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Short communication

Headspace-SPME-GC/MS as a simple cleanup tool for sensitive 2,6-diisopropylphenol analysis from lipid emulsions and adaptable to other matrices

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ABSTRACT

Due to increased regulatory requirements, the interaction of active pharmaceutical ingredients with various surfaces and solutions during production and storage is gaining interest in the pharmaceutical research field, in particular with respect to development of new formulations, new packaging material and the evaluation of cleaning processes. Experimental adsorption/absorption studies as well as the study of cleaning processes require sophisticated analytical methods with high sensitivity for the drug of interest. In the case of 2,6-diisopropylphenol – a small lipophilic drug which is typically formulated as lipid emulsion for intravenous injection – a highly sensitive method in the concentration range of μg/l suitable to be applied to a variety of different sample matrices including lipid emulsions is needed.

We hereby present a headspace-solid phase microextraction (HS-SPME) approach as a simple cleanup procedure for sensitive 2,6-diisopropylphenol quantification from diverse matrices choosing a lipid emulsion as the most challenging matrix with regard to complexity.

By combining the simple and straight forward HS-SPME sample pretreatment with an optimized GC–MS quantification method a robust and sensitive method for 2,6-diisopropylphenol was developed. This method shows excellent sensitivity in the low μg/l concentration range (5–200 μg/l), good accuracy (94.8–98.8%) and precision (intraday-precision 0.1–9.2%, inter-day precision 2.0–7.7%). The method can be easily adapted to other, less complex, matrices such as water or swab extracts. Hence, the presented method holds the potential to serve as a single and simple analytical procedure for 2,6-diisopropylphenol analysis in various types of samples such as required in, e.g. adsorption/absorption studies which typically deal with a variety of different surfaces (steel, plastic, glass, etc.) and solutions/matrices including lipid emulsions.

1. Introduction

During production and storage of pharmaceutical products as well as during their final clinical use, they are in contact with various surfaces which give raise to potential interact with either the excipients, the Active Pharmaceutical Ingredients (API) or both. These interaction may occur on the one hand with any surface in direct contact with the API in the manufacturing plant but on the other hand may also take place in any primary packaging container such as disposable single use syringes, prefilled syringes, cartridges, vials, plastic ampoules, flexible bags, stopper containing systems or currently newly developed innovative infusion devices or in the final clinical use like medical devices, infusion pumps and infusion tubes.

As a consequence, the study of API interaction with various solutions and surfaces is gaining interest in the pharmaceutical research field. Dennis Jenke provides an excellent review on the compatibility of plastic materials with pharmaceutical products, with specific emphasis on the safety aspects associated with extractables and leachables related to such plastic materials [1]. Reckzügel [2] presents an up-to-date overview on the regulatory, technical, and strategic requirements for polymers used for pharmaceutical packaging and medical devices. Moreover, the regulatory requirements of authorities (e.g. FDA) on manufacturing of APIs are increasing continuously during the last years which accounts for higher standards for cleaning procedures for production plants in contact with the API. This reflects in the relevant guidelines [3–5] to perform cleaning of equipment according to validated cleaning procedures especially when the manufacturing equipment is used to produce different products (multi-product equipment) [6].

To prove necessary cleaning efficiency in regard of the API, cleaning validation is required by the authorities. Cleaning vali-

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dations have to establish documented evidence that the applied cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size [7] which typically results in low acceptance criteria for the API of interest. As a consequence, to obtain reproducible and reliable data for cleaning validations highly sensitive and sophisticated analytical procedures and interaction studies according to the decision tree of the EMEA Guideline have to be developed and used [8].

Our model API of interest, 2,6-diisopropylphenol (DIP) is a lipophilic substance having a log *P* of 4.15 [9] that induces hypnosis and therefore serves as anesthetic and sedative drug. Because of its poor solubility in water, it is typically prepared in the form of an oil-in-water lipid emulsion using an oily component and an emulsifier. Hence, analytical procedures for sensitive DIP analysis in various matrices including lipid emulsions are required for the above stated reasons.

