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ORIGINAL RESEARCH ARTICLE

Determination of antibiotic residues in southern Baltic Sea sediments using tandem solid-phase extraction and liquid chromatography coupled with tandem mass spectrometry

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Summary The main objective of this study was to adapt analytical procedures for determining antibiotic residues in solid and aquatic samples to marine sediments and to investigate the occurrence of 9 sulfonamides, trimethoprim and 2 quinolones in southern Baltic Sea sediments. The analytical procedure was applied to sediment samples characterized as sand and silty sand. The validation results showed that a sensitive and efficient method applying tandem solid-phase extraction (SPE) and liquid chromatography coupled with tandem mass spectrometry (LC—MS/MS) was obtained. Analytes were determined in the lower ng g^{-1} range with good accuracy and precision. The proposed analytical procedure was applied to the analysis of 13 sediment samples collected from the Baltic Sea along the Polish coast. Concentrations of antibiotic residues in environmental samples were calculated based on external matrix-matched calibration. Residues of nine out of twelve of the above antibiotics were detected in sediment samples in a concentrations of up to 419.2 ng g^{-1} d.w. (dry weight). Sulfamethoxazole and sulfachloropyridazine were the most frequently detected compounds (58% of the analyzed samples). The

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occurrence frequency of trimethoprim was 42% and it was always detected simultaneously with sulfamethoxazole. Preliminary studies on the spatial distribution of the analyzed antibiotics indicate a high level of antibiotics occurring in the Pomeranian Bay and close to the mouths of Polish rivers. The study is the first one to demonstrate the occurrence of antibiotic residues in sediments of the Polish coastal area. The obtained results suggest that sediment can be an important secondary source of antibiotic residues in the marine environment.

1. Introduction

At the end of the second half of the twentieth century scientists started to treat pharmaceutical residues as environmental contaminants (Daughton and Ternes, 1999; Hirsch et al., 1999). The development and common use of sensitive analytical instruments like liquid or gas chromatographs coupled with mass spectrometers allowed the detection of trace concentrations of these compounds in different environmental matrices (Kot-Wasik et al., 2007; Mutavdžić-Pavlović et al., 2007). Special attention should be paid to antibiotic residues. In 2002, Wise estimated the world use of antibiotics at between 100 and 200 thousand tonnes per year. According to data published by Boeckel et al. (2014), global consumption of antibiotic drugs increased by 36% between 2000 and 2010. The main sources of antibiotics in the environment are animal farms, agriculture, and urban, municipal and hospital wastewaters (Boxall, 2008a; Hörsing et al., 2011; Kümmerer, 2008a; Łuczkiewicz et al., 2013; Minh et al., 2009; Sarmah et al., 2006). These bioactive compounds have only been detected in low concentrations in environmental samples, nonetheless, given their important, continuous input and only partial degradation, they are considered as 'pseudo-persistent' pollutants (Khetan and Collins, 2007). Prolonged exposure of organisms to antibiotic residues may strongly affect bacterial populations and induce biological effects in non-target organisms, potentially disrupting ecosystem processes (Arnold et al., 2014; Capone et al., 1996; González-Pleiter et al., 2013; Halling-Sørensen et al., 1998; Kotlarska et al., 2015; Kümmerer, 2008b; Molander et al., 2009; Nikolaou et al., 2007). Therefore, it has become of great importance to evaluate concentration levels of antibiotic residues and to understand their environmental fate.

Many studies have demonstrated that antibiotic residues are widespread in treated wastewaters, soils, groundwaters, river and lake water and sediments (Boxall et al., 2002; Kemper, 2008; Li et al., 2012; Sacher et al., 2001; Vazquez-Roig et al., 2012; Yang et al., 2010). The availability of data on antibiotic concentrations and their ecotoxicological properties in marine waters is still limited, while seas can be seen as the final sink of the most persistent antibiotic residues (Chen and Zhou, 2014; Claessens et al., 2013; McEneff et al., 2014). Once discharged into coastal waters, antimicrobial residues, like other contaminants, can undergo biotic and abiotic transformations (including degradation), sorb to suspended particulate matter and sediment, or accumulate in the tissues of organisms (Gaw et al., 2014; Ramirez et al., 2009). The fate of antibiotic residues varies depending on the physicochemical properties of compounds and matrices, in addition to environmental parameters also playing an important role. Freshwater and marine ecosystems differ significantly in terms of physicochemical conditions e.g. salinity, pH and organic matter content. Therefore, the conclusions generated for freshwater ecosystems on the environmental fate of antibiotics may not necessarily be transferable to marine environments (Weigel et al., 2002). The mobility of compounds greatly depends on water solubility, the octanol–water partitioning coefficient, and pK_a values governed by their chemical structure. Antibiotics are mostly hydrophilic compounds and should be present with relatively high frequency and concentrations in marine waters. This statement can be confirmed by several studies reporting the presence of these emerging contaminants in seawater (Borecka et al., 2013, 2015; Na et al., 2011; Nödler et al., 2014; Wille et al., 2010; Zhang et al., 2013). However, Bu et al. (2013) suggest that antibiotics could also accumulate in sediments, which could thus serve as a sink and secondary source of antibiotics in the aquatic environment. Several complex processes can be involved in the sorption mechanism of antibiotics in sediments. These comprise not only hydrophobicity but also cation bridging, cation exchange, hydrogen bonding and surface complexation (Kim and Carlson, 2005). All these factors may play important roles in retaining antibiotic residues on a sediment matrix. The sorption of antibiotics like sulfonamides is also governed by the property to ionize numerous compounds from this class depending on the pH of a medium. The log K_{ow} coefficients of ionizing compounds change considerably in a pH range around the pK_a (Mutavdžić-Pavlović et al., 2012).

