 % ethyl acetate (*v/v*) should be selected, since for the four compounds where it was significant, two of them showed a clear difference between the low (50 % of acetonitrile) and high (100 % of acetonitrile) levels, as seen in Fig. 3**B** for LIM. NaCl addition did not improve analyte

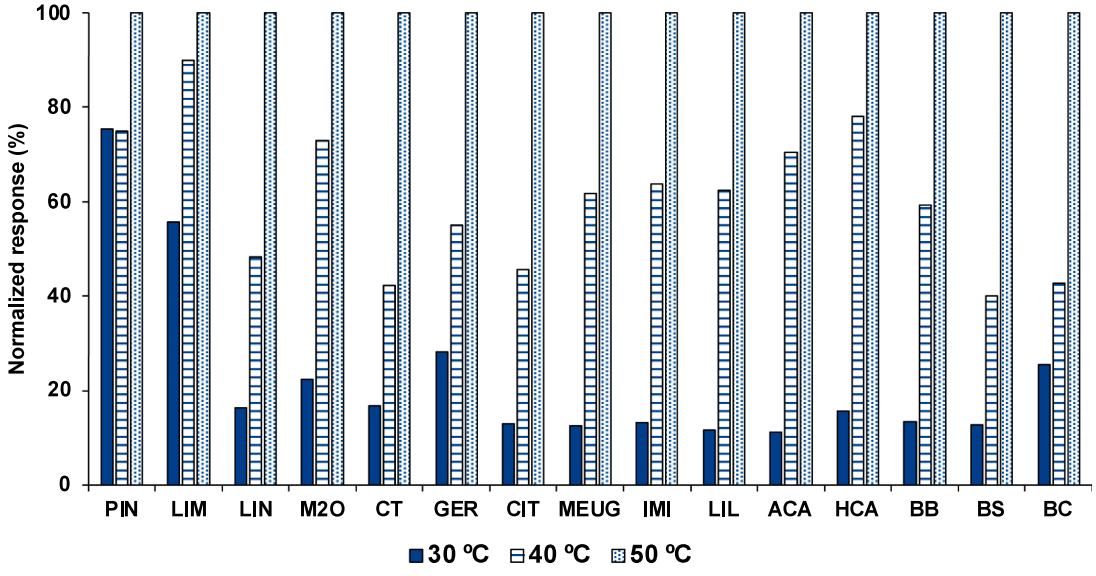

Fig. 2. Responses (normalized) obtained at different extraction temperatures for each fragrance allergen.

