Field evaluation of diffusive gradients in thin-film passive samplers for wastewater-based epidemiology

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HIGHLIGHTS

- Total drug abuse in Hanoi was one order of magnitude higher than in Guangzhou.
- Methamphetamine and heroin were two the most consumed illicit drugs.
- DGT is a promising sampling tool for better understanding of drug usage in large scale.

GRAPHICAL ABSTRACT
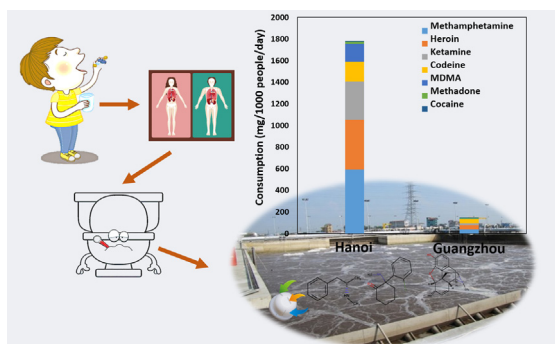
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ABSTRACT

There is a need for a simple water sampling technique to enable routine monitoring of community drug consumption through wastewater-based epidemiology (WBE). This study investigates the potential use of diffusive gradients in thin films to sample organic compounds (o-DGT) for WBE. Three types of resin gels (HLB, XAD 18, and XDA-1) within o-DGT samplers each were deployed in triplicate at the inlets of two sewage treatment plants of Southern Asian cities. The target compounds included 15 illicit drugs and 18 antibiotics. A comprehensive evaluation was undertaken regarding each resin's ability to accumulate the target compounds and accuracy by comparing active samples. The organic compounds accumulated on each resin gel were characterised at the molecular level using Fourier transform ion-cyclotron-resonance mass spectrometry (FT-ICR MS). The results showed that the HLB resin performed better than the XAD 18 and XDA-1 resins. Based on calculations using the HLB-DGT data, methamphetamine and heroin were the two most popular illicit drugs consumed among the studied populations, and were followed by ketamine and codeine, which agreed well with the authoritative reports and reference data. The total drug consumption in Hanoi was one order of magnitude higher than that in Guangzhou, thus implying a probably more serious drug situation in the former. Overall, the findings of this study demonstrate that o-DGT passive samplers are a promising tool for WBE studies, particularly at WWTPs or in urban streams where an automatic sampler for taking composite water samples is absent.

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1. Introduction

Wastewater-based epidemiology (WBE) has become a powerful complementary tool that can provide quantitative and qualitative information on the population consumption or exposure to chemicals in a defined sewer catchment. This approach relies on the principle that traces of target substances consumed by the population are excreted either unchanged or as a mixture of metabolites, which may ultimately enter the sewage system. Thus, by analysing the target parent and/or metabolic products in the influent wastewater of a domestic wastewater treatment plant (WWTP), the collective consumption/exposure to certain chemicals can be estimated (Zuccato et al., 2005). Over the past decade, many efforts have been made to improve the reliability of the WBE approach (Castiglioni et al., 2013; Castiglioni et al., 2006; Gracia-Lor et al., 2016; Ort et al., 2010; Thai et al., 2016); however, its application is geographically restricted. Although WBE has been applied on a large scale in Europe since 2010 to estimate illicit drug consumption (González-Mariño et al., 2020), it has hardly been applied in South/Southeast Asian countries (Du et al., 2020; Fallati et al., 2020; Nguyen et al., 2018). These countries are considered to have severe drug problems due to their proximity to the Golden Triangle region and inadequate governmental regulations. Few reports are available on additional applications of the WBE approach, for example, to assess the pharmaceuticals consumed by the populations of this region.

The first challenge facing South/Southeast Asia concerns the representativeness of the collected samples. Flow-proportional or time-proportional 24 h composite samples that are collected by an autosampler are adopted in most WBE studies to ensure valid conclusions (Ort et al., 2010). The preservation and transport of samples are essential to the validity of the results, but also increase the complexity of the system. However, in many developing countries of South/Southeast Asia, relatively few WWTPs are equipped with automatic sampling devices, or the installed autosampler does not work properly due to insufficient running expenses and erratic electricity supply. Running an autosampler has costs, generally referring to the cost of manpower and equipment maintenance. Passive sampling technology may address these issues by offering time-weighted average (TWA) concentrations of chemicals over an extended period of time, which can be easily obtained at a comparatively low cost (Mills et al., 2011). Passive sampling devices currently available for organic compounds mainly include the Polar Organic Chemical Integrative Sampler (POCIS) (Alvarez et al., 2004), diffusive gradients in thin films for tracing organic compounds (o-DGT) (Chen et al., 2012), Chemcatcher® (Kingston et al., 2000), microporous polyethylene membrane samplers (McKay et al., 2020; Verhagen et al., 2020), and semi-permeable membrane devices (SPMDs) (Huckins et al., 1993). Out of these devices, only POCIS has been demonstrated to be sufficiently robust to enable a reliable drug consumption assessment. The sampling rate of the compound should be calibrated in-situ as it is affected by environmental factors, including water flow rates, pH, and temperature (Baz-Lomba et al., 2017; Harman et al., 2011; Taylor et al., 2020). In contrast to POCIS, the chemical uptake by o-DGT passive sampler is governed by Fick's diffusion as the employment of agarose diffusive layer creates a diffusion pathway for the desired chemical and separates the receiving phase from the water body. The agarose diffusive layer rather than water boundary layer controls the sampling rate, which reduces the influence of varying hydrodynamic conditions (Chen et al., 2012; Chen et al., 2017; Chen et al., 2018; Fang et al., 2019; Guan et al., 2018; Li et al., 2019; Zou et al., 2018). A recent study demonstrated that o-DGT can be used to monitor three different illicit drugs (Guo et al., 2017a). However, despite the obvious need, o-DGT has not been sufficiently evaluated in the field, and more data are required to support its application for WBE studies.

