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Method for analysis of psychopharmaceuticals in real industrial wastewater and groundwater with suspended organic particulate matter using solid phase extraction disks extraction and ultra-high performance liquid chromatography/time-of-flight mass spectrometry☆

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ABSTRACT

A rapid and reliable analytical method was developed for the quantitative determination of psychopharmaceuticals, their precursors and by-products in real contaminated samples from a pharmaceutical company in Olomouc (Czech Republic), based on SPE disk extraction and detection by ultra performance liquid chromatography, combined with time-of-flight mass spectrometry. The target compounds were quantified in the real whole-water samples (water including suspended particles), both in the presence of suspended particulate matter (SPM) and high concentrations of other organic pollutants. A total of nine compounds were analyzed which consisted of three commonly used antidepressants (tricyclic antidepressants and antipsychotics), one antitussive agent and five by-products or precursors. At first, the SPE disk method was developed for the extraction of water samples (dissolved analytes, recovery 84–104%) and pressurised liquid extraction technique was verified for solid matrices (sludge samples, recovery 81–95%). In order to evaluate the SPE disk technique for whole water samples containing SPM, non contaminated groundwater samples were also loaded with different amounts (100 and 300 mg L^{-1}) of real contaminated sludge originating from the same locality. The recoveries from the whole-water samples obtained by SPE disk method ranged between 67 and 119% after the addition of the most contaminated sludge. The final method was applied to several real groundwater (whole-water) samples from the industrial area and high concentrations (up to 10^3 μg L^{-1}) of the target compounds were detected. The results of this study document and indicate the feasibility of the SPE disk method for analysis of groundwater.

1. Introduction

Pharmaceuticals play an important role in the prevention and treatment of various diseases in both human and animals and contribute to health improvements [1]. On the other hand, the growing use of pharmaceuticals is a relevant issue for environmental analysis [2–4]. Pharmaceuticals as well as personal care products can enter the aquatic ecosystems from municipal or industrial waste water treatment plant (WWTP) discharges or from industrial areas. The studies dealing with WWTPs effluents, activated sludge and river sediments show that WWTPs remove only a part of the organic pollutants including pharmaceuticals [5–7]. The occurrence of pharmaceuticals and psychopharmaceuticals in WWTP effluents has been reported in numerous articles [8–10]; however, only limited works relate to the presence of psychopharmaceuticals in waste waters and groundwaters from the areas where pharmaceutical industries are located.

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Depressive disorders are the most prevalent mental disorders in Europe and the United States.

Generally, consumption of antidepressants particularly of serotonin reuptake inhibitors and other new generation of psychoactive agents has increased worldwide over the last decade [11].Tricyclic antidepressants (TCAs) belong to the older class of pharmaceuticals which were primarily used as the antidepressant of first choice for treating clinical depression for many years in the past [12]. Although TCAs are still used occasionally to treat resistant depression and chronic pain, their consumption dramatically decreased in the last decade in the Czech Republic [13].

Ground water pollution can be caused by point sources such as industrial effluents or by diffuse inputs from surrounding contaminated areas [14,15]. Groundwater refers to protected water matrix because of the soil system above, which acts as a "safeguard". On the other hand, once the water bodies get contaminated, the effects become very often irreversible and/or very difficult and expensive to be remediated. In this context, an extensive remediation work has been running in an industrial area in Olomouc, Czech Republic, within the years 2007–2015. The area is highly contaminated with various organic solvents as well as pharmaceutical compounds formerly and in some cases currently produced there.

Concerning the techniques used in environmental analysis of pharmaceuticals, the most frequent is liquid chromatography coupled with mass spectrometry (LC–MS) [4,16] or with tandem mass spectrometry (LC–MS/MS) [17,18]. Due to low concentrations present in the environment, an extraction step is very often required. Solid phase extraction (SPE), using traditional SPE cartridges for determination of pharmaceuticals in wastewater and groundwater, was employed in the majority of published works (reviewed in Refs. [4,19]). Organic compounds discharged into the water bodies are subjected to partitioning between dissolved and suspended solid phases. It is noteworthy, that living organisms are exposed to contaminants present in both the phases; thus regarding ecosystem protection, it is important to analyze the total concentration of the target compounds [20]. Most of the published works report determination of pharmaceutical and other contaminants only in water bodies ('dissolved' or also called 'filterable matter'). Only in few cases, the literature report results from the whole-water samples. Whole-water is a synonym for the original water including the particles therein suspended [21]. Whole-water data may be generated by analysis of the whole-water samples, or by the analysis of liquid and suspended particulate matter (SPM) fractions in two independent extraction steps.

