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Determination of antihypertensive and anti-ulcer agents from surface water with solid-phase extraction–liquid chromatography–electrospray ionization tandem mass spectrometry

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ABSTRACT

Pharmaceuticals are emerging contaminants in surface water and they must be measured to follow their effects on the aquatic environment. We developed a solid-phase extraction and liquid chromatography–electrospray ionization tandem mass spectrometry (SPE-LC–ESI-MS/MS) method for the determination of twenty-six pharmaceutical compounds – which belong to antihypertensive and anti-ulcer agents – from surface water samples. The selection of pharmaceuticals was based on usage frequency in Hungary. During method development Oasis HLB, SampliQ Polymer SCX and Si-SCX SPE cartridges were tested. As LC eluent ammonium formate, ammonium acetate buffers at pH 3 and 5 were investigated and for quantitation both matrix-matched and internal standard calibration was used. For matrix effect assessment post-extraction spike method was applied which can separate the extraction efficiency from ion suppression for better determination of recovery. Method detection limits (MDLs) varied between 0.2 and 10 ng/L. Precision of the method, calculated as relative standard deviation (RSD), ranged from 0.2 to 14.6% and from 1.2 to 22.4% for intra- and inter-day analysis, respectively. The method was applied to analyze Danube water samples. Measured average concentrations varied between 2 and 39 ng/L for eleven compounds and another one could be detected under LOQ.

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1. Introduction

Due to growing consumption, improper disposal of unused or expired drugs and disability of waste water treatment plants to remove them entirely, pharmaceuticals are emerging contaminants in the environment [1,2]. Huge amount of drugs are used in medical and veterinary treatment. After excretion they can be found in the environment either in their parent forms or as metabolites or as transformation products, generated during the waste water treatment [3].

Acute toxicity is not the biggest concern, but over long periods of time the continuous inflow of pharmaceuticals in surface water even at low levels could cause changes in organisms. Moreover, mixtures of pharmaceuticals could also have even stronger negative impact on aquatic fauna and flora [4,5].

Consequently there is a need for reliable analytical methods, which enable the sensitive and selective determination of these substances, even at trace levels. Several methodologies are already available for the determination of different kinds of pharmaceuticals in surface and waste waters. Among them there are a few groups which are fairly well investigated such as antibiotics [6–10], endocrine disruptors [11–13], non-steroidal anti-inflammatories [14–17], psychiatric drugs [18,19] and X-ray contrast media [20–22]. Nevertheless, there are other increasingly applied types of pharmaceuticals, like antihypertensive drugs, which should also be studied.

Measuring polar compounds, such as polar pharmaceuticals and their even more polar metabolites, is a kind of challenge: applying GC–MS they have to be derivatized, which is very time-consuming and generally compromises the reliability of the method, while applying LC–MS derivatization can be avoided but one has to deal with matrix effects during the atmospheric pressure ionization of the molecules [23–28]. The already existing methods for pharmaceutical residue analysis are either based on gas chromatography–mass spectrometry [29–31] or liquid chromatography–tandem mass spectrometry [18,19,32–38], but there is a growing tendency of applying LC–MS/MS, due to its unique selectivity and sensitivity.

There are two common methods to assess matrix effects [39]: the post-column infusion method, defined by Bonfiglio et al. [40], and the post-extraction spike method, proposed by Matuszewski et al. [41,42]. The post-column infusion method provides a qualitative assessment of matrix effects, identifying chromatographic regions most likely to experience matrix effects [43]. In contrast,

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the post-extraction spike method quantitatively assesses matrix effects by comparing the response of an analyte in neat solution to the response of the analyte spiked into a blank matrix sample that has been carried through the sample preparation process. In this manner, quantitative effects on ion suppression or enhancement experienced by all analytes in the sample can be measured. So far, there are mostly bioanalytical methods applying the latter procedure to assess matrix effects [41,42,44] but environmental samples are also matrix loaded therefore it is worth to extend this approach for handling large volumes of surface water samples.

We developed a solid-phase extraction–liquid chromatography–electrospray ionization tandem mass spectrometry method for the determination of twenty-six basic pharmaceutical compounds. Since in Hungary the most often prescribed drugs are antihypertensive and anti-ulcer agents the following types of pharmaceuticals were chosen: four H_2-receptor antagonists, three proton pump inhibitors, nine β-blockers, three selective calcium-channel blockers, three angiotensin-converting enzyme inhibitors and four HMG-CoA reductase inhibitors (also called statins). During method development we evaluated four different solid-phase extraction methods with the application of three different kinds of sorbents (one silica-based and two polymeric types) and compared the effects of different modifiers and pH of the mobile phase. For matrix effect assessment post-extraction spike method was applied. Quantitation was done with internal standard calibration, with the application of three deuterium-labeled internal standard combined with matrix-matched calibration. The method performance parameters such as linearity, accuracy, precision and limit of detection and quantitation were determined before the method was applied to river water samples.