Detection of a lipophilic drug from a complex lipophilic matrix such as lipid emulsions, however, is an analytical challenge due to the need of an efficient sample-cleanup procedure. No publications to date have focused on DIP detection in the μg/l concentration range in lipid emulsion so far. Typically, 2,6-diisopropylphenol (DIP) is analyzed via HPLC–UV methods for the purpose of evaluation of drug content in lipid emulsions ranging at g/l concentrations. A variety of analytical methods deal with DIP analysis in the μg/l concentration range, however in biological matrices such as blood, plasma, serum, cerebrospinal fluid [10], bronchoalveolar lavage BAL [11] or breath [12–14] including HPLC combined with UV [15–17], fluorescence [11,18–20], or mass spectrometry detection [21–23], HS-SPME combined with GC–MS [13], thermodesorption combined with GC–MS [14] or GC/MS [24–26]; [27].

Typically, time-consuming sample preparation steps such as liquid–liquid extraction (LLE) or solid-phase extraction (SPE) are needed for matrix removal prior to analysis. Both cleanup procedures are not the ideal choice for DIP cleanup from lipid emulsions due the similarity of the analyte (DIP) and its matrix (lipid emulsion) with respect to hydrophobicity. However due to the semi-volatility of DIP [28], headspace-solid phase microextraction (HS-SPME) offers a promising alternative, being an easy and rapid sample preparation method, in particular for analysis of volatile compounds from complex matrices such as food or blood [29,30]. Moreover, HS-SPME is easily combined with GC/MS detection, can be automated via adequate autosamplers and is cost–effective due to organic solvent free analysis. HS-SPME was recently applied for sensitive 2,6-diisopropylphenol detection in breath [12,13] and blood samples [13].

We hereby present a headspace-solid phase microextraction (HS-SPME) approach as a simple cleanup procedure for sensitive 2,6-diisopropylphenol quantification from diverse matrices choosing a lipid emulsion as the most challenging matrix with regard to complexity.

By combining the simple and straight forward HS-SPME sample pretreatment with an optimized GC–MS quantification method, a robust and sensitive method for 2,6-diisopropylphenol was developed. This method shows excellent sensitivity in the low μg/l concentration range, comparable to previously presented procedures for 2,6-diisopropylphenol in biological matrices. The method can be easily adapted to other, less complex, matrices such as water or swab extracts. Hence, the presented method holds the potential to serve as a single and simple analytical procedure for 2,6-diisopropylphenol analysis in various types of samples such as required in, e.g. adsorption/absorption studies which typically deal with a variety of different surfaces (steel, plastic, glass, etc.) and solutions/matrices including lipid emulsions.

2. Materials and methods

2.1. Chemicals and reagents

2,6-Diisopropylphenol (DIP) was obtained from Cilag AG (Schaffhausen, Switzerland). The deuterated internal standard [$^2H_{17}$]-2,6-diisopropylphenol ([$^2H_{17}$]-DIP) was purchased from Alsachim (Illkirch Graffenstaden, France). A typical 20% lipid emulsion (Lipofundin) was from B. Braun (Melsungen, Germany), 1% DIP in 10% lipid emulsion was obtained from Fresenius Kabi Austria, Graz. Methanol HPLC gradient grade was purchased from Sigma–Aldrich, Steinheim, Germany. 2-Propanol seccosolv® was obtained from Merck (Darmstadt, Germany), glycerol-formal 99.7% was from Gabriel Performance Products (Ashtabula, OH, USA). Water was Milli Q grade (Millipore, Billerica, USA).

2.2. Preparation of calibration standards and QC samples

Stock solutions of 2,6-diisopropylphenol (c = 10 g/l) and [$^2H_{17}$]-2,6-diisopropylphenol (c = 100 mg/l) were prepared in methanol and stored at −20 °C.

Calibration solutions for lipid emulsion and water matrix were generated at concentrations of 0, 2, 5, 10, 20, 100 and 200 μg/l by dilution of the stock solution in the respective matrix (Milli Q water or Lipofundin for the matrix lipid emulsion).