Filtration or centrifugation is generally required when conventional SPE cartridges are used for extraction of turbid water samples, thus the SPM is removed during these steps. On the other hand, the analysis of the associated SPMs is of high importance due to their physico-chemical properties and the adsorption of the target organic compounds to SPM [20]. Baker et al. [22] determined high sorption (up to 89%) of some antidepressants, including dosulepin and amitriptyline, on SPM. Therefore, the results may be underestimated in many cases as a consequence of pre-filtration of SPM. A potential way how to overcome these problems is by using SPE disks for water extraction [23]. SPE disks represent a simple method for analysis of whole-water samples without time-consuming separation steps and subsequent extraction of solid phases. Although the advantages of SPE disk extraction of several organic compounds have been known for years [24], they are still not used as widely as SPE cartridges in routine water analysis. However, the SPE disks usually contain sorbent particles with smaller diameter than those in cartridges than those in cartridges and, considering the same height of the SPE column, the path of flow path is much more tortuous in case of the disk. This results in a larger available surface area and more rapid adsorption for the disks than for cartridges. In comparison to conventional SPE cartridges, the SPE disks often enable higher sample flow rates and lower elution volumes (depending on the disk format), these representing the two main advantages over conventional SPE cartridges [24,25]. The SPE disk procedures for whole water analysis are currently in focus, as evidenced from The European Directive 2000/60/EC and Directive 2008/105/EC which requires investigation of the whole-water samples [26,27].

Extraction methods for the environmental solid matrices, including the separated SPM, often employ pressurised liquid extraction (PLE). In comparison with other techniques, PLE requires shorter extraction time, low solvent consumption and high extraction recoveries for various solid matrices and broad group of chemicals depending on PLE conditions [28,29].

The main aim of this work was to develop a simple and robust analytical method for a set of psychopharmaceuticals, their precursors and by-products found in the pharmaceutical industrial area in the Czech Republic. The developed SPE disk method for whole-water samples and pressurized liquid extraction for sludge samples were followed by ultra high liquid chromatography coupled with time-of-flight mass spectrometry (UHPLC-ToFMS). The method was applied to study the occurrence of the target compounds in WWTP influent, groundwater and sludge related to the contaminated area.

2. Experimental

2.1. Chemical and reagents

2-Chloroprothioxanthen-9-one (CPTX), chlorprothixene hydrochloride (CPX), amitriptyline hydrochloride (AMP), and amitriptyline-d_3 hydrochloride solution (used as an internal standard; IS) were purchased from Sigma–Aldrich (Steinheim, Germany). Dibenzo[b,e]thiepin-11(6H)-one (thiepinon, THP) was purchased from Alfa-Aesar (Karlsruhe, Germany). Butamirate (BUT), dosulepin (DSL), dosulepin carbinol (DSL-C), melitracene carbinol (MEL-C) and 2-isoprophenylbenzophenon (IPB) were kindly provided by Ing. Monika Košíková, Aquatest, Czech Republic (Fig. 1).

Acetonitrile (ACN), methanol (MeOH) and formic acid used as the chromatographic mobile phase and for SPE extraction were of LC/MS grade and were obtained from Biosolve (Valkenswaard, The Netherlands). ENVI C18-DSK SPE disks (diam. 47 mm), hydrochloric acid (36.5–38.0%), sodium chloride, dimethyl sulfoxide ≥99.5%, and ethyl acetate 99.8% were purchased from Sigma–Aldrich (Steinheim, Germany). Ultrapure water was prepared using a Milli-Q water purification system (18.2 MΩ; Millipore; Billerica, USA).

2.2. Sample collection

Real contaminated samples containing the psychopharmaceuticals originated from a locality nearby the company Farmak a.s. situated in Olomouc, the Czech Republic. Real contaminated water samples consisted of a raw influent into a local WWTP in the Farmak a.s. locality and groundwater from this contaminated industrial area that were collected from 6 different boreholes, labelled DF-30, SM-41, SM-43, SM-45, SM-66 and SM-74 respectively. Two WWTPs influents (IF1 and IF2) were collected in the same place. The water samples were placed into methanol pre-washed 1L amber glass bottles rinsed with the sample on the site. The samples were stored at 4 °C. Additionally, blank (control) groundwater samples were collected from a non-contaminated locality in the Bohemian Paradise of the Czech Republic.

Sludge samples (labelled A–D—see bellow) originated from the local WWTP situated in the contaminated industrial locality. Blank (control) sludge from a municipal WWTP located in the Czech

