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Original Article

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Gas Chromatography-Mass Spectrometry (GC-MS) was Used for The Determination of Cyclic Volatile Dimethylsiloxane (D4) in Personal Care Products

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Abstract

Background and Aims: Compounds of low-molecular-weight cyclic volatile dimethylsiloxane (cVMS) are widely used in personal care products due to their beneficial properties for consumer goods. However, the European Chemicals Agency (ECHA) has proposed restrictions on two cyclic siloxanes, octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5), in rinse-off Personal care products that are rinsed off and discharged into drains. The main concerns with D4 and D5 are their persistence and accumulation in the water bodies. The goal of this restriction is to reduce their discharge into surface waters. According to the ECHA, these substances should not be sold or used in concentrations of 0.1% or more by weight in rinse-off personal care products. Analysing cyclic siloxanes in these products is vital for understanding human exposure to these substances. ECHA mandates dependable analytical methods for manufacturers and government agencies to verify adherence to the restrictions. A simple, fast, and easily applicable extraction method using gas chromatography-mass spectrometry (GC-MS) for the precise measurement of D4 at around 0.1% by weight of the total formulation in personal care products (PCPs) is proposed in this article.

Methods: Detection was performed using a GC-MS instrument equipped with an electron impact (EI) ion source and operated using the selected ion monitoring (SIM) mode. The mass-to-charge ratios (m/z) monitored for D4 were 281.0, 282.0, and 283.0. The monitored mass-to-charge ratios (m/z) for D4 were 281.0, 282.0, and 283.0.

Results: The proposed method showed excellent linearity, with a coefficient of determination (r^2) exceeding 0.999. The limit of detection (LOD) and limit of quantification (LOQ) were 0.2320 µg/mL and 0.7735 µg/mL, respectively. The precision and accuracy of D4 were evaluated at concentrations of 3.0 µg/mL, 15.0 µg/mL, and 25.0 µg/mL. The coefficients of variation (CV) were 5.07%, 7.24%, and 4.95%, respectively, while the accuracy values were 103.17±0.16, 100.44±1.09, and 101.13±0.07, respectively, for these concentrations. These values are within the acceptable limit of ±15%. The results show that this GC-MS method meets the regulatory standards and demonstrates satisfactory accuracy and precision. Real samples, such as beard oil and hair conditioner, were successfully analysed using this method.

Conclusion: The developed GC-MS method provides a simple, accurate, and sensitive approach for detecting D4 in rinse-off personal care products. It meets regulatory requirements and is suitable for routine analysis, supporting efforts to control environmental exposure to cyclic siloxanes.

Keywords Gas Chromatography · Octamethylcyclotetrasiloxane (D4) · Personal Care Products · Analytical Method Validation

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INTRODUCTION

Octamethylcyclotetrasiloxane (D4, CAS 556-67-2) is widely used for various purposes. In the food industry (Feng et al., 2019), it functions as a food additive, while in the personal care industry, it is used as an ingredient in products such as shampoo, hair conditioner, beard oil, body lotion, and sunscreens that are commonly used daily (Feng et al., 2019; Brothers et al., 2017; Aspromonte et al., 2020). D4 is employed in silicone rubber products such as infant feeding teats, soother teats, straws, and seal rings. In addition, it functions as a cleaning agent, lubricant, and penetrating oil in various applications (Vaparrath et al., 2000).

These personal care products frequently result in people's exposure to D4, where it acts as an emollient and solvent. Its absorption into the body varies depending on the application area (Biesterbos et al., 2014). Restrictions on the allowable levels of D4 and decamethylcyclopentasiloxane (D5) in rinse-off products, including shampoos and conditioners, have recently been proposed by the European Chemicals Agency (ECHA), which are washed away during use. This restriction requires manufacturers and government agencies to use dependable analytical methods to ensure compliance with these restrictions.