QC samples in lipid emulsion matrix were prepared by diluting a 10% lipid emulsion with 1% DIP to concentrations of 2000, 150, and 10 μg/l with 20% lipid emulsion. The QC with 2000 μg/l was diluted 1:20 with lipid emulsion prior to HS-SPME analysis and therefore served as a test for dilution steps in order to broaden the analytical range of the method to higher concentrations, if necessary. Prior to HS-SPME analysis of lipid emulsion or water samples, 50 μl of internal standard (2000 μg/l [$^2H_{17}$]-DIP) was added to 5 ml of either calibration solutions or QC samples.

For swab extracts, calibration solutions corresponding to 0, 4, 10, 20, 40 and 200 μg/l were prepared in 2-propanol. 500 μl of these solutions and 100 μl of internal standard (200 μg/l [$^2H_{17}$]-DIP) were pipetted each on a swab (Texwipe, Kernersville, USA). The swab was extracted in a 50:50 (v:v) % glycerol formal:water solution using ultrasonic for 10 min. 1 ml of the extract was diluted with 1:4 with water and analyzed via HS-SPME-GC/MS.

2.3. HS-SPME conditions

For headspace-solid phase microextraction, a DVB/CAR/PDMS fiber (SUPELCO, Bellefonte, USA) was used. Sample vials were incubated at 80 °C for 10 min prior to piercing through the septum of the headspace vial. Adsorption time was 30 min at 80 °C for lipid emulsion samples and 15 min for water samples and swab extracts. The fiber was withdrawn and transferred into the injection port of the GC. Desorption time was set to 1 min while the temperature of the injection port was set at 250 °C. After the chromatographic run, the fiber was removed from the injection port for a further HS-SPME cycle.

2.4. GC/MS conditions

GC/MS analysis was performed with a Thermoquest TRACE GC–MS. A (5%-phenyl)-methylpolysiloxane fused-silica capillary column (30 m, 0.25 mm ID, 0.25 μm film thickness, Agilent, Santa Clara, USA) with helium as carrier gas was used.

Starting temperature of the GC-program was set to 110 °C. Temperature was held for 1 min and was then raised to 170 °C at a rate of 10 °C/min, then again raised to 300 °C at a rate of 65 °C/min and held for 1 min. The analysis was performed with constant flow rate of 1 ml/min. Splitless time was 1.0 min. Source temperature was set

to 200 °C. Electron ionization (70 eV) was applied in the SIM mode with a dwell time of 0.1 min. Detection of 2,6-diisopropylphenol (DIP) was carried out at 163 and 178, [$^2H_{17}$]-DIP at 177 and 195 *m*/*z*.

2.5. Data analysis

Calibration of 2,6-diisopropylphenol was performed for each day via single injection of each calibration solution, followed by establishing a linear regression function of the DIP/[$^2H_{17}$]-DIP peak area ratio versus DIP concentration relationship. Peak area ratios of target analytes and internal standards were calculated by Xcalibur software. The detection limit (LoD) and limit of quantification (LLoQ) for lipid emulsion matrix was estimated from the mean calibration curve ($n = 6$) with mean + 3 × SD of mean blank response for LoD and mean+10 × SD for LLoQ.

3. Results and discussion

3.1. HS-SPME

It is well known that the extraction process in HS-SPME is influenced by various parameters such as the volatility of the analyte, the type of matrix (viscosity, lipophilicity, diffusion constant of the analyte in the matrix) and the extraction conditions (incubation time, extraction time, temperature, fiber chemistry) [29,31–33]. Miekisch et al. [13] successfully performed extraction of 2,6-diisopropylphenol from blood samples at 40 °C with 10 min incubation and 5 min adsorption time using a CAR/PDMS/DVB-fiber. For this reason, a brief optimization of HS-SPME parameters like temperature, incubation and extraction time was carried out with the same type of fiber. In the case of lipid emulsions, a highly lipophilic matrix compared to blood, a brief optimization showed a relative DIP peak area increase of around 27 when raising the incubation and extraction temperature from 40 °C to 80 °C (with 10 min incubation time and 5 min adsorption time; data not shown) indicating that lipid emulsion is a better solvent for 2,6-diisopropylphenol than blood. Longer adsorption times at 80 °C resulted in a further improvement of sensitivity (see Fig. 1) while rising the incubation time prior to adsorption did not have any

