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Development of potential candidate reference materials for drugs in bottom sediment, cod and herring tissues

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HIGHLIGHTS

- Candidate RMs for analysis of drugs in environmental samples were developed.
- Quantitative analysis was performed by two optimized UHPLC-MS/MS methods.
- A methods validation was performed.
- A homogeneity and stability studies were performed.

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ABSTRACT

Regular use of a reference material and participation in a proficiency testing program can improve the reliability of analytical data. This paper presents the preparation of candidate reference materials for the drugs metoprolol, propranolol, carbamazepine, naproxen, and acenocoumarol in freshwater bottom sediment and cod and herring tissues. These reference materials are not available commercially.

Drugs (between 7 ng/g and 32 ng/g) were added to the samples, and the spiked samples were freeze-dried, pulverized, sieved, homogenized, bottled, and sterilized by γ-irradiation to prepare the candidate materials. Procedures for extraction and liquid chromatography coupled with tandem mass spectrometry were developed to determine the drugs of interest in the studied material. Each target drug was quantified using two analytical procedures, and the results obtained from these two procedures were in good agreement with each other. Stability and homogeneity assessments were performed, and the relative uncertainties due to instability (for an expiration date of 12 months) and inhomogeneity were 10–25% and 4.0–6.8%, respectively. These procedures will be useful in the future production of reference materials.

1. Introduction

Thousands of tons of pharmacologically active substances are used yearly to treat illnesses. For decades, environmentalists have focused on the study of chemicals whose presence in the environment has been regulated by the various lists of criteria or priority pollutants included in different legislations (Petrie et al., 2015). The development of new and more sensitive methods for both detecting chemicals and determining their biological effects has, however, shifted the attention of the scientific community towards new unregulated contaminants including pharmaceuticals. Most drugs are measurable in drinking and river waters and

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sediments, suggesting that pharmaceutical products are widespread contaminants with possible implications for human health and the environment (Jørgensen and Halling-Sørensen, 2000; Rosi-Marshall et al., 2015). For this reason, analyses are routinely performed to test for a wide variety of residual pharmaceuticals in environmental samples, such as water, sediment and fish tissues that are under quarantine or on the market.

The analysis of drugs in environmental samples includes the complex extraction of the target pharmaceuticals, multi-step clean-up of the extracts, and sensitive and selective quantification via a chromatographic technique (Alda et al., 2003; Gros et al., 2006; Petrović et al., 2005; Ternes, 2001). A variety of methodologies is available for both the screening and confirmatory analysis of drugs, especially in the waters, e.g., gas chromatography (GC), mostly coupled to flame ionization or electron capture detectors (Ebrahimi et al., 2015; Migowska et al., 2012) or a mass spectrometer (GC-MS) (Duong et al., 2014; Kumirska et al., 2015; Racamonde et al., 2015), and liquid chromatography (LC) coupled to UV or diode array detectors (LC-UV or LC-DAD) (Baranowska and Kowalski, 2010; 2012; Tao et al., 2009) or a mass spectrometric system (LC-MS or LC-MS/MS) (Cahill et al., 2004; Huntscha et al., 2012; Leendert et al., 2015; Wode et al., 2012). Only certain methods have proven to be satisfactory for the analysis of drugs in the matrices proposed in this work (Díaz-Cruz et al., 2003; Magiera et al., 2015; Petrović et al., 2010; Wagil et al., 2015).

To ensure the reliability of the analytical results, validation of the performance of the method of drug analysis is essential, as noted in several reports and studies. Certified reference materials (CRMs) are a key element of the validation/verification of analytical methods, as well as of the quality assurance in individual laboratories (Griepink et al., 1991; Kiełbasa and Buszewski, 2015; Nogueira, 2015; Ulberth, 2006; Zakaria and Rezali, 2014). The complementary use of CRMs is useful for the evaluation of an analytical method in many testing laboratories because the conditions of the analytes in CRMs are more similar to those in actual samples (Maier, 1991). It is preferable, although not always possible, to obtain CRMs from natural materials that contain drugs, especially containing less popular pharmaceuticals. In this case, it is acceptable to spike the candidate matrix of interest with analytes if the grain size is reasonably small, the samples are homogeneous and the phase stability is under control (Sobiech-Matura et al., 2016; ISO Guide 35, Section 5.7.4).