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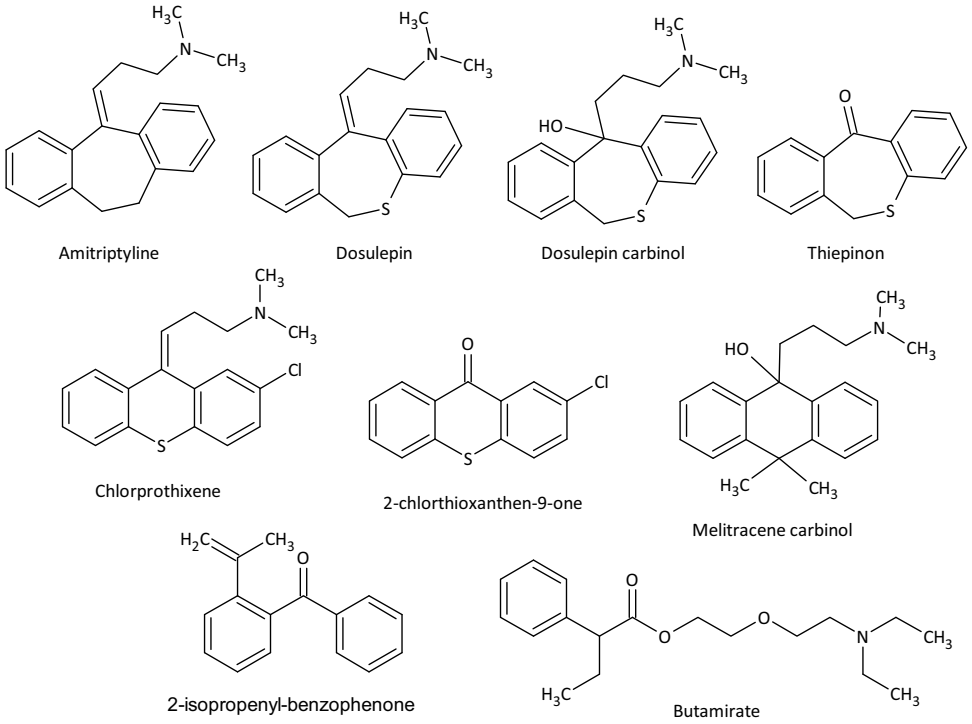

Fig. 1. Structures of the compounds involved in the study.

Republic (with an absence of any tested compound) was used for the method development and validation. All the solid samples were freeze–dried and stored at −20 °C until extraction.

Sampling was performed by Dekonta a.s. company using a standard sampling field manual [30] during the summer of 2015.

2.3. SPE disk procedure

Each water sample was acidified using 1 M HCl to pH 2.5 prior to the extraction. The ENVI C18-DSK SPE disk was conditioned with 20 mL of ethyl acetate, 20 mL of MeOH and 20 mL of H_2O. 500 mL of each water sample was passed through the SPE disk at a flow rate of 50 mL min^{-1}. The disks were then rinsed with 20 mL of Milli-Q water and afterwards, air-dried within 10 min. The analytes were eluted with 20 mL of MeOH and extracts were evaporated to dryness using a stream of nitrogen. The extracts were reconstituted in 1.9 mL of MeOH and 0.1 mL of the internal standard (100 ng mL^{-1}) was added. The blank groundwater sample extracts were reconstituted in 2 mL of MeOH and used for the preparation of matrix-matched calibration.

The recovery of the SPE procedure was tested using 3 replicates at two concentration levels (50 and 2000 ng L^{-1}). The recoveries were expressed as the percentage ratio of peak areas of the extracts and the corresponding standards. In order to validate the SPE disk method, artificial whole-water samples were prepared by loading aliquots of the blank groundwater with two different amounts of real contaminated dried sludge sample D (100 mg and 300 mg into 1 L). For calculation of the recovery, concentrations of the psychopharmaceuticals were determined employing PLE (see Section 2.5).

2.4. Groundwater characterization

The total organic carbon (TOC) was determined according to ČSN EN 1484 (1998) using a TOC analyzer (MULTI N/C 2100S, Analytik Jena, Germany). TOC concentrations were 98.0 mg L^{-1} in SM-74, 175.0 mg L^{-1} in SM-66 and 73.7 mg L^{-1} in SM-45, respectively. High concentrations of toluene (14 mg L^{-1} and 26.3 mg L^{-1}) were detected in SM-66 and SM-74 boreholes, respectively. Apart from this pollutant, dichloroethylene and trichloroethylene were also found to be present in concentrations higher than 5 mg L^{-1} in SM-74. Head-space analysis of the volatiles was performed employing GC–MS (450-GC, 240-MS, Varian, USA) equipped with CTC Combipal (CTC Analytics, USA) with a VF-624 ms column (Varian, USA).

2.5. PLE extraction and clean-up

Freeze-dried, homogenized sludge samples were extracted using ASE 200 accelerated solvent extractor (Dionex, Palaiseau, France) equipped with 11 mL stainless cells. Aliquots of sludge (2 g) were mixed in the extraction cell with sea sand (P-Lab, Prague, Czech Republic) as a dispersing agent. The extraction was carried out following a slightly modified published method where MeOH was used as the solvent for the extraction [31]. The methodological parameters were as follows: temperature, 80 °C; preheat period, 5 min; static cycles, 3; static time, 5 min; flush volume, 80%; purge time, 300 s; pressure, 1500 psi. The obtained extracts (approximately 30 mL) were transferred to 200 mL flasks and diluted using 150 mL of Milli-Q water (pH adjusted to 2.5, with HCl). The extracts were cleaned-up using the optimized SPE method (see Section 2.3).

The recovery of the ASE procedure was verified using 3 replicates of previously spiked blank sludge samples at two concentration levels (10 ng g^{-1} and 10 μg g^{-1}, respectively) of the target compounds. The sludge samples were spiked with standard mixtures of the analytes in MeOH (0.25 mL g^{-1}) and stirred vigorously in order to enable better contact of analytes with the matrix within 3 days. The recoveries were expressed as the percentage ratio of peak areas of the extracts with the corresponding standards. Due to high recovery of the PLE method (see Table 2), this extraction procedure was considered as a reference for the experiments with the artificially prepared whole-water samples.