The siloxane structure is a functional group formed by the condensation of two methyl-bonded silicon atoms and an oxygen atom (Feng et al., 2019). This monomer unit can be represented as [-Si(CH_3)2-O-]n, where the value of n indicates the number of silicon atoms in the compound, forming dimethylsiloxane compounds (Feng et al., 2019). Siloxanes are classified into two subclasses: cyclic, symbolised as D (e.g., D4 for octamethylcyclotetrasiloxane), which are cyclic condensations of siloxane monomers that may form polydimethylsiloxane oligomers (Brothers et al., 2017), and linear, symbolised as L (e.g., L6 for tetradecamethylhexasiloxane) (Feng et al., 2019; Brothers et al., 2017; Aspromonte et al. 2020).

In the nomenclature of siloxane compounds, the crucial factor is determining the number of repeat units the compound contains (Brothers et al., 2017). For example, hexamethylcyclotrisiloxane (CAS 541-05-9), octamethylcyclotetrasiloxane (CAS 556-67-2), decamethylcyclopentasiloxane (CAS 541-02-6), and dodecamethylcyclohexasiloxane (CAS 540-97-6) are commonly referred to as D3, D4, D5, and D6, respectively. Here, "D" represents the [-Si(CH3)2-O-] repeat unit, and the numeral following it indicates the number of these repeat units in the molecule. For instance, octamethylcyclotetrasiloxane (CAS 556-67-2) has four repeat units and is therefore named D4. Similarly, decamethylcyclopentasiloxane (CAS 541-02-6) has five repeat units and is abbreviated as D5. Dodecamethylcyclohexasiloxane (CAS 540-97-6) contains six repeat units; hence, it is called D6. In these instances, D denotes the repeat unit [-Si(CH3)2-O-]. D3, D4, D5, and D6 are known as Cyclic Volatile Methyl Siloxanes (cVMS) (Feng et al., 2019). The chemical structures of the cyclic siloxane compounds (D4, D5, and D6) are depicted in Figure 1.

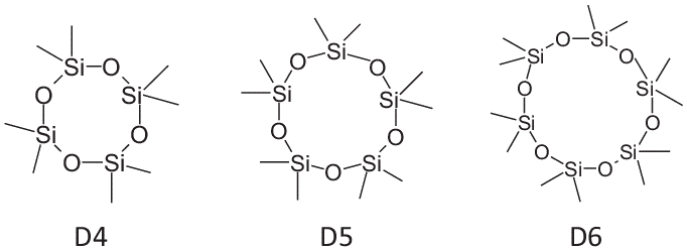


Figure 1. The molecular structures of cyclic D4, D5, and D6.

Octamethylcyclotetrasiloxane (D4) has a molecular weight of 296.61 and a specific gravity of 0.96. Its IUPAC name is 2,2,4,4,6,6,8,8-Octamethyl-1,3,5,7,2,4,6,8-Tetraoxatetrasilocane, and its molecular formula is $C_8H_{24}O_4Si_4$. Like other siloxane compounds, D4 is highly volatile and must be stored in tightly closed containers in dry, well-ventilated areas. Additionally, D4 is an odourless and colourless compound with a sufficient evaporation rate, low surface tension, and high compatibility with biological tissues and formulation ingredients (Vaparrath et.al 2000; Dekant et. al 2017; Franzen et.al. 2017).

Gas chromatography (GC) is a technique used to separate complex mixtures, especially organic compounds, by taking advantage of the different partitioning behaviours between a mobile gas phase and a stationary phase within the column (bin Abdullaha et.al. 2011).

Mass spectrometry provides an alternative approach for assays, using the selective capabilities of mass analysers to isolate specific analytes and quantify them through ion current measurements. Analytical chemistry routinely uses this method to quantify various small molecule analytes, including drug metabolites, protein degradation products, hormones, and pesticides, ensuring high throughput and excellent precision (Neşetoglu et al. 2020). Gas chromatography combined with mass spectrometry (GC-MS) is a unique technique for the quantification and identification of the chemical structures of organic compounds. Until now, only a small number of studies have documented the presence of D4 in personal care products (Lu et.al. 2011; Horii et.al. 2008; Wang et.al. 2009; Capela et.al. 2018).