To date, XAD 18 is the most widely used resin as a binding layer of o-DGT and has been tested for antibiotics (Chen et al., 2013; D'Angelo and Martin, 2018), household and personal care products (Chen et al., 2017), endocrine disrupting chemicals (EDCs) (Chen et al., 2018; Guo et al., 2017b), illicit drugs (Guo et al., 2017a), and perfluoroalkyl substances (Guan et al., 2018), thus being applicable to approximately 70 organic chemicals. The second most commonly used resin (Guibal et al., 2019) is HLB, which was used by Wang et al. (2019) and Zou et al. (2018) to monitor organophosphorus flame retardants in water. It has been suggested that HLB may accumulate chemicals with a higher accuracy compared to XAD 18, which is probably due to the competitive binding of chemicals on XAD 18 (Chen et al., 2017; Li et al., 2019). However, there is still insufficient field evidence to determine which type of resin is more widely applicable for o-DGT samplers.

Supported by the Belt and Road Initiative of the Chinese Academy of Sciences, we are planning to build a long-term, urban, wastewater monitoring network in selected developing countries in Asia. The present study was carried out in two typical South Asian cities with varying degrees of socio-economic features. The main objectives were to: i) assess the performance of o-DGT samplers comprising one of three types of resins based on each resin's ability to accumulate target compounds, as well as its precision, accuracy, and sampling cost; ii) estimate the drug consumptions in each of the two cities based on the o-DGT data; iii) compare the o-DGT estimates with survey reports and reference data. Additionally, the ultrahigh-resolution Fourier transform ion-cyclotron-resonance mass spectrometry (FT-ICR MS) was used to investigate discrepancies in basic molecular features accumulated by different o-DGT samplers, which has not been reported in previous o-DGT studies.

2. Materials and methods

2.1. Chemicals and reagents

According to current knowledge of the prevalence (UNODC, 2019b), metabolic fate (Zuccato et al., 2008), and stability of drugs in various types of wastewater (McCall et al., 2016), 15 illicit drugs including 9 parent drugs and 6 metabolites, were selected as the target compounds in this study, namely: cocaine (COC) and its metabolites benzoylecgonine (BEN) and cocaethylene (COCAE); codeine (COD); morphine (MOR) and 6-acetylmorphine (6ACE) as metabolites of heroin, fentanyl (FEN), methadone (MTD) and its metabolite ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP); amphetamine (AMP); methamphetamine (METH); ketamine (KET) and its metabolite norketamine (NKET); methylenedioxymethamphetamine (MDMA) and its metabolite methylenedioxyamphetamine (MDA). For licit drugs, we mostly considered parent antibiotics and hereby selected four sulfonamides, four fluoroquinolones, four tetracyclines, four macrolides, and two phenicols as follows: sulfamethoxazole (SMX), sulfadiazine (SDZ), sulfamethazine (SMZ), trimethoprim (TMP), norfloxacin (NOR), ciprofloxacin (CIP), ofloxacin (OFL), enrofloxacin (ENRO), tetracycline (TTC), oxytetracycline (OTC), doxycycline (DOX), chlortetracycline (CTC), erythromycin (ETM), clarithromycin (CTM), azithromycin (AZM), roxithromycin (RTM), chloramphenicol (CAP), and florfenicol (FF). More details, including the physicochemical properties and standard suppliers of drugs involved in this study, are shown in Table S1 of the Supporting Information (SI). Information on internal standards (ISs) and other reagents is given in Text S1.

2.2. o-DGT details

Standard o-DGT units were purchased from Nanjing Vision Environmental Science and Technology Co., Ltd. The standard o-DGT configuration consisted of a PES filter membrane (0.45 μm pore size, 0.14 mm thickness), an agarose diffusive layer (1.5% agarose, 0.8 mm thickness), and a resin binding layer (0.5 mm). Three different resins, HLB (Oasis, Waters Corporation, USA), XAD 18 (Sigma-Aldrich, USA), and XDA-1 (Sunresin Co. Ltd., China), were tested in the field for their suitability as a resin binding layer (Table S2). The area of the exposure window of the o-DGT plastic (ABS) moulding was 3.14 cm^2. The o-DGT

units were kept in clean, sealed plastic bags containing a few drops of 0.01 M NaCl at < 10 °C prior to field deployment.

2.3. Sample collections

We selected two WWTPs: one in Hanoi (hereafter WWTP$_{HAN}$) and one in Guangzhou (hereafter WWTP$_{GZ}$). Based on information provided by the personnel departments of the WWTPs, these WWTPs are the largest sewer facilities in their local areas, and mainly receive and treat domestic wastewater from households, workplaces, public sectors, and educational institutions. These two WWTPs serve approximately 500,000 people in an area of 55.6 km^2 in Hanoi, and approximately 2,130,000 people in an area of 141.5 km^2 in Guangzhou. Employees measured the real treatment capacity of the WWTPs during the sampling period (Table S3).

Both WWTP$_{HAN}$ and WWTP$_{GZ}$ were equipped with a refrigerated automatic sampler (Sigma SD900, Hach Company, USA) at the inlet after primary treatment, which includes screening of large-sized debris followed by grit removal. The sampler was equipped with a rack of 24 polyethylene bottles, which each collected 100 mL of wastewater every hour. The samples in the bottles were merged manually to provide a 24 h composite sample every day for seven consecutive days (11–17 May 2019 in Hanoi, and 11–17 June 2019 in Guangzhou). Aliquots (100 mL, in triplicate) of the composite samples were taken before 10:00 am each day and transferred to the laboratory within 30 min for further treatment. A temperature data logger (iButton®, Maximum Integrated, USA) was set to read the temperature every 15 min, and was placed simultaneously with the o-DGT units next to the autosampler at a depth of ~20 cm beneath the water surface of the influent channel to ensure that the samples were submerged for 7 days. Upon retrieval, the o-DGT units were washed with distilled water and then placed back into the original polythene bags. All of the retrieved DGTs were stored in a cool box and sent to the Guangzhou Institute of Geochemistry, Chinese Academy of Sciences, for extraction and chemical analysis. There was no rainfall during the sampling period.