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2.6. UHPLC-ToF analysis

UHPLC-ToF analyses were performed using a Waters Acquity UPLC System (Waters; Prague, Czech Republic) consisting of Acquity UPLC Sample Manager, Acquity UPLC Solvent Manager, Acquity UPLC Column Heater and Waters LCT Premier XE orthogonal accelerated ToFMS (Water MS; Machester, UK). MassLynx V4.0 software was used for data processing.

For the ionization of analytes, an ESI interface was employed (operating in the positive ion mode) using the following parameters: cone voltage, 40 V; capillary voltage, +2800 V; ion source block temperature, 120 °C; nitrogen desolvation gas temperature, 350 °C; desolvation gas flow, 800 L h^{-1}; cone gas flow, 50 L h^{-1}. Full scan spectra were acquired in the range of 100–1000 *m/z* with a scan time 0.15 s and an inter-scan delay of 0.01 s. Mass accuracy was maintained by lock spray using leucine-enkephalin (5 ng μl^{-1}; 5 $\mu L\ min^{-1}$).

Analytes were separated on an Acquity BEH C18 column (50 mm × 2.1 mm × 1.7 μm) with the mobile phase consisting of (A) formic acid–water (0.1:99.9, v/v), and (B) formic acid–acetonitrile (0.1:99.9, v/v). Linear gradient elution program was employed as follows (min/%B): 0/5; 15/70; 18/99 followed by 1.5 min step with 100% B and 2.0 min equilibration step. The mobile phase flow rate was 0.4 mL min^{-1}, the column temperature was 40 °C and the injection volume was 5 μL.

2.7. Method validation

Stock solutions containing 2 mg mL^{-1} of each of the 9 monitored compounds and the internal standard were prepared in ACN and stored in a refrigerator. The matrix-matched calibrations (whole-water and sludge samples) with addition of the internal standard were used for quantification. Amitriptyline-d_3 was used as the only IS for all the 9 monitored compounds due to a lack of other commercially available isotopically-labelled standards. The calibration solutions were prepared by diluting the stock solutions with the blank groundwater sample extract or with the PLE blank sludge extract. Concentrations of the calibration standards ranged from the instrument limit of quantification (ILOQ) for each analyte up to 5 μg mL^{-1}. The concentration of IS was 100 ng mL^{-1}. ILOQ was determined as the lowest point of calibration curve with precision less than 20% and trueness of 80–120% of six replicates.

The method limit of quantification (MLOQ) was determined as the lowest amount of each of the target compound that can be quantified in the whole-water sample extracts using SPE, or in sludge PLE extracts additionally purified with SPE. MLOQ comprises contributions of ILOQ, the enrichment factor, and the extraction recovery of each of the analytes.

The repeatability and reproducibility of the instrument was determined using 6 replicated injections of the analyte mixture (100 ng mL^{-1}) by comparing the peak areas within one day and five days, respectively.

In order to express the matrix effect on the ionization of the analytes, signal suppression was calculated according to the method described in Jelić et al. [32]. Peak areas from analyses of the spiked blank sludge extracts and the spiked blank groundwater extracts were compared with peak areas of the respective standard solution in MeOH at the same concentration level (0.1 μg mL^{-1}).

Short and long term stabilities were tested using spiked extracted blank groundwater samples (5, 0.1, and 0.05 ng mL^{-1}). The samples were stored at room temperature (RT, short term stability) or at 4 °C and −20 °C (long term stability) and analyzed after 0,2,4,6,8,12, and 24 h, or after 0,1,2,4,7 and 14 days, respectively.

3. Results and discussion

3.1. SPE disk recovery (without SPM)

At first, only the body of the blank groundwater samples (the filtered water), spiked with the target compounds, were used for the SPE extraction and recovery assessment. Great differences in recoveries were observed with differences in the pH of the sample matrix as well as in the volume of MeOH, which was used as a solvent for the elution. The studied psychopharmaceuticals possess different properties in terms of neutrality, acidity and basicity; therefore pH plays an important role during SPE procedure due to deprotonation of the acidic pharmaceuticals and protonation of the basic pharmaceuticals. Without previous pH adjustment (pH approximately 6.3), very low recoveries were achieved for all the target compounds (ND to 53%) with the exception of IPB, which was fully extracted (recovery 95%). Adjusting the pH of the sample (up to 3.5) using hydrochloric acid led to an increase in the extraction recovery; but the effectiveness of extraction of AMP and CPX remained lower than 30%. An addition of acetic acid (0.1%) into the elution solvent only increased the extraction efficiency (pH of sample 3.5) slightly and the recovery ranged between 45% and 101%. The best conditions were found when the pH of the samples were adjusted to 2.5, which led to enhanced recoveries even with pure MeOH and addition of acetic acid was not even necessary. Notably this method showed >80% recoveries for all the compounds (results listed in Table 2). The recoveries were analysed using the optimised UHPLC-ToFMS method and the LOQ parameters were determined (Table 1 and Table 2). In comparison to the present study, typical and most frequently used adsorbents for pharmaceutical extraction of water samples are polymeric materials like OASIS HLB or OASIS MCX [4,33,34]. It is noteworthy that in the current literature, there are only a limited number of articles that deals with SPE disks for environmental analysis of pharmaceuticals [35–37]. The methodology using SPE disks offers many advantages as compared to the conventional cartridges. Higher surface area for adsorbent/sample contact enables using higher of flow-rates and is very useful for high-volume samples often used in environmental analysis. ENVI-18 DSK disks contain a porous glass fiber membrane which deliver faster flow-rates in comparison with traditional PTFE disks [20].