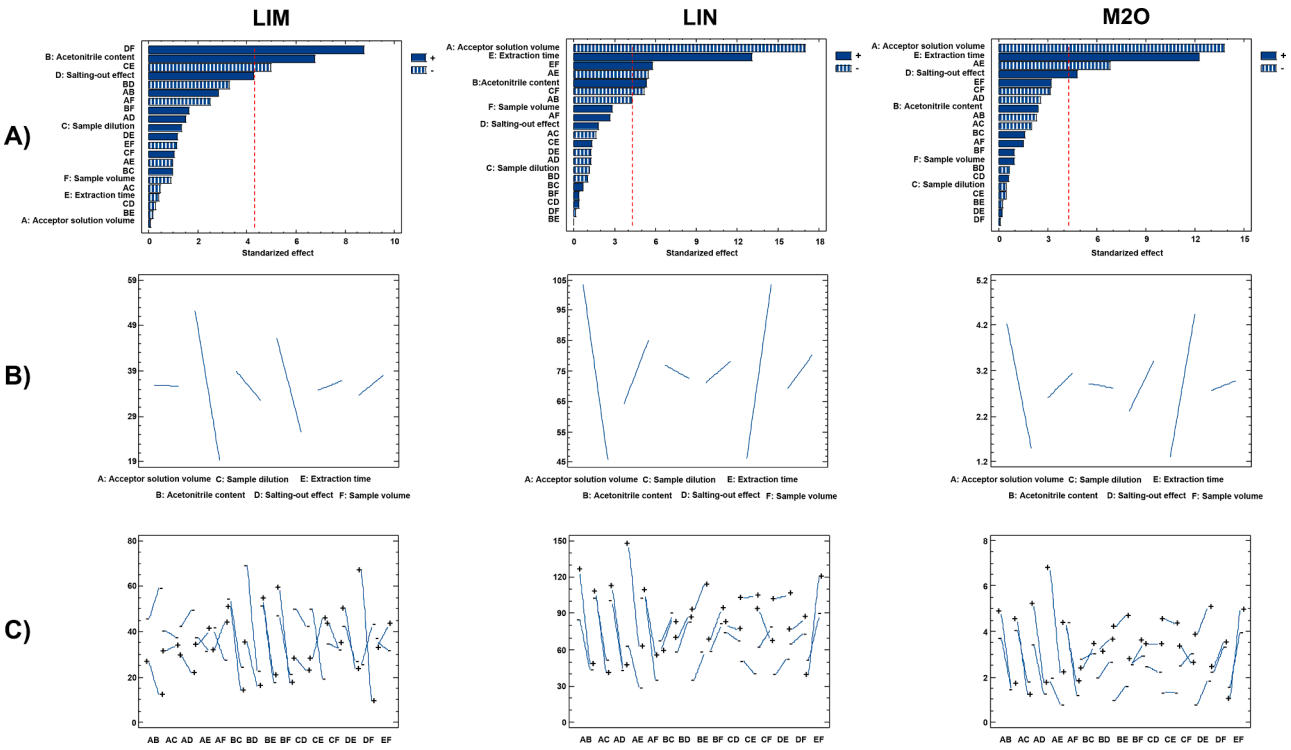

Fig. 3. A) Pareto charts, B) main effects plots, and C) two-factor interaction plots for LIM, LIN, and M2O.

extraction, as 0 % NaCl was optimal for two of the three compounds for which this factor was significant (PIN and IMI). Similarly, interaction DF (salting-out effect – sample volume) was significant for two compounds, with optimal conditions of 0 % NaCl and 1000 µL of sample volume, as can be seen for LIM in Fig. 3**C**. In the case of sample volume, this was significant only for PIN, with 1000 µL being the optimum. This conclusion is supported by significant interactions involving this factor (AF, CF, DF, and EF). As shown in Fig. 3**C**, the high level of sample volume is the optimum in the interactions CF (sample dilution – sample volume) and EF (extraction time – sample volume) interactions for LIN, and DF (salting-out effect – sample volume) interaction for LIM; with a 1:5 dilution, 15 min of extraction time, and 0 % NaCl, respectively. Finally, since the sample dilution factor was not significant, a 1:10 dilution was selected as the most favorable to minimize or avoid possible matrix effects. Regarding significant interactions involving sample dilution, the CE interaction (sample dilution – extraction time) for LIM, shown in Fig. 3**C**, yielded nearly identical responses when both factors were at their lowest levels (dilution 1:5 and 5 min as the extraction time) and at their high levels (dilution 1:10 and 15 min). Additionally, the previously mentioned CF interaction for LIN, upon selecting 1000 µL as the sample volume, showed only a 20 % difference between the 1:5 and 1:10 dilutions.

In conclusion, based on the experimental design results, the most favorable GDME conditions were determined to be: an acceptor solution volume of 300 µL consisting of ethyl acetate/acetonitrile 50/50 (*v/v*), a sample volume of 1000 µL, a subsequent dilution of 1:10 with ultrapure water, no NaCl addition, and an extraction time of 15 min.

3.3. Further experiments

Following the optimal conditions identified in the experimental design, an intermediate sample volume (500 µL) was tested and compared with the optimal volume (1000 µL), in accordance with the principles of green analytical chemistry, which aim to minimize sample size. This comparison was conducted with the same cosmetic spray sample used for the experimental design and the results are presented in **Figure S3A**. As shown in **Figure S3A**, the difference in response between the two sample volumes is very low, yielding comparable extractions for most of the compounds, except for PIN and BS, for which the sample volume of 1000 µL gave a higher response (around 35 %). Therefore, to minimize sample size, a sample volume of 500 µL was selected for the following analyses.

Additionally, the dilution factor, which was not a significant factor for any analyte during the experimental design, was further evaluated to increase the dilution in order to avoid or minimize potential matrix effects in cosmetic samples. Therefore, a higher dilution (1:20) was tested and compared with the optimal dilution identified in the experimental design (1:10). This comparison was performed by spiking the studied compounds into a real aqueous cosmetic sample at 10 µg mL^{-1}. **Figure S3B** presents the results for each compound, showing minimal differences between the sample dilutions, with a variation of less than 20 % for most compounds. Therefore, a 1:20 dilution was selected to minimize or avoid possible matrix effects.