2.4. Extraction and instrumental analysis

Wastewater samples were analysed using the methods described elsewhere with some modifications (Du et al., 2020; Samaraweera et al., 2019). Briefly, 100 mL of each water sample was filtered through 0.7-μm glass fibre filters (GF/F, Whatman, UK). The filtrate was then adjusted to pH to 2 using 4 M HCl before adding 0.2 g of Na$_2$EDTA and 50 ng of ISs. Although there were minor differences in the pretreatment procedures for illicit drugs and antibiotics, both procedures basically included two main steps: solid phase extraction (SPE) using an Oasis MCX or HLB cartridge (Waters Corporation, USA), and volume reduction under a gentle stream of N$_2$. The disassembled binding gels from the o-DGT units were ultrasonically extracted three times with methanol (Challis et al., 2018). Before instrumental analysis, the eluents from both the SPE cartridges and o-DGT binding gels were passed through 0.22 μm PES membranes (ANPEL Laboratory Technologies Inc., China). Sample analysis was performed using ultra performance liquid-chromatography tandem mass-spectroscopy (UPLC-MS/MS). Separation was achieved using an Agilent 1290 Infinity II instrument (Agilent Technologies, USA), and detections were performed using an Agilent 6470QQQ instrument equipped with an electrospray ionisation (ESI) source. The analytes were quantified by the internal standard method, which was carried out using an Agilent Mass Hunter Workstation (B.08.00). A full description of the pre-treatment procedure is available in Text S2. Optimised gradient elution methods and MS/MS conditions for all of the analytes are listed in Tables S4 and S5.

To explore the differences between the different o-DGT units at the molecular level, o-DGT extractions with methanol were measured using ultrahigh-resolution (10^7) FT-ICR MS (Bruker Daltonic GmbH, Bremen, Germany) equipped with a 9.4 T refrigerated,

actively shielded, superconducting magnet and a Paracell analyser cell. The samples were ionised in the negative-ion mode using an ESI source, and the detection mass range was set at m/z 150–1000. Procedure blanks were processed and analysed following the same procedure to detect possible contamination. The detailed analysis method is described in the Supporting Information and our previous studies (Mo et al., 2018; Tang et al., 2020).

2.5. Method validation

Extraction recoveries were determined by spiking 100 mL of ultrapure water and a blank o-DGT binding gel with a certain amount of each target compounds. First, 50 ng of IS mixtures were spiked into recovery-test samples before instrument analysis. The recoveries were calculated by comparing the concentrations obtained with the initial spiked concentration. To test for any matrix effects, a random influent sample from each WWTP that had gone through SPE was spiked with target and IS mixtures before instrument analysis. The difference between the spiked and obtained concentrations yielded the matrix effects of each analyte. The concentration of each analyte was obtained using a 7-points internal calibration curve with a correlation coefficient of >0.99. The instrumental accuracy and precision were assessed by injecting the standard mixtures at two levels (2 and 50 μg L^{-1} or 5 and 100 μg L^{-1}, by injecting 5 μL) every 12 samples. Carry-over was addressed by injecting a blank sample (10% aqueous methanol) after injecting the highest calibration level in the instrumental worklist. The carry-over was lower than the corresponding peak area of the lowest calibration level. The limit of quantification (LOQ) was based on the minimum measured concentration and extrapolated to a sound to noise ratio of 10. The conformity of the qualifier ion ratio and retention time with those of the standards were checked to be within the level of tolerance ($\pm$ 20% for the ion ratio and $\pm$ 5% for the retention time). All of the results for the method validation, including the recoveries, matrix effects, procedure blanks, method detection limits (MDLs), accuracy, and precision data of the instrument, are given in Tables S6 and S7.

2.6. Calculations

2.6.1. o-DGT

The o-DGT TWA concentration of each target compound in wastewater was calculated using Eq. (1):

$$C_{DGT} = \frac{M_{DGT}(\Delta g + \delta)}{DAt} \tag{1}$$

where M_{DGT} is the mass of the compound accumulated on the binding gel; Δg is the diffusion layer thickness, which includes the agarose diffusive layer and PES membrane; δ is the diffusive boundary layer (DBL) thickness of 0.2 mm (Chen et al., 2013); t is the o-DGT deployment time; A is the exposure area; and D is the diffusion coefficient of the compound, which depends on the chemical structure and is function of temperature. Among the variables, only D is not readily available; hence, the D values used in this study were based on measurements at 25 °C using a two-compartment diffusion cell by Chen et al. (2013) and Challis et al. (2016). For the compounds without experimental measurements, D was estimated using Archie's law, which is expressed as Eq. (2) (Challis et al., 2016; Chen et al., 2013):

$$D = \frac{3.3 \times 10^{-5} \varepsilon^m}{\sqrt[3]{M_W}} \tag{2}$$

where M_W is the molecular weight, ε is the porosity of the porous media, and m is the Archie's law exponent. Values of ε and m were taken from

Chen et al. (2013) as 0.98 and 2, respectively. Table S8 presents the D values for the temperatures during deployment (D_T), which were calculated based on that at 25 °C using Eq. (3):

$$log\, D_T = \frac{1.37023(T-25) + 8.36 \times 10^{-4}(T-25)^2}{109 + T} + log\, \frac{D_{25}(273+T)}{298} \quad (3)$$

2.6.2. Real-time population

Ammonia nitrogen (NH_4-N) is less affected by non-human sources in urban sewers and has been successfully applied to estimate dynamic populations (Been et al., 2014; Zhang et al., 2019); thus, we used the NH_4-N concentration of each 24 h composite sample to estimate the real-time population of the WWTP served area. The NH_4-N concentration was measured using an HACH HQ440D Laboratory Multi-Meter connected to an ammonium ion-selective electrode (Hach Company, USA). The population equivalents for the two WWTPs were calculated using Eq. (4):

$$Population = \frac{C_N \times F}{E_N} \quad (4)$$

where C_N (mg L^{-1}) is the NH_4-N concentration, F(m^3 d^{-1}) is the daily inflow rate of wastewater, and E_N (g d^{-1} people^{-1}) is the NH_4-N discharge coefficient. The data of C_N and F for the two WWTPs during the sampling period are listed in Tables S3 and S9. The selection of E_N values is mentioned in Section 3.3.1.