3.2. SPE disk recovery of whole-water (with SPM)

The SPE disks were tested on the groundwater from the contaminated locality in the presence of artificially added SPM using sludge D. Regarding the hydrophobicity of the target compounds, it is important to consider the impact of the SPM present in water samples. According to Ademollo et al. [20], the compounds with log K_{ow} > 5 should be measured in sediments or in SPM, while compounds with log K_{ow} <3 should be measured in water. Except CPTX (K_{ow} 5.2), all of the compounds considered in this study have K_{ow} within this range (Table 1). Therefore, the selected drugs could remain partly bound to the SPM and hence, the extraction of only the dissolved phase might lead to underestimation of the results. However, it is well known that chemical substances with similar K_{ow} can exhibit different behaviors in partitioning under different hydrological conditions, as in Baker and Kasprzyk-Hordern [22], who reported DSC and AMP adsorption on SPM in wastewater varying between 17% and 65% and 10 and 52%, respectively.

The SPM content in natural water is extremely variable and fluctuates in the range of 1–1000 mg L^{-1} [22,38]. The upper SPM load in real samples used in this study was 123.4 mg L^{-1} and therefore, two SPM load levels (100 mg L^{-1} and 300 mg L^{-1}) were concomitantly tested within this study. In this regard, the extraction recoveries were determined using the blank groundwater loaded with industrially contaminated sludge D, instead of artificially contaminated

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Table 1
List of the target pharmaceuticals including their precursors and by-products with corresponding properties and acquisition parameters.

Group	Compound	Abbreviation	CAS Number	Molecular Formula	Log K_{ow}	Molecular Weight (Da)	Acquisition parameters		
							RT (min)[a]	[M+H]+ (m/z)	Average mass error[b] (ppm)
Antidepressants	Amitriptyline	AMP	50-48-6	$C_{20}H_{23}N$	5.0	277.40332	7.75	278.190	3.4
	Dosulepin	DSL	113-53-1	$C_{19}H_{21}NS$	4.5	295.44174	7.33	296.146	6.1
Antipsychotic	Chlorprothixene	CPX	113-59-7	$C_{18}H_{18}ClNS$	5.2	315.86022	8.31	316.092	2.5
Antitussive	Butamirate	BUT	18109-80-3	$C_{18}H_{29}NO_3$	3.3	307.42776	6.89	308.222	5.8
By-products	Dosulepin carbinol	DSL-C	1531-85-7	$C_{19}H_{23}NOS$	3.4	313.45702	6.39	314.157	5.4
	Melitracene carbinol	MEL-C	85118-29-2	$C_{21}H_{27}NO$	4.2	309.44518	6.60	310.217	1.6
Synthesis precursors	Thiepinon	THP	1531-77-7	$C_{14}H_{10}OS$	3.5	226.29360	10.24	227.053	5.2
	2-isopropenyl-benzophenone	IPB	50431-89-5	$C_{16}H_{14}O$	4.7	222.28176	8.89	223.111	1.2
	2-chloroprothioxanthen-9-one	CPTX	86-39-5	$C_{13}H_7ClOS$	4.6	246.71208	13.10	246.998	7.0
Internal standard	Amitriptyline-d3	IS	342611-00-1	$C_{20}D_3H_{20}N$	5.0	280.42106	7.75	281.209	6.2

[a] Retention time.
[b] Average absolute mass error obtained as a mean value of 6 measurements (analytes mixture in the sample matrix; 200 ng mL^{-1}).

Table 2
Method performance parameters: reproducibility (RSD%, $n=6$), repeatability (RSD%, $n=6$), instrument limit of detection (ILOQ), extraction recoveries (%), matrix effects (%), and method quantification limits (MLOQ) obtained for spiked blank groundwater and spiked blank sludge samples using matrix-matched calibrations.