This study presents the process of developing and validating a gas chromatography (GC) method combined with mass spectrometry for quantifying D4 in personal care products (PCPs). The developed method is simple, highly sensitive,

and offers high-throughput capabilities with consistent reproducibility.

MATERIALS AND METHODS

Chemicals and the Test Substance

Octamethylcyclotetrasiloxane (98% D4; CAS 556-67-2) was procured from Sigma-Aldrich (St. Louis, MO, United States). The manufacturer indicated that a beard oil (50mL) and a hair conditioner (200mL) were obtained from an online retailer; the beard oil and hair conditioner did not contain any D4. Ethanol (99.9% purity; CAS 64-17-5) provided by Isolab (Eschau, Germany) was used to dissolve D4 for the preparation of the standards.

Materials

An Ohaus Explorer analytical balance (0.1 mg increments) was used to measure the standards and sample weights. Screw-cap glass vials (1.5 mL) were obtained from Agilent Technologies. The extraction procedures for the beard oil and hair conditioner samples were carried out using sterile polypropylene Falcon tubes (Isolab, Eschau, Germany), a vortex shaker operated continuously at 2500 rpm (MS1 Minishaker, IKA, Staufen, Germany), and a centrifuge at 3500 rpm with a relative centrifugal force of 2520g (3-16 KL, Sigma, Germany). The preparation of standards involved using Isolab volumetric flasks, Eppendorf adjustable pipettes, and microliter syringes.

Gas Chromatography Method and Mass Spectrometry Conditions

A 5% phenyl dimethylsiloxane capillary column (HP-5 MS, 30 m × 0.25 mm inner diameter × 0.25 µm film thickness) was used for separation in an Agilent 7890B gas chromatograph. Detection was conducted using an Agilent 5977A mass spectrometer equipped with an electron impact (EI) ion source operating in the selected ion monitoring (SIM) mode. Helium of 5.0 grade was used as the carrier gas at a flow rate of 1.0 mL/min. The solvent delay time was set to 3.0 min. The injector port operated at a split ratio of 50:1, with the inlet temperature, auxiliary-2 temperature, MS source temperature, and MS quad temperatures maintained at 180°C, 180°C, 230°C, and 150°C, respectively. The column temperature was ramped from 50°C to 150°C at a rate of 10°C per minute, then held at 150°C for 2.0 min. Mass spectra were generated using an electron impact at 70 eV across a scanning range of 50–500 m/z.

D4 was specifically detected using the selected ion monitoring (SIM) mode with ions monitored at 281.0, 282.0, and 283.0 m/z, rather than employing the scan mode. Under these experimental conditions, the retention time for D4 was approximately 5.29 ± 0.02 minutes. Chromatograms were collected and integrated using the Mass Hunter GC software (Agilent Technologies), and subsequent data analysis was performed using MS Excel 2016 (Microsoft, Redmond, WA, USA).

Preparation of Calibration Standards and Samples for Quality Control

Calibration standard solutions were prepared as follows: 50 mg D4 was weighed and made up to volume with ethanol in a 5.0 mL volumetric flask to prepare a stock solution at a concentration of 10 mg/mL. Then, a dilute solution with a concentration of 500 µg/mL was prepared from this solution by appropriate dilution. Calibration standard solutions (1.0, 5.0, 10.0, 20.0, 50.0 µg/mL) and quality control solutions (3.0, 15.0, 25.0 µg) were prepared by making appropriate dilutions from the prepared dilute solution. /mL) was prepared in ethanol. The solutions were found to be stable when stored in the refrigerator for at least 7 days. The regression equation was calculated using the least squares method.