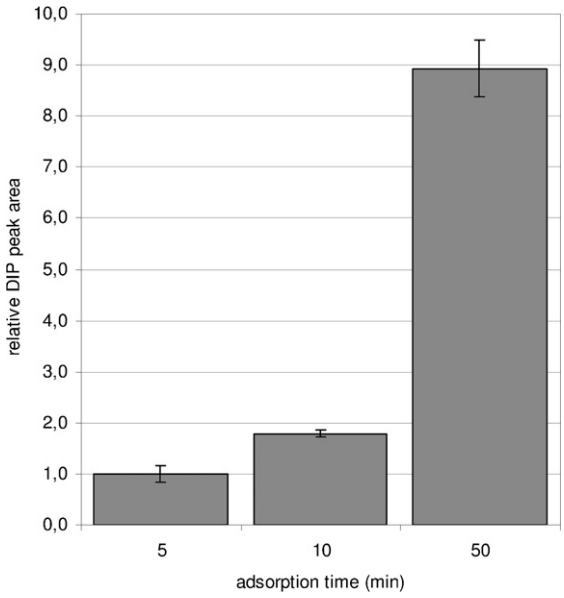

Fig. 1. Effect of adsorption time on sensitivity of DIP detection in lipid emulsion. Incubation and adsorption temperature: 80 °C, incubation time 10 min DIP peak area for 5 min adsorption time served as the reference.

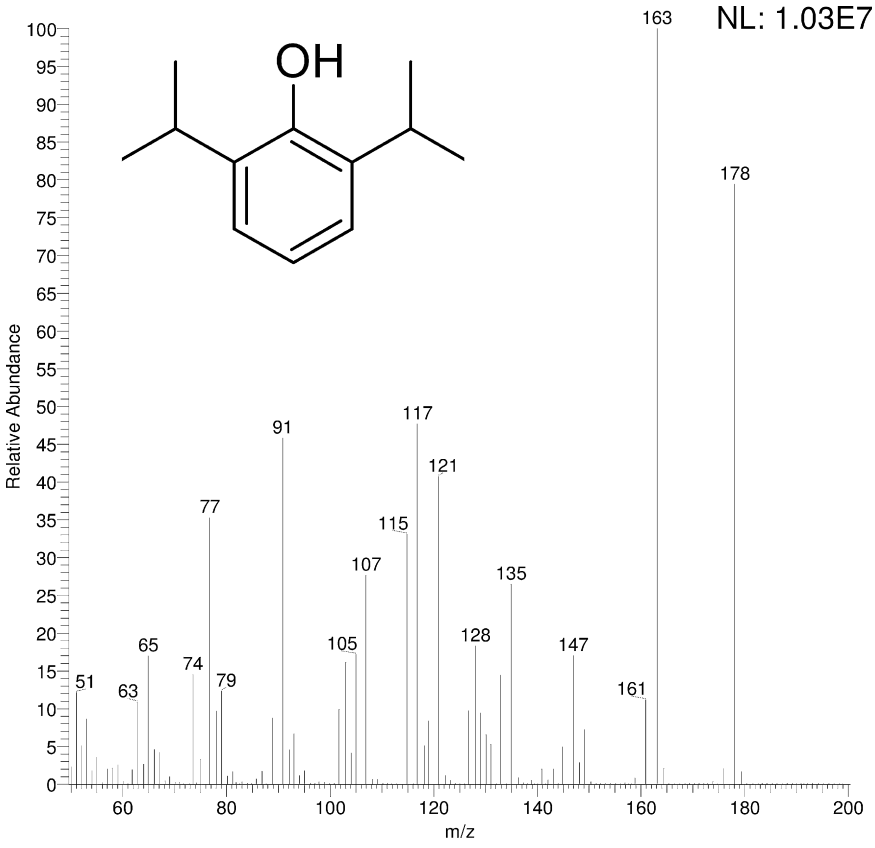

Fig. 2. Structure and EI full spectrum of 2,6-diisopropylphenol.

significant effect (data not shown). Because an adsorption time of 50 min would significantly increase the overall analysis time, 30 min was finally chosen as a compromise between sensitivity and analysis time.