Analyte	Repeat. (RSD, %)	Reprod. (RSD,%)	Calibration curve		Groundwater			Sludge		
			R^2	ILOQ (ng mL^{-1})[a]	Recovery (%)[b]	Matrix effect (%)	MLOQ (ng L^{-1})[c]	Recovery (%)[d]	Matrix effect (%)	MLOQ (ng g^{-1})[c]
Antidepressants										
Amitriptyline	2.4	2.1	0.995	2.5	97.6 ± 5.1	−17.8	3	92.8 ± 8.7	−25.0	2
Dosulepin	2.1	2.2	0.996	2.5	96.7 ± 10.5	−35.8	3	94.8 ± 9.6	−33.9	2
Antipsychotic										
Chlorprothixene	2.2	2.1	0.998	25	103.6 ± 13.7	−30.7	30	91.2 ± 7.8	−20.0	10
Antitussive										
Butamirate	1.7	1.6	0.998	2.5	89.5 ± 13.6	9.9	3	89.9 ± 9.6	−4.0	2
By-products										
Dosulepin carbinol	1.8	2.1	0.999	2.5	98.7 ± 13.5	−30.2	3	94.1 ± 10.5	−17.3	2
Melitracene carbinol	4.1	3.9	0.999	10	88.1 ± 7.8	20.8	10	86.8 ± 15.3	−7.7	10
Synthesis precursors										
Thiepinon	1.4	2.0	0.999	10	83.4 ± 5.0	24.1	10	82.7 ± 5.0	−9.9	10
2-Isopropenyl-benzophenone	1.1	1.5	0.997	5	101.5 ± 5.4	27.2	5	81.0 ± 7.7	−7.3	5
2-Chloroprothioxanthen-9-one	9.2	8.6	0.997	25	96.7 ± 11.4	27.7	25	89.5 ± 8.9	−39.9	25

[a] Instrument limit of quantification.
[b] Average recovery obtained as a mean value of 6 measurements (3 measurements at both 50 ng L^{-1} and 2000 ng L^{-1}).
[c] Method limit of detection obtained with the respect of ILOQ, and average recovery.
[d] Average recovery obtained as a mean value of 6 measurement (3 measurements at both 10 ng g^{-1} and 10 μg g^{-1}).

Table 3
Extraction yields of SPE disks from whole-water sample prepared with real sludge D as SPM matrix loaded with two different amounts of the sludge (100 and 300 mg). Deviation from the average values obtained by PLE are given as percentage.

	Farmak real sludge D			
	Load of 100 mg		Load of 300 mg	
	Analyte (μg g^{-1})	Deviation from PLE values (±%)	Analyte (μg g^{-1})	Deviation from PLE values (±%)
Antidepressants				
Amitriptyline	0.36 ± 0.0	8.5	0.40 ± 0.0	19.1
Dosulepin	681.13 ± 7.0	−2.5	735.06 ± 38.2	5.2
Antipsychotic				
Chlorprothixene	2993.24 ± 7.7	6.4	2816.87 ± 245.1	0.1
Antitussive				
Butamirate	61.65 ± 1.4	−25.6	59.31 ± 4.1	−28.4
By-products				
Dosulepin carbinol	290.17 ± 6.2	−18.6	311.82 ± 4.7	−12.5
Melitracene carbinol	35.24 ± 0.3	−27.8	42.88 ± 1.1	−17.6
Synthesis precursors				
Thiepinon	72.75 ± 1.1	−11.0	78.90 ± 5.4	−3.4
2-Isopropenyl-benzophenone	1080.50 ± 24.3	−29.0	1011.60 ± 113.3	−33.6
2-Chloroprothioxanthen-9-one	1551.32 ± 24.7	−24.7	2007.29 ± 250.9	−2.6

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Table 4
Average concentrations ($n = 3$) of the target compounds detected in the groundwater samples and WWTPs influents from the Farmak company industrial area.

Compound	Boreholes						WWTPS influents	
	DF-30	SM-41	SM-43	SM-45	SM-66	SM-74	IF1	IF2
	$\mu g\,L^{-1}$	$\mu g\,L^{-1}$	$\mu g\,L^{-1}$	$\mu g\,L^{-1}$	$\mu g\,L^{-1}$	$\mu g\,L^{-1}$	$\mu g\,L^{-1}$	$\mu g\,L^{-1}$
Antidepressants								
Amitriptyline	1449.44 ± 159.43	179.29 ± 8.97	0.16 ± 0.91	53.53 ± 4.76	3.07 ± 0.23	0.08 ± 0.01	ND[a]	ND[a]
Dosulepin	2227.02 ± 033.62	151.54 ± 13.03	ND[a]	52.74 ± 3.43	4.39 ± 0.43	0.01 ± 0.00	ND[a]	27.23 ± 16.07
Antipsychotic								
Chlorprothixene	500.98 ± 29.55	42.52 ± 1.74	0.11 ± 0.13	8.78 ± 0.11	19.70 ± 0.91	0.04 ± 0.01	ND[a]	2.26 ± 0.91
Antitussive								
Butamirate	2.10 ± 0.20	0.25 ± 0.03	ND[a]	1.03 ± 0.07	0.005 ± 0.00	3.98 ± 0.52	ND[a]	ND[a]
By-products								
Dosulepin carbinol	501.56 ± 26.08	186.64 ± 27.99	ND[a]	52.74 ± 3.64	0.65 ± 0.03	0.04 ± 0.01	ND[a]	1.15 ± 0.06
Melitracene carbinol	ND[a]	ND[a]	0.15 ±0.10	0.62 ± 0.04	ND[a]	0.18 ± 0.04	ND[a]	ND[a]
Snythesis precursors								
Thiepinon	773.32 ± 51.81	2262.18 ± 203.60	ND[a]	ND[a]	3199.58 ± 153.58	ND[a]	5.75 ± 0.66	2.66 ± 0.21
2-Isopropenyl-benzophenone	149.25 ± 14.63	6.56 ± 0.87	0.03 ± 0.00	7.75 ± 0.85	52.78 ± 2.59	1.58 ± 0.05	14.05 ± 0.87	5.69 ± 0.29
2-Chloroprothioxanten-9-one	4.24 ± 0.47	21.25 ± 1.06	ND[a]	60.48 ± 1.94	10.86 ± 0.54	1.88 ± 0.09	7.64 ± 1.19	2.66 ± 0.13