Sample Preparation and Extraction Procedure

A 500.0 mg personal care product sample was weighed into a 10.0 mL capped polypropylene tube, and 5.0 mL of ethanol was added and shaken gently. The tubes were tightly capped and the resulting solution was first vortexed at 2500 rpm for 5.0 min and then centrifuged at 3500 rpm for 5 min at 25 °C. Of the resulting phases, 2.0 mL of the supernatant ethanol phase was filtered using a 0.22 µm syringe filter and then transferred to a GC autosampler vial.

Method Validation

For the GC-MS analysis of the D4, the method was developed and validated with the standard of the relevant substances. In the validation, the study system suitability, selectivity, carry-over effect, linearity, precision and accuracy, limit of detection (LOD) and limit of quantification (LOQ) parameters were examined.

System Suitability

System suitability tests are essential components of both the gas chromatography (GC) and liquid chromatography (LC) methods. These tests are conducted to ensure that the chromatographic system is suitable and met the requirements for the intended analysis. The tests are designed on the principle that the equipment, electronics, analytical procedures, and samples analysed form a unified system that can be evaluated comprehensively. The resolution (RS) is influenced by the number of theoretical plates (N), which represents the

efficiency of the chromatographic separation, and k' (capacity factor).

Selectivity and the Carry-Over Effect

In the solvent chromatogram, no peak at the retention time of the active substance should be observed. Impurity peaks should be separated from the active substance. Carry-over in the solvent injection should not exceed 1% by area of known impurities.

Linearity

Linearity demonstrates the accurate measurement of the concentrations of the standard samples. For this purpose, samples prepared at 5 concentration levels (1.0, 5.0, 10.0, 20.0, 50.0 µg/mL). The calibration curves were generated using matrix-matched calibration standard solutions. This involved plotting the peak area corresponding to the quantitative ion of each analyte against their respective concentrations. Throughout the validation process, the determination coefficients (r^2) consistently exceeded 0.99.

Accuracy and Precision

The accuracy was evaluated using samples containing known quantities of the analyte, which served as quality control samples (QC samples). The QC samples were prepared separately from the calibration standards, with the analyte being spiked independently using separately prepared stock solutions. The accuracy was assessed by analysing a minimum of 6 samples per concentration level across at least 3 different concentration levels, ensuring coverage across the range of the calibration curve. Precision was evaluated for the low, medium, and high-quality control (QC) samples within a single analytical run, as well as between different runs. This assessment used the same runs and data used for demonstrating accuracy. Precision was expressed as percentage of coefficient of variation (CV%) () for 18 determinations. Intra-assay precision and accuracy of D4 were determined at concentrations of 3.0 µg/mL, 15.0 µg/mL, and 25.0 µg/mL, based on six replicates analysed within the same analytical run. Inter-assay precision and accuracy were calculated based on replicates analysed across three separate analytical runs. The %CV of the peak areas of each 6 consecutive injections of D4 (octamethylcyclotetrasiloxane) should not be more than 10%.

Limit of Detection (LOD)

For the limit of detection (LOD); signal-to-noise (S/N) ratio is considered 3:1.

LOD = 3 σ/S

σ: Standard deviation of the intercept

S: Slope

By calculating the LOD value statistically, it was found to be 0.2320 µg/mL.

Limit of Quantification (LOQ)

Limit of quantification (LOQ): Signal-to-noise ratio; for the limit of quantification (S/N) ratio should be greater than 10.

It can also be calculated from the slope of the calibration curve.

LOQ = 10 x σ /S

σ: Standard deviation of the intercept

S: Slope.

By calculating the LOQ value statistically, it was found to be 0.7735 µg/mL. The first level of the limit of the quantitation calibration curve was used as 1.0 µg/mL.