According to data published by Gaw et al. (2014) and Pazdro et al. (2016), until now only around twenty studies have evaluated the presence of antibiotics residues in marine sediments. Their presence has been reported in some coastal regions of the Pacific (mainly in China) and Atlantic Ocean (Beretta et al., 2014; Lara-Martín et al., 2014; Moreno-González et al., 2015; Na et al., 2013; Shi et al., 2014; Stewart et al., 2014; Yang et al., 2010; Yang et al., 2011; Zhou et al., 2011). As shown above, the information about spatial and seasonal distribution of antibiotic residues concentrations in many coastal areas is still very limited. This is particularly true for the Baltic Sea, a shallow inland sea with a large catchment area. There are only a few publications concerning the occurrence of pharmaceuticals in the Baltic Sea region and these are limited to water and fish (Beck et al., 2005; Borecka et al., 2013, 2015; HELCOM, 2010; Nödler et al., 2014). Borecka et al. (2013, 2015) reported the presence of antimicrobials from the sulfonamide and quinolone groups as well as trimethoprim, at concentrations

of up to ng L^{-1} in southern Baltic Sea waters. Apart from our preliminary study reporting the detection of hydrophilic antibiotics from the tetracyclines class in sediments from the Gulf of Gdańsk (Siedlewicz et al., 2014), to our knowledge, no study has been performed with regard to antibiotic residues in the sediments of the Baltic Sea.

The small amount of data available for marine sediments is also caused by the fact that the analysis of such a complex matrix is a very demanding task. The number of papers on the analytical methods of antibiotics residues determination in solid matrices is significant, but there is still a need for improvements in analytical procedures, aiming at reliable identification and quantification of these compounds in marine sediments (Białk-Bielińska et al., 2016). Moreover, the simultaneous analysis of compounds with quite different physicochemical properties in complex solid matrices like marine sediments also poses several problems (Mutavdžić-Pavlović et al., 2012).

The main objectives of the study were: (1) to adapt existing analytical extraction procedures for determining antibiotic residues concentrations in solid and aquatic samples to the analysis of Baltic sediments (Babić et al., 2006; Majka, 2010) and (2) to perform, by applying adapted, validated methods, preliminary studies on the concentration levels and spatial distribution of nine sulfonamides, trimethoprim and two quinolones in sediments from the southern Baltic Sea. The choice of target antibiotics was made due to their vast production and consumption worldwide (Dzierżawski and Cybulski, 2012; Kümmerer, 2008c; Sarmah et al., 2006). The target compounds represent a variety of structures and are characterized by different physicochemical properties (e.g. water solubility, pK_a values, hydrolytic stability) (Mutavdžić-Pavlović et al., 2012). Moreover their presence in southern Baltic surface waters has been observed (Borecka et al., 2013, 2015).

2. Material and methods

2.1. Chemicals and materials

Sulfathiazole (ST), sulfapyridine (SP), sulfamerazine (SRZ), sulfamethazine (SMZ), sulfamethiazole (SMT), sulfachloropyridazine (SCP), sulfamethoxazole (SMX), sulfisoxazole (SSX), sulfadimethoxine (SDM), trimethoprim (TMP), oxolinic acid (OA) and enrofloxacin (ENR) standards were purchased from Sigma-Aldrich (Germany). Methanol (MeOH) and acetonitrile (ACN) (HPLC grade) were obtained from Merck (Germany). Ammonium chloride (NH_4Cl), disodium ethylenediamine tetraacetate (Na_2EDTA), ammonium acetate (CH_3COONH_4), acetic acid (CH_3COOH) (all of analytical reagent grade) and filter paper were purchased from POCH (Poland). Milli-Q water was obtained from the Milli-Q water purification system (Millipore, Germany). Oasis HLB cartridges (Waters, Ireland) with 500 mg of packing material, a 6 mL reservoir, as well as Discovery DSC-SAX (Sigma-Aldrich) (500 mg/6 mL) cartridges were used for sample preparation. For sample processing, an SPE 12 position vacuum manifold (Phenomenex, Germany) was used.

Standard stock solutions of each compound were prepared in methanol at a concentration of 100 μg mL^{-1} and stored at −18°C. Stability tests show a minimum 6-month degradation resistance of the solutions under the presented conditions. Working solutions of pharmaceuticals were prepared before analysis by diluting the stock solution in ACN:H_2O (10:90, v/v) and stored at 4°C. To prepare calibration curves, the working solution was diluted with mobile phase A to an appropriate concentration.

2.2. Sediment sampling and sample characterization

Surface sediment samples were collected during the cruise of r/v Oceania in April 2010 and during the cruise of s/y Task in July 2010 using Reineck or Niemistö corers. The location of 10 sampling sites is shown in Fig. 1. During sampling, parameters of near bottom waters, such as temperature (*T*), pH, salinity (*S*) and dissolved oxygen concentration (O_2), were measured for all samples. Water parameter measurements were performed using a multimeter (Hach-Lange, HQ40D). The surface layer of sediment (0–5 cm) was retrieved, frozen (−18°C) in pre-cleaned glass jars and transported to the laboratory. Sediment samples were homogenized, freeze-dried (Labconco, 091118527 D) and used for chemical analyses. For each lyophilized sediment sample, a grain size analysis was performed. The sediment particle size was analyzed using meshes (% of grain < 0.063 mm), and the sediment type was classified according to the Shepard classification (1954) modified by Piekarek-Jankowska (2010). The organic matter content in sediments was measured by loss on ignition (LOI). Dry and homogenous samples of the sediments were weighed before and after heating for 5 h at 550°C (Ciborowski, 2010). Details of sampling sites and selected sediment characteristics are given in Table 1.

2.3. Sample preparation

The extraction procedure of the sediment samples consisted of two steps: (a) extraction of the analytes from the sediment by sonification and (b) the enrichment and clean-up of the extract applying SPE. The samples were extracted adopting the method used by Majka (2010) and clean-up procedure was performed adopting the method described by Babić et al. (2006). The extraction and the clean-up details are briefly described below.

In the case of the development of the method modification, before extraction 2.5 mL of a working solution of a mixture of antibiotics was spiked into the sediment to reach a final concentration in the sediment of 5 μg g^{-1} d.w. and kept in the dark at room temperature overnight to reach equilibrium, then the excess of the solvent was evaporated at room temperature.