[a] ND—not detected.

sludge. Such an approach provides more realistic evaluation of the method. All the SPE experiments were carried out three times. The calculation of the extraction yields were based on the comparison between the PLE and SPE results and the data is reported in Table 3. The 300 mg L^{-1} load of sludge D showed only a slight difference as compared to the 100 mg L^{-1} load and the method did not require any additional elution step. The obtained results, as listed in Table 4 document the suitability of the method for the analysis of whole-water samples bearing SPM load up to 300 mg L^{-1}.

3.3. PLE extraction and extract purification

To validate the extraction method for whole-water samples, direct extraction of SPM using PLE method was also evaluated. The verified PLE method was further applied in determining the concentrations of the target compounds in the real sludge samples from the contaminated industrial locality. The highest concentrations were found in the sludge D and therefore this sludge was further used as SPM for the evaluation of whole-water sample extraction.

The extraction efficiency of PLE can be influenced by a number of factors including a combination of solvents, temperature, flush volume and the number and the duration of extraction [39].

The extraction efficiency of the PLE method used in this study was verified using spiked blank sludge samples prepared at two concentrations (0.25 $\mu g\,g^{-1}$ and 25 $\mu g\,g^{-1}$, respectively) and three replicates for each of them. Non-spiked samples were also analyzed in order to exclude the possibility of the presence of psychopharmaceuticals in the blank sludge. The results of the PLE extraction including other purification steps, expressed as relative standard deviation and with the MLOQ, are listed in Table 2. The extraction recovery was higher than 80% for all the tested compounds.

Due to the lack of literature focusing on the determination of psychopharmaceuticals in soil and/or sludge, it is difficult to compare these results with other published reports. The methodology applied in this work was adopted from Baker and Kasprzyk-Hordern [19], which used PLE method for the determination of illicit drugs and other pharmaceuticals associated with suspended particulate matter present in the wastewater. For example, Jelić et al. [32] used PLE extraction for the determination of pharmaceuticals in solid sewage sludge and sediment samples. Out of 43 compounds involved in their study, three were psychiatric drugs—carbamazepine and two benzodiazepines.

3.4. UHPLC-ToFMS analysis

The standard stock solution in MeOH (100 ng mL^{-1}), fortified blank groundwater and blank sludge extracts (final concentrations of 500 ng mL^{-1} of each of the compounds, spiked in MeOH) were used for the development of the chromatographic and MS methods. ACN with formic acid as the additive was selected as the mobile phase and the gradient elution program was employed due to the differences of the polarities of the analytes. All of the nine target compounds were completely separated within 20 min of gradient elution. The final method was adjusted with respect to the separation efficiency of all the target analytes and matrix components, peak shape of the analytes and total analysis time. The ESI+ mode was used because higher intensity of protonated molecular ions $[M+H]^+$, in comparison to the ESI- mode were recorded. Different solvents were used for sample dilution, namely: 100% MeOH, MeOH:water 1:1, v/v and MeOH:water 1:3, v/v and finally, pure MeOH was selected because of the highest peak intensities.

3.5. Method validation

ESI–MS technique is susceptible to both inorganic and organic components present in the sample matrix and in the mobile phase. This may alter ionization (suppress or enhance the peak signal) and cause erroneous results during quantification [40,41]. The addition of isotopically labelled standards is a powerful strategy to diminish the suppressive effects and improve the accuracy. Unfortunately, due to the lack of commercially available standards applicable to this method, external matrix-matched calibrations and addition of one internal standard had to be employed to compensate the matrix related signal variations.

The calibration curves obtained using blank groundwater and blank sludge extracts with added standards were compared with those obtained in pure solvent (MeOH). All three curves were linear over the entire concentration range with determination coefficients $r^2 > 0.996$. The calibration curves were prepared over a linear range from ILOQ of each of the analytes to 5000 ng mL^{-1}. The concentrations used were 1, 2.5, 5, 10, 25, 50, 100, 250, 500, 1000 and 5000 ng mL^{-1} respectively. The lowest point of the calibration curve depended on the ILOQ of the individual analyte and the parameters of the calibration curves. The individual ILOQs and MLOQs are listed in Table 2.

ILOQ complied with precision (expressed as RSD %) lower than 20% and trueness ranging between 80 and 120%. With the respect to ILOQ, the recovery and the concentration factor, the corresponding

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Table 5
Average concentrations (n = 3) of the target compounds detected in the sludge samples from the Farmak company industrial area.

