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Development of a macroporous ceramic passive sampler for the monitoring of cytostatic drugs in water

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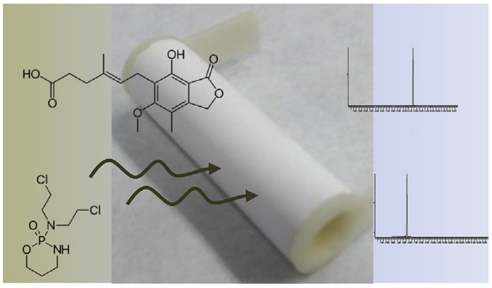
HIGHLIGHTS

- A Macroporous Ceramic Passive Sampler has been designed for monitoring cytostatic compounds in water.
- Water stability affects uptake, and sampling rate was calculated only for 5 out of 16 cytostatics.
- Similar performance was observed between Passive Sampler and grab sampling in WWTP effluents.
- Cytostatics were detected in WWTP effluents wastewaters at low levels.

GRAPHICAL ABSTRACT



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ABSTRACT

The aim of this study was to develop and calibrate a macroporous ceramic passive sampler (MCPS) for the monitoring of anticancer drugs in wastewater. This system was designed by the Spanish Research Council (CSIC) and consists in a porous ceramic tube to allow a high diffusion of contaminants. The MCPS has been calibrated for 16 cytostatic drugs over time periods up to 9 d in spiked water under controlled laboratory conditions. Optimal uptake was accomplished for 7 compounds, namely ifosfamide, cyclophosphamide, capecitabine, prednisone, megestrol, cyproterone and mycophenolic acid, whereas cytarabine was not adsorbed in the receiving phase and the rest were hydrolyzed over the deployment period. The sampling rate for these 7 compounds was between 0.825 and 3.350 mL day^{-1} and the diffusion coefficients varied from 1.01E-07 to 4.12E-07 $cm^2\ s^{-1}$. To prove the applicability of the MCPSs, samplers ($n = 3$) were deployed in influent and effluent waters of a WWTP for a period of 6 d and results were compared to grab sampling and extraction with Solid Phase Extraction (SPE). In influent waters, MCPS were clogged due to the high amount of suspended solids in these waters. In effluents, MCPS detected cyclophosphamide and mycophenolic acid at concentrations of 19 ± 3 and 136 ± 28 ng L^{-1} with a good agreement with the levels obtained by grab sampling. The study discusses the use and performance of the MCPS for the monitoring of stable cytostatic compounds in a complex matrix such as wastewater.

1. Introduction

Passive sampling techniques have emerged as an efficient and relatively inexpensive way of sample collection for the characterization of water pollutants. The main advantages of passive

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samplers are high capacity, time integrated response, versatility for the monitoring of different chemical families or types of water, autonomy as no external source of energy is required and easy deployment (Jones et al., 2015; Vrana et al., 2005). Many types of sampling techniques have been developed each providing specific advantages: dialysis membranes (Truitt and Weber, 1981), Polar Organic Chemical Integrative Sampler (POCIS) (Alvarez et al., 2004; Mazzella et al., 2010), Diffusive Gradient in Thin Films (DGT) (Zhang and Davison, 1995) and ceramic dosimeters (Martin et al., 2003). The uptake of the contaminants is usually achieved by means of sorption/binding onto a media which has specific retention properties. Because passive samplers can detect contaminants at ng-μg L^{-1}, they have been deployed for the monitoring of flame retardants in surface waters (Cristale et al., 2013), polycyclic aromatic hydrocarbons (PAHs) in groundwater (Bopp et al., 2005), pharmaceuticals in seawater (Martínez Bueno et al., 2016) and antibiotics in wastewaters (Chen et al., 2013), among other applications.

One of the main constrains in the deployment of passive samplers in environmental waters is the exposure time and the sorption kinetics without clogging the system. The diffusion coefficient (De) and the sampling rate (Rs), are key factors for determining the uptake efficiency and performance of a passive sampler. High De values means high free flow of contaminants to the receiving phase and, eventually, high Rs values if concentration efficiency at the receiving phase is high. The properties that govern the uptake of chemicals by a passive sampler are usually the polarity, water solubility and lipophilicity of target pollutants, and its performance depends on the type of water to be monitored and the sampler receiving phase.

This study is focused on diffusion-controlled ceramic dosimeters, first developed by Martin et al. (2001), which are characterized by an inert and rigid porous cylindrical ceramic membrane which operates as a diffusion barrier and a polymeric sorbent placed in the inner part capable to retain contaminants. Particularly, ceramic dosimeters developed by Martin et al. have a configuration of 50 mm of length, 1.5 mm of wall thickness and 10 mm outer diameter and they have been used to monitor PAHs. A similar structure of 50 mm, 2 mm of wall thickness and outer diameter of 10 mm with a porosity of 30% and lined with 5 μm layer of titanium dioxide (TiO_2) was used to determine dioxin contaminated water (Addeck et al., 2011). Those ceramic dosimeters have a pore diameter of 5 nm which makes diffusion slow and if deployed for wastewaters, clogging may occur.