Two grams of homogenized sediment sample were weighed in 30 mL polypropylene centrifuge tubes and subjected to the extraction. The procedure proposed by Majka (2010) for the analysis of 12 sulfonamides in soils and sediments consisted of extraction with 5 mL of a NH_4Cl:MeOH (1:1, v/v) mixture and 0.5 mL 0.1 M EDTA. NH_4^+ ions can increase the desorption efficiency by replacing antibiotic cations in a sediment matrix. Furthermore, a water solution of NH_4Cl enhances phase separation. The EDTA is added to prevent the analytes from complexing with metal ions (Lalumera et al., 2004). In this study, during the development

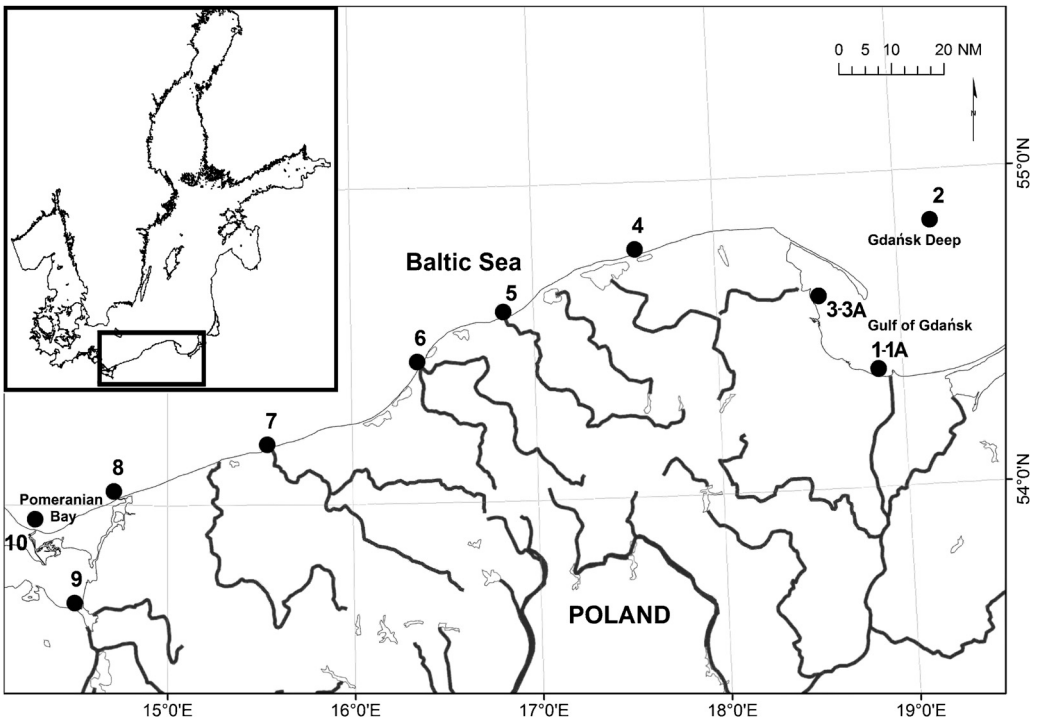

Figure 1 Locations of sampling sites.

of the method, different solutions and volumes of NH_4Cl or citrate/phosphate buffer (McIlvaine buffer) were used to test the extraction efficiency of antibiotics from the spiked sediment. The McIlvaine buffer was applied earlier in the extraction of tetracyclines from the Baltic Sea sediments (Siedlewicz et al., 2014). Eventually, according to the best recovery results, the extraction mixture consisted of methanol, supersaturated NH_4Cl and 0.1 M EDTA. 10 mL of methanol, 10 mL of supersaturated NH_4Cl water solution and 2 mL of 0.1 M EDTA were added to each tube. The samples were mixed on a vortex mixer for 1 min. The samples were then sonificated for 20 min and mixed on a vortex for 20 h in darkness in a cold place (different mix times were tested, and 20 h showed the best recoveries for all analytes). The samples were then centrifuged at 4000 rpm for 10 min. The supernatant from each tube was filtered using paper filter and collected in a glass flask. The extraction was repeated three times without the 20 h vortex stage. The supernatants were combined and 1440 mL of Milli-Q water (to dilute the organic solvent) were added before the clean-up step.

The clean-up procedure was based on the method of Babić et al. (2006) for wastewater samples, where a 60 mg OASIS HLB column was used and the following consecutive steps were performed: pre-conditioning: 5 mL MeOH, 5 mL H_2O pH = 4, washing: 2 mL 2% MeOH, elution: 2× 5 mL MeOH. In this study, the procedure was modified by using tandem SPE Discovery SAX – Oasis HLB, instead of single OASIS HLB SPE and the elimination of sample acidification. The application of strong anion exchange SPE – Discovery SAX, allowed the removal of negatively charged compounds like humic and fulvic acids, and therefore, a decrease in matrix effects.

Briefly, Discovery SAX (6 mL, 500 mg) and Oasis HLB (6 mL, 500 mg) were set up in tandem for the clean-up of the aqueous sediment extracts. Each tandem column was preconditioned with 8 mL of methanol and 10 mL of Milli-Q water. Each extract was passed through the tandem cartridge at a flow rate of 6 mL min^{-1}, without allowing the cartridge to dry out. After sample loading, the SAX cartridge was removed and the HLB cartridge was rinsed with 8 mL of 2% methanol. The HLB cartridge was then air-dried under a vacuum for about 20 min. The target compounds were eluted with 8 mL of methanol. The eluate was evaporated to dryness under a gentle nitrogen stream, and stored at −80°C until LC–MS/MS analysis. Just prior to LC–MS/MS, the residue was re-dissolved in 1 mL of mobile phase A, vortexed, centrifuged to remove particles and transferred to vials.