	Analyte concentrations—WWTPs sludges			
Compound	Sludge A ($\mu g\,g^{-1}$)	Sludge B ($\mu g\,g^{-1}$)	Sludge C ($\mu g\,g^{-1}$)	Sludge D ($\mu g\,g^{-1}$)
Dosulepin	0.204 ± 0.041	0.245 ± 0.028	0.101 ± 0.017	698.810 ± 9.55
Antipsychotic				
Chlorprothixene	4.954 ± 0.142	4.916 ± 0.477	4.297 ± 1.042	2813.811 ± 3.72
Antitussive				
Butamirate	0.154 ± 0.029	0.054 ± 0.002	0.062 ± 0.007	82.885 ± 0.80
By-products				
Dosulepin carbinol	0.068 ± 0.000	0.124 ± 0.011	0.052 ± 0.011	356.399 ± 23.73
Melitracene carbinol	ND[a]	0.005 ± 0.002	0.004 ± 0.001	52.012 ± 3.30
Synthesis precursors				
Thiepinon	0.682 ± 0.052	0.362 ± 0.015	0.264 ± 0.027	81.717 ± 0.52
2-Isopropenyl-benzophenone	7.359 ± 0.339	4.438 ± 0.584	2.289 ± 0.077	1522.415 ± 95.90
2-Chloroprothioxanthen-9-one	11.903 ± 0.079	4.813 ± 0.296	7.122 ± 0.338	2059.977 ± 75.11

[a] ND—not detected.

MLOQ of the SPE method ranged from 3.0 to 25 ng L^{-1} and the MLOQ for the PLE method ranged from 2.0 to 25 ng g^{-1}, respectively. The MLOQs were verified using the analysis of the blank groundwater extract and the PLE sludge extract spiked at the corresponding concentrations (4 samples in total).

Matrix effects were quantified by comparing areas of the compounds spiked in the blank matrix extracts (groundwater and sludge) with MeOH. The effects were expressed as the percentage of the signal suppression (Table 2). In the sludge matrix, all the compounds were subjected to signal enhancement with the percentage ranging from 4 to 40%. In the case of the groundwater matrix, the impacts of interferences were different for each of the compounds: signal intensities of five were suppressed and of four were enhanced.

All the target compounds except THP and CPTX were found to be stable. Peak areas ranged between 89.9 and 105.0% ($n = 3$) and 86.2 and 114.4% ($n = 3$) for short term and long term stability, respectively. Approximately 20% decrease (according to the peak area) was observed for THP after 6 hours and the areas measured after 14 days of storage decreased by a factor of 2 when the storage temperatures 4 °C and −20 °C were compared. CPTX degraded to the half of its initial value after three hours and the area decreased by a factor of 5 after 14 days of storage at 4 °C. Slower decomposition was observed when CPTX was kept at −20 °C; however, also in this condition, about 40% degradation was noticed after 1 day of storage. Therefore, fresh standard solutions were used for every experiment.

3.6. Method application

The developed method was used for the determination of selected pharmaceuticals and related compounds in groundwater collected from several boreholes and effluents of WWTP located in the contaminated industrial area. This monitoring revealed that all analyzed groundwater samples were positive for the tested compounds and their concentrations ranged between tens of ng L^{-1} and hundreds of mg L^{-1} (for detail see Table 4). The recorded concentrations of the analytes are higher than those previously found worldwide, which in general ranged between tens and hundreds of ng L^{-1} [4,22,42]. Out of the 9 compounds considered in this study, only two of them, DSL and AMP are commonly determined in environmental water bodies [22].

All the analyzed compounds were detected in the sludge samples originating from Farmak a.s. company WWTP. The average concentrations ($n = 3$) are listed in Table 5. The most contaminated sludge D originated directly from a technology hall.

Concentrations of CPTX, CPX and IPB detected in sludge D were three orders of magnitude higher than in the other three sludge samples and the total analyte concentration was 7.7 mg g^{-1}. Sludge samples A, B, and C originated from the WWTP in the locality (not directly connected to the technology hall) and the concentrations expressed as sums of all the target analytes did not exceed 25.3 $\mu g\,g^{-1}$, 15.0 $\mu g\,g^{-1}$ and 14.2 $\mu g\,g^{-1}$ in sludge A, B and C, respectively. However, these concentrations are still higher in comparison to reported concentrations of pharmaceuticals found in sludge elsewhere [32,43].

4. Conclusions

This study reports a SPE-UHPLC-ToFMS method which was developed for the determination of the most abundant pharmaceutically related chemicals in groundwater and WWTP sludge samples collected from the industrial locality of Farmak a.s. The validated method employed the SPE disk extraction which allows extracting the whole-water in “one-step”. The method enables quantitative analysis of analytes both dissolved in the liquid phase and adsorbed on the suspended particulate matter.

The method showed excellent reproducibility and achieved high recoveries for all of the nine compounds that were tested for their presence in both whole-water and sludge matrices.

The application of the method to groundwater samples collected from boreholes and WWTP sludge revealed a significant concentration of pharmaceutical compounds in this industrial area and emphasize a need for further remediation action to be undertaken in this locality.

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