



Application of polypropylene tubes as single-use and low-cost sorptive extraction materials for the determination of benzodiazepines and zolpidem in water samples



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ABSTRACT

This work presents a method for the simultaneous determination in water of 17 benzodiazepines (BZPs) and a related pharmaceutical (zolpidem) by extraction with low-cost polymeric sorbents followed by liquid chromatography–tandem mass spectrometry (LC–MS/MS). Different polymers were considered: polydimethylsiloxane (PDMS), polypropylene (PP), and polyethersulfone (PES), providing the second one (PP) higher responses. Hence, different operational parameters were considered and optimized using PP as polymeric material for the extraction: ionic strength (as NaCl addition), sample pH, sample volume, extraction time, amount of extractant phase, desorption solvent and desorption time. Under the optimized conditions, 70 mL of sample (pH 9) with 30% (w/v) of NaCl was extracted with four PP tubes (10 mm, ≈ 1 mg each) during 14 h at room temperature, the analytes eluted with 1 mL of acetone and the eluate concentrated to dryness, reconstituted in methanol and analyzed by LC–MS/MS. Under these conditions, extraction efficiencies ranged between 41 and 86%, leading to enrichment factors from 574 to 1204. Satisfactory trueness, expressed as relative recoveries, was obtained in the 87–117% range. LOQs ranged from 0.4 to 31 ng L⁻¹ and from 2 to 94 ng L⁻¹ for river and influent wastewater, respectively. None of the analytes were detected in river water while 6 of them were detected in wastewater samples in concentrations between 4 and 152 ng L⁻¹, being lorazepam and oxazepam the analytes detected at the highest concentration level. Thus, PP may become a good alternative to PDMS or PES for the extraction of basic analytes.

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1. Introduction

Benzodiazepines (BZPs) are psychoactive drugs whose core structure is the fusion of a benzene and a diazepine rings. The properties of BZPs make them useful in treating, for instance anxiety, insomnia, agitation, seizures, muscle spasms and alcohol withdrawal [1,2]. Long-term BZP use is controversial due to concerns about adverse psychological and physical effects since BZPs are prone to cause tolerance and physical dependence [3–5]. Recently zolpidem (ZOLP) has constituted a new generation of pharmaceuticals synthesized with similar action mechanism as classical BZPs but with different chemical structures and many times this compound is included into the reports about BZP consumption since it was included in the same therapeutical group as classical BZPs (N05–Psycholeptics) [6,7].

Besides health problems from the uncontrolled consumption of BZPs, they may also be an environmental problem, since these compounds are excreted partially unchanged or in the form of metabolites

[8]. Thus, BZPs have been detected in wastewaters [9–15] and surface waters [14–16] in several regions of Europe.

The most frequently method used for the enrichment and determination of BZPs is solid-phase extraction (SPE) followed by liquid chromatography–(tandem) mass spectrometry (LC–MS(/MS)) [8–10, 12–18]. However, SPE requires relative large volumes of sample (ca. 100–500 mL) to obtain low limits of quantification (LOQs) that can be translated in tedious filtration process, high possibilities of SPE cartridge clogging and problems with sample storage. Moreover the volume of organic solvents (10–50 mL each sample) [8–15,17] is high that means an eluate poor concentrated and further steps are required. All these disadvantages can be total or partially solved with the use of microextraction techniques.

Microextraction techniques can offer a lower intake of sample and hazardous organic solvents. Some of the most popular ones are solid-phase microextraction (SPME), developed by Pawliszyn et al. [19] in 1989 and stir-bar sorptive extraction (SBSE), introduced by Baltussen et al. [20] in 1999. Both of them rely on equilibrium extraction of a limited volume of sample (normally lower than 100 mL) with a small sorbent material (typically a few µL) than can be easily handled, minimizing or even eliminating solvent usage. Despite the high number of

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applications these techniques have gained in the last years [21–23], the main disadvantage of these procedures is the relatively high price of the extraction devices (SPME fibers and SBSE Twisters®) that involves their reutilization with the associated well-known carry over problems and the decreasing in the extraction efficiency by the chemical and mechanical degradation of the material due to successive uses. Because of this, in 2004, Popp et al. [24] presented an alternative to those devices: the use of disposable bulk silicone (polydimethylsiloxane, PDMS) sorbents for the extraction and concentration of organic compounds in water samples. Rapidly, this new extraction method increased its popularity due to its simplicity and the low price of each device (ca. 0.1 €), so that they could be used in a single and disposable mode, avoiding carry over problems and changes in the extraction efficiency and facilitating parallel extraction of many samples [25–27]. More recently, other sorbent materials with more polar properties, such as polyethersulfone (PES) [28,29] and polypropylene (PP) [28,30] in several formats (membranes, tubes or rods) have also been tested for the same purpose with better response for analytes with these characteristics. PP hollow fibers are widely used as inert solid support for liquid phase microextraction techniques (LPME) since the possibility of immobilizing a few μL of solvent (10–20 μL) in its lumen and pores [31,32], as recently has developed Rezaei et al. [33] for five BZPs in tap water, juices and biological matrix but also it can be used as sorptive material itself for compounds with high K_{ow} and low water solubility through a sorption process instead a liquid liquid mechanism as Müller et al. [34] have pointed. Following this last premise PP tubes as sorptive materials have been tested for the extraction of chloro and bromo toluene derivatives [35] and chlorinated anisoles [30]. So the extraction with polymers is established as a promising alternative for the extraction of organic compounds from water samples, broadening the application field towards more polar compounds.

Thus, the goal of this work was the assessment of the above mentioned three different low-cost disposable materials (PDMS, PES and PP) for the preconcentration of BZPs and ZOLP from water samples prior to their LC–MS/MS determination. The so-developed method would offer an easy-to-perform sample preparation procedure for the environmental determination of BZPs, due to its simplicity and inexpensive character. To the best of our knowledge, this is the first application of sorptive microextraction for BZP determination in environmental samples.