3.4. Validation of the methodology

The developed method GDME-GC–MS/MS has been validated for fifteen fragrance allergens in cosmetic samples in terms of linearity, repeatability (intra-day precision) and reproducibility (inter-day precision), trueness, and limits of detection (LODs) and quantification (LOQs), as summarized in Table 1.

The linearity study demonstrated good performance, with coefficients of determination (R^2) higher than 0.990 for most target fragrance allergens. **Figure S4** shows a SRM GDME-GC–MS/MS chromatograms of a standard solution. Intra-day and inter-day precision were assessed at concentrations of 20 µg mL^{-1} and 5 µg mL^{-1}, respectively. The intra-day precision was characterized by relative standard deviation (RSD, %) values ranging from 0.4 % to 13 %, while inter-day precision results ranged from 5.9 % to 14 %.

Trueness, expressed as recoveries (%), was evaluated as described in *Section 2.4*. As can be seen in Table 1, the recovery results were favorable, with values between 73 and 130 %, and deviations below 20 %,

Table 1
Validation of the developed GDME-GC–MS/MS method per analyte. Linearity (coefficient of determination and range), intra-day and inter-day precision (RSD, %) with specified replicates per day and number of days for inter-day, trueness (%), limits of detection (LOD) and quantification (LOQ) are displayed.

	Linearity		Precision		LOD (μg mL^{-1})	LOQ (μg mL^{-1})
	R^2	Range (μg mL^{-1})	Intra-day (n = 3) (RSD, %)	Inter-day (n = 4) (RSD, %)		
PIN	0.997	0.1 - 50	8.8	11	0.036	0.10
LIM	0.998	0.1 - 50	5.3	9.7	0.0010	0.0029
LIN	0.992	0.1 - 50	9.3	14	0.0061	0.020
M2O	0.994	0.5 - 50	8.6	13	0.048	0.16
CT	0.997	2 - 50	11	13	0.069	0.23
GER	0.995	0.1 - 50	7.1	12	0.0089	0.030
CIT	0.994	0.1 - 50	7.9	13	0.0021	0.0069
MEUG	0.994	0.5 - 50	3.8	9.4	0.028	0.10
IMI	0.996	0.1 - 50	13	13	0.0049	0.016
LIL	0.997	0.5 - 50	7.6	10	0.047	0.15
ACA	0.997	0.1 - 50	0.4	5.9	0.015	0.049
HCA	0.996	0.5 - 50	1.7	6.0	0.0089	0.030
BB	0.997	0.1 - 50	2.2	6.9	0.012	0.038
BS	0.992	0.1 - 50	9.5	12	0.0089	0.030
BC	0.991	0.1 - 50	10	14	0.0059	0.020

	Trueness (%)				
	Standard solutions		Real cosmetic samples		
	5 μg mL^{-1}	20 μg mL^{-1}	5 μg mL^{-1} (S12)	5 μg mL^{-1} (S11)	20 μg mL^{-1} (S11)
PIN	104.8 ± 4.9	126 ± 12	87.7 ± 3.4	124.3 ± 2.9	101.4 ± 0.2
LIM	102 ± 10	98.8 ± 9.6	94.1 ± 0.4	108.8 ± 6.9	107.1 ± 2.3
LIN	87.2 ± 4.1	107.9 ± 8.9	97.3 ± 9.0	107.9 ± 9.9	99.4 ± 8.1
M2O	102 ± 11	107 ± 11	99.1 ± 0.6	95.3 ± 1.2	90.8 ± 7.5
CT	93 ± 14	104 ± 19	105 ± 14	117.1 ± 9.8	97 ± 11
GER	110.9 ± 1.0	85.2 ± 9.4	86.3 ± 7.7	117 ± 19	117 ± 14
CIT	98.2 ± 9.5	106.9 ± 7.1	119 ± 13	119.9 ± 4.2	87 ± 12
MEUG	76.2 ± 7.8	110.3 ± 1.8	85.8 ± 3.7	130 ± 10	95.1 ± 3.0
IMI	95 ± 16	100.8 ± 2.6	104 ± 12	100.2 ± 0.6	97 ± 12
LIL	85 ± 13	106.8 ± 0.2	92.2 ± 1.4	91.7 ± 1.7	114 ± 12
ACA	78.9 ± 1.9	119.2 ± 5.6	86.6 ± 2.0	98.7 ± 2.2	109.4 ± 0.8
HCA	77.4 ± 6.0	110 ± 13	73.3 ± 1.4	98.4 ± 2.8	102.4 ± 2.9
BB	93 ± 12	122.4 ± 8.4	76 ± 11	93 ± 14	92.3 ± 1.7
BS	93 ± 16	79.6 ± 0.3	79.1 ± 7.8	114 ± 14	125.5 ± 9.7
BC	95.3 ± 9.7	78 ± 20	83.2 ± 4.0	113 ± 15	95 ± 14

demonstrating good method performance and suggesting no significant differences between the analysis of alcohol-based and aqueous cosmetic products.