2.6.3. Consumption rate

Population normalised drug consumption (mg (10^4 people)$^{-1}$ d^{-1}) at the community level was estimated from the drug mass load flowing into the WWTP using Eq. (5):

$$Consumption = Load \times \frac{MW_p}{MW_m} \times \frac{1}{EF} \times \frac{1}{Population} \quad (5)$$

where MW_p and MW_m are the molecular weights of the parent drug and its metabolite, respectively, and EF is the human excretion factor via urine. The selected EF values and molecular weight ratios of the illicit drugs are given in Table S10. As for the antibiotics, the consumption was estimated by directly considering the mass load of the parent substance because a large portion of consumed antibiotics is excreted via urine in an unchanged form (Carvalho and Santos, 2016). Moreover, it was unfeasible to include specific metabolites in this study; however, antibiotic usage based on WBE estimations would be more convincing if we use non-parent biomarkers (Choi et al., 2018). Table S10 shows the excretion factors of the antibiotics analysed in this study.

We used the NH_4-N equivalent population derived from Eq. (4) to calculate the consumption of each target compound. The mass load in Eq. (5) was obtained by multiplying the measured drug concentration (ng L^{-1}) and daily inflow rate (L d^{-1}), as reported previously (Gushgari et al., 2019; Khan et al., 2014; Samaraweera et al., 2019).

2.7. Statistical analyses

Statistical analyses were performed using SPSS 22 (IBM Co., USA). A one-way analysis of variance (ANOVA) with Tukey's post-hoc test was used to compare the drug concentrations measured by the o-DGT units and those in active samples. Significant differences were defined as a p-value of <0.05. Errors are presented as the standard deviation of the mean ($n = 3$). Values below the MDLs were replaced by 1/2 MDLs for statistical purposes.

3. Results and discussion

3.1. Occurrence of target drugs in the two WWTPs

The aim of the automatic sampling was to provide 1-week measurements that could be compared with those derived from o-DGT samplers. The concentrations of the individual analytes measured by the autosampler are presented in Table S11. Among the 33 analytes, 13 illicit drugs including metabolites as well as 14 antibiotics were found in both Hanoi and Guangzhou municipal wastewaters. Unlike the situation in Europe (González-Mariño et al., 2020; Lai et al., 2016), COC was rarely detected in the two cities with a concentration range of < LOQ to 2.11 ng L^{-1} and <LOQ to 1.86 ng L^{-1} in Hanoi and Guangzhou, respectively. As a metabolite of cocaine in the presence of ethanol, COCAE was not detected in any of the samples, which was also the case for tetracycline antibiotics. The results showed that FEN was only found at WWTP$_{HAN}$ (maximum concentration of 0.63 ng L^{-1}). To date, there have been limited reports of FEN in wastewater. Fentanyl is a powerful synthetic opioid analgesic that has been approved for treating severe pain, typically advanced cancer pain, which allows a lower clinical dosage than MOR (drugabuse.gov/drugs-abuse/fentanyl). Cases of FEN-related overdose deaths have increased drastically recently in the United States, which has increased global concern over its abuse and illegally made market. The maximum concentration of FEN found in this study was much lower than that reported in the United States (maximum of 4.4 ng L^{-1}) (Gushgari et al., 2019).

Overall, the mean total concentration of illicit drugs in samples collected by the autosampler from WWTP$_{HAN}$ (2110 ± 209 ng L^{-1}) was nearly 30 times higher than that detected in samples from WWTP$_{GZ}$ (72.8 ± 10.2 ng L^{-1}), whereas the mean total concentration of antibiotics at WWTP$_{HAN}$ (4180 ± 507 ng L^{-1}) was approximately 3.5 times higher than that at WWTP$_{GZ}$ (1190 ± 105 ng L^{-1}). Among the quantified illicit drugs, METH and KET were ubiquitous at relatively higher concentrations, which implies that the abuse of METH and KET are probably popular in the two cities.

3.2. o-DGT performance

3.2.1. General descriptions

Influent water conditions, including temperature, pH, concentrations of NH_4-N, total nitrogen (TN), total phosphorus (TP) and chemical oxygen demand (COD$_{Cr}$), for the days that sampling took place are given in Table S9. Temperature and pH are two key factors that may influence o-DGT sampling (Guibal et al., 2019), but only exhibited small weekly variations, with mean temperatures of 28.2 ± 1.84 °C and 27.3 ± 0.24 °C in WWTP$_{HAN}$ and WWTP$_{GZ}$, respectively, and mean pH values of 7.78 ± 0.24 and 7.54 ± 0.23 in WWTP$_{HAN}$ and WWTP$_{GZ}$, respectively. The water flow rate is another influencing factors because the DBL thickness may become significant under low-flow conditions, thus decreasing o-DGT sampling accuracy (Davison and Zhang, 2012). In this study, we deployed o-DGT samplers in water flow conditions of >10 cm s^{-1} with exposure windows parallel to the flow direction (Fig. S1). After 7 days, a recommended deployment time for many o-DGT applications (Chen et al., 2013; Chen et al., 2017; Fang et al., 2019), the o-DGT samplers were retrieved with no scarred surfaces observed. The PES membrane surface was covered with a layer of particulates. When we disassembled the o-DGT units, we did not observe any visible particulates within; the disassembled diffusive gels were clean and transparent, and the binding gels were all intact (Fig. S1).

In order to make a comparison with other passive samplers, the o-DGT sampling rate (Rs) of each compound was calculated using Eq. (6):

$$Rs = \frac{D_T A}{(\Delta g + \delta)} \quad (6)$$

D_T, A, Δg, and δ are described in Section 2.6.1. The calculated Rs values ranged from 14.0 to 20.8 mL d^{-1} and 4.20 to 17.2 mL d^{-1} for illicit drugs

and antibiotics, respectively. The sampling rates provided by o-DGT in this study were relatively low when compared to those reported for the same compounds in POCIS (Harman et al., 2011; Alvarez et al., 2004). It is suggested that increasing the sampling area of o-DGT can result in increased sampling rates and higher sensitivity (Buzier et al., 2019).

3.2.2. Comparison of the binding gels

The performance of the o-DGT samplers with each of the three binding gels was further assessed with respect to analyte precision, accuracy, and sampling cost. In particular, the FT-ICR MS was used to investigate the features of organic compounds enriched on each binding gel at the molecular level.