2. Material and methods

2.1. Reagents

Standards of 2-hydroxy-ethylflurazepam (2HEFLU), α -hydroxy-alprazolam (AHALP), α -hydroxy-triazolam (AHTRI), alprazolam (ALP), chlordiazepoxide (CHLOR), clonazepam (CLON), demoxepam (DEM), diazepam (DIA), flunitrazepam (FLUN), flurazepam (FLUR), lorazepam (LOR), lormetazepam (LORM), midazolam (MID), nordiazepam (NDIA), oxazepam (OXA), prazepam (PRA), temazepam (TEM) and ZOLP tartrate were purchased from Cerilliant (Round Rock, TX, USA) as 1000 mg L^{-1} solutions (expressed as neutral compounds) in methanol (MeOH) or acetonitrile (ACN). ALP- d_5 , DIA- d_5 , FLUN- d_7 , NDIA- d_5 , OXA- d_5 , 2HEFLU- d_4 , LOR- d_4 , and ZOLP- d_6 , used as internal standards (ISs), were purchased also from Cerilliant as 100 mg L^{-1} solution in MeOH or ACN. Stock solutions were prepared by dilution of the individual commercial compounds until obtaining a mixture of 18 analytes at 20 mg L^{-1} in MeOH/ H_2O (1:1). In the case of the ISs the stock mixture solution was prepared by dilution of the individual deuterated compounds until obtaining a mix of 5 mg L^{-1} in MeOH/ H_2O (1:1). Successive dilutions of these mixtures were performed to the desired concentrations necessary to spike the samples and to prepare the calibration curves.

LC-grade ACN, acetone and MeOH, glacial acetic acid (100%), hydrochloric acid (HCl) and sodium hydroxide (NaOH) were supplied by

Merck (Darmstadt, Germany). Sodium chloride (NaCl) was supplied by VWR (Llinars del Vallès, Spain). Ultrapure water was obtained in the laboratory by purifying demineralized water in a Milli-Q Gradient A-10 system (Millipore, Bedford, MA, USA). Nitrocellulose filters (pore size of 0.45 μm) and glass fiber pre-filters were purchased from Millipore.

PDMS flexible cord, with a diameter of 2 mm, was obtained from Goodfellow (Huntingdon, UK), Accurel Q3/2 PP (internal diameter of 0.6 mm, wall thickness of 0.2 mm) and PES (external diameter of 0.7 mm) tubular membranes were obtained from Membrana GmbH (Wuppertal, Germany). Pieces of these polymers with a length of 10 mm were manually cut with a scalpel, which represents a mass of sorbent of ca. 1 mg for PES and PP and of ca. 30 mg for PDMS. These tubes/rods were cleaned with MeOH by manual shaking for several minutes and then stored in clean solvent. Just prior to their use, they were dried with a lint-free tissue.

2.2. Samples

Grab wastewater samples of influent and effluent were taken during October 2013 from a local wastewater treatment plant (WWTP), also 24 h composite influent samples were collected in March 2014. The WWTP is located in the northwest of Spain serving a population around 130,000 inhabitants. Grab river samples were taken at river Sar (Santiago de Compostela, Spain) in October 2013.

Samples were collected in 250 mL amber glass bottles previously rinsed with MeOH, ultrapure water and finally with the sample. They were stored in the dark at 4 °C and analyzed prior 12 h after sampling to avoid any kind of degradation. Before analysis, samples were firstly filtered through a glass pre-filter and then with a 0.45 μm nitrocellulose filter.

2.3. Liquid chromatography–tandem mass spectrometry

The liquid chromatograph used in this work is equipped with two ProStar 210 high-pressure mixing pumps (Varian, Walnut Creek, CA, USA), a Metachem Technologies vacuum membrane degasser (Bath, UK), and an autosampler and a thermostated column compartment ProStar 410 module (Varian). A Synergi Fusion RP column (100 mm \times 2.0 mm with 4 μm particle diameter and 80 Å of pore size, Phenomenex, CA, USA) was selected for the analysis. It was protected with a guard column (4 \times 2 mm) of the same stationary phase (Phenomenex). Temperature was maintained at 35 °C. The injection volume was set to 10 μL . Analytes were separated using a flow rate of 0.2 mL min^{-1} of water (A) and MeOH (B), both containing 0.1% of acetic acid. The gradient was as follows: initial conditions 40% B; 0–20 min linear gradient to 50% B; 20–21 min, linear gradient to 100% B; 21–24 min isocratic conditions at 100% B and finally return to the initial conditions of 40% B with 5 additional minutes for column re-equilibration. The total run time is 29 min.

The LC instrument was coupled to a Varian 320-MS triple quadrupole mass spectrometer equipped with an electrospray interface (ESI) operating in positive mode. The ionization source working parameters were as follows: needle voltage 5000 V, ionization source temperature 50 °C, drying gas temperature (N_2) 200 °C, nebulizer gas pressure (N_2) 55 psi, drying gas pressure (N_2) 20 psi, collision gas pressure (Ar, 99.999%, Carbuos Metálicos, Spain) 1.5 mTorr and centroid mode for acquisition. Nitrogen was provided by a nitrogen generator (Domnick Hunter, Durham, UK). Instrument control and data acquisition were performed with the Varian MS Workstation 6.9 software.

Determination of BZPs was performed by recording two transitions for each analyte and just one for each IS in the multiple reaction monitoring mode (MRM) according to the 2002/657/EC decision [36]. Specific ESI-MS/MS parameters for each analyte are listed in Table 1. Validation parameters of the instrumental method were described in a previous work [18].

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