2.4. LC–MS/MS analysis

The instrumental analysis method was performed, according to the method developed by Białk-Bielińska et al. (2009) for the determination of 12 sulfonamides in soil samples. Chromatographic separations were performed using an Agilent 1200 Series LC system (Agilent Technologies Inc., Santa Clara, USA) with an Agilent Eclipse XDB C18 column (150 mm × 4.6 mm, 5 μm particle size) (Agilent Technologies Inc., Santa Clara, USA). H_2O:ACN (90:10, v/v, 1 mM NH_4Ac/AcH, pH 3.56) (A) and 100% ACN (B) were used as mobile phases. The flow rate was 0.3 mL min^{-1}. The gradient program started with 0% of mobile phase B, which was increased to 64% within 15 min. The injection volume was 50 μL. The mass spectrometric measurements were carried out on an HCT Ultra ion trap mass spectrometer (Brucker Daltonics, Bremen, Germany) equipped with an electrospray ionization source. For data acquisition, EsquireControl software was used. The source temperature was 350°C. Nitrogen was employed as the nebulizer gas (30 psi) and the dry gas (10 L min^{-1}). The capillary voltage was −4 kV. Helium (99.999%) was used as the collision gas in the ion trap. The best conditions for isolating the precursor ion were determined. Ions were acquired in the multiple reaction

Table 1 Location and characteristics of the sampling sites and the sediments collected from the southern Baltic Sea.

Station number/ sediment type	Sampling site	Sampling date	Coordinates	Depth [m]	LOI [%]	Fraction < 0.063 mm content [%]	S [PSU]	T [°C]	pH	O_2 [mg dm^{-3}]	SPM [mg dm^{-3}]
1 sand	Mouth of the Vistula, close to WWTP 'Gdańsk Wschód' outlet	April 2010	54°22.423 18°52.093	13	0.39	0.4	6.9	12.4	9.01	9.87	27.2
1A sand		July 2010			0.36	0.9	4.9	13.2	8.84	10.90	17.4
2 silty sand	Gdańsk Deep	April 2010	54°49.085 19°17.147	111	20.72	28.9	11.9	7.2	7.32	2.17	80.3
3 sand	WWTP 'Gdynia Dębogórze' outlet	April 2010	54°36.798 18°33.712	10	0.81	1.7	7.0	15.4	8.72	10.41	11.9
3A sand		July 2010			0.47	1.4	6.9	19.2	8.27	10.92	5.5
4 sand	Mouth of the Łeba river	April 2010	54°47.209 17°33.971	13	0.26	0.5	7.1	10.7	8.75	10.31	4.5
5 sand	Mouth of the Słupia river	April 2010	54°36.027 16°50.161	18	0.48	1.4	6.8	15.2	9.17	10.15	3.4
6 sand	Mouth of the Wieprza river	April 2010	54°26.897 16°21.595	10	0.99	0.7	6.2	10.2	8.89	10.12	5.3
7 sand	Mouth of the Parsęta river	April 2010	54°11.534 15°32.361	11	0.20	2.7	6.2	14.2	8.72	10.26	4.6
8 sand	Mouth of the Dziwna river	April 2010	54°02.703 14°42.626	10	0.18	0.2	6.7	13.2	8.62	10.15	7.4
9 silty sand	Szczecin Lagoon	April 2010	53°41.387 14°30.217	6	11.83	10.9	0.3	19.0	9.35	8.70	130.1
10 sand	Mouth of the Świna river	April 2010	53°57.315 14°17.253	10	0.77	1.5	5.6	12.1	8.46	9.60	62.1

LOI, loss on ignition; S, salinity; SPM, suspended particulate matter content; WWTP, wastewater treatment plant.

monitoring mode. After this, the full scan MS mode was used to record the product ion. For each compound, the fragmentation amplitude and isolation width were also optimized manually to increase the sensitivity and selectivity of the method and to select the three most intensive and characteristic fragmentation ions for qualitative analysis. For quantitative analysis, the ion of the highest intensity was selected. Analyses were performed in the positive mode for all compounds. The optimized MS/MS conditions are shown in Table 2.

2.5. Analytical procedure validation

The developed SPE-LC-MS/MS method was validated using sediment samples at eleven spiking levels (0.5, 1, 2, 5, 10, 20, 50, 100, 200, 500, 1000 ng g^{-1} d.w. of sediment). The sediments were spiked with a mixture of external standards of antibiotics. Each concentration was analyzed 5 times. Validation parameters such as linearity, method detection limit (MDL), method quantification limit (MQL), precision and accuracy of the whole procedure were determined. The

Table 2 Retention time, precursor and product ion used for LC–MS/MS analyses.

Compound	Retention time [min]	Precursor ion with isolation width	Product ions	Fragmentation amplitude [V]
ST	15.9	256 ± 2.0	**156**	0.55
			108	0.60
			92	0.65
SP	16.6	250 ± 0.9	**156**	0.50
			184	0.60
			108	0.55
SRZ	17.4	265 ± 2.0	**190**	0.65
			174	0.60
			156	0.55
SMZ	19.1	279 ± 1.9	**204**	0.60
			124	0.55
			156	0.55
SMT	19.3	271 ± 2.0	**156**	0.60
			108	0.70
			92	0.60
SCP	22.4	285 ± 2.0	**156**	0.65
			108	0.60
			92	0.65
SMX	23.8	254 ± 2.0	**156**	0.65
			188	0.65
			147	0.50
SSX	24.5	268 ± 2.0	**156**	0.70
			113	0.65
			108	0.65
SDM	26.5	311 ± 2.0	**156**	0.60
			245	0.60
			218	0.65
TMP	14.9	291 ± 2.0	**230**	0.90
			261	0.90
			123	0.90
OA	24.7	262 ± 2.0	**244**	0.75
			216	1.05
			234	1.05
ENR	16.9	360 ± 2.0	**316**	0.85
			245	0.75
			342	0.75

ST, sulfathiazole; SP, sulfapyridine; SRZ, sulfamerazine; SMZ, sulfamethazine; SMT, sulfamethiazole; SCP, sulfachloropyridazine; SMX, sulfamethoxazole; SSX, sulfisoxazole; SDM, sulfadimethoxine; TMP, trimethoprim; OA, oxolinic acid; ENR, enrofloxacin. Product ion selected for quantitative analysis marked in bold.