The limits of detection (LOD) and quantification (LOQ) for the fifteen fragrance allergens are displayed in Table 1, showing LOD values ≤ 0.069 μg mL^{-1} and LOQ values ≤ 0.23 μg mL^{-1}.

3.5. Greenness and practicability of the method

The development of extraction methodologies in line with the principles of green analytical chemistry (GAC) and green sample preparation (GSP) has increased significantly in recent years. These procedures include the employment of safe solvents, reagents, and materials, minimizing the experimental steps and reducing waste generation and energy consumption, while allowing high sample throughput. In 2022, a metric tool called AGREEPrep [49] was introduced to assess the greenness of sample preparation. The sustainability of the GDME methodology developed in this study to extract fragrance allergens from cosmetic samples was calculated. As can be seen in Fig. 4, a value of 0.61 as well as a green label was obtained, showing the greenness of the proposed GDME method.

The developed method is evaluated based on ten criteria, as detailed in Fig. 4: performed *ex situ* (criterion 1); the acceptor solution contains 0.15 mL of acetonitrile, which is considered toxic, while ethyl acetate is not since it is biodegradable (criterion 2); the GDME system can be reused multiple times (criterion 3); regarding the material consumption, 0.6 g corresponds to the insert, 0.3 g to the capsules, and 0.3 mL to the acceptor solution, generating a total of 1.2 g of waste (criterion 4); the sample amount is 0.5 mL (criterion 5); the duration of the sample preparation stage is approximately 15 min, and since three GDME systems can be prepared simultaneously, up to 12 samples per hour can be processed (criterion 6); the procedure consists of two steps – GDME extraction and extract dilution – and it is a semi-automated system (criterion 7); the energy consumption is around 11.45 Wh per sample due to the heating and magnetic stirring (criterion 8), GC–MS/MS is used as the analytical instrument (criterion 9) and, finally, two hazards are associated with the procedure – GHS02 (flammable) and GHS07 (harmful) – due to the use of organic solvents (criterion 10). The weights of each criterion were not modified (default weights given by AGREEPrep).

Besides, the practicability of the method was also evaluated by the metric tool Blue Applicability Grade Index (BAGI) [50], which was introduced in 2023. This metric is complementary to the green assessment tools (like AGREEPrep) and it is mainly related to practical aspects. As can be seen in Fig. 5, a value of 80.0 as well as a blue label was obtained, showing the practicability of the proposed GDME method.

As in the AGREEPrep protocol, the method was evaluated based on ten criteria, as detailed in Fig. 5: quantitative and confirmatory method (criterion 1); multi-element analysis targeting fifteen analytes (criterion 2); gas chromatography coupled to tandem mass spectrometry is the analytical instrumentation (criterion 3); simultaneous sample preparation of three samples (criterion 4); gas-diffusion microextraction is a miniaturized sample extraction technique (criterion 5); twelve samples can be analyzed per hour (criterion 6); common commercially available reagents are used (criterion 7); no pre-concentration is needed (criterion 8), semi-automated method with common device such as the