RESULTS AND DISCUSSION

A GC-MS/SIM method was established to identify and quantify D4 in the samples analysed in this study. The concentrations and compositions of the siloxanes can vary depending on the products and manufacturing practices. Three specific ions were chosen for D4 based on their full mass scan spectra. One ion was designated as the target ion for quantification, while the other two ions were used as the qualifier ions. Identification was accomplished by using the three ions and their relative ion ratios, in conjunction with the GC retention times specified in Table 1. A commercially available beard oil (50mL) and hair conditioner (200mL) were sampled and analysed with this method.

Table 1. Identification and quantification of fragments using GC-MS/SIM.

Quantitative and qualitative ion fragments m/z				
Analyte	**Ion 1**	**Ion 2**	**Ion 3**	**Retention Time[a]**
D4	281.0	282.0	283.0	5.290 ± 0.020

Note: [a]Retantion time ± SD (n=6)

According to the harmonised classification and labelling (ATP15) approved by the European Union, D4 is classified as very toxic to aquatic life with long-lasting effects and is also suspected of causing harm to fertility. It is important to highlight that D4 is classified as a reproductive toxicant, falling under the category 3 according to the ECB 2006 classification. The NOAEL (No Observed Adverse Effect Level) of 150 ppm for systemic toxicity used in this risk assessment also encompasses reproductive toxicity effects, with a specific NOAEL of 300 ppm as per the OECD 17 guidelines. The aim of this publication is to propose a GC-MS method for the straightforward and dependable detection of D4 in personal care products,

achieving detection levels down to approximately 0.1%. The analysis was conducted in the mass spectrometer using electron impact ionisation (EI). The method's reliability was evaluated based on its linearity, selectivity, limit of detection, limit of quantification, precision, and accuracy.

The selectivity and carry-over effects were carried out using a blank solvent (ethanol) and analysed using the proposed method. The batch did not show any interferences at the retention time of D4. Representative chromatograms of the blank and LOQ samples are given in Figure 2 and Figure 3.

The calibration curve regression (r^2) for D4 was found to be 0.9999. The coefficient of determination (r^2) for validation was greater than 0.99, which provides the requirements of the analytical method validation guideline. The calibration curve's equation is y = 378946x + 54536 (Figure 4).

The linear concentration range of D4 was found to be accurate and precise from 1.0 to 50.0 µg/mL. By calculating the LOD and LOQ values statistically; the results were found as 0.2320 µg/mL and 0.7735 µg/mL, respectively. The first level of the limit of the quantitation calibration curve was used as 1.0 µg/mL.

The accuracy and precision of D4 were calculated at 3.0 µg/mL, 15.0 µg/mL and 25.0 µg/mL levels for the six replicates. The coefficients of variation were 5.07%, 7.24% and 4.95%, re-