3.2.2.1. Analyte detection. The results showed that 20 of the 33 targeted analytes were 100% detected in the o-DGT samples (Table S11). For the other analytes, six, including three illicit drugs (6ACE, COC, and MDA) and three antibiotics (SDZ, ENRO, and DOX) were detected in 50–83% of the samples, while five (FEN, COCAE, TC, OTC, and CTC) were not detected in any samples. A slightly higher detection frequency of antibiotics was found for the XAD binding gel (72.2%) in comparison to the HLB (71.3%) and XDA (70.7%) binding gels. This minor difference was related to the detection of NOR, which was determined at the lowest concentration ($< 10 \, \text{ng} \, \text{L}^{-1}$) among the antibiotics at WWTP$_{HAN}$ and was not always quantifiable using HLB/XDA gel triplicates. Conversely, the XAD binding gel accumulated the least illicit drugs. With respect to the o-DGT concentrations, there was no significant difference between the three different o-DGT samplers for most of the analytes. The quantified concentration data ranged from 1.32 to 3980 ng L^{-1} for the HLB gel, 1.00 to 3310 ng L^{-1} for the XAD gel, and 1.11 to 2510 ng L^{-1} for the XDA gel. The fact that the data ranged over three orders of magnitude indicates a good capacity to measure a set of analytes over a wide range of concentrations.

3.2.2.2. Triplicate variability. The overall relative standard deviation (RSD) of quantifiable data for triplicate samples across all analytes was $<40\%$ ($n = 141$). Excluding the outliers, the RSD values were then less than 25% ($n = 131$), thus falling within the generally accepted thresholds for environmental measurements using this technique (Fig. S2). There was only one of these outliers occurred in Hanoi, and the rest were all for the Guangzhou data at low concentrations. Although the overall RSD was not significantly different between the three types of binding gels ($p > 0.05$, Tukey's post-hoc test), the precision of the HLB gel was the best when only data of illicit drugs were included (Fig. 1). Moreover, the RSD values were more concentrated around 10% when the XAD binding gel was used to monitor antibiotics in wastewater, which implies a better performance of the XAD resin for antibiotics in comparison to the other two resins.

3.2.2.3. Accuracy. To assess the accuracy of o-DGT for estimating the compound concentrations in water, we applied Eq. (1) using the temperature-corrected diffusion coefficients to calculate the TWA concentration of individual compounds (C_{DGT}) (excluding those compounds with a detection frequency $< 50\%$). Each derived C_{DGT} was compared to the corresponding TWA concentration measured by the autosampler (C_{Auto}) (Figs. 2 and S3). The concentrations were not significantly different (*t*-test, p > 0.05), and a very good correlation was observed for a range of illicit drugs and metabolites with R^2 = 0.964, 0.942, and 0.958 for the HLB-, XAD-, and XDA-measurements, respectively. Most of these compounds were present at lower o-DGT concentrations compared to the autosampler. A possible reason is the smaller pore size of the diffusive gel compared to the filter membrane used for active water samples. Because the nanopore size of the diffusive gel layer does not allow large particles to pass through, and the large particles may adsorb targeted chemicals.
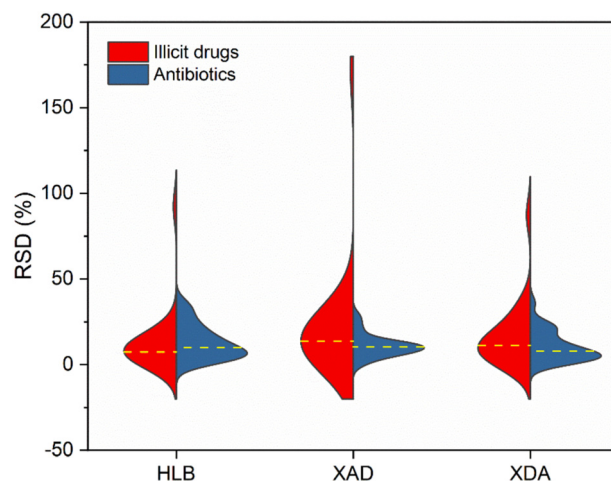

Fig. 1. Split-violin plot showing the relative standard deviation of o-DGT measurements across illicit drugs (red split) and antibiotics (blue split). The yellow dash line represents the median, and one each side of the black line is a kernel density estimation to show the distribution shape of the data.

We note that there were differences between the concentrations of some antibiotics. The mean concentrations of FQ antibiotics (OFL, NOR, and CIP) measured by the o-DGT samplers were much higher than those measured by the autosampler. This phenomenon has been observed in previous studies (Chen et al., 2013; Xie et al., 2018), but lacks a definitive explanation. Basically, the antibiotics selected in this study have relatively larger molecular weights and more complex functional groups than illicit drugs. The fact that illicit drugs are alkaline, while the acid-base property of antibiotics is compound-dependent, leads us to hypothesise that these differences may be due to the influence of pH. Because the pKa values of FQs are lower than the environmental pH (Tables S1 and S9), the FQs were in an ionic state and mainly in the form of zwitterion in wastewater, with a proportion of >75% among different species (neutral, cation, anion, and zwitterion) (Fig. S4, predicted by ACD/pKa). Therefore, there is a possibility that intramolecular repulsion among the FQ molecules decreased and molecular compression took place (Lead et al., 2003), thus leading to in-situ diffusion coefficients being higher than those measured in the laboratory. The effect of pH is difficult to elucidate unambiguously. We suggest further work to characterise the exact relationship between the analyte speciation and the governing uptake mechanism under real sewage conditions. Another possible reason for the difference is related to the non-continuous sampling of autosampler. The sampler started in time proportional at hourly intervals and stopped after it received a required sample volume. Continues flow proportional is the golden standard for WBE, but this is hard to achieve in most cases, as well as in our study.