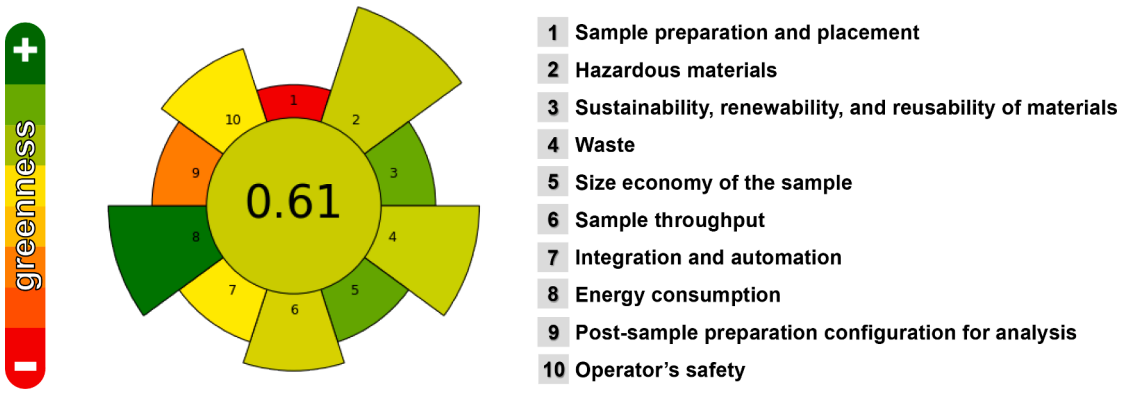

Fig. 4. AGREEPrep assessment of GDME as sample preparation under optimized conditions.

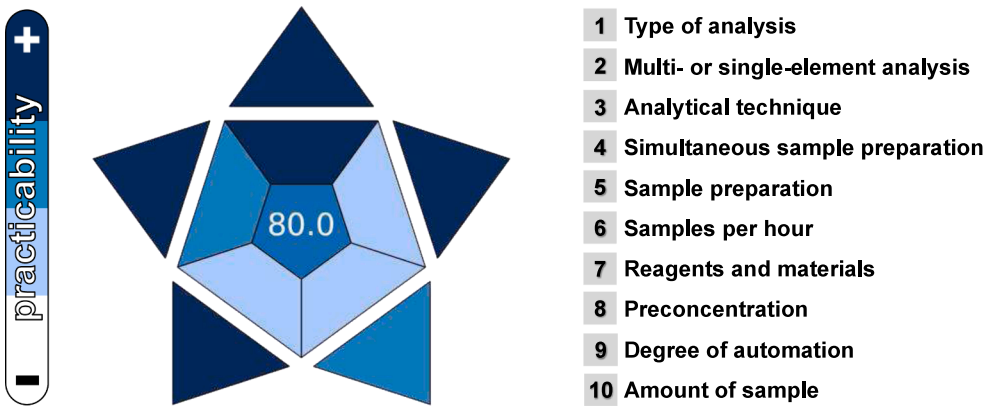

Fig. 5. BAGI assessment of GDME-GC–MS/MS as practicability of the method.

autosampler (criterion 9) and, finally, cosmetic samples can be classified as well as the environmental/food samples, and 500 µL is the sample volume, lower than 10 mL or g (criterion 10).

3.6. Sample analysis

The validated GDME–GC–MS/MS method was applied to twelve leave-on cosmetic samples to quantify fragrance allergens and assess compliance with Regulation EC No 1223/2009. Table 2 summarizes the quantification results for each analyte. Fig. 6 displays SRM GDME-GC–MS/MS chromatograms of a real cosmetic sample (S9). In addition, **Table S1** lists the analyzed cosmetic samples along with their ingredients as declared by the manufacturer and an assessment of regulatory compliance. Due to the varying concentrations of fragrance allergens across samples, different dilution levels were required to ensure that analyte responses fell within the linear range of the calibration curve.

All the target fragrance allergens, excluding MEUG, were detected in the analyzed cosmetic samples, excluding S12 where none of the studied compounds was detected. The most frequently detected compounds were LIN and BB, found in eleven samples; followed by LIM and GER, found in ten samples, and M2O, CT, and BS in nine samples each. These six fragrance allergens, along with PIN, CIT and BC (detected in eight samples each), IMI (detected in seven samples) were present in over 50 % of the analyzed samples. Furthermore, PIN, LIM, LIN, CT, and GER were the compounds with the highest concentrations in some of the analyzed cosmetic samples, with concentrations above 1000 µg mL^{-1}.

In terms of the number of fragrance allergens per sample, S1 contained almost all the studied fragrance allergens, as well as S5 and S6 with thirteen compounds. The presence of LIL in S5 is remarkable, as this fragrance allergen is prohibited in cosmetic products under Regulation EC No 1223/2009, demonstrating that sample S5 does not comply with this regulation, and its concentration is high, with a value of 460 µg mL^{-1}. S7 contained twelve compounds, followed by S8 with eleven compounds, S9 and S10 had ten each; S3 and S11 with seven; and finally, S4 contained six target compounds. Therefore, all the samples included over 50 % of the target fragrance allergens. Samples S7 and S8 contained the compounds with the highest concentrations (PIN, LIM, LIN, CT, and GER), up to 0.1 % - 0.6 %, and these samples correspond to deodorants which are typically applied all over the body, not just in the underarm area.