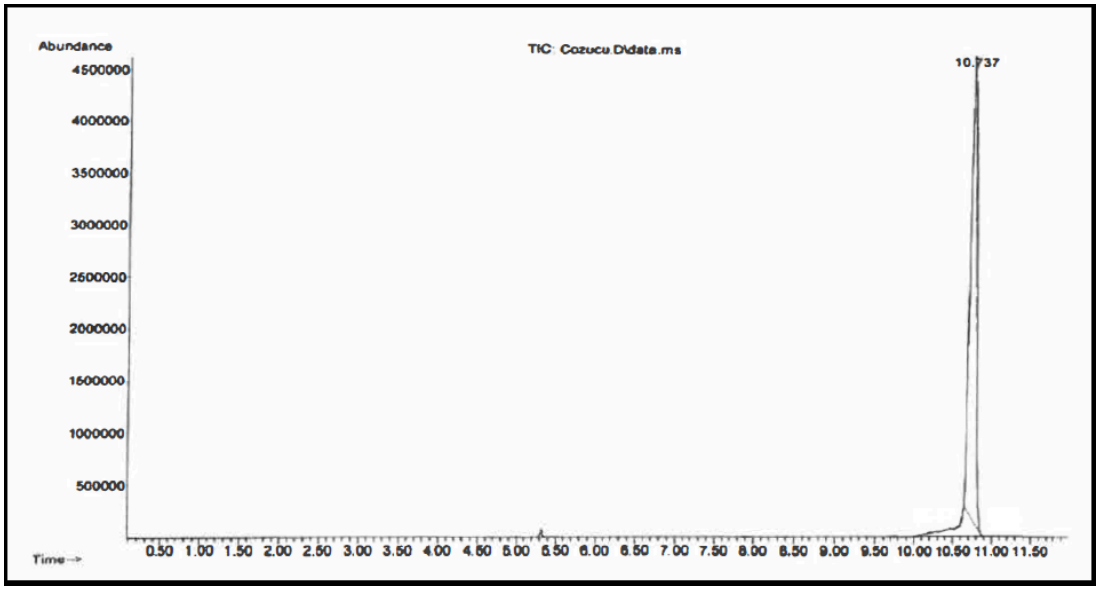


Figure 2. Chromatogram of blank sample (Ethanol).

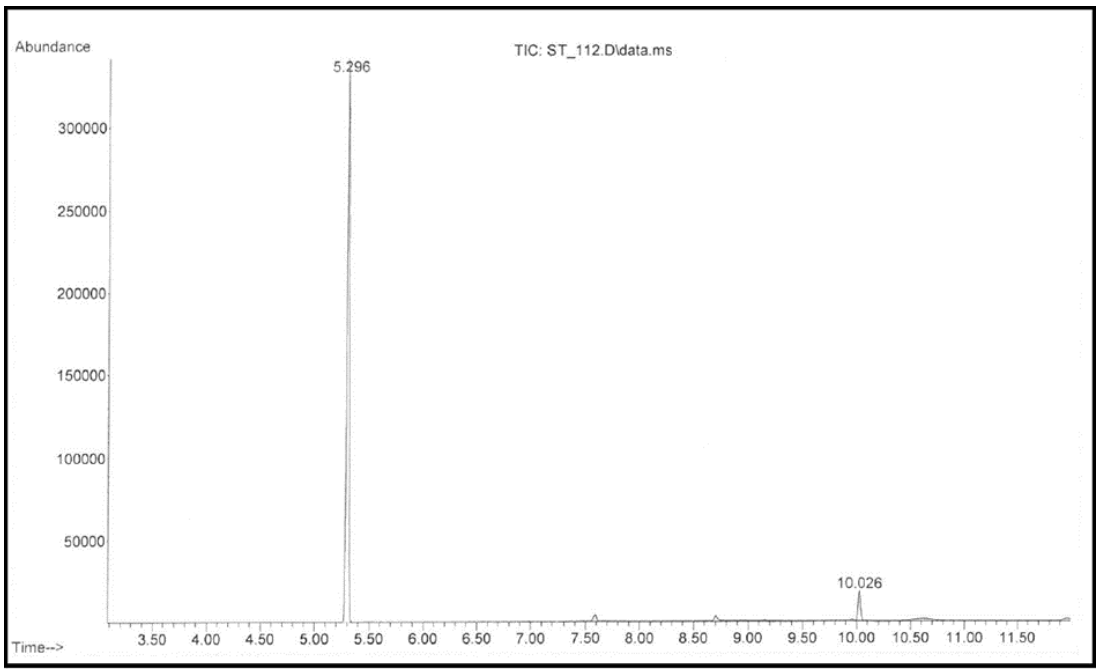


Figure 3. Chromatogram of standard sample (1,0 µg/mL)