In the frame of the present study, we have developed a Macroporous Ceramic Passive Sampler (MCPS) (Patent: P201530882, https://www.google.com/patents/WO2016207461A1?cl=es) whose main difference to previous ceramic dosimeters is its high connected porosity values and pore morphology consisting of large pore cavities connected by smaller pores. The idea was to allow for a high water volume inside the ceramic support. In addition, we have used a polymeric sorbent to enrich both polar and nonpolar cytostatic compounds, making the system versatile. As other ceramic dosimeters, the device is flow-independent and permits the sampling of the aqueous environment as diffusion constant through the wall will not be affected by the water flow. Finally, thanks to the high porosity, average weighed concentrations of cytostatics can be obtained in a complex matrix such as wastewater, provided the device is properly calibrated.

This study is focused on cytostatic compounds; class L for antineoplastic and immunomodulating agents according to the ATC classification (Drug Bank Database, 2013). They consist in a broad group of chemotherapy compounds with different chemical structure and modes of action used to treat different types of cancers. The environmental concern is related to the chronic effects that cytostatics may produce towards aquatic organisms as they bind directly to the genetic material or affect cellular protein synthesis affecting the growth and proliferation of both normal and cancer cells (Drug Bank Database, 2013). On a country-wide basis, consumption of the most commonly used anticancer drugs (~10–20 drugs) is in the order of tons/yr (Besse et al., 2012; Booker et al., 2014) and given their genotoxicity, concern has arisen on their emission and discharge to receiving waters (Buerge et al., 2006; Martín et al., 2011). In this sense, Wastewater Treatment Plants (WWTPs) have been identified as one of the main sources of pollution of cytostatic drugs, among other pharmaceuticals, to surface waters (Kosjek and Heath, 2011). Several compounds have been detected in wastewaters such as cyclophosphamide, tamoxifen and megestrol at concentrations in the range of 4.4–220 ng L^{-1} (Ferrando-Climent et al., 2014; Gómez-Canela et al., 2014; Negreira et al., 2014a). In these studies, grab or 24 h composite sampling are generally used and provide information on the compounds and levels detected in a given time. Alternatively, passive sampling provides time averaged concentrations on compounds present in a water body and it is especially suited for the control and time-integrated surveillance of contaminants. For cytostatic compounds, Fabrizi et al. (2012) used a printed glass slide as a passive sampler for surface monitoring. However, to our knowledge, passive sampling techniques have not yet been applied for the monitoring of cytostatic compounds in wastewaters.

The objective of the present study was to develop and assess the analytical capability of a home-made passive sampler (MCPS) for the analysis of cytostatic compounds in wastewater. First, the ceramic membrane was fabricated using alumina and the porogen agent using the slip casting method to obtain the desired high porosity. Then the polymeric sorbent was introduced inside the cylinder and preconcentration efficiency was evaluated. Then, it was calibrated and tested in terms of uptake rate considering the stability of 16 drugs in water. Based on these calibration studies, the Rs and De were determined for each compound to allow for the calculation of water concentrations (Cw) in the sampled medium. Finally, the system was deployed in WWTP influents and effluents, and simultaneously, grab samples from the same sampling points were collected during 4 days and analyzed by Solid Phase Extraction (SPE) to validate the method.

2. Experimental section

2.1. Chemicals and reagents

Sixteen pure analytical standards of cytostatic drugs (98–99%) purity were acquired from Sigma-Aldrich (St. Louis, USA) and from Toronto Research Chemicals (TRC, Ontario, Canada), namely cytarabine (CYT), ifosfamide (IFO), cyclophosphamide (CYC), capecitabine (CAP), prednisone (PRE), melphalan (MEL), doxorubicin (DOX), mycophenolic acid (MPA), tamoxifen (TAM), chlorambucil (CHL), cyproterone (CYP), megestrol acetate (MEG), leuprolide (LEU), irinotecan (IRI), vinblastine (VINB) and vincristine (VINC). Their molecular formula and relevant physicochemical properties are shown in the supplementary information (SI1). Cyclophosphamide-d_4 (CYC-d_4, Santa Cruz Biotechnology, USA) and mycophenolic acid-d_3 (MPA-d_3, Sigma-Aldrich, St. Louis, USA) were used as internal standards (IS). Stock solutions were prepared at 1000 μg mL^{-1} and working solutions at 10 μg mL^{-1} in methanol (MeOH). MeOH, acetonitrile (ACN) (SuperSolv grade) and HPLC water (LiChrosolv grade) were supplied by Merck (Darmstadt, Germany). Formic acid (HCOOH) and ammonium acetate (NH_4OAc) were supplied by Sigma-Aldrich (St. Louis, MO USA). Milli-Q water was produced from an Integral Water Purification System from Millipore (Billerica, MA, USA). Oasis HLB cartridges (200 mg) were purchased from Waters (Mildford, MA, USA) and were used for the solid phase