Since variations in matrix composition and HS-SPME conditions can have different effects for different substances [31], the ideal internal standard should have a structure very similar to that of the analyte, hence an isotopically labelled standard [$^2H_{17}$]-DIP was used in order to provide optimum robustness for this quantitative headspace SPME (HS-SPME) method.

3.2. GC/MS analysis

The EI spectrum of DIP shows two major peaks at *m*/*z* 178 (molecular ion) and *m*/*z* 163 (major fragment due to the loss of a methyl group) (see Fig. 2). The corresponding masses for the isotopically labelled internal standard [$^2H_{17}$]-DIP are *m*/*z* 195 and *m*/*z* 177, respectively. DIP was detected and quantified using selected-ion monitoring of *m*/*z* 163 while the internal standard [$^2H_{17}$]-DIP was monitored at *m*/*z* 195 because *m*/*z* 177 corresponding to the same major fragment was prone to interferences at higher concentrations of the DIP (see Fig. 3).

3.3. Linear range

The linear calibration equation was (mean ± SD, $n = 6$): $y = 0.0557\ (0.0459) + 0.051\ (0.0041)x$ with an average coefficient of determination $R^2 = 0.9991$ (0.0014). A typical calibration curve from 5 to 200 μg/l was $y = 0.0759 + 0.0470x$ with a coefficient of determination of 0.9999.

3.4. LoD and LLoQ

LoD and LLoQ was calculated from the calibration curve as mean blank response + 3SD (LoD) and mean blank response + 10SD (LLoQ) to be 3.3 μg/l and 9.4 μg/l respectively. Fig. 4 shows that even 2 μg/l DIP in lipid emulsion can be well distinguished from blank samples. The estimated LLoQ was well supported with excellent accuracy and precision data at a level of 10 μg/l (see Table 1).

3.5. Accuracy and precision

Accuracy and precision data for DIP detection in lipid emulsion samples is summarized in Table 1. QC samples at three different concentrations (10, 150 and 2000 μg/l) were prepared from a DIP pharmaceutical formulation (1%DIP in 10% lipid emulsion). Each QC sample, freshly prepared on each day of analysis, was analyzed two times each on six different days. Intraday-precision ranged from 0.1 to 9.2%, inter-day precision was 2.0 to 7.7%. Accuracy was 94.8 to 98.8%.

3.6. Potentials for adaption of HS-SPME conditions for further matrices

The method development for DIP analysis via HS-SPME GC/MS primarily focused on the most challenging matrix such as lipid emulsions representing a lipophilic, non-volatile matrix which shows excellent solubility for DIP. Hence, adaption of typical HS-SPME parameters such as incubation time, adsorption time or temperature is easily achieved for simpler matrices such as, e.g. water or swab extracts containing organic solvents. A typical linear calibration curve from 2 to 200 μg/l DIP in water using an adapted HS-SPME setup was $y = -0.0115 + 0.0661x$ with $R^2 = 0.9998$, a spiked sample with 2 μg/l DIP in water is well detectable (Fig. 4).

Table 1
Accuracy and precision (intraday, inter-day) data for lipid emulsion matrix from six different days ($n = 12$).