3.2.2.4. FT-ICR MS characteristics. FT-ICR MS can provide 10–100 times higher ability in resolving power, resolution, and mass-to-charge measurement accuracy than other mass analyser instruments (Marshall, 2000). It was utilized in this study to compare molecular features of chemical substances in wastewater acquired by different o-DGT samplers. The FT-ICR mass spectral profiles of the extracts with methanol from the o-DGT samplers with the three binding gels were remarkably similar. As shown in Fig. S5, the largest number of ions that were identified in negative ESI mode were within a *m/z* of 300–400 and 600–700, and the average molecular formula was $C_{18}H_{29}O_{3.3}S_{0.94}N_{0.011}$, $C_{18}H_{29}O_{3.3}S_{0.94}N_{0.006}$, and $C_{18}H_{29}O_{3.3}S_{0.94}N_{0.010}$ for HLB-, XAD-, and XDA-DGT, respectively (Table S12). These identified molecular formulae were classified into four groups based on their elemental compositions: CHO, CHON, CHOS, and CHONS. They were compared with respect to relative abundance, which was defined as
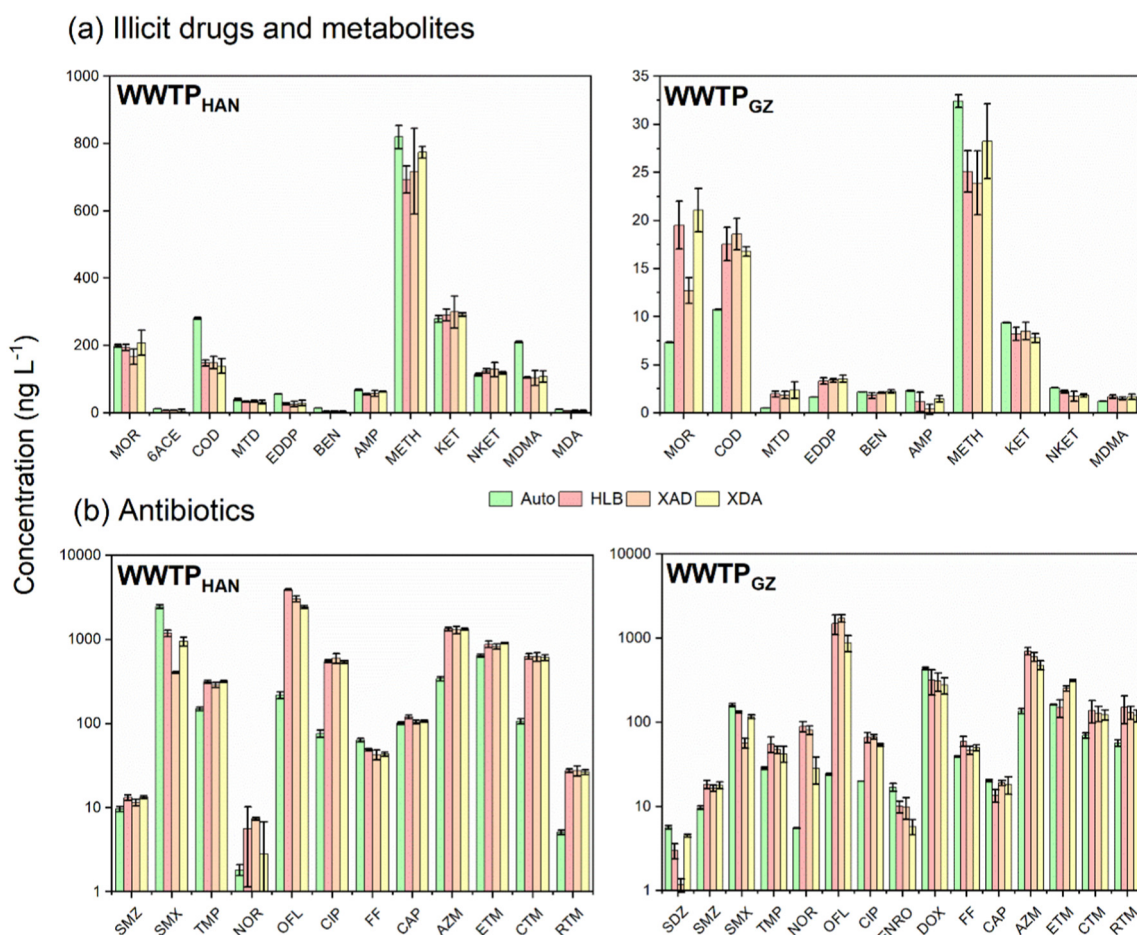
(a) Illicit drugs and metabolites

(b) Antibiotics

Fig. 2. Concentrations of the compounds measured by two sampling methods at Hanoi and Guangzhou wastewater treatment plants. Error bars are standard deviation of the mean ($n = 3$). Abbreviations: MOR = morphine; 6ACE = 6-acetylmorphine; COD = codeine; MTD = methadone; EDDP = ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; BEN = benzoylecgonine; AMP = amphetamine; METH = methamphetamine; KET = ketamine; NKET = norketamine; MDMA = methylenedioxymethamphetamine; MDA = methylenedioxyamphetamine; SDZ = sulfadiazine; SMZ = sulfamethazine; SMX = sulfamethoxazole; NOR = norfloxacin; OFL = ofloxacin; CIP = ciprofloxacin; ENRO = enrofloxacin; DOX = doxycycline; FF = florfenicol; CAP = chloramphenicol; AZM = azithromycin; ETM = erythromycin; CTM = clarithromycin; RTM = roxithromycin.

the intensity of each peak divided by the sum of intensities of all identified peaks (Fig. S5). It is obvious that the extracts were all dominated by CHOS compounds. This result agrees well with the findings of a study in which the dissolved organic matter of municipal wastewater effluent was dominated (90%) by CHOS formulae (Gonsior et al., 2011). The high abundance of CHOS can be ascribed to the presence of the most intense O_3S_1-containing components and their high ionisation efficiencies. The O_3S_1-containing components with the highest relative abundances were detected as those between $C_{16}H_{25}O_3S$ and $C_{19}H_{31}O_3S$. These molecular formulae were identical to those of linear alkyl benzene sulfonates (LAS) (Fig. 3), which are the world's largest volume synthetic surfactant, and are widely used in household detergents as well as in numerous industrial applications. In a previous study, Schymanski et al. (2014) applied FT-ICR MS to screen for polar organic contamination in the wastewater of a Swiss WWTP, and found that the screened suspects included LAS with the molecular formula $C_{16-20}H_{26-34}O_3S$. In fact, LAS cannot be efficiently removed by wastewater treatment plants; they are persistent polar pollutants that have been widely found in surface and coastal waters (Sakai et al., 2017; Sanderson et al., 2006).