calibration curves were constructed by plotting peak areas against analyte concentrations. Linearity was determined for the whole range of concentrations, but for better accuracy of the results two concentration ranges were applied (0.5—50 and 50—1000 ng g^{-1} d.w.). The method detection limit was calculated as three times the standard deviation of the lowest acceptable concentration of analytes (Białk-Bielińska et al., 2009; Taverniers et al., 2004). The method quantification limit was set as three times the MDL value. The precision was determined as a coefficient of variation (CV) for the repeated measurements for each spiking level. The accuracy was calculated as the agreement between the measured and known concentrations of each sample analyzed in the applied linear ranges. The validation of the whole analytical procedure was applied to the two types of sediment samples from the Baltic Sea. For this purpose, sediments differing in granulometry and organic matter content were analyzed (silty sand from station 2 — Gdańsk Deep — with high organic matter content, sand from station 3A — WWTP 'Gdynia Dębogórze' outlet — with low organic matter content). Sediments used as blank samples were burned at 450°C for 8 h to eliminate organic contaminants and analyzed in the same way as other samples. Antibiotic residue concentrations in environmental samples were calculated based on an external matrix-matched calibration.

2.6. Statistical analysis

Linear regression analysis was used to evaluate the influence of environmental factors on the distribution of frequently detected antibiotic residues. A level of $p < 0.05$ was considered statistically significant. The statistical analysis was performed using Statistica 10 software (Stat Soft®, Poland).

3. Results and discussion

3.1. Method development

The target antibiotic residues are present in the environment in low concentrations, which, together with the complexity of the sediment-like matrix, makes their reliable determination difficult. Sample preparation is therefore a key step in analysis. In this study sediment samples were extracted and cleaned up adopting the modified analytical method developed by Majka (2010) and Babić et al. (2006). The extraction procedure described by Majka (2010) (MSc thesis in Polish language) included the application of supersaturated NH_4Cl, 0.1 M EDTA and methanol for the extraction of sulfonamides from soils and sediments. The modification of the extraction method used in this study consisted of increasing the volume of methanol, supersaturated NH_4Cl and 0.1 M EDTA compared to the original extraction procedure. The application of the clean-up procedure described by Babić et al. (2006) for wastewater analyses resulted in low recoveries, ranging from 8% for SSX in the Baltic silty sands to 154% for SMZ in the sand sediments. Subsequently, the SPE clean-up procedure was modified. The main part of the modification concerned the use of tandem coupled SPE columns and an increased volume of solvent used for column conditioning and purification. The step of the acidification of the sample was also eliminated. The modified method was characterized by higher accuracy than the starting procedure.

The proposed analytical procedure was applied to two types of sediment samples from the Baltic Sea. The sediments used in the validation procedure (from station 2 — silty sand and station 3A — sand) were almost completely free from antibiotic residues. Only in sample 3A, was SCP concentration < MQL level, and it was taken into account in the calculation of the validation parameters. The validation parameters of the whole analytical procedure for sand and silty sand are presented in Table 3.

The MDL values were very low for both types of sediments. For the sand, the values were generally lower (MDL = 0.15—1.86 ng g^{-1} d.w.) than the values for the silty sand (MDL = 0.23—10.2 ng g^{-1} d.w.). The method detection limit and method quantification limit for the target compounds were similar to, or lower than, the values of these parameters reported in the literature (Löffler and Ternes, 2003; Na et al., 2013; Xu et al., 2014; Zhou et al., 2011). However, Shi et al. (2014) obtained lower limit of detection (LOD) values for some target compounds ranging from 0.05 ng g^{-1} d.w. for SP to 0.1 ng g^{-1} d.w. for SMX. Similarly, Chen and Zhou (2014) described the limit of quantification (LOQ) of their target antibiotic in the range of 0.01—0.5 ng g^{-1} d.w. The higher MDL and MQL values observed for Baltic sediments were probably caused by matrix effects. For example, Gdańsk Deep sediments are characterized by a high content of organic matter and accumulated persistent organic pollutants, heavy metals or anionic surfactants (Hampel et al., 2012; Konat and Kowalewska, 2001; Szefer et al., 1995). Those compounds can affect the ionization efficiency (Caban et al., 2012; Van De Steene and Lambert, 2008; Zhou et al., 2011). Furthermore, the strong sorption properties of OA and ENR could be a reason for their high MDL/MQL values in silty sand type sediments (Kümmerer, 2008a, 2008c; Le-Minh et al., 2010). The calibration curves obtained for all compounds were linear in the assayed range, with the correlation coefficients $r \geq 0.98$. Linear concentration ranges were applied for most of the compounds except OA and ENR in silty sand. For these analytes the accuracy of spiking levels located beyond the linear range (presented in Table 3) increased or decreased enormously. The calibration curves were proved to be linear within the range of the linear regression parameters of both the matrix-matched and standard calibration curves. The accuracy of the method was expressed as the mean recoveries with standard deviations (SD) of spiked antibiotics in the sediment matrix. Good accuracies, ranging from 89 to 119%, were obtained for the two spiking levels in both sediment types assayed. This accuracies are very satisfactory compared to the methods described in the literature, where the reported accuracy for sulfonamides and quinolones were in the range of 51—141% (Chen and Zhou, 2014; Luo et al., 2011; Na et al., 2013; Raich-Montiou et al., 2007). However, some accuracies of target compounds were relatively high. At the lowest spiking level of OA in sand sediment and the highest spiking level of ST, SP, SRZ and SMT, in silty sand, the standard deviations obtained were higher than 20%. The physicochemical properties of the target substances and the influence of the matrix may affect the accuracy (Caban et al., 2012; Zhou et al., 2011). According to Kim and Carlson (2005) cation exchange, cation bridging, surface complexation and hydrogen bonding may play important role in retaining pharmaceuticals on a solid matrix. Białk-Bielińska et al. (2012) and Maszkowska

Table 3 Validation results for the entire analytical procedure (SPE-LC-MS/MS) applied to determination of 12 antibiotics in Baltic sediments.