Nominal conc. [μg/l]	Measured conc (%RSD) [μg/l] ([%])						Average measured conc. [μg/l]	Accuracy [%]	Average intra-day precision [%RSD]	Inter-day precision [%RSD]
	d1	d2	d3	d4	d5	d6				
10	9.1 (5.9)	9.4 (0.3)	9.1 (0.1)	9.2 (1.2)	10.6 (9.2)	10.6 (0.4)	9.7	96.8	2.8	7.7
150	146.5 (1.9)	149.7 (1.4)	148.5 (1.4)	144.3 (4.0)	152.9 (4.7)	147.4 (2.2)	148.2	98.8	2.6	2.0
2000	1873.0 (0.6)	1893.0 (0.0)	1910.3 (5.7)	1834.2 (2.4)	1925.0 (3.4)	1936.2 (3.1)	1895.3	94.8	2.5	2.0

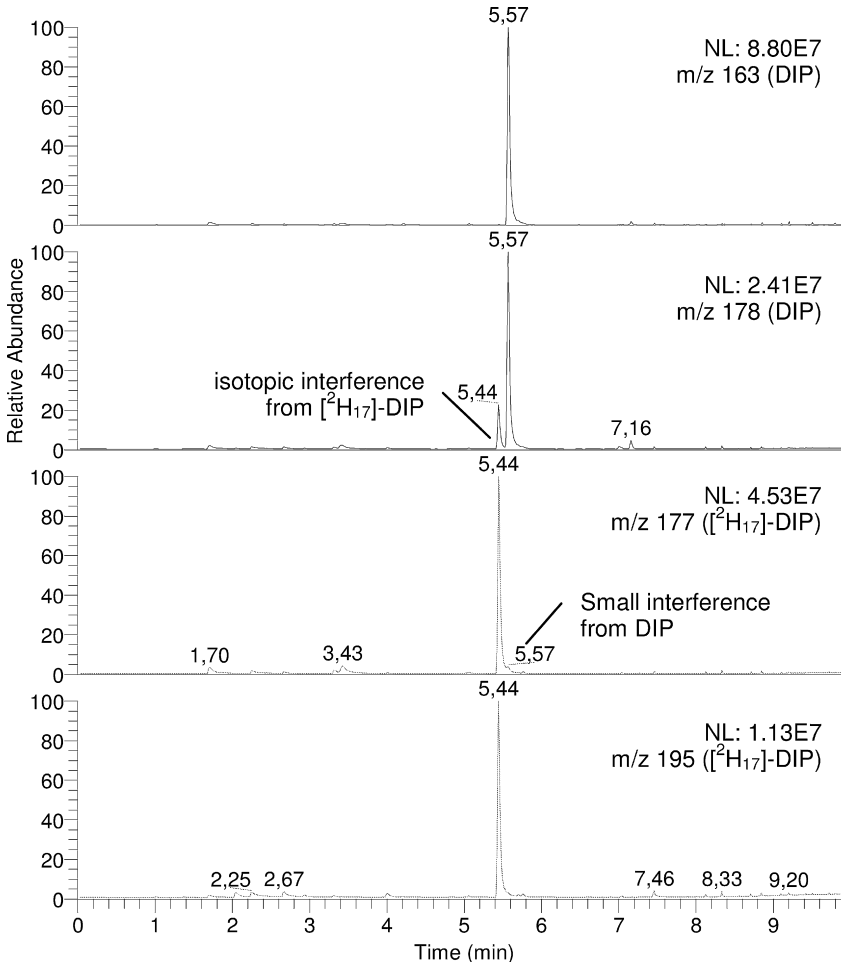

Fig. 3. SIM chromatogram of 200 μg/l DIP with 19.8 μg/l [$^2H_{17}$]-DIP from lipid emulsion.

With respect to organic solvents, a mixture of water with glycerol formal was chosen for DIP extraction from swabs because glycerol formal [CAS 5464-28-8] is a low toxic water miscible solvent with a high boiling point (>190 °C) and therefore potentially suitable for HS-SPME with respect to swelling of the SPME fiber coating. As a short proof of concept, swabs were spiked with DIP amounts ranging from 2 ng up to 100 ng, subsequently extracted and analyzed via HS-SPME-GC/MS resulting in a linear calibration curve with $y = 0.0329 + 0.0468x$ ($R^2 = 1.0000$). The sensitivity of this method is underlined by the peak area corresponding to 2 ng DIP on swabs which was more than three times higher than a small detected blank peak (Fig. 4). In conclusion, the presented HS-SPME-GC/MS shows excellent sensitivity for various different matrices.