The target compounds in this study, particularly illicit drugs, are mostly CHON-class compounds (Table S1). The HLB- and XAD-DGT samples both had the highest abundance of O_3N_1 species, which was followed by O_1N_1. Moreover, the number of molecular formulae assigned to the CHON group was slightly higher in the HLB-DGT sample

than in the XAD-DGT sample, thus implying that more diverse CHON compounds accumulated on the HLB gel at the molecular level. Although Guo et al. (2017a) used XAD-based o-DGT to monitor three
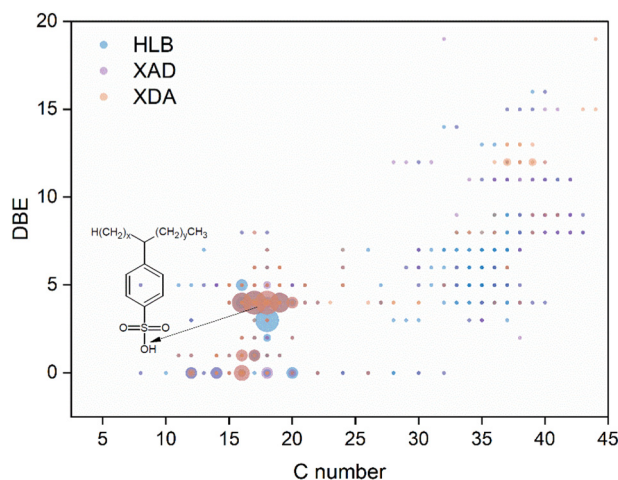

Fig. 3. Double bond equivalent (DBE) vs C number for all the CHOS compounds of the three DGT extracts. The marker size denotes the peak intensities of the compounds. Note: the proposed structure is representative, not determined.

types of illicit drugs in wastewater, we found that XAD was not the best binding gel for measuring the concentrations of illicit drugs.

3.2.2.5. Cost. Although there are differences between the autosampler and o-DGT measurements, the consistent results for most compounds suggest that o-DGT samplers can perform well in situ, especially considering that this approach allows us to easily sample at a large-scale and low cost. Chen et al. (2013) compared the costs of different sampling approaches. The most pronounced differences between o-DGT and auto-sampling involved the costs associated with sampling equipment and regular travel to the sampling site. For different types of DGT samplers, the main differences involve the cost of o-DGT materials (e.g. resin, filter membrane, and ABS moulding), along with the time and labour required for making gels. As there is no price difference between HLB and XAD-based devices at the present DGT website, we prefer to use HLB-DGT samplers based on our study findings.

3.3. Application of o-DGT to wastewater-based epidemiology

3.3.1. Estimated drug consumptions

Ammonia N is considered to offer a more suitable parameter for real-time population estimation than other water quality indicators, for example, COD, biochemical oxygen demand, and TP, which may also be influenced by industrial discharge (Been et al., 2014; Zheng et al., 2017). In China, the per capita discharge coefficients vary between different regions, although the variation range is relatively small across the country (7.16–9.94 g d^{-1} people^{-1}) according to estimations in the report of the national general survey of pollution sources (MEP, 2011). Normally, megacities in China are characterised by high NH_4-N discharge coefficients, including that for Guangzhou (9.80 g d^{-1} people^{-1}). According to the external drainage/sewage networks and facility design standards of Vietnam, E_N in Eq. (4) was set to 8.0 g d^{-1} people^{-1} for Hanoi, which corresponds to the level of third- and fourth-tier cities in China. Consequently, the mean NH_4-N equivalent population (P_{NH4-N}) was calculated as 340,900 ± 69,800 (range of 303,600–497,400) in Hanoi and 2,308,800 ± 265,300 (range of 1,899,000–2,581,000) in Guangzhou, which are comparable to the reported populations (Table S3). The peak values of P_{NH4-N} both occurred on weekends, which agrees with local living habits that increase the weekend population, because people like to do activities with friends and families in the city centre on the weekend.

As mentioned, the performance of the HLB binding gel was the best for monitoring illicit drugs; hence, the HLB-DGT data were used to assess the consumption of illicit drugs in the two study areas. Additionally, the good agreement between the consumption profiles of the autosampler and HLB-DGT further indicated its reliability (Fig. S6). The consumption of each antibiotic was estimated using the XAD-DGT data based on the wide application of XAD resin for measuring antibiotics (Chen et al., 2013; Chen et al., 2015; Xie et al., 2018). The influent mass loads of drug residues and estimated drug consumption in two communities of Hanoi and Guangzhou are displayed in Table S13. Statistical analysis revealed that the daily consumption per 10^4 people was significantly different (*t*-test, *p* < 0.05) for the majority of the drugs assessed here, while the overall drug consumption in Hanoi was one order of magnitude higher than that in Guangzhou.

The seizure and consumption of drugs have been found to show generally geographic discrepancies. For example, COC is reported as the most prevalent and most frequently seized illicit stimulant drug in southern and western Europe (EMCDDA, 2018). On the contrary, AMP and MDMA have been found to be the most frequently consumed stimulants in northern and eastern countries (González-Mariño et al., 2020). There is an ongoing opioid crisis in the United States, where the use of FEN in two cities (based

on wastewater analysis) has been reported to be much higher than that in other countries (Gushgari et al., 2019). However, in the present study, COC and FEN were rarely detected, thus suggesting a low prevalence of these drugs in the study area. Previous studies in South Asia also rarely detected COC and FEN (Du et al., 2020; Fallati et al., 2020). On the contrary, METH and HER were the illicit drugs with the highest consumption rates in the present study, which were followed by KET and COD (Fig. 4). Regarding antibiotics, macrolides (ETM, CTM, AZM, and RTM) exhibited the highest consumption rates among all of the antibiotics assessed in this study in both Guangzhou and Hanoi, despite the difference in the TWA concentrations of the two sampling methods. This also agrees well with findings for a South Asian touristic city (Samaraweera et al., 2019).