Compound	Sand					Silty sand				
	Range	R^2	MDL [ng g^{-1} d.w.]	MQL [ng g^{-1} d.w.]	Accuracy [%] Mean (SD) (n = 5)	Range	R^2	MDL [ng g^{-1} d.w.]	MQL [ng g^{-1} d.w.]	Accuracy [%] Mean (SD) (n = 5)
ST	0.5–50	1.000	0.38	1.14	96.5 (12.9)	0.5–50	1.000	0.43	1.29	100.5 (9.4)
	50–1000	1.000			95.1 (18.4)	50–1000	0.975			101.0 (21.0)
SP	0.5–50	1.000	0.19	0.57	91.2 (16.9)	1–50	0.999	0.77	2.31	93.9 (9.5)
	50–1000	0.999			109.9 (9.6)	50–100	0.999			92.1 (28.2)
SRZ	0.5–50	1.000	0.25	0.75	94.1 (11.1)	0.5–50	1.000	0.23	0.69	100.8 (6.6)
	50–1000	0.999			107.7 (7.8)	50–1000	0.999			102.5 (22.9)
SMZ	1.0–50	0.999	0.49	1.47	103.4 (9.8)	1–50	1.000	0.59	1.77	90.5 (15.6)
	50–1000	0.984			112.1 (12.6)	50–1000	0.999			109.0 (11.9)
SMT	1–50	1.000	0.79	2.37	101.4 (6.3)	0.5–50	0.999	0.88	2.64	103.8 (11.7)
	50–1000	0.999			88.8 (17.7)	50–1000	0.985			118.8 (23.4)
SCP	0.5–50	1.000	0.15	0.45	97.6 (6.1)	0.5–50	1.000	0.37	1.11	105. (17.2)
	50–1000	1.000			100.2 (3.0)	50–1000	0.999			104.3 (9.5)
SMX	0.5–20	1.000	0.31	0.93	99.3 (4.4)	1–50	1.000	0.83	2.49	101.3 (7.2)
	50–1000	1.000			95.9 (16.9)	50–1000	0.999			104.8 (8.2)
SSX	0.5–50	0.999	0.26	0.78	101.1 (12.2)	2–100	0.984	0.58	1.74	96.5 (11.8)
	50–1000	0.999			107.9 (12.0)	100–1000	1.000			104.8 (8.4)
SDM	0.5–50	0.999	0.53	1.59	103.5 (6.6)	1–50	1.000	0.54	1.62	98.7 (10.6)
	50–1000	0.999			104.8 (7.8)	50–1000	0.984			106.0 (14.9)
TMP	0.5–50	1.000	0.34	1.02	103.1 (11.7)	0.5–50	1.000	0.34	1.02	102.7 (9.2)
	50–1000	0.984			103.8 (12.3)	50–1000	0.984			102.3 (16.6)
OA	2–50	0.999	1.86	5.58	108.7 (24.5)	50–1000	0.999	10.2	30.6	113.8 (12.7)
	50–1000	0.984			104.5 (16.7)					
ENR	2–50	0.985	1.22	3.66	98.5 (18.7)	2–200	0.999	1.38	4.14	97.7 (18.6)
	50–1000	1.000			101.8 (4.0)					

n, number of replicates; MDL, method detection limit; MQL, method quantification limit; R^2, determination coefficient; SD, standard deviation; ST, sulfathiazole; SP, sulfapyridine; SRZ, sulfamerazine; SMZ, sulfamethazine; SMT, sulfamethiazole; SCP, sulfachloropyridazine; SMX, sulfamethoxazole; SSX, sulfisoxazole; SDM, sulfadimethoxine; TMP, trimethoprim; OA, oxolinic acid; ENR, enrofloxacin.

et al. (2013) reported a strong dependence between the sorption/desorption of selected sulfonamides and the organic carbon content in soils. In the light of these investigations it can be assumed that similar dependencies could be a reason for the difference in accuracies observed for analyzed types of Baltic sediments. Matrix effects like ion suppression and/or ion enhancement are ubiquitous during LC–MS/MS analysis, due to ionization competition between eluting compounds in a chromatographic system (Na et al., 2011; Van De Steene and Lambert, 2008). To reduce high values of the standard deviation and to fully determine the influence of the sample matrix on the obtained results, the use of internal, isotope-labelled standards is recommended (Löffler and Ternes, 2003; Na et al., 2011; Yang et al., 2010). However, these were not applied at this stage. The exact values of matrix effects were not calculated as they were compensated by working with a matrix-matched calibration. Studies on matrix effects in different types of Baltic sediments will be continued in future research applying isotope-labelled analogues. This approach was demonstrated to be the most advantageous approach for an accurate determination of target compounds in environmental complex samples (Na et al., 2013). The selection of an internal standard has to be based on its similarity to the compounds of interest, with regard to chemical structure, mass spectrometric response, chromatographic retention time and matrix effect (ion suppression or enhancement) (Bayen et al., 2013). However, the commercial availability of reference standards is still low, thus according to the literature satisfactory results can be obtained using only one or two internal standards to correct for all compounds (Wille et al., 2012).

In the applied method, the precision (CV) values were in general less than 20%. The sediment matrix and the properties of some target analytes could explain the differences in the validation parameters between both types of sediments. Analyses of the blank samples, in which none of the analyzed compounds were detected, in comparison with spiked sediment samples showed that the method also exhibited good selectivity.

The obtained validation results showed that a sensitive and efficient extraction procedure and analytical method, applying tandem SPE and LC–MS/MS, has been developed to determine 12 antibiotics in Baltic sediments. The described procedure allows the determination of 9 sulfonamides, 2 quinolones and trimethoprim in Baltic sediments down to the lower ng g^{-1} range, with good accuracy and precision.

3.2. Results of the real samples analysis

The proposed analytical procedure was applied to the analysis of 12 sediment samples collected from the southern Baltic Sea. Environmental samples were analyzed in duplicate, and the reported data are the average of the two analyses. The detected compounds together with their concentrations are shown in Table 4. Nine of the twelve target antibiotics were detected in the sediment samples. Among the analyzed antibiotics, SMX and SCP were the most frequently detected (58%) in sediment samples. The occurrence frequency of TMP was 42% and it was detected in the samples simultaneously with SMX. SMT, SRZ, SSX and SDM were found in the monitored area but only in single samples. No residues of SP, OA, ENR were detected in any of the samples analyzed.