According to Cosmetic Regulation EC No 1223/2009, seven out of the twelve analyzed cosmetic samples did not comply with this regulation. Specifically, samples S2, S4, S5, S6, S7, S8, and S9 did not list some of the individual names of fragrance allergens on their cosmetic labels when their concentration exceeded the regulatory limit of 10 µg mL^{-1} (0.001 %) in leave-on cosmetic products, and S5 also contained the mentioned prohibited compound LIL (**Table S1**). As an example, PIN was detected in samples S2, S7, and S8 at concentrations higher than 10 µg mL^{-1}. The same applies to the analytes M2O, CT, GER, CIT BB, and BS in other samples, as shown in the mentioned table, which were not listed on the cosmetic labels even though their concentration exceeded regulatory limits.

4. Conclusions

A GDME-GC-MS/MS method has been developed and validated for the simultaneous determination of fifteen fragrance allergens in cosmetic products. The key critical factors affecting GDME were optimized through a preliminary experiment studying the extraction temperature and through a design of experiments, resulting in the following optimal operating conditions: 300 µL of acceptor solution volume

Table 2
Concentration (µg mL^{-1}) of the target fragrance allergens in cosmetic products.

	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12
PIN	0.51	124	0.14		4.00	0.48	630	1808		1.72		
LIM	5.51	1007		0.42	1540	1.52	2503	3246	0.20	54.6	0.16	
LIN	2.35	6638	10.6	4.66	842	2.08	6340	4376	1296	199	0.22	
M2O	1.82	11.7		2.24	19.2	1.78	3.34	6.24	5.91	2.66		
CT	37.0	450	4.92		590	40.2	2155	708	441	25.4		
GER	4.14	514	0.26		152	0.26	3.35	952	8.81	18.0	0.38	
CIT	0.60	43.5	0.93		5.02	17.1	5.14	0.28	37.5			
MEUG												
IMI	5.92	0.21			12.8	11.0		0.36	24.4	0.76		
LIL					460							
ACA	46.0					4.50	0.36	0.12	0.29		0.10	
HCA	21.8				4.20	6.30	0.58		16.9			
BB	8.44	16.9	1.42	7.94	3.70	7.78	4.46	0.32	3.97	1.84	0.63	
BS	54.6	2.42		27.8	11.4	8.23	15.0	4.16		2.20	0.58	
BC	2.10		1.58	1.56	2.00	2.16	1.52			0.16	0.98	

