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Multi-residue determination of psychoactive pharmaceuticals, illicit drugs and related metabolites in wastewater by ultra-high performance liquid chromatography-tandem mass spectrometry

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ABSTRACT

This study presents a new multi-residue analytical method for the simultaneous determination of 38 psychoactive drugs (including benzodiazepines, antidepressants and drugs of abuse) and related metabolites in raw wastewater. Potential analyte losses during sample filtration and stability in wastewater were evaluated. Analyte losses, especially for 12 compounds, were observed during filtration, indicating a strong sorption onto the filter material. In order to overcome this effect, filtered water samples were combined with methanolic washes of the corresponding filters and the resulting solutions were solid-phase extracted on mixed-mode (reverse-phase plus cation-exchange) sorbents. Extracts were analyzed by ultra-high performance liquid chromatography-tandem mass spectrometry. Quantification was performed by the internal standard method with isotopic labeled analogs. Recovery percentages varied between 65% and 137%; method quantification limits ranged between 0.2 and 22 ng/L in ultrapure water and between 0.3 and 30 ng/L in wastewater for all the analytes but three (for which they were ~60–80 ng/L). The analysis of 24 h-composite samples collected during one week in the city of Santiago de Compostela demonstrated the ubiquity of 31 analytes, which were positively quantified in all samples. The highest concentrations were found for some of the antidepressants, with mean and maximum levels exceeding, in some cases, the levels previously reported in literature. This fact could be related to the additional washing step of the filters using methanol, which allowed to desorb retained analytes highlighting the importance of this step during the sample preparation protocol.

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1. Introduction

Psychoactive pharmaceuticals, drugs of abuse and their metabolites are widely known to be present in urban wastewaters due to their high rates of production and consumption [1–9]. According to the Health Indicators of the Organization for Economic Co-operation and Development (OECD) [10], the use of antidepressants has increased considerably in most OECD countries since the year 2000, with selective serotonin reuptake inhibitors (SSRIs, e.g. fluoxetine, paroxetine, sertraline, citalopram) being the most popular in Spain [11]. Anxiolytics and hypnotics, particularly benzodiazepines (lorazepam, diazepam, alprazolam), are another group of medicines with remarkable rates of prescription [12]. And,

among drugs of abuse, cannabis accounts for the largest estimate of abuse in the European Union, followed by cocaine, ecstasy, other amphetamine-derived compounds and opioids [13]. Following this widespread consumption, residues of licit and illicit psychoactive substances enter sewage systems continuously [1–9], a fact that may imply environmental consequences (if they end in surface waters [9,14,15]) and act as a measurable indicator of their use in different communities [2,5,16,17].

Most of the analytical methodologies developed for the determination of psychoactive substances in wastewater remove suspended particles by filtration or centrifugation prior to solid-phase extracting the aqueous phase. However, organic molecules may get adsorbed onto solids following a process that depends on the properties of both the substance (pK_a , K_{ow} , etc.), the suspended particle matter (SPM) and the water itself (pH, Total Organic Carbon - TOC) and the filtering materials. Therefore, sorption is very hard to predict and, if a proper evaluation of the portion of sub-

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stance adsorbed is not performed, it is possible to underestimate its levels in real samples [18–24]. In the case of drugs and pharmaceuticals, Baker et al. [18] assessed the sorption onto wastewater SPM for 16 out of the 38 analytes included in our study and concluded that it was >10% for methadone and 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and >30% (up to 89% in one of the samples) for some antidepressants like fluoxetine and norfluoxetine. This result highlighted the need to take sorption processes into consideration for the development of future sample preparation protocols for these analytes.

In this line, this study presents a novel sample preparation strategy for the solid-phase extraction (SPE) of 38 psychoactive drugs and metabolites in wastewater. Particular attention was paid to pretreatment steps, including water filtration, washing of the filters and in-sample stability, in order to avoid the under-reporting of concentrations in real wastewater. The analytes were carefully selected to be the most frequently prescribed psychoactive pharmaceuticals, the most frequently abused drugs in Spain and their most relevant metabolites: i) seven benzodiazepines and two of their metabolites; ii) methylphenidate - a psycho-stimulant drug used in the treatment of attention deficit hyperactivity disorder - and its main metabolite ritalinic acid; iii) eight antidepressants and five of their metabolites; and iv) eight illicit drugs, five metabolites and levamisole, the most common adulterant of cocaine. Analytes were separated and detected by ultra-high performance liquid chromatography (UHPLC) coupled to tandem mass spectrometry (MS/MS). Parameters affecting UHPLC separation and MS/MS detection were carefully optimized and the final method was validated in terms of trueness, precision and quantification limits. Finally, it was applied to the analysis of 24 h-composite raw wastewater samples collected during one week in the city of Santiago de Compostela (NW of Spain).