The concentrations of the analyzed antibiotics ranged from <MDL to 419 ng g^{-1} d.w. for sulfonamides and from <MDL to 2.46 ng g^{-1} d.w. for TMP. The highest concentrations were observed for SMX up to 419.2 ng g^{-1} d.w. Compounds observed sporadically were found at low concentrations, with one exception – SMT. In the case of SMT, notable concentrations were observed (12.85 and 20.84 ng g^{-1} d.w.).

This preliminary study has demonstrated for the first time the occurrence of the analyzed compounds in sediments collected in the Polish coastal area. It is worth noting that very little information is available on the concentrations of antibiotic residues in marine sediments. Most of the available data has been reported for Asian coastal seas. In general, the maximum concentrations of sulfonamides in marine sediments in other geographical areas were lower than in the present study. For example, Na et al. (2013), investigating the

Table 4 Occurrence of target compounds in sediment samples collected from the southern Baltic Sea.

Sampling station	Concentration, mean value (SD) [ng g^{-1} d.w.]											
	ST	SP	SRZ	SMZ	SMT	SCP	SMX	SSX	SDM	TMP	OA	ENR
1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	11.12 (0.42)	n.d.	n.d.	<MQL	n.d.	n.d.
1A	<MQL	n.d.	<MQL	1.76 (0.23)	n.d.	1.07 (0.32)	2.34 (0.61)	<MQL	<MQL	2.46 (0.12)	n.d.	n.d.
2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3	n.d.	n.d.	n.d.	n.d.	n.d.	0.54 (0.04)	7.83 (0.40)	n.d.	n.d.	<MQL	n.d.	n.d.
3A	n.d.	n.d.	n.d.	n.d.	n.d.	<MQL	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
4	n.d.	n.d.	n.d.	<MQL	n.d.	0.55 (0.06)	67.24 (5.32)	n.d.	n.d.	<MQL	n.d.	n.d.
5	1.77 (0.03)	n.d.	n.d.	n.d.	20.84 (0.52)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
6	n.d.	n.d.	n.d.	n.d.	12.85 (0.23)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
7	n.d.	n.d.	n.d.	<MQL	n.d.	0.47 (0.23)	275.8 (13.1)	n.d.	n.d.	1.74 (0.03)	n.d.	n.d.
8	n.d.	n.d.	n.d.	n.d.	n.d.	<MQL	185.7 (5.4)	n.d.	n.d.	n.d.	n.d.	n.d.
9	n.d.	n.d.	n.d.	n.d.	n.d.	<MQL	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
10	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	419.2 (2.6)	n.d.	n.d.	n.d.	n.d.	n.d.

n.d. not detected (<MDL below method detection limit), <MQL below method quantification limit, ST, sulfathiazole; SP, sulfapyridine; SRZ, sulfamerazine; SMZ, sulfamethazine; SMT, sulfamethiazole; SCP, sulfachloropyridazine; SMX, sulfamethoxazole; SSX, sulfisoxazole; SDM, sulfadimethoxine; TMP, trimethoprim; OA, oxolinic acid; ENR, enrofloxacin; SD, standard deviation.

occurrence of 20 antibiotics in the coastal areas of Dalian (China), reported different patterns in the maximum concentration and frequency of sulfonamides: ST, SRZ and SMZ were at maximum levels in the range of 1.8–3.7 ng g^{-1}, whereas SMT, SCP, SMX, SSX and SDM were not detected in any sediment sample, despite some of them being present in seawater. Seasonal variations in the detection frequency of ST, SP, SRZ, SMZ, SMX and ENR, and a maximum concentration range of <LOQ to 9.1 ng g^{-1}, were observed by Shi et al. (2014) in the Yangtze Estuary. In the same area, Yang et al. (2011) observed SMX in water but not in sediments. Low levels of SMZ and ENR, and an absence of SMX, were also observed by Liang et al. (2013) in sediments of the Pearl River Estuary. In sediments of the Mar Menor Lagoon (Spain), the concentration of SMX was <LOD and that of TMP was <LOQ (Moreno-González et al., 2015). Low concentrations (<1 ng g^{-1}) of SMT and TMP were measured in sediments around Auckland in New Zealand (Stewart et al., 2014). Higher concentrations of SMX, TMP and OA than reported in this article have been detected in sediment collected near aquacultures. Le and Munekage (2004) observed levels of these compounds in the range of 1.8–820 μg g^{-1} in Viet Nam shrimp ponds, where these antibiotics are popular components of shrimp feed (Le and Munekage, 2004). The authors also observed higher concentrations of antibiotic residues in sediments than in water samples in the vicinity of these shrimp farms (Le and Munekage, 2004).

The observed levels of sulfonamides and trimethoprim in the collected sediments were higher than those reported for Baltic seawaters (Borecka et al., 2013; Nödler et al., 2014) and Polish river waters (Gbylik-Sikorska et al., 2014). The spatial distribution of the analyzed antibiotics indicates a high level of antibiotics occurring in the Pomeranian Bay and in the mouths of rivers. The highest SMX levels were found at station 10 (Pomeranian Bay) close to the mouth of the Świna river (station 10 – 419.2 ng g^{-1} d.w.). A high level of SMX was also observed close to the mouths of the Parsęta river (station 7 – 275.75 ng g^{-1} d.w.) and the Dziwna river (station 8 – 185.70 ng g^{-1} d.w.). To exclude the influence of artificial interference resulting in the detection of high concentrations of SMX, the analyses of samples from stations 7, 8 and 10 were repeated by independent analysts. In the case of the Gulf of Gdańsk, samples collected in summer from the station in the mouth of the Vistula, close to the Wastewater Treatment Plant (WWTP) 'Gdańsk Wschód' outlet (1A), were characterized by the highest frequency of antibiotics. These results were quite different from those for samples collected from the same place in April (1), where only SMX and TMP were detected. Samples collected in April and June (stations 3 and 3A), near to the WWTP 'Gdynia Dębogórze' outlet, demonstrated much lower antibiotic frequency than stations 1 and 1A. There was only one sample – collected from the Gdańsk Deep station – where none of the analytes were detected.