The objective of this work was to evaluate analytical procedures and methods for measurement of the mass fractions of the drugs metoprolol (MET), propranolol (PRO), carbamazepine (CBZ), naproxen (NAP), and acenocoumarol (ACE) in candidates environmental reference materials (RMs) for bottom sediment (BS), cod tissue (CT) and herring tissue (HT). The procedures included sample preparation, qualitative analysis, quantitative analysis, verification, and studies of homogeneity and stability.

2. Materials and methods

2.1. Chemicals

High-purity-grade (>95%) pharmaceutical standards including: (±)-metoprolol (+)-tartrate salt (MET), (±)-propranolol hydrochloride (PRO), carbamazepine (CBZ), naproxen (NAP) and ketoprofen (KET) (IS, internal standard, positive ionization) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Acenocoumarol (ACE) was obtained from U.S. Pharmacopeia (Rockville, MD, USA). (±)-Carvedilol (CAR) (IS, internal standard, negative ionization) was purchased from Toronto Research Chemicals Inc. (North York, Canada). HPLC-grade formic acid, water, ammonium acetate and acetonitrile were obtained from Merck (Darmstadt, Germany). Analytical-grade methanol and acetonitrile were purchased from POCH S.A. (Gliwice, Poland).

2.2. Standard solutions, calibration standards and quality control (QC) sample

Primary stock solutions of the analytes and ISs (1 mg/mL) were prepared in methanol, stored at 4 °C and brought to room temperature before use. Working solutions from 1 to 5000 ng/mL were used to prepare the calibration standards. The working solutions were prepared by diluting the stock solutions of all analytes with methanol. A working standard solution of the ISs (10 μg/mL) was prepared by diluting the stock solution with water and storing it at 4 °C.

To obtain calibration standards (CS), the working solutions were added to drug-free bottom sediment and cod and herring tissues as blank samples. In this way, calibration samples for the analyzed compounds were prepared from 1.0 to 100 ng/g or from 1.0 to 200 ng/g (Method I) and from 5 to 30 ng/g or from 5 to 40 ng/g (Method II).

Quality control (QC) samples were prepared in the same way as the calibration samples at three mass fractions: 5 ng/g (low, LQC); 50 ng/g (middle, MQC); and 80 ng/g or 150 ng/g, depending on the compound and the matrix (high, HQC) (Method I) and 7 ng/g (low, LQC); 15 ng/g or 20 ng/g depending on the compound and the matrix (middle, MQC); and 25 ng/g or 35 ng/g, depending on the compound and the matrix (high, HQC).

2.3. Samples

Three candidates for RMs with different matrix compositions, identified as BS (bottom sediment), CT (cod tissues) or HT (herring tissues), were prepared by spiking the matrices with the drugs of interest.

The bottom sediment was taken from the Vistula River near Włocławek, Poland, by a professional company with diving equipment. Then, gravel and leaves were removed from the bottom sediment, and the material was frozen. Before use, the collected material was lyophilized, ground and sieved through a nylon sieve, and the fraction with a particle size below 90 μm was separated. The particle size distribution of the collected fraction was tested evaluated microscopically and using the laser diffraction method.

The lyophilized bottom sediment (1.0 kg) was placed in a beaker. A mixed solution of drugs was prepared in methanol with each of the compounds at a concentration between 20 μg/mL and 32 μg/mL. The mixture was further diluted with methanol to obtain solutions with concentrations between 2 μg/mL and 3.2 μg/mL. Ten milliliters of this reference drugs solution was quantitatively transferred to a volumetric flask (1 L) and brought up to volume with acetone. The bottom sediment was flooded with 1 L of the drug solution in acetone. The beaker was protected from light and stirred with a mechanical stirrer, and inert gas was applied to the surface of the solvent and overly rapid evaporation of the acetone. When the acetone was at a height of 1 cm above the precipitate, a solvent evaporation was interrupted. The beaker was then placed in a vacuum oven at 25 °C for 24 h.

The powdered material thus obtained was homogenized by mixing for 16 h in a homogenizer that rotated the container in three planes, providing good mixing of the samples. Then, the material was distributed into amber glass bottles. All bottles containing samples were sterilized by electron beam irradiation (energy of 13 MeV) using the linear accelerator LAEA-13 with a dose of 28 kGy to ensure the long-term stability of the material.

Herring (*Clupea harengus*) were taken from the North Sea, and cod (*Gadus morhua*) were obtained from the Baltic Sea. Muscle