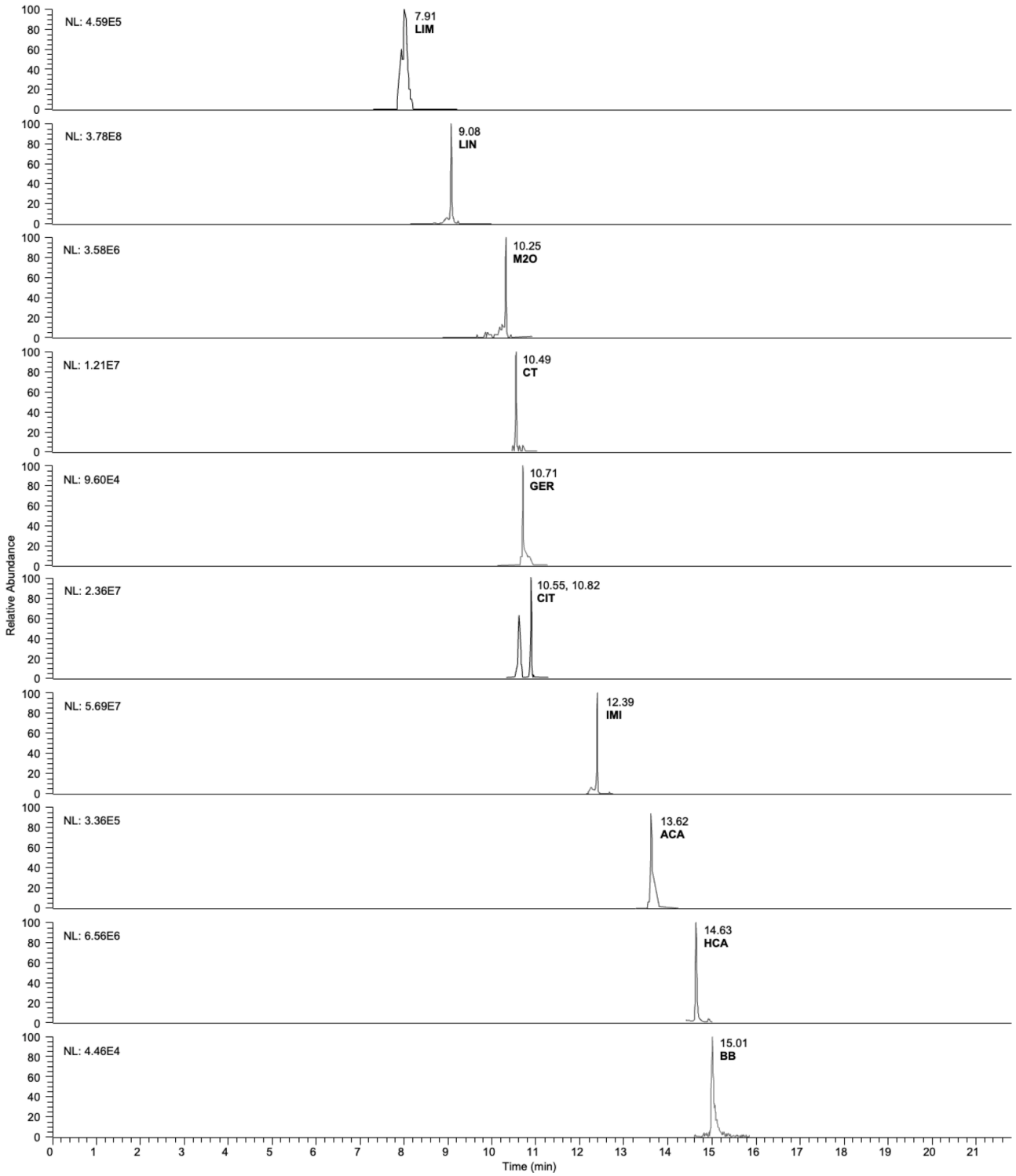

Fig. 6. SRM reconstructed GDME-GC–MS/MS chromatograms of a real cosmetic sample (S9).

consisting in ethyl acetate/acetonitrile 50/50 (*v/v*), a sample volume of 500 μL, a subsequent dilution of 1:20 with ultrapure water, no NaCl addition for salting-out effect, an extraction time of 15 min, and an extraction temperature of 50 °C.

Upon optimization, the methodology was validated, showing good trueness, precision, and linearity. Recovery studies were performed in two simulated cosmetic samples and two real cosmetic samples at two different concentration levels, yielding quantitative recoveries for all fragrance allergens. The analysis of twelve real cosmetic samples revealed that seven out of the twelve analyzed samples did not comply with Regulation EC No 1223/2009 since they did not list the individual names of fragrance allergens on their cosmetic labels despite their concentrations exceeded the regulatory limit of 10 μg mL^{-1} (0.001 %) in leave-on cosmetic products, and one sample even contained the prohibited compound LIL.

Therefore, the analytical methodology based on gas-diffusion microextraction followed by gas chromatography coupled to tandem mass spectrometry (GDME-GC-MS/MS) is an effective alternative for the

simultaneous determination of fragrance allergens in cosmetic products. The main characteristics of the optimized method are the compatibility of the acceptor solution with GC-MS/MS, avoiding additional steps during sample preparation, and its novelty, as this is the first application of GDME for the extraction of fragrance allergens from cosmetic products. Besides, this methodology represents a sustainable approach in accordance with the green analytical chemistry (GAC) and green sample preparation (GSP), as well as demonstrating a strong practicability according to the AGREEPrep and BAGI metrics, respectively.

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CRediT authorship contribution statement

Ana Castiñeira-Landeira: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Data curation, Conceptualization. **Angel Gomez-Feas:** Writing – original draft, Validation, Methodology, Investigation, Data curation. **Antonia M. Carro:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Thierry Dagnac:** Writing – review & editing, Funding acquisition. **Paulo J. Almeida:** Writing – review & editing, Conceptualization. **Maria Llompart:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing 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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sampre.2025.100187.

Data availability

Data will be made available on request.

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