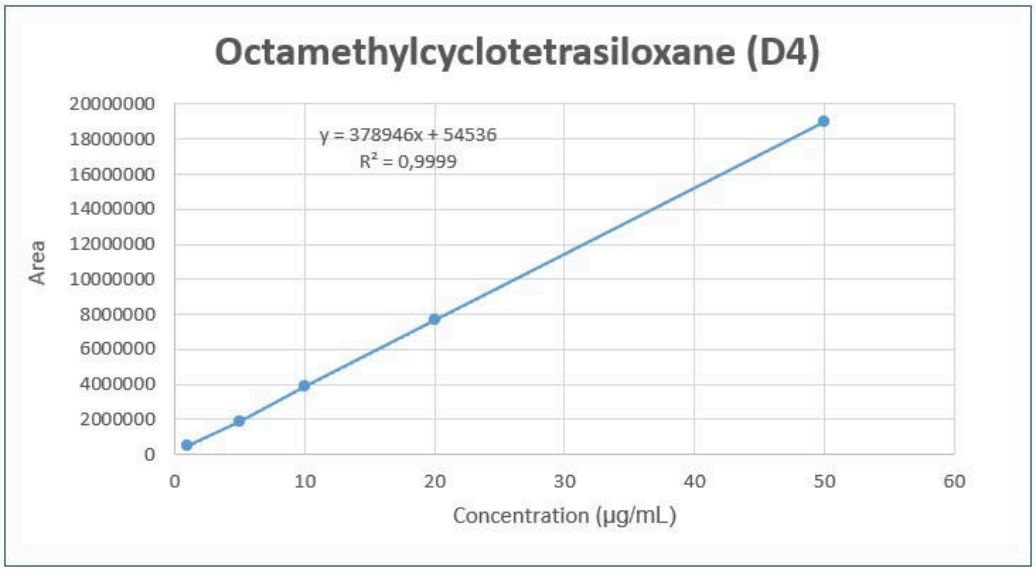


Figure 4. Octamethylsiloxane (D4) area-concentration sample calibration curve

spectively, whereas the accuracies were 103.17±0.16, 100.44±1.09 and 101.13±0.07, respectively (Table 2). Values are within the acceptance limit of ±15%. The results suggest that the method demonstrates good precision and accuracy.

Table 2. Accuracy and precision data on QC samples

Intra-day and inter-day accuracy and precision calculations of validation (n=18)				
Analyte	Cons. (µg/mL)	Calculated Cons. (µg/mL) ± SD	% Error	CV (%)
D4 Samples Validation 1-3	3,0	3.095±0,157	103.170	5.072
	15.0	15.066±1,090	100.439	7.235
	25.0	25.282±0,072	101.126	4.946

The system suitability parameters were determined as per the guideline specifications. The theoretical plate number (N) was calculated as 7240, the capacity factor (k') was 9.8, and the tailing factor (T) for D4 was 1.1. Detailed parameters are given in Table 3.

Table 3. System suitability testing results

	Retention Time[a]	**Response**	**Peak Width**	**Plate Number**
D4_1	5.296	10692195	0.150	6894
D4_2	5.296	10796084	0.145	7415
D4_3	5.296	10767527	0.145	7413
D4_4	5.296	10703911	0.145	7415
D4_5	5.296	10417873	0.150	6894
D4_6	5.296	10524835	0.145	7412
Mean	**5.296**	**10650404**	**0.146**	**7240.500**
SD	**0.000**	**147910**	**0.002**	**268.400**
%RSD	**0.000**	**1.380**	**1.760**	**3.700**

The prepared beard oil and hair conditioner samples were analysed 3 times. By taking the average of the analyzes, the amount in the samples was found to be 123.33 µg/mL and 23.40 µg/mL (ppm), respectively, and in between the acceptable limit.

CONCLUSION

A novel, straightforward, cost-effective, high-throughput, and highly sensitive GC-MS method was successfully developed and validated for quantifying D4 in personal care products (PCPs). The method included a straightforward single-step extraction process for preparing the PCP samples and a short analysis runtime (12.0 minutes). The proposed method could be considered practical and reliable for manufacturers and government agencies to use in ensuring compliance with the restrictions on D4.

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