3.3.2. Comparisons with other studies/drug reports

Comparison of the consumption rates in Hanoi with other regions revealed that the METH consumption in Hanoi is higher than that reported for Europe (González-Mariño et al., 2020), South Korea (Kim et al., 2015), China (Shao et al., 2020) and the republic of Maldives (Fallati et al., 2020), but similar to that reported for Australia (Lai et al., 2016) and the city of Kuala Lumpur (Du et al., 2020). The consumption rate of HER in Hanoi was found to be higher than that in Kuala Lumpur (Du et al., 2020), but much lower than that reported for the United states (Gushgari et al., 2019). As a recreational drug, the mean consumption rate of MDMA per 10^4 people was considerably higher in Hanoi (168 mg d^{-1}) than in Guangzhou (4.87 mg d^{-1}), which implies that the situation of MDMA use is probably more serious in Vietnam than in southern China. According to the UNODC report in 2019 (UNODC, 2019a), the market for amphetamine-type stimulants, especially that of METH, continues to expand in Vietnam, and heroin remains the drug of primary concern. Compared with the monitoring results of a European multi-city study, the corresponding drug usage in Guangzhou was of a low to median levels (González-Mariño et al., 2020). The consumption rate of METH per 10^4 people in the same study area decreased by nearly 70% between 2012 (114 mg d^{-1}) (Khan et al., 2014) and 2019 (this study, 38.4 mg d^{-1}). The Chinese Drug Situation Report in 2018 (Commission, 2018) stated that, although METH had replaced heroin as the drug of primary concern in China, the quantity of METH seized in China and its manufacturing scale had greatly decreased at that time in comparison to previous years.
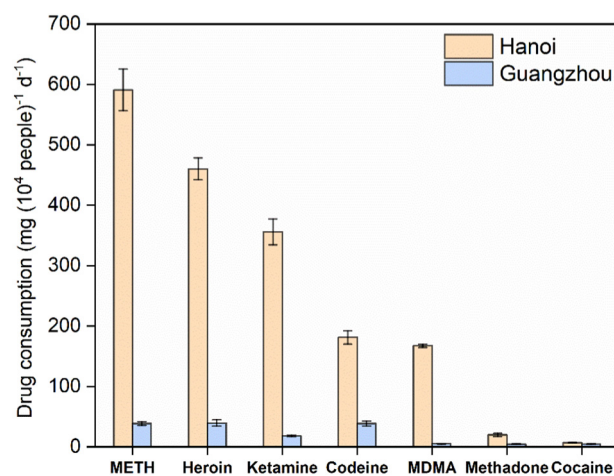

Fig. 4. Estimated consumption rates per 10^4 people from communities of Guangzhou and Hanoi. Error bars are standard deviation of the mean (n = 3). Abbreviations: METH = methamphetamine; MDMA = methylenedioxymethamphetamine.

4. Limitations and implications

The 24 h composite samples from the autosampler could not provide a 'true' mean concentration of the chemical compounds when the flow or chemical concentration varied due to episodic discharges (Ort et al., 2010). Consequently, although there was a difference in the chemical concentrations determined by the o-DGT samplers to that determined by the autosampler, the epidemiologic information extracted from the o-DGT data agreed well with authoritative reports/reference data. This demonstrates the applicability of the o-DGT method for providing complementary information to gain a better understanding of drug use. An obvious merit of o-DGT is that it helps to provide a relatively cleaner sample by capturing fewer analytical interferences including ion suppression and enhancement (Fig. S7). With respect to the three resins used in this study to make binding gels, HLB performed better than XAD and XDA. This could relate to the fact that HLB is a macroporous polymeric sorbent, which provides a reversed-phase capability with a special 'polar hook' to enhance the capture of polar analytes. As a preliminary study that applied o-DGT for WBE, future work should be conducted to i) measure precise diffusion coefficients by two-compartment diffusion cells, and ii) better understand the capacities and kinetics uptakes for different compounds.

Nevertheless, this study provides new perspectives regarding the following issues:

(i) To date, only a few investigations have aimed to apply passive sampling devices to the long-term assessment of community drug usage. These studies primarily used POCIS as the sampling technique (Baz-Lomba et al., 2017; Harman et al., 2011); however, this approach is considered to be a semiquantitative measurement tool because it lacks a fundamental uptake model and the sampling rate is affected by exposure conditions (e.g. temperature and water flow rate); thus, it has to be calibrated in-situ for a 'new compound'. In contrast, the o-DGT sampler does not require extra calibration for in-situ monitoring. Although the temperature-dependent diffusion coefficient must be determined, the procedure has been well established and is relatively easy to perform. Even when using the modelled diffusion coefficients based on Archie's law, good approximations can be made, as reported by Challis et al. (2016) and the present study. From the WBE perspective, we therefore recommend that o-DGT passive samplers be considered in future monitoring when sample collection by an autosampler is insufficient or inconvenient.

(ii) To date, o-DGT passive samplers have been successfully developed and tested in field trials for more than 100 organic compounds. However, we noticed that the main application proposed is to understand the occurrence, fate, and behaviour of organic pollutants in water bodies. Given that WBE has become a powerful complementary tool for surveying human exposure and consumption to a broad suite of chemicals, we suggest that future work on the development of o-DGT could shift to sampling urinary metabolites in urban wastewater. In addition, it would be particularly useful to establish an o-DGT-based monitoring network to provide valuable information for public health in the near future.

CRediT authorship contribution statement

Xin Liu: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. **Ruiling Zhang:** Methodology, Investigation, Writing – review & editing. **Hao Cheng:** Resources, Writing – review & editing. **Mahdi Safaei Khorram:** Methodology, Writing – review & editing. **Shizhen Zhao:** Resources, Writing – review & editing. **Trinh Thi Tham:** Resources, Investigation, Writing – review & editing. **Tran Manh Tri:** Resources, Investigation, Writing – review & editing. **Tu Binh Minh:** Project administration, Funding acquisition, Writing – review & editing. **Bin Jiang:** Formal analysis, Investigation, Writing – review & editing. **Biao Jin:** Formal analysis, Writing – review & editing. **Gan Zhang:** Supervision, Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.145480.

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