The presence of SMX and TMP most probably results from their application in medicine (commonly used together in the ratio 5:1) (Chang et al., 2008). The main source of these compounds in the investigated samples may be wastewaters from WWTPs. Łuczkiewicz et al. (2013) proved that the removals of TMP and SMX in Gdańsk WWTP were only in the range of 7–38% and 47–65% respectively. Another source of compounds like SCP or SMZ may be used in livestock, further surface runoff from soil, and final discharge to the sea (Xu et al., 2014). The results from station 10 (mouth of the Świna river), which show high concentrations of SMX, were very surprising and may be caused by different factors like, for example, the impact of the Odra and Świna rivers or the city of Świnoujście (a point source of pollution). Such phenomena were also observed by Nödler et al. (2014) for caffeine in the Cape Arcona area (western Baltic Sea). It is suggested that, as this location includes popular tourist destination places, the detected concentrations may be attributed to tourist activities. The influence of tourist activity on pharmaceutical levels was also observed by Moreno-González et al. in the Mar Menor lagoon (western Mediterranean Sea) (Moreno-González et al., 2015). The mouth of the Świna river has a high shipping throughput and the coast nearby is a popular tourist attraction, so the high level of pollution may be caused by tourists and sewage dumping by ships near the sampling location. This hypothesis about tourist activity influencing contamination could also explain the higher frequency of antibiotic residue occurrence at station 1A in the coastal area of the Gulf of Gdańsk in summer compared to spring. However, to verify this hypothesis, a greater volume of data would be necessary.

Table 5 The Pearson linear correlation between environmental parameters and SMX, TMP, SCP (measurable intensity) in sediment samples collected from the southern Baltic Sea.

Compound	LOI [%]	<0.063 mm [%]	*S* [PSU]	*T* [°C]	pH	O_2 [mg dm^{-3}]	SPM [mg dm^{-3}]
SMX	0.1144	0.4279	−0.2815	−0.1220	−0.8012*	−0.6280	0.5374
	n = 7	*n* = 7	*n* = 7	*n* = 7	*n* = 7	*n* = 7	*n* = 7
	p = 0.807	*p* = 0.338	*p* = 0.541	*p* = 0.794	*p* = 0.030	*p* = 0.131	*p* = 0.213
TMP	−0.3975	0.3444	−0.9619*	0.2067	−0.1127	0.7057	−0.0761
	n = 5	*n* = 5	*n* = 5	*n* = 5	*n* = 5	*n* = 5	*n* = 5
	p = 0.508	*p* = 0.570	*p* = 0.009	*p* = 0.739	*p* = 0.857	*p* = 0.183	*p* = 0.903
SCP	−0.1373	−0.1323	−0.0939	−0.4345	0.3111	0.5496	−0.0665
	n = 7	*n* = 7	*n* = 7	*n* = 7	*n* = 7	*n* = 7	*n* = 7
	p = 0.769	*p* = 0.777	*p* = 0.841	*p* = 0.330	*p* = 0.497	*p* = 0.201	*p* = 0.887

n, number of samples; LOI, loss on ignition; *S*, salinity; SPM, suspended particulate matter content; SMX, sulfamethoxazole; TMP, trimethoprim; SCP, sulfachloropyridazine.

* $p < 0.05$.

Statistical analyses showed that SMX concentrations correlate with bottom water parameters like pH (Table 5). Białk-Bielińska et al. (2012) confirmed that sulfadimethoxine and sulfaguanidine had lower K_d values with increasing pH. The inverse Pearson correlation between TMP and the salinity of bottom waters may be caused by the dilution of this compound in marine waters (Liang et al., 2013; Zhang et al., 2012). No significant correlation existed between the concentrations of the target compounds and the sediment properties, which is in contrast with the situation for persistent organic pollutants (POPs). The content of POPs, which are hydrophobic compounds, in sediments, in general, strongly correlates with organic matter content and fine grain content (Pazdro, 2004). Although the obtained results indicate that the sediment composition is not the determining factor in the retention of the analyzed antibiotics, it should be remembered that the number of samples is low for statistical analyses and that a larger database would help in drawing conclusions. Due to the hydrophilic properties of the target antibiotics, sorption on sediment particles is more complex than that of hydrophobic organic contaminants (Beretta et al., 2014). Antibiotics like sulfonamides or trimethoprim are generally persistent in the marine environment and are sparingly adsorbed by sediment due to their physicochemical properties (Benotti and Brownawell, 2009; Boxall, 2008b; Hektoen et al., 1995; Sukul and Spiteller, 2006; Thiele-Bruhn, 2003; Tolls, 2001). On the other hand, quinolones are easily photodegraded and strongly adsorbed by solid matrices (Khetan and Collins, 2007; Kümmerer, 2008a, 2008c; Le-Minh et al., 2010; Zhang et al., 2012). García-Galán et al. (2010) concluded that the high presence of some antibiotic residues in the environment has more to do with the high quantities employed than with physicochemical properties such as the solubility of the compound in water. This could be the reason why SMX, TMP and SCP were detected more frequently than OA, ENR or other sulfonamides.

4. Conclusions

A reliable method for the simultaneous determination of sulfonamides, trimethoprim and selected quinolones has been developed. Nevertheless, the employment of isotope-labelled internal standards should be considered in the future research to further compensate for matrix effects. The obtained method has been applied to analyze the Baltic Sea sediments. This preliminary study demonstrates for the first time the occurrence of antibiotic residues in the southern Baltic Sea. The obtained results suggest that sediment can be an important sink and, in some cases, a secondary source of antibiotic residues like sulfamethoxazole, sulfachloropyridazine or trimethoprim in the marine environment. Consequently, the studies will be continued to establish a more extensive database of the occurrence of antibiotic residues in the southern Baltic Sea and to identify factors governing their spatial and temporal distribution.

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