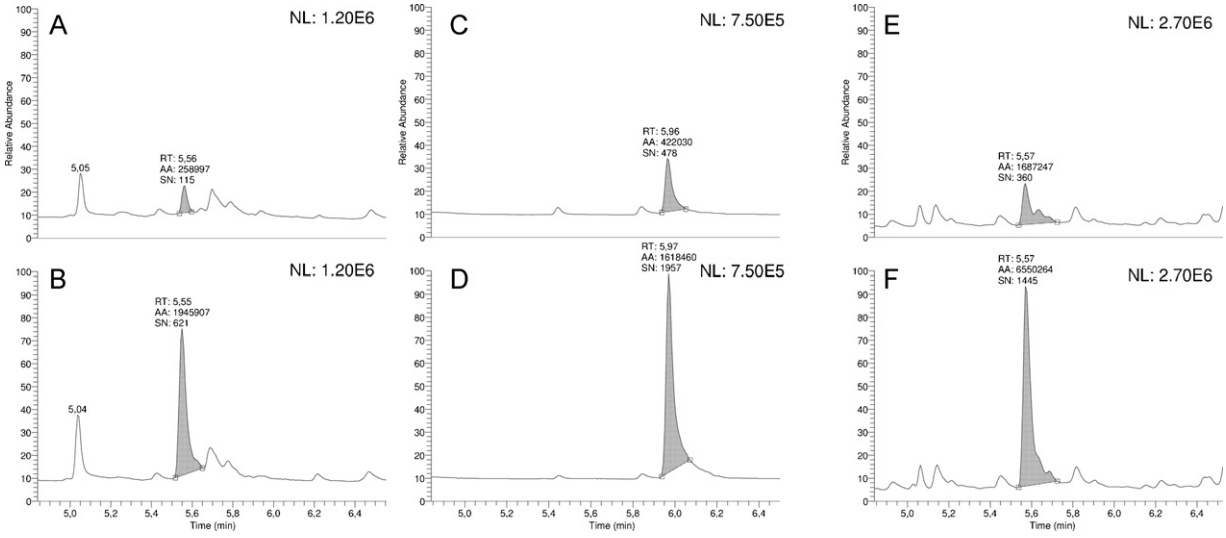

Fig. 4. SIM chromatograms (*m*/*z* 163) of DIP obtained in lipid emulsion (A, B), water (C, D) and from swabs (E, F) with blank samples (A, C, E) versus spiked samples (2 μg/l DIP (B, D), 2 ng on swab (F)).

4. Conclusion and outlook

We have shown for the first time that HS-SPME is a fast and easy sample cleanup tool in combination with GC/MS showing excellent sensitivity down to the low μg/l concentration range (LoD 3.3 μg/l) even for moderately volatile compounds like 2,6-diisopropylphenol in a complex and lipophilic matrix such as a lipid emulsion. The method is further characterized by excellent accuracy and precision.

The reported sensitivity is comparable to previously published procedures for 2,6-diisopropylphenol quantification in biological matrices (LODs of 2 μg/l for blood and plasma [18] and BAL [11] respectively using HPLC with fluorescence detection, 72.2 nmol/l corresponding to 12.9 μg/l for blood using HS-SPME GC/MS [13]) as well as a previously presented HS-SPME GC/MS method for analysis of volatile oxidation compounds in a fish oil emulsion (0.12–6.58 ng/g) [30]. Due to its high sensitivity, the presented method has the potential to be applied in the evaluation of cleaning processes in pharmaceutical industry.

Moreover it was shown that HS-SPME parameters can easily be adapted to further – less complex – types of matrices such as water or swab extracts which is a prerequisite for adsorption/absorption studies dealing with a variety of solutions/matrices and different surfaces for the analyte of interest.

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