2. Material and methods

2.1. Chemicals and materials

All pharmaceutical standards were of high purity grade (>90%). Acebutolol, atenolol, betaxolol, carvedilol, cimetidine, esmolol, metoprolol, nifedipine, nizatidine, oxprenolol, propranolol and sotalol were purchased from Sigma-Aldrich (Hungary). Atorvastatin–calcium, famotidine, lisinopril·$2H_2O$, lovastatin, pantoprazole–sodium, ranitidine·HCl, ramipril and simvastatin were from Wessling NCo. by courtesy. Atenolol-d_7, enalapril-d_5 and lansoprazole-d_4 were purchased from CDN Isotopes (Quebec, Canada). Nimodipine and omeprazole were from Calbiochem (Darmstadt, Germany). Fluvastatin–sodium was from USP (Rockville, MD). Amlodipine besylate and enalapril maleate were from Richter Gedeon Co. by courtesy. Lansoprazole was from LGC Standards (Wesel, Germany).

Acetonitrile, methanol of HPLC gradient grade quality; acetone, n-hexane and dichloromethane for gas chromatography; diethyl-ether and ethyl-acetate for chromatography were from Merck (Darmstadt, Germany). Water was deionized in our laboratory using a Millipore (Billerica, MA, USA) Milli-Q water purification system. Ammonium formate (cryst. Extra pure, Ph Eur), ammonium acetate (cryst. Extra pure, Ph Eur), formic acid (Extra pure, Ph Eur) and acetic acid (Extra pure, Ph Eur) were form Merck (Darmstadt, Germany). 25% aqueous NH_4OH (analytical grade) was also from Merck (Darmstadt, Germany). Paper filters (3hw type) were purchased from Spektrum-3D (Hungary).

Standard and internal standard stock solutions of 1 mg/mL were prepared in methanol, with the exception of statin compounds (atorvastatin, fluvastatin, lovastatin and simvastatin), which were prepared in acetonitrile because they proved to be degradable in methanol [45,46]. All stock solutions were stored at −18 °C in a refrigerator for a maximum time of two months. Working and calibration solutions were prepared in 10% methanol in Millipore water and stored in the dark below 4 °C.

2.2. Solid-phase extraction

Pharmaceuticals were extracted from 500 mL of tap or surface water with the application of four different extraction methods using Waters Oasis HLB (500 mg, 6 mL), Agilent SampliQ Polymer SCX (150 mg, 6 mL) and Agilent SampliQ Si-SCX (500 mg, 6 mL) solid phase extraction cartridges. Particles in the water were removed by filtering through paper filter. Before extraction 50 ng of internal standards were added and in the case of spiked samples 500 μL solution containing all the compounds at a concentration of 25, 50, 100 or 300 ng/mL was also added.

2.2.1. Extraction Method I

pH of the water samples was adjusted to 10 with 25% aqueous NH_4OH. SampliQ Polymer SCX cartridges were conditioned with 5 mL of methanol and equilibrated with 5 mL of Millipore water pH adjusted to 10 with 25% aqueous NH_4OH. Samples were introduced onto the cartridges through PTFE tubes at a flow rate of 3–4 mL/min. After sample loading the cartridges were washed with 5 mL of Millipore water pH adjusted to 10 with 25% aqueous NH_4OH. Cartridges were then dried for at least 10 min with vacuum, and subsequently, the pharmaceuticals were eluted with 2.5 mL of methanol and 2.5 mL of methanol–25% aqueous NH_4OH (1:1, v/v) in the same collection vial.

2.2.2. Extraction Method II

pH of the water samples was adjusted to 10 with 25% aqueous NH_4OH. SampliQ Si-SCX cartridges were conditioned with 5 mL of methanol and equilibrated with 5 mL of Millipore water pH adjusted to 10 with 25% aqueous NH_4OH. Samples were introduced onto the cartridges through PTFE tubes at a flow rate of 3–4 mL/min. After sample loading the cartridges were washed with 5 mL of Millipore water pH adjusted to 10 with 25% aqueous NH_4OH. Cartridges were then dried for at least 10 min with vacuum, and subsequently, the pharmaceuticals were eluted with 2.5 mL of methanol and 2.5 mL of methanol–25% aqueous NH_4OH (1:1, v/v) in the same collection vial.

2.2.3. Extraction Method III

Oasis HLB cartridges were conditioned with 5 mL of methanol and equilibrated with 5 mL of Millipore water. Samples were introduced to the cartridges through PTFE tubes at a flow rate of 3–4 mL/min. After sample loading, the solid phase was washed with 5 mL of Millipore water. Cartridges were then dried for at least 10 min with vacuum, and subsequently, the pharmaceuticals were eluted with 5 mL of methanol.

2.2.4. Extraction Method IV

pH of the water samples was adjusted to 10 with 25% aqueous NH_4OH. Oasis HLB cartridges were conditioned with 5 mL of n-hexane, 5 mL of acetone, 10 mL of methanol, and then equilibrated with 10 mL of Millipore water, pH adjusted to 10, with 25% aqueous NH_4OH. Samples were introduced to the cartridges through PTFE tubes at a flow rate of 3–4 mL/min. After sample loading, the solid phase was washed with 5 mL of 5% methanol in 2% aqueous NH_4OH. Cartridges were then dried for at least 10 min with vacuum, and subsequently, the pharmaceuticals were eluted with 5 mL of methanol.

In all four cases extracts were evaporated to dryness by a gentle stream of nitrogen and reconstituted in 500 μL of 10% methanol in Millipore water, with the exception of the post-extraction spiked

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