2. Experimental

2.1. Reagents and materials

Analyte standards were supplied by Cerilliant (Round Rock, TX, USA) as individual solutions of 100 µg/mL of norsertraline and O-desmethylvenlafaxine, or 1000 µg/mL in methanol (MeOH) of alprazolam, α-hydroxyalprazolam, diazepam, nordiazepam, oxazepam, temazepam, lorazepam, lormetazepam, chlordiazepoxide, methylphenidate, ritalinic acid, citalopram, N-desmethylcitalopram, fluoxetine, norfluoxetine, sertraline, venlafaxine, mirtazapine, N-desmethylmirtazapine, duloxetine, paroxetine, trazodone, amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), cocaine, benzoylecgonine, cocaethylene, levamisole, 11-hydroxy-Δ9-THC (THC-OH), 11-nor-9-carboxy-Δ9-THC (THC-COOH), meta-chlorophenylpiperazine (mCPP), mephedrone, ketamine, methadone and EDDP. Isotopic labeled analogs (α-hydroxyalprazolam-D5, alprazolam-D5, diazepam-D5, nordiazepam-D5, oxazepam-D5, temazepam-D5, lorazepam-D4, methylphenidate-D9, ritalinic acid-D10, citalopram-D6, N-desmethylcitalopram-D3, fluoxetine-D6, norfluoxetine-D6, sertraline-D3, norsesertraline-¹³C6, venlafaxine-D6, O-desmethylvenlafaxine-D6, duloxetine-D3, paroxetine-D6, trazodone-D6, amphetamine-D6, methamphetamine-D5, MDMA-D5, cocaine-D3, benzoylecgonine-D3, cocaethylene-D3, THC-OH-D3, THC-COOH-D3, mCPP-D8, mephedrone-D3, ketamine-D4, methadone-D3 and EDDP-D3) were also supplied by Cerilliant as 100 µg/mL solutions in MeOH and used as internal standards (IS). Mixed stock solutions containing all the analytes (10 µg/mL) or all the IS (2 µg/mL) were prepared in MeOH and stored in the dark at -20 °C until use.

HPLC-grade MeOH, acetonitrile (ACN), acetic acid (100%) and ammonia solution in ultrapure water (25%) were supplied by Merck (Darmstadt, Germany). Formic acid (95–97%) and NH₃ solution in MeOH (7 M) were supplied by Sigma-Aldrich (San Luis, MI, USA). Ultrapure water was obtained in the laboratory by purifying demineralized water in a Milli-Q Gradient A-10 system (Merck-Millipore, Bedford, MA, USA).

2.2. Filtration tests

Potential sorption of analytes onto different filter materials was assessed by vacuum filtering 100 mL aliquots of ultrapure water, spiked with 5 ng/mL of all the analytes, through different types of filters: 0.7 µm glass microfiber filters GF/A (Whatman, Kent, U.K.), 0.45 µm mixed cellulose membranes (Millipore, Bedford, MA, USA), 0.45 µm hydrophilic nylon membranes (Millipore) and 0.45 µm hydrophilic PVDF membranes (Millipore). IS were added after filtration and samples (n = 3 in every case) solid-phase extracted as detailed in Section 2.4. Losses were calculated as:

$$\text{Filtration loss (\%)} = \left(1 - \left(\frac{\text{Response}}{\text{Average (Response}_{\text{No filtr}})}} \right) \right) \times 100$$

Where *Response* is the IS-corrected response in a filtered sample and *Average (Response_{No filtr})* is the average of the IS-corrected responses in non-filtered samples. One-way ANOVA (α = 0.05) were performed to compare the mean losses of every analyte with the four types of filters.

For the filters providing the best performance (GF), experiments were repeated with raw wastewater in order to assess the combined sorption onto the filter and the SPM. Aliquots (100 mL, n = 3) were spiked with 5 ng/mL of all the analytes before and after being filtered, IS added after filtration and losses calculated as:

$$\text{Filtration loss (\%)} = \left(1 - \left(\frac{\text{Average (Response}_{\text{Before}})}}{\text{Average (Response}_{\text{After}})}} \right) \right) \times 100$$

Where *Average (Response_{Before})* is the average of the IS-corrected responses in samples spiked before filtration; and *Average (Response_{After})* is the average of the IS-corrected responses in samples spiked after filtration. Individual Student's t-tests (α = 0.05) were run for all the analytes to assess whether there were statistically significant differences between their mean filtration losses in ultrapure water *versus* in raw wastewater, *i.e.*, whether there were differences between their sorption onto filters (exclusively) or their combined sorption onto filters and SPM.

Finally, potential recovery of the analytes adsorbed by means of a methanolic wash of the filter was assessed with raw wastewater samples spiked with 2 ng/mL of all the analytes before and after filtration (n = 3). Filters were washed with 2 × 5 mL of MeOH. Washes were collected, spiked with IS and made to a final volume of 1 mL for instrumental analysis.

2.3. Antidepressant biodegradation tests

Biodegradation of benzodiazepines and drugs of abuse was not assessed since it had been already reported in the literature [25,26].

Potential biodegradation of antidepressants was evaluated by spiking 10 mL of raw wastewater (n = 3) with 500 ng/mL of these analytes and collecting 0.7 mL aliquots at the beginning of the experiment and at different times up to 48 h. Each aliquot was passed through a 0.22 µm GHP membrane syringe filter (Pall laboratory, NY, USA). Subsequently, 0.7 mL of MeOH were used to wash the filter and collected over the water fraction. The resulting solutions were spiked with 100 ng/mL of IS and kept at -20 °C until analysis (by direct injection into the UHPLC-MS/MS system).

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